A STUDY OF THE FACTORS AFFECTING TABLET LUBRICANT EFFICIENCY.

A Thesis Submitted in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

of the

COUNCIL FOR NATIONAL ACADEMIC AWARDS.

by

GLENDA MOODY, B.Sc., M.P.S.

1981

School of Pharmacy,
Liverpool Polytechnic.
Byrom Street.
Liverpool. L3 3AF.

E.R. Squibb & Sons Ltd.
Reeds Lane.
Moreton, Wirral.
Merseyside. L46 1QW.

PAGE

NUMBERING

AS ORIGINAL

ABSTRACT.

Variation in lubricity, and its relationship to the various physical parameters of different batches of commercial samples of magnesium stearate, was investigated using an Instron Universal Testing Instrument. The lubricity evaluating parameter used was ejection energy. The distribution of the lubricant within the tablet was also determined using atomic absorption analysis. Samples of pure magnesium stearate, magnesium palmitate and varying stearate to palmitate ester mixtures were also examined to determine the influence of fatty acid composition upon lubricity.

Tests upon lubricant material alone and in the presence of excipients yielded different rank orders for relative lubricant efficiency. A magnesium stearate batch therefore, was concluded to have an inherent lubricity, the expression of which was modified by parameters such as particle size, surface area, crystal shape and ease of breakdown during mixing, to produce the practical lubricant efficiency (judged by excipient tests). Fatty acid composition was concluded to determine the inherent lubricity of a magnesium stearate batch.

This phenomenon was not specific to magnesium stearate because other lubricants investigated, both alone and in admixtures behaved similarly.

All magnesium stearate batches migrated to the die wall during the tableting process, producing a lubricant gradient across the tablet matrix, varying from approximately 1% in the core to 10% or more in the outer 0.2mm of the tablet surface. The lubricant distribution did not appear to be influenced by the compaction speed or the lubricant batch, although the E.S.C.A. analyses indicated that differences may be seen if only the outer 30Å of the surface is examined.

Thus it appears that the lubricity ability exhibited by a magnesium stearate batch, is the practical expression of its inherent lubricity. A poor batch can therefore be improved by modification of those parameters (such as particle size) which control the extent to which the inherent lubricity can be expressed.

LIST OF CONTENTS

	PAGE No.
Title page	i
Abstract	ii
List of contents	iii
List of tables	x
List of figures	xiii
List of plates	xvii
Acknowledgements	xviii
Abbreviations	xix

CHAPTER 1. INTRODUCTION.

1.1.	Definition of a Lubricant.	1
1.1.1.	In General.	1
1.1.2.	Application to Tableting.	1
1.2.	Lubrication Process.	1
1.2.1.	Welded Junction Theory of Friction and Application to Tableting.	1
1.2.2.	Types of Lubrication	3
1.2.2.1.	Fluid Lubrication	3
1.2.2.2.	Boundary Lubrication	3
1.2.2.3.	Application to Tableting	5
1.3.	Theories and Modes of Action of Lubricants	6
1.3.1.	Shear Strength Theory.	6
1.3.1.1.	Adsorption/Reaction with the Die Wall	7
1.3.1.2.	Slip of Laminar Plates	7
1.3.1.3.	Orientation of Plates at 45°	8
1.3.1.4.	Roller Bearing Action	8
1.3.2.	Antistatic Action	9
1.3.3.	Electron Distribution Theory for Laminar Solids	9
1.4.	Lubricants Used in Tableting	9
1.4.1.	Soaps	10
1.4.2.	Hydrocarbons	13
1.4.3.	Fatty Acids	13
1.4.4.	Fatty Alcohols	13
1.4.5.	Fatty Acid Esters	14

1.4.6. Alkylsulphates 14
1.4.7. Inorganic Oxides 15
1.4.8. Polymeric Compounds 15
1.4.9. Carbohydrates 16
1.4.10. Miscellaneous 16
1.4.11. Choice of Lubricant 16
1.5. Incorporation and Distribution of a Lubricant in a Tablet 17
1.5.1. Lubrication of Granules prior to Compression 17
1.5.1.1. Distribution of Lubricant and the Influence on Tablet Properties 17
1.5.1.2. Effect of Mixing Time 18
1.5.1.3. Comparison of Lubrication Methods 19
1.5.2. Incorporation Method 20
1.6. Effect of Lubricants on Tablet Properties 20
1.6.1. Hardness of Tablets 21
1.6.2. Dissolution and Disintegration 22
1.6.3. Incompatibility with Active Ingredient or Other Excipients. 23
1.6.4. Adhesion of Film Coatings 24
1.7. Alternative Methods of Applying and Using Lubricants to Overcome Adverse Lubricant Effects on Tablet Properties 24
1.7.1. Application of Lubricants to the Die Wall 24
1.7.1.1. Automatic Lubrication of Punches and Dies. 25
1.7.1.2. Lubricant Carrier Compression Cycle 26
1.7.1.3. Die Linings and Inclusions 26
1.7.2. Elimination of Lubricants 26
1.7.2.1. High Frequency Vibration 26
1.7.2.2. Composition of Die Wall 27
1.7.3. Reduction of Amount of Lubricant Required 28
1.7.3.1. Novel Roller Compactor 28
1.7.3.2. Reduction of Die Wall and Tablet Surface Contact Area 28
1.7.4. Alternatives to Hydrophobic Lubricants 28
1.7.4.1. Water Soluble Lubricants 28
1.7.4.2. Decreasing Hydrophobicity by the use of Sodium Chloride 29
1.7.4.3. Enrobed Solid Hydrophobic Tablet Lubricants 29
1.7.4.4. Modification of Magnesium Stearate and Stearic Acid 29

1.8. Batch Variation 30
1.8.1. Batch Variation of Magnesium Stearate 30
1.8.2. Manufacture of Magnesium Stearate 32
1.8.2.1. Precipitation Method 33
1.8.2.2. Direct Reaction 33
1.8.2.3. Alcoholic Metathesis 34
1.9. Methods to Evaluate Tablet Lubricants 34
1.9.1. Trial and Error 34
1.9.2. Use of Instrumented Machines 35
1.9.2.1. Instrumentation 35
1.9.2.2. Forces Involved in the Tableting Process 35
1.9.2.3. Parameters Evaluated 37
1.9.3. Shear Strength Measurements 41
1.9.4. Heat/Temperature Changes of the Tablet Surface 42
1.9.5. Extrusion Forces 43
1.9.6. Miscellaneous 43
1.10 Approach and Scope of the Present Study. 44

CHAPTER 2. METHODS AND MATERIALS.

2.1. Measurement of Lubricity of Lubricants 46
2.2. Measurement of Physico-chemical Properties of Magnesium Stearate. 48
2.2.1. Particle Size Analysis. 48
2.2.2. Surface Area Determination. 49
2.2.3. Crystal Shape 49
2.2.4. Purity Determinations 49
2.2.5. Assay 50
2.2.6. Percent Loss on Drying 50
2.2.7. Bulk Densities 50
2.3. Preparation of Admixtures of Lubricant and Excipient 51
2.3.1. Mixing Process 51
2.3.2. Uniformity of Mix Analysis Method 51
2.4. Analysis of Distribution of Magnesium Stearate 52
2.4.1. Quantity on Tablet Surface 52
2.4.2. Quantity on the Die Wall 52
2.4.3. Distribution in Tablets 53
2.4.4. Skimming Method 53

2.5. Humidity Measurements 54
2.6. "Blowability" Test 54
2.7. Manufacture of Magnesium Stearate/Palmitate Samples 55
2.8. Milling 56
2.9. Sieve Analysis 56

CHAPTER 3. MATERIALS AND THEIR PROPERTIES.

3.1. Tablet Excipients 58
3.1.1. Lactose B.P. 58
3.1.2. Dicalcium Phosphate Dihydrate B.P. 58
3.1.3. Cornstarch B.P. 59
3.2. Lubricants Other Than Magnesium Stearate 59
3.2.1. P.T.F.E. 59
3.2.2. Sodium and Zinc Ricinoleates 60
3.2.3. Palmitic Acid 60
3.2.4. Stearic Acid 61
3.3. Magnesium Stearate 61
3.3.1. Commercial Samples 62
3.3.2. Laboratory Prepared Lubricants 62

CHAPTER 4. LUBRICITY EVALUATION OF MAGNESIUM STEARATE

4.1. Work Involving Commercial Lubricants 66
4.1.1. Lubricant Material Alone Tests 66
4.1.2. Lubricants in Admixture with Excipients Tests 68
4.1.2.1. One Percent in Lactose--Single Test 68
4.1.2.2. One Percent in Lactose--Plateau Value 71
4.1.2.3. Varying Lubricant Concentration in Lactose 72
4.1.2.4. Estimate of Lubricant Carryover on die 75
4.1.2.5. One Percent Lubricant in Dried Dicalcium Phosphate Dihydrate. 77
4.1.2.6. One Percent Lubricant in Cornstarch 79
4.1.2.7. Comparison of Lubricant Behaviour in the Various Excipients. 79
4.1.3. Comparison of Lubricant Alone Tests with Admixture Tests. 83

4.2. Lubricity Evaluation of Laboratory Prepared Lubricants. 85
4.2.1. Tests upon Lubricant Material Alone 85
4.2.2. One Percent Admixture with Lactose. 88
4.2.3. Comparison of Commercial and Laboratory Prepared Lubricants. 94
4.3. Discussion 95
4.4. Summary.

CHAPTER 5. PHYSICAL CHARACTERISTICS OF THE LUBRICANTS. 110
5.1. Commercial Lubricants 110
5.1.1. Appearance of Crystals. 110
5.1.2. Particle Size. 117
5.1.3. Surface Area 123
5.1.4. Summary for Commercial Lubricants. 126
5.2. Laboratory Prepared Lubricants. 127
5.2.1. Particle Size. 127
5.2.2. Appearance of Lubricant Crystals. 129
5.3. Summary 133

CHAPTER 6. DISTRIBUTION OF LUBRICANT DURING THE TABLETING PROCESS. 135
6.1. Indications of Behaviour 135
6.1.1. Estimates of Lubricant "Carry Over" on Die. 135
6.1.2. Blowability Test 135
6.2 Further Investigation of Lubricant Distribution Through the Tablet Matrix. 142
6.2.1. Commercial Lubricants. 142
6.2.1.1. Concentration of Lubricant on the Tablet Surface. 142
6.2.1.2. Amount of Magnesium Stearate on the Die Wall 147
6.2.1.3. Distribution of Magnesium Stearate through the Tablet Matrix. 153
6.2.2. Laboratory Prepared Lubricants. 167
6.2.2.1. Amount of Lubricant on Die Wall. 167
6.2.2.2. Distribution of Magnesium stearate through the Tablet. 171
6.3. Summary 181

CHAPTER 7. WORK WITH LUBRICANTS OTHER THAN MAGNESIUM STEARATE. 186
7.1. Lubricant Materials Compressed Alone. 186
7.2. Lubricants One Percent in Lactose. 188
7.3. Lubricants Three Percent in Lactose. 188
7.4. Blowability Tests. 190
7.5. Summary. 191

CHAPTER 8. CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER WORK. 192
8.1. Conclusions. 192
8.2. Recommendations for Further Work. 198

APPENDIX 1. INSTRON WORK.
1.1. Validation of Instron Test. xxi
1.1.1. Choice of Ejection Energy as Evaluating Parameter. xxi
1.1.2. Die Cleaning xxi
1.1.3. Variability in Results. xxii
1.2. Calculation of Compaction Pressure. xxiv
1.3. Calculation of Ejection Energy from Instron Readings. xxv
1.4. Examples of Instron Traces xxvi

APPENDIX 2. VALIDATION OF MIXING CONDITIONS.
2.1. To Determine the Effective Lubricant Concentration. xxviii
2.2. Determination of Optimum Mixing Time. xxix

APPENDIX 3. GAS LIQUID CHROMATOGRAPHY WORK.
3.1. Calculation of Percentage Mix from G.L.C. Traces. xxxi
3.2. Calculation of Purity of Laboratory Prepared Lubricants. xxxiii

APPENDIX 4. ATOMIC ABSORBTION WORK.
4.1. Validation of Atomic Absorbtion Method. xxxv
4.1.1. Influence of Presence of Lactose upon results. xxxv
4.1.2. Influence upon Readings of the Amount of Lactose Present. xxxvi
4.1.3. Influence of Time on Readings. xxxvii
4.1.4. Effect of Magnesium Ion Concentration. xxxviii
4.1.5. Reproducibility of Results. xxxviii
4.2. Determination of Breakdown Factors. xl
4.3. Calculation of Amount of Magnesium Stearate in a Sample xlii

APPENDIX 5. CALCULATION OF MEDIAN PARTICLE SIZE USING THE MICROSCOPE METHOD OF ANALYSIS. xliv

APPENDIX 6. MODIFIED IDENTITY TESTS FOR LABORATORY PREPARED LUBRICANTS. xlv

6.1. Testing for Presence of Magnesium Ions. xlv

6.2. Testing the Melting Point of the Fatty Acid Layer. xlv

APPENDIX 7. PRACTICAL USE OF LUBRICITY TEST. xlvii

7.1. To Estimate Probable Behaviour of Batches of Magnesium Stearate. xlvii

7.2. To Estimate Mixing Efficiency of a Turbula Blender. xlviii

7.3. To Determine the Best Milling Method to Obtain Optimum Lubricity Performance from Stearic Acid. xlviii

APPENDIX 8. SURFACE AREAS OF MAGNESIUM STEARATE BATCHES. l

LIST OF REFERENCES li

LIST OF TABLES.

Table 2.1.	Quantities of materials required for lubricant manufacture.	56
3.1.	Properties of various batches of commercial magnesium stearate.	63-64
3.2.	Properties of laboratory prepared lubricants.	65
4.1.	Lubricity evaluation of samples of eleven commercial batches of magnesium stearate.	67
4.2.	Lubricity evaluation of samples of 1% lubricant in lactose.	67
4.3.	Lubricity evaluation of batches 1 to 7 magnesium stearate of varying concentration in lactose.	74
4.4.	Estimates of lubricant carryover on the die.	78
4.5.	Mean ejection energies of the eleven commercial batches of magnesium stearate in common tablet excipients.	78
4.6.	% Lubricant excipient factors for eleven batches of magnesium stearate in various excipients.	81
4.7.	Relative classification of eleven commercial batches of magnesium stearate.	80
4.8.	Mean ejection energies of lubricant samples in micronized and unmicronized forms in Jm^{-2}.	86
4.9.	Mean ejection energies in Jm^{-2} of 1% lubricant in lactose samples.	89
4.10.	Correlation coefficients and their levels of significance for various physical properties of magnesium stearate and relative lubricity.	102
5.1.	S.E.M. comparison of lubricant material alone and in mixtures with lactose.	111
5.2.	S.E.M. comparison of tablet surfaces of lubricant only and 1% lubricant admixture with lactose.	113
5.3.	S.E.M. comparison of lubricant material at various stages during tableting process.	115
5.4.	Surface areas of various lubricant samples.	124
5.5.	Percentage change in surface area before and after mixing with lactose.	125.

Table 5.6.	Particle Size Analyses of Lubricants Before and After Mixing with Lactose.	128
5.7.	Appearance of Crystals of Unmicronized Lubricant at Various Stages in the Tableting Process.	131
5.8.	Crystal Appearance of Micronized Lubricant During Various Stages in the Tableting Process.	132
6.1.	Mean Blown Distance in Centimetres for Various Lubricant Batches..	136
6.2.	Mean Blown Distance in Cms. for the Remaining Magnesium Stearate Batches.	137
6.3.	Information Obtained from E.S.C.A. Analysis.	143
6.4.	Amount of Magnesium Stearate Remaining on Die after Compression and Ejection of Lubricated Sample.	148
6.5.	Amount of Lubricant Remaining on the Die, for Eleven Batches of Magnesium Stearate.	149
6.6.	Influence of Tableting Process upon Amount of Lubricant Remaining on Die Wall.	150
6.7.	Lactose Skim Test Results	155
6.8.	Cornstarch Skim Test Results.	156
6.9.	Effect of Tableting Process on Amount of Lubricant on Die Wall.	169
6.10	Amount of Magnesium Stearate on the Die after Compaction at Different Compaction Speeds.	170
7.1.	Ejection Energy Measurements for Various Lubricant Batches Alone and in 'Admixtures'.	187
7.2.	Variation in Stearic Acid Batches.	189
7.3.	Estimation of Ease of Movement of Lubricants in Powder Bed	190
A2.1.	Mean Ejection Energies in Jm^{-2} for Different Concentrations of Magnesium Stearate in Lactose	xxviii
A2.2.	Percentage Mix Values for Various Mixing Times of One Percent Lubricant in Lactose.	xxix
A4.1.	Influence of Lactose on Atomic Absorbtion Readings.	xxxvi

A4.2.	Influence of Time on Atomic Absorption Readings.	xxxvii
A4.3.	Percentage Increase in Atomic Absorption Readings with Lactose.	xxxvii
A4.4.	Reproducibility of Sample Results Using Atomic Absorbtion Analysis.	xxxix
A4.5.	Breakdown Factors for Commercial Batches of Magnesium Stearate.	xli
A4.6.	Breakdown Factors for Laboratory Prepared Lubricants.	xli
A6.1.	Solidification Temperatures of Fatty Acids Obtained From Various Lubricant Batches.	xlvi
A7.1.	Ejection Energies of Various Magnesium Stearate Batches.	xlvii
A7.2.	Lubricant Excipient Factors for Various Magnesium Stearate Batches.	xlvii
A8.1.	Properties of Two Magnesium Stearate Batches.	l

LIST OF FIGURES

Figure 1.1.	Fluid film lubrication of two surfaces.	4
1.2.	Boundary film lubrication of two surfaces.	4
1.3.	Mechanism of boundary lubrication.	5
1.4.	Schematic illustration of rollers.	8
1.5.	Classification of lubricants.	11
1.6.	Orientation of "in situ" soap lubricant of stearic acid on iron oxide.	10
1.7.	Diagram of tablet section as obtained by Strickland et al. (83)	17
1.8.	Forces involved in tableting. a) compression b) ejection	36
1.9.	Ejection force-displacement curves. a) magnesium stearate b) talc.	38.
2.1.	Universal Testing Instrument. (Model 1122).	47
2.2.	"Blowability" test apparatus.	54
2.3.	"Blown" distance.	55
3.1.	Particle size distribution of lactose.	58
3.2.	Particle size distribution of dicalcium phosphate dihydrate.	59
4.1.	Instron traces for ejection of tablets containing 1% lubricant (Magnesium stearate) in lactose.	69-70
4.2.	Effect of consecutive compressions of lubricated samples upon ejection energy of sample.	73
4.3.	Ejection energy curves for cleaning magnesium stearate off the die.	76
4.4.	Scattergram of lubricant excipient factor for dicalcium phosphate and lubricant excipient factor for cornstarch for eleven commercial batches of magnesium stearate.	82
4.5.	Scattergram of ejection energy of lubricant alone samples and lubricant excipient factor for dicalcium phosphate.	84

Figure 4.6. Scattergram of ejection energies of unmicronized laboratory prepared lubricants compressed alone and in 1% admixture with lactose. 90

4.7. Scattergram of ejection energies of micronized laboratory prepared lubricants compressed alone and in 1% admixture with lactose. 91

4.8. Instron traces for ejection of tablets containing 1% lubricant in lactose for lubricant batches prepared in the laboratory. 93

4.9. Scattergram of percentage magnesium oxide in assay for commercial lubricants.
a) against ejection energies of lubricants tested alone.
b) against lubricant excipient factor for dicalcium phosphate. 96

4.10. Percentage moisture loss scattergrams for commercial lubricants.
a) against ejection energy of lubricant alone samples.
b) against lubricant excipient factor for dicalcium phosphate. 97

4.11. Scattergrams for the ratio of stearate to palmitate for commercial lubricants.
a) against lubricant alone ejection energies
b) against lubricant excipient factor for dicalcium phosphate. 98

4.12. Scattergrams for bulk density before and after tapping.
a) against ejection energies for lubricant alone samples
b) against lubricant excipient factor for dicalcium phosphate. 99

4.13. Scattergrams for particle size for commercial lubricants.
a) against ejection energy of lubricant alone samples.
b) against lubricant excipient factor for dicalcium phosphate. 100

4.14. Scattergrams for surface areas for commercial lubricants.
a) against ejection energy for lubricant alone samples.
b) against lubricant excipient factor for dicalcium phosphate. 101

4.15. Relationship between stearate to palmitate ratio in the lubricant material and its lubricant ability. 105

Figure 4.16. Relationship of particle size of lubricant material and ejection energy for the three mixture laboratory prepared lubricants. 107

5.1. Particle size distribution of Batch 1 lubricant before and after mixing with lactose. 118

5.2. Particle size distribution of Batch 4 lubricant before and after mixing with lactose. 119

5.3. Particle size distribution of Batch 6 lubricant before and after mixing with lactose. 120

5.4. Particle size distribution of Batch 7 lubricant before and after mixing with lactose. 121

6.1. Air movement during compaction. 136

6.2. Scattergram of 'blown distance' against lubricant excipient factor for dicalcium phosphate. 138

6.3. Scattergram of particle size and 'blown distance' 140

6.4. Scattergram of surface area and blown distance. 141

6.5. Ejection of tablet from die. 145

6.6. Compression of lubricated sample. 145

6.7. Ejection of a lubricated compact. 146

6.8. E.S.C.A. analysis of ejected and non ejected tablets. 146

6.9. Effect of compaction speed upon amount of magnesium stearate remaining on die wall. 152

6.10. Mid point skim radius. 157

6.11. Lubricant gradient across lactose admixture tablets. 158

6.12. Lubricant gradient across cornstarch admixture tablets. 159

6.13. Magnesium stearate distribution across a tablet compressed at 2mm/min. 161

6.14. Magnesium stearate distribution across a tablet compressed at 0.1mm/min. 163

6.15. Magnesium stearate distribution across a tablet compressed at 10mm/min. 164

6.16. Magnesium stearate distribution across a tablet compressed at 1000mm/min. 165

Figure 6.17. Effect of compaction speed on magnesium stearate distribution across a tablet 166

6.18. Lubricant distribution across tablets compressed at 0.1mm/min. 172

6.19. Lubricant distribution across tablets compressed at 0.1mm/min 173

6.20. Lubricant distribution across tablets compressed at 2mm/min. 174

6.21. Lubricant distribution across tablets compressed at 2mm/min. 175

6.22. Lubricant distribution across tablets compressed at 10mm/min. 176

6.23. Lubricant distribution across tablets compressed at 10mm/min. 177

6.24 Lubricant distribution across tablets compressed at 1000mm/min. 178

6.25. Lubricant distribution across tablets compressed at 1000mm/min. 179

6.26. Comparison of magnesium stearate needles distribution with varying compaction speed. 180

6.27. Effect of compaction speed on lubricant distribution across a tablet for pure stearate and palmitate plates. 182

6.28. Effect of compaction speed on lubricant distribution across a tablet for the mixed stearate and palmitate lubricants. 183

A1.1. Graphs of ejection energies of successive samples when varying cleaning solvents are used. xxii

A2.1. Effect of mixing time on ejection energy for three batches of magnesium stearate. xxx

A3.1. Typical G.L.C. trace for lubricant assay. xxxi

A3.2. Examples of traces to determine purity. xxxiii

A4.1. Effect of lactose on calibration curves. xxxv

A7.1. Influence of mixing time in a turbula blender on lubricity. xlviii

LIST OF PLATES

		Adjacent to page
Plate 1.	Commercial batches of magnesium stearate.	110
2.	Powder samples after half a minute mixing of 1% lubricant in lactose.	110
3.	Powder samples after ten minutes mixing of 1% lubricant in lactose.	110
4.	Lubricant material from powder sample after ten minutes mixing.	110
5.	Lubricant material from tablets.	110
6.	Lubricant material from curved surface of tablet.	110
7.	Curved surface of lubricant tablet.	110
8.	Curved surface of tablets of 1% lubricant in lactose.	110
9.	Curved surface of lactose tablet.	110
10.	Non micronized batches of laboratory prepared lubricants.	130
11.	Micronized batches of laboratory prepared lubricants.	130

ACKNOWLEDGEMENTS

I wish to express my grateful thanks to my academic supervisor Dr. M. H. Rubinstein, for his invaluable advice and guidance during the experimental work and his advice and constructive criticism during the writing of this thesis.

My thanks to E. R. Squibb and Sons Ltd. for the use of the Instron and especially to Mr. R. A. FitzSimmons, my Industrial supervisor.

I also thank all the staff, both at the Liverpool School of Pharmacy and the International Development Laboratories at E. R. Squibb and Sons Ltd. for their practical help, advice, and moral support during the three years required to carry out the experimental work. A special thanks to Steve Parry, Biology Department, Liverpool Polytechnic for his invaluable assistance in the preparation of the S.E.M. data.

With thanks, I acknowledge S.R.C. who funded the CASE award, without which this work could not have been possible.

My sincerest thanks to my parents for their interest and support throughout my career and to Chris who encouraged me in the final stages of the writing of this thesis. Last, but not least, my special thanks to my mother who cheerfully undertook the mammoth task of typing it.

ABBREVIATIONS.

Capital Letters

Å	Angstrom
B.P.	British Pharmacopoeia
B.S.	British Standard
^{o}C	Degrees Centigrade
D.T.A.	Differencial Thermal Analysis
E.S.C.A.	X ray Photoelectron Spectroscopy
G.L.C.	Gas Liquid Chromatography
J	Joules
Jm^{-2}; J/m^{2}	Joules per square metre
MNm^{-2}	Mega Newtons per square metre
MN	Mega Newton
MPa	Mega Pascal
N	Newton
R	Registered trade mark
P.T.F.E.	Polytetrafluoroethylene
P.V.C.	Polyvinylchloride
S.E.M.	Scanning Electron Microscopy
St : P	Stearate to Palmitate ratio
T.G.A.	ThermoGravimetric Analysis
U.S.P.	United States Pharmacopoeia

Small Letters

cm	centimetre
conc.	concentration
g	gram
gcm^{-2}; g/cm^{2}	grams per square centimetre
hr	hour
kg	kilogram
lb	pound
m	metre
mcg	microgram
mg	milligram
$m^{2}g^{-1}$; m^{2}/g	square metres per gram

min	minute
ml	millilitre
$ml\ min^{-1}$; ml/min	millilitres per minute
mm	millimetre
mm^2	square millimetre
$mm\ min^{-1}$; mm/min	millimetres per minute
nm	nanometre

Symbols

µg	microgram
$\mu g\ ml^{-1}$; µg/ml	microgram per millilitre
µm	micron
>	greater than
<	less than
≥	equal to or greater than
%	percentage
°	degree
"	inch
#	mesh

CHAPTER 1. INTRODUCTION

1.1. Definition of a Lubricant.

1.1.1. In General.

A Lubricant is a suitable material, a small amount of which, interposed between two rubbing surfaces, will reduce friction arising at the interface (1,2). It should also be capable of reducing wear of the rubbing surfaces.(3). To perform this function, the lubricant must provide a film, that will prevent solid - solid contact and is itself easily sheared. (4).

1.1.2. Application to Tableting.

Lubricants are added to tablet formulations primarily to reduce friction between the die wall and granules as the tablet is formed and ejected. (1,5,6). The other main activities attributed to a lubricant are a) prevention of sticking of granules to tooling -- antiadherent and b) improvement of flow properties -- glidant. (7,8,6). A given lubricant may provide one or more of these actions to varying degrees (6), but no material is highly efficient in all three categories. (9,10,5). Accordingly combinations of lubricants are often selected to provide the necessary total lubricant effect. (11,12). Careful selection is necessary since some lubricants may interact adversely when in combinations, for example, magnesium stearate and talc (13), although not all authors agree. (14,15).

1.2. Lubrication Process.

1.2.1. Welded Junction Theory of Friction and Application to Tableting

When two solids in "contact" are displaced relatively to each

other parallel to the plane of contact, a resistance, known as friction, must be overcome. (16,17,18). Surfaces are not "smooth" but consist of irregularities known as asperities which are large compared to molecular dimensions. (19). When two surfaces are brought together, they initially "touch" at points corresponding to the highest asperities. Application of a load causes deformation of the asperities, initially elastically, then plastically, till the load is supported. At this point the real contact area between the two surfaces is established. (20). For tangential motion to occur, between the two, these interfacial junctions must be sheared. This is the welded junction theory of Bowden and Tabor, 1958. (8). This is applicable to tableting since sliding friction is involved as 1) granules slide over each other and across the die wall during compression and 2) the tablet slides across the die wall during ejection. Frictional resistance is interpreted as the shearing of welded junctions formed between points of contact and the ploughing out of the softer material by the harder material riding over it. (3) This can readily be seen in an inadequately lubricated granulation, because the tablets will bear vertical striations along their edges reflecting the high frictional force of ejection along the die wall. (5,6). The total frictional force is

$$F = SA$$

F = Frictional force
S = Shear strength of junction
A = Surface area in contact.
(20,18,16)

and the relative value assigned to the friction of contacting surfaces is the coefficient of friction μ where

$$\mu = \frac{S}{W}$$

S = Shear strength of junction
W = Yield strength of softer material

(3,17)

The purpose of lubrication, therefore, is to reduce S by preventing the formation of welded junctions by preventing asperity contact or lowering the shear strength of the junctions that are formed. (3).

1.2.2. Types of Lubrication.

1.2.2.1. Fluid Lubrication.

The moving surfaces are completely separated by a continuous film of lubricant and the resistance to motion arises solely from the viscosity of the lubricant itself - Fig. 1.1 It is not a surface phenomenon. A fluid lubricant has a coefficient of friction of approximately 0.001 and wear is negligible.

1.2.2.2. Boundary Lubrication.

This is a surface phenomenon. The sliding surfaces are separated by lubricant films only a few molecules in thickness and the nature of the underlying surface will also affect the friction. (16). The surface asperities support much of the load - Fig. 1.2. Friction coefficients are much higher approximately 0.05 - 0.15 and wearing does occur. (19). Boundary lubrication is provided by natural surface films for example water vapour, contaminants, or low shear strength laminar solids, referred to as solid lubricants, for example metallic stearates. Since the main function of a boundary lubricant is to interpose between the sliding surfaces, a film that is able to reduce the amount of surface interaction and is in itself easily sheared, the solid must a) have a low shear strength, b) have the ability to adhere to the surface to be lubricated and c) be tough enough in film form to resist rupture

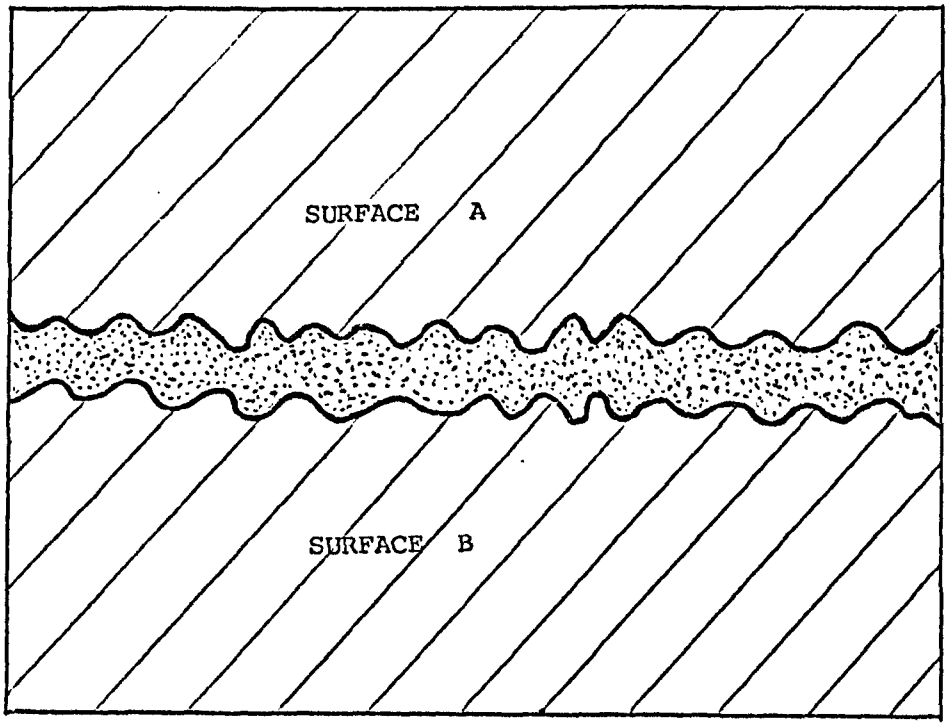


Fig. 1.1. Fluid film lubrication of two surfaces.

Boundary layer Bulk fluid

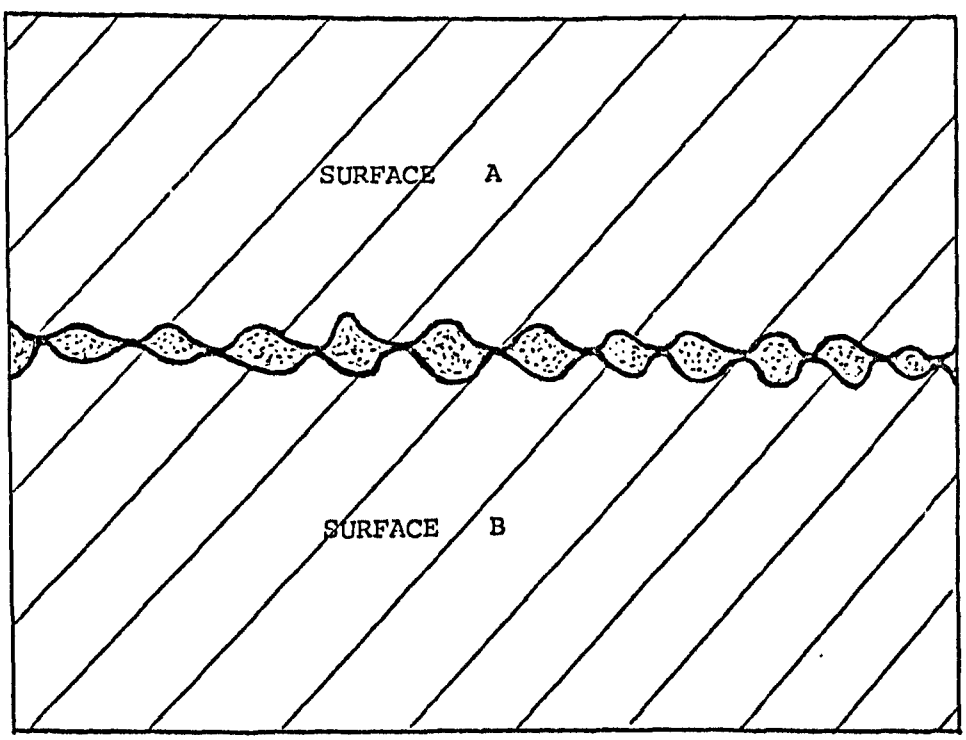


Fig. 1.2. Boundary film lubrication of two surfaces

Boundary layer Bulk fluid

and minimize wear. (21,22). Under boundary lubrication the load is now supported over an area A by the lubricant film -- Fig.1.3. and by minute junctions formed where the lubricant film has been penetrated.

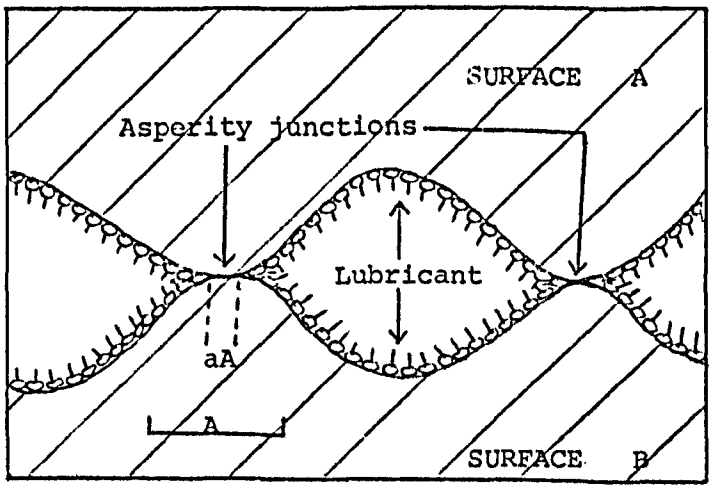


Fig. 1.3. Mechanism of boundary lubrication.

The frictional force F is the sum of the force required to shear the junction and the force to shear the lubricant film:-

$$F = aAs + A(1-a)s_1$$

s = Shear strength of surface
s_1 = Lubricant shear strength
a = Fraction over which junction is formed.

For a good boundary lubricant a is very small so that the major sliding resistance comes from shearing of the lubricant itself, hence the low shear strength requirement. (16).

1.2.2.3. Application to Tableting.

Strickland, 1959, (1,10), was the first to attempt to correlate general lubrication theories to the behaviour of a lubricant in tableting. Mineral oils were stated to be examples of fluid type lubricants being dependent upon viscosity for their

effectiveness. Mineral oils lubricated the die wall and prevented seizure of the two surfaces in proportion to their ability to maintain the continuous layer between the surfaces. The main problem with fluid lubrication was the increase in tackiness of the granules (reduced rate of flow) and a reduction in tablet strength (6,22). Boundary lubrication results from the adherence of polar portions of molecules with long carbon chains to the opposing surfaces, for example magnesium stearate. The latter type is most commonly used in tableting because it is more effective, requires smaller quantities and is more easily applied to granules (10). From his study Strickland (1) concluded that tablet lubrication appeared to be generally amenable to the theory of lubrication reported for other systems.

1.3. Theories and Modes of Action of Lubricants.

1.3.1. Shear Strength Theory.

This is the most commonly accepted mechanism of lubrication based on the Bowden and Tabor theory of friction. (section 1.2.1). With respect to tableting, the theory suggests that the frictional force at the tablet - die wall interface results from the shearing of junctions between the tablet and die wall materials (6). Thus the lubricant is thought to offer a lower shear interface than that characteristic of the die wall - tablet surfaces and will thus readily shear when tangential motion is initiated between the tablet and the die (ejection process) and hence the friction is less (6,10).

Shear strength values for various lubricants have been measured by Train and Hersey using a punch penetration test (23) (section 1.3.1.3). Scruton et al (24) measured the shear strength of calcium stearate monolayers and multilayers and other materials

and concluded that shear strength could not be simply interpreted in terms of molecular structure and orientation but was perhaps more closely related to bulk rheological properties even though the film may be only one or two molecules thick. This view was supported by Jentgen (4), who concluded that lubrication of solids cannot be ascribed to any one property of the materials; thermal and oxidative stability, chemical reactivity, mobility, hardness and crystal structure all affecting lubricant function and performance.

Use of shear strength measurements to evaluate lubricants (section 1.9.) has been attempted (25,26), but absence of a correlation between the two was reported by Lewis and Shotton. (25). Various modes of action have been proposed for these lubricants.

1.3.1.1. Adsorption/Reaction with the Die Wall,

Chemisorbed films are most suitable for boundary lubrication (27) because of the strong adherence to the surface to be lubricated (20), for example soap formation (18). Next in order of lubricant ability are physically adsorbed films provided by polar molecules on non-chemically reactive surfaces (27). Adhesion is not as strong but lateral cohesion is high. Adsorption of non polar molecules on a metal substrate is usually very weak, since adhesive and cohesive forces are small (27). However the latter has been reported to be more effective than a fatty acid or soap above its melting point (28). Thus metallic soaps are very effective boundary lubricants because they have high melting points and suitable shear properties.

1.3.1.2. Slip of Laminar Plates.

One crystalline structure that seems particularly favourable for low shear strength is a kind of laminar structure in which

there are strong bonds between atoms within a layer and weak bonds between atoms in adjacent layers. This layer-lattice shears easily because bonds between layers break easily and the layers slide over each other (29,30). However, this type of structure does not by itself ensure lubricating properties (20).

1.3.1.3. Orientation of Plates at 45°

Some lubricants,eg. graphite, were thought to form layers which were orientated at 45° to the moving surface, because altering direction of motion produced a very high frictional resistance, until re-orientation within the lattice had been achieved (23).

1.3.1.4. Roller Bearing Action.

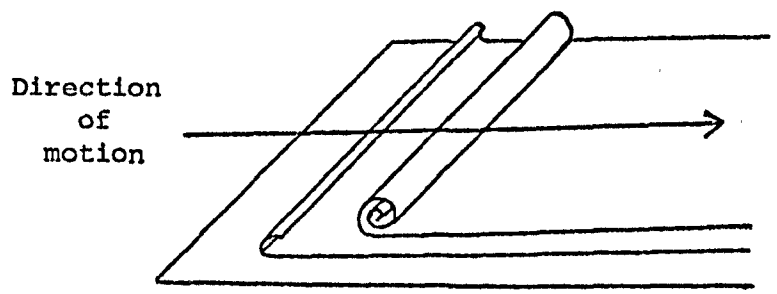


Fig. 1.4. Schematic illustration of rollers.

Electron microscopy work (31) indicated that laminar lubricants "roll up" in the direction of motion. It was suggested that there was a loosening of the interlayer binding forces first at the edge then within the crystal. This process would not be stopped by grain boundaries or pores in the crystal unlike the slipping plane theory. Train and Hersey (23) suggested that these lubricants would therefore only work efficiently where there is sufficient space for the roll to form eg. at low pressures. In a well fitting punch and die assembly, the necessary space is not available so they

are less efficient than the polar types.

1.3.2. Antistatic Action.

In 1947 Wolff et al. (32) suggested that a lubricant might act as a conductor by providing more points of contact or it might act as an insulator, which would reduce the high charge built up during the rapid compression of some compounds. Work by Gold and Palermo (33) showed that magnesium stearate and talc reduced the static charges generated by flow of particles through a tablet hopper. The authors carried out a further study on the antistatic properties of tablet lubricants themselves (34). Magnesium stearate, polyethylene glycol 4000, sodium lauryl sulphate and talc had the ability to lower accumulation of static charge. The antistatic properties decreased with decrease in lubricant concentration and was independent of the material accumulating the charge. Similar behaviour for magnesium stearate was also reported by Bhatia and Lordi (35).

1.3.3. Electron Distribution Theory for Laminar Solids.

A theory was postulated by Jamison (36) that lubricating efficiency is impaired when non-bonding electrons are on surface layers which must slide over each other. Non-bonding electrons which are unpaired are able to promote adsorption and decrease shear resistance but paired non-bonding electrons are less able to do this.

1.4. Lubricants used in Tableting.

The ideal lubricant has yet to be discovered. It should be white or colourless, odourless, tasteless, soluble in water, non toxic and efficient at low concentration. It will probably be a

synthetic compound (37). Lubricants in general can be fluids, semisolids or solids (38) (Fig. 1.5.) but tablet lubricants are generally solids (section 1.2.2.3.).

1.4.1. Soaps.

These are the metallic salts of fatty acids. A preformed soap will act as a boundary lubricant on both reactive and non-reactive metals but an "in situ" soap is only effective on reactive metals. (39). The latter is produced by reaction of a fatty acid with a reactive metal to form the metallic soap. Above the melting point of the soap, the lubricity efficiency decreases (39,18,16). On reactive surfaces moisture and metallic oxide films must be present (39) to form an in situ soap. A minimum of eight carbon atoms in the fatty acid is required. On non reactive surfaces at least twelve carbon atoms are required (18). The soap molecules are orientated as shown in Fig. 1.6.

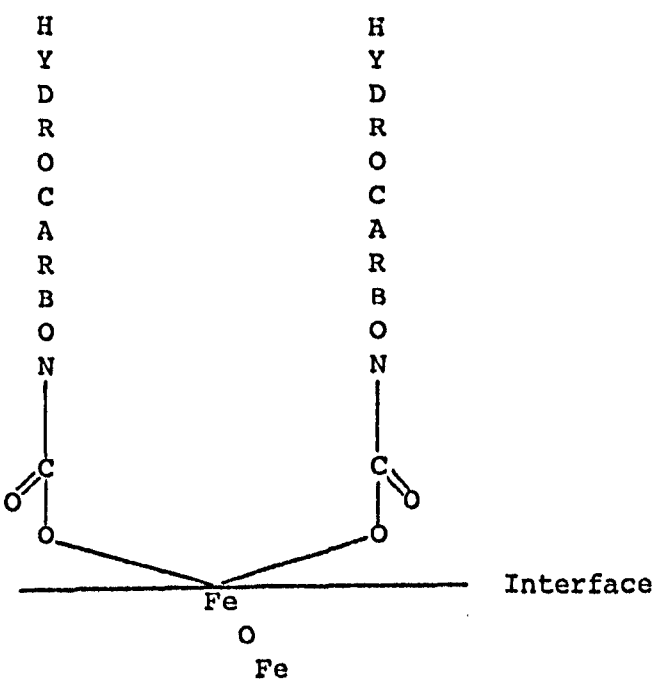


Fig. 1.6. Orientation of "in situ" soap lubricant of stearic acid on iron oxide.

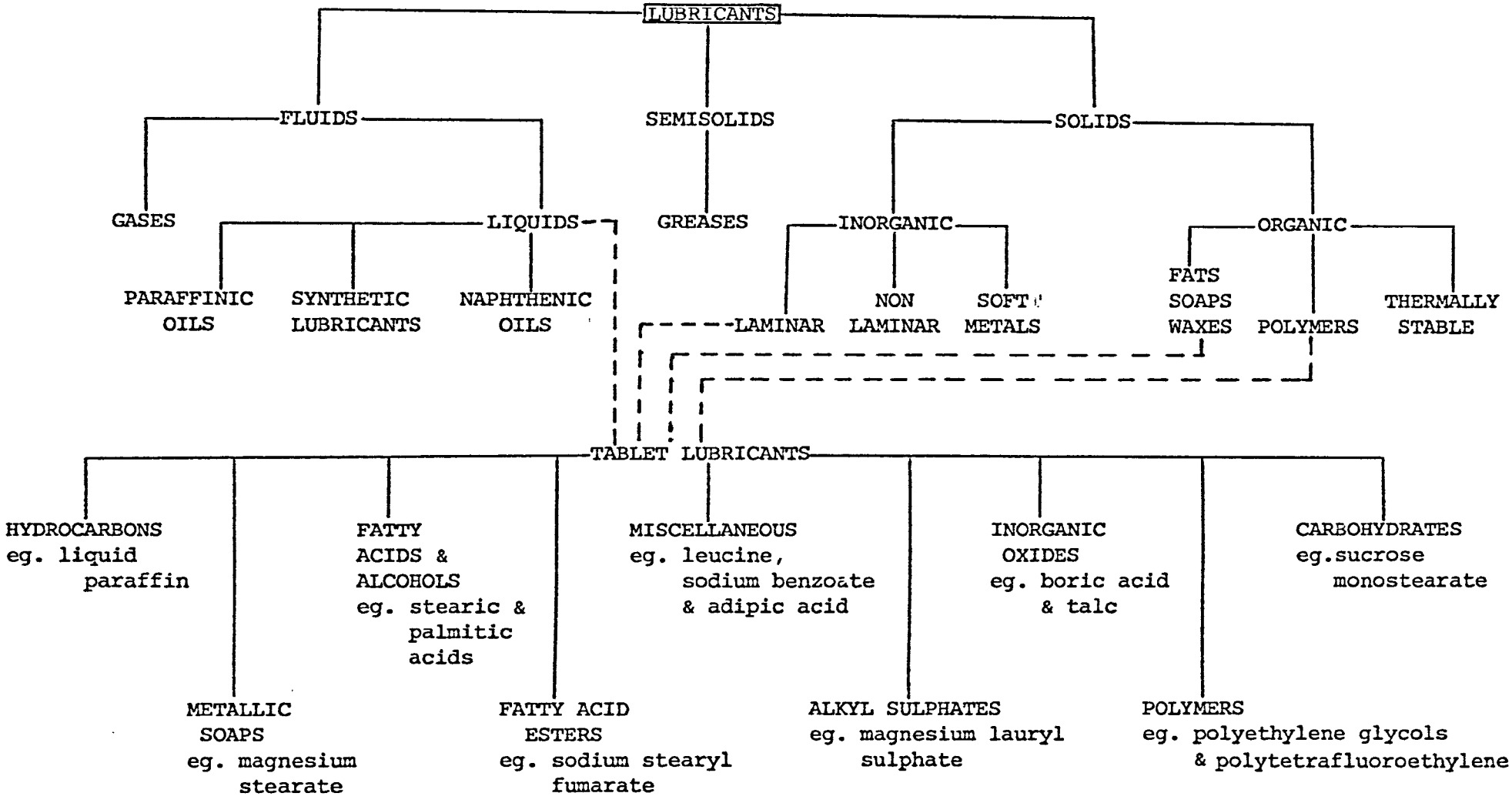


Fig. 1.5. Classification of Lubricants.

This orientation leads to two phenomena:- a) it provides close molecular packing thereby minimizing metal to metal contact, (20) and b) increase in chain length in the 12-18 carbon range decreases friction by increasing the separation of the two surfaces to be lubricated. (20, 27, 1). This type of soap film is chemisorbed onto the substrate (monolayer) as well as physically adsorbed (multilayer). Next in lubricating ability order are physically adsorbed films e.g. soaps on non reactive surfaces. Adhesion is not as strong although cohesion is high, so it will not be as effective as an in situ soap (27). Strong hydrogen bonding forces between fatty acid molecules produces thicker more stable films. Evidence and theories for multilayer formation are presented by Allen and Drauglis (27); the most relevant resulting in the formation of a liquid like film consisting of loosely bound layers of long chain molecules orientated normally to the substrate, due to induced dipole and hydrocarbon mutual interaction forces. Materials in this state are more viscous in the direction of molecular orientation, thus soaps will readily support a normal load but will shear easily when sliding occurs. The best lubrication is provided by lubricant films which have high melting points and suitable shear properties, and for these reasons metallic soaps are effective lubricants (28). A melted soap film can still function as a lubricant until it is desorbed, the stronger the surface adhesion the higher the temperature of desorption.

The best (1) and most commonly used soaps are the metallic stearates, especially magnesium stearate (section 3.3.). Calcium, zinc, sodium and aluminium stearates have also been investigated, (22, 1, 25) as well as metallic oleates, elaidates, laurates and myristates (1,6). With metallic stearates, lower melting points generally favour lower ejection force (22) and the polyvalent

(bivalent especially) salts are superior to the monovalent salts. (1,9). These compounds are hydrophobic and usually have a deleterious effect on tablet disintegration, hardness and dissolution (section 1.6). The nature of the cation affects the thermal stability of the salt (40,41,42). There are no general rules for incompatibilities, each has to be individually assessed (43) but all hydrolyse aspirin due to their alkaline nature (section 1.6.3) (44).

1.4.2. Hydrocarbons.

These are not commonly used but have been investigated (1,25,26) Juslin and Krogerus investigated hydrocarbons of C_{16} to C_{22} and C_{28} chain length. They were found to be poorer lubricants than fatty acids or alcohols (45,46,47,48) but they have less effect on tablet hardness and disintegration.(49). Generally as the carbon chain length increased, the lubricant efficiency increased (45,46,47,48).

1.4.3. Fatty Acids.

Two types of lubrication can occur, either by fatty acid itself or by soap formation as described in section 1.4.1. The fatty acid is ineffective above its melting point.(50). The longer the carbon chain length, the better the lubricity. Juslin and Krogerus (45,46 47,48) concluded that these compounds were more efficient than the alcohols or hydrocarbons. Tablet hardness and disintegration are adversely affected.(49). Examples of this group are lauric, myristic, palmitic and stearic acid (section 3.2.4), the latter the most commonly used.

1.4.4. Fatty Alcohols.

Saturated straight chain alcohols generally appear to exhibit properties of fluid type lubricants probably due to their low polarity.

Lubricity decreases as carbon chain length decreases corresponding to a decrease in viscosity (1). Juslin and Krogerus (45,46,47,48) showed that these compounds are less efficient than fatty acids but more efficient than hydrocarbons. Tablet hardness may be slightly decreased (49). Examples are lauryl, myristic and stearyl alcohol.(1).

1.4.5. Fatty Acid Esters.

Sodium stearyl fumarate has been investigated by Suren (51), and Lindberg (52) and reported to compare favourably with magnesium stearate. Particle size was reported to be very important by Hölzer et al. (53) during their evaluation of this compound as a lubricant. Glyceryl monostearate is an ester of glycerol and stearic acid and is reported to be suitable for aspirin tablets provided no alkaline impurities are present (54,55). Sorbitan monostearate, a mixture of the partial esters of sorbitol and its mono and di anhydrides with stearic acid,(10) and Precirol^{R},a mixture of palmitic-stearic esters of glycerols of known composition (56,57) have also been investigated. The latter is reported to be as effective as magnesium stearate but at higher concentration. It has little effect on tablet properties (57) including aspirin stability provided alkaline impurities are absent (54,55).

1.4.6. Alkylsulphates.

These are magnesium and sodium salts of lauryl sulphate. Caldwell and Westlake (58,59) claimed similar lubricity to magnesium stearate and that the magnesium salt was better than the sodium salt although Strickland (1) did not agree. A higher concentration than magnesium stearate is required for the same lubricity. The magnesium salt is claimed to be a more efficient lubricant than magnesium stearate but does not have the antiadherent properties (60,22). Both are

soluble in water and therefore are expected to have less effect on tablet dissolution and disintegration than magnesium stearate.(61,62).

1.4.7. Inorganic Oxides.

These compounds tend to be antiadherents rather than lubricants (1) and although they feel slippery, they are unable to exert their beneficial effects with the forces employed in tableting (23). Boric acid is used but not for tablets for internal use because of its toxicity (6,8). Talc is commonly used. It is a native hydrous magnesium silicate (63,64), insoluble in water and batch to batch variation will occur due to impurity variation (64). It is a poorer lubricant than magnesium stearate (26,51,65) but is a good glidant and antiadherent (10). It has a retardant effect on tablet dissolution and disintegration (66,51,67) and hardness (68,69). Concentration used is between 1 and 5%^{w}/w. (8)

1.4.8. Polymeric Compounds.

The main group are the polyethylene glycols of varying molecular weights, being the polycondensation products of ethylene oxide and water (70,63). They are soluble in water and used for soluble tablets at a concentration of 1-4%^{w}/w (6). Decreasing particle size can improve lubricity (71) but they are not as effective as magnesium stearate (72, 10, 37). They are reported to have retardant effects on disintegration (66,68), tablet hardness(68), and aspirin stability (54).

Polyoxyethylene glycols, also known as polyoxyethylene monostearates, are direct reaction products of alkylene oxide and stearic acid. They are water soluble (73). They are slightly less effective than the polyethylene glycols,(74) and poorer than sucrose esters (75) and magnesium stearate. Concentration for use is 3%^{w}/w (72). Tablet hardness and disintegration areaffected but

to a lesser extent than with the polyethylene glycols.

The other main lubricant in this group is polytetrafluoroethylene which is described in section 3.2.1.

1.4.9. Carbohydrates.

The two major carbohydrate lubricants are sucrose monostearate and sucrose monopalmitate. They increase mechanical strength of tablets (74,75,76) and enhance disintegration (76,75). The stearate ester is more efficient than the palmitate.(74) They are better lubricants than polyethylene glycols (74,75) but at 2.5%^{w}/w concentration are less efficient than magnesium stearate (52,74).

1.4.10. Miscellaneous.

Many compounds have been tried as lubricants including sodium benzoate (77c,22), leucine and isoleucine (78), adipic acid (79), fumaric acid(77a,b and c) and amides (1,30,80) as well as many other combinations of fatty acids and waxes.

1.4.11. Choice of Lubricant.

The basic requirements of a boundary lubricant are a) resistance to penetration under load and b) ability to shear easily (section 1.1). Selection of the solid lubricant depends upon load requirements, sliding velocity, cost, operational temperatures and abrasiveness of the environment. Lubricant purity and particle size must also be considered (81). In tableting, in addition, considerations such as colour, toxicity, machine type, type of granulation, drug stability, effect on tablet properties and the need to make the medicament rapidly and entirely bioavailable are important. (9). Thus magnesium stearate is the most widely used because it is a good lubricant. It does however adversely affect tablet properties.

1.5. Incorporation and Distribution of a Lubricant in a Tablet.

With the exception of a few materials which themselves possess some lubricant action e.g. microcrystalline cellulose (82), tableting on production equipment is not possible without proper lubrication of the granules (5).

1.5.1. Lubrication of Granules Prior to Compression.

This is the method normally employed (5,6,7).

1.5.1.1. Distribution of Lubricant and the Influence on Tablet Properties.

In 1915, Wolff et al (32) reported that when granules were lubricated using boric acid coloured with amaranth, the coloured lubricant lodged in roughened cavities of granules, but did not envelop them. Munzel and Kagi 1954 (12) reported that talc adhered well to carbon granules and could be dispersed efficiently but this was not so with stearic acid. Strickland et al (83) doubted the validity of these conclusions and studied the distribution of a lubricant in a tablet during and after formation. They reported that lubricants added as dry powders, served to form a coat around individual granules.

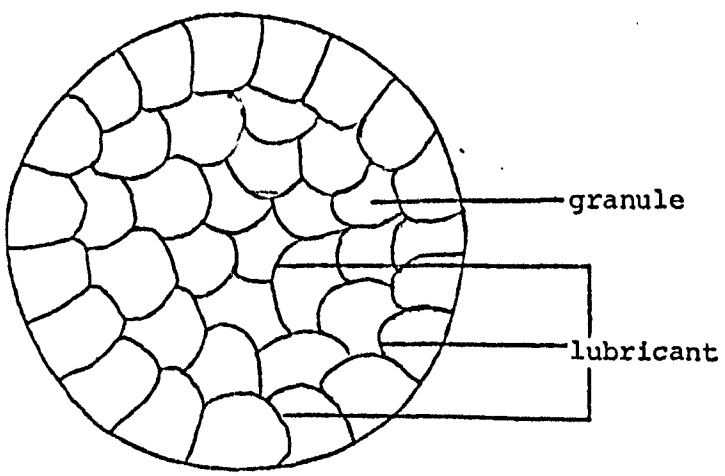


Fig. 1.7. Diagram of tablet section as obtained by Strickland et al.(83).

There was no evidence of marked tendency of lubricants to mix intimately with the contents of granules during the compressional process. Lubrication is therefore a surface phenomenon. Film formation has been further demonstrated by Bolhuis and others (84,85, 86,87). This lubrication method leads to problems, since the majority of lubricants in common use are hydrophobic and consequently the hydrophobic film formed around the granules inhibits dissolution of soluble components (87,85,88,5,62) and reduces tablet strength (87,86,84) (see section 1.6). Addition of colloidal silica will prevent formation of, or disrupt an already formed magnesium stearate film (84,85), which produces a negative effect on lubricity but not necessarily an improvement in tablet properties. Therefore its use as a general remedy for magnesium stearate problems is doubtful (89). Since lubricant function is related to surfaces, the greater the degree of subdivision of the lubricant the greater its covering power and hence its greater efficiency (5,90,91). For this reason lubricants are usually added to the granulation as a fine powder; 60 mesh(6) or finer (7).

1.5.1.2. Effect of Mixing Time.

Bolhuis et al (87) showed that increased mixing time will obviate the effect of lubricant particle size, suggesting that the magnesium stearate is sheared off larger particles during mixing and is adsorbed at the granule surface until a film is formed completely around the granules. They were able to photograph such a film from around sodium chloride crystals. Work by Shotton and Lewis (92) was consistent with these observations. Thus an increase in mixing time means a more uniform distribution of lubricant in tablets (93) but adversely affects dissolution (87,93,62,89,84,85).

De Boer et al (94) investigated the effect of mixing on bonding properties of blends of magnesium stearate and tablet excipients, and reported that bonding was dependent upon compression behaviour and bonding mechanisms of the excipients. They found that the greater the degree of fragmentation, the less the effect. This view was supported by Egermann (95). Shah and Mlodozeniec (96) extensively studied this phenomenon and concluded that prolonged mixing decreased bulk density, ejection force and tablet hardness and increased dissolution and disintegration, the mechanism being film formation as postulated by Bolhuis et al. Bossert and Stamm (97) investigated mixing speed; high speed mixing gave good lubricant distribution, resulting in lower tablet hardness. Low speed mixing had to be carried on longer to give thorough distribution of lubricant but resulted in a continuous film about the granules.

Hersey (98) suggested that the mixing process is that of ordered mixing, which requires an interaction between particles such that adherence or coating occurs to give an homogenous mix (99) such as between mixtures with a large proportion of large particles (granules) and a small portion of fine cohesive particles (lubricant). (section 2.3.1.)

1.5.1.3. Comparison of Lubrication Methods.

The manner of granule lubrication would be expected to influence lubricant activity and this has been studied. Spraying or tumbling granules with a nearly saturated aqueous solution of lubricant was reported to be more effective than dusting the lubricant onto granulations (32). Strickland, (83), however, did not verify this conclusion when investigating the application of lubricants as 100 mesh powders or in an ethereal spray. Bogs and Moldenhauer (100) supported Strickland et al, finding no difference between application as a spray, powder or impregnated starch. Thus it appears that

the application method is unimportant, the kind and amount of lubricant being the decisive factors.

1.5.2. Incorporation Method.

The lubricant can be added to the formulation before wet granulation and the lubricant functions just as well, apparently, because enough is exposed during the final milling of the granulation (6). Such "internal" lubricants (2) are generally added as suspensions, solutions or emulsions (7,101). Several authors have investigated this method of granule lubrication and compared it with the customary process (101, 102,72,103,104,). From their work it would appear that whilst the lubricant can be successfully incorporated into the binding agent,as an emulsion, suspension or solution, and obviate the necessity of a separate lubrication step, unless the lubricant concentration is increased, their effectiveness is less than that when lubricants are employed conventionally. This was explained by the fact that for a given lubricant concentration there would be a lower surface concentration of lubricant in the incorporation method, since some of the lubricant would be present within the granules. Thus mobility of the lubricant particles and their frequency of contact with the die wall during compression and ejection would be lower than with conventional lubrication methods.

1.6. Effect of Lubricants on Tablet Properties.

Lubricants are primarily process aids but, because of their nature they may tend to produce weaker or softer tablets (antibonding properties) and may increase dissolution and disintegration rates (hydrophobic properties).

1.6.1. Hardness of Tablets

In 1956 Strickland et al (83) reported a reduction in tablet hardness by magnesium stearate, and to a lesser extent, stearic acid. Concentrations below 1%^{w}/w did not appear to have significant effects. In 1964, Shotton and Lewis (92) investigated magnesium stearate particle size and concentration on tablet crushing strength. Reduction of particle size below 435 microns had little effect and contrary to Strickland et al (83) they reported 0.25%^{w}/w lubricant produced a maximum reduction in tablet strength. The effect of the lubricant concentration depended upon the nature of the base material. Since the strongest bonds are formed between clean surfaces (18), Shotton and Lewis suggested that the lubricant might be expected to interfere with the adhesive bond between particles, by the formation of a physical barrier and so reducing the amount of clean reactive surface. Higuchi (105) showed that the granule surface area increases to a maximum and then decreases as compaction pressure increases. This new surface would remain uncontaminated by the lubricant and hence relatively strong bonds could be formed. In tablets where fragmentation during compression does not occur to the same extent, tablet strength will be more greatly affected (reduced). Work by De Boer (94) was in agreement with this. Other authors investigating other lubricants effects on tablet hardness include Yumioka and Makita (69), Asker et al (106), Jaminet and Hazée (56), Delattre and Gillard (57), and LaManna and Shotton (107). It is reported that water soluble lubricants have either a less deleterious effect on tablet hardness than magnesium stearate or can increase tablet hardness. (74).

Bolhuis et al (87) showed that prolonged mixing decreases tablet hardness by magnesium stearate, again dependent upon the base material (94,95).

Paris et al (108) concluded that lubricants giving tablets with poor cohesive properties were those showing high elasticity. However, this property was a characteristic of a good lubricant.

Thus the effect of lubricant on tablet hardness depends upon a) the nature of the lubricant b) its method of incorporation (section 1.5.) c) its concentration d) mixing time, and e) nature of the base material, but not upon particle size of the lubricant.

1.6.2. Dissolution and Disintegration.

Strickland (83) reported a marked adverse effect on disintegration by lubricants even at low concentration used. Increasing the concentration, increased the effect. Levy and Gumtow (67) reported that the hydrophobic lubricants decreased the effective drug solvent interfacial area and thereby reduced dissolution rate, but sodium lauryl sulphate enhances water penetration into tablets and hence increased dissolution rate. Fuchs et al (109) also reported increased dissolution by the use of surface active agents as lubricants. Marlowe and Shangraw (110) investigated the effect of a water soluble lubricant combination compared with conventional lubricants but little difference was noted. Osseekey and Rhodes (61) compared magnesium lauryl sulphate and magnesium stearate and were surprised to find that magnesium lauryl sulphate prolonged disintegration time longer than magnesium stearate, since the magnesium lauryl sulphate has surfactant properties and was expected to decrease disintegration times (58,59). They concluded that particle size of the sulphate was responsible and should be reduced below 50 microns to give a more efficient disintegrant/lubricant.

Several authors have investigated water penetration in tablets and shown that water penetration is adversely affected by lubricants (111,112,113). However water penetration cannot be used as a measure

of disintegration time (114,115) though obviously involved in the process. Cid and Jaminet (55) claimed that there was a narrow relationship between lubricant action on dissolution and its melting point, but lubricant effect was obviated after aging. Ahmed and Enever (116,117) reported a significant increase in disintegration and a decrease in dissolution of sulphadiazine due to hydrophobic lubricant coating of the particles, but these differences were virtually eliminated in vivo. The effects of lubricants other than magnesium stearate on disintegration and dissolution have been investigated by Stamm et al (118) and extensively reviewed by Lowenthal (66).

1.6.3. Incompatibility with Active Ingredient or other excipients.

The most widely documented interaction is that between metallic stearates and aspirin. The mechanism of the accelerated hydrolysis of the aspirin is explained by Kornblum and Zoglio (44). Commercial stearic acid (impure) was found to have a greater deleterious effect than reagent grade acid (119). The effect could be inhibited by inclusion of 20%$^{W}/_{W}$ malic or hexaminic acids (120). Jaminet and Louis (54) reported effective use of Precirol^{R} with aspirin provided alkaline impurities were absent. Strongly hydrophilic lubricants however, caused marked degradation. Talc has been recommended as a lubricant for aspirin tablets (44) but being of natural origin, its composition varies. Gold and Campbell (64) investigated this and reported a high calcium content was associated with increased aspirin decomposition.

Lubricants low in metallic content confer maximum colour stability to ascorbic acid tablets (121), the alkaline stearates and minerals (talc) causing excessive colour reversion.

Asker et al (122) reported loss of antimicrobial activity of tetracycline and chloramphenicol with magnesium stearate, stearic acid and talc by the presence of impurities, complexation or adsorption of drug by lubricants. The latter occurs if cyancobalamin tablets are lubricated with talc (123). Oxytetracyline has been shown to be incompatible with stearates (124) and digoxin to be adsorbed by magnesium stearate (125).

Thus great care needs to be taken when selecting a lubricant for a formulation.

1.6.4. Adhesion of Film Coatings.

Lubricants will interfere with adhesion of film coatings to tablets (126) by presenting a surface consisting mainly of non polar hydrocarbons, polar groupings being required for bond formation between tablet and coating. The extent of the effect depends upon the lubricant. If some polar groups are present on the lubricant then some interaction will occur between such groups and the coating film.

1.7. Alternative Methods of Applying and Using Lubricants to Overcome Adverse Lubricant Effects on Tablet Properties.

1.7.1. Application of Lubricants to the Die Wall.

The absence of a lubricant within the tablet matrix means that bonding of granules and water penetration is not inhibited. Application of a lubricant to the die wall is the most efficient utilisation of lubricant; requiring less than 2mcg of 100 micron size lubricant for 100mg tablet of diameter 6mm (127). The lubricant can be applied as a fine aerosol spray but the main problem is automation of process. Work by Nelson (65,128,129) supported the idea that die wall lubrication was more efficient than granule lubrication.

The difference between upper and lower punch pressures (which is used as a measure of lubricant efficiency --section 1.9), is related to the coefficient of friction between the die wall and tablet, and pressure transmitted to the die wall by the following expression:-

$$\Delta P = \mu P_w$$

ΔP = difference between upper and lower punch pressure
μ = coefficient of friction
P_w = pressure transmitted to the die wall.

In his work, Nelson showed that granule lubrication caused an increase in P_w as well as a decrease in μ but die wall lubrication only decreased μ. Therefore, ΔP is reduced to a greater extent by die wall only lubrication, than by granule lubrication, since in the latter case, the decrease in μ is partially offset by the increase in P_w resulting in a smaller decrease in ΔP and hence lower lubricity efficiency.

1.7.1.1. Automatic lubrication of Punches and Dies.

Raff (130) patented an adapted rotary tablet machine system in which the periodic spraying of the punches and dies with a tablet lubricant was achieved automatically during machine operation. Lubricants are applied in an aerosol spray after every 250 to 300 revolutions of punch and die "head", during one revolution. Spray nozzles are so positioned, that they do not interfer with the tableting process. The punches and die should have a porous chromium plating as this retains the lubricant and reduces frequency of lubricant application. The disadvantages are that it requires elaborate mechanical components, probably does not precisely or uniformly deposit lubricant film where needed and probably difficult to regulate and adjust for changes in tableting rate. (131)

In an engineering method (132) for compression of iron powder it was found that it was only necessary to provide a supply of fluid lubricant to the punch and die clearances as the movements of punch and die assemblies during the ejection sequence allowed adequate lubricant flow so that, in effect, the tooling lubricated itself. Applicability to tableting is unknown.

1.7.1.2. Lubricant Carrier Compression Cycle.

Leal et al (133) patented this method, whereby the tablet lubricant is applied to the die wall by compressing, in the die, a lubricated carrier material and then ejecting the "lubricating" tablet. Enough lubricant is left behind to lubricate the die for compression of the unlubricated product composition. Any suitable carrier material may be used with any convential tablet lubricant. Particle size of carrier is not critical and tableting pressures are variable. The invention is operable with all types of compressed tableting machines. The composition of the tooling is not critical though carbide tooling in general has given the best results.

1.7.1.3. Die Linings and Inclusions.

Hersey (127) used bonded P.T.F.E die linings and dies made from steel with lubricant inclusions. Unfortunately the erosive nature of the granules at high pressures, either rapidly stripped the linings or were forced into the softer inclusions of the die metal. Since both these actions will result in extremely high frictional forces, the erosive nature of the granules must be overcome before these methods can be used successfully.

1.7.2. Elimination of Lubricants.

1.7.2.1. High Frequency Vibration.

Mechanical aids such as high frequency or ultrasonic vibrations

are reported to reduce friction and may eventually prove effective as a means to eliminate lubricants. (2) The main problem would be separation of fines within the tablet hopper leading to non-uniformity in tablet weight.

1.7.2.2. Composition of Die Wall.

In engineering high-carbon, high chromium steels, tungsten carbide and chromium plated surfaces were reported to reduce friction (134) and Schey and Newnham (135) found that die composition had a pronounced effect on efficiency of solid and boundary lubricants. Tungsten carbide was reported to produce higher compact-die contact than a high chromium steel die (136). In tableting, Alimov (137) found differences in performances of dies of various steels used for compression of drugs such as rhubarb, caffeine and codeine. Strickland (10), utilizing various metals as die wall materials, showed that only the silver die amalgamated with mercury and rubbed to a good polish, showed an appreciable reduction in friction. Since this study, a technique of chrome plating of punch faces and die walls has been employed to reduce the need for tablet lubricants (5). Polytetrafluoethylene which has a very low coefficient of friction (18) has been used to manufacture dies (138) and to tip tablet punches (139). The latter has been successfully used to overcome sticking and picking associated with the production of an effervescent tablet. Cleavage of the "tip" from the metal punch may occur after a period of use. The P.T.F.E. die (138) was not so successful. A simple P.T.F.E. sleeved die can only be used at a few hundred lb./sq.inch because of plastic flow of P.T.F.E. which is extruded from ends of the die. An improved die was developed by containing the P.T.F.E. in a fixed volume but distortion of die wall occurs at pressures

above 3 ton per square inch (470 kg/cm). This therefore is not useful in tableting since upper punch pressures are in the range up to 2000kg/cm. (140).

1.7.3. Reduction of Amount of Lubricant Required.

1.7.3.1. Novel Roller Compactor.

In slugging (dry granulation), ample use of lubricants often impairs the binding properties of powders as well as weight fluctuations in tablets. The new roller compactor devised by Funakoshi et al (141) processes powders where less lubricant is needed, and there is uniform compacting pressure, so that all the advantages of the dry process can be obtained without the disadvantages.

1.7.3.2. Reduction of Die-wall and Tablet Surface Contact Area.

Nelson (129) demonstrated that 80% of the friction exhibited by a poorly lubricated granulation occurred at the tablet-die wall interface as the tablet is ejected. Thus reduction of this area will reduce total friction and permit the use of low concentrations of hydrophobic lubricants. This can be accomplished by the use of deep cupped punches or making thin tablets of large diameter (10).

1.7.4. Alternatives to Hydrophobic Lubricants.

1.7.4.1. Water Soluble Lubricants.

Boric acid 1%^{W}/w, sodium benzoate 5%^{W}/w, sodium acetate 5%^{W}/w (6,7) or combination of the latter two (90), leucine 1-5%^{W}/w (78), polyethylene glycols 1-4%^{W}/w (75), and derivatives, magnesium and sodium lauryl sulphate (58,61) and others have been used. Polyethylene glycols and derivatives are wax like materials, soluble in water (37) but only dissolve slowly (66). Lubricant composition studies indicate that the water soluble materials are not as good as conventional

lubricants and are required in higher concentrations (22,74). However, their effects on dissolution, disintegration, and tablet hardness are equivalent to, or less than, those of magnesium stearate. It is not likely that highly water soluble compounds eg. salts and carbohydrates, can be effective lubricants, although some sucrose derivatives have been used (76,52). Water soluble lubricants have been the subject of several patents (142) in an attempt to derive a highly efficient lubricant.

1.7.4.2. Decreasing Hydrophobicity by the use of Sodium Chloride.

Haupt (143) reported that the presence of a small amount of sodium chloride greatly increased magnesium soap solubility. Zink (144) refuted this claim.

1.7.4.3. Enrobed Solid Hydrophobic Tablet Lubricants.

Hersh (131) reported the use of conventional solid hydrophobic tableting lubricants enrobed in a hydrophilic sheath (designed to rupture only at areas of high shear eg. die wall) in conventional tableting equipment. Harder, less friable and more rapidly disintegrating tablets were obtained, using this method of lubrication.

1.7.4.4. Modification of Magnesium Stearate and Stearic Acid.

The lubricants were modified by dispersion onto high surface area, amorphous silica by liquid addition or attrition. Also, estersils were prepared by reacting normal fatty alcohols with silica surface silanols. However, such modifications did not improve hydrophobicity of the lubricants and were less efficient as lubricants (22).

1.8. Batch Variation.

Tableting problems also occur because of batch variation of materials. Cassie et al (145) reported that starch source variation had a significant effect on tablet properties. Talc's compatibility with aspirin also depends upon its composition (64). "Improvement" of quality by a raw material supplier can cause problems, for example magnesium stearate of higher grade and smaller particle size to usual caused serious compressibility problems, necessitating reformulation of the product and adoption of a particle size specification for the raw material (146). Thus routine characterisation of batches of particulate materials is therefore good practice during research, formulation, development or production(147). This viewpoint is echoed by Hess (43) who considers that careful choice of supplier of raw materials as well as defined chemical composition and physical properties are essential pre-requisites for excipients.

1.8.1. Batch Variation of Magnesium Stearate.

Batch variation manifests itself as an inability of the lubricant to adequately fulfill its role in tablet manufacture. To overcome this problem, the lubricant concentration is increased, which often leads to problems with dissolution, disintegration and hardness of tablets (section 1.6). Nevertheless, little work appears to have been carried out on this aspect of lubricity. In 1948 Lien and Miller, (148) who carried out a comparative study of ten commercial samples of magnesium stearate involving physical and chemical tests, reported that the variable results obtained indicated that the samples were not identical in composition. Unfortunately they did not evaluate lubricity of the batches. In 1972, Butcher and Jones (149) investigated particle densities, packing changes

sieving properties, tensile strengths and frictional properties of five commercially available samples of magnesium stearate. They reported marked physical dissimilarities between the batches, which they accounted for by the nature of the material as shown by scanning electron microscopy (S.E.M.). Four samples contained needle crystals the other consisted of plate-like structures. The authors concluded that such tests yield useful quantitative data for comparison of sample variation. However, again, lubricity efficiency of the batches was not evaluated. Hanssen et al (150) showed that grade variation of magnesium stearate produces large differences in the compression properties of bulk solids at 0.1%^{W}/w lubricant concentration but no relationships between physical data and experimental results were established.

In 1975, Müller (151) reviewed interface friction and lubrication with respect to tableting and concluded that hydrodynamic lubrication is impossible during tablet production, and in consequence solid lubricants have to be used. A characteristic feature of a good adjuvant is that it has no amorphous fraction (152) but rather a well orientated layered lattice. Therefore in 1976, Müller (152) carried out studies on the structure of lubricant layers, using magnesium stearate. Physicochemical tests showed that lubricant behaviour was directly related to the fatty acid composition. Infra-red spectra did not differenciate between the batches but combined differencial thermal analysis (D.T.A.) and thermogravimetric analysis (T.G.A.), indicated that lubricant properties improved with increasing amounts of adsorbed water. In 1977, Müller (153) carried out, D.T.A.,T.G.A., X ray and infra-red spectroscopic studies on magnesium and calcium soaps, produced using pure stearic acid. In the process method, two types of crystalline products (or mixture of

the two) could be formed. These were lamellar particles and needle shaped particles (section 2.7). From T.G.A. and X ray analyses, Müller concluded that the needle crystals were richer in water, (the trihydrate) and the lamellae crystals poorer in water (the dihydrate). Powder diffraction studies indicated that magnesium stearate should not contain any trihydrates for lubrication purposes (7% ^{w}/w water). Expansion of the crystal layers due to more water molecule incorporation causes the lubricant to lose its stress resistance ability. The ideal form for use as a lubricant is the dihydrate (4.9%^{w}/w water). Thus the product obtained by precipitation (section 2.7) should be dried below 80^{o}C to give the dihydrate (below 60^{o}C if shorter chain fatty acids present). According to the altitude of the chosen temperature and duration of the process, the soaps of different origins contain different amounts of particles with a non-layered structure, which Müller (154) states is the true explanation for observed grade variations.

In conclusion, Müller (153) states that a magnesium stearate used as a lubricant should have a water content between 3-6%^{w}/w (5%^{w}/w preferably) and should not show diffuse or broadened lines at 30-50Å and 4.5Å on X ray diffractograms.

1.8.2. Manufacture of Magnesium Stearate.

From Müller's work it would appear that the manufacturing method could play an important role in determining the lubricant efficiency of the commercial product. On the commercial scale, the soaps are prepared from grades of stearic acid which almost always contain about 10% amounts of other long chain fatty acids and thus are not exact chemical entities with which to start (155).

1.8.2.1. Precipitation Method

A fatty acid dispersion is treated with aqueous sodium or potassium hydroxide

$$CH_3(CH_2)_{16}COOH + NaOH \longrightarrow CH_3(CH_2)_{16}COONa + H_2O$$

and the resulting alkaline soap is converted into the metal soap by precipitation with a metal salt solution and the product is repeatedly washed to remove residual salts, dried and ground to the required fineness (155,156).

$$2CH_3(CH_2)_{16}COONa + MgCl_2 \longrightarrow \left[CH_3(CH_2)_{16}COO\right]_2Mg + 2NaCl$$

These soaps are fine, fluffy powders with a crystalline structure. Their purity and properties depend considerably upon reagent purity and experimental conditions of temperature, concentration, rate of stirring, washing etc. that have been employed by the different manufacturers (155).

1.8.2.2. Direct Reaction

Direct reaction between the fatty acid and oxide, hydroxide, carbonate or acetate of the desired metal is best carried out at elevated temperatures so that any evolved vapours are flashed off into the atmosphere (155,156). This makes the method suitable for soaps which readily hydrolyse.

$$Ca(OH)_2 + 2CH_3(CH_2)_{16}COOH \longrightarrow \left[CH_3(CH_2)_{16}COO\right]_2Ca + 2H_2O$$

The resultant soap is cooled and ground. The advantage of this method is the avoidance of filtering an often sticky precipitate which

is difficult to free from contaminants. Direct reaction soaps generally have a lower metal content and higher acid content than precipitated soaps (155).

1.8.2.3. Alcoholic Metathesis.

The appropriate metal hydroxide is reacted with the fatty acid in hot alcoholic solution (155,156).

$$Mg(OH)_2 + 2CH_3(CH_2)_{16}COOH \xrightarrow[\text{solution}]{\text{alcoholic}} \left[CH_3(CH_2)_{16}COO\right]_2Mg + 2H_2O$$

Thus whilst the metal soaps can be standardised within certain limits, with respect to metal content, contaminant metal content, free acidity, total ash, moisture content, etc, the different conditions and methods of manufacture will result in different crystal forms and other properties.

1.9. Methods to Evaluate Tablet Lubricants.

Any investigation into lubricant behaviour requires a standard test for evaluating lubricity and there are many methods by which lubricity is evaluated. The common feature is that a parameter representing lubricity is evaluated, there being no actual test for lubricity itself.

1.9.1. Trial and Error

In the past materials were evaluated in a qualitative manner by observing the tablet machine in operation and the tablets being produced, and many excellent lubricants were found eg. magnesium stearate (32,10).

1.9.2. Use of Instrumented Machines.

These enable more rapid and precise evaluation by enabling measurement of various forces during tableting (65). They are of great use in the development of tablets (157).

1.9.2.1. Instrumentation

Many authors have described instrumentation of single punch (158,159), or rotary (140, 160,161,162,163) tablet machines and detailed reviews on the various methods have been carried out by Salpekar (22) and Sixsmith (164). Basically instrumentation can be strain gauge or with the use of piezo-electric transducers. Strain gauges are short lengths of resistance wire bonded onto various parts of the machine, and distortions due to pressures, alters the resistance, which is detected by a wheatstone bridge arrangement. Advantages are their simplicity, sensitivity, reproducibility, reliability, versatility, durability, and short recovery time. The limiting factor is the time required for recording response changes (165). Piezo-electric transducers are quartz crystals which develop an electrical charge proportional to the applied external force. Their advantages over strain gauges are greater sensitivity, greater flexibility in inter or intra machine use, less temperature sensitivity, involve minimum amount of structural alteration to rotary machines, when used, and any initial loading can be cancelled simply by earthing it. The instrumentation chosen depends mainly upon the forces to be evaluated (166).

1.9.2.2. Forces involved in the Tableting Process.

The frictional force (F_d) at the die wall resists downward movement of the top punch and can be expressed as follows:-

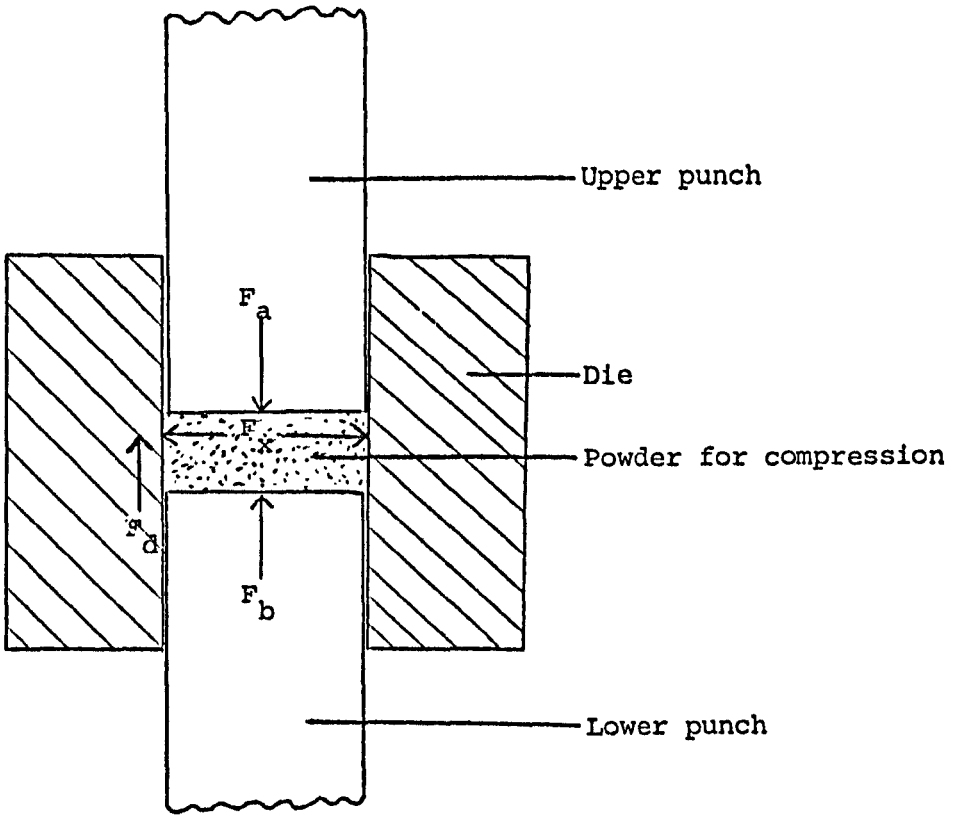


Fig. 1.8. a)

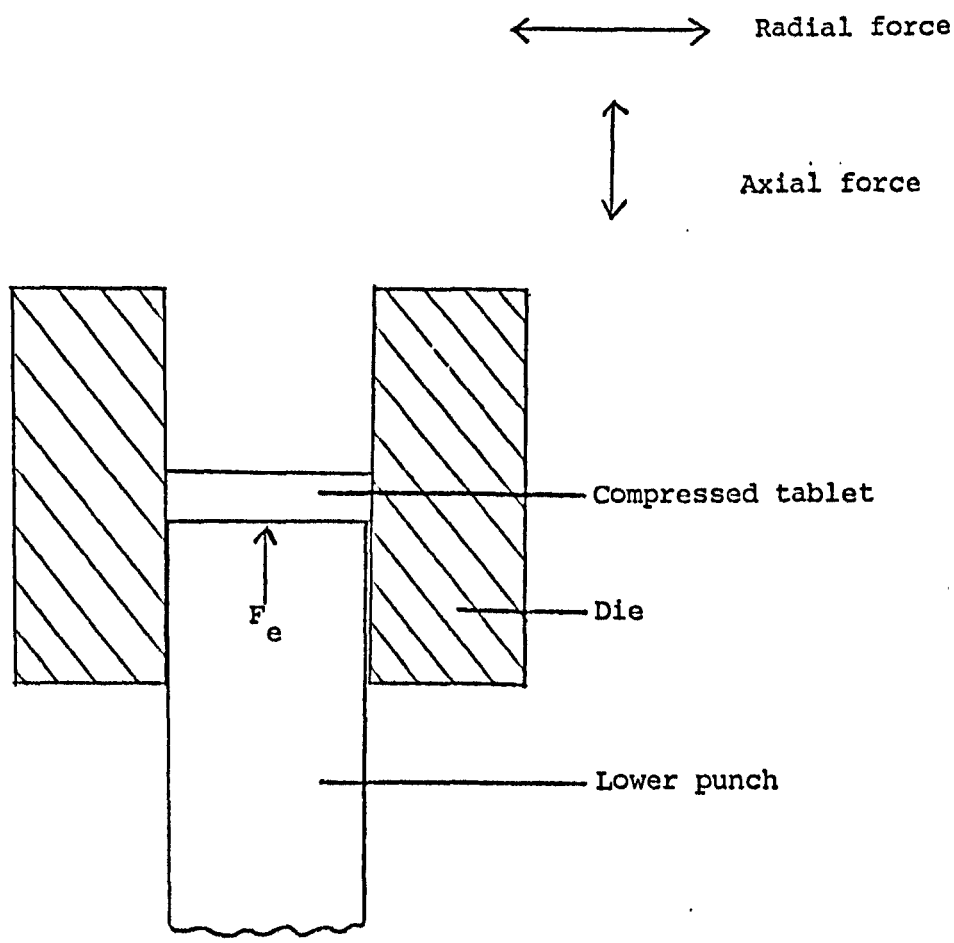


Fig. 1.8. b)

Fig. 1.8. Forces involved in tableting. a) compression, b) ejection.

$$F_d = F_a - F_b$$

F_a = Force applied to upper punch.

F_b = Force transmitted to the lower punch.

When compressing a solid the force transmitted to the die wall (F_x) (167), is less than that received by the lower punch (F_b) (128). For a given tablet, F_d depends only upon F_x and the coefficient of friction between the die wall and tablet (μ). Thus

$$F_d = \mu F_x$$

Hence with suitable instrumentation F_d and μ may be calculated from F_a, F_b, and F_x measurements. The ejection force (F_e) is the force required to "break" the tablet from the die wall. Use of a tablet lubricant is expected to increase F_b and F_x, and reduce μ and F_e. See Fig. 1.8. for summary of these forces.

1.9.2.3. Parameters Evaluated.

1. R value is the ratio of upper and lower punch forces $\left[\frac{F_b}{F_a}\right]$ (57,168) and can vary between zero (no lubricant properties) and unity (perfect lubrication) (1,168). R values should be greater than 0.88 (52). Larger values are obtained using rotary tablet machines (140). It increases with a) increase in lubricant concentration (169,52,170) to a certain limit (83), b) increase in compaction load (170,171,1) and c) decrease in particle size (71). It is dependent on the nature (172) and electrostatic charge of base material used (169) and is not representative of the entire compression process (173,165,174). It is widely used to compare lubricants but because it is dependent on many factors, absolute values cannot be determined. Another disadvantage is that it can only distinguish between "good" and "bad" lubricants and not between two "good" lubricants (45,25).

2) Force lost to die wall, (F_d), is reduced in the presence of lubricant (169,175) but will vary irrespective of the nature of the lubricant when compaction pressure varies (45), showing an almost linear relationship (170), and is proportional to the die-wall tablet contact area (171). Cumulative changes in F_d were utilised by Rees and Shotton (176) in their investigations.

3) Ejectability. The force required to propel the tablet out of the die is smaller than the force required to "break" the tablet loose from the die wall (F_e) which is usually evaluated (160). It is claimed that ejectability is a measure of a combination of tablet ejection and lower punch friction (177); the smaller the force the better the lubricant (1). It decreases with increase in lubricant concentration (169) and a decrease in particle size (71). It increases with increase in compaction load, and tablet thickness (163,170) and machine speed (162). At slow ejection speeds the phenomenon of slip stick is seen (178). A linear relationship between F_e and F_d is reported (65,175) and also between F_e and F_m (mean compaction pressure) (158,175) until a limiting value of F_e is obtained (175).

Energy consumption (area under F_e, displacement curve) during the entire ejection process was measured by Matsuda et al (103), since difference in shapes of ejection curves (Fig. 1.9) for varying

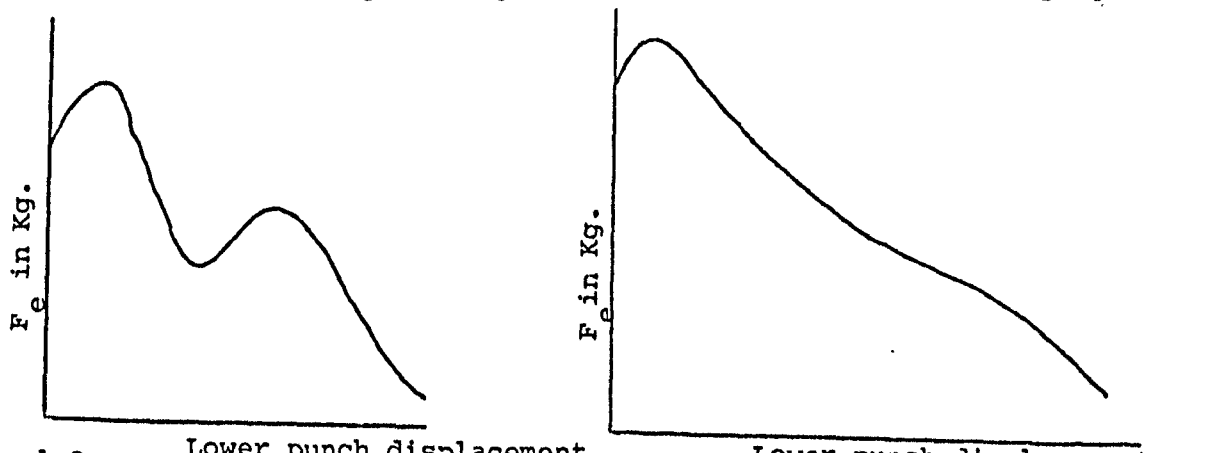


Fig. 1.9a Fig. 1.9b

Fig. 1.9. Ejection force-displacement curves.
a) magnesium stearate b) talc.

lubricants was noted. Ejection energy differed even when F_e was the same. Therefore ejection energy was considered more accurate. Ejectability is the most commonly used parameter in tablet friction studies, even before instrumentation of tablet machines (179,73,101) and appears to give the best prediction of tendency to stick to the die wall. It is able to differenciate between "good" lubricants.

5) M value which is a ratio of ejection forces (107,25),

$$M = \left[1 - \frac{F_2}{F_1}\right] 100$$

F_1 = Ejection force of unlubricated sample
F_2 = Ejection force of lubricated sample.

has no advantage over use of ejection force.

6) Force remaining on lower punch is the force exerted on the lower punch by the tablet (180) due to its elastic recovery after compression (170,158), reported to be the minimum force required to eject tablets (181) but usually less than ejection energy (170). It is greater, the higher the compaction load and the thicker the tablet (170). It decreases as lubricant concentration increases to a limiting value, but more so than ejection energy (150). Suren (51) used this parameter in his lubricant comparison study. It is claimed to measure antiadherent action (93) but ejection energy is thought to be more suitable (170 , 171).

7) Mean compression force (F_m) is given by

$$F_m = \frac{F_a + F_b}{2}$$

F_a = Upper punch force
F_b = Lower punch force

but is little used. It is linearly related to F_d and F_e (175) and very dependent on F_a. For good lubrication F_m should approach F_a.

8) Lower punch pulldown force is the force occurring during travel of the lower punch during tableting (177). Poor lubrication increases this force due to binding or sticking at punch and die wall interface (162). Higher forces are obtained with high compressional forces and faster machine speeds. However this is not a specific method for lubricant evaluation.

9) Area compensated forces. Hölzer and Sjögren (170,171) and others report that all parameters investigated are influenced by tablet dimensions and therefore values should be corrected for differences in contact area between tablet and die wall. Stamm et al (93) also took mean compaction pressure into account to produce values independent of experimental conditions, and therefore comparable between themselves eg.

$$F_e\% = \frac{F_e \times 100}{F_m S}$$

F_e = Ejection force
F_m = Mean compaction force
S = Surface area

10) Work involved in tablet compression is the area beneath the force-displacement curve (129). Force displacement curves were studied quantitatively by DeBlaey and Polderman (173). The data showed that a lubricated granulation produced the lowest value for work involved in tablet compression. In further studies (165,174,13), comparison of work and R value led to the conclusion that R values were not representative of the whole compression process and that work lost to the die wall could differentiate better between lubricants than R values.

11) Transmission of force to die wall (P_w). Nelson (128) first attempted measurement of die wall forces using a modified conventional punch and die arrangement. He reported that about 30% compaction

pressure appeared on the die wall. The die wall was lubricated throughout the test. Since

$$\Delta P = \mu P_w$$

ΔP = Difference between upper and lower punch forces

μ = Coefficient of friction

and granule lubrication was shown to <u>increase</u> P_w, he concluded that die wall lubrication was best (ΔP greater) (section 1.7.1.). Windheuser et al (167), improved the measuring system and from their work concluded that the change in magnitude of die wall transmission was not a simple linear function of the lubricant concentration. Ridgway et al (182,183), reported that P_w is proportional to the compacting pressure and inversely depends upon the surface hardness of the compacted material, stearic acid, a soft material, giving high transmission. Although lubricants increase P_w, the larger the radial force the greater the die wall friction. Thus lubricant effectiveness is a balance of its axial and radial force transmissions and friction reducing properties.

Although all these parameters have been used to evaluate lubricants, they do not always give correlating results because they measure the friction during different phases of the compression cycle (157).

1.9.3. <u>Shear Strength Measurements.</u>

A theory of lubricant action is that lubrication is a function of shear strength (section 1.3.1.). A punch penetration test was developed by Train and Hersey (23) using a moving die technique (184). They concluded that high shear strength values for talc

and graphite indicated that they were poor lubricants especially at high compaction loads, probably having a crystal lattice orientation lubrication mechanism (section 1.3.1.). Shear strengths of the majority of other lubricants are independent of compaction pressure (26). Shear strength values depend upon the method used (172). However, Lewis and Shotton (25) reported that there was no correlation between ejection energy and shear strength. Juslin and Erkkila (48) reported that whilst decrease in shear strength corresponded to increase in lubricant efficiency for fatty acids, for alcohols and hydrocarbons, the situation was more complex.

1.9.4. Heat/Temperature Changes of the Tablet Surface

Nelson (129), assuming all energy expended in the tableting process appeared as heat, stated that

$$\Delta T = Q/CM$$

ΔT = Temperature rise in ^{o}C
Q = Heat input in calories
C = Thermal capacity of the material
M = Weight in grams of granulation

Lubrication will reduce ΔT and thus temperature changes can be used to evaluate lubricants. Juslin (185) reported that ΔT was dependent upon lubricant used, was directly related to log compression time and best measured at the die wall. Small differences in lubricant effectiveness could not be demonstrated (47). Temperature increase is proportional to compaction pressure and lubricants changed the start of the temperature rise at higher pressures. (186). However, not all authors agree that ΔT is reduced by lubricants (187).

1.9.5. Extrusion Forces.

Extrusion forces of lubricant materials were ten times lower in comparison to other materials and the assumption that the lower the extrusion force the better the lubricant resulted in its excellent correlation with ejection force measurements (188).
This property could be used as a measure of both slip and antiadherence effects of a lubricant.

1.9.6. Miscellaneous.

A 'lubrication factor' defined as the percentage reduction in friction after addition of lubricant compared with unlubricated material, was used by Maly (189,11,190). A patent by Gruszczynski (191) evaluated lubricity by the difference in rotation angles between two drums in the presence of the lubricant. A simple sliding test where the lubricant is placed between the two sliding surfaces has been used by Graham and Jenkins (192). The lubrimeter, developed by Levy and Schwarz,(193) relies upon friction between a motorised roller and stationary drum to rotate the latter, the extent of the rotation being measured. The better the lubricant the less friction and the smaller the drum rotation. Finally a coefficient of weight variation of tablets lubricated with the investigated lubricants was used to compare magnesium stearate and magnesium lauryl sulphate (58).

To summarize, measurement of the properties of lubricants can indicate to some extent, lubricant performance. Tests have to be carefully standardised because few (if any) measure fundamental properties independent of the test method. If the method or equipment used for the test is changed, the result also will change (38).

1.10. Approach and Scope of the Present Study.

Much of the research on lubricants has dealt with methods to identify possible lubricant materials, and their effects upon tablet characteristics. Magnesium stearate, the most widely used tablet lubricant, is very efficient but has adverse effects upon dissolution, disintegration and tablet hardness.

In the present study, batch to batch variation of magnesium stearate has been investigated. Batch variation is seen as an inability of the lubricant to adequately fulfill its role in tablet manufacture. At present the problem cannot be solved prior to the tableting process, and since the solution normally employed is to increase the concentration of lubricant in the tablet formulation, this can lead to dissolution or compression problems.

Although it has been shown that marked physical dissimilarities exist between different batches of magnesium stearate there is, as yet, no method for predicting lubricity behaviour of a lubricant batch from physical data. Alternative methods for lubrication of tooling used in tableting, to eliminate granule lubrication, have been investigated but no method has been practically effective.

In the present study it was intended to.....

a) Develop a relatively simple lubricity test with available equipment so that various lubricant batches could be evaluated. The test had to be sufficiently sensitive to detect differences between the various magnesium stearate batches.

b) Use the test developed in a) to evaluate eleven batches of magnesium stearate, obtained from commercial sources and try to relate their lubricity behaviour to one or more physical properties, ultimately to try to develop a specification for a batch of magnesium stearate to ensure a certain level of lubricity.

c) Manufacture batches of the lubricant containing different ratios of stearate to palmitate and to investigate these materials with respect to lubricity to determine the effect of purity and manufacturing process upon lubricity.

d) Investigate the distribution of magnesium stearate in the tablet after the tableting process, to determine the behaviour of the lubricant during tableting and to try to relate the results to the lubricant ability of the investigated batches.

e) Finally to try to establish the exact lubrication mechanism, how physical properties of the lubricant material will affect this process and how, if possible, to modify any adverse properties.

CHAPTER 2. METHODS AND MATERIALS.

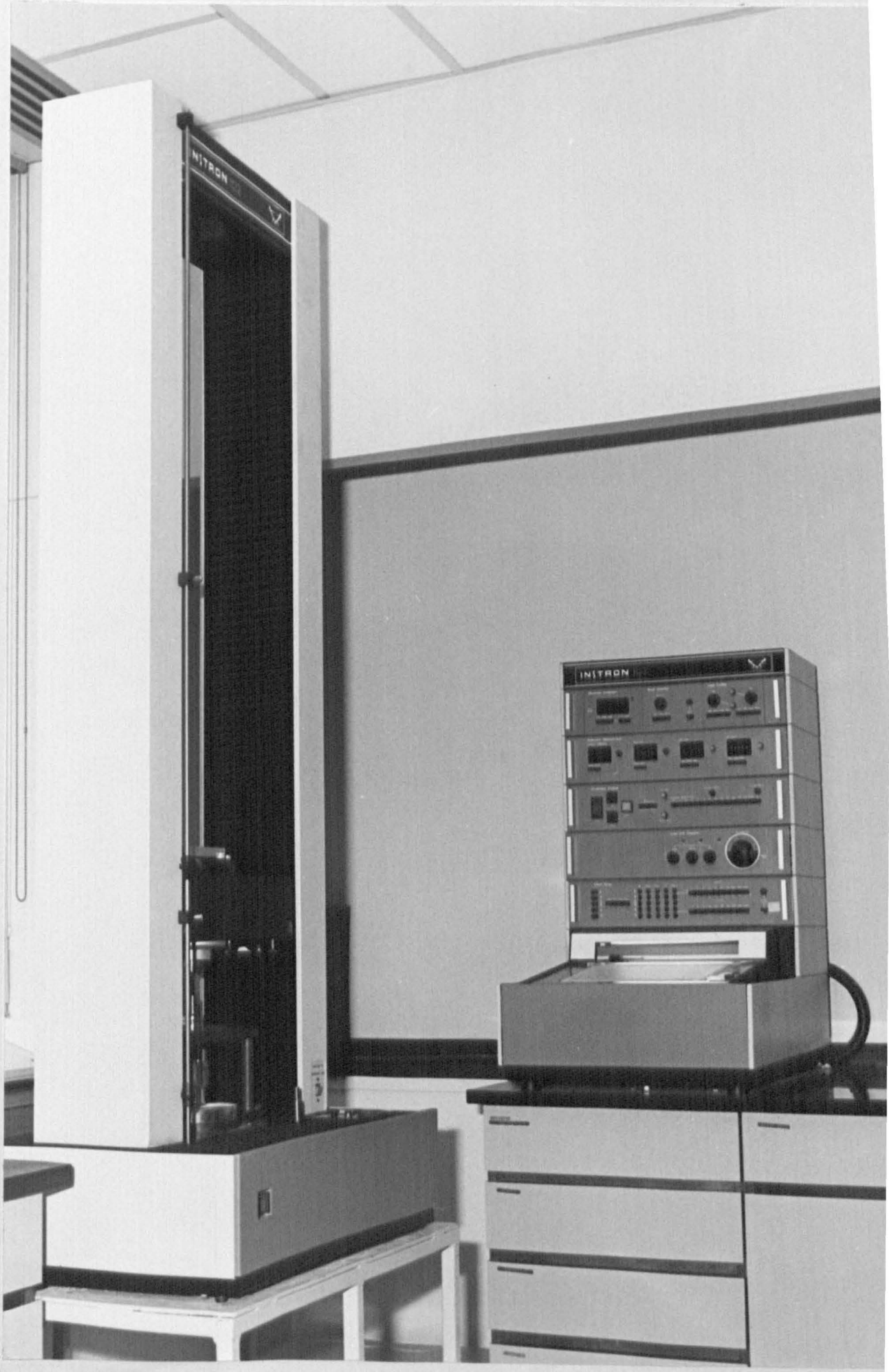
This chapter describes the methods for the various experimental techniques utilised during this investigation.

2.1. Measurement of Lubricity of Lubricants.

A Universal Testing Instrument (model 1122, Instron Ltd., High Wycombe) was utilised to determine lubricity values. The major considerations for selecting the Instron machine were its accuracy, versatility, operational convenience and relative compactness, which make it a valuable tool for both investigational and routine measurements. It has been utilised by other workers (194, 195, 196) for compression and ejection evaluations and can be adapted to represent single punch or the double acting compression of a rotary tableting machine.

The instrument is shown in Fig. 2.1. (197). A compression-tension load cell of maximum load capacity 500kg was mounted through the movable crosshead. The punch and die set, a ⅜" (9.46mm) tungsten carbide steel die and flat faced punches, were not clamped. The die was placed on a specially constructed table, so that the bottom punch, when resting on the Instron compression table, extended 4mm into the die. Powder samples (200mg) were placed into the cleaned die cavity, the top punch fitted into position and compacted at a crosshead speed of 2mm per minute, until a 58MPa pressure had been applied. When this maximum load was attained, the instrument was programmed to automatically reverse direction of movement of the crosshead. The punches and die were then set up for the ejection process. The bottom punch was removed, the die reversed on the table and the top punch repositioned in the die, so that ejection would

Fig. 2.1. Universal Testing Instrument (Model 1122).



occur in the same manner as on a tableting machine. Ejection was carried out at a speed of 5 mm per minute and full scale load of 20kg (admixture samples) or 2kg (lubricant only samples). Energies for the compaction and ejection cycles were monitored by the integrator module built into the instrument. Compaction and ejection speeds were selected as a compromise between the number of samples that could be tested in a day, and accuracy. Validation tests for lubricity evaluation are described in Appendix 1. For each investigation at least six samples were measured and the mean ejection energy in Jm^{-2} (Appendix 1.3) used for comparative purposes. For admixture tests (lubricant and excipient) two such evaluations were performed.

2.2 Measurement of Physico-chemical Properties of Magnesium Stearate.

2.2.1. Particle size Analysis.

Particle size analysis was performed by Double Image microscopy using the '526' particle size micrometer and analyser (Fleming Instruments, Crawley) (198) and technique described in B.S. 3406 part 4. (199). Original lubricant samples were prepared by dispersing the lubricant in a mixture of water and glycerol, but lubricant samples from admixture tests were obtained by placing a sample of the admixture in water, and transferring the lubricant film, formed on the water surface, onto a microscope slide. Only lubricant from lactose admixture tests could be evaluated since lactose was the only soluble excipient. The number of particles in each of the ten size ranges employed (0 to 25 microns) were recorded and the cumulative weight percentage above stated size was recorded and median particle size estimated. (Appendix 5). However, results, when plotted on log probability paper, did not produce straight lines, indicating that lubricant particle size did not follow a log normal distribution. In fact graphs of percentage of particles

present in the various size ranges, showed negative skewness, that is a predominance of smaller particles. Thus the median particle size is used as an estimate of particle size for each lubricant batch but for comparisons of lubricant particle size before and after mixing, percentage particle size distributions were used.

2.2.2. Surface Area Determinations.

Surface areas were evaluated by the Strohlein nitrogen adsorption technique (200) using 2.0g samples. Surface area determinations were performed on lubricant material before and after mixing with lactose B.P. Lubricant material from admixtures with lactose was obtained by adding 300g of mixture to water, to dissolve the lactose, the hydrophobic lubricant material being removed from the water surface, suction filtered, washed with acetone and allowed to dry at room temperature. Samples of lubricant material were also treated in this manner to try to eliminate any variations in surface area being due to sample preparation.

2.2.3. Crystal Shape.

Crystal shape was observed by scanning electron microscopy (stereoscan). Samples were prepared by one of three methods. Original lubricant material and samples of mixtures were prepared by dusting a small amount of powder onto double sided sticky tape on a sample stub. Portions of tablets were mounted in a "blob" of glue on the stubs. To obtain lubricant material from lactose mixtures, a sample was added to water and the lubricant film formed on the surface, transferred onto a sample stub. Lubricant material from the curved tablet surface was transferred onto a stub from a water surface onto which the tablet surface had been touched.

2.2.4. Purity Determinations.

The ratio of stearate to palmitate in magnesium stearate samples

was determined by G.L.C. investigation (Pye series 104 with Flame ionization detector). Column used was 2% Carbowax on gas chrome Z at a temperature of 160°C and nitrogen flow rate of 50 ml per min.

The 'stearate' samples were assayed as the methyl derivatives by complexation of the liberated fatty acids with BF_3/Methanol complex and removal of the methyl derivatives into an organic solvent (201a). The ratio of the areas under the stearate and palmitate peaks was calculated (Appendix 3) to determine the stearate/palmitate ratio.

2.2.5 Assay.

Assay values were determined by the USP XIX (202) method.

2.2.6 Percent Loss on Drying.

Approximately one gram, accurately weighed, of the lubricant material was dried in a hot air oven at 105°C to constant weight. Samples were removed from the oven every hour, cooled in a desicator and weighed, until two readings were within 0.0005g. The loss in weight was then calculated as a percentage of the original weight.

2.2.7. Bulk Densities.

Bulk densities were determined before and after tamping. Five grams of lubricant material were placed in a 100ml measuring cylinder and the volume recorded, from which was calculated the original bulk density. The cylinder was then tapped at a rate of 60 taps per minute over a distance of 1cm and the volume of the powder noted at 10 tap intervals for 2 minutes, then every 30 taps for a minute and finally every 60 taps for another 7 minutes by which time the volume had attained its limiting value. The final volume was used to calculate the tamped bulk density value.

2.3. Preparation of Admixtures of Lubricant and Excipient.

2.3.1. Mixing Process

Since samples to be mixed consisted of a large amount of material of large particles and a small amount of cohesive material of small particle size, they fulfilled the requirements for ordered mixing as postulated by Hersey (98, 99). Thus the best type of mixer to use is a tumbling mixer (99). Also, since only small amounts of lubricant samples were available for investigations, mixing was restricted to 100gram batches. The mixer was specially constructed and consisted of a variable speed motor, set to rotate a 700ml capacity, large mouthed, screw top, glass bottle, at a speed of 26 revs per minute. A loop strip of corrugated P.V.C. sheet inside the jar acted as a baffle to cause tumbling of the powder sample. The appropriate quantities of lubricant and excipient (depending upon lubricant concentration) were mixed for 10 minutes in this apparatus. Validation tests for this mixing arrangement are described in Appendix 2.

2.3.2. Uniformity of Mix Analysis Method.

Uniformity of mix was determined by assaying 100milligram samples of mixtures for magnesium stearate content by G.L.C. (Pye series 104 with flame ionization detector). Column used was 5% E.G.S.P.—Z on chromatogram Q 100-120, at a temperature of 180^{o}C and a nitrogen flow rate of 60ml per minute.

Samples were treated as described in section 2.2.4. with the inclusion of an internal standard—n-eicosane.(20lb). A sample of the magnesium stearate used in the mixing tests was also prepared for determination of the ratio of stearate to palmitate esters. The percentage mix values were calculated from the traces obtained from G.L.C. analysis of the prepared samples, as described in Appendix 3.

2.4. Analysis of Distribution of Magnesium Stearate.

2.4.1. Quantity on Tablet Surface.

The percent by weight of magnesium stearate present in the outermost 30Å of the curved tablet surface was evaluated by E.S.C.A. analysis (203) (Loughborough Consultants Ltd.). Tablet samples were prepared using the Instron (section 2.1) from 1% lubricated lactose mixtures. One set of tablets underwent the normal ejection process, the other set being 'broken' out of the die after compaction. At least 5 tablets of each lubricated sample were prepared since an area of approximately one square centimetre was required for efficient E.S.C.A. analysis.

2.4.2. Quantity on the Die Wall.

Samples were analysed for magnesium ion content by atomic absorption (Universal Instruments Ltd.). Calibration graphs, and validation tests of process are described in Appendix 4.

Samples for analysis were prepared by compressing or compressing and ejecting (depending upon test - chapter 6) a lubricated powder sample and then removing the magnesium stearate left on the die by successive compressions of lactose tablets. These "cleaning" tablets were retained and the curved surface of each, skimmed (section 2.4.4) and the skimmings bulked. It was assumed that all the stearate that was left on the die was now present in this powder sample.

These powder samples were prepared for atomic absorption analysis by boiling for two minutes with 5mls of 0.1N hydrochloric acid, adding water, when necessary to maintain the original volume. Five mls of distilled water were added, the solution cooled (to solidify the fatty acids) and the resultant solution analysed. The amount of magnesium stearate originally in the sample was then calculated (Appendix 4.3).

2.4.3. Distribution in Tablets.

Samples were analysed for magnesium ion content by atomic absorption. (Appendix 4).

Samples were prepared by compressing and ejecting a lubricated excipient tablet. This tablet was retained and the curved surface skimmed several times (section 2.4.4) each skimming being collected separately in a previously weighed sample bottle. Finally the remaining core of the tablet was placed in a weighed sample bottle. The bottles were then reweighed so that the weight of material in each skim could be evaluated.

These powder samples were prepared for atomic absorption as described in section 2.4.2. except that for samples containing cornstarch, the solutions had to be centrifuged to sediment the insoluble starch. The clear supernatent was then analysed. The prepared solutions had to be appropriately diluted so that the magnesium ion concentration was within the atomic absorption range. The dilution depended on the amount of material present in the original sample. Usually a 1 in 50 dilution and a 1 in 100 dilution were suitable for 'skims' and 'core' samples respectively. The amount of magnesium stearate originally in the sample was then calculated from the dilution corrected magnesium ion concentration value. (Appendix 4.3)

2.4.4. Skimming Method.

Skimming was performed by holding the tablet with tweezers and gently scraping the curved surface, using a sharp bladed craft knife. The powder produced was collected directly in the previously weighed sample bottles. Because of the friability of the tablets, extreme care was required to avoid either a) an excessive quantity of powder in any particular skimming, or b) causing complete disintegration of the tablet.

2.5. Humidity Measurements.

Humidity was measured at regular intervals throughout the day using a whirling hygrometer. (Brannan Thermometers, Cumberland).

2.6 "Blowability" Test.

This apparatus (Fig. 2.2) was designed to give an estimate of the ease with which the lubricant could be wafted through the powder bed during the compression process.

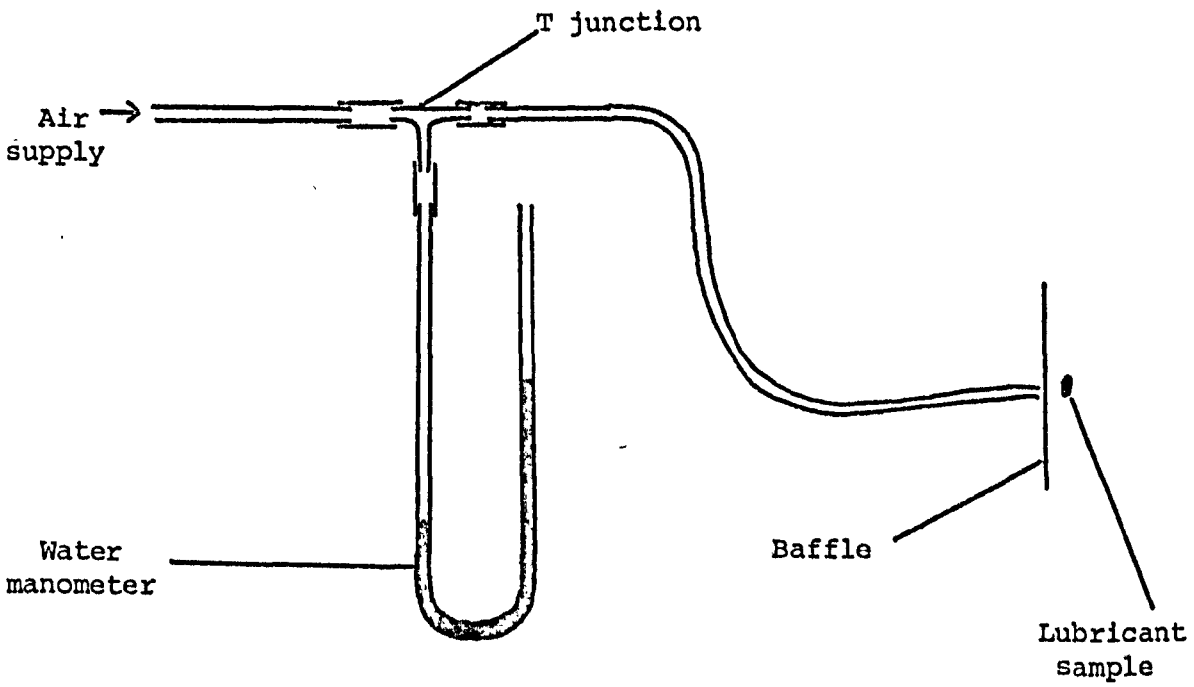


Fig. 2.2. "Blowability" test apparatus.

The manometer was used to control the air pressure so that the air jet applied to the powder is uniform for each test. The rubber tubing was taped to the working surface to maintain it in the correct position. The baffle was readily movable. When the air pressure was at the required pressure (as indicated by previously determined scales on the manometer) the baffle was raised to allow the air jet to impinge

on the lubricant powder sample and then lowered again to prevent undue scattering of the powder. The distance over which the lubricant material

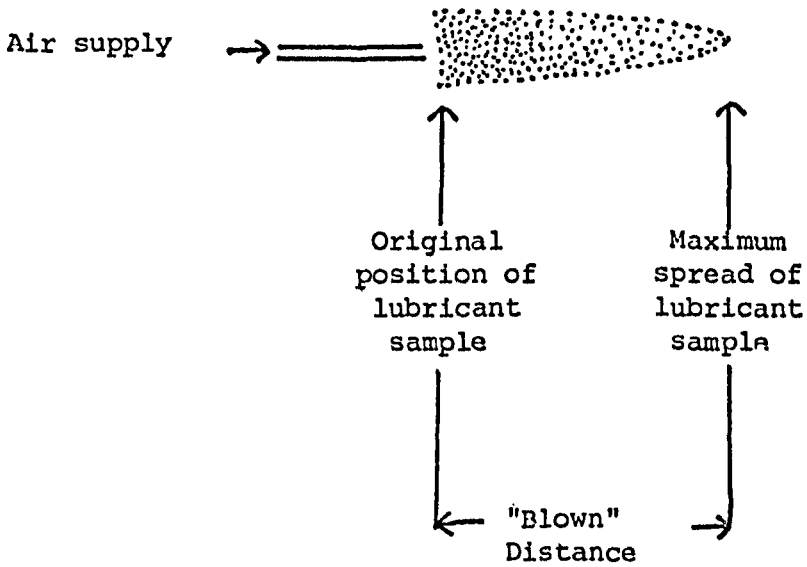


Fig. 2.3. "Blown" distance.

had been scattered was measured as shown in Fig. 2.3. and referred to as the 'blown distance'. Three determinations were made and the mean 'blown distance' calculated.

2.7. Manufacture of Magnesium Stearate/Palmitate Samples.

The manufacture was based upon the method used by Müller in 1977.(153) Six different products were manufactured. The fatty acids (Table 2.1. for quantities) in approximately 1.2 litres of distilled water were heated to 86°C and the corresponding ammonium soap was produced by the addition of 140mls of 1% ammonia solution. The metallic soap was then precipitated by addition of 400ml of 1% magnesium chloride solution, added at a rate of 20 mls per minute, the mixture being stirred throughout the entire process. The mixture was then allowed to cool overnight after which the crystallizate was suctioned off, refluxed with acetone for half an hour (to remove free fatty acid), suctioned off again

TABLE 2.1. QUANTITIES OF MATERIALS REQUIRED FOR LUBRICANT MANUFACTURE.

Materials used	Product					
	Magnesium stearate plates	Magnesium stearate needles	Magnesium palmitate	St. : P 25 : 75	St : P 50 : 50	St : P 75 : 25
Pure stearic acid	22.76g	22.76g	——	5.69g	11.38g	17.07g
Pure palmitic acid	——	——	20.52g	15.39g	10.26g	5.13g
Volume of 1% Ammonia solution	140ml	200ml	140ml	140ml	140ml	140ml
Volume of 1% magnesium chloride solution	400ml	400ml	400ml	400ml	400ml	400ml

and washed with hot acetone and finally dried at room temperature (22°C) for 24 hours. For preparation of magnesium stearate needles, 200ml ammonia solution was used, to provide an excess of ammonia to render the precipitating medium alkaline. For the other products the excess of magnesium chloride solution rendered the precipitating medium acidic which was expected to result in plate-like crystal formation.

A sample of each material was milled as described in section 2.8.

Physical properties and purity of these materials were evaluated as described in section 2.2.

2.8. Milling

Milling was performed by an air jet micronizer. A five gram sample was micronized to below 5 micron particle size.

2.9. Sieve Analysis

A hundred gram sample was sieved on a Fritsch sieve shaker for

ten minutes. Sieves of 30# (500μm); 60# (250μm); 85# (180μm); 100# (150μm); 120# (125μm); 170# (90μm) and 200# (75μm) were used to size analyse the samples. The weight of powder retained on each sieve was determined and the percent weight retained calculated.

CHAPTER 3. MATERIALS AND THEIR PROPERTIES.

3.1. Tablet Excipients.

These materials were used to form binary mixtures with the various lubricant batches.

3.1.1. Lactose B.P.

This was the main excipient used, chosen because it is commonly used in tablets and is readily soluble in water. It complied with B.P. requirements, having a moisture content of 1%w/w. It was a white crystalline material with a bimodal particle size distribution as shown in Fig. 3.1. (section 2.9.)

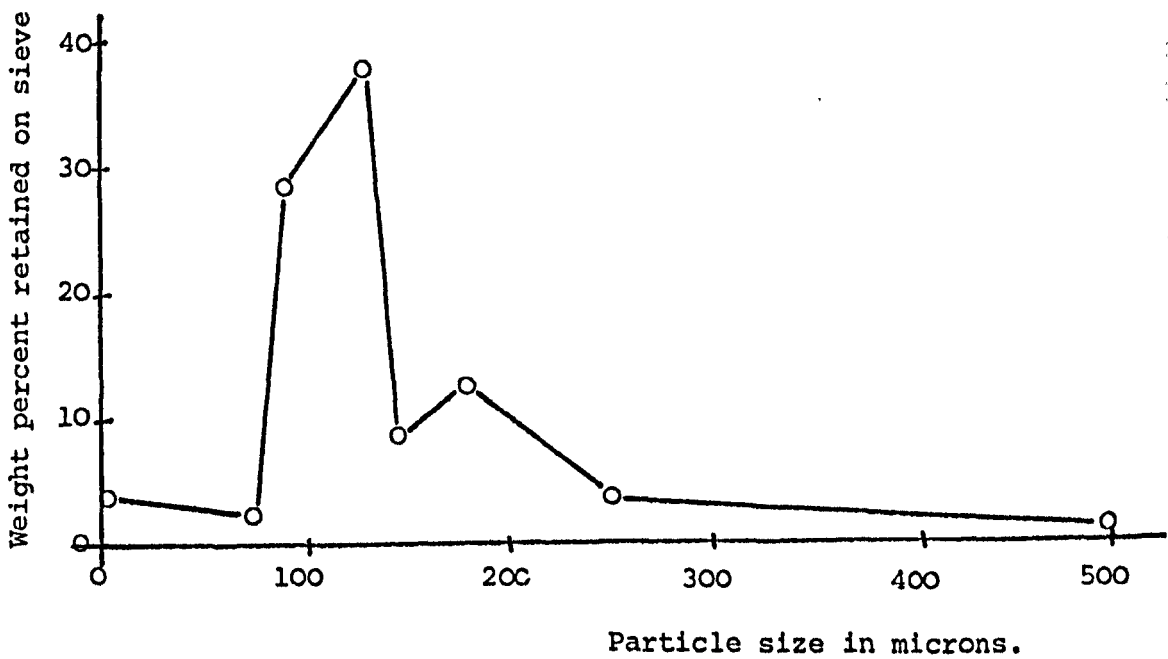


Fig. 3.1. Particle size distribution of lactose.

One batch was used throughout to eliminate possible batch to batch variation. Samples of particle size 90-125μm and below 600μm (22mesh) were used in the investigations.

3.1.2. Dicalcium Phosphate Dihydrate B.P.

This is another commonly used tablet excipient. It was a white

crystalline material with a particle size distribution as shown in Fig. 3.2. and moisture content of 0.8% w/w.

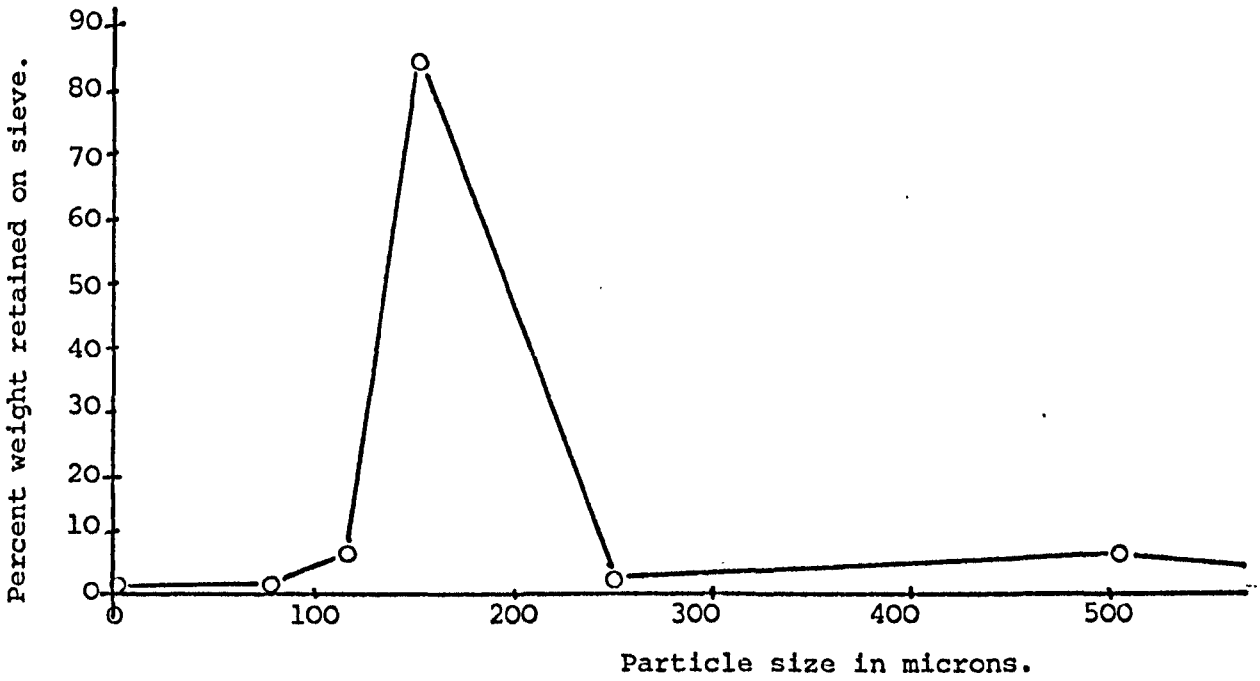


Fig. 3.2. Particle size distribution of dicalcium phosphate dihydrate.

One batch was used throughout, to eliminate batch to batch variation. Material was sieved through a 22 mesh sieve and dried overnight at 50°C which resulted in a moisture loss of 0.52%.

3.1.3. Cornstarch B.P.

This was chosen because it is another commonly used excipient but in contrast to lactose and dicalcium phosphate, is non crystalline, consisting of granules less than 40μm in diameter. (70). Cornstarch will undergo complete plastic deformation without any fragmentation (cohesion bonding) whereas the crystalline materials undergo fragmentation during compression (cold-bonding bonding). (94) It is insoluble in cold water.

3.2. Lubricants Other Than Magnesium Stearate.

3.2.1. P.T.F.E.

It is reputedly non toxic and chemically inert below 250°C,

possessing a low coefficient of friction, low shear strength and high yield pressure. (204,107,205) It seems to meet all the requirements of an ideal lubricant because it facilitates granule flow in dies, reduces intergranular friction, prevents sticking to punches, reduces ejection force and is compatible with easily degradable substances. However, it is more expensive than other lubricants. (9). It is a clean white colour (206) and optimum concentration for use is 2 to 10% with a particle size of 2-25μm.(9) Lubricity efficiency is reported to be approximately the same as magnesium stearate, but tablet crushing strength and disintegration time is unimpaired. (204, 107,169) A possible explanation for this behaviour is that it does not become smeared over the tablet surface by shear forces at the die wall and punch faces. (205) However, the nature of the thermal decomposition products above 250^{o}C have led to doubts as to its toxicity. (204).

The P.T.F.E. used for this investigation was in fine powder form with a particle size of approximately 5μm.

3.2.2. Sodium and Zinc Ricinoleates.

They are white or yellowish, almost odourless powders consisting of mixtures of the sodium or zinc salts of the fatty acids from castor oil. (207) Sodium ricinoleate has been suggested as a water soluble lubricant and for this reason was included in the investigation.

3.2.3. Palmitic Acid.

It is a white greasy flaky crystalline material being a 16 carbon saturated acid of formula $CH_3(CH_2)_{14}COOH$. (208). It is reported to have a low shear strength (26,6) and a similar lubricity to stearic acid. In this investigation the purified material (G.L.C. assay $\geqslant$99%, melting point 62-63^{o}C) was used in the manufacture of lubricants of varying stearate to palmitate ratios. Its molecular weight is 256.43.

3.2.4. Stearic Acid.

This is an 18 carbon saturated acid of formula $CH_3(CH_2)_{16}COOH$. (208) Commercial stearic acid, (70) a white greasy flaky crystalline material is in fact a mixture of fatty acids, chiefly stearic and palmitic. It is insoluble in water. It is used at a concentration between 0.5 to 2% (37,103) and reduces particle movement and interparticle friction in all directions during compression, (209) undergoing plastic deformation at extremely low applied pressures. (210) It possesses no glidant properties (58,6,) and poor antiaherent properties. (6,10) It retards drug dissolution and tablet disintegration (66,67,68,52), reduces tetracycline and chloramphenicol activity (122) and hydrolyses aspirin. (119) It is reported to decrease tablet strength (209) but other reports indicate it has no effect (152). It is recommended for use in tablets where lettering or a design is present (8). It is reported to be a better lubricant than talc but worse than magnesium stearate.

In this investigation both the commercial and purified grades were used, the latter for manufacturing lubricants of various ratios of stearate to palmitate. Its molecular weight is 284.8.

3.3. Magnesium Stearate.

It is the most widely used tablet lubricant, because of its availability. (43). It is the magnesium salt of commercial stearic acid (section 3.2.4) and is a fine white powder, insoluble in water, with faint characteristic odour. (63,211). Commercial batches produced by different methods have different properties (149,151,148), and crystal structure can be needle shaped or plate like (section 1.8). During mixing, the lubricant forms a continuous film around granules (section 1.5) and because of this has a deleterious effect on tablet disintegration and dissolution. (section 1.6.2). The effect increases with concentration

to a certain limit (212) but appears to be eliminated in vivo (116). A deleterious effect is observed on tablet hardness (section 1.6.1), the extent of the effect depending upon the base material used due to different bonding mechanisms undergone during compaction. (94). The lubricant film can be disrupted by admixture with aerosil 200 both during and after film formation (84,85,86). Magnesium stearate can also adversely affect the active ingredient in a tablet (section 1.6.3). It is thought that conversion to stearic acid may account for some of its deleterious effects (213). It is effective in concentrations below 1% (103,6,83,22) possessing some glidant (58) and antiadherent properties (60,10) as well as being an antistatic compound (34,33). It is the most efficient of the tablet lubricants alone, but in combination with talc, however, it is reported to lose its lubricant action (6,13). It has a low shear strength (25,6). Using this lubricant, tablets with a high gloss are produced (179,37).

3.3.1. Commercial Samples.

Since batch variation of magnesium stearate was the problem under investigation, eleven commercial batches were obtained from varying sources for evaluation. Their physical properties are summarized in table 3.1.

3.3.2. Laboratory Prepared Lubricants.

These were prepared in 20g batches as described in section 2.7. Identity tests for the presence of magnesium ions and fatty acids were performed as described in Appendix 6 and proved positive. Exact stearate to palmitate ratios were determined by G.L.C. (section 2.2.4) and examples of the traces obtained are shown in Appendix 3. The main properties of these manufactured lubricants are summarized in table 3.2.

TABLE 3.1. PROPERTIES OF VARIOUS BATCHES OF COMMERCIAL MAGNESIUM STEARATE.

Property	Commercial Batch of Magnesium Stearate.										
	1	2	3	4	5	6	7	8	9	10	11
Source	Squibb Australia	Squibb Australia	Squibb Italy	Squibb Germany	Squibb S. Africa	Squibb Brazil	Squibb England	Wyeth England	Wyeth England	Wyeth England	B.D.H. Tech. grade England
Odour	Fairly strong	Very faint	Fairly strong	Faint	Very strong waxy odour	Quite strong	Faint	Faint	Faint	Very very faint	____
Assay as % Magnesium Oxide	7.24	7.61	7.80	6.90	7.15	7.40	7.30	7.43	7.59	7.26	____
% Loss on drying	3.43	5.06	3.18	4.53	5.06	4.23	3.85	3.34	4.14	3.33	____
% Fatty acid content	77.3	84.6	84.9	88.6	87.3	87.5	82.3	____	____	____	____
Ratio of stearate to palmitate	65:35	52:48	71:29	69:31	50:50	68:32	67:33	____	____	____	____
Bulk Density,											
a) before taps	0.200	0.147	0.154	0.208	____	0.169	0.143	____	0.135	____	____
b) after taps	0.357	0.315	0.313	0.368	____	0.294	0.219	____	0.242	____	____

TABLE 3.1. (cont) PROPERTIES OF VARIOUS BATCHES OF COMMERCIAL MAGNESIUM STEARATE.

Property	Commercial Batch of Magnesium Stearate.										
	1	2	3	4	5	6	7	8	9	10	11
Particle size in microns	27.50	15.80	26.00	16.60	14.20	15.50	5.50	21.75	16.00	18.00	15.30
Particle size Distribution											
< 5.0 microns	46.75%	67.94%	47.63%	63.96%	73.14%	63.39%	97.67%	82.22%	72.58%	79.52%	77.79%
5.0-15.0microns	38.35%	29.77%	39.08%	32.85%	25.43%	33.60%	2.33%	15.91%	24.93%	18.25%	20.29%
> 15.0 microns	14.90%	2.29%	13.29%	3.19%	1.42%	3.01%	0.00%	1.87%	2.49%	2.22%	1.91%
Surface area in m^2/g	2.83	8.00	3.47	6.93	5.70	7.90	15.36	5.66	14.52	5.98	7.99
Crystal Shape	Large sheets of plates	Plate-like	Large sheets of plates	Plates	Needles Few plates	Needles and plates	Very small plates	Plates	Plates	Plates	Plates

TABLE 3.2. PROPERTIES OF LABORATORY PREPARED LUBRICANTS.

Property	Batch of Lubricant					
	Magnesium Stearate plates	Magnesium Stearate needles	Magnesium Palmitate	St : P 25 : 75	St : P 50 : 50	St : P 75 : 25
Fatty acid solidifying temperature.	67.5°C	67.5°C	61.0°C	54.0°C	55.0°C	60.5°C
Stearate to Palmitate ratio in lubricant	100 : 0	100 : 0	0 : 100	27 : 73	53 : 47	74 : 26
% Loss on drying	4.05	6.05	6.28	6.13	5.53	5.11
Crystal shape of unmicronized material	Very thin sheets of plates	Needles. Few Plates	Large plates very thin	Very thin plates	"Chunky" plates	"Chunky" plates
Crystal shape of micronized material	Rounded plates	"Blunt" needles Few plates	Rounded plates	Rounded plates	Rounded plates	Rounded plates
Particle size of unmicronized material	70-100 microns	40-50 microns	50-60 microns	70% below 5μm Rest 5-10μm	20-25 microns	100-200 microns
Particle size of micronized material	Less than 5μm	Less than 5μm	Less than 5μm	Less than 5μm	Less than 5μm	Less than 5μm

CHAPTER 4. LUBRICITY EVALUATION OF MAGNESIUM STEARATE.

This chapter describes the work undertaken using the Instron machine as described in section 2.1.

4.1. Work Involving Commercial Lubricants.

Having established the test procedure (section 2.1.), lubricity evaluations were performed upon the eleven commercial magnesium stearate batches, The material was tested alone and in admixtures with various tablet excipients.

4.1.1. Lubricant Material Alone Tests.

Using the established test and die cleaning procedures, the eleven lubricant batches were evaluated in random order. The mean ejection energy values per unit area of tablet - die wall contact are summarized in table 4.1. Examples of traces are shown in Appendix 1.

The main conclusion from this test was that the batches of magnesium stearate are different and variations in lubricity do exist. From the results, an arbitary classification of the lubricants into good, poor, and mediocre could be established. Lubricants with an ejection energy of $800 Jm^{-2}$ or below were classified as GOOD, that is batches 3, 7, and 10. Those lubricants having ejection energies in the range 1000-1100 Jm^{-2} were classified as MEDIOCRE, namely batches 1, 2, and 9 whilst batches 4 and 6, having ejection energies above 1400 Jm^{-2} were classed as POOR. Batches 5, 11, and 8, whose ejection energies lie in the 900-950 Jm^{-2} range could be classed as mediocre to good in expected performance.

Thus it would appear that ejection energy measurements for the lubricant material only, could be used to estimate the lubricity efficiency of a batch of magnesium stearate.

TABLE 4.1. LUBRICITY EVALUATION OF SAMPLES OF ELEVEN COMMERCIAL BATCHES OF MAGNESIUM STEARATE.

Batch of Magnesium Stearate	1	2	3	4	5	6	7	8	9	10	11
Ejection energy in Jm^{-2}	1110	1050	655	1600	920	1460	750	900	1080	800	950

TABLE 4.2. LUBRICITY EVALUATION OF SAMPLES OF 1% LUBRICANT IN LACTOSE.

Batch of Magnesium Stearate	1	2	3	4	5	6	7	8	9	10	11
Ejection energy in Jm^{-2} of first sample.	5319	3036	4612	4434	4456	3222	2371	4938	2767	4105	3444
Ejection energy in Jm^{-2} at plateau	2500	1530	2000	1950	1750	1550	1350	1950	1350	1850	1500

4.1.2. Lubricants in Admixture with Excipients Tests

Since in practice, lubricant material is usually used in the presence of other excipients, it was thought appropriate to evaluate the eleven batches of magnesium stearate in the presence of common tablet excipients. Samples were mixed as described in section 2.3. and lubricity evaluated by the established test (section 2.1.).

4.1.2.1. One Percent Lubricant in Lactose - Single Test.

Each sample was evaluated in a clean die, and mean ejection energies per unit area of tablet - die wall contact are summarized in table 4.2.

Differences between the lubricant batches, were again, readily observed. From these results the arbitary classification of lubricants into good, poor, and mediocre, establishes batches 7 and 9 as good, 10, 4, and 5 as mediocre and batches 1 and 8 as poor, the other batches falling in between. The most interesting conclusion is that there is no correlation of lubricant classification, with the preceeding tests, when the lubricants were compressed alone. Thus the lubricant batches are different, and behave differently when mixed with lactose at 1% concentration. Therefore ejection energy measurements on lubricated tablet excipients could also be used as an estimate of lubricity of a magnesium stearate batch, and this test is probably a more reliable guide to practical lubricant efficiency, since it more closely resembles a tablet formulation.

Matsuda et al.(103) studied the energy consumption during ejection of tablets lubricated with various materials. They found that the shape of the ejection force against punch displacement curve, changes, with a close relationship to lubricity, depending upon the kind of lubricant and application conditions. The curve rapidly reaches a peak, after which the ejection force tends to decrease rapidly with further movement of the punch. It then shows a plateau or second peak for magnesium

Fig. 4.1. Instron traces for ejection of tablets containing 1% lubricant (Magnesium stearate) in lactose.

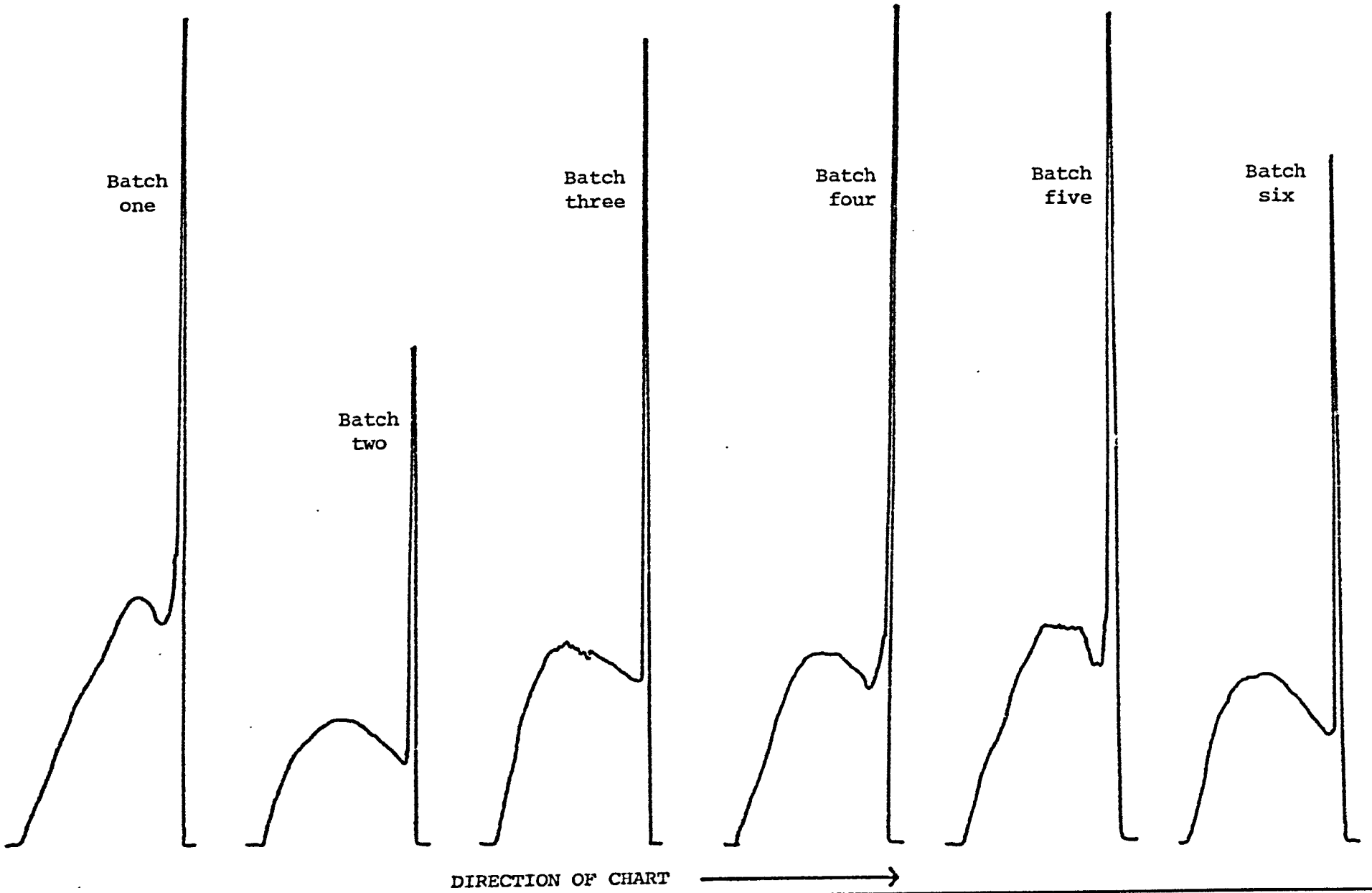
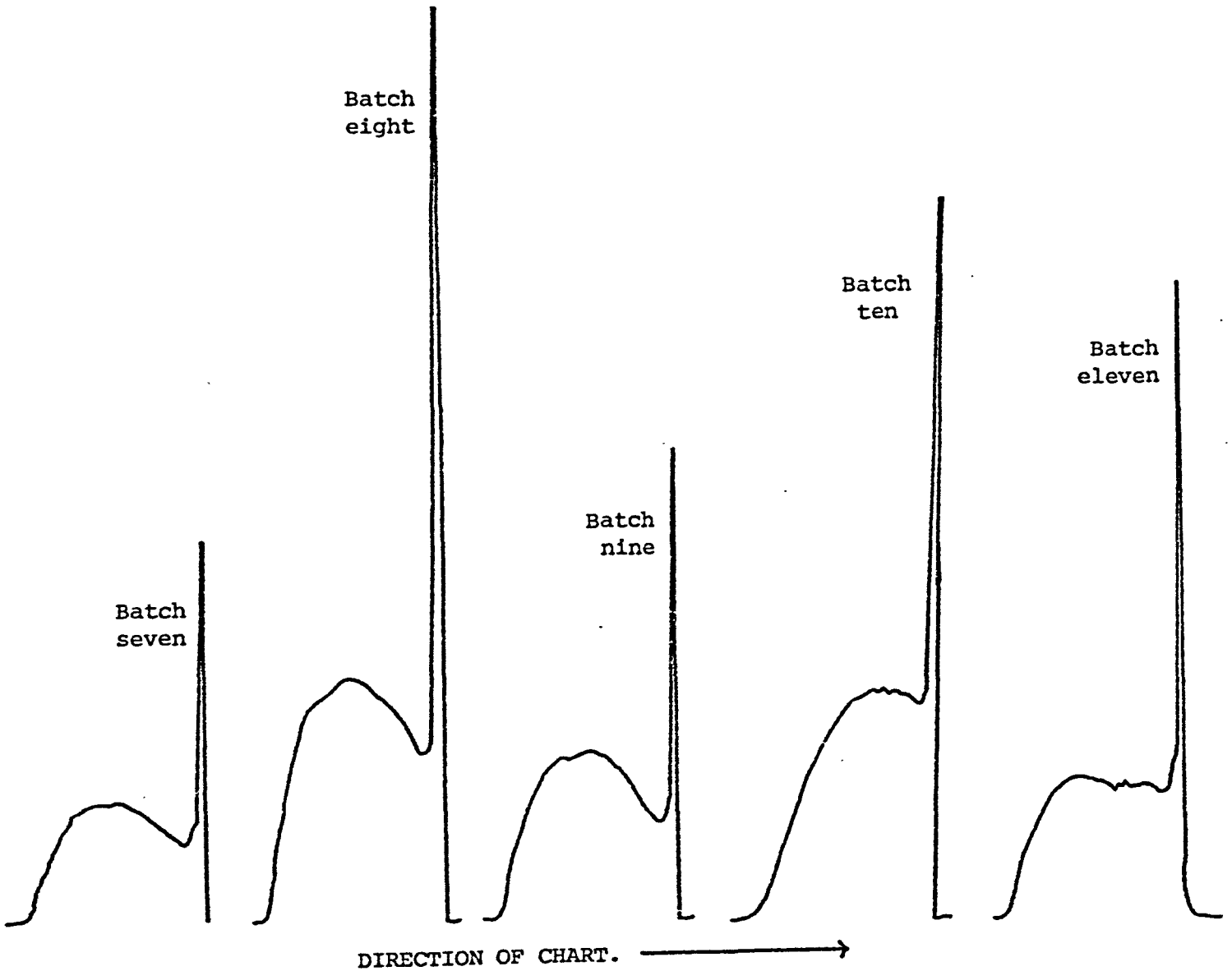


Fig. 4.1. (cont.) Instron traces for ejection of tablets containing 1% lubricant (Magnesium stearate) in lactose.

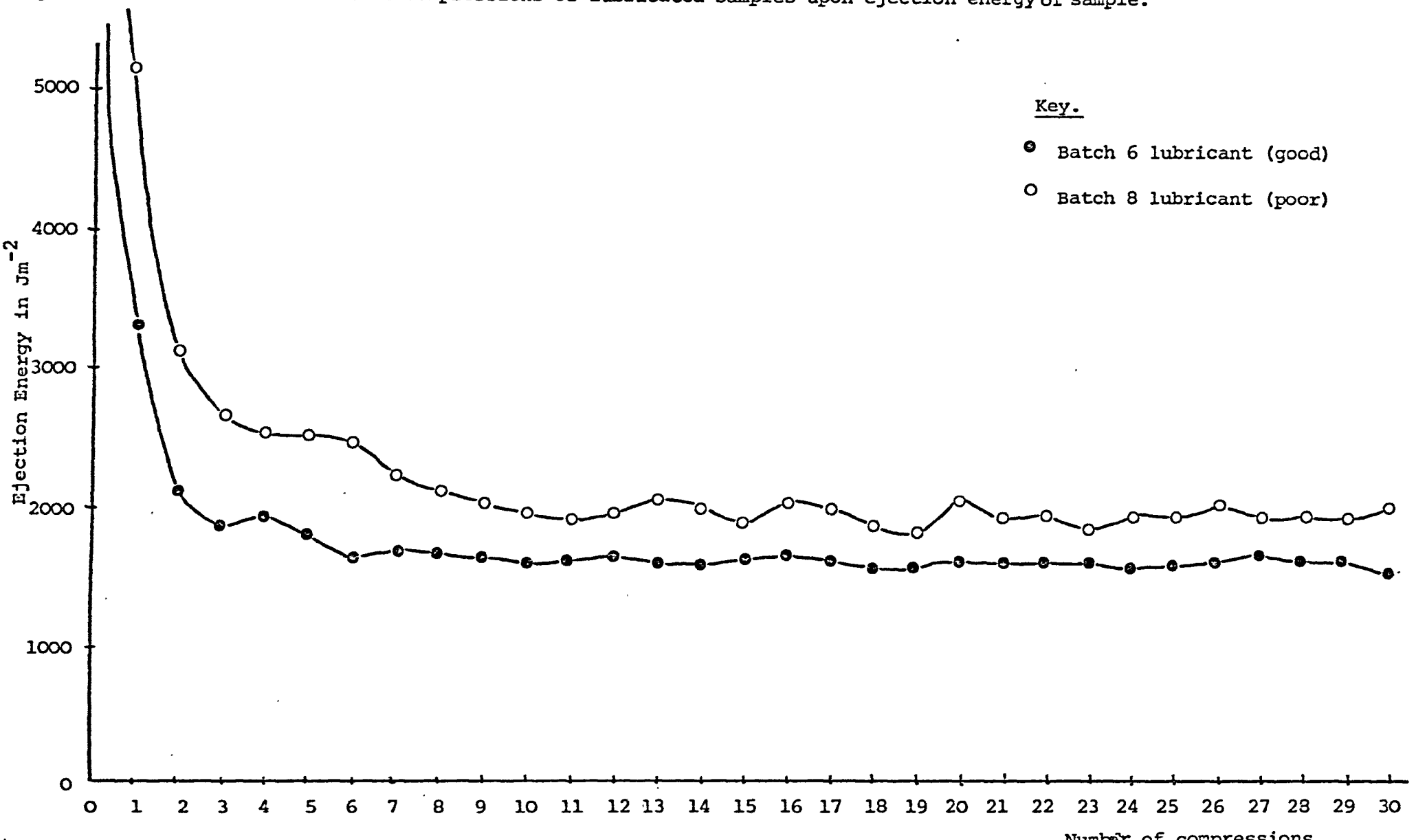


stearate but decreases continuously for talc. Studies indicated that the second peak shows the elastic recovery of a tablet inside the tapered outlet of the die and is closely related to the lubricity of a tablet. Good lubricants show high elasticity (108), therefore the more pronounced the second peak, the greater the elastic recovery of the tablet and hence the more efficient the lubricant. Thus the ejection energy curves for the eleven commercial batches 1% in lactose were examined for presence of the second peak.(Fig. 4.1.) Batches 1, 3, 10, and 11 yield traces with a "flattened" secondary peak, indicating poor elasticity and hence these batches could be classified as 'poor' relative to the other magnesium stearate batches. Batches 2, 6, 7, 9, and 8 yield traces with a well defined second peak which indicates a high degree of elastic recovery and that these batches, relatively, are good batches. Batches 4 and 5, yield traces with a definate second peak but not as pronounced as batches 6, 7, 2, 9, and 8. Thus batches 4 and 5 could be classified as mediocre. This classification, based upon shape of ejection curve, correlates reasonably well with the classification based on ejection energies themselves. The major exception is batch 8, which apparently has a high elasticity but also a high ejection energy.

4.1.2.2. <u>One Percent Lubricant in Lactose - Plateau Value.</u>

In practice, in a production run, dies are not cleaned between each tablet compression so that for each tablet formed, the die would have been lubricated by the formation of the preceeding tablets. Therefore to determine the effect of lubricant "carry over" on the die, upon the lubricity evaluations, samples of 1% magnesium stearate in lactose were compressed in an unwashed die until a constant value for ejection energy had been obtained. (Fig. 4.2.) Thirty compressions were found to be sufficient for all batches. Results are summarized in Table 4.2.

Fig. 4.2. Effect of consecutive compressions of lubricated samples upon ejection energy of sample.



As expected, the presence of magnesium stearate on the die wall, reduced the ejection energy of subsequent samples, to a limiting value, which was not that value obtained when lubricant materials were compressed alone. In fact the plateau ejection energy value was dependent upon the original ejection energy so that a "poor" lubricant has a higher plateau value than a "good" lubricant. Therefore the "carry over" of magnesium stearate on the die, does not affect the relative lubricity ability of the magnesium stearate batches investigated although the differenciation between the batches is reduced.

4.1.2.3. Varying Lubricant Concentration in Lactose.

This investigation determined the extent of the influence of the excipient present upon the lubricant. Only lubricant batches 1 to 7 were examined since there was insufficient material in batches 8 to 11 to use for this investigation. Samples were mixed as described in section 2.3.1. using lubricant concentrations of 1, 3, 5, and 10%. Mean ejection energies for all samples are summarized in table 4.3

The results show that increasing the lubricant concentration up to 10%, results in a decrease in ejection energy of all samples, initially, but whilst batch 1 ejection energy continually decreases, batches 2, 3, 4, and 5 attain plateau values and for batches 6 and 7 the ejection energy increases. However the relative lubricity ability order of the magnesium stearates, even at 10% concentration is not altered from that obtained when the lubricants are compressed alone, in fact there is very little change from the 1% concentration order. Therefore, it would appear that the presence of the excipient has a marked influence on the lubricity ability of magnesium stearate batches.

TABLE 4.3. LUBRICITY EVALUATION[a] OF BATCHES 1 to 7 MAGNESIUM STEARATE at VARYING CONCENTRATIONS IN LACTOSE.

Percentage of lubricant	Batch of Magnesium Stearate						
	1	2	3	4	5	6	7
1%	5651	3211	4628	4337	4456	2674	2524
3%	3339	1774	2823	1964	2610	1678	1443
5%	2573	1717	2194	1795	1819	1497	1345
10%	2368	1784	2126	1713	1819	1623	1687
100%	1110	1050	655	1600	920	1460	750

[a] Lubricity evaluation was by means of the mean ejection energy measured in Jm^{-2}

4.1.2.4. Estimate of Lubricant Carryover on Die.

Lubricated samples, 1% in lactose, were compressed and ejected under standard test procedures, then, without washing the die, lactose only samples were compressed and ejected until the original ejection energy value for lactose tablets had been attained. Graphs of ejection energy against the number of the lactose compression were plotted for each lubricant batch as shown in Fig. 4.3.

All curves showed the same basic shape, that of a Type $\overline{V}$ adsorption/desorption isotherm. (214,215). Type $\overline{V}$ isotherms indicate adsorption onto a porous surface by multilayer formation but not in a uniform manner that is, some parts of the surface undergo multilayer formation before monolayer formation is completed. Application of this theory to lubrication would suggest that the lubricant molecules pass to the die wall during the compression process and 'adhere' to it. Since the die wall will not be smooth but consist of asperities (section 1) of molecular dimensions, the lubricant molecules can "fill up" the hollows between asperities (adsorption into capillaries) as well as adhering to the asperities. Depending upon the amount and distribution of lubricant at the die wall, multilayer film formation will occur to varying degrees. Thus the ease with which the magnesium stearate batch will undergo this process would be indicative of its lubricant ability. In this investigation, the quicker the magnesium stearate is removed from the die wall, the less a) that is there and b) it adheres to the metal surface, and therefore the poorer the lubricant. The rate of removal from the die wall was estimated by calculating the gradient of the first portion of the graphs. Results are summarized in Table 4.4.

It is assumed that the greater the gradient value, the quicker the lubricant is removed from the die. Therefore batches 10 and 11 are

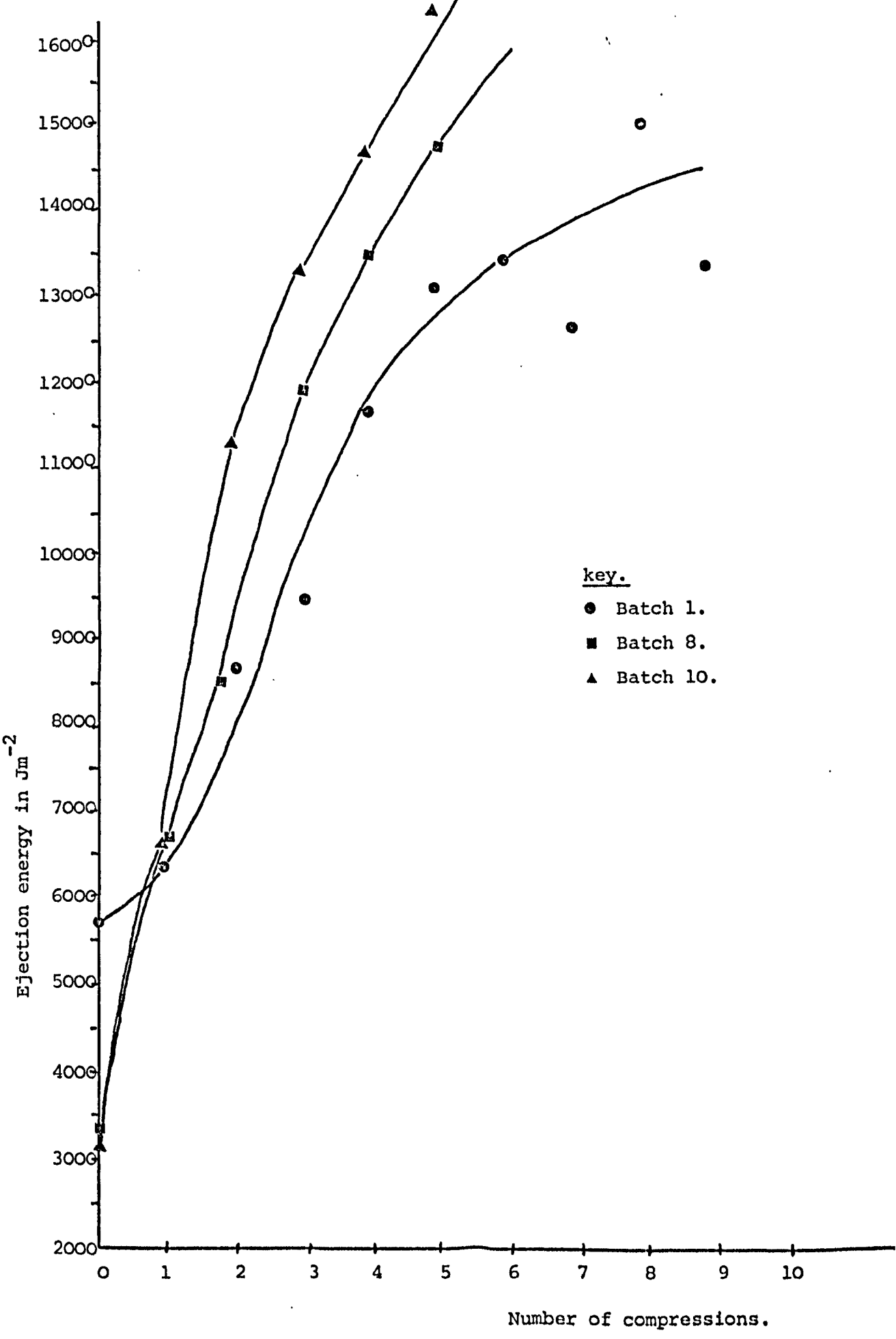


Fig. 4.3. Ejection energy curves for cleaning magnesium stearate off the die

removed quickly whereas batches 1, 7, and 6 are harder to remove, indicating that batches 10 and 11 are less efficient than batches 6, 7, and 1. Batch 1, however, has previously been reported as a poor batch as judged by ejection energy measurements. Thus, although the general trend in these results is that the more efficient batches are more slowly removed from the die, whilst the less efficient batches are removed quickly, this is not an absolute guide to practical lubricant ability. However, the results do indicate that there are differences in "carry over" of the lubricants, a factor which will affect the efficiency of the lubricant.

4.1.2.5. <u>One Percent Lubricant in Dried Dicalcium Phosphate Dihydrate.</u>

Each of the lubricant batches was evaluated as described in section 4.1.2.1. but using dried dicalcium phosphate dihydrate as the base material. Dried material (section 3.1.2.) was used, because preliminary tests with dried and undried materials indicated that distinction between the good and poor lubricant batches was best with the dried material. Mean ejection energy values are summarized in Table 4.5.

Differences between the eleven batches were again apparent and the lubricants could be divided into three distinct categories. Those with ejection energies in the range 8000-9000Jm^{-2}, that is batches 9, 6, 2, and 7, could be classified as good. Batches 5, 4, and 11, which had ejection energies in the range 10000 to 11000Jm^{-2} could be classified as mediocre whilst batches 3, 8, 1, and 10 could be classified as poor, having ejection energies greater than 12000Jm^{-2}. The relative lubricity ability classification of the lubricants, therefore, is very similar to that obtained from 1% in lactose tests (section 4.1.2.1.) but bears little correlation to the classification obtained

TABLE 4.4. ESTIMATES OF LUBRICANT CARRYOVER ON THE DIE.

Batch of Magnesium stearate	1	2	3	4	5	6	7	8	9	10	11
Gradient of graph in Jm^{-2} per compression	1573	2250	3077	3019	2176	1882	2041	2535	2432	4250	3750

TABLE 4.5. MEAN EJECTION ENERGIES[a] OF THE ELEVEN COMMERCIAL BATCHES OF MAGNESIUM STEARATE IN COMMON TABLET EXCIPIENTS

Tablet Excipient	Batch of Magnesium Stearate 1	2	3	4	5	6	7	8	9	10	11
Dicalcium phosphate dihydrate	13462	8739	12178	10559	10558	8251	8806	12343	8082	12386	10935
Cornstarch	3594	1798	2608	2898	2731	1461	2102	3716	1904	3059	3158

[a] Ejection energies were measured in Jm^{-2}

when the lubricants were compressed alone. Thus the lubricity ability of the magnesium stearate batches does not significantly depend upon the excipient used.

4.1.2.6. One Percent Lubricant in Cornstarch.

To determine whether an excipient which undergoes a different mechanism of bonding during compaction, will affect the relative lubricity performance of the magnesium stearate batches, section 4.1.2.5. was repeated but using cornstarch as the base material. Cornstarch (section 3.1.3.) undergoes complete plastic deformation without any fragmentation during compression, (known as cohesion bonding) whereas lactose and dicalcium phosphate dihydrate undergo fragmentation during compression (known as cold-bonding). Mean ejection energies are summarized in Table 4.5.

From the results, differences between the batches were apparent but there was no division of the batches into definate categories, since the ejection energies observed, covered the entire range rather than clustering around upper, lower and middle sections. It could be concluded that relatively, batches 6, 2, 9, and 7 were good, batches 8, and 1 were poor and the other batches were in between. The relative lubricity ability classification corresponds to that obtained with lactose as excipient rather than that obtained when lubricants were compressed alone. Thus the different bonding mechanism during compaction does not significantly affect the relative lubricant ability of batches of magnesium stearate although distinction between the batches is not as clear.

4.1.2.7. Comparison of Lubricant Behaviour in the Various Excipients

For the three materials used, categorization of the lubricants was very similar, Thus a batch classed as poor with lactose would be

classed as poor with the other two materials, cornstarch and dicalcium phosphate dihydrate.

For each set of results for the different base material investigations, a relative lubricant excipient factor was calculated where:-

$$\text{Lubricant excipient factor} = \frac{\text{Ejection energy of base material x 100\%}}{\text{Ejection energy of 1\% lubricated base material}}$$

the higher the percentage, the more efficient the lubricant. Results are summarized in Table 4.6. Graphs were plotted of each set of values against each of the other two sets and the correlation coefficients calculated. (Fig. 4.4.) For dicalcium phosphate dihydrate values against lactose values and cornstarch values against dicalcium phosphate dihydrate values (Fig.4.4.), correlation coefficients were 0.84 and 0.90 respectively which indicates good agreement between the two sets of values. For cornstarch values against lactose values, a lower correlation of 0.68 was obtained. However, from these values, it can be concluded that the three sets of results do show a high degree of correlation. Thus the eleven batches of commercial magnesium stearates could be classified as shown in Table 4.7 and it would be expected that this classification would accurately predict their performance in actual production batches.

TABLE 4.7. RELATIVE CLASSIFICATION OF ELEVEN COMMERCIAL BATCHES OF MAGNESIUM STEARATE.

Relative classification	GOOD	MEDIOCRE	POOR
Batches of magnesium stearate	9, 6, 7, & 2	4, 5, & 11	1, 8, 3, & 10

Therefore it can be concluded that the nature of the excipient does not influence the relative lubricity ability of the batches of magnesium stearate although the actual ejection energies themselves are affected.

TABLE 4.6 % LUBRICANT EXCIPIENT FACTORS FOR ELEVEN BATCHES OF MAGNESIUM STEARATE IN VARIOUS EXCIPIENTS.

Excipient	Batch of Magnesium Stearate										
	1	2	3	4	5	6	7	8	9	10	11
Lactose	282.01%	494.07%	325.24%	338.29%	336.62%	465.55%	632.64%	303.77%	542.10%	365.41%	435.54%
Cornstarch	297.72%	595.11%	410.28%	369.22%	391.80%	732.38%	509.84%	287.94%	561.97%	349.79%	338.82%
Dicalcium phosphate dihydrate	111.42%	171.64%	123.17%	142.06%	142.07%	181.80%	170.34%	121.53%	185.63%	121.10%	137.17%

Note. Mean ejection energies for the base materials themselves are 15000, 15000, and 10700 Jm^{-2} for lactose, dried dicalcium phosphate, and cornstarch respectively.

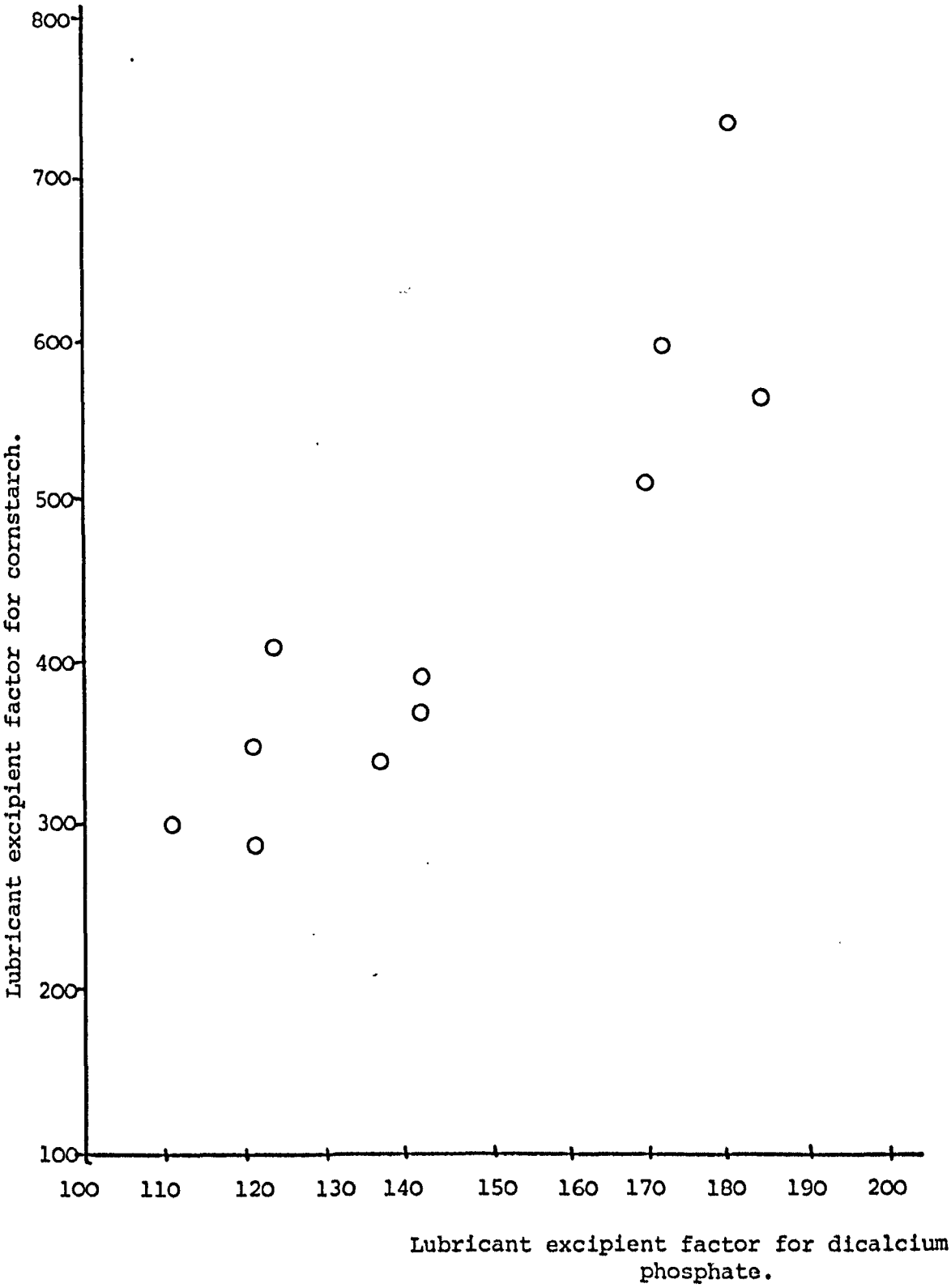


Fig. 4.4. Scattergram of lubricant excipient factor for dicalcium phosphate and lubricant excipient factor for cornstarch for eleven commercial batches of magnesium stearate.

4.1.3. Comparison of Lubricant Alone Tests with Admixture Tests.

A graph of lubricant excipient factor for dicalcium phosphate dihydrate against ejection energies of lubricant materials tested alone yielded a scattergram as shown in Fig. 4.5. indicating a very low correlation between the two sets of values. The actual correlation coefficient was calculated as 0.32 which confirms that there is little relationship between lubricant alone tests and admixture test classifications of lubricant ability. The same conclusion is obtained from scattergrams of lubricant excipient factors of lactose or cornstarch against lubricant alone ejection energies.

Increasing the lubricant concentration in admixtures (section 4.1.2.3) did not alter the relative lubricity ability order of the batches, to that obtained from lubricant alone tests, so it was concluded that the presence of the excipient significantly influences lubricant performance. Thus the behaviour of lubricants in admixtures cannot be predicted from lubricant alone behaviour and vice versa.

Overall, it was concluded that the lubricant alone tests evaluated the "inherent" lubricity of a magnesium stearate batch and that other factors such as particle size, crystal shape, hardness etc, may modify the ability of the lubricant to express that lubricity practically. Thus a lubricant batch which may have a good inherent lubricity but is not readily sheared and distributed during the mixing process would be less effective in actual production runs.

Therefore, since all tablets consist of other materials beside the lubricant, the best test for the prediction of lubricant behaviour in production batches would be the 1% admixture tests, preferably using the base material to be used in the production batch. Lubricant alone tests would not be a reliable guide for prediction of practical lubricant efficiency.

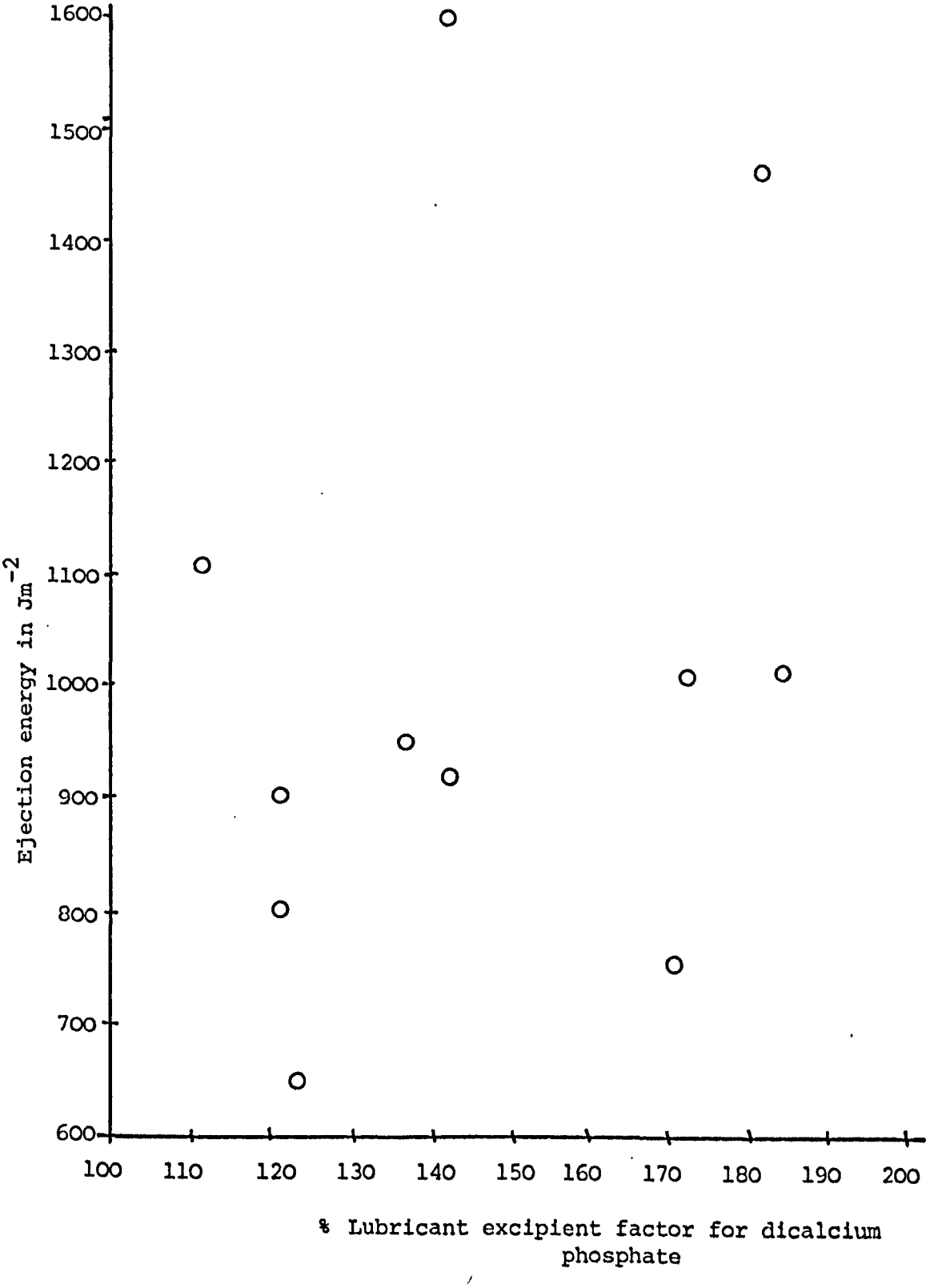


Fig. 4.5. Scattergram of ejection energy of lubricant alone samples and lubricant excipient factor for dicalcium phosphate.

4.2. Lubricity Evaluation of Laboratory Prepared Lubricants.

The materials were manufactured as described in section 2.7. Six samples were prepared and these were:-

a) 100% magnesium stearate as plate-like crystals

b) 100% magnesium stearate as needle crystals

c) 100% magnesium palmitate

d) magnesium stearate : palmitate ratio 25 : 75

e) magnesium stearate : palmitate ratio 50 : 50

f) magnesium stearate : palmitate ratio 75 : 25.

Their physical properties are described in section 3.3.2. Lubricity was evaluated by the Instron test (section 2.1.), tests being performed on lubricant material alone, (micronized and unmicronized) and 1% admixture with lactose (micronized and unmicronized). The aim of these investigations was to determine the effect of the lubricant composition upon its lubricant efficiency. For comparative purposes commercial batches 1 and 6 were simultaneously investigated.

4.2.1. Tests upon Lubricant Material Alone

Ejection energies of samples were measured by the established test for both micronized (below 5μm) and unmicronized material, the results being summarized in Table 4.8.

From the results it could readily be seen that there were differences in lubricity efficiency between the manufactured batches, in both micronized and non micronized states. For the unmicronized material all laboratory prepared batches were less efficient at reducing ejection energy than even the poorest commercial lubricant batch examined. An arbitary classification of the manufactured lubricants into "more efficient" and "less efficient" could be established. Those lubricant batches producing ejection energies below 2200 Jm^{-2}, that is magnesium stearate plates, magnesium palmitate and the 25 : 75 stearate to palmitate

TABLE 4.8. MEAN EJECTION ENERGIES OF LUBRICANT SAMPLES IN MICRONIZED AND UNMICRONIZED FORMS IN Jm^{-2}

Sample state	Lubricant batch.							
	100% stearate plates	100% stearate needles	100% palmitate	25 : 75 St : P[a]	50 : 50 St : P[a]	75 : 25 St : P[a]	Magnesium stearate Batch 1	Magnesium stearate Batch 6
Unmicronized	1903	2833	2053	2196	3251	3129	1110	1460
Micronized	2596	2243	1815	1363	1938	2166	1996	1153

a=St : P is the ratio of stearate to palmitate esters in the "Magnesium stearate" sample.

lubricant, could be classed as the "more efficient" lubricants whereas the other batches produced ejection energy values greater than 2800Jm^{-2} and therefore could be considered as "less efficient". Micronization of the lubricant batches, including commercial batches 1 and 6, caused an increase in lubricant efficiency as judged by the reduction in ejection energy values, except for magnesium stearate plates and commercial batch 1, both of which showed an increase in the ejection energy values. Batch 1 is, in fact, large sheets of plate-like material such as is found in the manufactured magnesium stearate plates lubricant. Thus the two lubricants are similar in form and therefore could be expected to behave similarly. Magnesium palmitate, however, which is also in large plate-like crystal form, does not show an increase, but a reduction, in ejection energy. This reduction, however, is not as great as with the other manufactured lubricants. Micronization thus produces a change in the relative lubricant ability of the manufactured lubricant batches. The 25 : 75 stearate to palmitate lubricant is now almost as efficient as batch 6, the most efficient of the commercial batches. Magnesium palmitate and the 50 : 50 mixture are less efficient than the 25 : 75 mixture but more efficient than the 75 : 25 stearate to palmitate and magnesium stearate lubricants. Magnesium stearate plates are least efficient.

Thus lubricant alone ejection energy measurements can distinguish between batches of lubricant material, as previously established and thought to indicate inherent lubricity. Micronization improved lubricant ability for the majority of materials. This was as expected since lubrication is a surface phenomenon and therefore the finer the lubricant, the greater its covering power and therefore the greater its efficiency. However, the increase in ejection energy for plate-like material lubricant samples after micronization, indicates that some other parameter,

besides particle size is involved, perhaps, for example, electrostatic attraction between the lubricant particles.

4.2.2. One Percent Admixture with Lactose.

Samples were prepared and evaluated by the established techniques using both micronized and unmicronized lubricant material at 1%w/w concentration. Mean ejection energies in Jm^{-2} are summarized in Table 4.9.

From these results it can be concluded that the influence of the excipient is again significant, since the relative lubricant ability of the laboratory prepared lubricants is changed from that obtained when lubricant material is compressed alone. Scattergrams (Fig. 4.6 and Fig.4.7) of ejection energies of material alone and in admixture form confirm this conclusion, showing a very low degree of correlation between these two parameters, the correlation coefficients being 0.62 for micronized material and 0.05 for unmicronized material. Micronization of the lubricant reduces the ejection energies measured, but does not drastically change the relative lubricity order obtained from tests using unmicronized material. The relative lubricity orders can be summarized as follows in increasing lubricant efficiency order:-

Unmicronized material	Micronized material
Stearate to palmitate 75 : 25	Stearate to palmitate 75 : 25
100% stearate plates	Stearate to palmitate 50 : 50
Commercial batch 1	Commercial batch 1
100% palmitate plates	100% stearate plates
100% stearate needles	100% stearate needles
Stearate to palmitate 50 : 50	100% palmitate plates
Commercial batch 6	Commercial batch 6
Stearate to palmitate 25 : 75	Stearate to palmitate 25 : 75

Thus the 25 : 75 stearate to palmitate lubricant is more efficient than the most efficient of the commercial batches but the 75 : 25 stearate to palmitate lubricant is less efficient than the least efficient of the

TABLE 4.9. MEAN EJECTION ENERGIES IN Jm^{-2} OF 1% LUBRICANT IN LACTOSE SAMPLES.

Sample state	Lubricant Batch. 100% stearate plates	100% stearate needles	100% palmitate	25 : 75 St : P[a]	50 : 50 St : P[a]	75 : 25 St : P[a]	Magnesium stearate Batch 1	Magnesium stearate Batch 6
Unmicronized	6460	3590	4225	1842	3307	7194	5952	2504
Micronized	2943	2822	2349	1562	3476	3999	3239	1821

a = St : P is the ratio of stearate to palmitate esters in the "Magnesium stearate" sample.

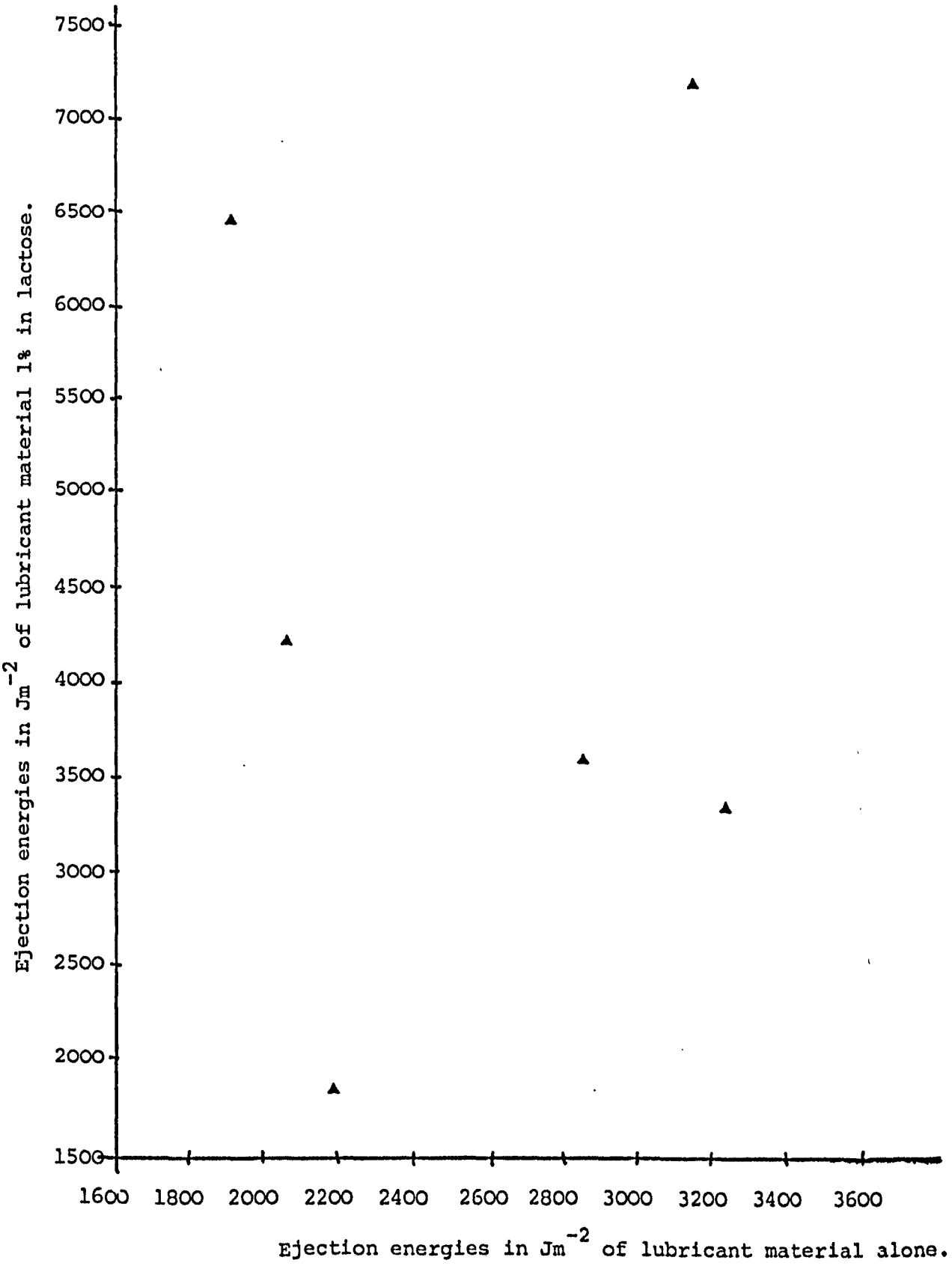


Fig. 4.6. Scattergram of ejection energies of unmicronized laboratory prepared lubricants compressed alone and in 1% admixture with lactose.

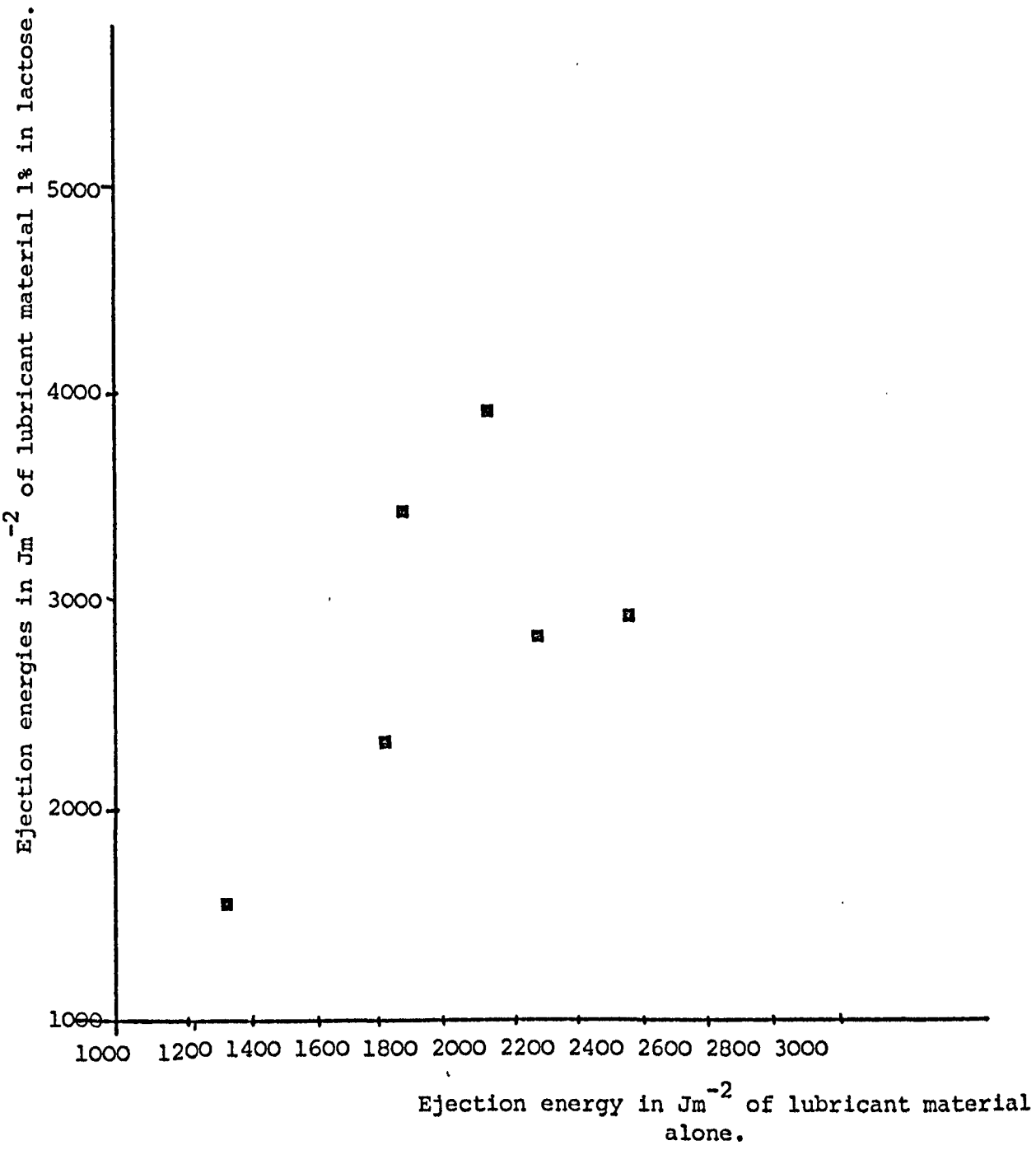


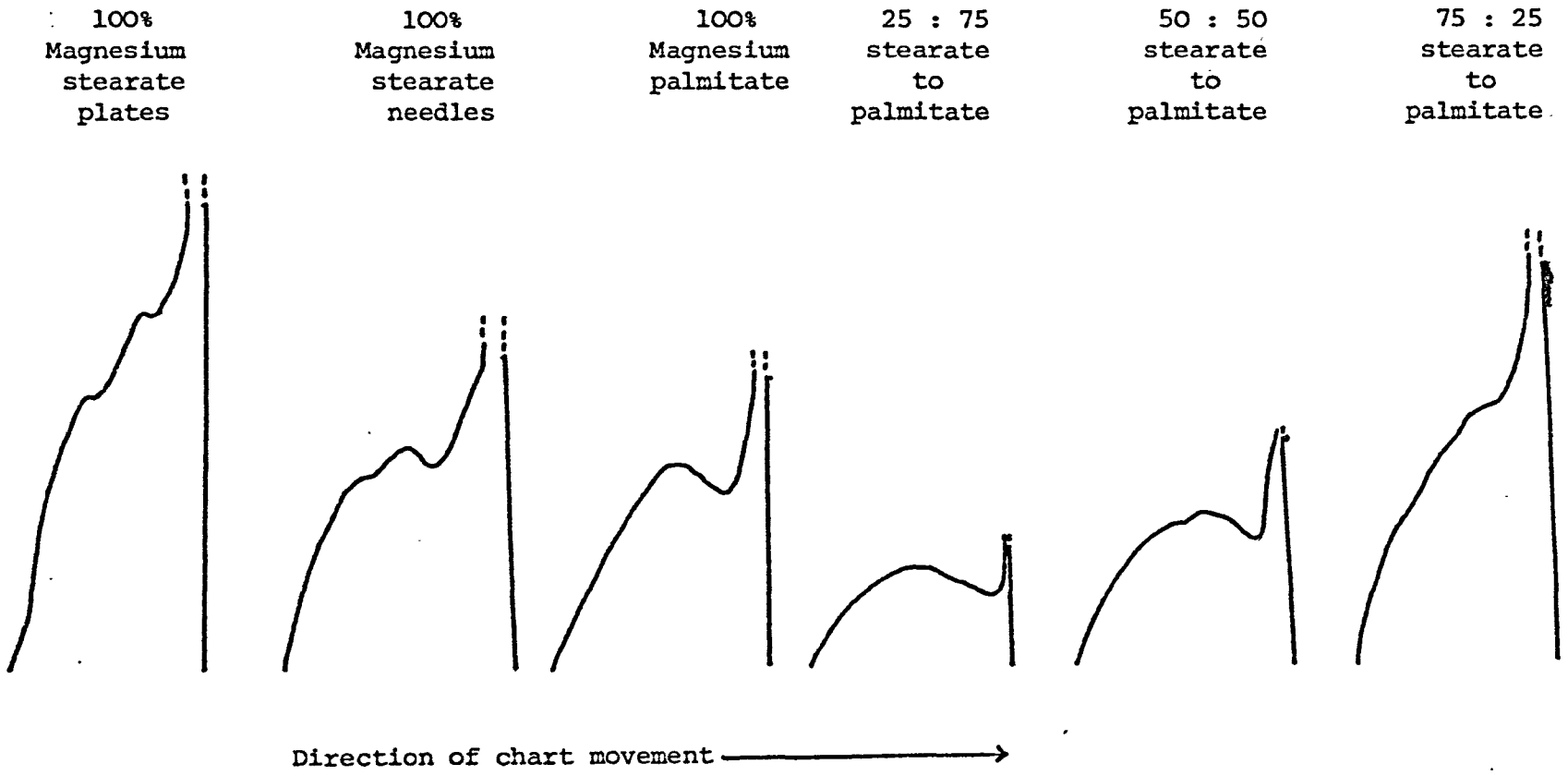
Fig. 4.7. Scattergram of ejection energies of micronized laboratory prepared lubricants compressed alone and in 1% admixture with lactose.

commercial batches. Stearate plates are much less efficient than the stearate needles although Müller (151,152,153,154) stated that dihydrate material (plates) was the more efficient lubricant. However, since micronization reduced the ejection energies produced by these two lubricants to almost the same value, indicating similar lubricant efficiency, it would appear that the difference in lubricant ability may be due to a difference in physical properties such as particle size, rather than crystal structure.

For plate-like material the relationship between stearate to palmitate ratio in the lubricant material, and its lubricant ability, can be evaluated. It was found that in the mixtures, as the concentration of stearate is increased, the ejection energy is also increased. This is true whether or not the lubricant material is micronized. With the pure materials, palmitate produces lower ejection energies than the stearate for both micronized and non micronized states. However, the pure material appears to be more efficient as a lubricant than the 75 : 25 stearate to palmitate mixture but not as efficient as the 25 : 75 stearate to palmitate mixture. In the unmicronized state the pure material is also poorer than the 50 : 50 mixture but micronization reverses this order, indicating that perhaps the large particle size of the unmicronized pure material prevents these lubricants exerting their full lubricity potential

Examination of the ejection energy curves of the unmicronized lubricants, 1% in lactose (Fig. 4.8) as described in section 4.1.2.1. reveals that 25 : 75 stearate to palmitate and 50 : 50 mixture batches have pronounced secondary peaks indicating good elastic recovery of the tablets and therefore are good lubricants, whereas magnesium stearate plates and 75 : 25 stearate to palmitate mixture do not have a pronounced secondary peak indicating poor elastic recovery of the tablets and

Fig. 4.8. Instron traces for ejection of tablets containing 1% lubricant[a] in lactose for lubricant batches prepared in the laboratory.



[a] Lubricant material is in the non micronized form.

hence are less efficient as lubricants. This confirms the conclusions from the actual ejection energy values themselves.

Thus it would appear that the magnesium salt of a 25 : 75 stearate to palmitate mixture is the most efficient lubricant, being more efficient than the pure materials, themselves. This material appears to be very efficient even in the unmicronized state probably because of its inherent small particle size.

4.2.3. Comparison of Commercial and Laboratory Prepared Lubricants.

As shown with the commercial batches of magnesium stearate the presence of an excipient such as lactose greatly influences the relative lubricity behaviour of the lubricants. Micronization of the lubricant material, however, increases its efficiency but does not greatly influence the relative lubricity of the material. Thus the laboratory prepared lubricants behave in a similar manner to the commercial batches, under similar test conditions.

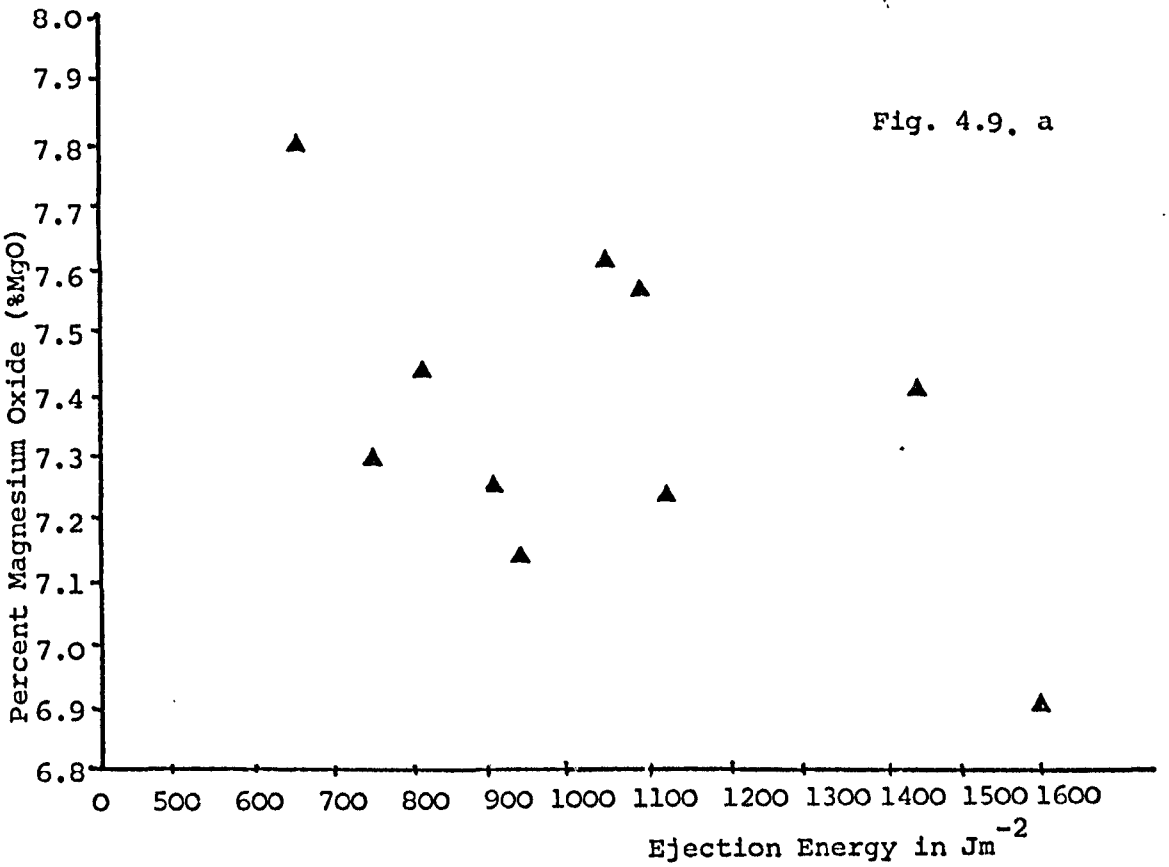
With the exception of the 25 : 75 stearate to palmitate mixture lubricant, the laboratory prepared lubricants are not as efficient as the most efficient of the commercial lubricants (batch 6). However, only the 50 : 50 and 75 : 25 stearate to palmitate mixture lubricants are less efficient than the least efficient of the commercial lubricants (batch 1). The 25 : 75 stearate to palmitate mixture lubricant is, in fact, more efficient than the commercial batch 6.

In practice, commercial magnesium stearate is prepared from commercial stearic acid which contains about 90% stearic acid, palmitic acid and other fatty acids (section 1). Thus the commercial magnesium stearate is, in fact, a mixture of stearate and palmitate esters, but with a high stearate to palmitate ratio. Thus it was thought that the lubricant efficiency of the magnesium stearate could be improved by reducing the contaminants. The laboratory prepared lubricants were

produced using purified stearic acid and palmitic acid. Thus the magnesium stearate samples contained 100% magnesium stearate. (Appendix 3.2) However, by comparison of results it can be seen that increased stearate purity does not automatically produce increased lubricant efficiency. In fact, except for 100% stearate material, increasing the stearate proportion, decreases the lubricant efficiency. It would therefore appear that a greater palmitate to stearate ratio is more efficient as a lubricant, all other factors being equal. Thus the ratio of the fatty acid constituents in the lubricant does appear to influence lubricant ability but can be overshadowed by other parameters such as particle size etc.

4.3. Discussion

Tests on commercial lubricant material alone, and in admixture with excipients, yielded two lubricity classifications for the lubricants. It was concluded that the lubricant material alone tests indicated the relative inherent lubricity of the batches, whereas the admixture tests indicated the relative practical lubricity of the batches. In the latter case, parameters such as particle size, crystal shape, crystal hardness etc. will have modified the ability of the lubricant to express practically its inherent lubricity, by affecting the ease with which the lubricant is distributed in the mix. Thus scattergrams of the physical properties of the lubricants (section 3.3.1.) were plotted against lubricant alone ejection energy values and percent lubricant excipient factor for dicalcium phosphate dihydrate to determine whether there was any relationship between relative lubricity and any physical property of magnesium stearate. (Fig. 4.9 to 4.14) Correlation coefficients and their levels of significance were calculated for each pair of parameters investigated, and are summarized in Table 4.10.



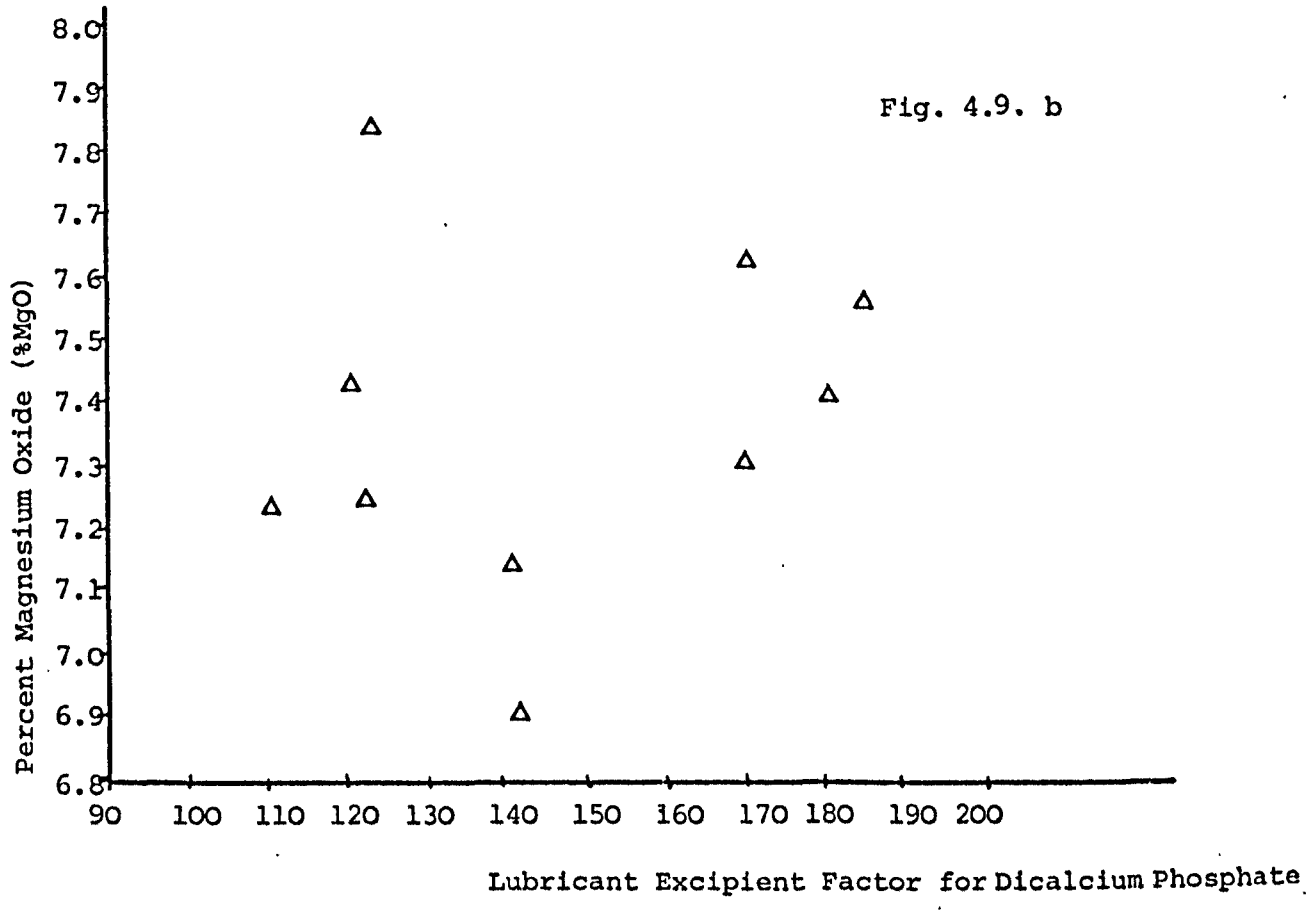
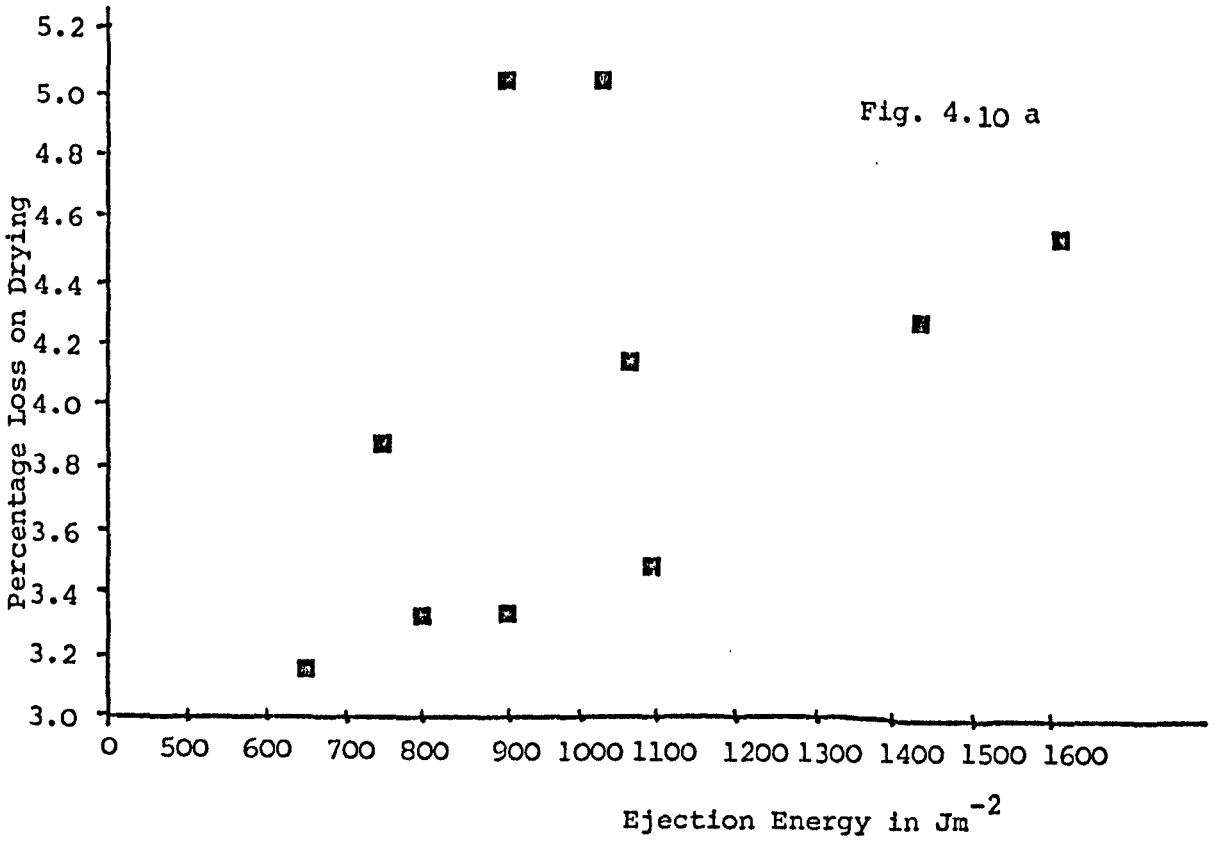


Fig. 4.9. Scattergram of percentage magnesium oxide in assay for commercial lubricants.
a) against ejection energies of lubricants tested alone,
b) against lubricant excipient factor for dicalcium phosphate.



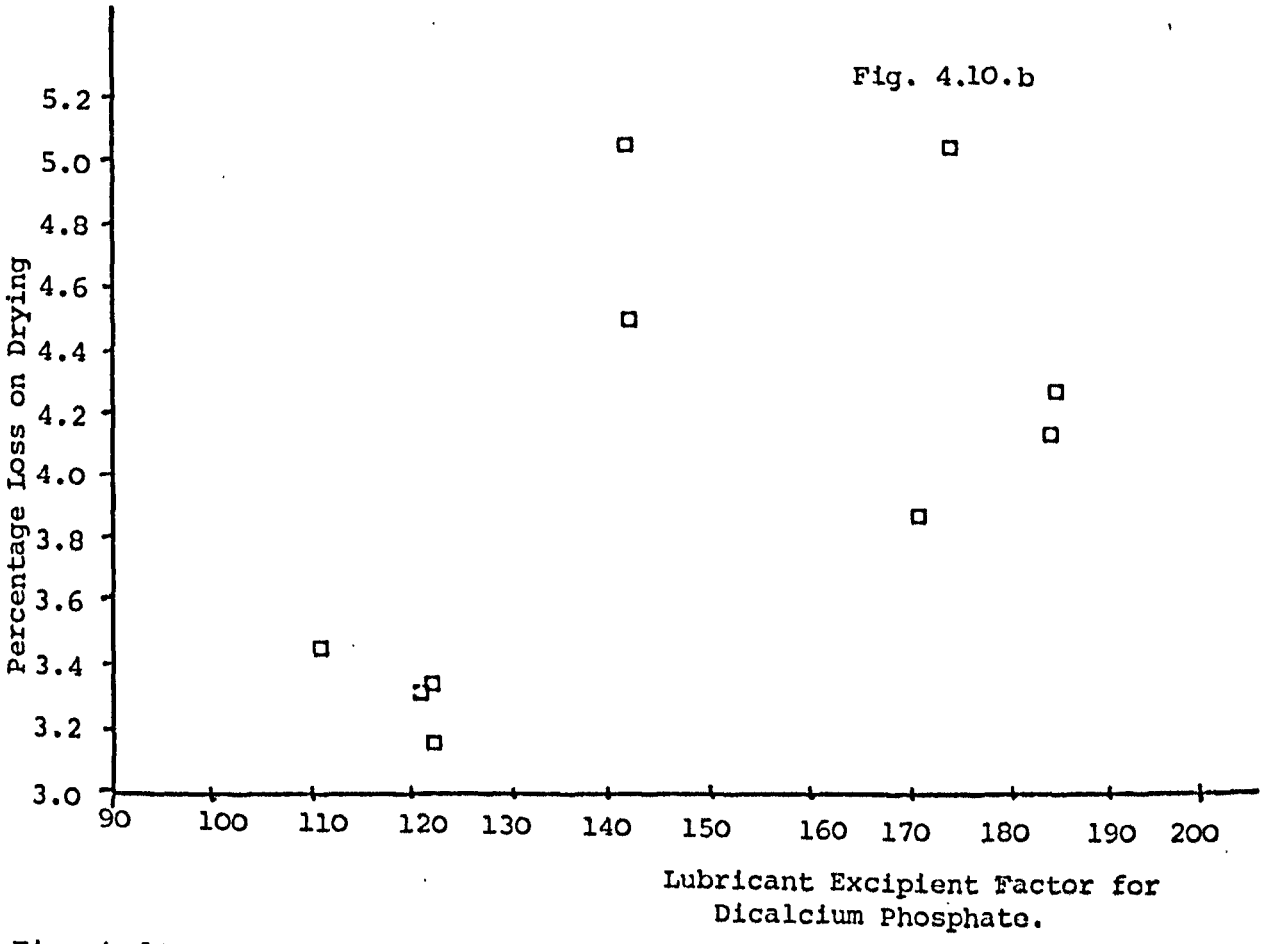
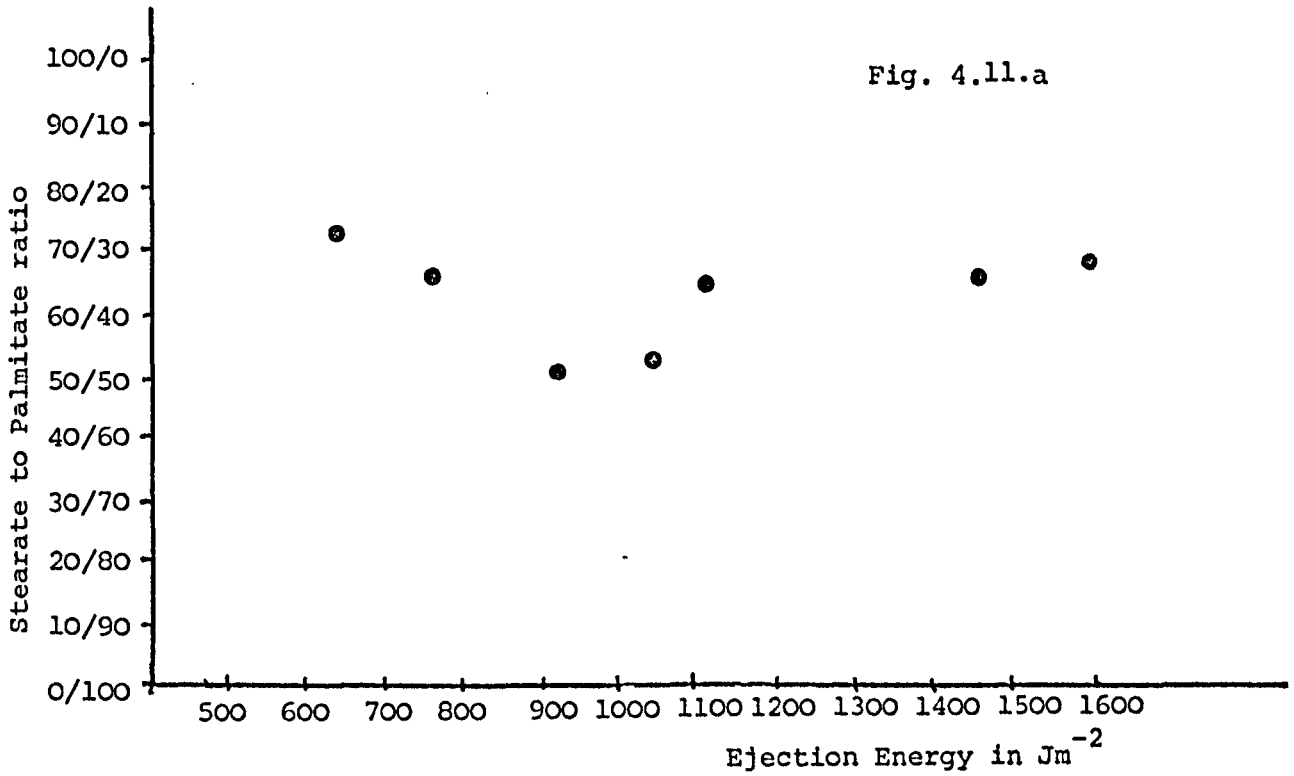


Fig. 4. 10 Percentage moisture loss scattergrams for commercial lubricants.
a) Against ejection energy of lubricant alone samples
b) Against lubricant excipient factor for dicalcium phosphate.



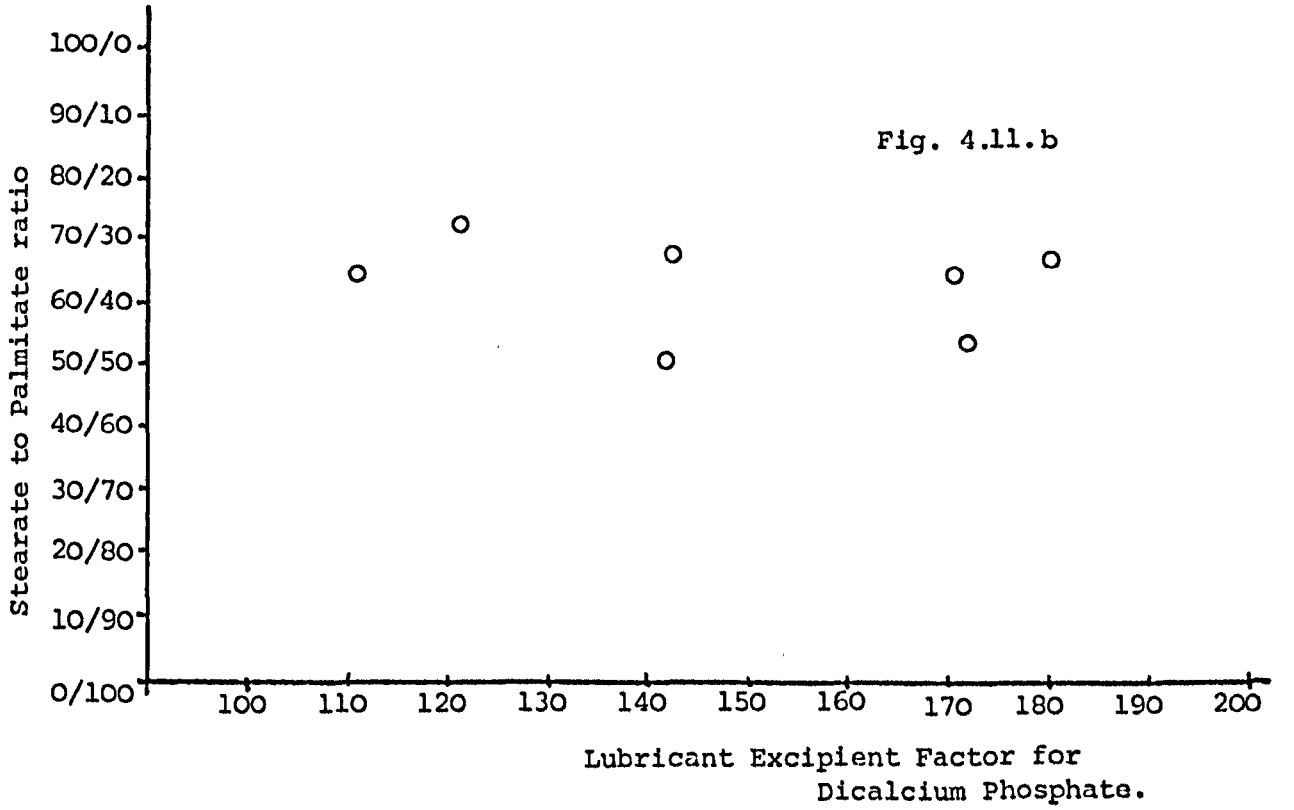
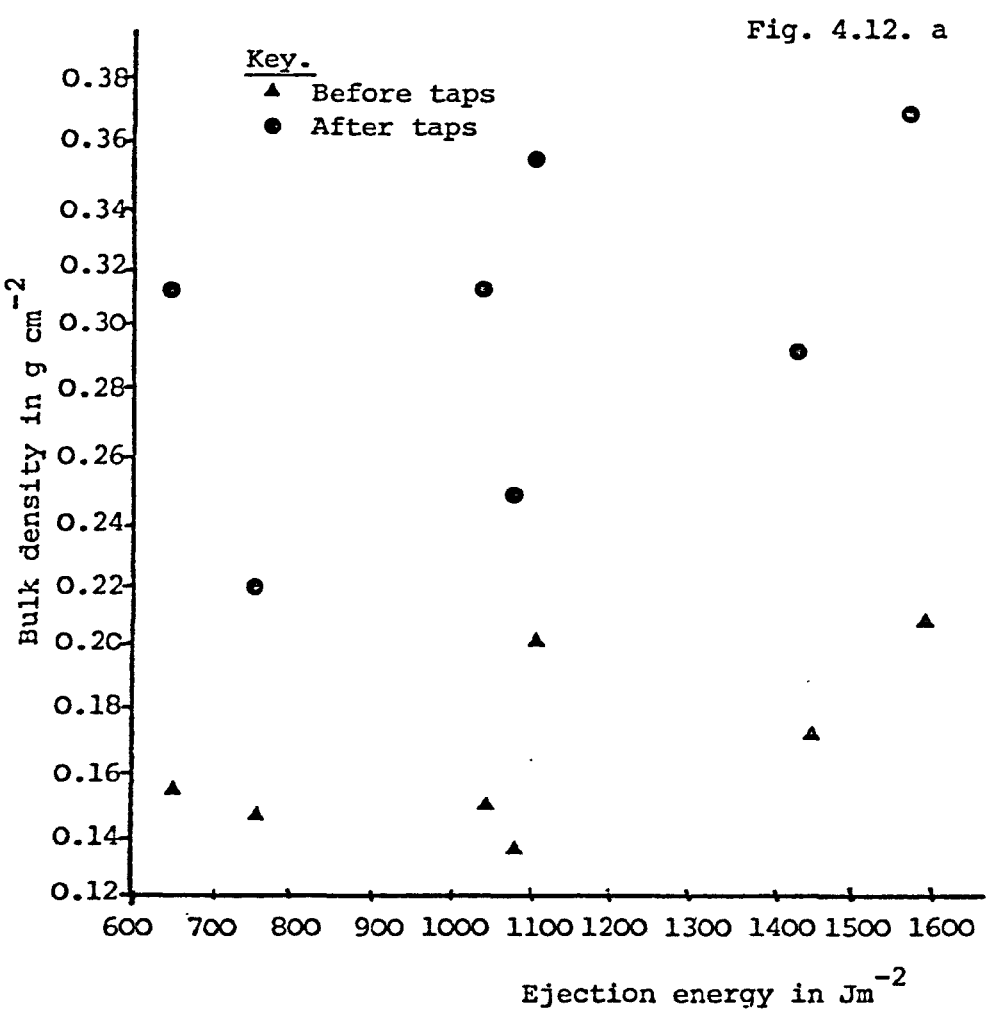


Fig. 4.11. Scattergrams for the ratio of stearate to palmitate for commercial lubricants.
a) Against lubricant alone ejection energies &
b) Against lubricant excipient factor for dicalcium phosphate



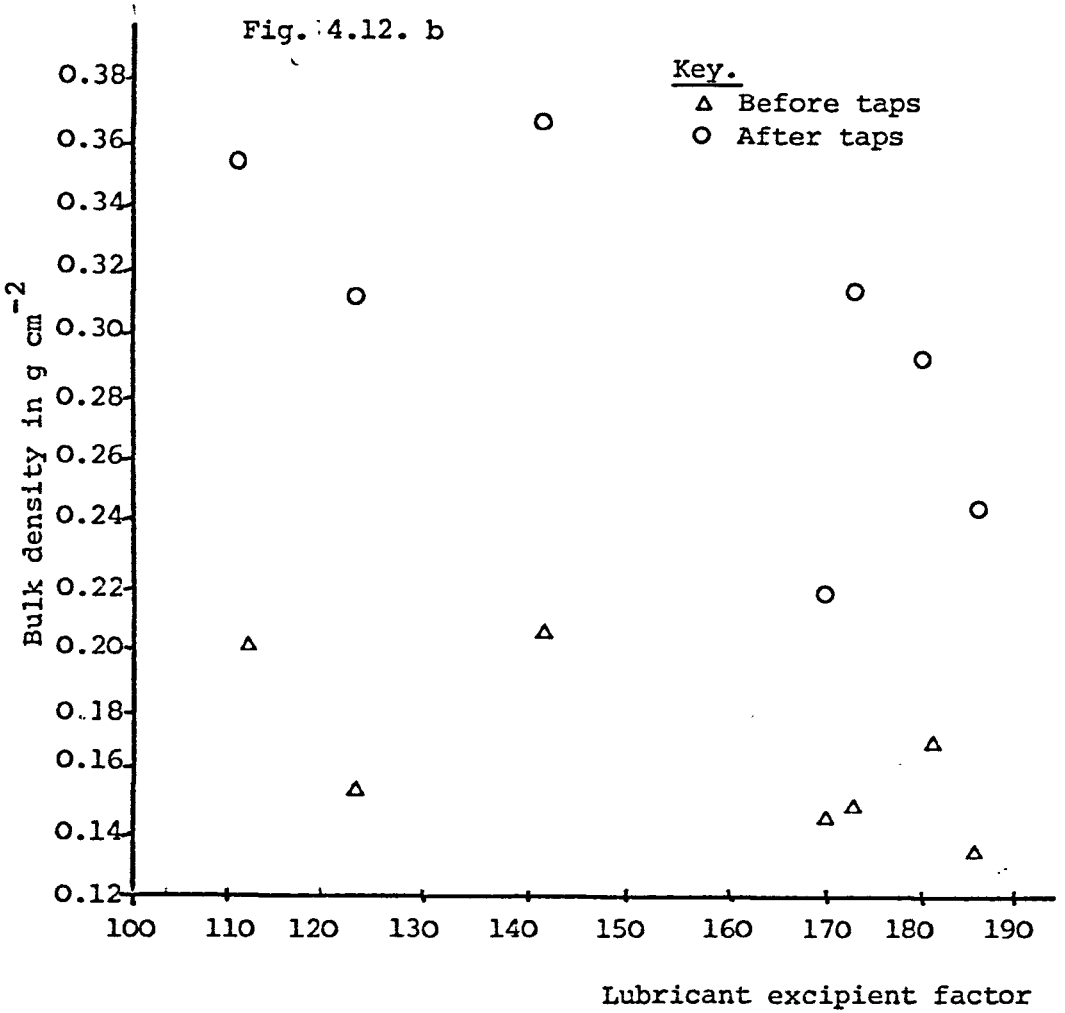
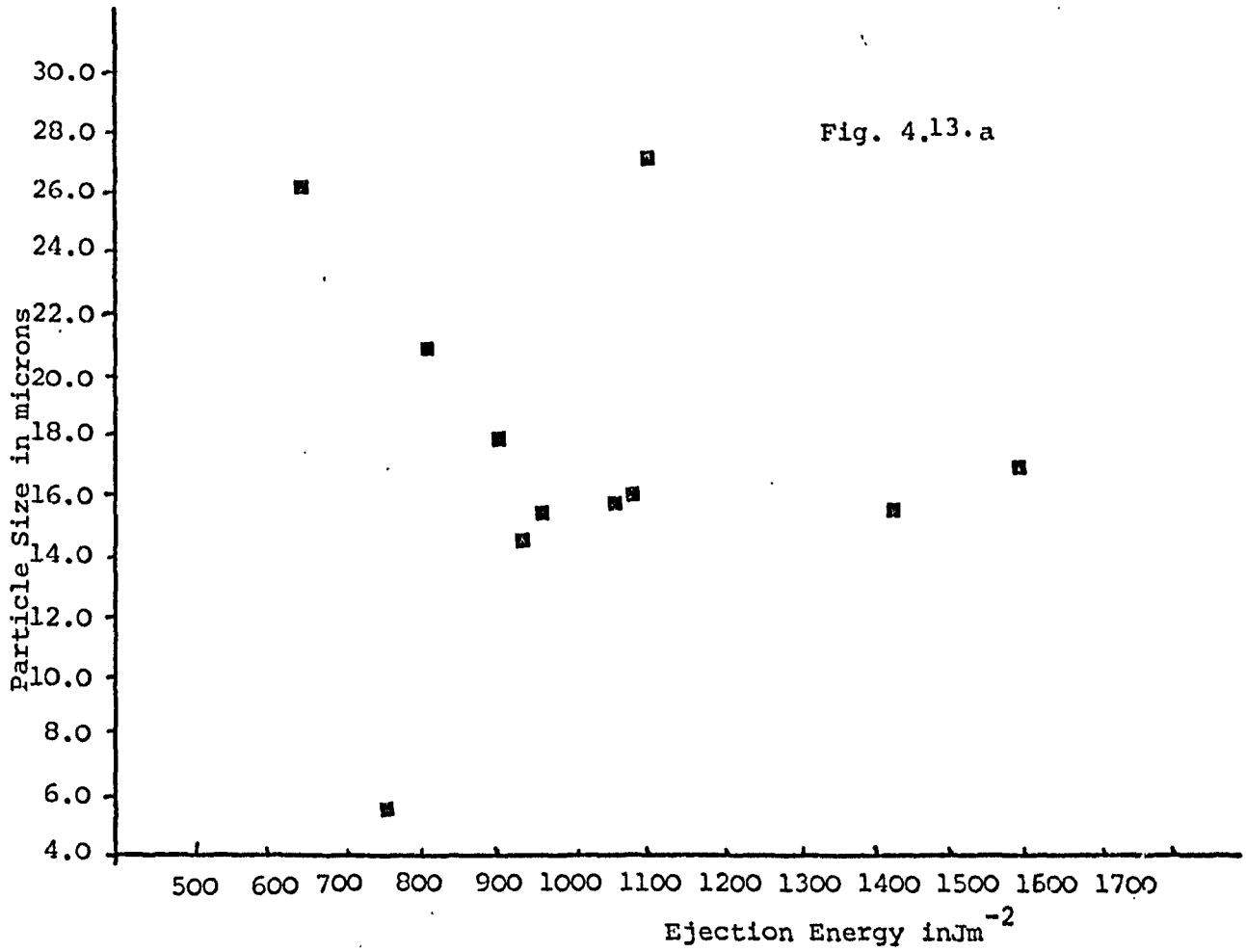


Fig. 4.12. Scattergrams for bulk density before and after tapping, a) against ejection energies for lubricant alone samples and b) against lubricant excipient factor for dicalcium phosphate.



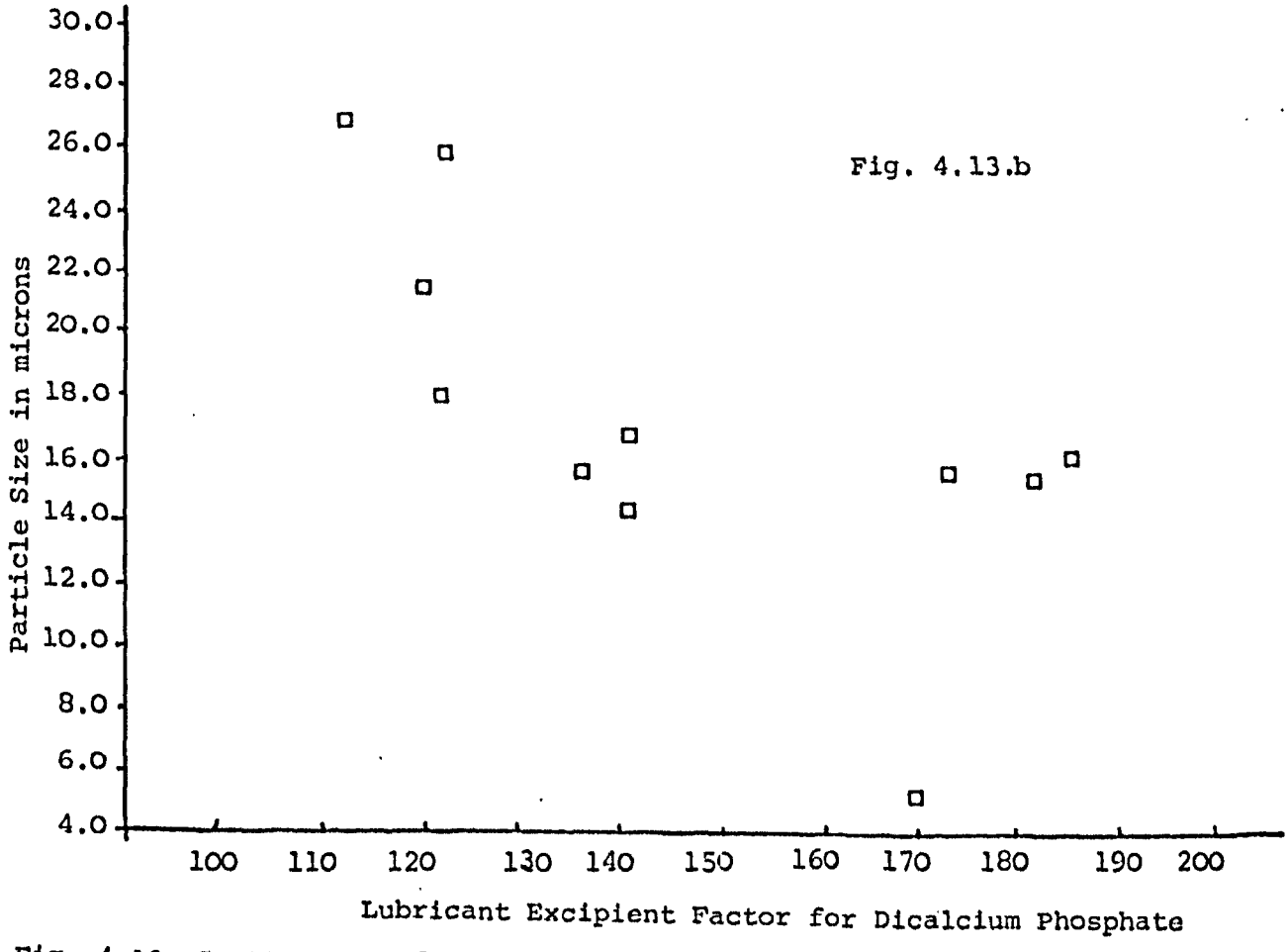
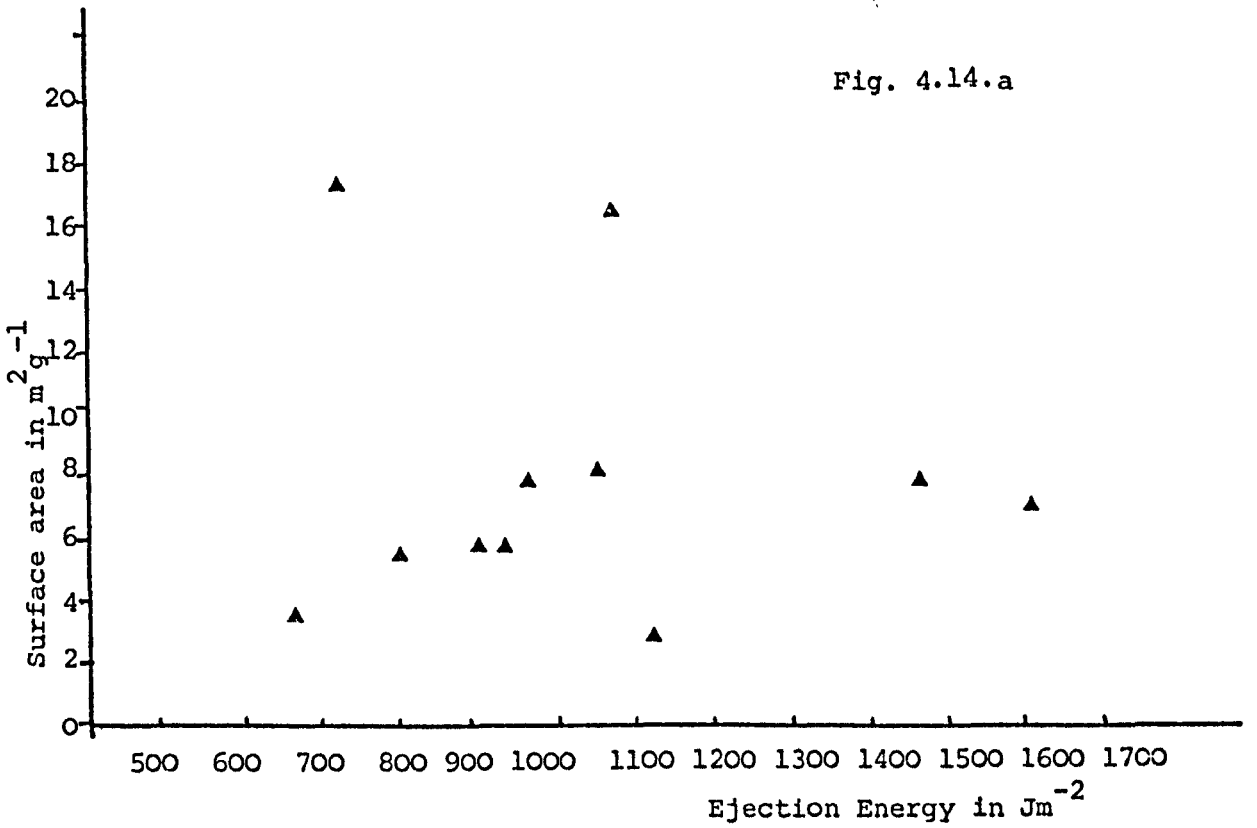


Fig. 4.13 Scattergrams for particle size for commercial lubricants
a) against ejection energy of lubricant alone samples
b) against lubricant excipient factor for dicalcium phosphate.



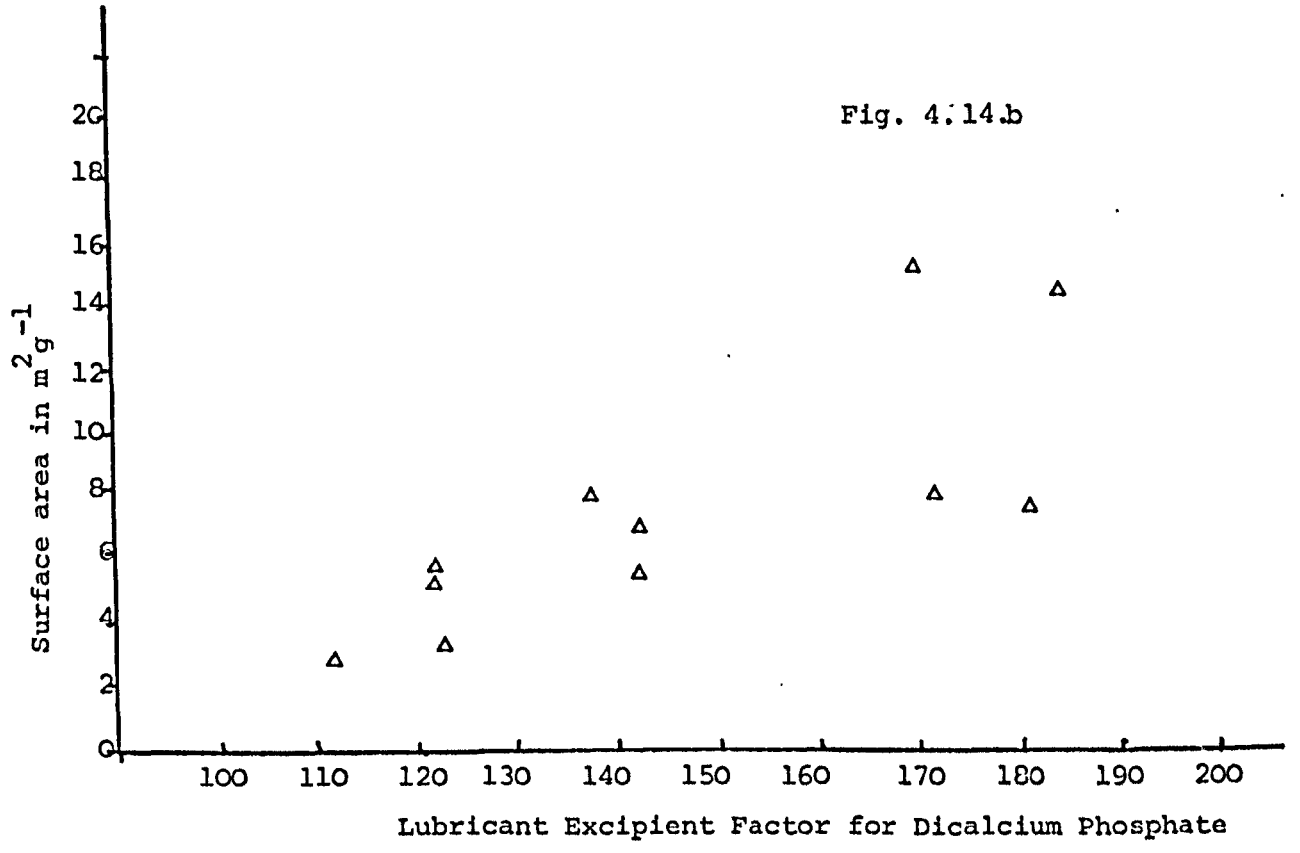


Fig. 4.14. Scattergrams for surface areas for commercial lubricants
a) against ejection energy for lubricant alone samples
b) against lubricant excipient factor for dicalcium phosphate

TABLE 4.10. CORRELATION COEFFICIENTS AND THEIR LEVELS OF SIGNIFICANCE FOR VARIOUS PHYSICAL PROPERTIES OF MAGNESIUM STEARATE AND RELATIVE LUBRICITY.

	Physical Property.						
	Percentage of magnesium oxide in assay.	Percentage moisture loss	Ratio stearate[a] to palmitate	Bulk density before tapping	Bulk density after tapping	Particle size	Surface area
Lubricant alone ejection energy							
Correlation Coefficient	0.5566	0.4461	0.1554	0.6357	0.4893	-0.0588	-0.0058
Level of significance	0.100	Greater than 0.100	Greater than 0.100	0.100	Greater than 0.100	Greater than 0.100	Greaterthan 0.100
Percent Lubricant Excipient Factor							
Correlation Coefficient	0.1989	0.5732	-0.1720	-0.6259	-0.6861	0.6776	0.6887
Level of Significance	Greater than 0.100	0.100	Greater than 0.100	0.100	0.100	0.050	0.020

a. Correlation coefficient was calculated using the percentage presence of stearate.

From the correlation coefficients it can be concluded that there is little correlation between assay value, % moisture loss, stearate to palmitate ratio and bulk density values with either of the relative lubricity orders. Particle size and surface area measurement, however, do show some correlation with practical lubricity efficiency. The best correlation occurred between surface area and practical lubricity efficiency. There is no correlation between particle size or surface area, and inherent lubricity efficiency.

It can be seen that practical lubricity efficiency of a batch of magnesium stearate can be predicted with 95% accuracy from particle size measurements or with 98% accuracy from surface area measurements but not from any other of the investigated parameters. The smaller the particle size of the lubricant, the better the lubricant activity of the material.

Practical lubricity efficiency of a magnesium stearate batch therefore is significantly dependent upon the particle size and surface area of the lubricant material but may be influenced by other parameters such as % moisture, bulk density, assay etc. It must be remembered, however, that other factors, not investigated, such as shear strength of the material, may also significantly affect lubricity.

The lubricant samples prepared in the laboratory were investigated primarily to determine whether there was any significant relationship between stearate to palmitate ratio and lubricant efficiency. As described in section 4.2.2. the pure palmitate material was more efficient than the pure stearate material. Also, in the mixture lubricants, increasing the stearate concentration resulted in a decreasing lubricant efficiency as judged by ejection energy measurements. In fact, of the three mixtures examined the 25 : 75 stearate to palmitate mixture was the most efficient lubricant. This implies that the

palmitate ester is more efficient as a lubricant than the stearate ester, but the presence of a small percentage (25%) of the stearate ester will improve the lubricity of the pure palmitate material. However, the reverse does not hold true. A small percentage of palmitate ester, with the stearate (75 : 25 stearate to palmitate mixture) apparently decreases the lubricant efficiency of the pure stearate material. Fig. 4.15. plots the relationship between stearate to palmitate composition, and ejection energy values. It should therefore be possible to predict the relative lubricant ability of any stearate/palmitate mixture from such a graph, all other factors being equal.

Examination of the fatty acid solidifying temperature, (Table 3.2) determined during identity tests on the lubricant materials, (Appendix 6) revealed that the most efficient lubricant, the 25 : 75 stearate to palmitate mixture, had the lowest solidification temperature. In fact, as the ratio of stearate to palmitate increased, so did the solidification temperature but not in a uniform manner. The same was true of the pure materials, the pure palmitate having a lower solidification temperature than the pure stearate material. This could indicate that lubricity may be dependent upon the relative ease of softening of the lubricant material under tableting conditions. Since solidification temperatures of the fatty acid mixtures do not merely reflect the proportion of palmitate and stearate present, it would appear that the lubricant mixtures produced in the laboratory are not just simple mixtures of the two fatty acid esters. To test this hypothesis, a physical mix of 25% magnesium stearate plates and 75% magnesium palmitate was prepared and used at 1% concentration to lubricate lactose, as described in section 2.3. Lubricant efficiency of the mixture was evaluated by ejection energy measurements using the Instron (section 2.1.)

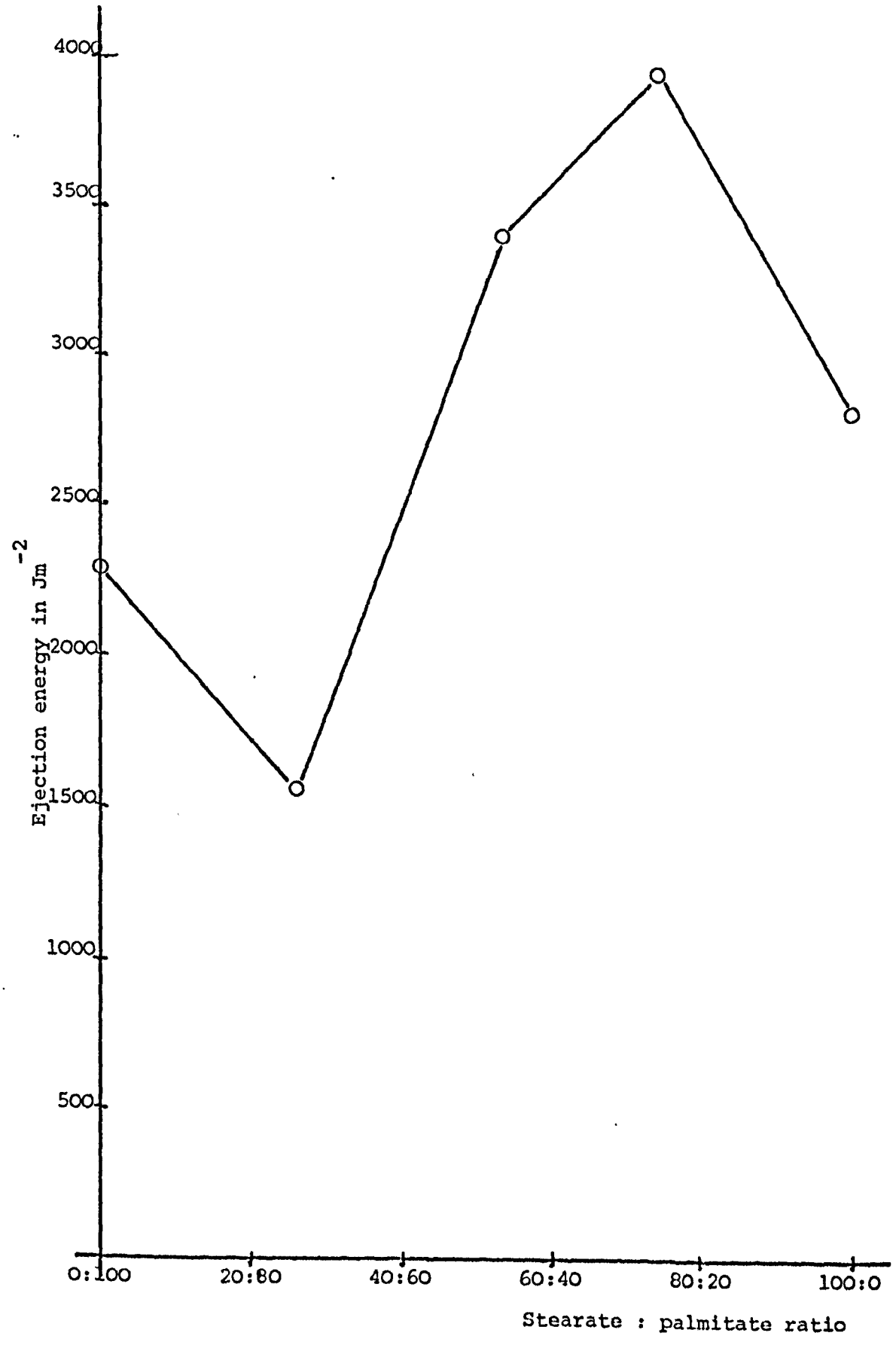


Fig. 4.15. Relationship between stearate to palmitate ratio in the lubricant material and its lubricant ability.

The mean ejection energy was found to be $6012Jm^{-2}$. The mean ejection energy for the laboratory prepared 25 : 75 stearate to palmitate mixture lubricant, however, was $1842Jm^{-2}$ which indicates that the prepared mixture lubricant is much more efficient as a lubricant than the physical mix lubricant. Therefore, it would appear that the 25 : 75 stearate to palmitate laboratory prepared lubricant is not simply a mixture of the two fatty acid esters but is a more complex structure of the two. The small particle size of this material may therefore be an integral property of this stearate to palmitate ratio, the presence of the other ester preventing the large plate crystal formation as seen in the pure stearate and palmitate.

Calculation of the contribution of each fatty ester to the overall lubricity efficiency of the physical mix (that is 75% x $4225Jm^{-2}$ and 25% x $6460Jm^{-2}$) produces a theoretical ejection energy value of $4785Jm^{-2}$. This value is lower than the actual ejection energy obtained ($6012Jm^{-2}$) which could indicate that in the physical mixture, one ester has an inhibitory effect upon the other, so that overall the lubricant efficiency of both is reduced. This is the reverse of the chemical mixture of the two esters in this ratio.

Examination of crystal size of unmicronized lubricant material leads to the conclusion that particle size could explain the changes in relative lubricity behaviour of the pure materials before and after micronization. The ejection energy values for the unmicronized pure materials, 1% in lactose, correlate with particle size. Magnesium stearate plates, which has the highest ejection energy, has the largest particle size and magnesium stearate needles has the lowest ejection energy and the smallest particle size. (Fig. 4.16.)

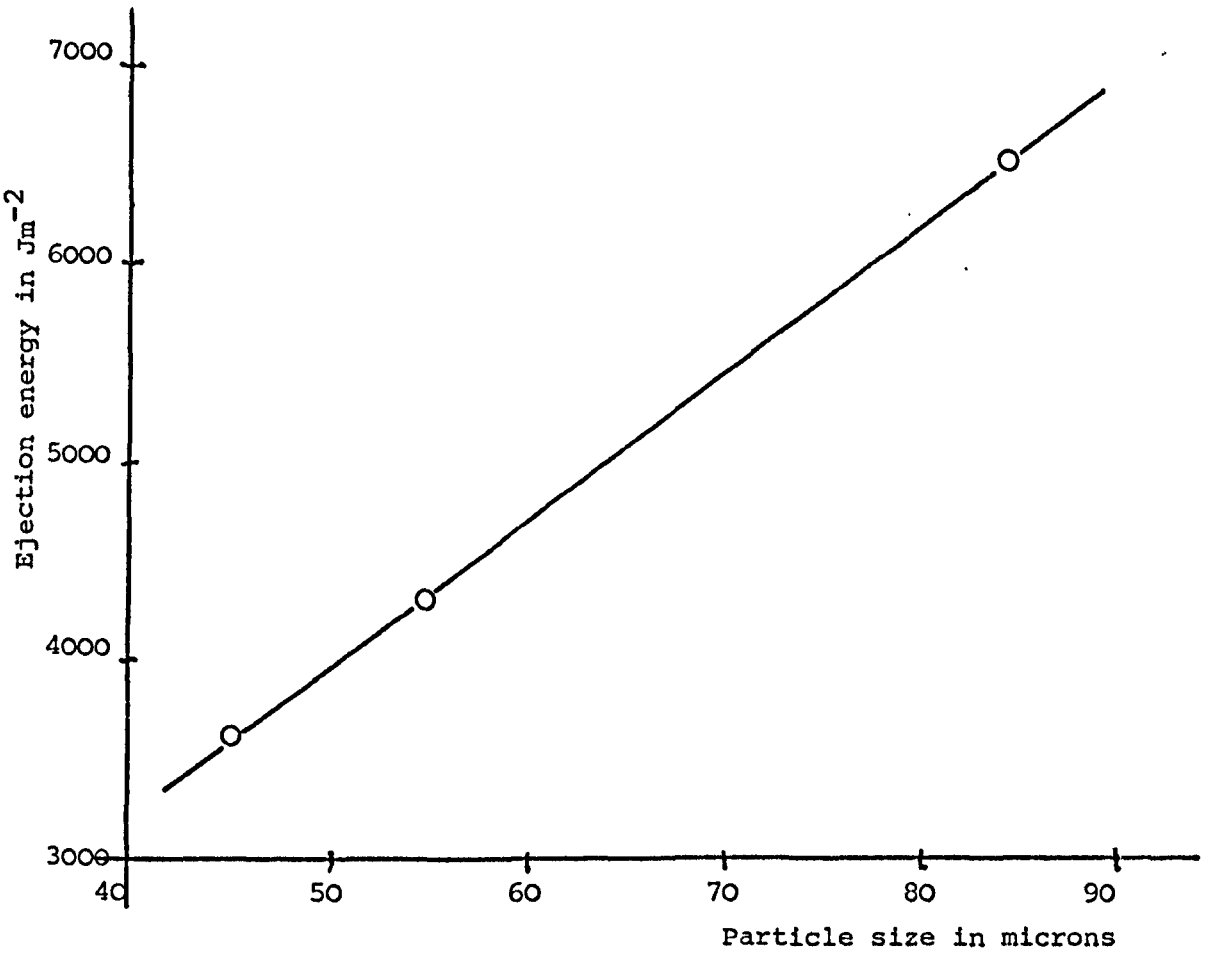


Fig. 4.16. Relationship of particle size of lubricant material and ejection energy for the three pure laboratory prepared lubricants.

Magnesium stearate needles material therefore appears to be a more efficient lubricant than magnesium stearate plates. Also the particle sizes are much larger than for 25 : 75 and 50 : 50 mixtures. However, micronization reduces the particle size of all 3 pure materials to below 5μm and lubricity efficiency is greatly improved. Since the effect of particle size is obviated it would be expected that the micronized 1% in lactose evaluations would more accurately reflect the relative lubricant efficiency. Thus the pure materials are now shown to be more efficient than the 50 : 50 mixture although they are still not as good as 25 : 75 stearate to palmitate mixture. The two stearate samples now have approximately the same lubricant efficiency

which would indicate that this relative efficiency is due to the presence of the stearate molecule only and not influenced by particle size or crystal shape. Therefore it would appear that the palmitate molecule, in the pure state, is more efficient as a lubricant than the stearate molecule.

4.4. Summary

For all materials examined there was no relationship between the relative lubricity behaviour of the materials tested alone and in 1% admixture with another tablet excipient. The lubricant alone tests are thought to indicate inherent lubricant efficiency but the practical expression of this lubricity is modified by other parameters. Thus the admixture tests are a more accurate guide to probable lubricant behaviour in production.

Parameters such as moisture content, bulk density, assay value, crystal shape etc. may influence the expression of inherent lubricity, but particle size and surface area appear to exert a significant influence since there is a high degree of correlation between ejection energy values of lubricants and these two parameters.

The lubricant efficiency of a magnesium stearate batch can be improved by increasing the concentration of the lubricant, but modification of the material itself, for example, by micronization, can improve the practical lubricant efficiency; that is increase the ability of the lubricant to express its inherent lubricity.

The ratio of stearate to palmitate in the lubricant also appears to be important, the 25:75 stearate to palmitate mixture being the most efficient lubricant. However, the relationship between stearate to palmitate content and lubricity efficiency is not straight forward (Fig.4.15) although the palmitate molecule appears to be more efficient than the

stearate molecule. The lubricant efficiency could be related to the relative ease of softening of the lubricant material, provided that the melting point of the material is not exceeded under tableting conditions.

In addition, the lubricants of varying stearate to palmitate ratio are not simple mixes of the specified ratio of the two constituent esters, but are complexes of the two materials. Therefore to produce the most efficient mixture lubricant the proportions of the constituents must be carefully controlled during manufacture of the compound. Thus lubricant efficiency is dependent upon the manufacturing process itself.

It would appear, therefore, that lubricity efficiency is dependent upon many factors, some, such as particle size, having a greater influence on performance, than others. Practical lubricant efficiency is more accurately evaluated by testing the material in the presence of other tablet excipients and can be improved to a certain extent by modification of the physical properties of the lubricant material so that the inherent lubricity can be expressed more efficiently. The inherent lubricity efficiency, however, cannot be modified once the lubricant material has been prepared. Careful control during manufacture would be required to ensure production of a lubricant with good inherent lubricity.

CHAPTER 5. PHYSICAL CHARACTERISTICS OF THE LUBRICANTS.

This chapter investigates the effects of the tableting process upon the size and shape of the magnesium stearate particles in an attempt to explain the changes in lubricity ability when the lubricants are mixed with a tablet excipient.

5.1. Commercial Lubricants.

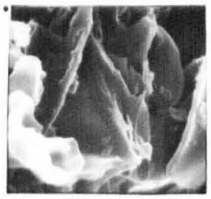
The three properties examined in this investigation were crystal appearance, particle size and surface area, at various stages in the tableting process.

5.1.1. Appearance of Crystals.

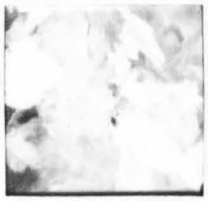
Crystal appearance and the effect of mixing and tableting upon this parameter was investigated by Scanning Electron Microscopy. (S.E.M) Samples were prepared as described in section 2.2.3, and results are summarized in Tables 5.1. to 5.3. Batches 3, 6, 9, 1, 4, 7, and 5 were examined, which are respectively a good, poor and mediocre batch when lubricants tested alone and a poor, mediocre and good batch when lubricants tested in admixture. Batch 5 is an example of needle material. Actual S.E.M. photographs are displayed in Plates 1 to 9.

Examination of mixtures of lubricants and lactose indicates that 10 minutes mixing produces a more uniform distribution of lubricant in the mixture than ½ minute mixing. The very large sheets of laminar crystals of batches 1 and 3 do appear to be broken down but only into large sized particles. Batch 3 lubricant appears to be poorly mixed in that it is not uniformly distributed through the powder mass during mixing. This could explain why the lubricant is not able to express its good inherent lubricity, practically. Batches 6, 7, and 9 appear to be well mixed and are considered to be good lubricants

PLATE 1. COMMERCIAL BATCHES OF MAGNESIUM STEARATE.

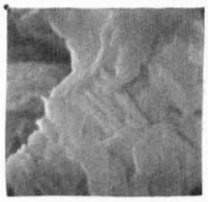


Batch 1 X5250



Batch 2 X5000

Batch 3 X4600



Batch 4 X5000

Batch 5 X4500

Batch 6 X4750

Batch 7 X5000

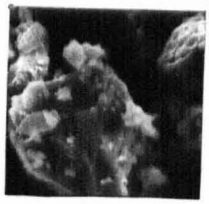
Batch 8 X5000

Batch 9 4500

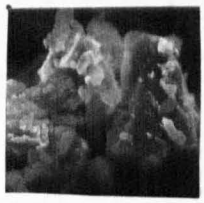
Batch 10 X5000

Batch 11 X5200

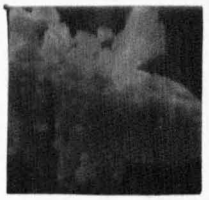
PLATE 2. POWDER SAMPLES AFTER HALF A MINUTE MIXING OF 1% LUBRICANT IN LACTOSE.



Batch 1 X950

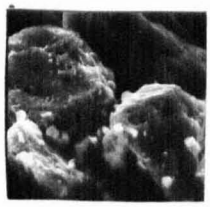


Batch 4 X1000

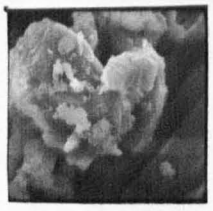


Batch 6 X1850

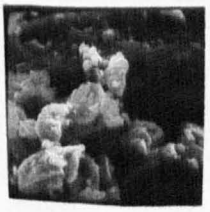
PLATE 3. POWDER SAMPLES AFTER TEN MINUTES MIXING OF 1% LUBRICANT IN LACTOSE.



Batch 1 X1000

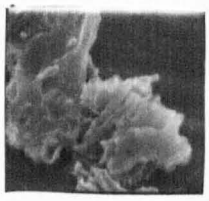


Batch 4 X1000

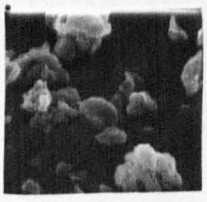


Batch 6 X1000

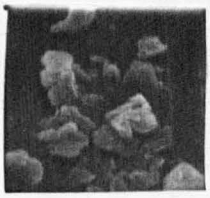
PLATE 4. LUBRICANT MATERIAL FROM POWDER SAMPLE AFTER TEN MINUTES MIXING.



Batch 1 X1800

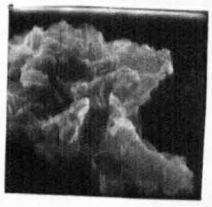


Batch 4 X1650

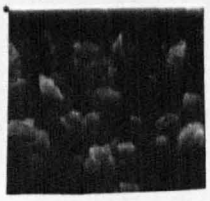


Batch 6 X1800

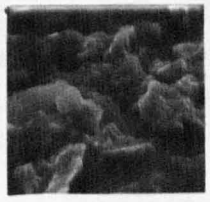
PLATE 5. LUBRICANT MATERIAL FROM TABLETS.



Batch 1 X1700



Batch 4 X1650

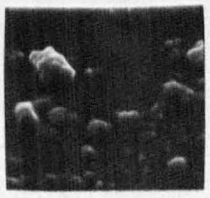


Batch 6 X2150

PLATE 6. LUBRICANT MATERIAL FROM CURVED SURFACE OF TABLET.

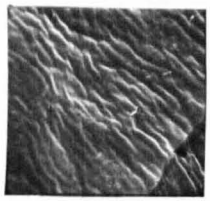
Batch 1 X1650

Batch 4 X1800



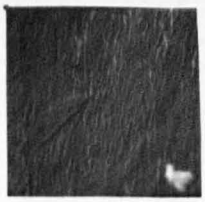
Batch 6 X1750

PLATE 7. CURVED SURFACE OF LUBRICANT TABLET



Batch 1 X1300

Batch 4 X1200



Batch 6 X1100

PLATE 8. CURVED SURFACE OF TABLETS OF 1% LUBRICANT IN LACTOSE.

Batch 1 X950

Batch 4 X1050

Batch 6 X1050

PLATE 9. CURVED SURFACE OF LACTOSE TABLET.

X1050

TABLE 5.1. S.E.M. COMPARISON OF LUBRICANT MATERIAL ALONE AND IN MIXTURES WITH LACTOSE.

Sample examined	Lubricant Batch 1	3	4	5	6	7	9
Lubricant material alone	Large sheets of laminar crystals	Large sheets of laminar crystals	Laminar material. Some broken plates	Laminar material in clumps and needle material	Large and small laminar material. Much needle material	Laminar material. Very small.	Large and small laminar material
1% lubricant in lactose mixed for half a minute	Large lactose particles with adhering lubricant which has a distinct laminar shape	Does not appear well mixed. Clumps of lubricant on lactose particles	Large lactose particles with adhering lubricant which has a distinct laminar shape	Appears well mixed	Better mixed than batch 3 but still some clumping	Large lactose particles with adhering lubricant but not excessively so.	Large lactose particles with adhering lubricant
1% lubricant in lactose mixed for ten minutes.	As for half minute mixing but more lubricant present on lactose surface	Better mixed than at half minute mixing but still clumping of lubricant and lactose.	Similar to half minute mixing	As for half minute mixing	Appears to be well mixed	As for half minute mixing but more lubricant present on lactose surface.	As for half minute mixing but more lubricant present on lactose surface

practically. Since their inherent relative lubricities are poor, good and mediocre respectively, the mixing process must modify the physical properties of batches 6 and 9 so that lubricity efficiency becomes as good as batch 7.

Examination of the tablet surface in contact with the die for lubricant only tablets and 1% admixture tablets, (Table 5.2) indicates differences in distribution of lubricant at the tablet - die wall interface.

Examination of the lubricant only tablets reveals that the overall appearance of the tablet surface is smoother, the more efficient the lubricant batch, (with the exception of batch 4) as judged by ejection energy measurements. The presence of striations on a tablet surface indicates poor lubrication and again it can be seen that the poorer the lubricant batch, relatively, the more striations that are present on the tablet surface. Thus the relative lubricant ability of the lubricants when tested alone is reflected in the appearance of the tablet surface.

Examination of the 1% admixture tablets reveals irregular distribution of lubricant on the tablet surface. Patches of smooth surface exist indicating the presence of lubricant film and patches of rough surface are present indicating unlubricated lactose material. During the ejection process, therefore, where lubricant is present, the lubricant material will "smooth" out asperities on the die and tablet surfaces and being readily sheared, will be smeared over the tablet surface. Where lubricant is not present, then the asperities on the die surface (being the harder material) will plough out material from the tablet surface giving it a rough appearance. The greater the proportion of lubricant at the die wall - tablet interface, therefore, the more efficient the lubricant. The relative amount of lubricant

TABLE 5.2 S.E.M. COMPARISON OF TABLET SURFACES OF LUBRICANT ONLY AND 1% LUBRICANT ADMIXTURE WITH LACTOSE.

Sample examined	P	P	M	M	G	G	G
	Lubricant Batch						
	1	3	4	5	6	7	9
Lubricant only tablet surface	Wrinkled Surface. Large and small striations	Wrinkled surface. Some striations	Very smooth surface. Some large striations	Wrinkled surface. Some minor striations	Wrinkled surface Striations present	Very smooth surface. Minor striations	Reasonably smooth surface Some minor striations
1% admixture tablet surface	Rough surface Lubricant particles can be seen more so than lactose	Large patches of smooth surface (lubricant) Other parts rough & deeply pitted.	Rough surface with some smooth patches	Areas of rough and smooth on surface	Large patches of smooth surface (lubricant). Other parts are rough	Some rough but large proportion of smooth surface	Large area of smooth surface Other parts quite rough. Not as smooth as batch 7.

at the die wall for the examined lubricant batches can be estimated from the S.E.M. photographs of 1% admixture tablets, by the differing proportions of smooth surface present on the tablet surface. Tablets from batches 6, 7, and 9 lubricants have a higher proportion of smooth surface, than tablets from batches 4 and 5. Tablets with batches 1 and 3 as lubricants have the highest proportions of rough surface. Thus batches 1 and 3 are poor compared to batches 4 and 5 which are not as efficient as batches 6, 7, and 9. This is in agreement with the classification suggested by lubricity tests on admixtures (section 4). Thus lubricity efficiency of a magnesium stearate batch depends upon its concentration at the tablet surface - die wall interface during the tableting process. This in turn indicates that the lubricant must move through the tablet mass during tableting since all mixtures started at the same concentration level but different amounts apparently are present at the die wall after the tableting process. This phenomenon is further investigated in chapter 6.

Finally, lubricant material a) alone b) after mixing with lactose for 10 mins, and c) after tableting, was examined and compared. (Table 5.3). The greatest change observed (if any) is after tableting. Batch 6 material has a "squashed" or smeared appearance which indicates that it is a soft material with low shear strength. These are the properties required for good lubricant efficiency. However, batch 6 has a relatively poor inherent lubricity although it is relatively good when mixed with excipients. An explanation for this could be that when tableted alone, all the particles will undergo plastic deformation to produce a cohesive mass which tends to adhere to the die and deform rather than shear. However, during mixing with a harder material, shear will readily occur to uniformly distribute the lubricant throughout the powder mass and allow film formation

TABLE 5.3. S.E.M. COMPARISON OF LUBRICANT MATERIAL AT VARIOUS STAGES DURING TABLETING PROCESS.

Sample examined	Lubricant Batch. 1	3	4	5	6	7	9
Lubricant alone	Large sheets of plate crystals.	Large sheets of plate crystals.	Clumps of fairly large plates & some broken pieces.	Range of size in plates Needle crystals present.	Large & small plates and much needle crystals.	Very small plates	Some large but mostly small plates.
Lubricant after 10 minutes mixing with lactose	Clumps of large plate crystals.	Clumps of large plate crystals.	Clumps of plate crystals	Large clumps of plate crystals and needle crystals	Clumps of laminar crystals and needle crystals	Small plate crystals, well separated	Small well separated plate crystals
Lubricant after tableting of admixture	Some very large clumps Small angular plates.	Some large clumps. Smaller plates	Small clumps of plates. Not as angular as batch 1	Largish clumps Some evidence of smearing or rubbing off of angular points of clumps Needles and plates.	Largish clumps "squashed" & distorted laminar crystals & evidence of smearing during ejection process	Small well separated plates	Some clumps & small plates. Some signs of flattened material.

to occur. Subsequently during tableting, the thin magnesium stearate film will much more readily deform and undergo shear than the two harder materials and hence the low shear strength is more noticeable than when the lubricant is compacted en mass.

Batches 7 and 9 consist of small particles which are well separated during mixing and tableting and will therefore cover a greater proportion of lactose surface than larger particles and thus are good lubricants. Batch 9 shows some evidence of being smeared during compression and ejection and therefore may behave in a similar manner to batch 6, but to a lesser degree. Lubricants from batches 1 and 3 do not appear to change greatly during the mixing and tableting processes. Therefore mixing probably does not break down the lubricant which is also probably unevenly dispersed in the mixture and hence poor lubrication results. Batch 3 is not as poor as batch 1, perhaps because of its better inherent lubricant ability.

With batch 4, mixing has some effect, in that the clumps of material are reduced in size. After compression, the lubricant material is fairly well separated which could indicate fracture of material during compression. Therefore the crystals may shear easily in the presence of harder materials, similar to batch 6 but not to the same extent, so that batch 4 is only a mediocre lubricant compared with batch 6.

To summarize, it would appear that in those batches which are poor, as judged by admixture tests, the magnesium stearate particles tend to be clumped together and very angular. With the good batches, however, the lubricant particles tend to be smaller, more separated and show evidence of smearing or rounding off of the crystal edges. Those batches classed as mediocre tend to be a combination of the two extremes. Thus S.E.M. observations on lubricant batches at

various stages during tableting can be used to explain the lubricity behaviour of various batches of magnesium stearate.

From the S.E.M. work, it was thought that particle size changes during the mixing process may play an important part in determining practical lubricant efficiency and so particle size and surface area analyses were performed on representative lubricant batches. The batches chosen were 1, 4, and 6 being poor, mediocre and good respectively as judged by admixture tests. Batch 7 (good) was also examined because it already consists of very fine material and is classed as good by both lubricity tests.

5.1.2. Particle Size.

Samples of lubricant material, before and after mixing with lactose for 10 minutes, were prepared and size analysed as described in section 2.2.1. Graphs of percentage number of particles in size range against particle size were plotted for both samples for each of the four investigated batches. (Figs. 5.1. to 5.4.)

Particle size distributions of the lubricant batches prior to mixing with lactose were varied. Batch 1 showed a bimodal distribution with approximately 18% of the particles below 2.5μm and 27% of the particles between 2.5 - 5.0μm, with a secondary peak of approximately 7% of the particles in the 22.5 - 25.0μm range. Batches 4 and 6 contained higher percentages of particles below 5.0μm, approximately 20 - 30% below 2.5μm and 35 - 40% between 2.5 and 5.0μm. They contain very few particles of larger dimensions. In batch 7, virtually all the particles are below 5μm in size, 82% being less than 2.5μm in size.

During the mixing process with lactose, all 4 batches underwent a change in particle size distribution but to varying degrees. For batch 7 little change was noticed except that the percentage of particles

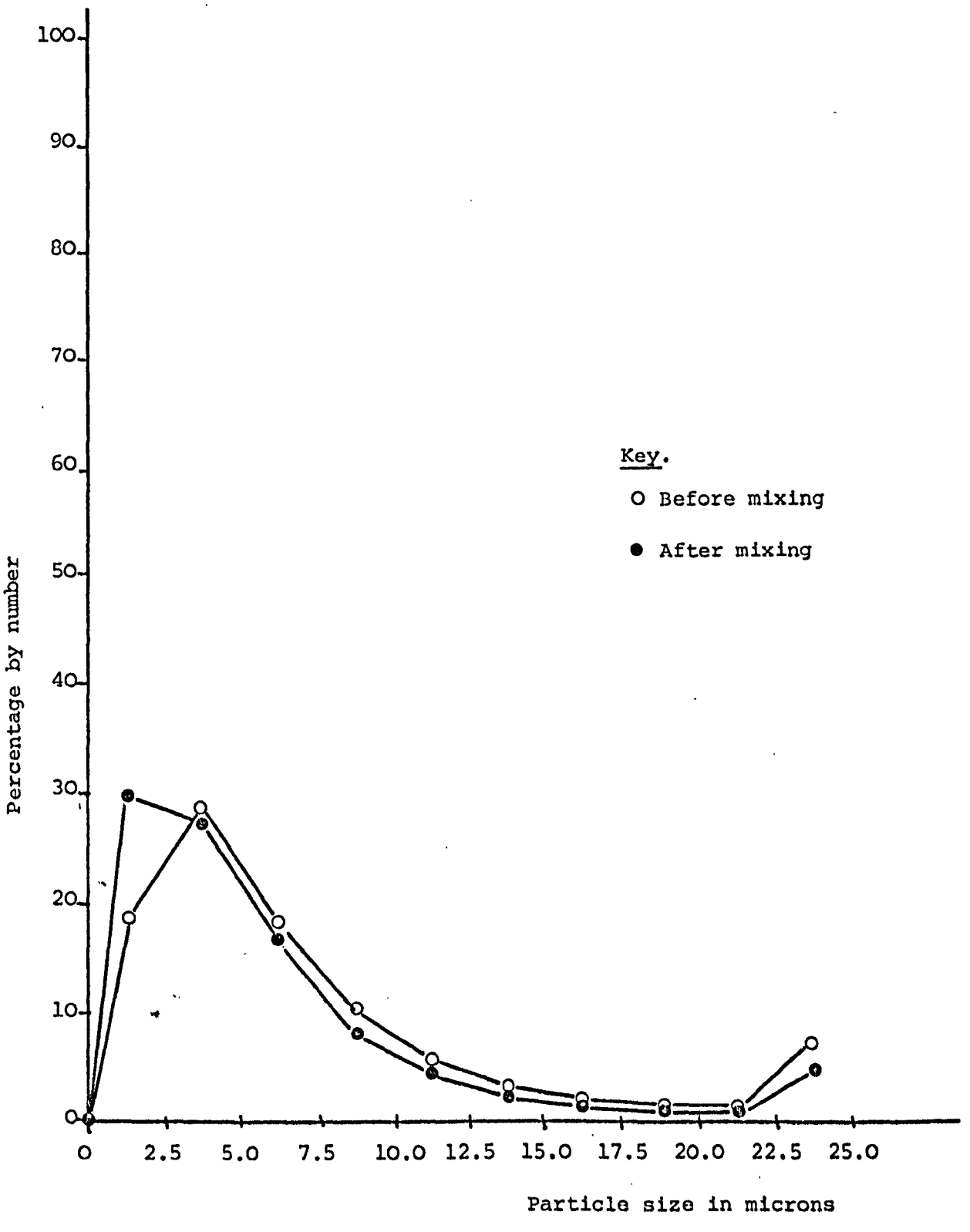


Fig. 5.1. Particle size distribution of Batch 1 lubricant before and after mixing with lactose.

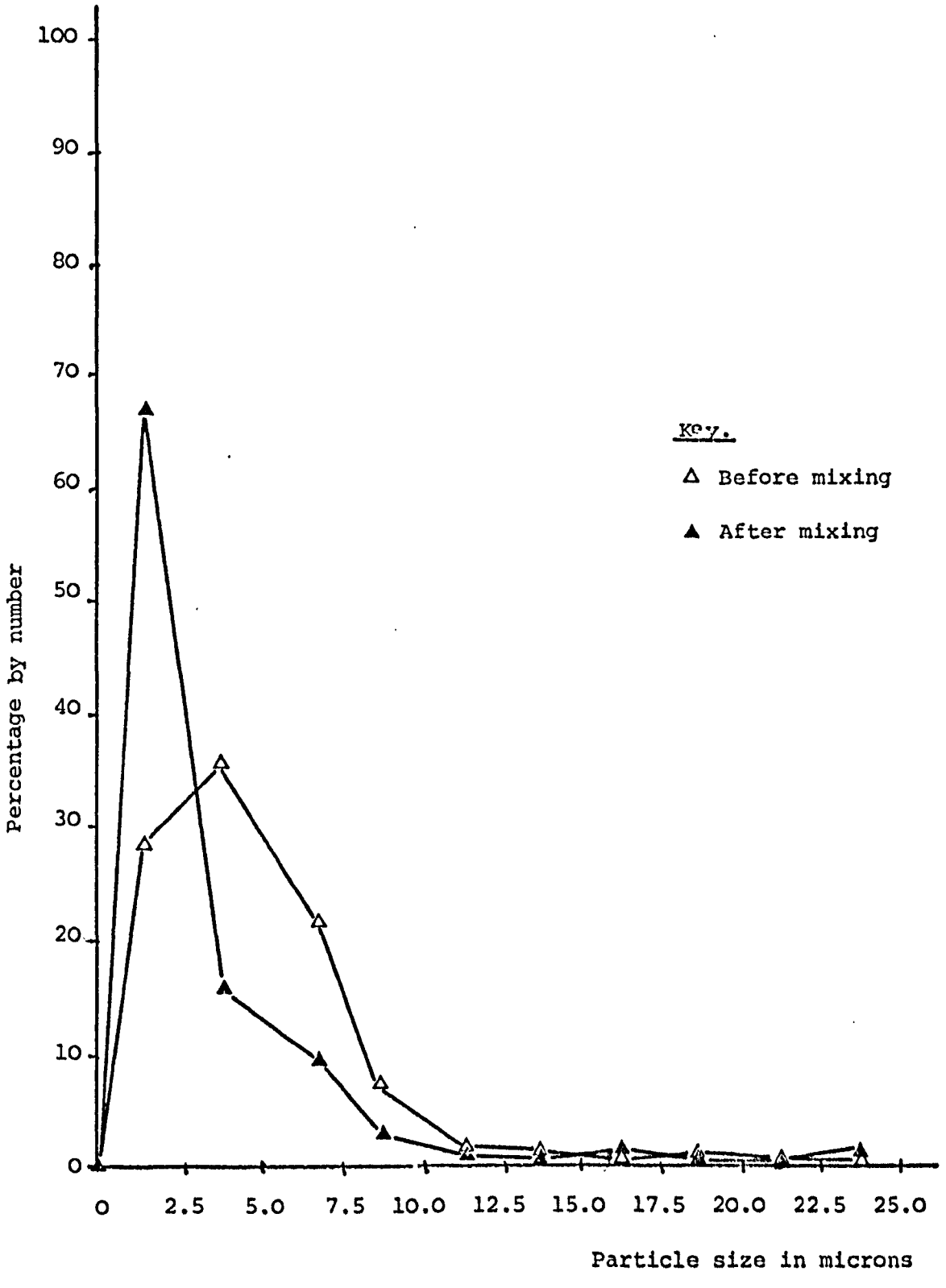


Fig. 5.2. Particle size distribution of batch 4 lubricant before and after mixing with lactose.

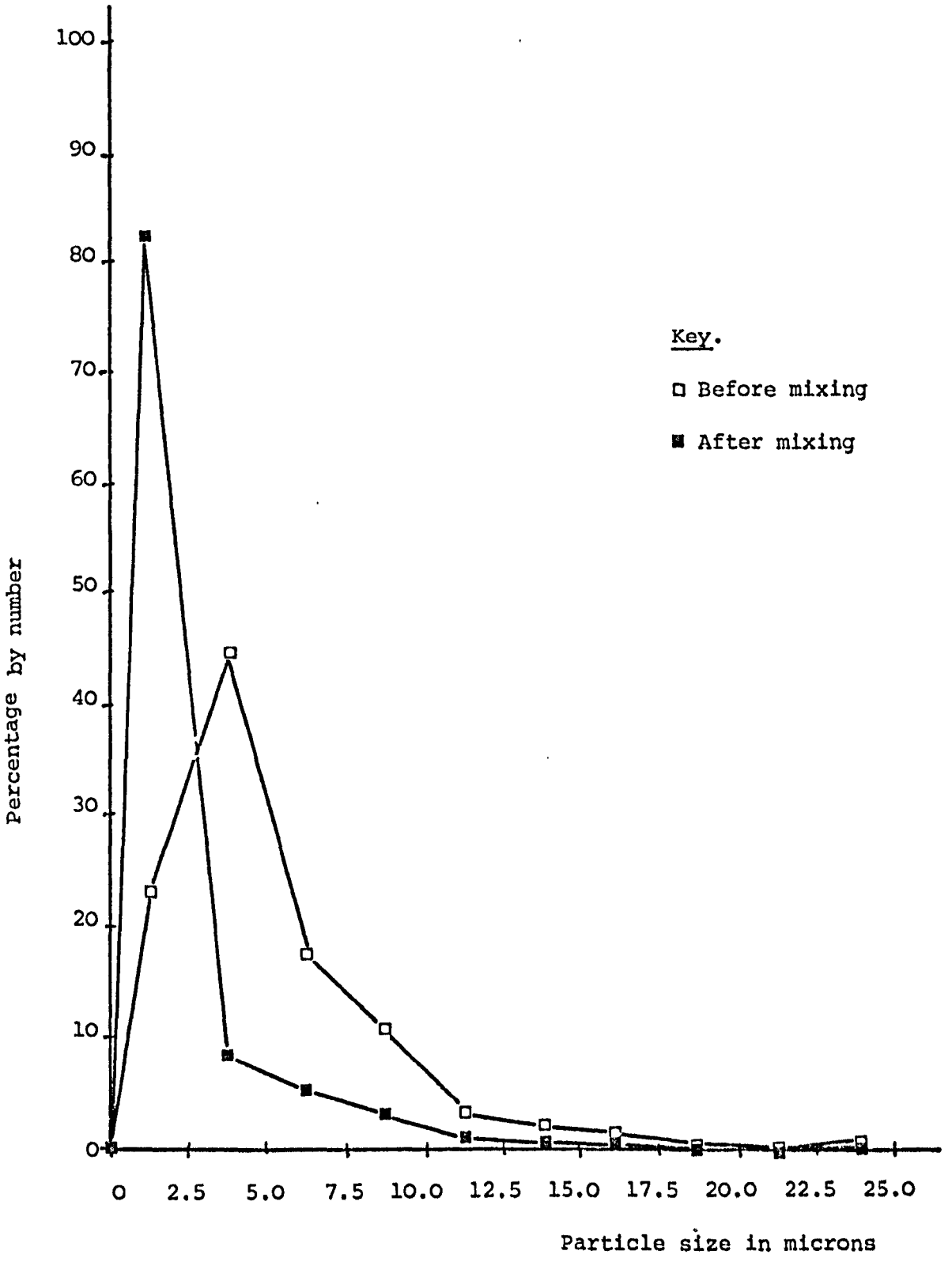


Fig. 5.3. Particle size distribution of batch 6 lubricant before and after mixing with lactose.

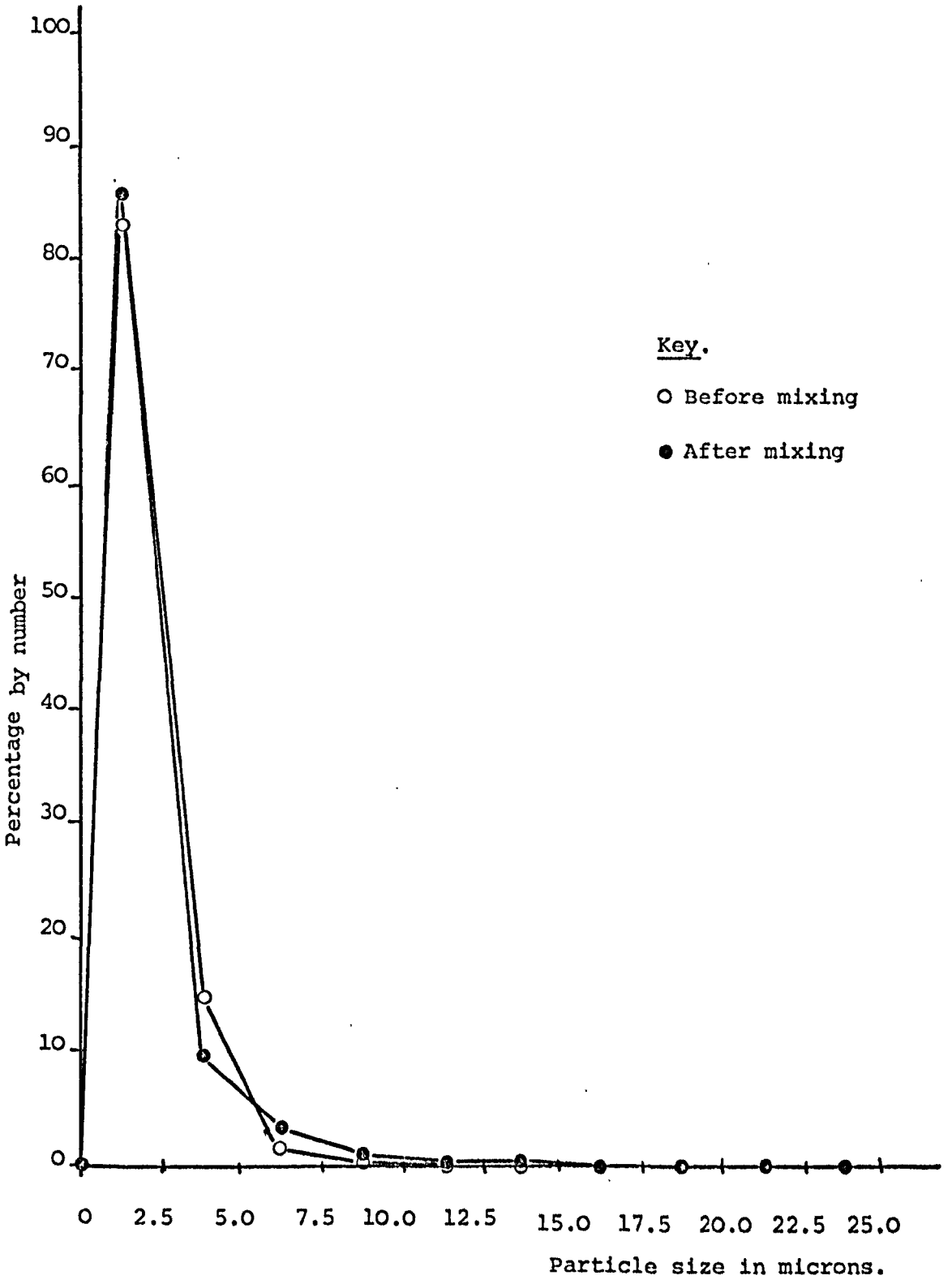


Fig. 5.4. Particle size distribution of batch 7 lubricant before and after mixing with lactose.

below 2.5μm increased by 3%. This small change is probably due to the fact that smaller crystals will contain less impurities and therefore less cracks or faults etc. and thus are less susceptible to break down during mixing. The smaller the crystals the greater the shearing force required and probably under these mixing conditions insufficient shear is produced to cause significant break down. For batch 1 there is an increase in fine material (<5.0μm) of approximately 10% but there is still more than 40% of material of larger particle size. It would appear that batch 1 does not readily breakdown under the conditions of shear which occur during the mixing process. This conclusion, however, does not apply to batches 4 or 6. In batch 4, mixing produces an increase in fine particles from 64% to 83%, 68% of this material being below 2.5μm, whilst in batch 6, mixing produces an increase in fine particles from 64% to 91%, 82% of this material being below 2.5μm. Thus these two batches, 6 in particular, readily undergo shear during the mixing process.

Lubrication is reported to be a surface phenomenon (section 1) and thus the finer the lubricant particles the greater the lubricant's surface covering power and hence the greater its efficiency at the same concentration. Therefore a lubricant batch which is readily broken down during mixing will have a greater surface covering potential and therefore would be expected to be a more efficient lubricant than a batch which is not readily broken down. Thus with batches 1, 4, 6, and 7, particle size distribution changes before and after mixing could provide the explanation for change in relative lubricant efficiency of the batches after admixture with a tableting excipient. Batch 7 has a good inherent lubricity and is able to express it practically because of its fine particle size which gives it a good covering power. The fact that it is little affected by the mixing

process is irrelevant, since uniform distribution throughout the powder mass obviously occurs. Batch 1, however, has a mediocre inherent lubricity but does not readily undergo breakdown during mixing, thus its surface covering power is not great compared with the other batches. Also since a smaller number of larger particles will be present rather than a large number of fine particles, uniform distribution of the lubricant throughout the powder mass may not occur. Thus this batch exhibits poor lubricant efficiency when combined with the other tablet excipients.

Batches 4 and 6, both of which have poor inherent lubricity, readily undergo shear and fracture during mixing, therefore their surface covering power is greatly increased, especially so with batch 6. In fact batch 6, after mixing, has a similar particle size distribution to batch 7. Therefore, practically, batch 6 is rated a good lubricant of similar efficiency to batch 7. Batch 4 is only rated as mediocre, probably because it does not break down to the same extent as batch 6.

Thus it would appear that particle size distribution does play a major part in determining practical lubricant efficiency but it is the particle size distribution after mixing not before mixing which is relevant. Therefore to attempt to predict practical lubricant efficiency from physical properties of the lubricant batch, it would be necessary to know at least the particle size distribution and the ability of the lubricant particles to undergo breakdown due to the shear produced during the mixing process.

5.1.3. Surface Area.

Samples of lubricant material before and after mixing were prepared and the surface areas determined as described in section 2.2.2. Results are summarized in Table 5.4.

TABLE 5.4. SURFACE AREAS OF VARIOUS LUBRICANT SAMPLES

Sample tested	Batch of lubricant material 1	4	6	7
Lubricant material alone	2.86m^2/g	6.93m^2/g	7.90m^2/g	15.28m^2/g
Lubricant material[a] prior to mixing	3.05m^2/g	7.36m^2/g	8.90m^2/g	7.80m^2/g
Lubricant material after mixing	3.01m^2/g	5.12m^2/g	3.99m^2/g	5.33m^2/g

[a] To eliminate possible variation in particle size due to sample preparation of lubricant material after mixing, a sample of lubricant material itself was treated to the same extraction process. However magnesium stearate is very hydrophobic and therefore very difficult to wet. Therefore this sample was not wet to the same extent as lubricant material from the admixture samples and therefore has not strictly undergone the same extraction procedure.

Surface area values for batches 1, 4. and 6 appear to be low for this type of material but they were concluded to be representative of the particle size of the material. (Appendix 8)

From Table 5.4., it would appear that the separation process does affect the lubricant material. The material cakes when filtered and it is thought that the particles "weld" together in such a manner that the surface area available for nitrogen adsorption is reduced. If small particles weld together, then the reduction in surface area is much greater than if larger particles weld together, to produce approximately the same size masses. Lubricant samples were sieved through a 22 mesh (B.S.) sieve prior to surface area measurement, to break down agglomerates. A finer sieve was not used so as to avoid the possibility of attrition of the particles due to sample preparation.

The lubricant material, not mixed with lactose but added to water was not readily wetted except for batch 7 and thus surface area determinations were approximately the same as for untreated material

with the exception of batch 7. Here it was assumed, that "welding" of the fine particles in batch 7 caused the drastic reduction in surface area observed. Lubricant samples from the admixture tests were compared with the original results and reductions in surface area were noted for batches 4, 6, and 7 but not batch 1. The percentage changes in surface area are summarized in Table 5.5.

TABLE 5.5. PERCENTAGE CHANGE IN SURFACE AREA BEFORE AND AFTER MIXING WITH LACTOSE.

Lubricant batch	1	4	6	7
Percentage change before to after mixing	+6.43%	-26.13%	-49.47%	-65.29%

Assuming that the greater the percentage of fine material present in the sample, the greater the reduction in surface area due to massing and welding of the particles, it could be concluded that there are a large proportion of fines in batches 4, 6, and 7 but not in batch 1. From particle size analysis of the original material it was known that batches 4 and 6 contained approximately 64% fines, batch 7 approximately 83% fines, but batch 1 only approximately 50% fines. Therefore in batch 7, massing (and welding) of fine material could account for its drastic reduction in surface area. For batches 4 and 6, massing of the fines would be expected to reduce the surface areas to the same extent but this is not the case. It is therefore concluded that these two batches have undergone breakdown during mixing, batch 6 more so than batch 4, so that the percentage of fines present has increased and hence massing of the fine material has produced the different reductions in surface area. With batch 1 it would appear that the mixing process has little effect on the lubricant material.

Thus to summarize, it is assumed that reduction in surface area is indicative of an increase in the percentage of fine material present, which, in conjunction with the particle size distribution knowledge of original material, leads to the conclusion that batch 1 is unaffected by mixing whilst batches 4 and 6 are broken down, more so batch 6 than batch 4. The relationship between effect of mixing and lubricity of batches has already been discussed in section 5.1.2. under particle size analysis. However taken alone, surface area determinations are not very useful because they are too greatly influenced by the sample preparation technique.

5.1.4. Summary for Commercial Lubricants.

Thus from S.E.M. and particle size analysis, it is apparent that the mixing and tableting processes play a major role in determining the practical lubricant efficiences of batches of magnesium stearate. For good practical lubricant efficiency, the lubricant batch must be of small particle size or readily undergo breakdown during the mixing process, without agglomeration, so that it can be uniformly distributed in the tablet mix. A very low shear strength is advantageous so that the lubricant will readily smear over the excipient to form a lubricant film around the excipient particles. During the compaction process it appears that the lubricant must be able to migrate through the powder mass to the tablet die wall interface, and be readily sheared when the tablet is ejected. It would appear that the greater the migratory ability of the lubricant the more efficient the lubricant, but certainly the more easily the migrated lubricant is smeared (as seen by S.E.M.) the more efficient the lubricant.

Poor lubricant batches tend to consist of large sized particles which do not readily break down during mixing, perhaps because their

shear strengths are not so low, and hence are not uniformly distributed in the powder mass. They apparently do not readily move through the powder mass during compaction, so are not present in large quantities at the die wall at the time of tablet ejection.

5.2. Laboratory Prepared Lubricants.

With the results from the investigations of the commercial magnesium stearate batches in mind, all six laboratory prepared lubricant samples were investigated with respect to particle size and crystal appearance and the relationship of these parameters to lubricity behaviour of the batches.

5.2.1. Particle Size.

Particle size analyses were performed (where possible, as described in section 2.2.1. otherwise obtained from S.E.M. photographs) on both micronized and unmicronized material before and after mixing with lactose for 10 mins. Results are summarized in Table 5.6.

As expected, for the micronized material, there was no apparent difference between the lubricant material before and after mixing, all particles being less than 5.0μm in size. No change was expected due to the fact that small crystals will contain less impurities and therefore less cracks or faults etc. (and these were pure materials) and thus are less susceptible to breakdown during mixing. In addition, having undergone the milling process to be size reduced to below 5μm, it was unlikely that the shear forces produced during the mixing process would equal the milling shear forces and hence further breakdown would be unlikely. This is reflected to a certain extent in the similarity of relative lubricant efficiency orders of the micronized material when tested alone compared with admixture tests. The slight

TABLE 5.6. PARTICLE SIZE ANALYSES OF LUBRICANTS BEFORE AND AFTER MIXING WITH LACTOSE.

Sample examined	Lubricant Batch					
	100% stearate plates	100% stearate needles	100% palmitate plates	25 : 75 St : P[a] plates	50 : 50 St : P[a] plates	75 : 25 St : P[a] plates
Lubricant before mixing unmicronized	70-100 microns	40-50 microns	50-60 microns	70% below 5μm Rest 5-10μm	20-25 microns	100-200 microns
Lubricant after mixing unmicronized	25-30 microns	20-25 microns	50-60 microns	<7.5 microns	20 microns	100-200 microns
Lubricant before mixing micronized	<5.0 microns	<5.0 microns	<5.0 microns	<5.0 microns	<5.0 microns	<5.0 microns
Lubricant after mixing micronized	No apparent change. <5.0 microns	No apparent change <5.0 microns	No apparent change. <5.0 microns	No apparent change. <5.0 microns	No apparent change. <5.0 microns	No apparent change. <5.0 microns

a. St : P = stearate to palmitate ratio present in the lubricant sample.

changes in the order are probably due to variations in uniformity of mix.

For the unmicronized material, particle sizing was carried out by measurements from S.E.M. photographs, due to the large sizes of the particles. The relative lubricity ability of the lubricant materials when tested alone did not bear any relationship to particle size of the material. However, when the materials were tested in admixture with lactose, with the exception of the palmitate material, the relative lubricity ability order was directly related to the particle size of the material after mixing. Consideration of the particle size before mixing also revealed that for all the lubricant materials, the relative lubricity ability, as judged by admixture tests, was in the same order as particle size of the lubricant material. Although this conclusion is not the same as for the commercial batches examined (section 5.1.) this could be due to the fact that, unlike the commercial lubricants, none of these materials, with the exception of the stearate plates, undergo much breakdown during mixing with the lactose. Thus, again, it would appear that the particle size of the lubricant material does significantly affect the relative lubricant efficiency and to a greater extent than does the composition of the lubricant. However, it could be that the particle size of the lubricant particles is an inherent property of the particular lubricant composition i.e. 25 : 75 mixture has a small particle size whereas a 75 : 25 mixture will have a large particle size and it is only when the lubricant materials are micronized that the influence of composition (i.e. stearate to palmitate ratio) can be seen.

5.2.2. Appearance of Lubricant Crystals.

This was investigated by S.E.M. Samples examined were lubricant

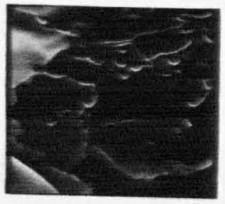
material alone, from admixture, and from tablet surface for both micronized and unmicronized material. Results are summarized in tables 5.7. and 5.8. Actual S.E.M. photographs are shown in plates 10 and 11.

Examination of the unmicronized lubricant material showed that only the pure stearate plates appeared to have undergone any change during mixing with lactose, the material having undergone fracture into largish plates from sheets of the material and showing evidence of smoothing off of irregularities in the crystal. This conclusion agrees with the particle size analysis findings. (section 5.2.1) The tableting process also appears to exert little effect upon the lubricant materials except perhaps for the needle material which shows some evidence of being compressed. Thus the overall conclusion appears to be that the unmicronized material appears to be relatively unaffected by mixing with lactose or by compression of the admixture into tablets. It would therefore appear that the stearate : palmitate composition of the lubricant does not influence the susceptibility of the unmicronized material to the tableting process.

Examination of the micronized material immediately reveals the effect of the milling process, all the lubricant particles having "rounder" or "blunt" features rather than retaining their angular shape. Crystal shape however is still intact i.e. plate-like materials are still plate-like and the needle material is still in the form of needles, albeit blunt needles. In addition all batches show evidence of flattening after the compression process, the needle material, in fact, losing its shape and being no longer recognizable as such. However, although it can generally be seen that the lubricant material has been affected by the tableting process, there is no distinction between the varying compositions of the lubricant.

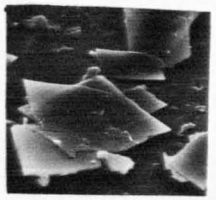
PLATE 10. NON MICRONIZED BATCHES OF LABORATORY PREPARED LUBRICANTS.

Lubricant material

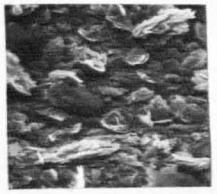


Plates X1000

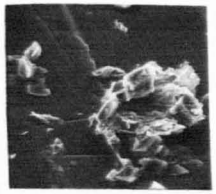
Needles X1000



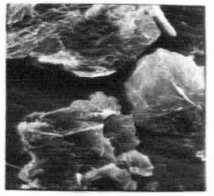
Palmitate X1000



25:75 X1000

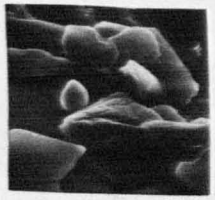


50:50 X5000

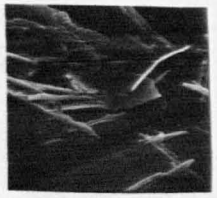


75:25 X5000

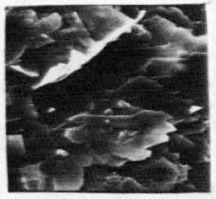
Lubricant Material from Lactose Admixture



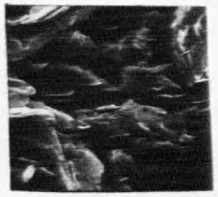
Plates X2000



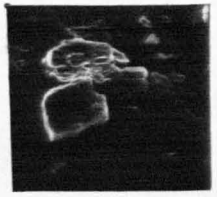
Needles X2000



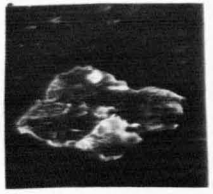
Palmitate X475



25:75 X2000

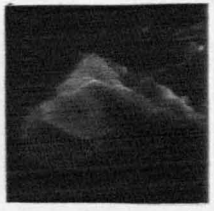


50:50 X2000



75:25 X200

Lubricant Material from Curved Surface of Admixture Tablet.



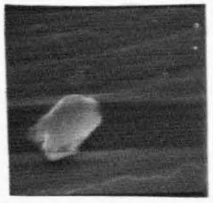
Plates X450

Needles X420

Palmitate X920

25:75 X5000

50:50 X1800

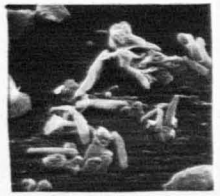


75:25 X1900

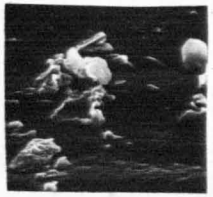
PLATE 11. MICRONIZED BATCHES OF LABORATORY PREPARED LUBRICANTS.

Lubricant Material

Plates X5000

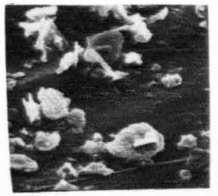


Needles X4500

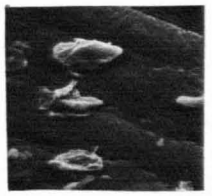


Palmitate X4700

25:75 X5000

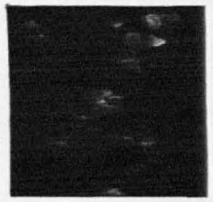


50:50 X2000

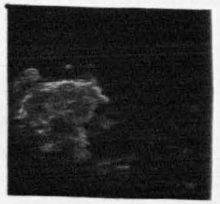


75:25 X5000

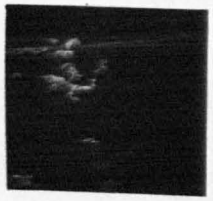
Lubricant Material from Lactose Admixture.



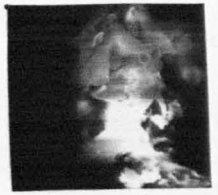
Plates X2100



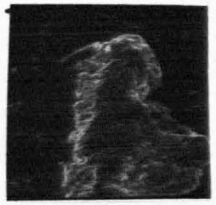
Needles X900



Palmitate X1800



25:75 X1100



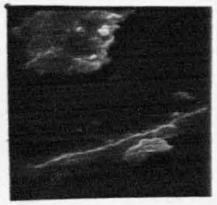
50:50 X500

75:25 X525

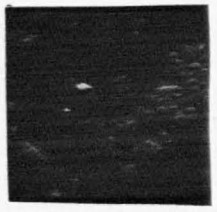
Lubricant Material from Curved Surface of Admixture Tablet.

Plates X1100

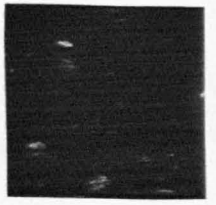
Needles X4900



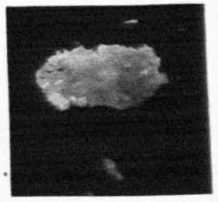
Palmitate X2200



25:75 X1100



50:50 X1050



75:25 X1050

TABLE 5.7. APPEARANCE OF CRYSTALS OF UNMICRONIZED LUBRICANT AT VARIOUS STAGES IN THE TABLETING PROCESS.

Sample examined	Lubricant Batch. 100% stearate plates	100% stearate needles	100% palmitate plates	25 : 75 St : P[a] plates	50 : 50 St : P[a] plates	75 : 25 St : P[a] plates
Lubricant alone	Sheets of very thin plates	Needles. Few plates.	Large very thin plates	Very thin small plates	Chunky plates	Chunky plates
After mixing	Large plates with rounded edges. A little small material.	No apparent change	Thin plates. Quite angular Jagged - parts broken off-not just rectangular or square.	Small thin plates and broken plates	Chunky plates Some fine material	Chunky plates Not much change
After tableting	Large thin overlapping plates. Quite angular	Appears to be some flattened plate - like material. Some flattened needle shaped material.	Thin overlapping plates. Large but not as large as stearate	Small very thin plates	Chunky overlapping plates.	Chunky plates

[a] St : P is the ratio of stearate to palmitate in the manufactured batch of lubricant.

TABLE 5.8. CRYSTAL APPEARANCE OF MICRONIZED LUBRICANT DURING VARIOUS STAGES IN THE TABLETING PROCESS.

Sample examined.	Lubricant Batch					
	100% stearate plates	100% stearate needles	100% palmitate plates	25 : 75 St : P[a] plates	50 : 50 St. : P[a] plates	75 : 25 St : P[a] plates
Lubricant material alone	Rounded plates	Blunt needles Few plates.	Rounded plates	Rounded plates	Rounded plates	Rounded plates
After mixing	As above	As above	As above	As above	As above	As above
After tableting	Thin flattened plates	Flattened material Shape not distinguishable	Flattened plates	Flattened plates	Flattened plates	Flattened plates

[a] St : P is the ratio of stearate to palmitate in the batch of laboratory prepared lubricant.

Thus in the micronized state, it does not appear that the composition or shape of the lubricant particle greatly influences its mechanical performance, although in the unmicronized state it appears that needle shaped crystals may be more susceptible to deformation than the plate-like crystals. This could explain the fact that the pure stearate needle material is a more efficient lubricant than the pure stearate plate material.

Thus overall it would appear that the composition of a lubricant material pre-determines the inherent lubricity of the lubricant material, and, also the particle size of the original material. The latter however can be modified to enable the lubricant to express its inherent lubricity more efficiently. Also needle shaped crystals appear to undergo deformation more readily than plate-like material and thus needle material would be expected to be more efficient, lubricity wise, than laminar material.

5.3. Summary.

Overall it would appear that the composition of a lubricant material pre-determines its inherent lubricity but the mixing and tableting processes play a major role in determining the extent of the expression of that lubricity practically.

For good practical lubricant efficiency it would appear that the batch should be of small particle size, that is 80% plus below 5μm, or readily undergo breakdown during the mixing process, without agglomeration, so that it can be uniformly dispersed through the tablet mix. During mixing and tableting, a low shear strength is advantageous, so that the lubricant will readily smear over the excipient to form a lubricant film. Needle shaped material appears to be more efficient than laminar material since it appears to be more susceptible to

deformation during compaction indicative, perhaps, of a lower shear strength. Since it also appears that the lubricant migrates through the tablet to the tablet/die wall interface during compaction, it would be expected that the greater ability of the lubricant to undergo migration, and the more easily it can be sheared at the die wall, the more efficient it will be.

CHAPTER 6. DISTRIBUTION OF LUBRICANT DURING THE TABLETING PROCESS.

This chapter investigates the movement of lubricant particles within the tablet mass during the tableting process.

6.1. Indications of Behaviour

6.1.1. Estimates of Lubricant "Carry Over" on Die.

The lubricant carryover investigation was described in section 4.1.2.4. It was found that the different batches of magnesium stearate varied in their ease of removal from the die wall (by compression of lactose samples). It was concluded that the variation was due to different amounts of magnesium stearate remaining on the die wall after ejection of the lubricated sample. Since all samples originally contained the same proportion of lubricant, it would appear that the lubricant particles must be able to move within the powder mass during the tableting process, in order to produce differing lubricant concentrations at the tablet - die wall interface. This phenomenon is also indicated by the S.E.M. investigation of tablet surfaces from tablets originally containing 1% magnesium stearate. (section 5.1.1.) Differing proportions of smooth and rough surface (lubricated areas and unlubricated respectively) led to the conclusion that lubricant material migrates to the die wall during the compaction process, the greater the amount at the die wall, the more efficient the lubricant.

6.1.2. Blowability Test.

Based upon the suppositions expressed in section 6.1.1., it was thought that, during the compression of the powder in the compaction process during tableting, as the air was expelled from the powder mass (Fig. 6.1) the lubricant might also be wafted towards the die wall. The ease with which lubricant particles could be wafted to the die wall

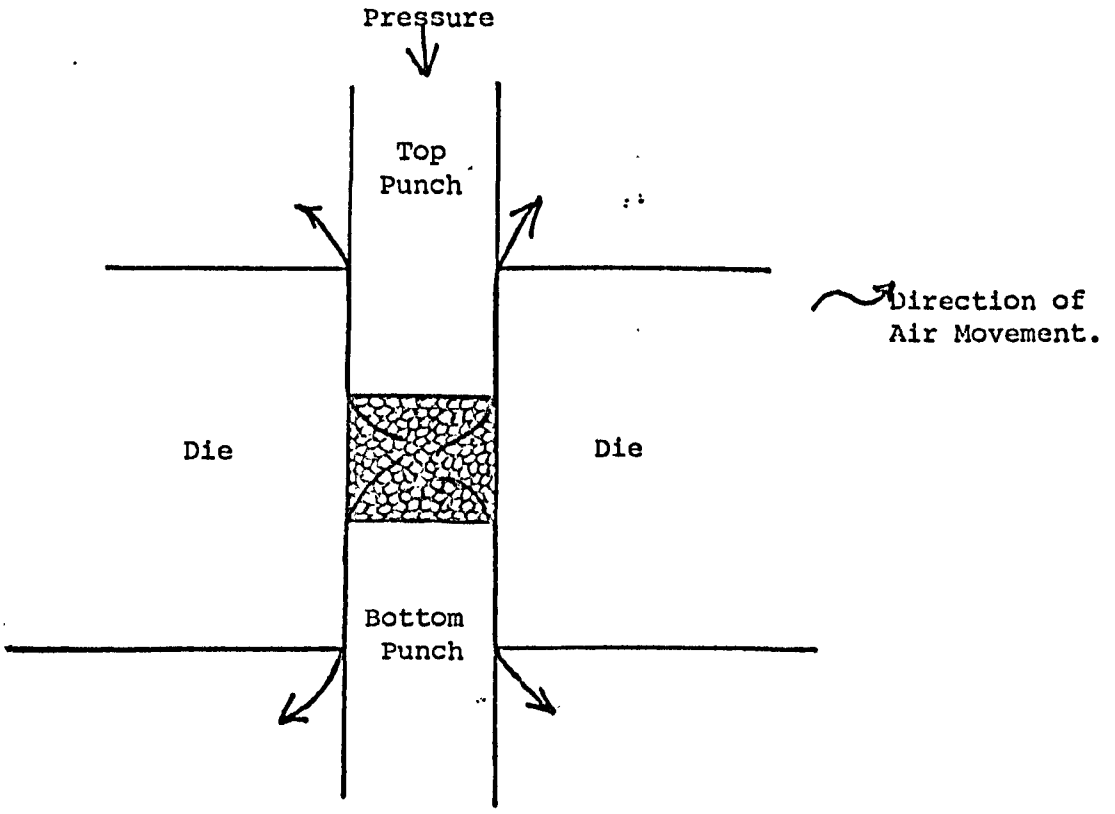


Fig. 6.1. Air movement during compaction.

could be an indication of lubricant ability. Therefore a simple blowability test was developed (described in section 2.6) to indicate whether differences did in fact exist in the blowability of lubricant material and, if so, how this parameter relates to lubricity.

Initially representative batches 1, 4, 6, and 7 only, were investigated, at two different air pressures. Mean blown distance is summarized in Table 6.1.

TABLE 6.1. MEAN BLOWN DISTANCE IN CENTIMETRES FOR VARIOUS LUBRICANT BATCHES.

Air pressure [a] in cms. water	Lubricant Batch 1	4	6	7
6	22.0	25.0	30.5	35.67
12	33.33	36.83	41.33	44.17

[a] Air pressure was measured as height of water column in the manometer tube of cross sectional area of 12.6mm^2.

It was concluded that variations in ease of movement of lubricant material did exist. Also the samples blown the furthest were the good lubricants, that is batches 6 and 7, and the sample blown the shortest distance was the least efficient lubricant, that is batch 1. Batch 4, the mediocre lubricant is inbetween. This conclusion is true for both air pressures. Therefore the force applied to waft the lubricants will affect the distance moved by the lubricant material but not the relative ease with which the lubricants are moved.

Since it appeared that blowability may indicate lubricity behaviour of a batch of magnesium stearate, the other seven batches were then subjected to this test, the results being summarized in Table 6.2. Again it could be concluded that the good lubricants are blown the furthest (batches 2 and 9) whereas the poor batches are blown the shortest distances (batches 3, 10, and 8).

TABLE 6.2. MEAN BLOWN DISTANCE IN CMS. FOR THE REMAINING MAGNESIUM STEARATE BATCHES.

Lubricant batch	2	3	5	8	9	10	11
Blown distance	29.10	22.17	26.60	24.67	32.83	26.00	27.87

Thus it does appear that blowability could be used to predict relative lubricant efficiency of magnesium stearate batches. To determine the reliability of the test, the degree of correlation between the two parameters was investigated. Fig. 6.2. shows the scattergram of the two parameters from which it can be concluded that, in general, lubricant efficiency increases as ease of blowability increases. The correlation coefficient was calculated as 0.86 from 11 samples which indicates a good degree of correlation between the two parameters. In fact, from statistical tables the significance level for this value is 0.001 which

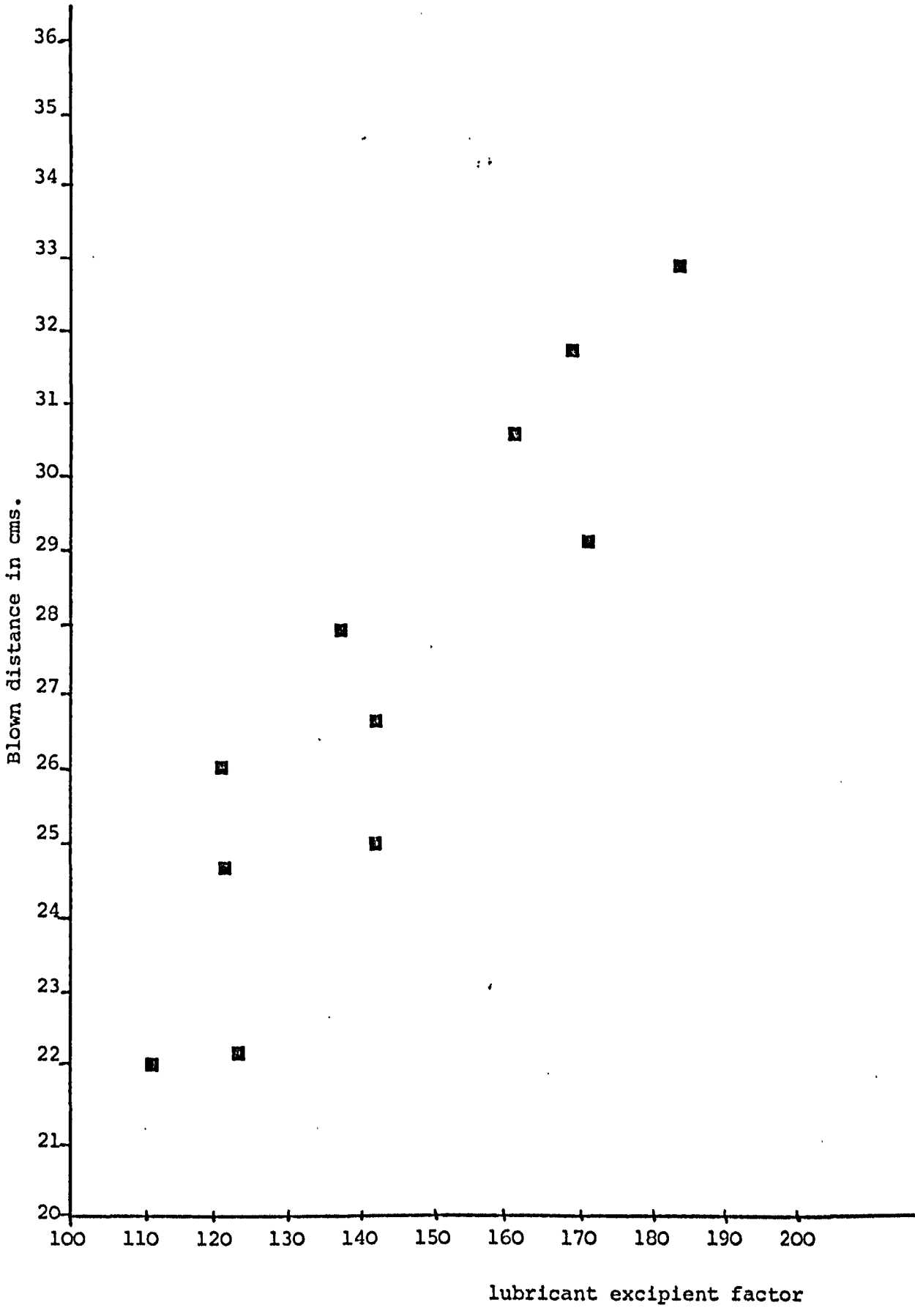


Fig. 6.2. Scattergram of 'blown distance' against lubricant excipient factor for dicalcium phosphate.

means that relative lubricity of a batch of magnesium stearate could be predicted from blown distance with a 99.9% probability of being correct. Therefore it is confirmed that blowability can be used as a measure of lubricity.

It was thought that blowability was probably very dependent upon particle size. To determine the relationship between blowability and particle size, scattergrams of blown distance against particle size (Fig. 6.3) and surface area (Fig. 6.4) were plotted and the correlation coefficients calculated. The scattergrams indicated that, in general, blown distance decreased with increase in particle size but increased with increase in surface area. Correlation coefficients were -0.87 and 0.95 respectively, for eleven samples, indicating a direct relationship between the parameters, especially surface area. From the Fisher - Yates statistical tables (216) it was concluded that both particle size and surface area could be predicted from blown distance with a 99.9% degree of accuracy.

The fact that blowability correlates with surface area and particle size, also indicates that the latter two parameters should correlate with lubricant efficiency. This was tested in chapter 4 and correlation coefficients of 0.68 (particle size) and 0.69 (surface area) were obtained, which indicates that there is good correlation between surface area or particle size and lubricant ability. However, blowability is the better parameter to use to predict lubricant behaviour, and, being dependent upon surface area and particle size, will reflect the influence of these parameters upon lubricant ability.

Thus, blowability can be used to estimate particle size, surface area and relative lubricity efficiency of a batch of magnesium stearate with a 99.9% degreee of accuracy. This is very useful because blowability is very simple to measure and will give a good idea of the

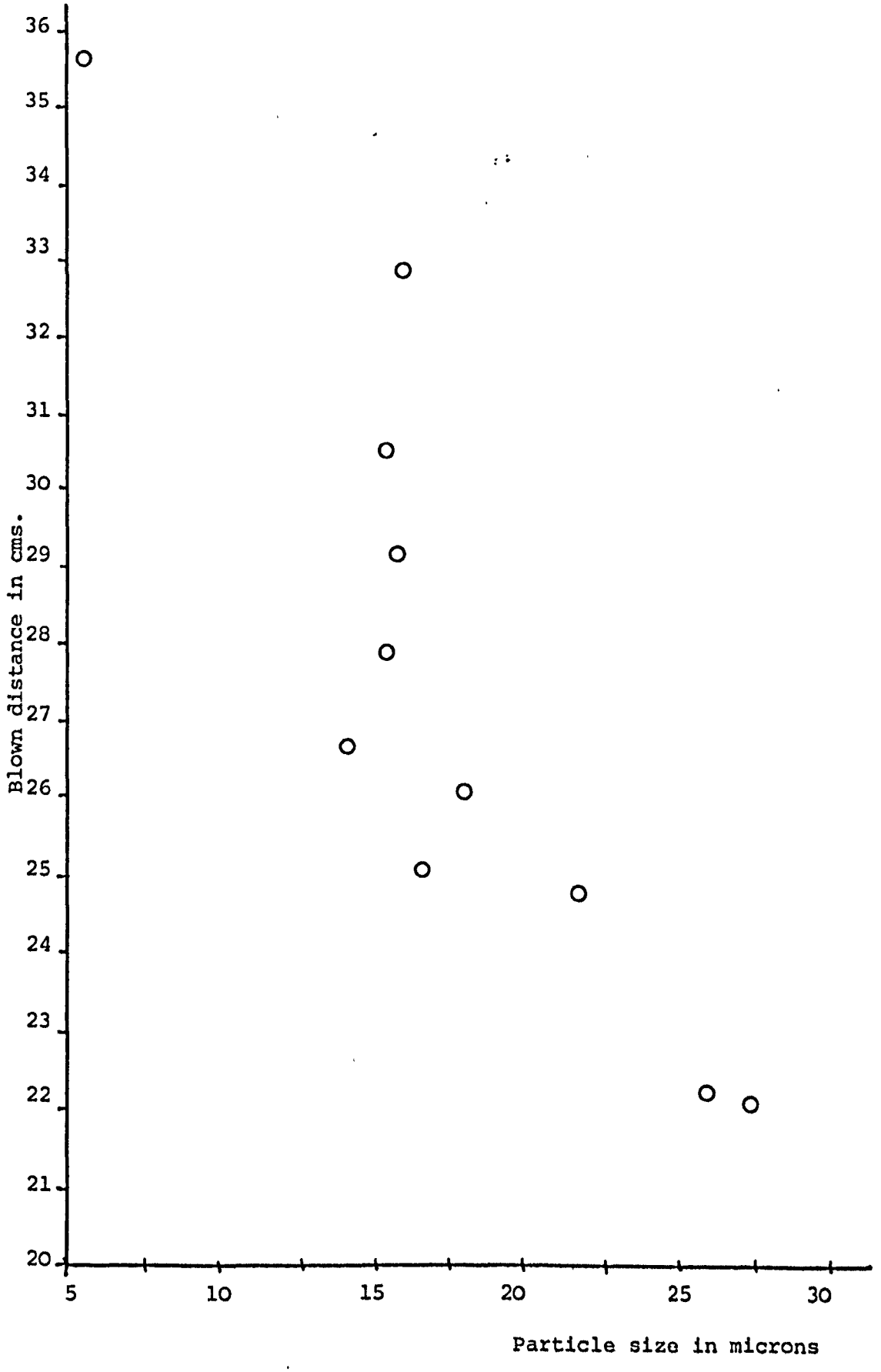


Fig.6.3. Scattergram of particle size and 'blown distance'.

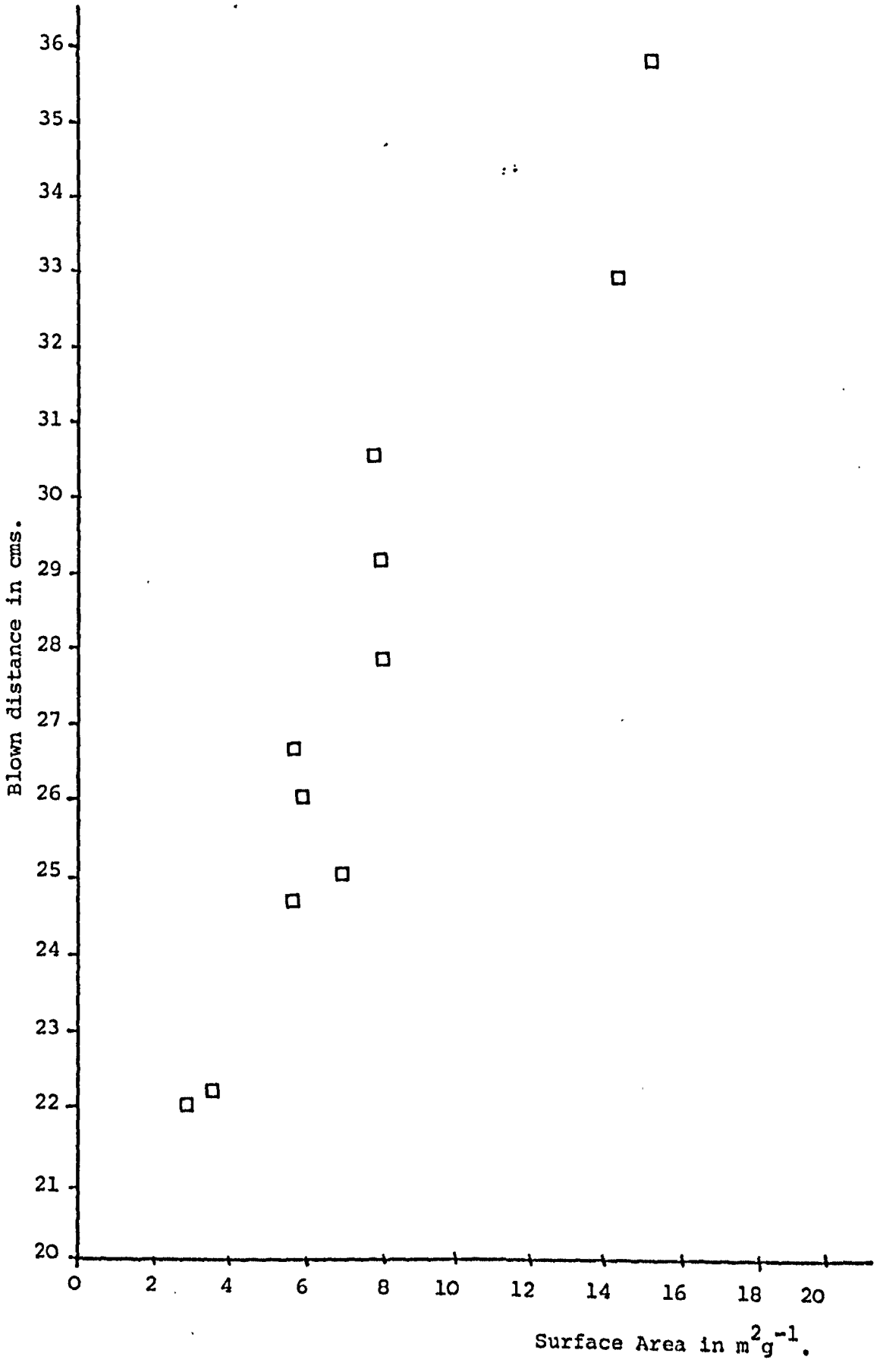


Fig. 6.4. Scattergram of surface area and blown distance.

practical lubricity efficiency of a magnesium stearate batch before it is used in production batches.

6.2. Further Investigation of Lubricant Distribution Through the Tablet Matrix.

The amount of magnesium stearate on the die wall and tablet surface and its distribution through the tablet matrix were investigated.

6.2.1. Commercial Lubricants.

6.2.1.1. Concentration of Lubricant on the Tablet Surface.

Samples were prepared (section 2.4.1.) and subjected to E.S.C.A. analysis. Lactose tablets lubricated with batches 1, 6, 3, 9, and 10 were examined after a) undergoing compaction only and b) undergoing both compaction and ejection processes. Information obtained from the analyses is summarized in Table 6.3. The oxygen, carbon, and magnesium percentage weight compositions are approximate but intercomparison of the samples is, however, quite valid. Additional information indicated that there was no significant differences in oxidation state or chemical environment between the samples of the elements magnesium and oxygen. The carbon however, was present in two different environments namely carbon-oxygen (from lactose) and aliphatic - CH_2 — (from stearate) species. It was shown that the variations in magnesium and oxygen contents of the ten samples arose from variations in the surface concentration of magnesium stearate. From the results it could be concluded that:-

a) tablet surface concentrations of magnesium stearate greatly exceeded 1%.

b) tablets undergoing compression and ejection showed greater surface concentrations of magnesium stearate than tablets which were compacted only, and

TABLE 6.3. INFORMATION OBTAINED FROM E.S.C.A. ANALYSIS.

Parameter measured	Magnesium Stearate Sample. Tablets compacted only. 1	3	10	6	9	Tablets compacted & ejected. 1	3	10	6	9
% weight carbon	56.8	56.7	58.6	59.8	63.1	55.7	57.8	59.8	59.9	64.0
% weight oxygen	42.7	42.8	40.5	39.1	35.5	43.6	41.4	39.2	39.0	34.3
% weight magnesium	0.51	0.51	0.89	1.09	1.34	0.69	0.82	1.04	1.15	1.73
% weight* magnesium stearate concentration.	12.5	12.5	21.9	26.8	33.0	17.0	20.2	25.6	28.3	42.6
Magnesium* stearate film thickness in nanometers.	1.4	1.4	2.5	3.2	4.1	1.9	2.3	3.0	3.4	5.7
Batch classification by admixture tests.	POOR	POOR	POOR	GOOD	GOOD	POOR	POOR	POOR	GOOD	GOOD

* Estimated from percent weight of magnesium present on the surface.

c) the more efficient the lubricant, the higher the magnesium stearate surface concentration.

These findings confirm the supposition that the lubricant migrates through the powder mass to the die wall during the tableting process. It would also appear to confirm that the greater the lubricant ability to migrate to, and accumulate at, the die wall, the greater its efficiency as a tablet lubricant.

A surprising conclusion was that ejected tablets have higher magnesium stearate surface concentrations than non ejected tablets, because it was assumed that magnesium stearate was sheared from the tablet surface as it passed over the fresh die surface during its ejection from the die cavity. It would appear, however, that in practice, the tablet picks up lubricant during the ejection process. Thus, during the compaction process, lubricant migrates to the die wall - tablet surface interface, then during the ejection process, the lubricant is picked up on the tablet surface rather than left behind on the die wall. Hence the ejected tablet possesses a greater surface concentration of stearate than a non ejected tablet. To test the validity of this theory it would be necessary to measure surface concentrations of tablets ejected equidistance through either the pre-lubricated section of the die (normal ejection manner) or the clean section of the die (reversed ejection direction) - see Fig. 6.5.

An alternative explanation is that the results are dependent upon the analysis method. During compaction the lubricant moves to the die wall - tablet surface interface and accumulates there.(Fig. 6.6.) If the tablet is then broken out of the die without undergoing ejection then the lubricant distribution on the tablet surface would be uneven, some parts having a higher concentration than others. However, if the tablet undergoes the ejection process, then the accumulated lubricant

is smeared over the tablet surface as the tablet moves over the die surface when the ejection force is applied. (Fig. 6.7.)

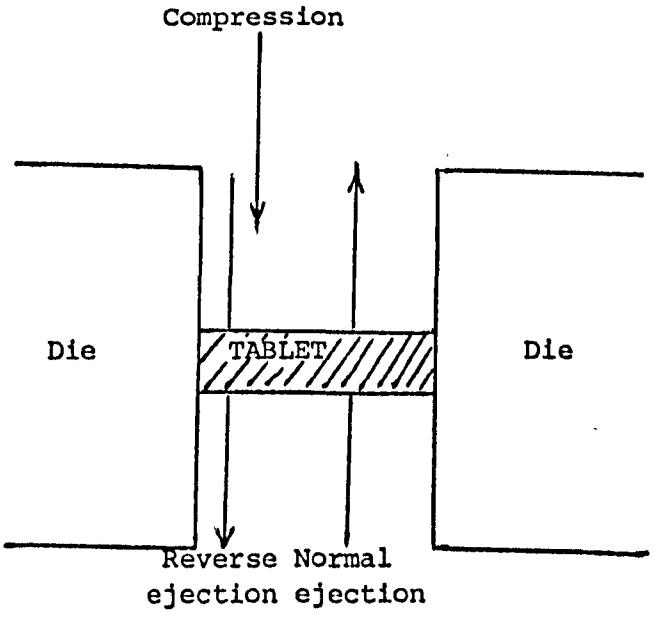


Fig. 6.5. Ejection of Tablet from Die.

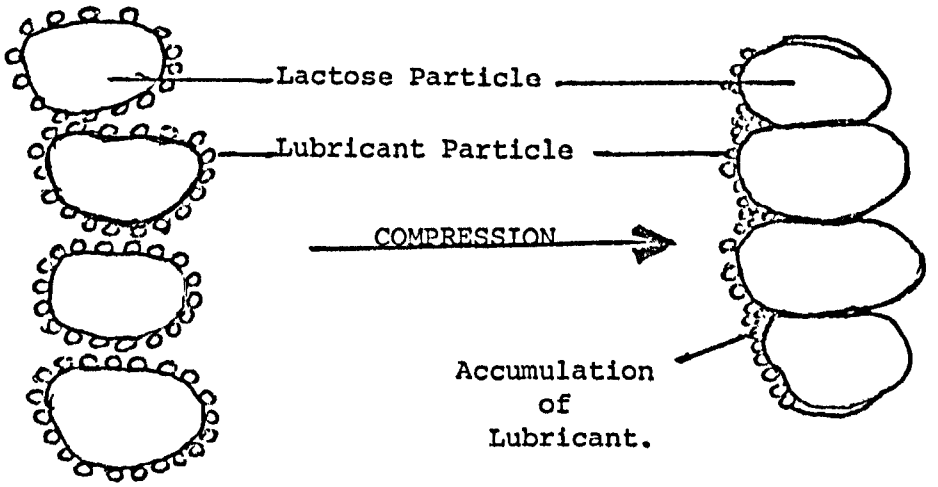


Fig. 6.6. Compression of lubricated sample.

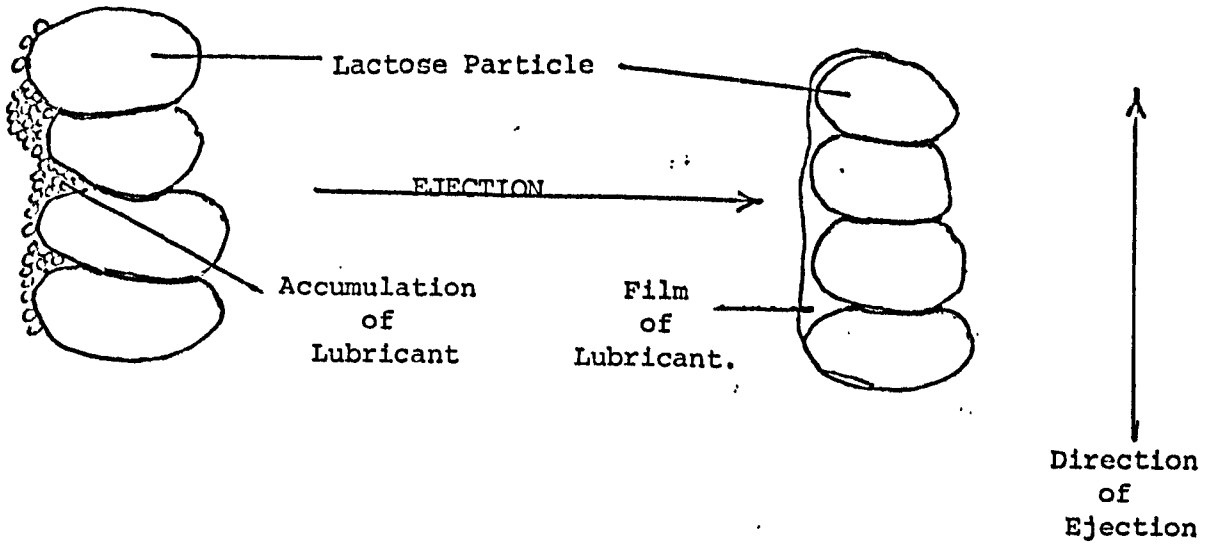


Fig. 6.7. Ejection of a lubricated compact.

The extent to which the lubricant film is formed will depend upon the relative efficiency of the lubricant, that is the ease with which it can migrate to the die wall. Thus the ejected tablet surface would be expected to be more uniformly covered with lubricant. From the E.S.C.A. analyses, such a film could be up to 5.7nm (57Å) in thickness.

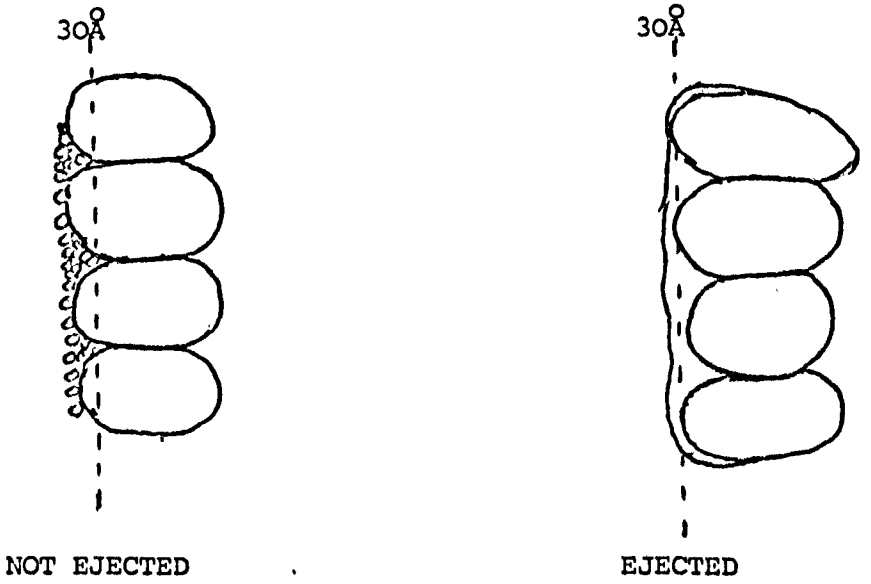


Fig. 6.8. E.S.C.A. analysis of ejected and non ejected tablets.

Thus as shown in Fig. 6.8. the same amount of lubricant can be present at the tablet surface but with non-ejected tablets, it is present in large clumps whereas with ejected tablets, it is present as a more uniform film.

Since E.S.C.A. analysis is performed only on the top 30Å of the surface, then the more uniformly the lubricant is distributed on the tablet surface and the thicker the lubricant film that is formed, the greater the apparent magnesium stearate concentration. The less uniform the lubricant distribution, then the more lactose that is present in the top 30Å available for inclusion in the analysis, and the greater the amount of magnesium stearate present below 30Å which is not included in the analysis.

Thus the difference in magnesium stearate surface concentration between ejected and non-ejected tablets could be a measure of the uniformity of lubricant distribution over the tablet surface rather than an accurate quantitative assessment of the amount present.

To summarize, the relative lubricant efficiency depends upon the relative ability of the lubricant to migrate to the die wall during compaction and smear over the tablet surface and die wall during ejection. The greater the amount of lubricant that migrates to the die wall, the greater its efficiency.

6.2.1.2. Amount of Magnesium Stearate on the Die Wall.

The actual quantity of magnesium stearate present on the die wall after various tableting procedures could be estimated by atomic absorption analysis on samples obtained as described in section 2.4.2. Three investigations were carried out to determine a) the relationship between batch lubricity and amount of lubricant remaining on the die, b) the relationship between the stages in the tableting process and

amount of lubricant transferred to the die wall and c) the effect of compaction speed upon the transfer of lubricant to the die wall.

a) Relationship between batch lubricity and amount of lubricant on the die.

Each lubricant batch was mixed 1% in lactose as described in section 2.3.1. and 200mg samples compressed and ejected using the Instron (section 2.1). Samples were prepared for atomic absorption as described in section 2.4.2. Representative batches 1, 4, and 6 were investigated being respectively classified as poor, mediocre, and good by the lubricant admixture tests (section 4). Results are summarized in Table 6.4.

TABLE 6.4. AMOUNT OF MAGNESIUM STEARATE REMAINING ON DIE AFTER COMPRESSION AND EJECTION OF LUBRICATED SAMPLE.

Lubricant batch	1	4	6
Mean amount of magnesium stearate in µg.	24.90	35.23	26.73

From these results there was no conclusive evidence that lubricity ability was related to amount of lubricant remaining on the die wall. Further investigations involving all eleven batches of magnesium stearate also proved inconclusive. Results of this investigation are summarized in Table 6.5.

Thus it would appear that the amount of magnesium stearate remaining on the die wall after compression and ejection of a lubricated tablet is not indicative of the lubricity of the utilised lubricant batch.

b) Relationship between tableting process and lubricant on the die wall.

Using the same procedure as described under (a) three stages in

TABLE 6.5. AMOUNT OF LUBRICANT REMAINING ON THE DIE, FOR ELEVEN BATCHES OF MAGNESIUM STEARATE.

Lubricant batch	8	9	10	4	1	5	2	7	6	11	3
Mean amount of magnesium stearate on die	19.34	22.06	22.22	22.78	24.50	25.45	28.67	29.43	30.18	31.51	38.90
Lubricant ability classification	POOR	GOOD	POOR	MEDIOCRE	POOR	MEDIOCRE	GOOD	GOOD	GOOD	MEDIOCRE	POOR

the tableting process were investigated, namely (i) after the sample had been packed into the die but not compressed, (ii) after the sample was compressed but not ejected and (iii) after the sample underwent normal compaction and ejection process. Results are summarized in Table 6.6.

TABLE 6.6. INFLUENCE OF TABLETING PROCESS UPON AMOUNT OF LUBRICANT REMAINING ON DIE WALL.

Tableting process.	Mean amount of lubricant on die wall in μg.		
	Batch 1	Batch 4	Batch 6
Packing	42.20	54.13	65.51
Compaction	24.90	35.23	26.73
Compaction and ejection	25.11	34.40	25.88

From these results it would appear that the lubricant is maximally transferred to the die wall during the packing stage in the tableting process and is then removed from the die wall during compaction. This may be due to the fact that the loose packing of the powder in the die results in a greater adherence of lubricated lactose particles to the die wall (all of which is subsequently analysed) whereas after compaction, the lubricant is present only as a thin film, all the lubricated lactose particles being incorporated into the compact. Also during the initial stages of compaction, lubricant could be removed from the die surface to aid consolidation of the powder bed. An interesting conclusion is that the compaction and ejection processes leave approximately the same amount of lubricant behind in the die, which indicates that there is no overall exchange of lubricant between the tablet surface and the die wall surface, and that the ejection process is a smearing of the lubricant already present at the

die wall - tablet surface interface, over the asperities on both surfaces. This finding also supports the explanation for the E.S.C.A. results. (section 6.2.1.1.)

The relative amounts of lubricant remaining on the die after the packing process (i.e. lubricant film and lubricated powder) for the three batches, correlates with lubricity ability of the batches, the greater the amount of lubricant remaining, the better the lubricant ability. Thus the ease with which the lubricant adheres to the die wall surface may be the parameter which significantly controls lubricity of a magnesium stearate batch. Thus the distribution of lubricant on the die wall during the tableting process appears to be at a maximum during packing but is reduced during consolidation and compaction of the powder bed and apparently remains unaffected by the ejection process. However the latter process is thought to smear the lubricant already present over the die wall and tablet surfaces.

c) Effect of Compaction Speed upon amount of lubricant remaining on die wall after compaction.

Representative batches 1, 4, and 6 were investigated as 1% admixtures in lactose (section 2.3.1.). Samples, 200mg in size, were compressed at various speeds, 0.1mm/min, 2mm/min, 10mm/min, and 1000mm/min, using the Instron (section 2.1.). However, the tablets were not ejected from the die but "broken out" at the end of the compaction stage, through the clean part of the die. This was done to avoid the results being influenced by the ejection process. Samples were prepared for atomic absorption as described in section 2.4.2. Results are summarized in Fig 6.9.

From the graph it would appear that compaction speed does influence the amount of lubricant remaining on the die wall but not in a uniform manner. At low speed i.e. 0.1mm/min. compaction, the amount of lubricant

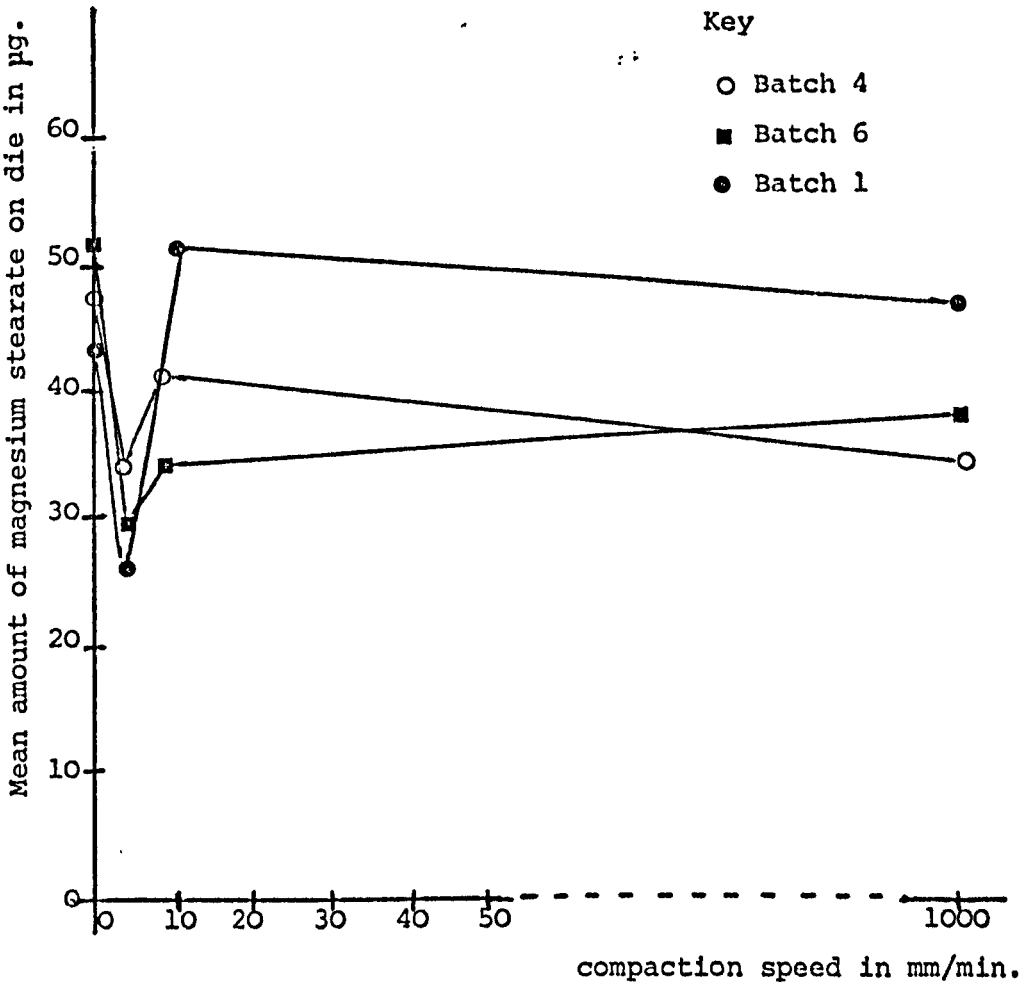


Fig. 6.9. Effect of compaction speed upon amount of magnesium stearate remaining on die wall.

remaining on the die wall is directly related to the lubricity ability, in that the lower the amount on the die wall the poorer the lubricity. However, at 10mm/min compaction speed, this trend is completely reversed. At 2mm/min and 1000mm/min compaction speeds, there is no relationship between lubricity and amount of lubricant on die wall. Thus there is not a constant relationship between compaction speed and amount on the die wall for each batch. However, each batch does appear to behave in a similar manner as compaction speed is altered, in that the amount of lubricant left on the die reaches a minimum at 2mm/min compaction speed.

It was expected from blowability tests that increasing the compaction speed would waft more lubricant to the die surface and thus a direct relationship would be expected between compaction speed and amount of lubricant on die wall. The actual relationship appears to be a reduction in the amount of lubricant left on the die wall as the compaction speed increases, reaching a minimum at 2mm/min followed by an increase as compaction speed is further increased until a plateau value is reached afterwhich further increases in compaction speed do not significantly change the amount of lubricant remaining on the die.

Thus to summarize, it would appear that the amount of lubricant remaining on the die wall after the tableting process, is not indicative of the lubricity ability of the lubricant batch but is affected by very low compaction speeds. Compaction speeds above 10mm/min do not significantly alter the amount of lubricant remaining on the die from those amounts obtained at 10mm/min. It is thought, therefore, that lubricity efficiency of a lubricant batch will not be affected by the compaction speed used in the tableting process.

6.2.1.3. Distribution of Magnesium Stearate through the Tablet Matrix.

The distribution of lubricant throughout the tablet matrix was investigated as described in section 2.4.3. The investigation was divided into three parts, a) preliminary tests to establish whether there was a lubricant gradient across the tablet and if so, which are the areas of high lubricant concentration, b) to repeat the test in (a) but intensifying the investigation to examine areas of high lubricant concentration, and c) to examine the distribution in the tablet when compacted at different speeds.

In the preliminary investigation, representative batches 1, 4 and 6, that is poor, mediocre and good respectively, were examined, both as

1% mixtures in lactose and 1% mixtures in cornstarch. Four or five skims were obtained from each tablet and analysed for magnesium stearate concentration. From the weight of the powder actually present in each of the skimmings, and assuming uniform mix of the lubricant and excipient, the theoretical amount of lubricant and actual amount of lubricant present in each skimming could be compared. Table 6.7. summarizes the results for lactose admixtures whilst Table 6.8. summarizes the results for the corn starch admixtures. Examination of both sets of results leads to the conclusion, that during the tableting process lubricant material is wafted from the centre of the tablet to the tablet surface. Thus it appears that a lubricant gradient does exist across the tablet, being high at the tablet surface and low at the tablet centre. This gradient is probably established during the compaction process, when air is expelled from the powder mass.

To obtain a realistic comparison between the different batches, and to relate the lubricant concentration to actual tablet dimensions, graphical representation of the results was required. The experimental results, as such, were not considered to be in a very useful form. Therefore the weight of powder present in each skimming was used to calculate the radius of the remaining portion of tablet after the skim had been performed. The calculation is explained in Appendix 4.4. It was assumed that the skimmed material was removed in a uniform manner, that is the remaining portion of the tablet is circular in cross section. The concentration of lubricant material in each skimming was calculated from the following equation:-

$$\text{Lubricant concentration} = \frac{\text{weight of lubricant in } \mu g \times 100\%}{\text{weight in } \mu g \text{ of powder in skimming}}$$

TABLE 6.7. LACTOSE SKIM TEST RESULTS.

Sample analysed		Amount of magnesium stearate in micrograms present in skimming. Batch 1 Test 1	Batch 1 Test 2	Batch 4 Test 1	Batch 4 Test 2	Batch 6 Test 1	Batch 6 Test 2
Skim 1	Expected	126	104	148	156	151	161
	Obtained	342	249	183	251	425	265
Skim 2	Expected	213	313	250	190	282	286
	Obtained	249	296	255	379	357	558
Skim 3	Expected	161	196	221	184	—	—
	Obtained	313	146	413	286	—	—
Skim 4	Expected	—	145	252	206	—	—
	Obtained	—	109	300	217	—	—
Core	Expected	1464	1190	1125	1136	1550	1556
	Obtained	1169	615	772	620	844	1034
Total	Expected	1964	1948	1996	1872	1983	2003
	Obtained	2073	1415	1923	1753	1626	1857
Percentage	$\frac{\text{Obtained}}{\text{Expected}}$	105.6%	72.6%	96.3%	93.6%	82.0%	92.7%

TABLE 6.8. CORNSTARCH SKIM TEST RESULTS.

Amount of magnesium stearate in micrograms present in skimming.

Sample analysed		Batch 1 Test 1	Batch 1 Test 2	Batch 4 Test 1	Batch 4 Test 2	Batch 6 Test 1	Batch 6 Test 2
Skim 1	Expected	78	83	162	250	167	184
	Obtained	200	200	317	327	316	653
Skim 2	Expected	88	91	144	231	229	156
	Obtained	363	363	358	217	384	418
Skim 3	Expected	—	239	214	—	—	125
	Obtained	—	641	228	—	—	582
Skim 4	Expected	—	160	—	—	—	—
	Obtained	—	762	—	—	—	—
Core	Expected	1765	1481	1436	1482	1616	1455
	Obtained	983	655	606	772	952	626
Total	Expected	1931	2054	1976	1963	2012	1920
	Obtained	1546	2626	1509	1316	1652	2279
Percentage	$\frac{\text{Obtained}}{\text{Expected}}$	80.1%	127.8%	76.8%	67.0%	82.1%	118.7%

This value was plotted against the radius of the tablet at the midpoint of the skimming. (Fig. 6.10.)

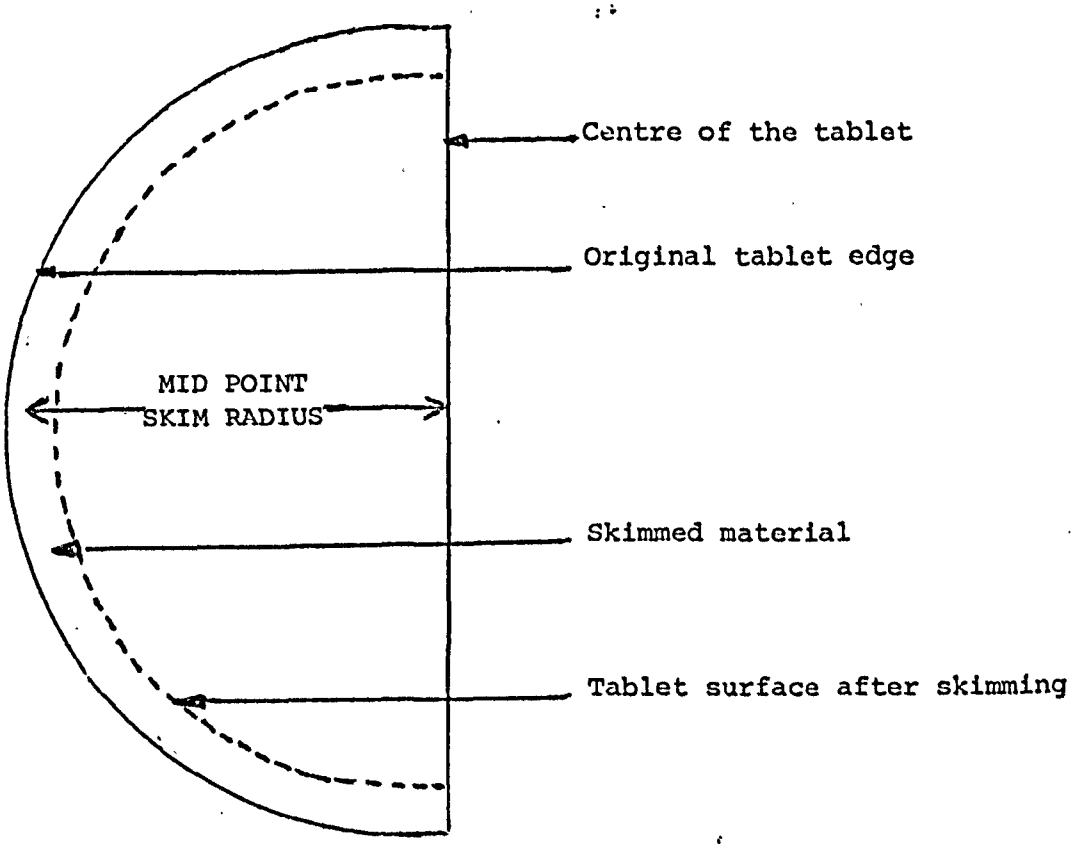


Fig. 6.10. Mid point skim radius.

Graphs for each lubricant batch with lactose as excipient are shown in Fig. 6.11. and graphs with cornstarch as excipient are shown in Fig. 6.12.

From the graphs it can be confirmed that a lubricant gradient does exist across the tablet. The first skim of some of the tablets has a lower magnesium stearate concentration than the next skim. This was thought to be accounted for, by the fact that some of the lubricant from this skim will be left behind on the die surface. The centre of the tablet contains less than 1% of lubricant and the surface contains greater than 1%. With lactose as excipient the surface concentration

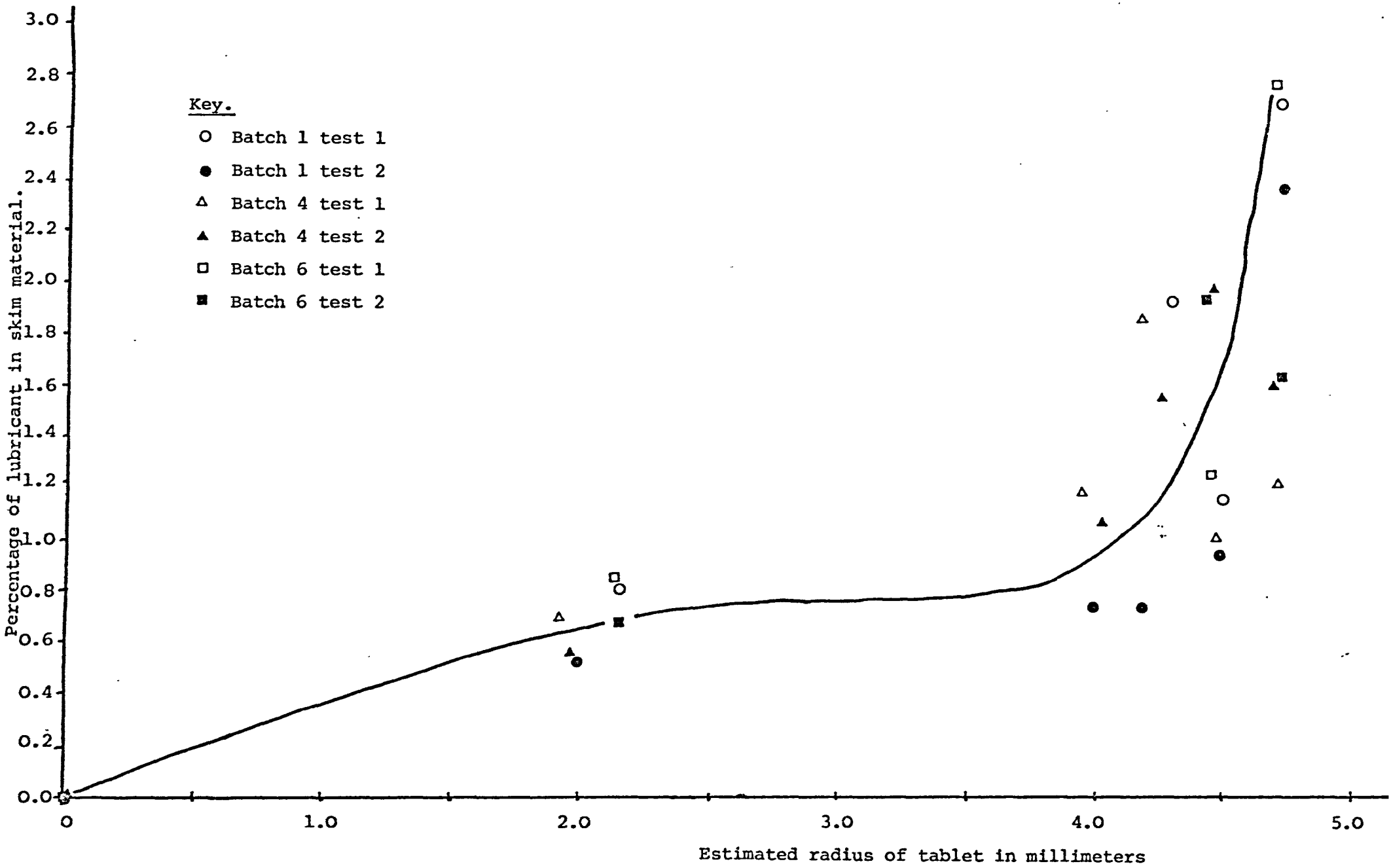


Fig. 6.11. Lubricant gradient across lactose admixture tablets

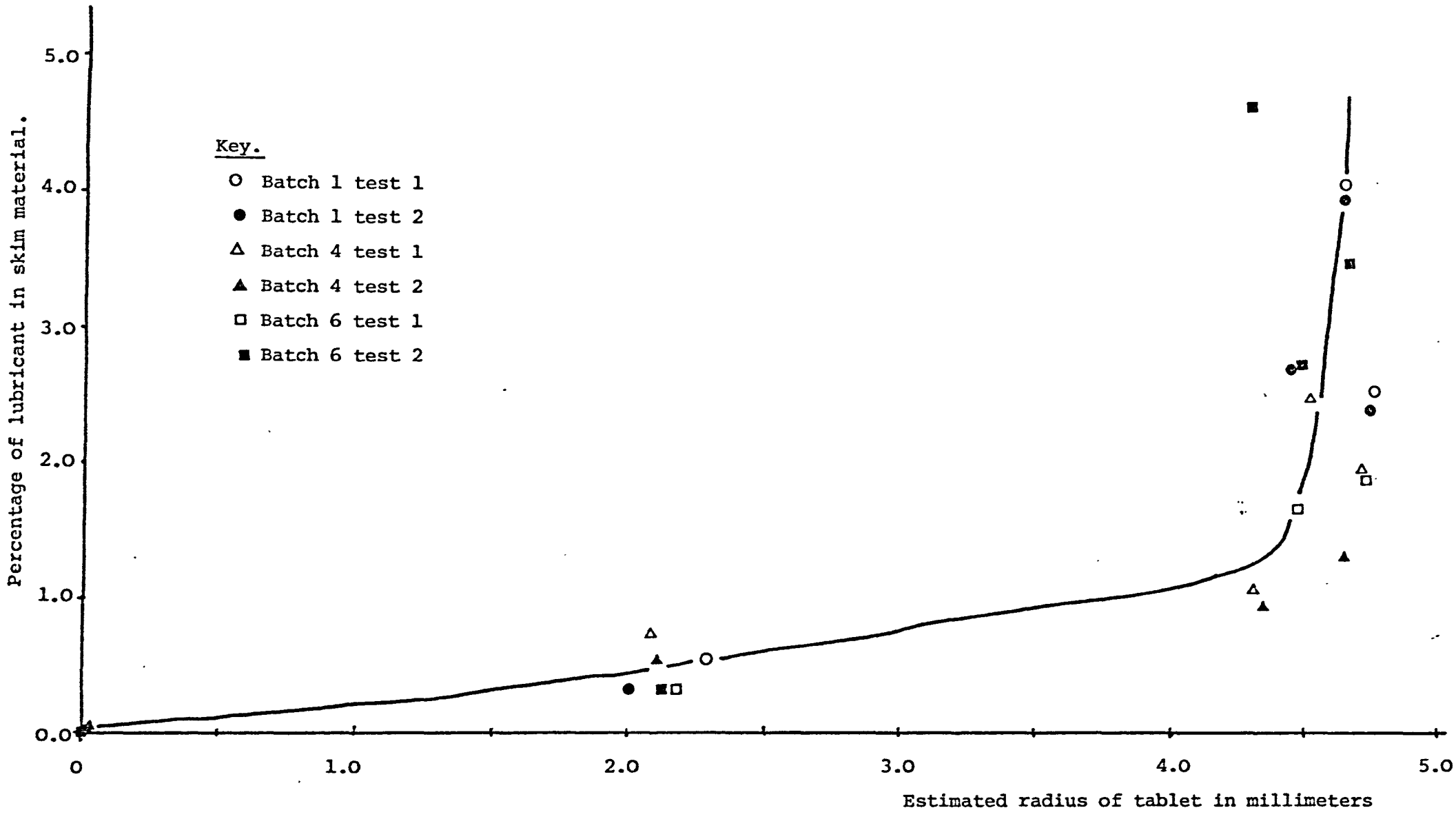


Fig. 6.12. Lubricant gradient across cornstarch admixture tablets

is not as great as with cornstarch as the excipient. This implies that lubricant is wafted through the cornstarch powder mass more easily than through the lactose powder mass. The shape of the lubricant gradient curves supports this hypothesis. The lubricant tends to concentrate in the outer 0.2mm of the tablet surface.

It was thought that the ease with which the lubricant is wafted to the die wall may account for the differences in lubricity behaviour. However, from this investigation, with respect to lubricant ability, the results are inconclusive. This is mainly due to the fact that the graphs only approximately represent the lubricant gradient because of the small number of skims performed. Therefore, in order to obtain a more accurate representation of the lubricant gradient, and to try to establish a relationship between lubricant ability and ease of movement of the lubricant through the tablet, the preceeding investigation was repeated using admixtures lubricated with batches 1, 4, and 6, but increasing the number of skims performed upon each tablet, especially within the first 0.2mm of the tablet surface.

For the second part of the investigation, representative batches 1, 4, and 6 were again used but only as 1% admixtures in lactose. Between 6 to 8 skims were obtained from each tablet and analysed for magnesium stearate concentration as described previously. (section 2.4.3.) Two tests were performed for each lubricant batch. As described for the preliminary tests, the results obtained were mathematically treated so that the information could be summarized graphically as shown in Fig. 6.13.

From these results it was concluded that a lubricant gradient did exist across the tablet, lubricant concentrations being below 1% in the tablet core and above 1% at the outer surface. The thinner the skimming removed from the outer surface, the greater the concentration

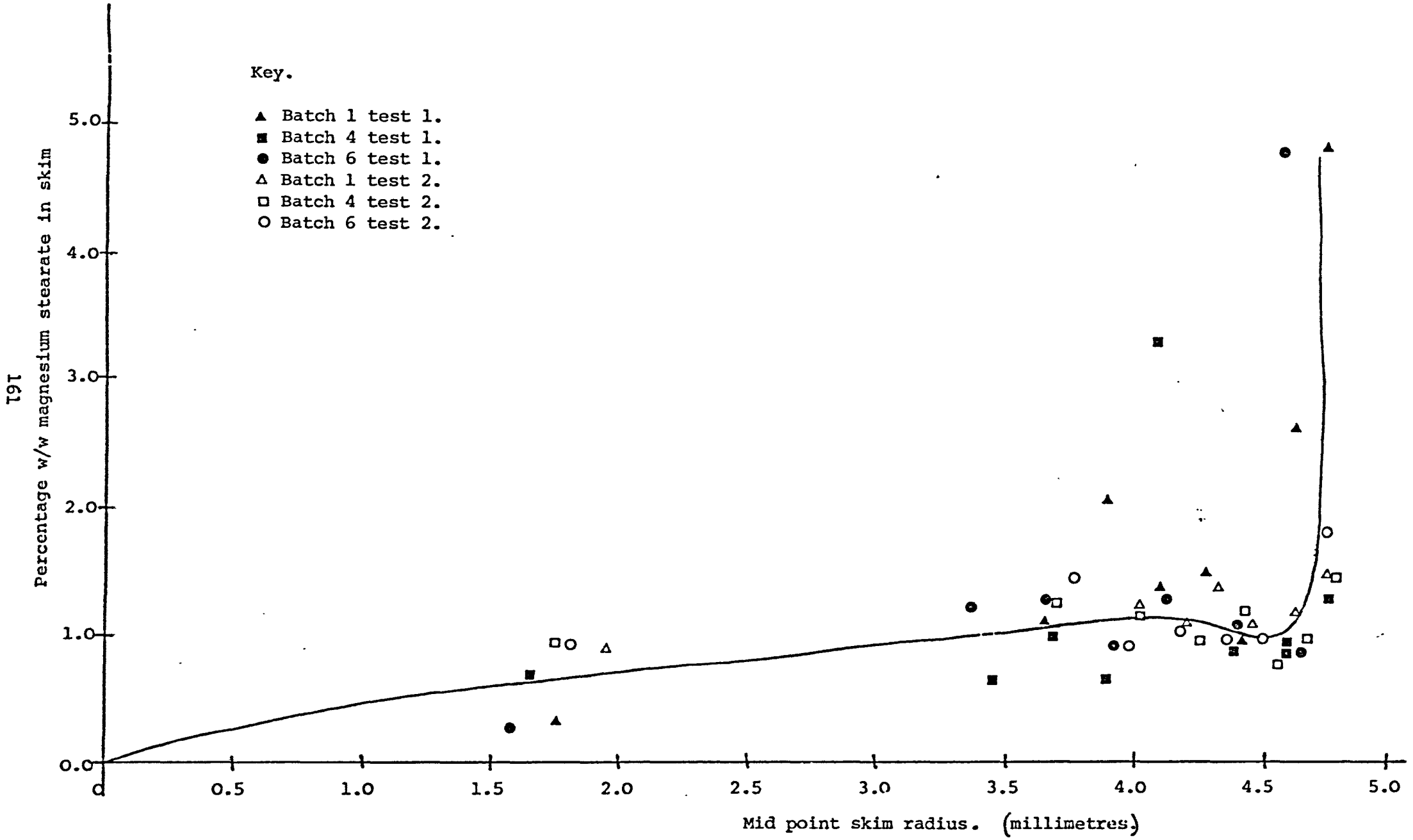


Fig. 6.13. Magnesium Stearate Distribution Across a Tablet Compressed at 2mm/min.

of lubricant appeared to be the general trend. However, there did not appear to be any significant difference between the different batches of lubricant so that it does not appear that a more efficient lubricant is wafted further through the tablet than a less efficient lubricant. This would indirectly imply that the amount of lubricant transferred to the die wall would not be dependent upon the relative lubricant ability of the magnesium stearate batch, which supports the conclusions from section 6.2.1.2. It was therefore concluded that all the points on the graphs in Fig 6.13. could be represented by the one curve which could be used to represent lubricant distribution at a compaction speed of 2mm/min when comparing lubricant distribution at different compaction speeds.

The above investigation was therefore repeated but using compaction speeds of 0.1mm/min, 10mm/min, and 1000mm/min. Results are summarized graphically (after mathematical treatment) in Figs 6.14, 6.15, and 6.16. Again, for each set of results, it was concluded that there was no significant difference between the batches with respect to the lubricant distribution, that is, no relationship between lubricant distribution and lubricant ability. Therefore, all the points plotted could be represented by the one general curve for each compaction speed. Comparison of these curves for the four compaction speeds is shown in Fig. 6.17. From this graph it can readily be seen that there is no significant difference in distribution of magnesium stearate throughout the tablet matrix when the tablet is compacted at different speeds.

Thus the overall conclusion is that compaction of the lubricated powder in a die causes the magnesium stearate material to be wafted through the tablet matrix to the die wall during consolidation of the powder. This results in a lubricant gradient across the tablet, the lowest lubricant concentration occurring at the tablet core

Fig. 6.14. Magnesium Stearate Distribution Across a Tablet Compressed at 0.1mm/min.

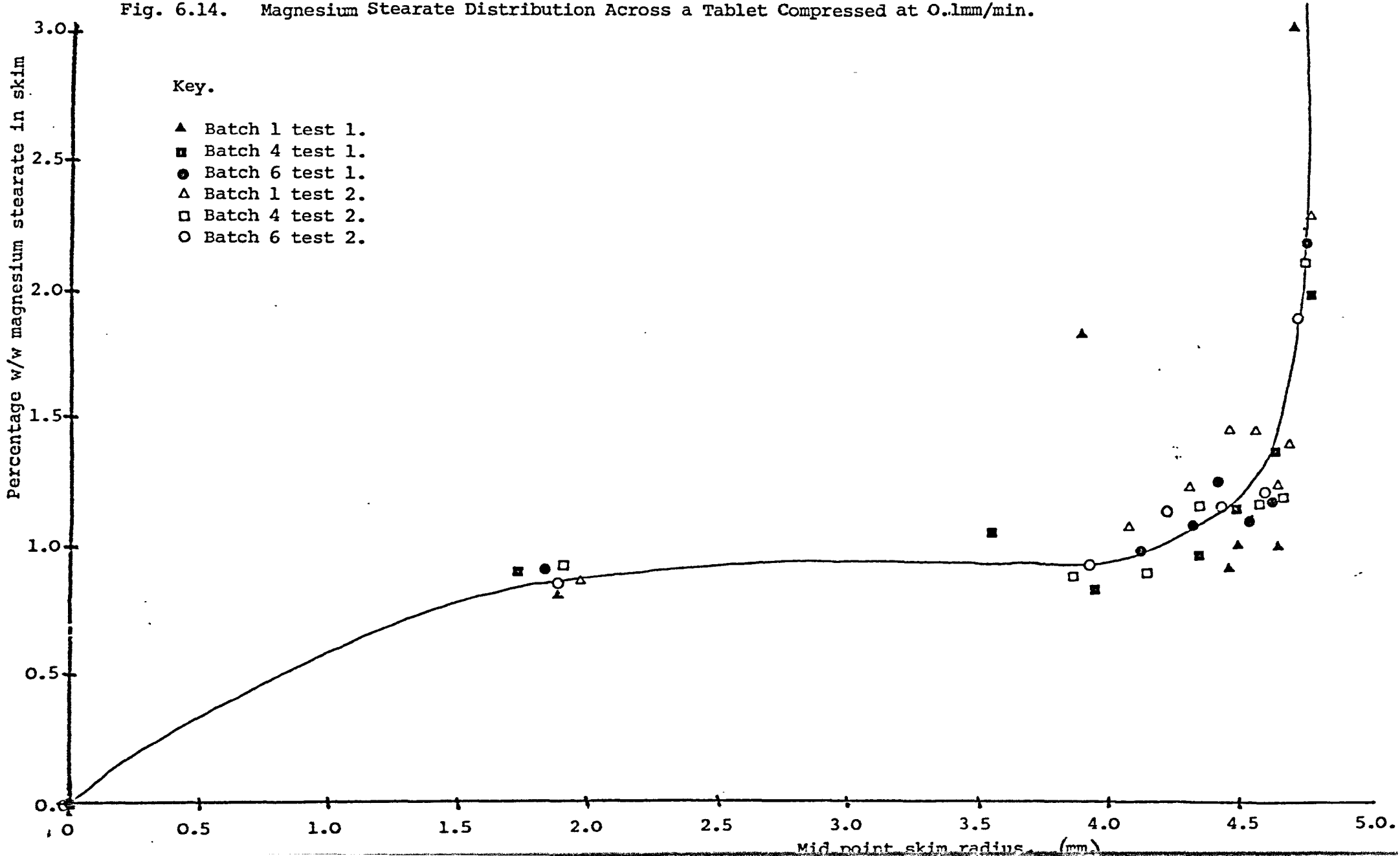


Fig. 6.15. Magnesium Stearate Distribution Across a Tablet Compressed at 10mm/min.

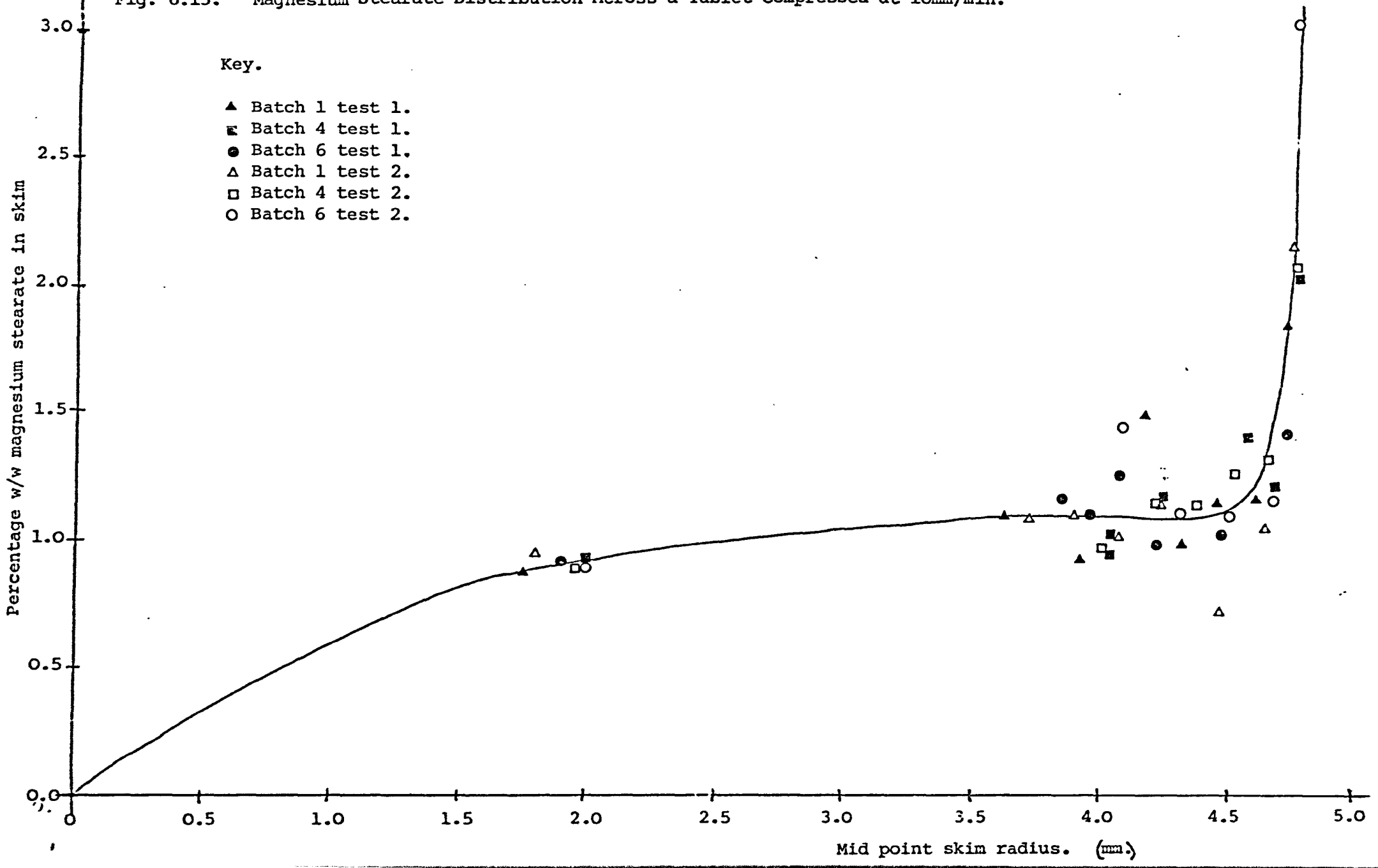


Fig. 6.16. Magnesium Stearate Distribution Across a Tablet Compressed at 1000mm/min.

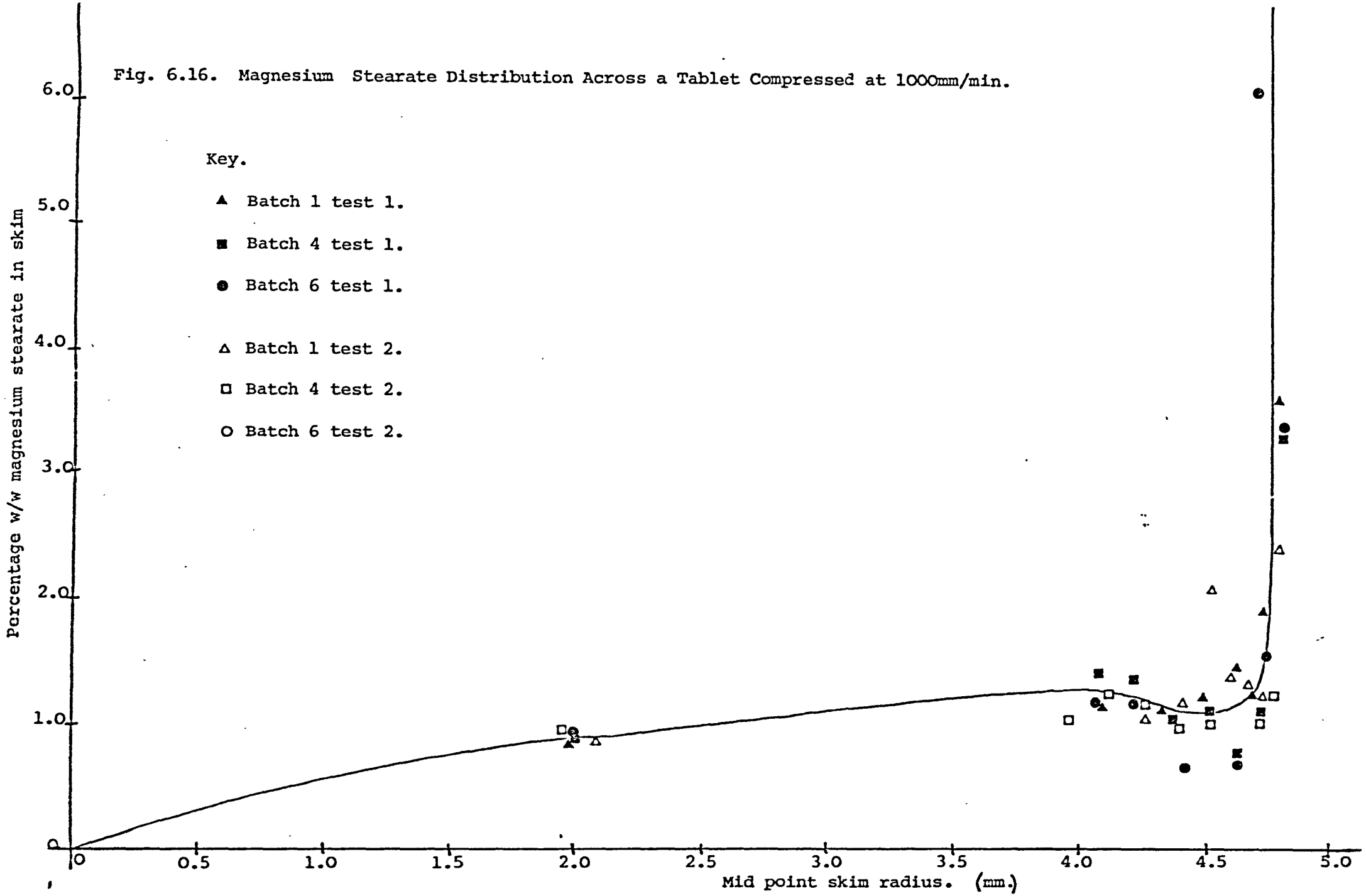
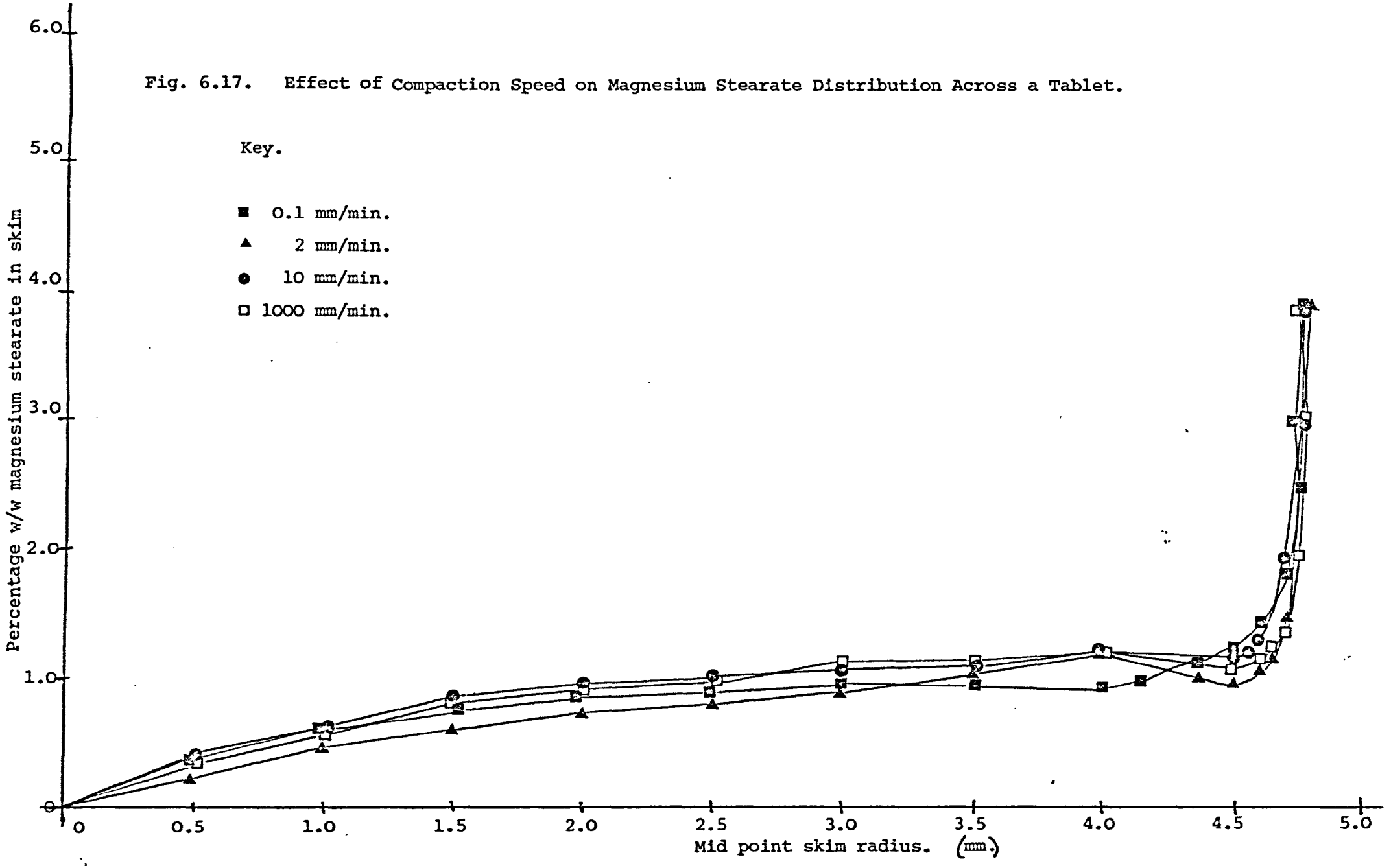


Fig. 6.17. Effect of Compaction Speed on Magnesium Stearate Distribution Across a Tablet.



and increasing gradually across the tablet until reaching the tablet surface when the concentration rises rapidly within the outer 0.2mm of the tablet. It would be expected that the greater the lubricant concentration at the surface of the tablet, the more efficient the lubricant. However this does not appear to be the case for the different batches of magnesium stearate. Since the lubricant gradient is not significantly affected by compaction speed, a particular batch of magnesium stearate should be equally efficient whether the tableting machine is operating at high or low speeds.

Thus the batch variation in magnesium stearate would appear to be inherent within the material rather than on its ability to move within the powder/tablet mass and accumulate at the die wall, although it is probable that for general lubrication, the greater the lubricant's migratory potential, the more effective it will be as a lubricant. However, this must reach a limiting value since once the minimum concentration of lubricant required for efficient lubrication is at the die surface, any further lubricant migration is superfluous.

It would appear that for magnesium stearate this minimum concentration at the die wall is readily obtained even at slow compaction speeds and thus it is a very good lubricant.

To determine whether the magnesium stearate distribution was affected by crystal shape or composition, the laboratory prepared lubricants were also investigated.

6.2.2. Laboratory Prepared Lubricants.

All six batches were investigated. Admixtures of 1% micronized lubricant in lactose were used for sample preparation.

6.2.2.1. Amount of lubricant on die wall.

Analysis was carried out as described in section 2.4.2. The

amount of lubricant left on the die wall was determined under standard test conditions and for different compaction speeds as for the commercial lubricants (section 6.2.1.2.). Results are summarized in Table 6.9. and Table 6.10. From Table 6.9. it can be concluded that, as found for the commercial lubricants, the greatest amount of magnesium stearate remains on the die after the packing process. Also it would appear that the ejection process does not significantly alter the amount of magnesium stearate deposited on the die wall after the compaction process but, as concluded for the commercial batches, smears the already present lubricant over the die wall and tablet surfaces. The results also indicate that there is no relationship between lubricant efficiency and amount of material deposited on the die wall during tableting. This again supports the conclusion obtained from the investigation of the commercial lubricant batches. Apart from the pure palmitate values obtained after compaction and ejection, there does not appear to be any influence of lubricant composition upon the amount of lubricant left on the die. Also, crystal shape does not appear to have any influence, since pure stearate plates and needles tend to behave in the same manner.

The influence of compaction speed upon lubricant distribution was also investigated (Table 6.10.) but did not appear to be directly related to lubricant distribution. The mixture lubricant materials tended to follow a similar behavioural pattern to the commercial lubricant batches 1, 4, and 6, (section 6.2.1.2) although for the 50 : 50 mixture the minimum value is at 1000mm/min compaction speed. For the pure materials the minimum of magnesium stearate transfer to the die wall occurs at 10mm/min. The exception is the palmitate which virtually shows no change in lubricant amount with changing compaction speed.

TABLE 6.9. EFFECT OF TABLETING PROCESS ON AMOUNT OF LUBRICANT ON DIE WALL.

Tableting process	Amount of lubricant on die wall in µg.					
	Plates	Needles	Palmitate	25 : 75	50 : 50	75 : 25
Packing	55.66	52.10	59.18	41.78	88.44	65.85
Compaction	44.86	49.02	32.48	32.76	56.35	56.34
Compaction and ejection.	46.58	41.51	23.20	41.06	44.30	45.38

TABLE 6.10. AMOUNT OF MAGNESIUM STEARATE ON THE DIE AFTER COMPACTION AT DIFFERENT COMPACTION SPEEDS.

	Amount of magnesium stearate in μg.					
Compaction Speed	Plates	Needles	Palmitate	25 : 75	50 : 50	75 : 25
0.1mm/min.	29.01	37.69	23.4L	51.14	56.03	49.84
2mm/min.	46.58	41.51	23.20	24.69	44.30	45.38
10mm/min.	32.84	18.09	28.15	39.16	67.76	71.95
1000mm/min.	39.63	33.38	24.64	34.13	29.95	48.35

Thus the overall conclusion appears to be that the lubricity ability of the lubricant is not reflected by the amount remaining behind on the die wall, and there is no direct relationship between compaction speed and amount of magnesium stearate transferred to the die wall. These conclusions are the same as those obtained from the investigations using commercial batches 1, 4, and 6 of magnesium stearate.

6.2.2.2. Distribution of magnesium stearate through the tablet.

The investigation described in section 6.2.1.3. was repeated using all 6 batches of the laboratory prepared lubricants but omitting the preliminary tests. One percent admixtures of lubricant in lactose were used. Results are summarized in Figs. 6.18. to 6.25. Again, as for the commercial batches, it was concluded that each set of points could be represented by a single curve. From these curves it could readily be seen that there was a lubricant gradient across the tablet surface both for the pure materials and for the admixture lubricants. It was noticed that the values for the needle material did not conform to the general behaviour pattern and so these values for each compaction speed were replotted on a separate graph, Fig. 6.26. From this graph it was concluded that the peak lubricant accumulation area of the needle material depended upon the compaction speed at which the powder was compressed. At 0.1mm/min the lubricant accumulated at about 3.4mm from the centre of the tablet, at 4.1mm at 2mm/min and 10mm/min, and 4.6mm at 1000mm/min, the latter being similar to the behaviour of the other pure lubricants under these conditions. This dependence of the lubricant distribution upon compaction speed was thought to be due to the needle shape of the lubricant particles which would be surmised to hinder the wafting of the lubricant through the powder mass. This was not thought to occur with the more regular

Fig. 6.18. Lubricant Distribution Across Tablets Compressed at 0.1mm/min.

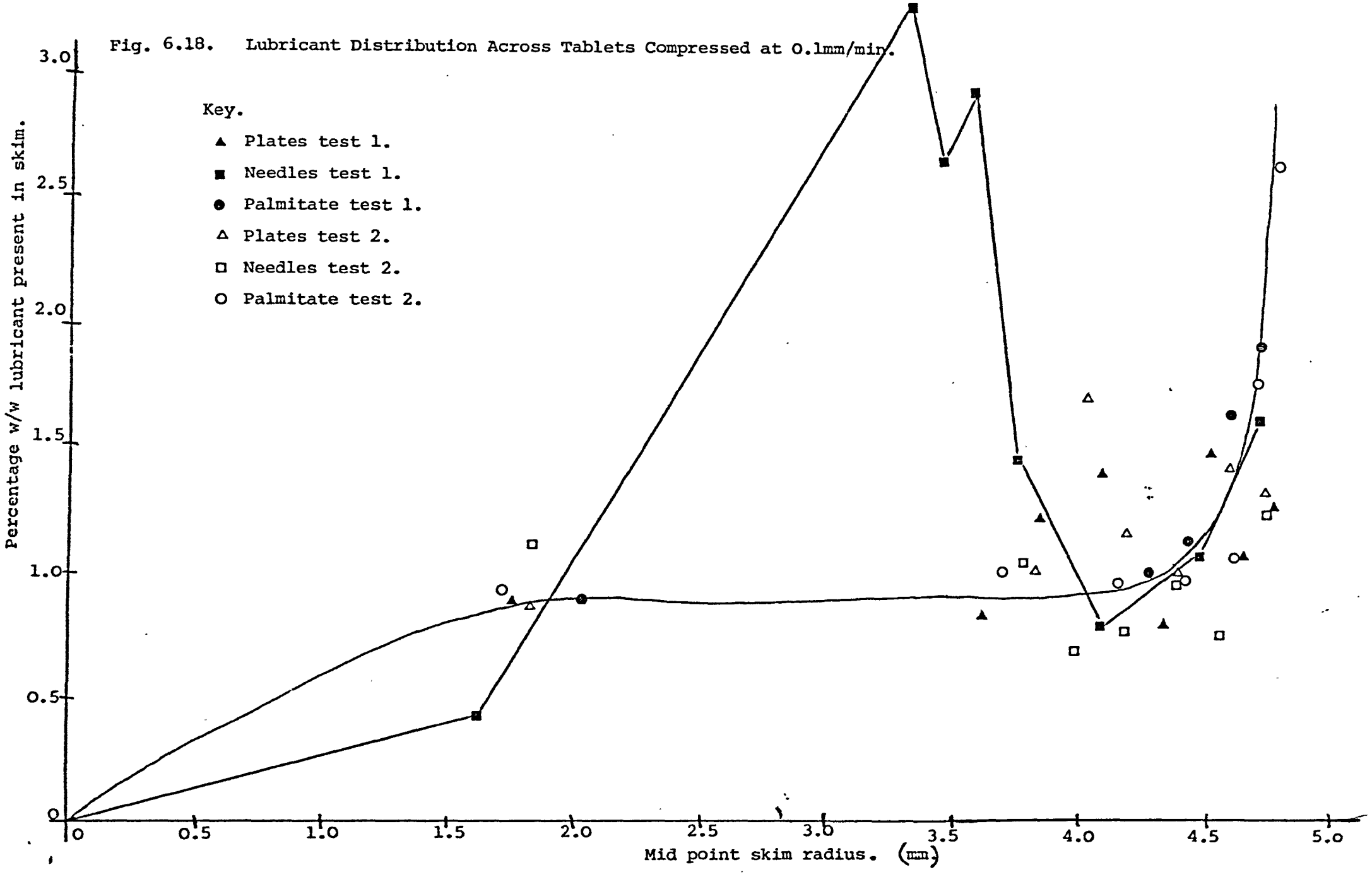


Fig. 6.19. Lubricant Distribution Across Tablets Compressed at 0.1mm/min.

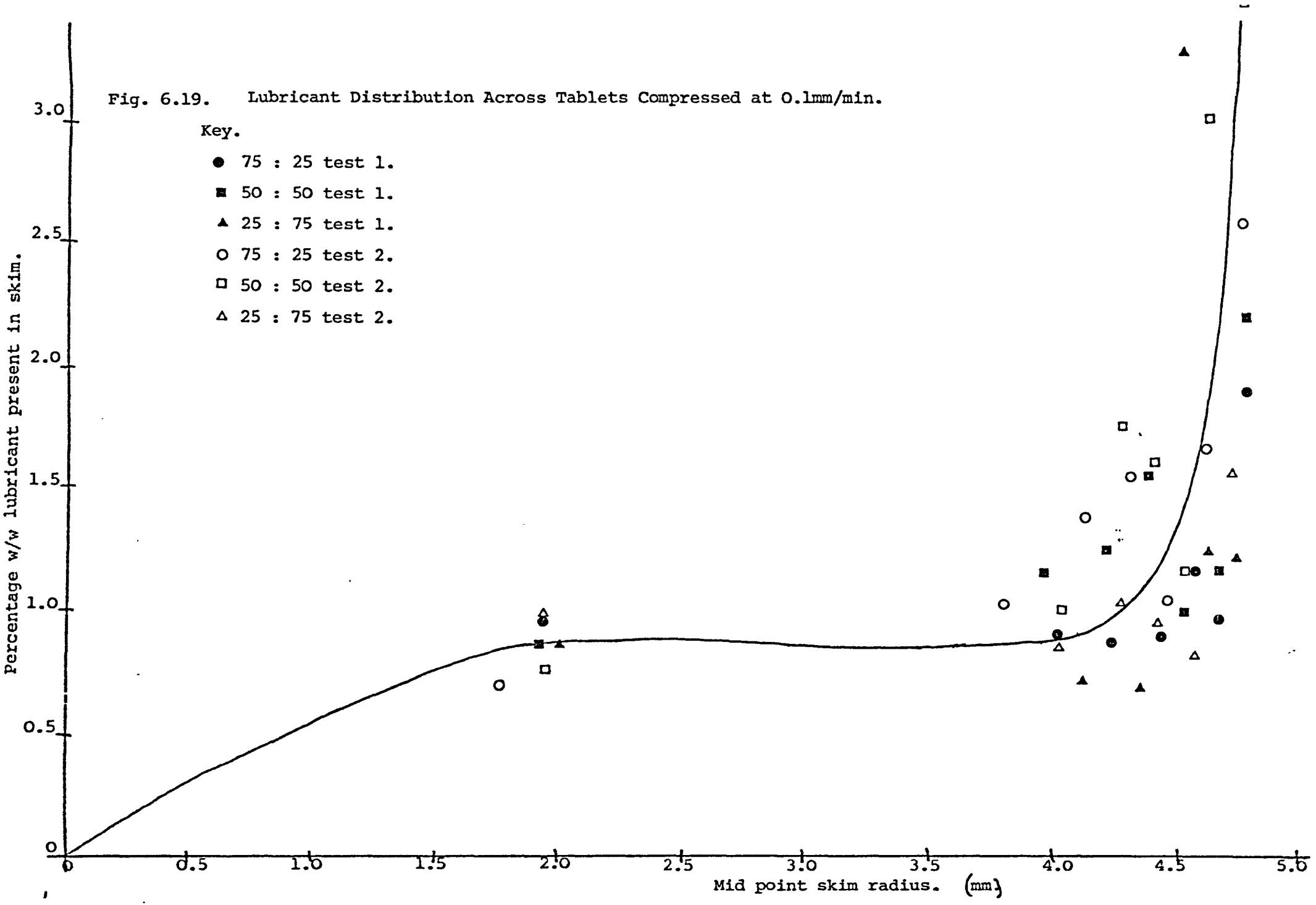


Fig. 6.20. Lubricant Distribution Across Tablets Compressed at 2mm/min.

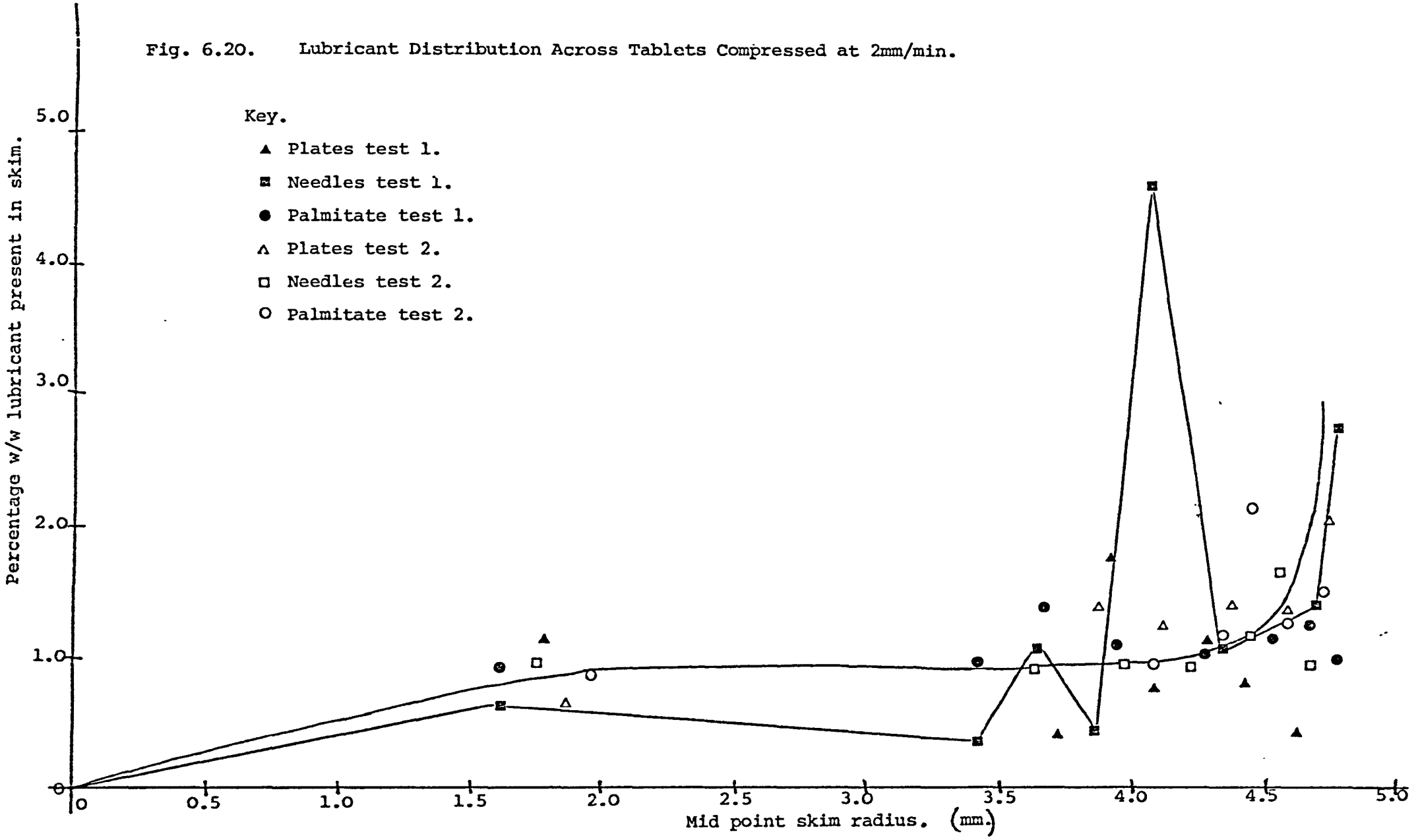


Fig. 6.21. Lubricant Distribution Across Tablets Compressed at 2mm/min.

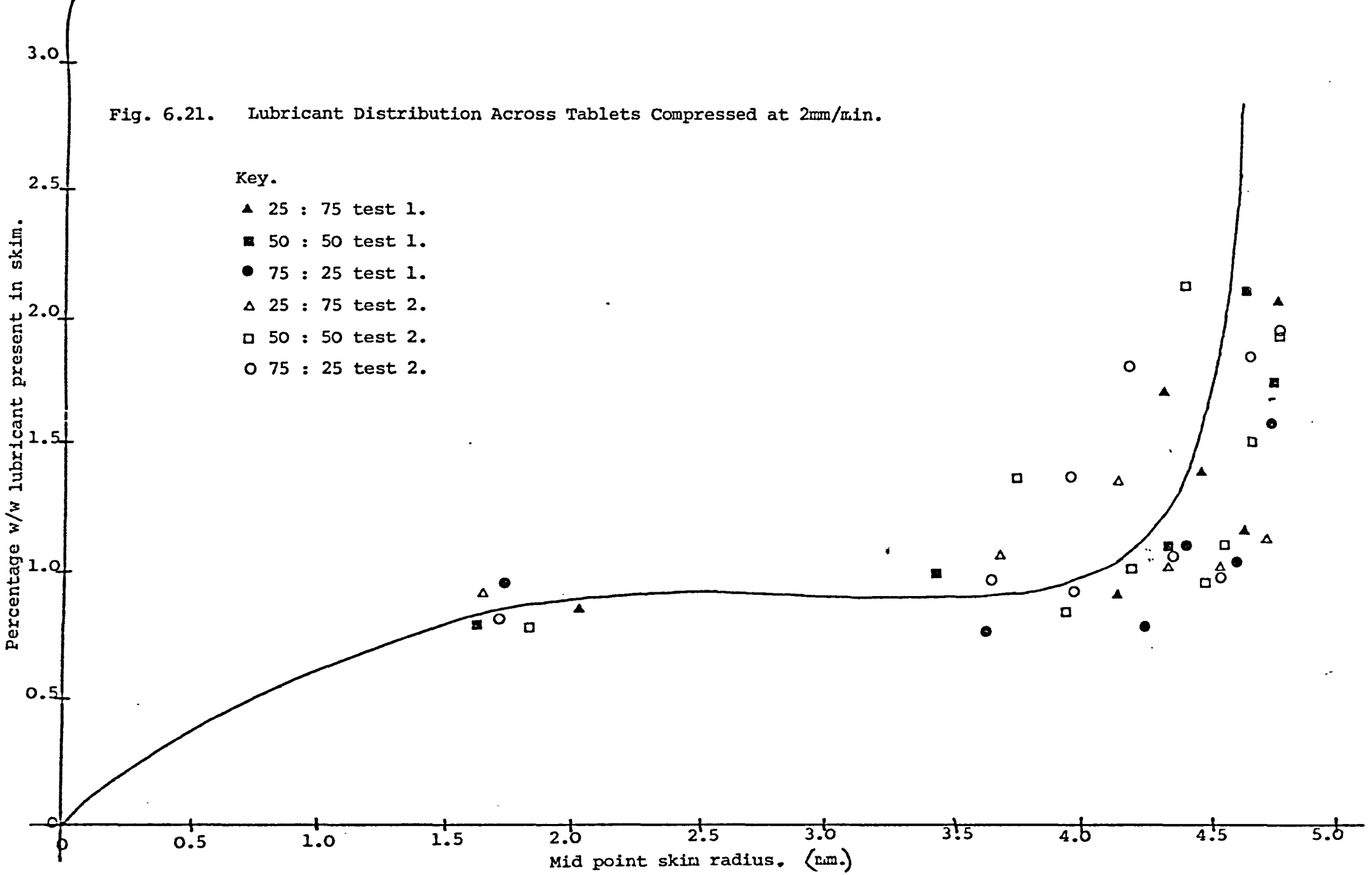


Fig. 6.22. Lubricant Distribution Across Tablets Compressed at 10mm/min.

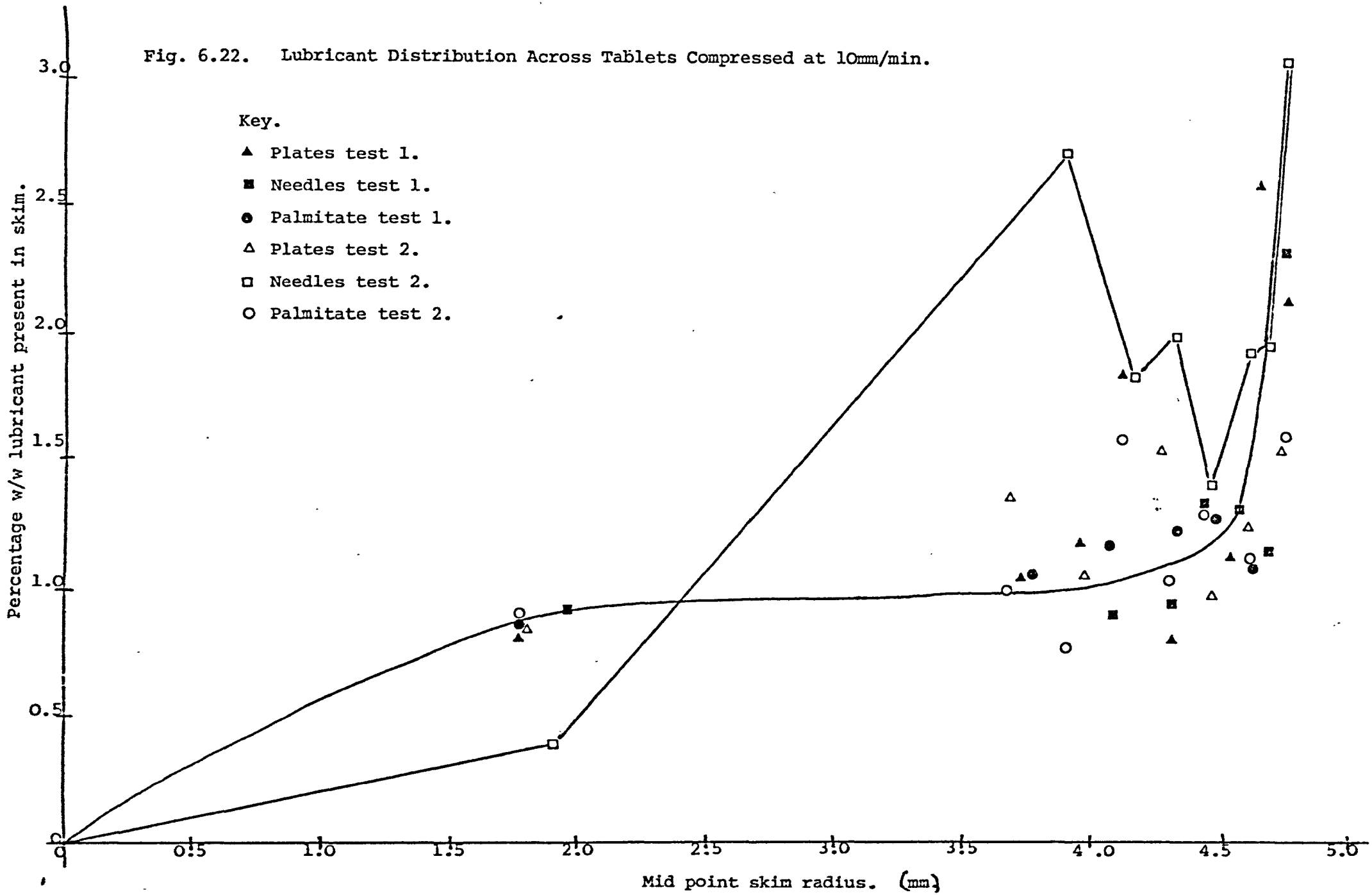


Fig 6.23. Lubricant Distribution Across Tablets Compressed at 10mm/min.

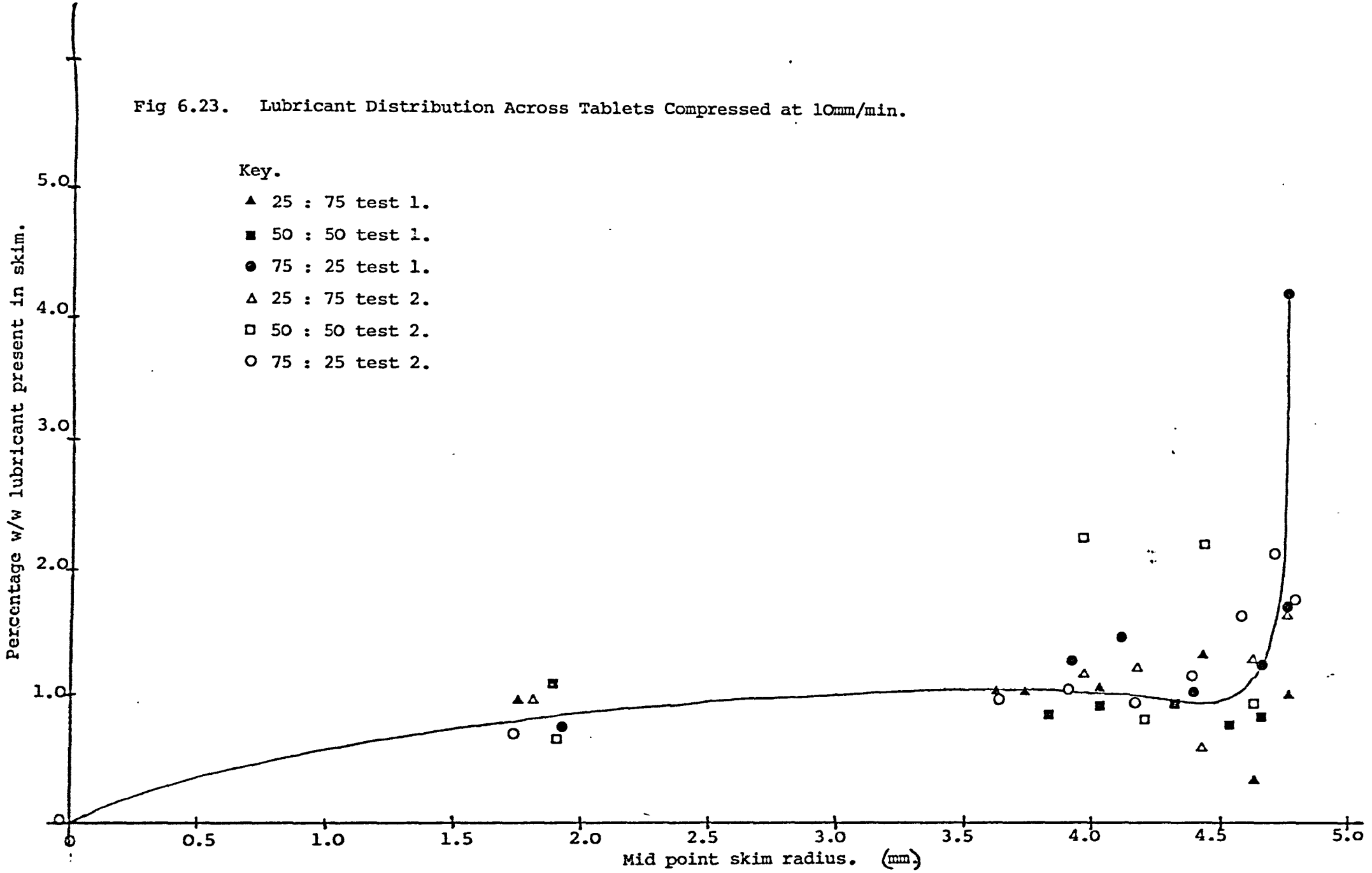


Fig. 6.24. Lubricant Distribution Across Tablets Compressed at 1000mm/min.

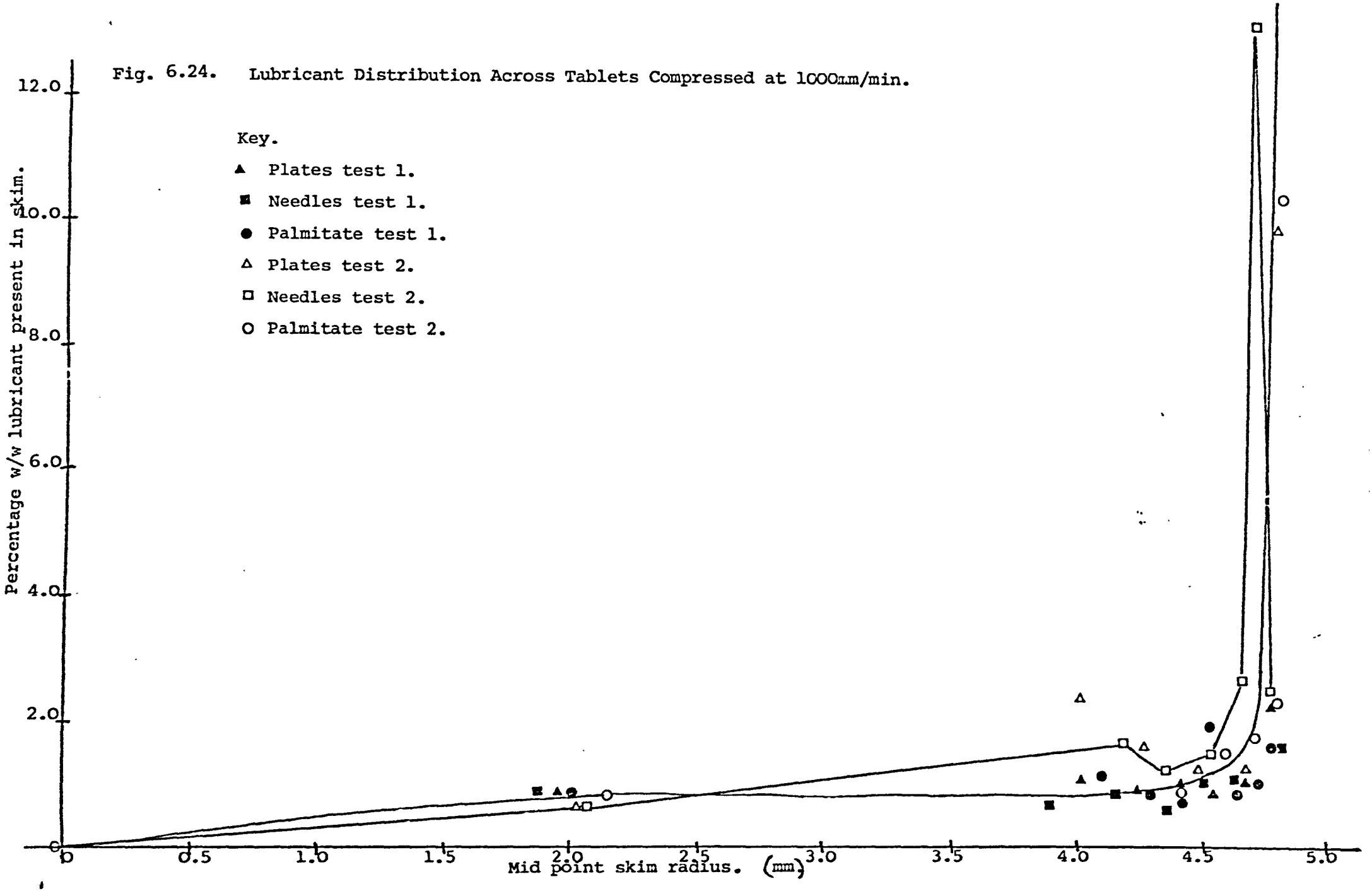


Fig. 6.25. Lubricant Distribution Across Tablets Compressed at 1000mm/min.

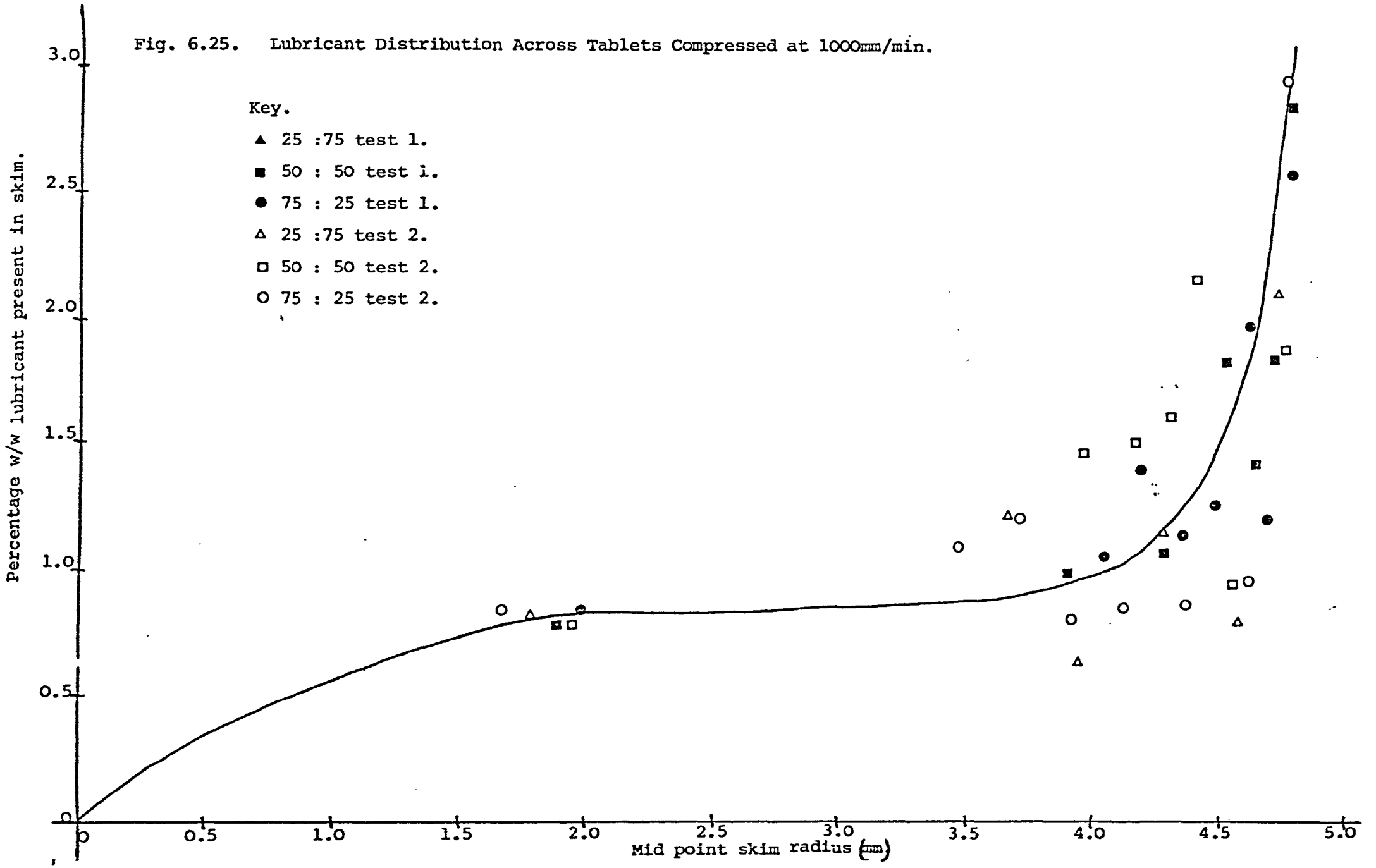
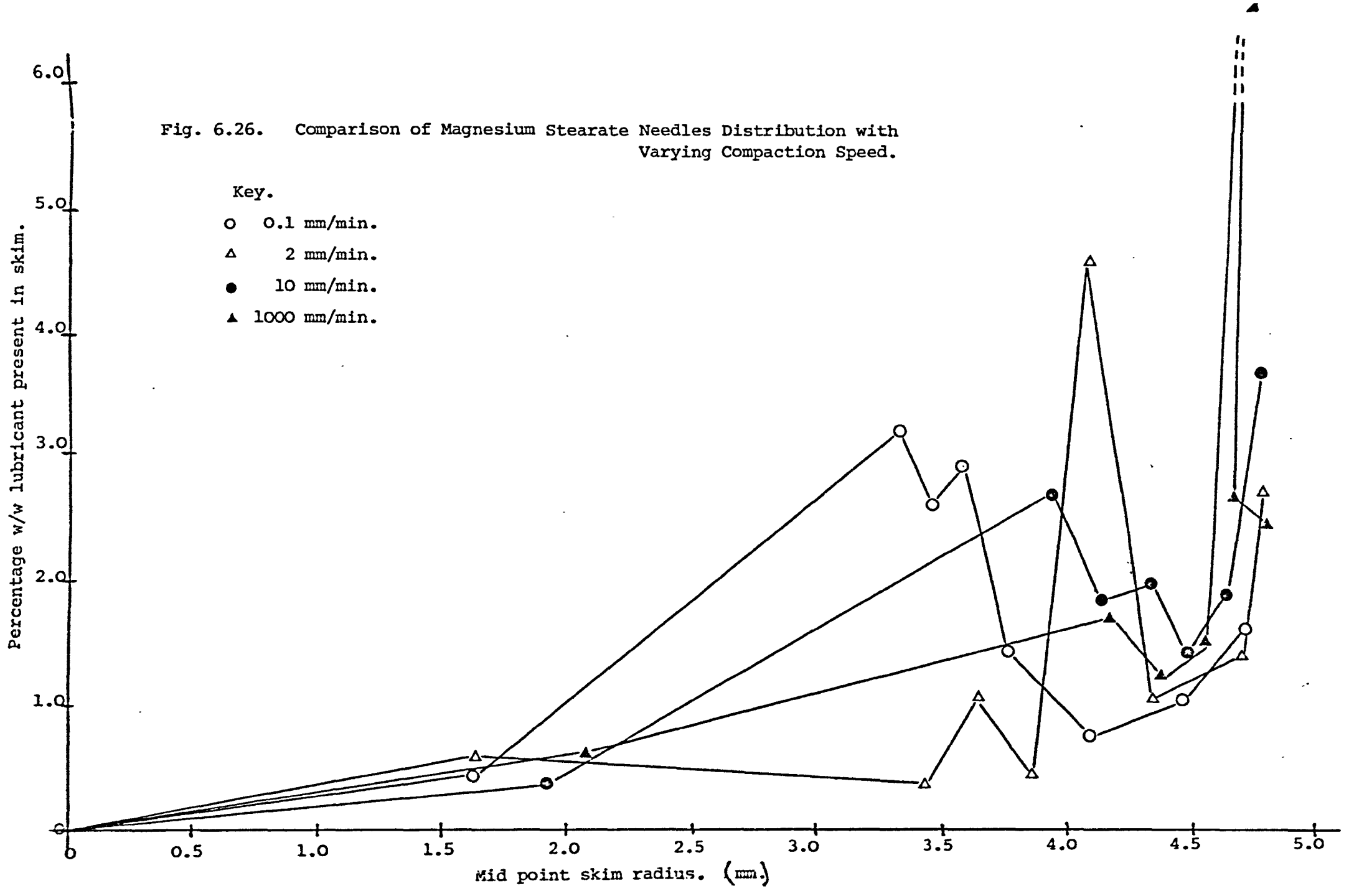


Fig. 6.26. Comparison of Magnesium Stearate Needles Distribution with Varying Compaction Speed.



shaped plate-like material of which the other 5 lubricant batches were composed. Comparison of lubricant distributions of the plate-like materials at different compaction speeds (Fig. 6.27. Fig. 6.28.) showed that in fact there was no significant difference between the curves , and thus it was concluded that the lubricant distribution was unaffected by rate of compaction.

Comparison of these curves with those for the commercial batches of magnesium stearate showed that the commercial batches of magnesium stearate and the laboratory prepared samples (except the needle material) redistributed themselves in the tablet in a similar manner during the consolidation process.

6.3. Summary.

Simple tests indicated that different batches of magnesium stearate would leave different amounts of lubricant on the die wall after compression of a lubricated sample, and blowability tests indicated that this could be related to the ease of wafting of lubricant through the powder bed during expulsion of the entrapped air during consolidation. Blowability was found to show a high degree of correlation with lubricant ability and so it was hypothesized that the greater the amount on the die wall (the easier the lubricant could be wafted there), the better the lubricant ability. E.S.C.A. analyses of the top 30Å of the tablet surface tended to confirm this hypothesis, the more efficient lubricants containing a higher percentage of magnesium stearate in the surface layer. However, evaluation of the amount of lubricant remaining on the die wall after tableting indicated that there was no relationship between the amount of lubricant and lubricant ability. Compaction speed was not found to increase the amount of lubricant wafted to the die wall as was expected.

Fig. 6.27. Effect of Compaction Speed on Lubricant Distribution Across a Tablet for pure Stearate and Palmitate Plates.

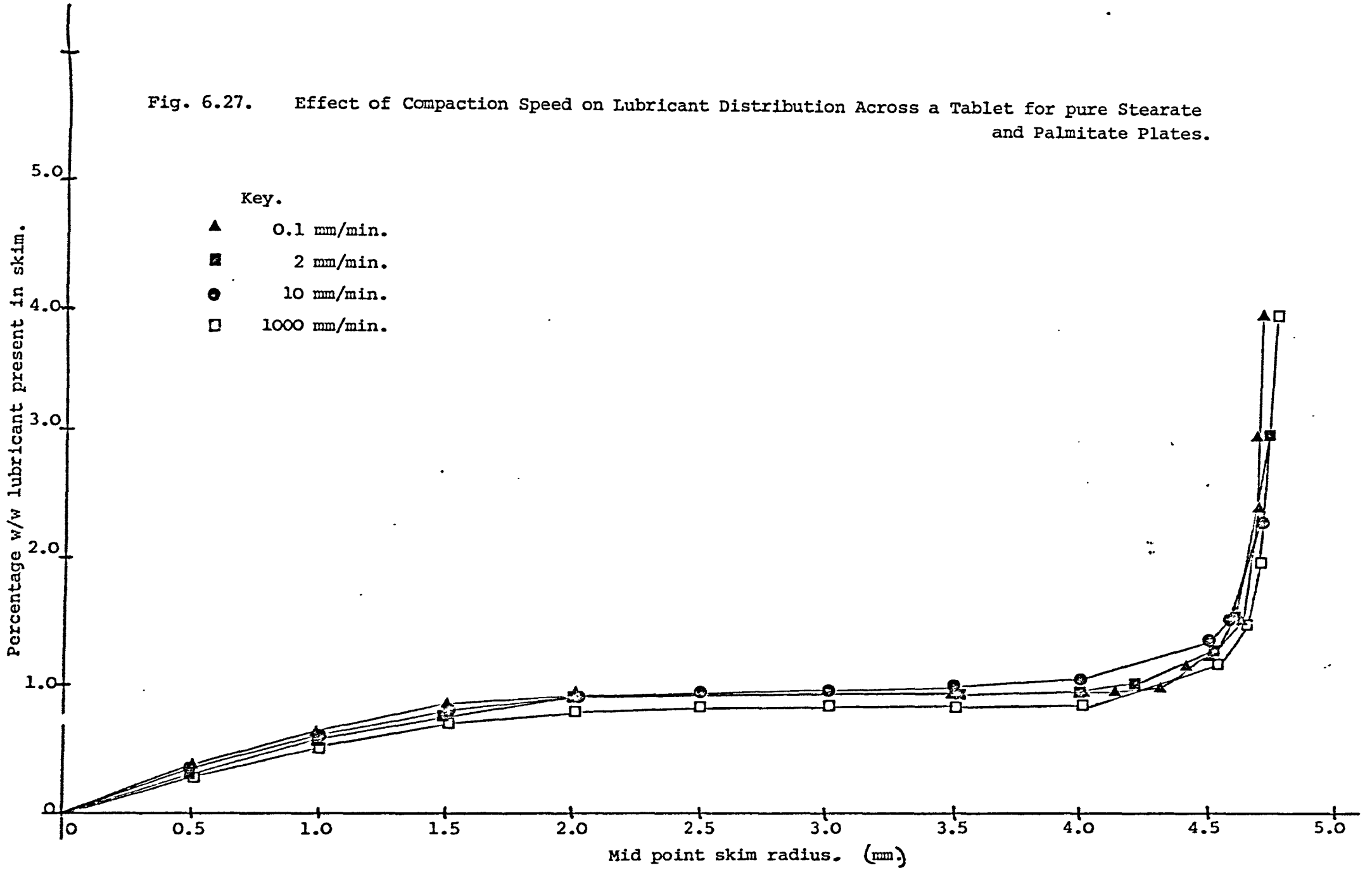
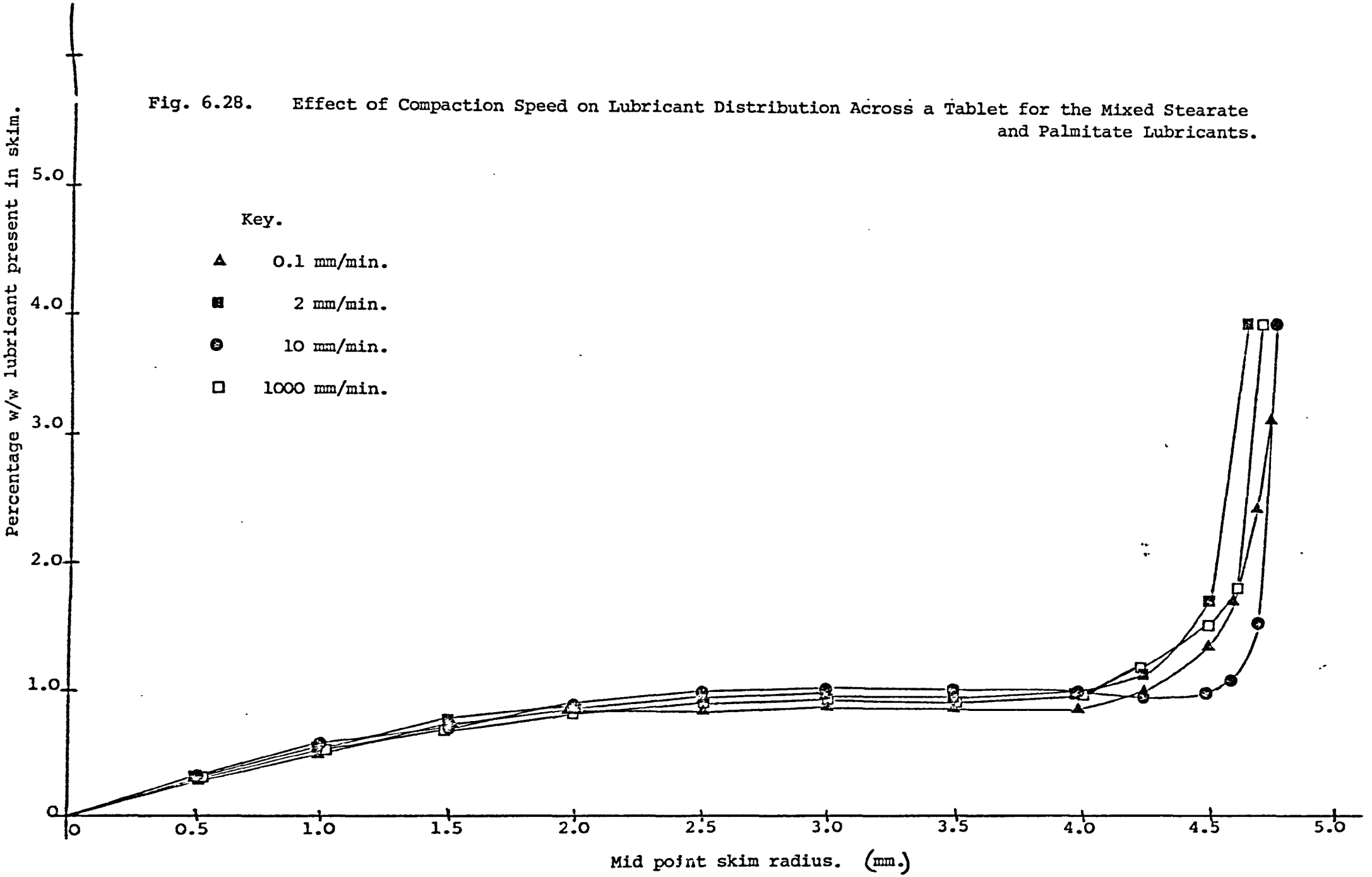


Fig. 6.28. Effect of Compaction Speed on Lubricant Distribution Across a Tablet for the Mixed Stearate and Palmitate Lubricants.



Analysis of the actual distribution of magnesium stearate in the tablet after the tableting process proved that the lubricant material was wafted through the powder bed during consolidation, and a definite lubricant gradient was established across the tablet. At 1% lubricant concentration originally present in the powder, the amount of lubricant in the centre of the tablet was below 1% gradually increasing to slightly more than 1% at approximately 4.5 mm from the tablet centre. The lubricant concentration then rose rapidly to 10% or more within the outer 0.2mm of the tablet. The nearer to the tablet surface the lubricant concentration was determined, the higher the percentage lubricant concentration that was recorded. This distribution behaviour, however, did not depend upon the lubricant batch tested, that is, it was not related to lubricity ability, and was not affected by compaction speed. Thus the amount of lubricant wafted through the powder bed during its consolidation is the same, irrespective of the speed at which the wafting takes place. The one exception was the needle material which did show a distribution dependency upon compaction speed, thought to be due to the needle shape of the lubricant particles. However, at 1000mm/min the hindering effect of the needle shape was overcome and this material then behaved in a similar manner to all the other investigated magnesium stearate batches.

Thus it would appear that magnesium stearate is wafted through the consolidating powder bed to the die wall surface to exert its lubricating effect, the latter being the same whether slow speed or high speed tableting was performed. Under the testing conditions described here, the extent of this process appears to be the same for each lubricant batch examined. However, as indicated by E.S.C.A. analyses, it could be that the distribution in the outermost few

angstroms of the tablet surface could be indicative of the relative lubricity ability. It would be expected that magnesium stearate concentrations within this region would be very high.

CHAPTER 7. WORK WITH LUBRICANTS OTHER THAN MAGNESIUM STEARATE.

Although most of the work involved investigation of the behaviour of magnesium stearate, polytetrafluoroethylene, stearic acid and sodium and zinc ricinoleate were also investigated.

7.1. Lubricant Materials Compressed Alone.

Lubricity evaluations of the lubricant materials alone were attempted using the test as described in section 2.1. However, sodium ricinoleate adhered so strongly to the punch surfaces that in trying to remove the punches the tablet was moved in the die. This of course meant that the subsequent ejection energy reading would be inaccurate. Therefore the basic test was modified. The punch used as the top punch was now used as the bottom punch for the compression process. For ejection, the entire punch and die assembly was reversed so that the situation was basically the same as that for the original test. The ejection energy value now measured the energy for ejection of the lubricant tablet together with the lower punch. To enable comparison of these lubricants with commercial magnesium stearate, it was necessary also to evaluate the magnesium stearate batches using this modified method. Results are summarized in Table 7.1.

The ejection energy values are higher than previously, as expected, but the relative lubricity ability of the magnesium stearate batches is unchanged, confirming that modification of the lubricity test does not significantly affect the results. Comparison of the other four lubricants with the commercial stearates leads to the conclusion that polytetrafluoroethylene and sodium ricinoleate are better lubricants than magnesium stearate, stearic acid is approximately the same lubricity, but zinc ricinoleate is a poorer lubricant. However, as shown in chapter four, lubricant alone tests may not be a reliable guide

TABLE 7.1. EJECTION ENERGY[a] MEASUREMENTS FOR VARIOUS LUBRICANT BATCHES ALONE AND IN 'ADMIXTURES'

Test	Lubricant.										
	Sodium Ricinoleate	P.T.F.E.	Zinc Ricinoleate	Stearic Acid	Magnesium stearate Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7
Material compressed alone	663	weight of the top punch.	2264	1477	1406	1376	1387	1992	1416	1912	1264
Lubricant 1% in lactose	7919	13000	10243	11486	5651	3036	4612	4434	4456	2674	2524
Lubricant 3% in lactose	4396	7977	5413	5659	3339	1774	2823	1964	2610	1678	1443

a = Ejection energy measurements are in Jm^{-2}

Ejection energy of lactose material alone is $15000Jm^{-2}$.

to lubricity behaviour in practice.

7.2. Lubricants One Percent in Lactose.

Samples were prepared as described in section 2.3.1. and tested using the established Instron test (section 2.1). Results are summarized in Table 7.1. From these results it can immediately be established that the presence of the excipient drastically influences practical lubricant efficiency, all four lubricants producing ejection energy values greater than those obtained for the poorest batches of magnesium stearate. From lubricant alone tests polytetrafluoroethylene would be expected to be a very efficient lubricant, but in the presence of lactose it virtually has no lubricant action. Stearic acid also has a very poor practical lubricant efficiency. As observed with the magnesium stearate batches, there is no relationship between relative lubricant efficiency of material compressed alone and in admixture with lactose. Polytetrafluoroethylene is the best lubricant alone, and worst when tested with lactose but sodium ricinoleate which is second most efficient alone, is the most efficient lubricant of these four in the presence of lactose. Magnesium stearate, however, is still the most effective lubricant in the presence of lactose (Table 7.1).

7.3. Lubricants Three Percent in Lactose.

The samples were prepared and tested as described in section 7.2 using 3% of lubricant instead of 1%. Results are summarized in Table 7.1. As expected the values for ejection energy are lower than for 1% concentrations and the relative lubricant efficiency order of the four materials is unchanged by the increase in lubricant concentration. Three percent stearic acid and 3% polytetrafluoroethylene are not as efficient as lubricants, as is 1% of the poorest batch of magnesium stearate.

Zinc ricinoleate at 3% is as effective as 1% of the poorest magnesium stearate batch and sodium ricinoleate at 3% is as efficient as 1% of a mediocre batch of magnesium stearate. However, even at 3% concentration, none of the lubricants are as efficient as 1% of a good batch of magnesium stearate.

From the investigations into batch variation of magnesium stearate it is highly probable that batch variation will occur with polytetrafluoroethylene, stearic acid, sodium ricinoleate and zinc ricinoleate, so that the ejection energy values obtained in this particular investigation may not be reproduced exactly if different batches are used in succeeding investigations. However, although the relative lubricity efficiency of these four lubricants may be changed, at 1% concentration they will always be poorer lubricants than 1% of a good batch of magnesium stearate.

An investigation of two batches of stearic acid confirms that variation in batches does exist, the results being summarized in Table 7.2.

TABLE 7.2. VARIATION IN STEARIC ACID BATCHES.

	Stearic Acid Sample	
	Batch 1	Batch 2
Ejection energy of material alone in Jm^{-2}	701	2251
Ejection energy of material 2% in lactose in Jm^{-2}	9182	7350

As can be seen from these results, one batch is as efficient a lubricant as magnesium stearate alone, whereas the other is much poorer, but both batches at 2% concentration are much less efficient as lubricants than any batch of magnesium stearate.

7.4. Blowability Tests.

The ease with which these lubricants could be wafted through a powder bed during compaction (used as a measure of lubricity ability) was estimated using the blowability test (section 2.6) and compared with results obtained for commercial magnesium stearate batches. Results are summarized in Table 7.3.

TABLE 7.3. ESTIMATION OF EASE OF MOVEMENT OF LUBRICANTS IN POWDER BED.

Lubricant Batch	Sodium Ricinoleate	Zinc Ricinoleate	P.T.F.E.	Stearic Acid
Mean 'blown' distance	32.58cms	32.50cms	34.67cms	35.83cms

The blown distances of these four lubricants, when compared with the commercial magnesium stearate values, indicated that these lubricants are as effective if not more efficient lubricants than any of the magnesium stearate batches. However, this conclusion is not supported by lubricity test evaluations, which indicate that all the lubricants are less efficient than any magnesium stearate batch at the same concentration.

Thus it would appear that this test is only suitable for evaluating lubricity of different batches of the same lubricant and not suitable for comparing different materials. Thus it would appear that blowability is more dependent upon such factors as particle size as suggested in section 6. Since particle size is related to lubricant behaviour, blowability could be used to estimate lubricity in a similar manner to particle size but is quicker and simpler to measure.

7.5. Summary.

The four lubricant materials, polytetrafluoroethylene, stearic acid, sodium ricinoleate, and zinc ricinoleate, are less efficient as lubricants than the poorest batch of magnesium stearate, at the same concentration. Polytetrafluoroethylene and sodium ricinoleate, however, show a greater inherent lubricity than any magnesium stearate batch. Thus the change of lubricity behaviour of lubricant tested alone compared with admixture in lactose is not a phenomenon of magnesium stearate alone but applies to other lubricants. This phenomenon has also been observed by Hölzer (217). Thus lubricant alone tests are not a reliable guide to practical lubricant efficiency.

In addition the simple blowability test for predicting lubricant efficiency was shown to be of limited value. It can be used to distinguish between different batches of the same lubricant but not between different lubricants. It is probably a measure of particle size rather than lubricant ability.

CHAPTER 8. CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER WORK.

8.1. Conclusions.

The use of the Instron (model 1122) as an investigational technique for evaluation of lubricity of lubricants by measurement of ejection energy values was found to be extremely satisfactory.

Tests on lubricant material alone indicated that the lubricity of commercial magnesium stearate did vary according to the batch used and that the batches could generally be arbitarily classified into poor, mediocre and good. However, tests on lubricant material 1% admixtures with lactose, whilst indicating batch variation in lubricity, also produced a different lubricity rank order for the batches. There was no correlation between the two relative lubricant ability orders. Other excipients such as Dicalcium phosphate dihydrate and cornstarch 1% admixtures with the lubricant batches showed similar results to those obtained with lactose admixtures. Obviously the actual presence of the excipients significantly altered the relative lubricity order but the nature of the excipient used, did not significantly influence this rank order. Dicalcium phosphate dihydrate and cornstarch undergo brittle fracture and plastic deformation respectively during compaction, and whilst the influence of lubricant upon ejection energy of the admixtures is different, the relative lubricant ability is not significantly altered. Thus it was hypothesized that the lubricant alone tests indicated the inherent lubricity of a magnesium stearate sample but other parameters modify the extent of expression of this lubricity, the practical lubricity efficiency obtained, being indicated by the admixture tests. Since, in practice, tablet formulations contain several other excipients besides lubricant, the admixture tests are a more accurate guide to probable lubricant behaviour in production.

The modification of the rank order of relative lubricity ability of the magnesium stearate batches by admixture with excipients is not just a phenomenon of magnesium stearate alone but applies to other lubricants. The other four lubricant materials investigated, polytetrafluoroethylene, stearic acid, sodium ricinoleate, and zinc ricinoleate, were less efficient as lubricants than the poorest batch of magnesium stearate at the same concentration, but polytetrafluoroethylene and sodium ricinoleate showed a greater inherent lubricity than any magnesium stearate batch.

The relative lubricity order for the lubricants tested alone could not be changed to that obtained for the admixture tests by using a pre-lubricated die (ejection energy values decreased similarly for each batch) or by increasing the lubricant concentration up to 10%. The presence of the excipient therefore has a marked influence on lubricant ability.

The shape of the ejection energy curves obtained from the admixture tests showed correlation with the lubricity order, in that the more pronounced the secondary peak, the greater the elastic recovery of the tablet in the tapered outlet of the die and the better its lubricity ability. Graphs of the rate of removal of magnesium stearate from the die wall, as determined by ejection energy values for sequential lactose alone compressions, indicated that the lubricant appears to move to the die wall and fill any asperities present at the tablet die-wall interface to give monolayer and multilayer film formation.

Micronization of magnesium stearate batches, in general, tends to decrease lubricant material alone ejection energies except for large plate-like crystalline material, for which an increase in ejection energy may be observed. Manufacture and examination of

pure magnesium stearate (plate-like and needle crystals), magnesium palmitate and 25 : 75, 50 : 50, and 75 : 25 stearate : palmitate mixtures led to the conclusions that a 25 : 75 stearate to palmitate mixture lubricant was the most efficient magnesium stearate batch to use for lubricity purposes. Pure magnesium palmitate was shown to be more efficient than pure magnesium stearate whilst for the mixed lubricants, increasing the stearate content, decreased the lubricant efficiency. It therefore appeared that magnesium palmitate was a more efficient lubricant than magnesium stearate but the presence of a small amount of impurities in the form of magnesium stearate, enhanced the lubricity efficiency. These lubricant mixtures were not just physical mixes of the two esters but a more complex structure of the two since a physical mix of the two esters had a higher ejection energy than the manufactured mixture. It was thought that the stearate impurity could be responsible for the small particle size of the 25 : 75 stearate to palmitate lubricant, compared with the large plate-like crystals obtained with pure magnesium palmitate. This small particle size of the 25 : 75 mixture lubricant appears to be an inherent property of the material. The ratio of stearate to palmitate in the magnesium stearate batch does therefore influence lubricant ability but this can be overshadowed by other parameters such as particle size. It was noted that the solidification temperature of the fatty acids obtained by acid hydrolysis of the magnesium ester, exhibited a relationship to lubricity ability that was similar to that seen between the stearate to palmitate ratio in the lubricant and the lubricant ability. Therefore the lubricity could be dependent upon the relative ease of softening of the lubricant during tableting. Although there appeared to be very little correlation between assay value, percentage moisture loss and bulk density values, and lubricant ability, there was a high degree of correlation

between particle size and surface area and practical lubricant efficiency. The smaller the particle size and the larger the surface area, the more efficient the lubricant. The particle size and surface area values were those for the original magnesium stearate material but examination of these two parameters after mixing with excipient indicated that the particle size distribution of the lubricant material could drastically alter, and the greater the percentage of small particular material (i.e. $< 5.0\mu m$) after the mixing process, the more efficient the lubricant. For good practical lubricity efficiency it would appear that the magnesium stearate batch should be of small particle size i.e. 80% or more particles below $5.0\mu m$ or readily undergo breakdown during the mixing process, without agglomeration, so that it can be uniformly dispersed through the tablet mix. S.E.M. investigation of mixtures and tablets containing representative batches of magnesium stearate (good, poor, and mediocre relatively) and examination of the lubricant material extracted from the mixtures and tablets could be used to explain variations in lubricity efficiency. Some of the poorer batches tended not to undergo uniform mixing or readily breakdown during mixing, whilst the more efficient lubricants appeared to be more uniformly mixed and break down more readily during mixing. They also tended to move to the die wall to a greater extent during tableting, and often showed signs of having been smeared during the ejection process.

To summarize, it appeared that with poor batches, the lubricant particles tended to be clumped together and were angular after the mixing and tableting processes whereas with the good batches, the lubricant particles tended to be more separated and uniformly dispersed during mixing and show evidence of smearing or rounding off of the crystal edges. Particles of mediocre batches tended to show a

combination of these two extremes.

During mixing a low shear strength is advantageous so that the lubricant material will readily smear over the excipient to form a lubricant film. Needle material appears to be more efficient than laminar material since it appears to be more susceptible to deformation during compaction, indicative perhaps of a lower shear strength.

Overall it would therefore appear that the fatty acid composition of a magnesium stearate batch, pre-determines its inherent lubricity but the mixing and tableting processes play a major role in determining the extent of the expression of that lubricity, practically.

It appeared that the lubricant material migrated through the tablet matrix to the tablet surface-die wall interface during compaction and it was expected that the greater the ability of the lubricant to migrate then the greater its lubricant efficiency. Simple blowability tests confirmed that the more efficient magnesium stearate batches could be wafted further by an air jet, than the poorer batches, showing a high degree of correlation between the lubricant ability and blown distance. The results also implied that a simple test such as blowability could be used to determine the lubricity of a batch of magnesium stearate prior to production runs. However, there was also a high degree of correlation between blowability and particle size of the lubricant material and therefore it seemed highly probable that it was the relationship between lubricity and particle size which was being reflected by the blowability tests. Use of the test for the other four lubricant materials investigated proved the blowability test to be of limited value since it failed to distinguish between magnesium stearate and the other lubricant materials. Thus it was finally concluded that the blowability test could be of use to predict relative lubricity efficiency of different batches of the same lubricant

but not between different lubricants, due to the correlation between lubricity ability, lubricant particle size and blowability.

Neverless E.S.C.A analyses confirmed that tablets lubricated with the more efficient batches of lubricants contained a higher concentration of lubricant at the tablet surface than did tablets lubricated with the less efficient batches of lubricant. Also tablet surfaces which had been subjected to the ejection process showed higher lubricant concentrations than those not subjected to the ejection process. However, evaluation of the amount of lubricant remaining on the die wall after tableting indicated that there was no relationship between the amount of lubricant and lubricant ability. Compaction speed did not increase the amount of lubricant wafted to the die wall as was expected. However, analysis of the actual distribution of magnesium stearate in the tablet after the tableting process proved that the lubricant material was wafted through the powder bed, during consolidation and a definite lubricant gradient was established across the tablet. Using 1% lubricant admixture powder samples, the amount of lubricant in the centre of the tablet was less than 1%, gradually increasing to a little more than 1% at about 4.5mm distance from the tablet centre, and then rising rapidly to 10% or more within the outer 0.2mm.

The closer to the tablet surface that the lubricant concentration was evaluated, the higher the percentage lubricant concentration that was recorded. However, the observed distribution behaviour did not depend upon the lubricant batch tested, that is, it was not related to lubricity ability, and was not affected by compaction speed. Thus the amount of lubricant wafted through the powder bed during its consolidation was the same, irrespective of the speed at which the wafting takes place. The one exception was the needle material

for which distribution within the tablet was dependent upon compaction speed. This was thought to be due to the needle shape of the lubricant particles. However, at 1000mm/min the hindering effect of the needle shape was overcome and the material then behaved in a similar manner to all the other investigated magnesium stearate batches.

Thus it appears that magnesium stearate is wafted through the consolidating powder bed to the die wall surface to exert its lubricant effect. The extent of this process appears to be independent of the batch of lubricant used and the speed at which the tableting process is occurring. The lubricity ability exhibited by the magnesium stearate batch is the practical expression of its inherent lubricity, parameters such as stearate : palmitate fatty acid ratio, particle size, surface area, crystal hardness etc. significantly affecting the extent to which the inherent lubricity (as measured by lubricant alone tests) could be expressed.

8.2. Recommendations for Further Work.

Since this work has shown that, during the tableting process, magnesium stearate migrates to the die wall, to exert its lubricant effect, and that the lubricant efficiency is significantly dependent upon particle size of the crystals, it would be reasonable to hypothesize that relative lubricant ability could be determined by the amount of lubricant transferred to the tablet surface - die wall interface. This did not appear to be the case from the skimming analyses but did appear to be true from the E.S.C.A. analyses. Since E.S.C.A. analyses examine only the top 30Å of the tablet surface it could be concluded that any lubricant concentration differences may be seen only in the very outermost layers of the tablet surface and, therefore, several successive E.S.C.A. analyses on the tablet surface from tablets

compacted at various compaction speeds would yield more positive information on magnesium stearate distribution in the critical outer 0.1mm of tablet surface. Particle size analysis of lubricant at different points in the tablet, after compaction at varying speeds, would also indicate how particle size influenced the distribution of magnesium stearate in the tablet during tableting. Alteration of the particle size range, by milling or micronization and examining the resultant lubricant distribution patterns in tablets compacted at various speeds would also provide information about the influence of particle size on lubricity ability.

A concentration of 1% magnesium stearate was used for this work and it could be that this concentration was too high for differences in lubricant distribution in the tablet to be distinguished. Therefore the skimming analyses could be repeated using excipient samples lubricated with 0.25, 0.5, and 0.75% w/w lubricant. It is thought that if the more efficient lubricants are more efficient because they waft to the die wall more easily, then as the lubricant concentration is reduced, there will be a greater distinction between the good and poor lubricants.

Lubricant distribution analyses upon tablets manufactured under normal tablet production conditions could be used to determine the degree of correlation between experimental findings and actuality, and thus establish whether simple simulation tests such as using an Instron or instrumented tablet machines could be used to accurately predict lubricity ability of a batch of magnesium stearate.

Further work on the fatty acid composition of magnesium stearate batches and the relationship to lubricity would determine the best composition for maximum inherent lubricity and enable batch to batch variation to be reduced if manufacturing conditions are more strictly controlled. If a graph of stearate : palmitate ratio and lubricant

ability can be established, then analysis of the fatty acid composition as a quality control test, would enable prediction of lubricity ability of the batch.

If it appears unlikely that lubricant ability can be predicted or batch variation cannot be reduced, then other lubricants could be evaluated, not only for relative lubricity, but also the ability to move through the tablet matrix (distribution in tablet) and degree of batch variability. Ultimately, if a similar problem exists with other lubricant materials as established with magnesium stearate, which is highly probable, then an investigation of a) methods to apply lubricant to the die wall only or b) techniques which will enable elimination of lubricants completely, would be required.

APPENDIX 1. INSTRON WORK.

1.1. Validation of Instron Test.

Initial tests using the Instron (section 2.1.) gave rise to two major problems, namely inefficient die cleaning and excessive variability in results. Therefore preliminary work was carried out to overcome these problems.

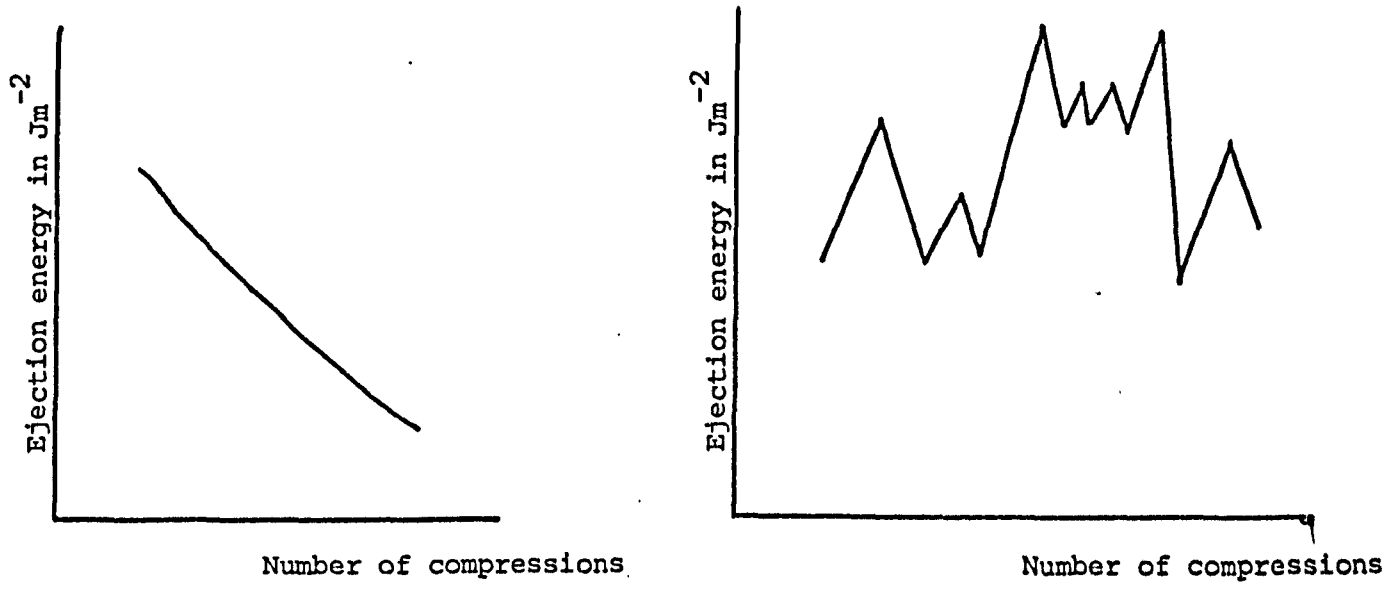
1.1.1. Choice of Ejection Energy as Evaluating Parameter.

A review of the lubricity evaluating parameters was carried out (section 1.9.2.3.) Since ejection energy measurement, which can be readily evaluated by the Instron, will differentiate between similar lubricants and appears to give the best prediction of tendency to stick to the die wall during the entire ejection process, it was chosen as the lubricity evaluating pa_ameter for this investigation.

1.1.2. Die Cleaning.

For comparative purposes each lubricity test was to be carried out in a clean die but removal of the magnesium stearate from the die wall proved a major problem. Many cleaning solvents were used but all proved ineffective as did the cleaning methods employed by other authors, which were also investigated.

Two types of solvent categories were observed. In type A, incomplete removal of lubricant means that each succeeding compression occurs in a partially lubricated die whereas in type B, lubricant is removed in an inconsistent manner. Several compressions of lactose material alone, successfully cleaned the die but was a slow and tedious process. Eventually an acetone and water combination was found to be effective and therefore adopted as the cleaning method.



A.Cleaning solvent Acetone

B. Cleaning solvent D.M.S.O.

Fig. A1.1. Graphs of ejection energies of successive samples when varying cleaning solvents are used.

1.1.3. Variability in Results.

Several factors thought to be contributory to the excessive variability, were investigated.

Humidity was measured at varying times throughout the day (section 2.5) Variation was ±3%. Graphs of humidity against ejection energy showed no relationship between these two parameters over the small range recorded. Increasing ejection speed results in an increase in variability. A sample weight variation of 200 ± 0.2mg had been observed but upon investigation, samples up to 0.5mg below nominal weight produced no difference in ejection energy compared to 200mg samples. Variation in lubricated samples would be produced by inefficient sample mixing but G.L.C. tests indicated that samples were uniformly mixed (Appendix 2.2). Variability of lubricated samples was reduced to below ±10% by establishing an effective solvent die cleaning system (Appendix 1.1.2.). Ejection energies of lactose only samples were also investigated.

When a specified size fraction (90 to 125μm) of lactose was compared with material sieved below 22# (600μm), the variability in ejection energy values increased from ±6% to ±12%. A repeat test confirmed this result.

Since a variability of ±5% to ±10% was obtained with lactose only tests, it was concluded that this variability was due to the sensitivity of the Instron, a sensitivity necessary, however, to distinguish between magnesium stearate batches.

1.2. Calculation of Compaction Pressure.

For the calculation of compaction pressure it is necessary to know:-

1. The full scale load range.....500kg
2. Diameter of the top punch.....9.468mm
3. Kilogram force to Newtons conversion factor.....9.807
4. One Mega Pascal (MPa) is equivalent to one Mega Newton per square metre(MNm^{-2})

Maximum force that can be exerted = 500 x 9.807 N

= 4903.5N

The force is exerted over the flat surface of the punch;-

Therefore, area of punch face = πr^2 mm^2

= 3.142 x 4.734^2 mm^2

= 70.415 mm^2

= 70.415 x 10^{-6} m^2

Thus:-

Pressure exerted by punch at maximum = $\frac{\text{maximum force}}{\text{punch area}}$ Nm^{-2}

= $\frac{4903.5}{70.415 \times 10^{-6}}$ Nm^{-2}

= 69.64 x 10^6 Nm^{-2}

= 69.64 MNm^{-2}

= 69.64 MPa

However, maximum compaction pressure was not used but 83.3% of this value.

Thus compaction pressure used = $\frac{83.3 \times 69.64}{100}$ MPa

= 58 MPa

1.3. Calculation of Ejection Energy from Instron Readings.

Ejection energy is given by:-

$$E = X\ L\ S \times 9.807 \times 10^{-7}$$

E = Ejection energy in J
X = Integrator reading
L = Maximum full scale load in kg
S = Crosshead speed in mm/min.

Ejection energy values for lubricated and unlubricated samples, however, are quoted per unit area of contact between die wall and tablet surface.

Thus contact area between tablet and die wall is the curved area of the tablet given by:-

Curved area of tablet = πDt

D = Die diameter = 9.468 mm
t = tablet thickness in mm

$$= 29.75t\ mm^2$$

$$= 29.75t \times 10^{-6}\ m^2$$

Thus ejection energy per unit contact area is:-

$$\frac{\text{Ejection energy in J}}{\text{Contact area in } m^2} = \frac{X\ L\ S \times 0.9807}{29.75t}\ Jm^{-2}$$

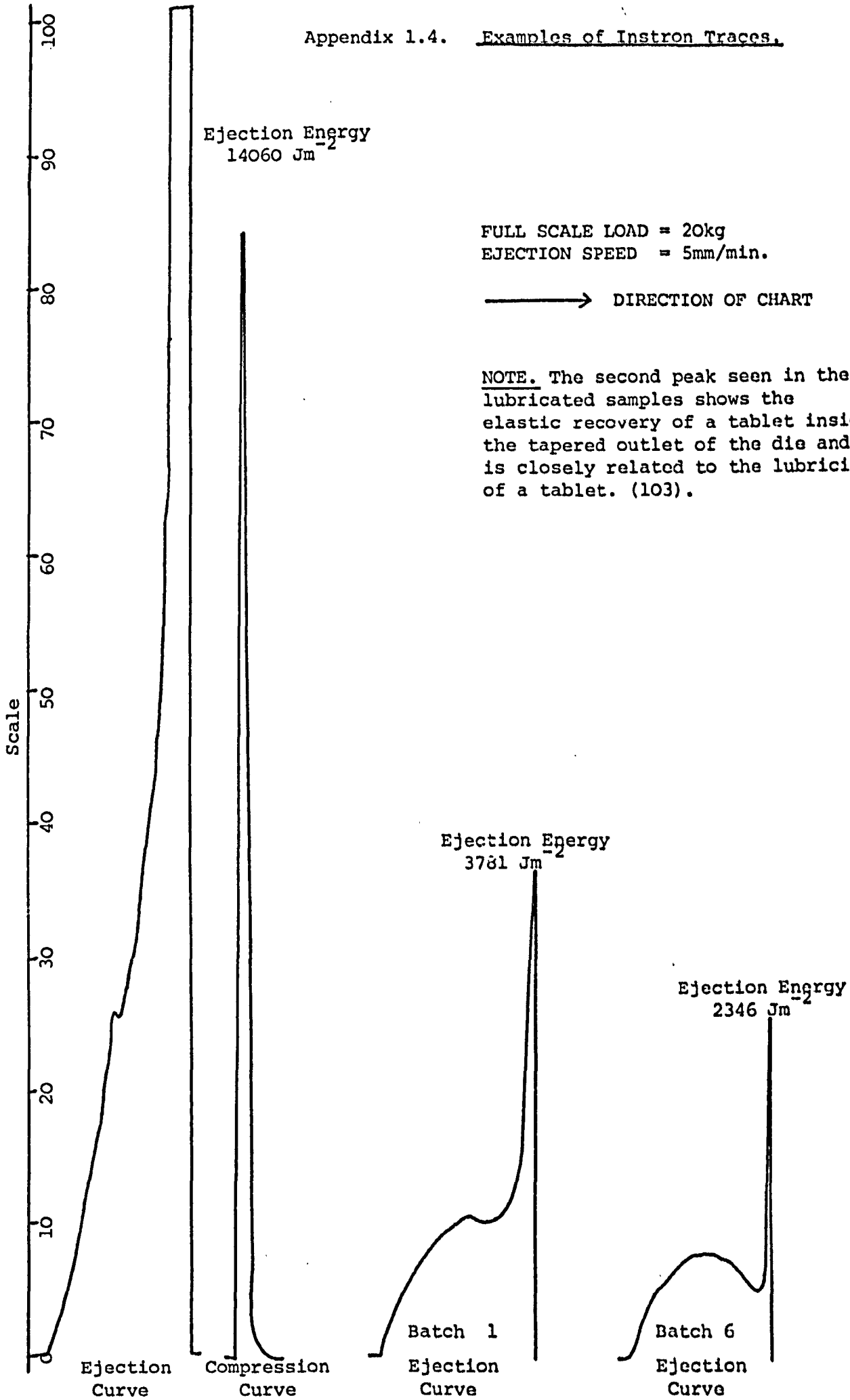
For example:-

Ejection of a tablet of 1% batch 7 magnesium stearate in lactose at 5mm/min. and full scale load 20kg, produced an integrator reading of 1165 units. Tablet thickness was 2.158mm.

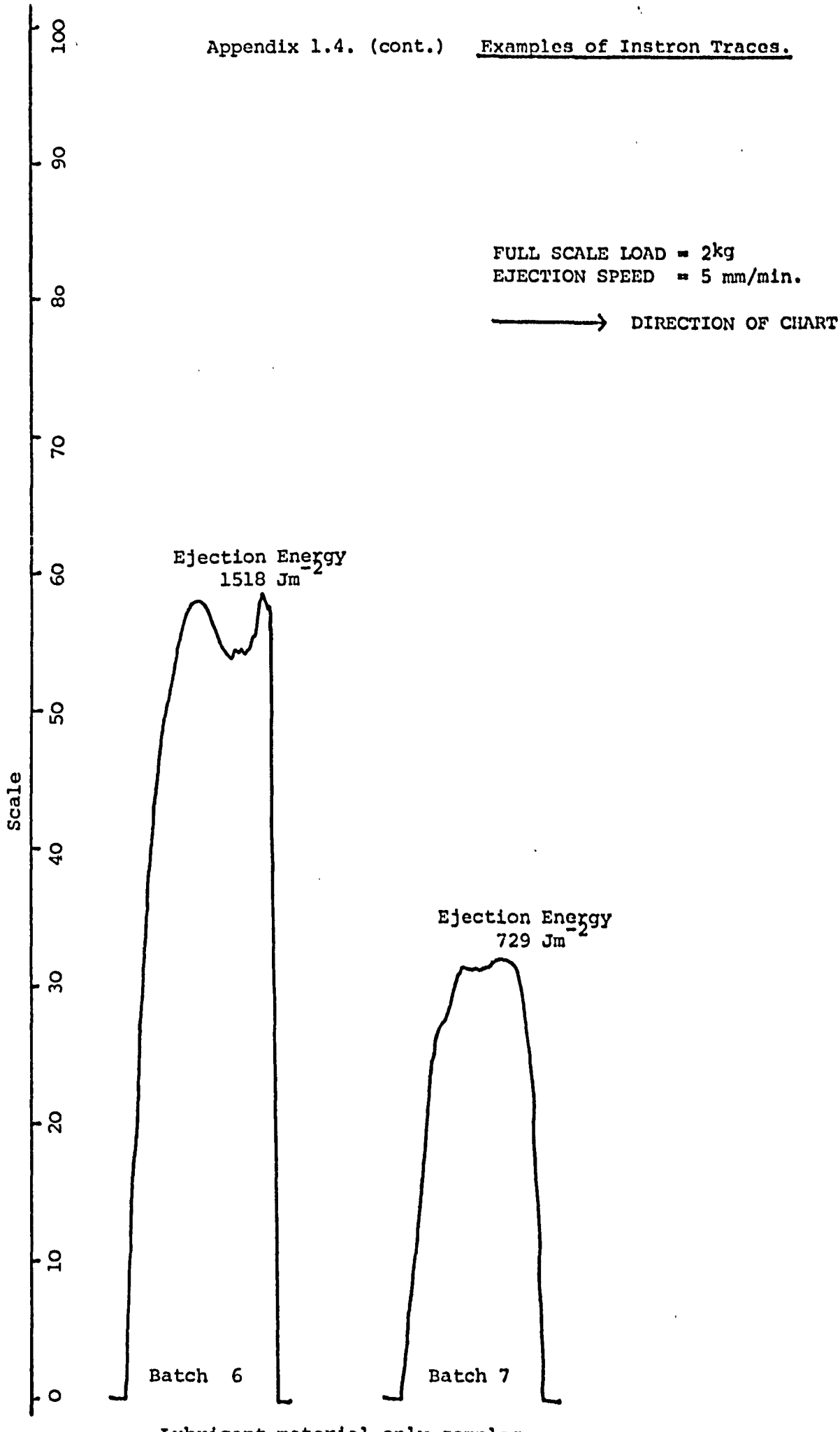
Calculation.

1. Area of contact = $29.75t \times 10^{-6} m^2$ = $64.20 \times 10^{-6}\ m^2$
2. Ejection energy = $1165 \times 20 \times 5 \times 9.807 \times 10^{-7}$ J = 0.1143J
3. Ejection energy per unit contact area = $\frac{0.1143}{64.2 \times 10^{-6}}\ Jm^{-2}$ = 1780 Jm^{-2}

Appendix 1.4. Examples of Instron Traces.



Appendix 1.4. (cont.) Examples of Instron Traces.



Lubricant material only samples

APPENDIX 2. VALIDATION OF MIXING CONDITIONS.

The mixing apparatus described in section 2.3.1. was used.

2.1. To Determine the Effective Lubricant Concentration.

Since G.L.C. tests (section 2.3.2.) indicated 10 minutes mixing time produced uniform mixing of lubricant and lactose, this mixing time was used for this test.

Since in practice magnesium stearate is used in the minimum concentration possible (section 1.6), concentrations of 0.5%, 1.0% and 2.0% were investigated by ejection energy evaluation as described in section 2.1., using a "good" and "poor" lubricant batch as judged by lubricant alone tests (section 4.1.1). The results are summarized in Table A2.1.

TABLE A2.1. MEAN EJECTION ENERGIES IN Jm^{-2} FOR DIFFERENT CONCENTRATIONS OF MAGNESIUM STEARATE IN LACTOSE.

Batch of magnesium stearate	Percentage lubricant present				
	0.0%	0.5%	1.0%	2.0%	100%
C	17100	7859	3216	2221	1500
Variability	±10%	±20%	±10%	±6%	±10%
3	17100	10949	4525	3252	655
Variability	±10%	±20%	±10%	±6%	±10%

It can be concluded that the greater the lubricant concentration the lower the ejection energy and the smaller the variability in results. Based on these results, a 1% lubricant concentration was chosen for admixture tests because a) a reasonable integrator reading is obtained, b) variability of results is within accepted limits (±10%) and c) differences between the ejection energy values for the batches are more marked than at the 2% level.

2.2. Determination of Optimum Mixing Time.

Mixing time is very important (section 1.5.1.2.), the shortest time to produce satisfactory sample lubrication being preferred. Satisfactory mixing means uniform distribution of the lubricant throughout the sample and satisfactory lubricant effect.

Uniformity of mix was investigated by G.L.C. as described in section 2.3. Percentage mix values were calculated as described in Appendix 3.1. Results are summarized in Table A2.2.

TABLE A2.2. PERCENTAGE MIX VALUES FOR VARIOUS MIXING TIMES OF ONE PERCENT LUBRICANT IN LACTOSE.

Mixing time in minutes	Percentage mix values	Range
5	90.10%; 93.60%; 107.9%; 106.5%	17.8%
7.5	93.4%; 94.3%; 105.8%; 106.1%	12.7%
10	99.2%; 100.1%; 100.8%; 99.1%; 99.4%; 101.4%	2.2%

From these results it was concluded that 10 minutes mixing gives a uniform distribution of lubricant.

The effect of mixing time on lubricity efficiency was investigated by ejection energy evaluations of 1% mixes of lubricant in lactose using the Instron (section 2.1). Three representative lubricant batches were used. Results are summarized in Fig. A2.1.

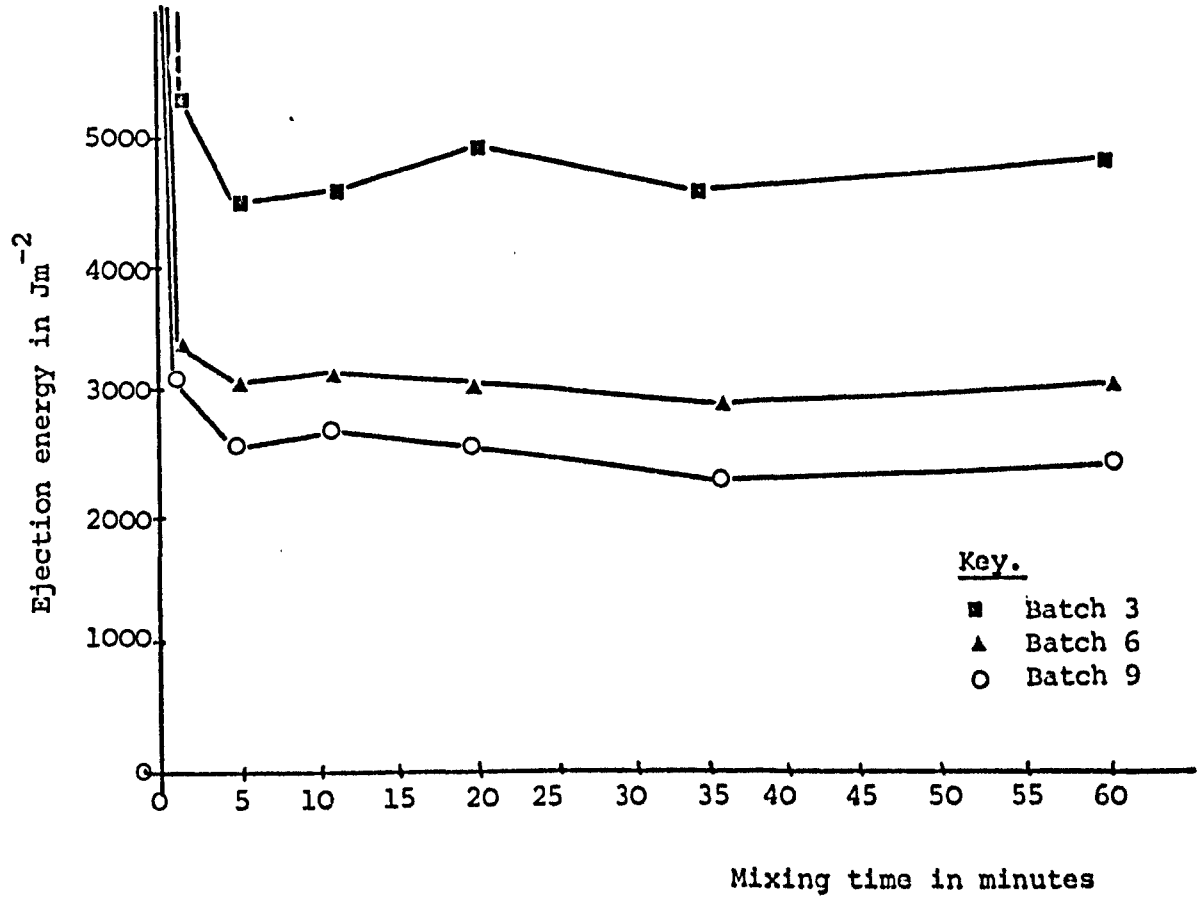


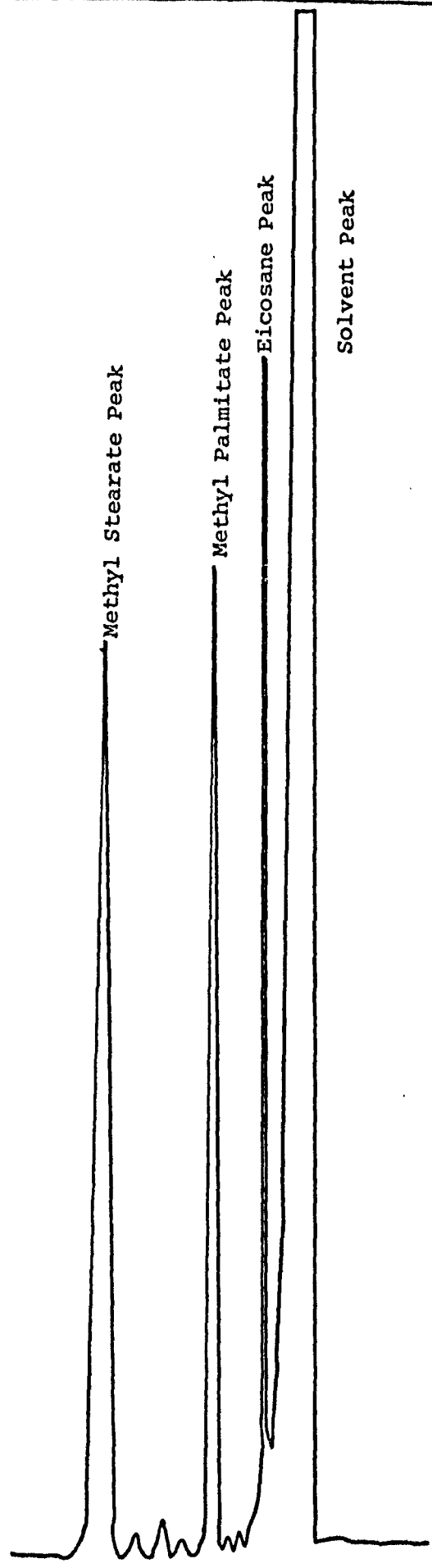
Fig. A2.1. Effect of mixing time on ejection energy for three batches of magnesium stearate.

It was concluded that mixing times longer than 5 minutes do not significantly improve the lubricant efficiency.

Thus a mixing time of 10 minutes at 1% magnesium stearate concentration is a valid combination to use for admixture tests.

APPENDIX 3. GAS LIQUID CHROMATOGRAPHY WORK.

Appendix 3.1. Calculation of Percentage Mix from G.L.C. Traces.



NOTE. Eicosane was used as the Internal Standard.

→ DIRECTION OF CHART.

Fig. A3.1. Typical G.L.C. trace for lubricant assay.

Calculation.

Peak heights of all three peaks for standard and for sample are recorded.

The ratio of stearate to palmitate is given by the ratio of peak heights of the standard, thus:-

$$\text{Amount of stearate in batch} = \text{Percentage of stearate present} \times \text{sample weight of standard.}$$

$$\text{Amount of palmitate in batch} = \text{Percentage of palmitate present} \times \text{sample weight of standard.}$$

Since the volume of standard and sample analysed is not identical sample peak heights are accordingly corrected:-

$$\text{Corrected stearate peak height of sample} = \text{Peak height of sample} \times \frac{\text{Peak height of eicosane standard}}{\text{Peak height of eicosane sample}}$$

$$\text{Corrected palmitate peak height of sample} = \text{Peak height of sample} \times \frac{\text{Peak height of eicosane standard}}{\text{Peak height of eicosane sample}}$$

The amounts of stearate and palmitate in sample can then be calculated:-

$$\text{Amount of stearate in sample} = \text{stearate sample reading} \times \frac{\text{eicosane standard}}{\text{eicosane sample}} \times \frac{\text{weight of stearate in standard}}{\text{stearate standard reading.}}$$

$$\text{Amount of palmitate in sample} = \text{Palmitate sample reading} \times \frac{\text{eicosane standard}}{\text{eicosane sample}} \times \frac{\text{weight of palmitate in standard}}{\text{palmitate standard reading}}$$

Thus the amount of lubricant present in the sample is the amount of stearate plus the amount of palmitate present.

Percentage mix is given by $\frac{\text{Amount of lubricant in sample}}{\text{Expected amount in sample}} \times 100\%$

where the expected amount in the sample is equivalent to 1% of the sample weight.

Appendix 3.2. Calculation of Purity of Laboratory Prepared Lubricants

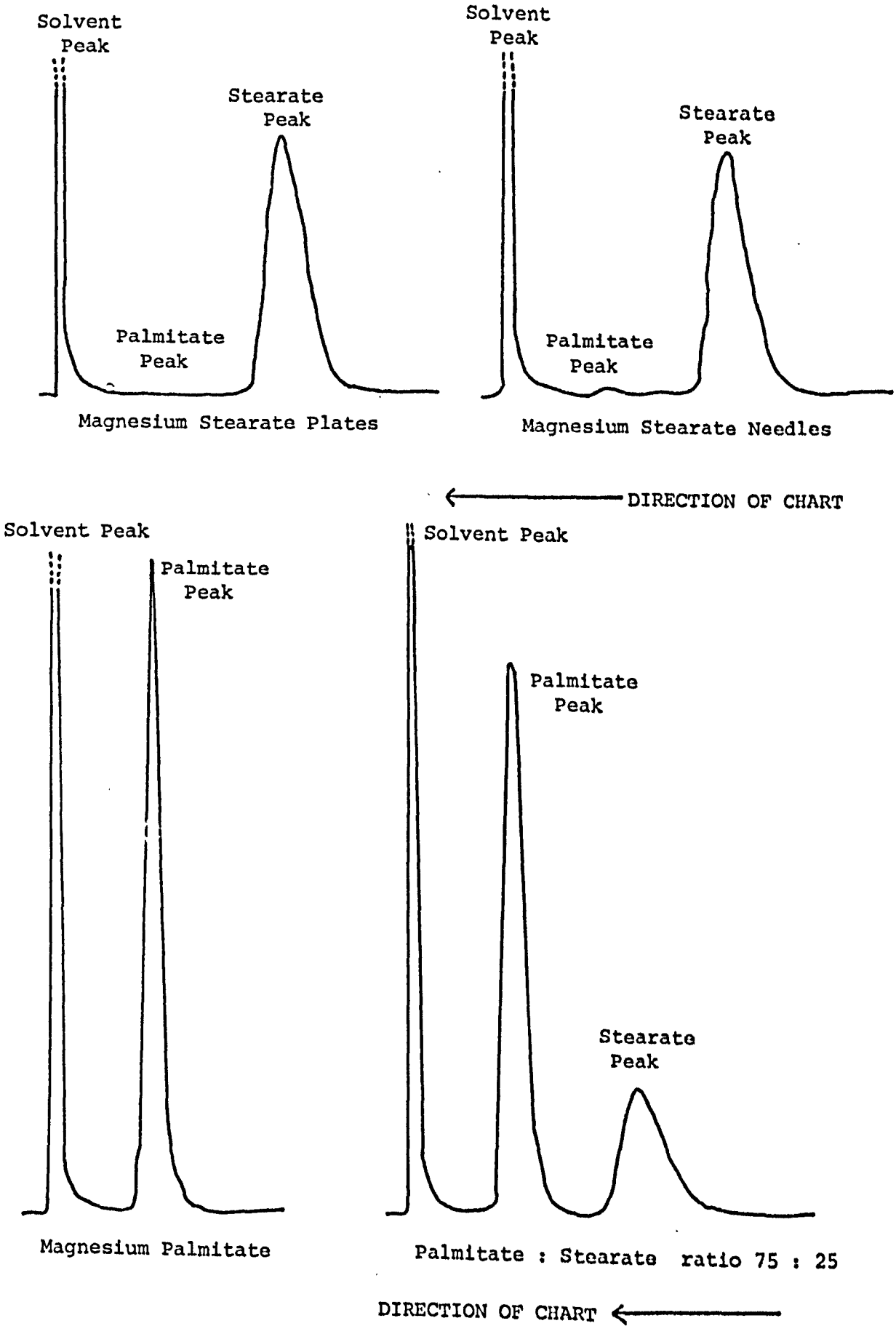


Fig. A3.2. Examples of traces to determine purity.

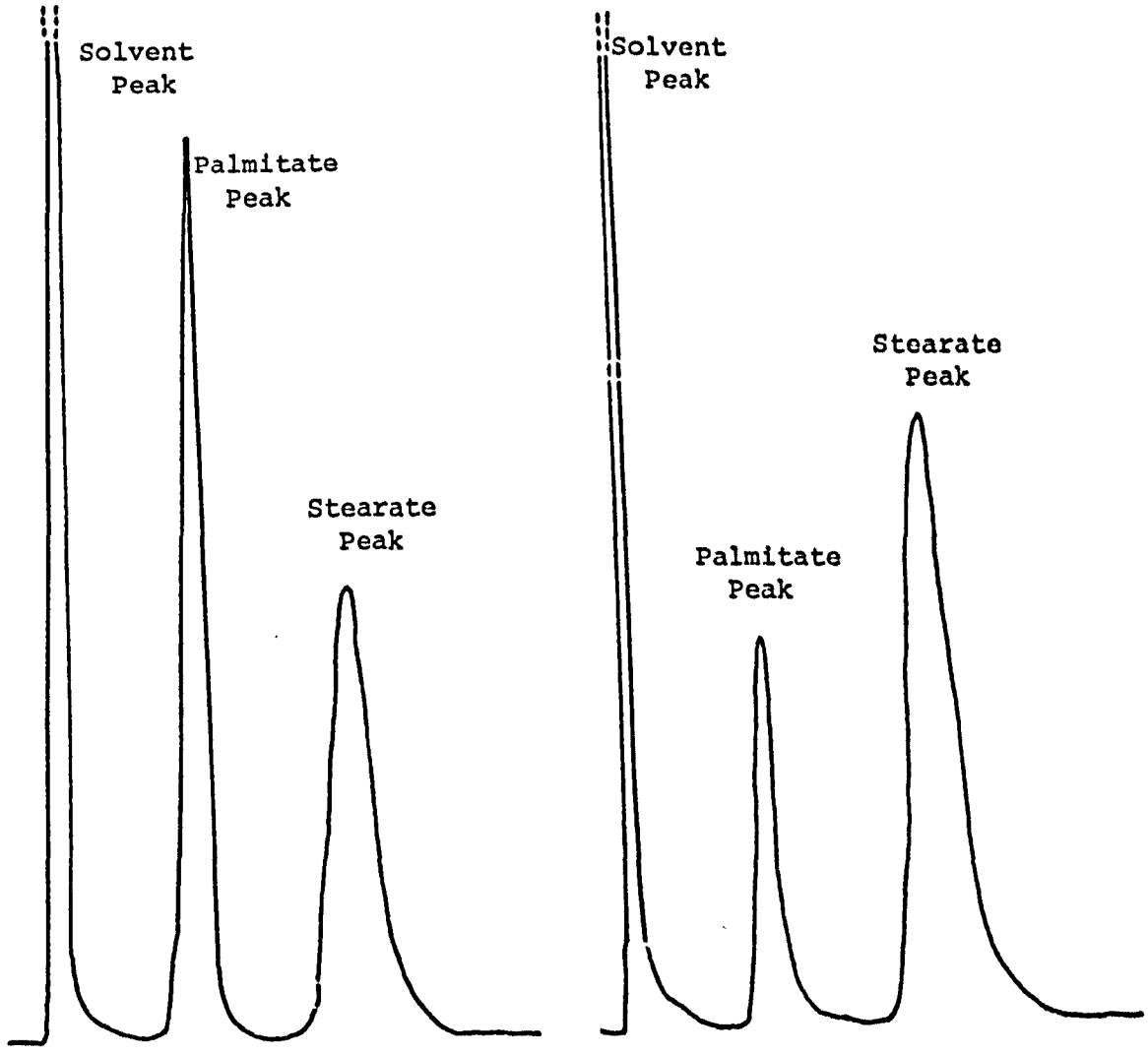


Fig. A3.2. (cont.) Examples of traces to determine purity.

Calculation.

The peaks, for each sample were cut out and weighed, the ratio of peak weights being assumed to be the same as the ratio of the peak areas.

Molecular weights of methyl esters are.....298.5 for methyl stearate
and.....271.0 for methyl palmitate

Therefore ratios were adjusted for molecular weight, thus:-

$$\% \text{ palmitate in sample} = \frac{\text{Peak weight palmitate}}{\text{Total peak weights}} \times \frac{271.0}{298.5}\%$$

$$\% \text{ stearate in sample} = \frac{\text{Peak weight stearate}}{\text{Total peak weights}} \times \frac{298.5}{271.0}\%$$

APPENDIX 4. ATOMIC ABSORBTION WORK.

Appendix 4.1. Validation of Atomic Absorbtion Method.

Appendix 4.1.1. Influence of Presence of Lactose upon results.

Standard solutions of known Magnesium ion concentration were analysed alone, and in the presence of 50mg of lactose.

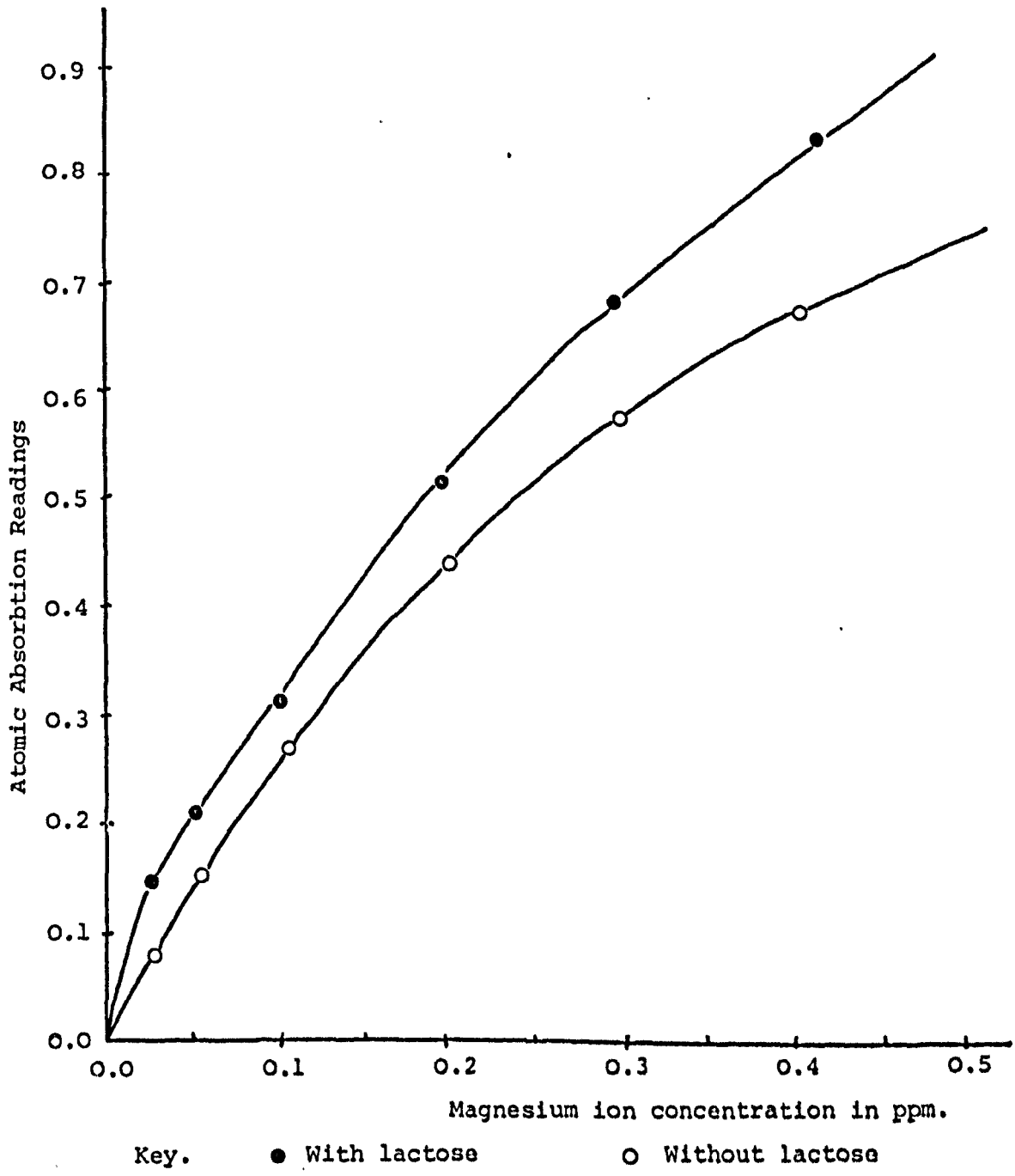


Fig. A4.1. Effect of lactose on calibration Curves.

The mean results from several tests are depicted graphically in Fig. A4.1.

Thus the presence of lactose increases the reading obtained. Therefore standards should always contain lactose unless breakdown factors are being determined. (Appendix 4.2)

4.1.2. Influence upon Readings of the Amount of Lactose Present.

The amount of lactose present in a sample for analysis is inevitably variable due to the sample preparation technique (section 2.4), so this investigation established whether the presence of differing amounts of lactose would influence the results obtained.

A hundred mls of standards representative of the magnesium ion concentration range investigated, were prepared. To 8ml portions of these standards were added varying quantities of lactose and the series analysed by atomic absorbtion. Three determinations were carried out.

TABLE A4.1. INFLUENCE OF LACTOSE ON ATOMIC ABSORBTION READINGS.

Standard conc. in p.p.m.	Atomic absorbtion reading in presence of varying amounts of lactose.					
	None	10mg	25mg	50mg	100mg	None
0.03	0.106	0.217	0.176	0.183	0.220	0.126
0.10	0.235	0.312	0.35L	0.319	0.292	0.260
0.40	0.565	0.742	0.756	0.726	0.765	0.580

From these results it was concluded that:-

a) lactose does increase the readings especially at low concentration of magnesium ion, 0.03ppm values being increased by 50% but only a 28% increase for 0.1 and 0.4ppm standards.

b) there does not appear to be any relationship between the amount of lactose present and the absorption reading although greater variability in results is shown at low magnesium ion concentrations.

Therefore, the samples will not be significantly affected by

variations in lactose content but low concentrations of magnesium ions should be avoided if possible.

4.1.3. Influence of Time on Readings.

A set of standard magnesium ion solutions were analysed at varying times after preparation to determine the effect of time upon reading.

TABLE A4.2. INFLUENCE OF TIME ON ATOMIC ABSORPTION READINGS.

Standard conc. in p.p.m.	Readings obtained at varying times after preparation.				
	Ohrs	1hr	2hrs	3hrs	4hrs
0.5	1.118	1.111	OFF SCALE	OFF SCALE	OFF SCALE
0.3	0.763	0.777	0.794	0.794	0.807
0.1	0.290	0.306	0.319	0.319	0.327
0.05	0.180	0.201	0.198	0.203	0.208
0.03	0.135	0.149	0.145	0.144	0.152

TABLE A4.3. PERCENTAGE INCREASE IN ATOMIC ABSORPTION READINGS WITH LACTOSE.

Standard conc. in p.p.m.	Percentage increase in reading at varying times after preparation.		
	1hr	3hrs	4hrs
0.03	20.00%	16.67%	23.22%
0.05	10.00%	1200%	14.60%
0.10	1.700%	6.700%	10.00%
0.30	1.670%	4.430%	6.000%

It was concluded that the time at which a sample is read after its preparation will affect its apparent concentration. The longer the sample is left before reading, the greater the apparent concentration.

This effect is most noticeable with the low concentration samples. Therefore it is necessary to prepare a few samples together with a set of standards and measure their absorbances in the same order in which prepared, as quickly as possible.

4.1.4. Effect of Magnesium Ion Concentration.

Low concentrations appear to be more affected by presence of lactose and effects of time. Therefore, where possible, the samples for analysis should be kept as concentrated as possible to produce absorption readings in the 0.1 to 0.4ppm range.

4.1.5. Reproducibility of Results.

Ten accurately weighed 100mg samples of 1% batch 4 magnesium stearate in lactose were analysed by atomic absorption to check reproducibility of results. Each sample was boiled with 5mls 0.1N hydrochloric acid for 2 minutes, solution volume then being adjusted to 10mls with distilled water and allowed to cool. A 1 in 50 dilution was performed and the diluted solution analysed for magnesium ion content. From the results the amount of magnesium stearate present in the sample was calculated (Appendix 4.3) and expressed as a percentage of the amount expected to be present at a 1% concentration level. Results are summarized in Table 4.4.

It was concluded that the atomic absorption method was reproducible since the % magnesium stearate content of all ten samples lay within 6% of the mean value of 81.42%. Some of this variation will be due to variation of the amount of lubricant in the sample as well as process variability.

The percentage of magnesium stearate calculated to be present in the samples was only 80% of the expected amount which indicates that under these test conditions not all the magnesium stearate is recovered from the sample and analysed. However the results do indicate

TABLE A 4.4. REPRODUCIBILITY OF SAMPLE RESULTS USING ATOMIC ABSORBTION ANALYSIS.

	Sample Number									
	1	2	3	4	5	6	7	8	9	10
Atomic Absorbtion Reading	0.148	0.137	0.148	0.142	0.147	0.136	0.144	0.136	0.139	0.139
Amount of Magnesium Stearate present in micrograms.	878.1	793.7	878.1	821.3	867.8	775.0	847.1	775.0	813.5	813.5
Amount present as a percentage of the expected amount.	86.94%	78.35%	85.84%	80.44%	85.84%	76.13%	83.79%	76.66%	78.98%	81.19%

that provided the samples are treated identically, the results obtained will be comparable.

4.2. Determination of Breakdown Factors.

The breakdown factor is the percentage of magnesium present in a batch of magnesium stearate. This value is required in calculations of amount of stearate in samples since the analysis method only measures the concentration of magnesium ions (Appendix 4.3).

Approximately 10mg, accurately weighed of the magnesium stearate batch, was boiled with 5mls of 0.1N hydrochloric acid, maintaining original volume, until the fatty acid layer was clear. Five mls of distilled water were then added and the solution cooled until the fatty acids solidified. One ml of the aqueous solution was then diluted to 100ml and one ml of this dilution further diluted to 10mls. The latter solution was then analysed by atomic absorption.

Calculation.

Let the concentration of the analysed solution be Zppm.

Therefore the concentration is equivalent to $Z\mu g/ml$ magnesium ions.

Since the overall dilution was 1ml in 10 litres,

$$\text{concentration of magnesium stearate in analysed sample} = \frac{\text{sample weight}}{10{,}000} \text{ mg/ml} = \frac{\text{sample weight}}{10} \mu g/ml$$

Thus:-

$\frac{\text{sample weight}}{10}\mu g$ magnesium stearate contains $Z\mu g$ magnesium ions

$\therefore$ 1g magnesium stearate contains $\frac{Z \times 10}{\text{sample weight}}$ g magnesium ions

$\therefore$ 1g magnesium stearate contains $\frac{Z \times 10 \times 100\%}{\text{sample weight}}$ magnesium ions

Thus breakdown factor is $\frac{1000 \times Z}{\text{sample weight}}\%$ where Z is the concentration of magnesium in assayed sample.

TABLE A4.5. BREAKDOWN FACTORS FOR COMMERCIAL BATCHES OF MAGNESIUM STEARATE.

Lubricant Batch	1	2	3	4	5	6	7	8	9	10	11
Breakdown Factor	4.68%	4.71%	4.52%	4.84%	4.95%	4.90%	4.28%	4.55%	4.76%	4.17%	4.21%

TABLE A4.6. BREAKDOWN FACTORS FOR LABORATORY PREPARED LUBRICANTS.

Lubricant Batch	Stearate Plates	Stearate Needles	Palmitate	St : P[a] 25 : 75	St : P[a] 50 : 50	St : P[a] 75 : 25
Breakdown Factor	4.24%	4.06%	4.85%	4.38%	3.07%	3.03%

a. St : P = Stearate to Palmitate present in the manufactured batch of lubricant.

4.3. Calculation of Amount of Magnesium Stearate in a Sample.

Let concentration of magnesium ions in analysed solution be Yppm

Therefore the concentration is equivalent to Yμg/ml

The original sample was dissolved in 10mls acid solution

Therefore the amount of magnesium ions in sample = 10 x Yμg

The amount of magnesium ions in a magnesium stearate batch is given by the breakdown factor (Appendix 4.2.)

$$\text{Therefore the amount of magnesium stearate} \times \text{breakdown factor} = 10 \times Y\mu g$$

If the breakdown factor is P% then:-

$$\text{Amount of magnesium stearate} \times \frac{P}{100} = 10 \times Y\mu g$$

$$\text{amount of magnesium stearate} = \frac{10 \times Y \times 100}{P}\mu g$$

$$= \frac{Y}{P}mg$$

Therefore, the amount of magnesium stearate in the sample = $\frac{Y}{P}$mg

where Y is the sample concentration of magnesium ions, and P is the numerical value of the breakdown factor.

4.4. Calculation for Estimating Diameter of Tablet in Skim Test.

Volume of tablet = $\pi \times r^2 \times t$ mm^2 t = tablet thickness in mm
r = radius of tablet in mm

This volume is equivalent to the weight of the tablet (W).

Therefore, 1mg of tablet is equivalent to $\frac{\pi \times r^2 \times t}{W}$ mm^3

Now, from skim tests, the weight of powder used in each test is known (Ymg).

Therefore Ymg is equivalent to $\frac{\pi \times r^2 \times t \times Y}{W}$ mm^3

This is equivalent to the volume change between the original tablet and remaining tablet core of radius r_1

Volume change = $\pi \times r^2 \times t - \pi \times r_1^2 \times t$

$$\therefore \frac{\pi \times r^2 \times t \times Y}{W} = \pi \times t(r^2 - r_1^2)$$

$$\therefore \frac{\pi \times r^2 \times t \times Y}{W \times \pi \times t} = r^2 - r_1^2$$

$$\therefore r_1^2 = r^2 - \frac{r^2 \times Y}{W}$$

$$\therefore r_1 = \sqrt{r^2 - \frac{r^2 \times Y}{W}}$$

Thus:-

Radius of tablet after skimming = $\sqrt{r^2 - \frac{r^2 \times Y}{W}}$

where r = original radius of tablet in mm before skimming
W = total weight of tablet in test = total weight of skims
Y = accumulative weight of tablet in mg in skimming.

APPENDIX 5. CALCULATION OF MEDIAN PARTICLE SIZE USING THE MICROSCOPE METHOD OF ANALYSIS.

Values measured are:-

a). the number of particles in each size range (N_r)

b). the mean size for each size range (d_r)

The percentage by weight in each size class is then:-

$$\frac{100 \times N_r \times d_r^3}{\sum (N_r \times d_r^3)}$$

The cumulative weight percentage above stated size (abscissa) is then plotted on log probability paper and the median particle size is the 50% value.

APPENDIX 6. MODIFIED IDENTITY TESTS FOR LABORATORY PREPARED LUBRICANTS.

6.1. Testing for Presence of Magnesium Ions.

Magnesium stearate contains approximately 4% magnesium and thus the magnesium content may be insufficient under B.P. or U.S.P. conditions to yield positive results for identity tests. Therefore the test was modified as below:-

Approximately 200mg magnesium stearate was boiled with 0.5ml sulphuric acid (202) until the fatty acid layer was clear. Cooling, solidified the fatty acids and the aqueous solution was decanted, and neutralised with dilute ammonia solution (63). Ammonium carbonate solution (63) was added and the solution boiled. Sodium hydrogen phosphate solution (63) was then added and the resultant mixture again boiled.

All 6 lubricants yielded positive magnesium tests, a slight white precipitate being obtained with ammonium carbonate, becoming a heavy gelatinous precipitate upon addition of sodium hydrogen phosphate.

6.2. Testing the Melting Point of the Fatty Acid Layer.

Samples were prepared as described in U.S.P. XIX (202), (1g quantity) and the temperature at which the fatty acid layer solidified was recorded. These solidification temperatures are shown in Table A6.1.

TABLE A6.1. SOLIDIFICATION TEMPERATURES OF FATTY ACIDS OBTAINED FROM VARIOUS LUBRICANT BATCHES.

Material	Solidification temperature.
Magnesium stearate	67.5°C
Magnesium palmitate	61.0°C
Stearate to palmitate 25:75	54.0°C
Stearate to palmitate 50:50	55.0°C
Stearate to palmitate 75:25	60.5°C
Stearic acid*	68-71°C
Palmitic acid*	60-63°C

* Quoted values.

All lubricant batches conform to the U.S.P. test since solidification temperatures were not below 54°C.

APPENDIX 7. PRACTICAL USE OF LUBRICITY TEST.

7.1. To Estimate Probable Behaviour of Batches of Magnesium Stearate.

Ejection energies of 1% mix of the lubricants in lactose were evaluated by the established test (section 2.1) and compared with representative research batches. Batch 32609 was known to cause production problems.

TABLE A7.1. EJECTION ENERGIES OF VARIOUS MAGNESIUM STEARATE BATCHES

Lubricant material	Batch 32609	Batch 34454	Batch 36470	Research Batch 1	Research Batch 7
Mean ejection energy in Jm^{-2}	3216	2220	2330	3754	1509

TABLE A7.2. LUBRICANT EXCIPIENT FACTORS FOR VARIOUS MAGNESIUM STEARATE BATCHES.

Lubricant material	Lubricant excipient factor
Good lubricant	500%+
Mediocre lubricant	330% - 430%
Poor lubricant	330%-
Batch 1	266%
Batch 7	663%
Batch 32609	311%
Batch 34454	450%
Batch 36470	430%

Batch 1 is poor and batch 7 is good, therefore 32609 is poor, 34454 is mediocre to good and 36470 is mediocre. Thus in production, batches 36470 and 34454 should behave similarly but should not prove as problematic as batch 32609.

7.2. To Estimate Mixing Efficiency of a Turbula Blender

Samples of 0.5% magnesium stearate in anhydrous lactose were mixed for various times in a Turbula blender and evaluated for lubricant efficiency by the established test (section 2.1).

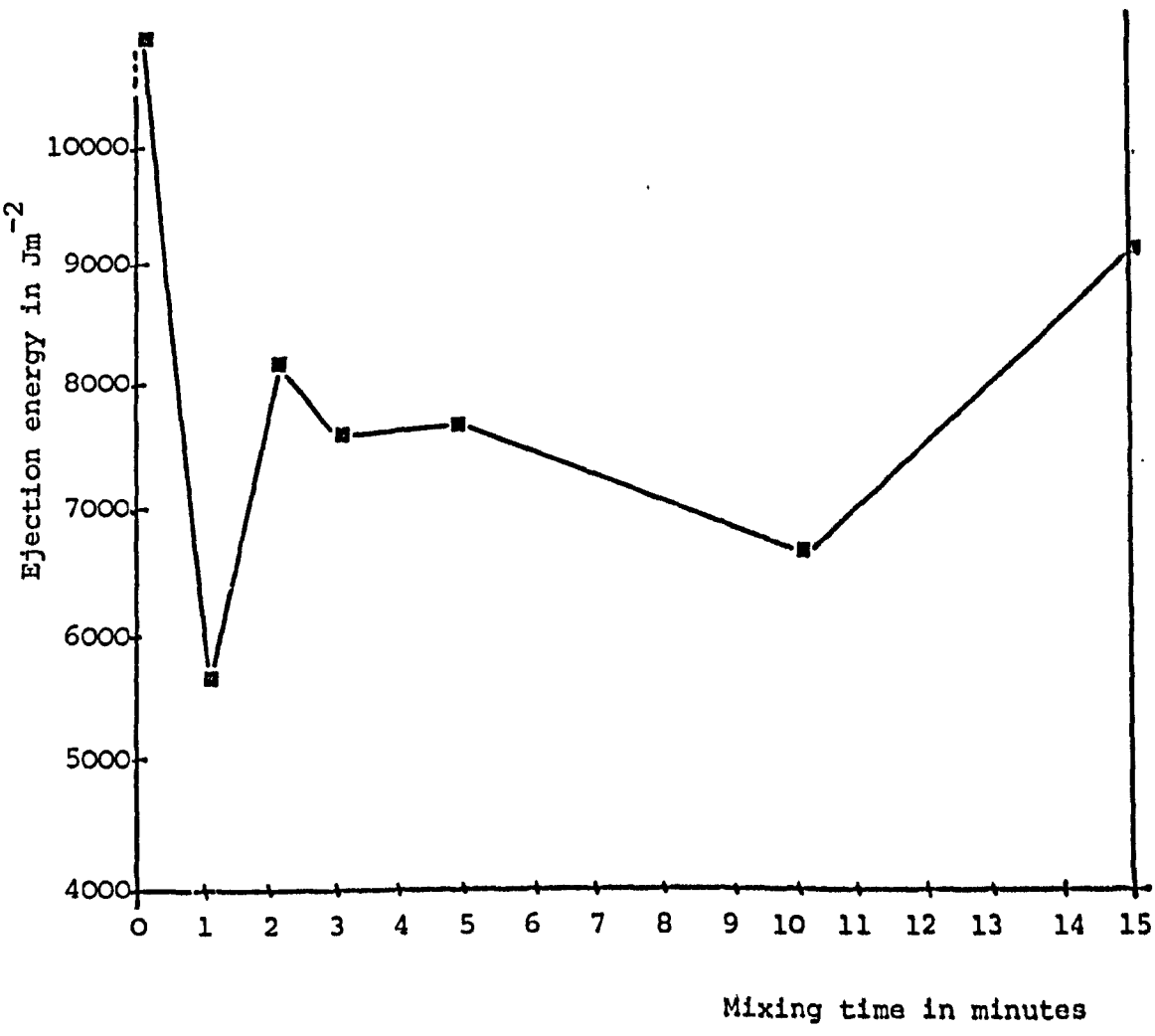


Fig. A7.1. Influence of mixing time in a Turbula blender on lubricity.

It was concluded that prolonged mixing does not exert a beneficial effect upon lubricity.

7.3. To Determine the Best Milling Method to Obtain Optimum Lubricity Performance from Stearic Acid.

Two percent mixtures of milled stearic acids and lactose were

prepared and evaluated in the usual manner (section 2).

TABLE A7.3. EFFECT OF MILLING PROCEDURE ON STEARIC ACID LUBRICITY

Milling procedure	Unmilled	Ball milled	Apex milled
Mean ejection energy Jm^{-2}	10475	11342	10992
Standard deviation	2600	1850	2300

It was concluded that the milling process did not significantly affect the lubricity performance of the stearic acid.

APPENDIX 8. SURFACE AREAS OF MAGNESIUM STEARATE BATCHES.

The work described in this appendix was carried out independently by Pfizer Central Research, Sandwich, Kent.

Two batches of magnesium stearate were investigated by Pfizer, and surface area determinations using the Strohlein equipment, were performed. Approximate particle size of the materials could also be estimated from scanning electron micrographs at x 20,000 magnification. The results are summarized in Table 8.1.

TABLE A8.1. PROPERTIES OF TWO MAGNESIUM STEARATE BATCHES.

Magnesium stearate sample	3-5379	352-21
Surface area in m^2g^{-1}	20.42	11.18
Approximate particle size	less than 2μm	5μm or less

From the results it can be seen that the surface area values are greater than those obtained for the majority of magnesium stearate batches investigated in this research work, (section 3) with the exception of batch 7. However, this is thought to be due to the differences in particle size, since the majority of the research batches were of much larger particle size than the two Pfizer batches. In fact, batch 7 is the only research batch of similar particle size, and this is reflected in its larger surface area, which is comparable to the surface areas obtained for the Pfizer materials.

Thus it was concluded that the surface areas obtained for the majority of the research magnesium stearate batches were representative of the lubricant materials and only appeared to be low because of the large particle size of the crystals.

LIST OF REFERENCES.

1. Strickland, W.A. Jnr., Higuchi, T., and Busse, L.W. (1960). J. Am. Pharm. Assoc., 49, 35-40.

2. Komarek, K.R. (1967). Chem. Eng. 74(25). 154-155.

3. Silvershер, H.I. (1969). NASA. Spec. Publ. SP-3051 199-239

4. Jentgen, R.L. (1971). I.E.E.E. Trans. Parts. Hybrids. Packag. 7 (2) 86-93.

5. Sprowl, (1974). In: Sprowl's American Pharmacy, 7th Ed.. J.B. Lippincott Co. Philadelphia. Toronto. Pages 311, 337, 338, 359,360, 366 &367.

6. Lachman, L., Lieberman, H.A., and Kanig, J.L. (1970). In: Theory and Practice of Industrial Pharmacy. Lea and Febiger. 2nd. Ed.

7. Remington's Pharmaceutical Sciences. 14th. Ed. Mack Publishing company. Page 1652.

8. Little, A., and Mitchell, K.A. (1949). In: Tablet Making. Liverpool Northern Pub. Co.

9. Sperandeo, F., and DeMarchi, G. (1976). Boll. Chim. Farm. 115(12). 801-809.

10. Strickland, W.A. Jnr. (1959). Drug Cosmet. Ind. 85 318

11. Maly, J. (1963). Pharm. Ind. 25(10) 573-578.

12. Munzel, K., and Kagi, W., (1954). Pharm. Acta. Helv. 29 53-71.

13. De Blaey, C.J. (1972). Pharm. Weekblad. 107 233-242.

14. Rubio, G.I., (1957). Anales. Fac. Quim. Y. Farm. Univ. Chile. 9 249-254.

15. Esnaud, J.M., Clerc, J., Tebbi, H., Duchêne, D., Levy, J., and Puisieux, F. (1973). Ann. Pharm. Fr. 31(2) 103-116

16. Bowden, F.P., and Tabor, D. (1967). In: Friction and Lubrication. Methuen & Co. Ltd.

17. Bikerman, J.J. (1950). In: Surface Chemistry. Theory and Applications. 2nd. Ed. Academic. New York. Pages 388-395.

18. Bowden, F.P., and Tabor, D. (1958). In: The Friction and Lubrication of Solids. Clarendon Press, Oxford.

19. Fein, R.S. (1971). Lubrication. 57(1). 1-12.

20. Buckley, D.H., and Johnson, R.L. (1972). Chem. Technol. 2(5) 302-310.

21. Carver, S.E. (1974). Lubrication. 60 61,62,70,& 71.

22. Salpekar, A.M. (1975). Ph.D Thesis.

23. Train, D., and Hersey, J.A. (1960). J. Pharm. Pharmacol. 12 97T-104T.

24. Scruton, B., Tabor, D., and Willis, R.F. (1972). Nature. 236 59-60.

25. Lewis, C.J., and Shotton, E. (1965)1 J. Pharm. Pharmac. 17 suppl. 82s-86s.

26. Lewis, C.J., and Train, D. (1965), J. Pharm. Pharmac. 17 577-583.

27. Allen, C.M., and Drauglis, E. (1969). Wear. 14(5). 363-386.

28. Rabinowicz, E., and Tabor, D. (1951). Proc. Roy. Soc. A208 455-475.

29. Boes, D.J. (1966). Intern. Sci. Tech. 54 80-84 & seq.

30. Ling, F.F., Klaus, E.E., and Fein, R.S. (1969). In: Boundary Lubrication: An Appraisal of World Literature. 197-223.

31. Bollman, W., and Spreadborough, J. (1960). Nature. 186 29-30

32. Wolff, J.E., Dekay, H.G., and Jenkins, G.L. (1947). J. Am. Pharm. Assoc. 36 407-410.

33. Gold, G.,and Palermo, B.T. (1965). J. Pharm. Sci. 54 310-312

34. Gold, G., and Palermo, B.T. (1965). J. Pharm. Sci. 54 1517-1519.

35. Bhatia, R.P., and Lordi, N.G. (1979). J. Pharm. Sci. 68(2). 222-226.

36. Jamison, W.E. (1972). A.S.L.E. Trans. 15(4). 296-305.

37. Burlinson, H. (1968). In: Tablets and Tableting. W. Heinmann Med. Books Ltd. London. Pages 10-11.

38. Robertson, W.S. (1972). In: Lubrication in Practice. Macmillan-Esso Publ. Pages 15-21.

39. Pilpel, N. (1966). Chemical Reviews. 66 39-44.

40. Dauron, B.K. (1971). Neftepererab. Neftekhim. Nr. 4 96-100

41. Man'kovskaya, N.K., and Daurov, B.K. (1968). Maslozhir. Prom. 34(6). 20-23.

42. Man'kouskaya, N.K., and Daurov, B.K. (1968). Neftoporerab. Neftekhim. 7 38-41.

43. Hess, H. (1977). Drug Devel. and Ind. Pharm. 3(6). 491-506.

44. Kornblum, S.S. and Zoglio, M.A. (1967). J. Pharm. Sci. 56 1569-1575.

45. Juslin, M.J., and Krogerus, V.E. (1970). Farm. Aikak. 79 191-202.
Juslin, M.J., and Krogerus, V.E. (1970). Farm. Notisblad. 11 191 and seq.

46. Juslin, M.J., and Krogerus, V.E. (1971). Farm. Aikak. 80 255-262.

47. Juslin, M.J., and Krogerus, V.E. (1971). Farm. Aikak. 80 197-209.

48. Juslin, M.J., and Erkkila, E.S. (1972). Farm. Aikak. 81 (11-12). 189-93.

49. Juslin, M.J., and Krogerus, V.E. (1971). Farm. Aikak. 80 323-331.

50. Clayfield, E.J., and Galvin, G.D. (1969). Inst. Mech. Eng. (Lon) Pro. 1968-1969. 183(3p) 152-163.

51. Suren, G. (1971). Dansk. Tidsskr. Farm. 45 331-338.

52. Lindberg, N-O. (1972). Acta Pharm. Sueica. 9 207-214.

53. Hölzer, A.W., and Sjögren, J. (1979). Int. J. Pharm. 2(314) 145-153.

54. Jaminet, F., and Louis, G. (1968). Pharm. Acta. Helv. 43 153-157.

55. Cid, E., and Jaminet, Fr., (1971). J. Pharm. Belg. 26(4). 360-368.

56. Jaminet, Fr, and Hazée, A. (1966). Pharm. Acta. Helv. 41 530-550.

57. Delattre, L., and Gillard, J. (1972). Bull. Tech. Gattefosse. S.F.P.A. 67 67-69.

58. Caldwell, H.C., and Westlake, W.J. (1973). Can. J. Pharm. Sci. 8(2). 50-53.

59. Caldwell, H.C., and Westlake, W.J. (1972). J. Pharm. Sci. 61 984-985.

60. Salpekar, A.M., and Augsburger, L.L. (1974). J. Pharm Sci. 63 289-293.

61. Osseekey, K.B., and Rhodes, C.T. (1976). Pharm Acta. Helv. 51(3) 71-72

62. Murthy, K.S., and Samyn, J.C. (1977). J. Pharm. Sci. 66(9). 1215-1219.

63. British Pharmacopoeia (1973). H.M.S.O.

64. Gold, G., and Campbell, J.A. (1964). J. Pharm. Sci. 53 52-54.

65 Nelson, E., Naqvi, S.M., Busse, L.W., and Higuchi, T., (1954). J. Am. Pharm. Assoc. 43 596-602.

66. Lowenthal, W. (1972). J. Pharm. Sci. 61 1702-1703.

67. Levy, G., and Gumtow, R.H. (1963). J. Pharm. Sci. 52 1139-1144.

68. Munzel, K., and Kagi, W. (1957). Pharm. Acta. Helv. 32 321.

69. Yumioka, E., and Makita, H. (1966). Yakueaigaku. 26(3) 201-3

70. British Pharmaceutical Codex. (1973). H.M.S.O.

71. Tsumura, J., Imaseki, I., and Nagasawa, M. (1972). U.S. Patent 3,692,896.

72. Munden, B.J., Dekay, H.G., and Banker, G.S. (1960). Drug Standards 28(1) 12-17.

73. Smilek, M., Cosgrove, F.P., and Guth, E.P. (1955). Drug Standards. 23 87-91.

74. Maly, J., and Jaros, A. (1967). Pharm. Ind. 29(6) 399-404.

75. Maly, J. (1969). Acta. Fac. Pharm. Univ. Comeniana. 17 181-185.

76. Burda, L., Novak, J., and Sajvera, J. (1969). Czech. Patent 133,277.

77a. Cox, P.H. (1971). U.S. Patent 3,577,491.

77b. Cox, P.H. (1970). U.S. Patent 3,518,346.

77c. Cox, P.H. (1970½. Brit. 1.178,294.

78. Shinozaki, I., Sugihara, M., Nagai, T., and Nogami, H. (1971). Yakuzaigaku. 31(3) 232-234.

79. Hoss, G.C. (1971). U.S. Patent 3,584,099.

80. Tabor, D. (1974). Am. Chem. Soc. Div. Org. Plast. Chem. Pap. 34(1) 203-218.

81. Disapio, A. (1970). Machine Design 42(15). 56.

82. Fox, C.D., Richman, M.D., Reier, G.E., and Shangraw, R. (1966). Drug Cosmet. Ind. 92 161.

83. Strickland, W.A. Jnr., Nelson, E., Busse, L.W., and Higuchi, T. (1956) J. Am. Pharm. Assoc. 45 51-55.

84. Lerk, C.F., Bolhuis, G.K., and Smedema, S.S. (1977). Pharm. Acta. Helv. 52 Nr. 3 33-39.

85. Lerk, C.F., and Bolhuis, G.K. (1977). Pharm. Acta. Helv. 52 (3) 39-44.

86. Bolhuis, G.K., and Lerk, C.F. (1977). Acta. Pharm. Technol. 23(1) 13-20.

87. Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T., andDe Boer, A.H. (1975). Pharm. Weekblad. 110 317-325.

88. Iranloye, T.A., and Parrott, E.L. (1978). J. Pharm. Sci. 67(4). 535-539.

89. Ragnarsson, G., Hölzer, A.W., and sjögren, J. (1979). Int. J. Pharmaceutics. 3 127-131.

90. Sperandio, G.J., and Dekay, H.G. (1952). J. Am. Pharm. Assoc. 41 245-248.

91. Travers, D. (1975). Powder Technology. 12 189-190.

92. Shotton, E., and Lewis, C.J. (1964). J. Pharm. Pharmac. 16 suppl. 111T-120T.

93. Stamme, A., Bobbe, O., and Kleinknecht, A. (1977). Labo. Pharma. Probl. Tech. 25(261) 45-50.

94. De Boer, A.H., Bolhuis, G.H., and Lerk, C.F. (1978). Powder Technology. 20(1) 75-82.

95. Egermann, H. (1978). Sci Pharm. 46(2) 137-138

96. Shah, A.C., and Mlodozeniec, A.R. (1977). J. Pharm. Sci. 66(10). 1377-1382.

97. Bossert, J., and Stamm, A. (1978). Bull. Soc. Pharm. Strsbourg. 21(2). 159-170.

98. Hersey, J.A. (1975). Powder Technology. 11 41-44.

99. Yip, C.W., and Hersey, J.A. (1977). Drug Devel. and Ind. Pharm. 3(5). 429-438.

100. Bogs, U., and Moldenhauer, H. (1965). Pharm. Ind. 27(1). 6-13.

101. Appino, J.B., Banker, G.S., and Dekay, H.G. (1957). Drug Standards. 27 193-200.

102. Bogs, U., and Moldenhauer, H. (1965). Pharm. Ind. 27(2). 76-80.

103. Matsuda, Y., Minamioa, Y., and Hayashi, S.I. (1976). J. Pharm. Sci. 65 1155-1160.

104. Faber, J. (1947). Arch. Pharm. Chem. 54 599-604.

105. Higuchi, T., Rao, N., Busse, L.W., and Swintosky, J.V. (1952). J. Am. Pharm. Assoc. 42 194-200.

106. Asker, A.F., Saied, K.M., and Abdel-Khalek, M.M. (1975). Pharmazie. 30(6) 378-382.

107. La Manna, A., and Shotton, E. (1970). Farmaco Ed. Prat. 25 689-699.

108. Paris, J., Duchêne, D., and Puisieux, F. (1977). J. Pdr. Bulk Solids Tech. 1 47-56.

109. Fuchs, P., Schottky, E., and Schenck, G. (1970). Pharm. Ind. 32(7). 581-583.

110. Marlowe, E., and Shangraw, R.F. (1967). J. Pharm. Sci. 56 498-503.

111. Samyn, J.C., and Jung, W.Y. (1970). J. Pharm. Sci. 59 169-175.

112. Ganderton, D. (1969). J. Pharm. Pharmac. 21 suppl. 9s-18s.

113. Carli, F., and Simioni, L. (1977). Drug Dev. and Ind. Pharm. 3(1) 1-21.

114. Khalil, S.A., and Ali, L.M.M. (1972). Acta. Pharm. Suecica 9 563-572.

115. Rowley, G., and Newton, J.M. (1970). J. Pharm. Pharmac. 22 966-967.

116, Ahmed, M., and Enever, R.P. (1970). J. Pharm. Pharmac. 22 5P.

117. Ahmed, M., and Enever, R.P. (1978). Pharm. Acta. Helv. 53(12). 358-364.

118. Stamm, A., Kleinknecht, A., and Bobbe, D. (1977). Labo.- Pharma.- Probltech. 25(263) 215-225.

119. Maulding, H.V., Zoglio, M.A., and Johnston, E.J. (1968). J. Pharm. Sci. 57 1873-1876.

120. Zoglio, M.A., Maulding, H.V., Haller, R.M., and Briggen, S. J. Pharm. Sci. 57 1877-1880.

121. Wortz, R.B. (1967). J. Pharm. Sci. 59 1169-1173.

122. Asker, A.F., Elnakeeb, M., Motawi, M., and Elginoy, N. Pharmazie 28 476-478.

123. Trolle-Lassen, C. (1960). Arch. Pharm. Chemi. 67 504-505.

124. Lee, K.C., and Hersey, J.A. (1977). J. Pharm. Pharmac. 29 515-516.

125. Khalil, S.A.H. (1978). Indian J. Pharm. Scir. 40 109-112.

126. Rowe, R.C. (1977). J. Pharm. Pharmac. 29 723-726.

127. Hersey, J.A. (1972). Aust. J. Pharm. Sci. 1 76-78.

128. Nelson, E. (1955). J. Am. Pharm. Assoc. 44 494-497.

129. Nelson, E., Busse, L.W., and Higuchi, T. (1955). J. Am. Pharm. Assoc. Sci. Ed. 44 223-225.

130. Raff, A.M. (1964). U.S. Patent 3,158,111.

131. Hersh, M. (1975). U.S. Patent 3,908,003.

132. Haeckl, R.S. (1968). Int. J. Powder Met. 4(1). 13-23.

133. Leal, E.J., Irvington, and Pinto, P.J. (1962). U.S. Patent 3,042,531.

134. Seelig, R.P., and Wulff, J. (1946). Trans. Aime. 166 492-505.

135. Schey, J.A., and Newnham, J.A. (1970). Lubric. Eng. 26(4) 129-137.

136. Dangerfield, C.J., and Coleman, D.S. (1977). J. Pdr. and Bulk Solids Tech. 1(1) 36-41.

137. Alimov, Yu. A. (1975). Khim.-Farm. Zh. 9 30-33.

138. Miller, C.A. (1967). J. Sci. Instrum. 44 565.

139. Siegal, S., Hanus, E.J., and Carr, J.W. (1963). J. Pharm. Sci. 52 604-605.

140. Shotton, E., Deer, J.J., and Ganderton, D. (1963). J. Pharm. Pharmac. 15 106T-114T.

141. Funakoshi, Y., Asogawa, T., and Satake, E. (1977). Drug. Dev. and Ind. Pharm. 3(6) 555-573.

142. Crivellaro, G.B., and Olandi, F. (1971). German Patent 2,057,753.

143. Haupt, W. (1914). Z. Angew. Chem. 27(1). 535-536.

144. Zink, J., and Liere, R. (1915). Z. Angew. Chem. 28(1). 229-32.

145. Cassie, J., Ryder, J., and Smith, D. (1977). J. Pharm. Pharmac. 29 suppl.36P.

146. Shangraw, R.F. (1978). Drug and Cosmet. Ind. Part 1 (June) pages 68 and seq., Part 2 (July) pages 34 and seq.

147. Rees, J.E. (1977). Boll. Chim. Farm. 116 125-141.

148. Lien, M.L., and Miller, C.E. (1948). J. Am. Pharm. Assoc. Sci. Ed. 37 238-239.

149. Butcher, A.E., and Jones, T.M. (1972). J. Pharm. Pharmac. 24 Suppl. 1P-9P.

150. Hanssen, D., Führer, C., and Schaefer, B. (1970). Pharm. Ind. 32(2) 97-101.

151. Müller, B.W. (1975). Pharm. Ind. 37 567.

152. Müller, B.W. (1976). Pharm. Ind. 38(4) 394-398.

153. Müller, B.W. (1977). Pharm. Ind. 39(2) 161-165.

154. Müller, B.W. (1977). Zentrabl. Pharm. Pharmakother, Laboratoriumsdiagn. 116(12) 1261-1266.

155. Pilpel, N. (1971). Mfg. Chem. Aerosol News. 42 37-40.

156. Pilpel, N. (1963). Chem. Rev. 63 221, 223, & 233.

157. Doelker, E. (1978). Pharm. Acta. Helv. 53(6) 182-188.

158. Shotton, E., and Ganderton, D. (1960). J. Pharm. Pharmac. 12 Suppl. 87T-92T.

159. Lindberg, N-O. (1972). Acta. Pharm. Suecia. 9 135-140.

160. Knoechnel, E.L., Sperry, C.C., Ross, H.E., and Linter, C.J. (1967). J. Pharm. Sci. 56 109-115.

161. Deer, J.J., Ridgway, K., Rosser, P.H., and Shotton, E. (1968). J. Pharm. Pharmac. 20 Suppl. 182s-184s.

162. Goodhart, F.W., Mayorga, G., Mills, M.N., and Ninger, F.C. (1968). J. Pharm. Sci. 57 1770-1775.

163. Knoechel, E.L., Sperry, C.C., and Linter, C.J. (1967). J. Pharm. Sci. 56 116-130.

164. Sixsmith, D. (1977). Mfg. Chem. & Aerosol News. 48 17-21.

165. Polderman, J., and DeBlaey, C.J. (1971). Farm. Aikak. 80(1-2) 111-118.

166. Ho, A., Greer, H., and Clare, D. (1978). J. Pharm. Pharmac. 30 Suppl. 95P.

167. Windheuser, J.J., Misra, J., Eriksen, S.P., and Higuchi, T. (1963). J. Pharm. Sci. 52 767-772.

168. Cooper and Gunn. In: Cooper and Gunn's Tutorial Pharmacy. 6th Edt. Pitman Medical. Northern Ireland Universities Press, Belfast. Pages 216,218, 232, & 231.

169. Conte, U., Colombo, P., Caramella, C., and La Manna, A. (1972). Farmaco. Ed. Prat. 27(8). 440-452.

170. Hölzer, A.W., and Sjögren, J. (1977). Drug Dev. and Ind. Pharm. 3(1) 23-37.

171. Hölzer, A.W., and Sjögren, J. (1978). Acta Pharm. Suec. 15 59-66.

172. Lewis, C.J., and Train, D. (1965). J. Pharm. Pharmac. 17 1-9.

173. DeBlaey, C.J., and Polderman, J. (1970). Pharm. Weekblad. 105 241-250.

174. DeBlaey, C.J., and Polderman, J. (1971). Pharm. Weekblad. 106(8) 57-65.

175. Lewis, C.J., and Shotton, E. (1965). J. Pharm. Pharmac. 17 Suppl. 71s-81s.

176. Rees, J.E., and Shotton, E. (1971). J. Pharm. Sci. 60 1704-1708.

177. Goodhart, F.W., Mayorga, G., and Ninger, F.C. (1969). J. Pharm. Sci. 58 248-251.

178. Hersey, J.A., Cole, E.T., and Rees, J.E. (1973). Aust. J. Pharm. Sci. 2(1) 21-24.

179. Patel, B.C., and Guth, E.P. (1955). Drug Standards. 23 37-42.

180. Führer, C., Hanssen, D., and Schafer, B. (1970). Pharm. Ind. 32 17-21.

181. Higuchi, T., Nelson, E., and Busse, L.W. (1954). J. Am. Pharm. Assoc. 43 344-348.

182. Ridgway, K., and Rosser, P.H. (1971). J. Pharm. Pharmac. 23 Suppl. 202s-209s.

183. Ridgway, K., Glasby, J., and Rosser, P.H. (1969). J. Pharm. Pharmac. 21 Suppl. 24s-29s.

184. Lewis, C.J., and Train, D. (1965). J. Pharm. Pharmac. 17 33-41.

185. Juslin, M.J. (1969). Farm. Aikak. 78(9) 201- 210.

186. Bogs, U., and Lenhardt, E. (1971). Pharm. Ind. 33(11a) 850-4.

187. Travers, D.N., and Merriman, M.P.H. (1970). J. Pharm. Pharmac. 22 Suppl. 11s-16s.

188. Salisbury, R., and Higuchi, T. (1960). J. Am. Pharm. Assoc. 49 284-288.

189. Maly, J. (1963). Acta. Fac. Pharm. Bohemoslov. 8 81-101.

190. Maly, J. (1963). Pharm. Ind. 25 257-262.

191. Gruszczynski, C. (1966). Pol. Patent 51.733.

192. Graham, J.D.P., and Jenkins, M.E. (1952). J. Pharm. Pharmac. 4 392-398.

193. Levy, G., and Schwartz, T.W. (1957). J. Am Pharm. Assoc. 46 558-561.

194. Varsano, J., and Lachman, L. (1966). J. Pharm. Sci. 55 1128-1133.

195. Rees, J.E., Hersey, J.A., and Cole, E.T. (1972). J. Pharm. Sci. 61 1313-1315.

196. Cole, E.T., Rees, J.E., and Hersey, J.A. (1971). J. Pharm. Pharmacol. 23 258s

197. Instron instruction manual.

198. Instruction manual for the use of the microscope particle size analysis apparatus.

199. British Standard 3406 Part 4.

200. Strohlein instruction manual.

201a. Squibb G.L.C. analysis method for magnesium stearate.

201b. Squibb G.L.C. analysis method for magnesium stearate involving the use of an internal standard.

202. United States Pharmacopoeia XIX (1975).

203. E.S.C.A. analysis information booklet.

204. Alpar, O., Deer, J.J., Hersey, J.A., and Shotton, E. (1969). J. Pharm. Pharmac. 21 Suppl. 6s-8s.

205. Shotton, E. (1972). Pharm. Ind. 34(4). 256-262.

206. Arkles, B. (1972). N.L.G.I. Spokesman. 35(11) 390-398.

207. Martindale. (Extra Pharmacopoeia). 27th Edt.

208. Taylor, R.J. (1973). In: The Chemistry of Glycerides. Unilever Educational Booklet Adv. series 4. 4-5.

209. Hüttenrauch, R., and Jacob, J. (1977). Pharmazie 32 Part 1 49-50.

210. York, P. (1978). J. Pharm. Pharmac. 30 6-10.

211. Merck Index (1968). 8th. Edt. Merck and Co. Inc. page 638.

212. Newton, J.M., Rowley, G., and Törnblom, J-F.V. (1971). J. Pharm. Pharmac. 23 452-453.

213. Kassem, A., and Said, S. (1975). Can. J. Pharm. Sci. 10 92-94.

214. Martin, A.N., Swarbrick, J., and Cammarata, A. (1973). In: Physical Pharmacy. 432-435. Lea and Febiger, Philadelphia

215. Glasstone, S., and Lewis, D. (1966). In: Elements of Physical chemistry. 558-566. Macmillan and Co. Ltd. London.

216. Fisher, R.A., and Yates, F. (1970). In: Statistical Tables For Biological, Agricultural, and Medical Research. 6th Edt. Oliver and Boyd. Edinburgh.

217. Hölzer, A.W., (1981). Symposium on Tablet Technology, Stockholm, Sweden.