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RESEARCH

Towards Rational Excipient Selection: Assessing Lactose-Based Co-Processed Excipients with APIs of Differing Solubilities

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Abstract

Purpose This research was designed to systematically investigate the performance of three lactose-based co-processed excipients (CPEs): SuperTab® 40LL, StarLac®, and MicroceLac® 100 in immediate-release tablet formulations prepared by direct compression. The objective was to evaluate their suitability with drugs of varying solubility and mechanical properties and provide practical guidance for excipient selection in tablet formulation.

Methods Each co-processed excipient (CPE) was evaluated for flowability, tabletability, compressibility and compactibility. Formulations were prepared using four model drugs (promethazine, theophylline, hydrocortisone, and paracetamol) at drug loadings of 20 and 30% w/w. A single-punch tablet press was employed to prepare the tablets and were evaluated under harmonised conditions for strength, friability, disintegration and dissolution.

Results Different performance profiles were observed among the excipients. SuperTab® 40LL exhibited the strongest flow properties. StarLac® demonstrated superior disintegration speed and dissolution performance but had the weakest tensile strength, failing friability testing at 30% paracetamol loading. MicroceLac® 100 demonstrated enhanced mechanical strength and compactibility, coupled with consistently low friability values for all APIs tested, but generally failed British Pharmacopoeia criteria for disintegration and dissolution. Regardless of the excipient used, tablets containing hydrocortisone exhibited the poorest disintegration and dissolution. Overall, most formulations complied with friability specifications, confirming good manufacturability.

Conclusion Excipient performance depended on API properties, drug loading, and formulation strategy. StarLac® provides optimal performance in terms of fast disintegration and high dissolution rates, SuperTab® 40LL improves flow, and MicroceLac® 100 enhances mechanical strength. This comparative evaluation provides a framework for rational excipient selection and supports Quality-by-Design approaches in tablet formulation.

Keywords Co-processed excipients · direct compression · StarLac® · SuperTab® 40LL · MicroceLac® 100

Introduction

Oral solid dosage forms, particularly tablets, remain the most widely used method for drug delivery due to their convenience, stability, ease of administration, and cost efficiency during industrial-scale manufacturing. Among tablet manufacturing techniques, direct compression (DC) has become increasingly popular because it eliminates granulation steps, shortens production time, and reduces costs [1]. However, successful DC technique depends strongly on the physicomechanical characteristics of the active pharmaceutical ingredient (API), especially at high drug concentrations [2]. Many APIs exhibit poor flowability and compressibility, which can lead to problems such as weight variability, capping, lamination, or poor mechanical strength [3]. Therefore, the selection of suitable excipients is a key factor influencing the final tablet's performance.

Excipients constitute the bulk of most tablet formulations and perform multiple roles including acting as fillers, binders, disintegrants, glidants, and lubricants [4]. For DC, excipients should ideally retain key characteristics when combined with APIs, including good flowability to

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minimise processing issues at high tablet press speeds [5, 6]. Additionally, optimal excipients need to be stable, safe, colourless, and economically viable, while exhibiting low sensitivity to moisture and lubricants, as well as high dilution potential [2, 4, 7]. Traditional single excipients such as microcrystalline cellulose (MCC) and lactose have well-known limitations: MCC has poor flowability and lubricant sensitivity, whereas lactose, although brittle and free-flowing, has limited binding capacity [8–10].

To overcome these challenges, co-processed excipients (CPEs) have emerged as a promising alternative. CPEs are combinations of two or more excipients that are physically co-processed by a special particle engineering technique to create new particles with superior functional properties compared to simple physical mixtures [11]. These systems typically combine plastic and brittle components to improve compressibility, reduce elastic recovery, and enhance flow without chemical modification [12]. Since their constituents are already approved, CPEs often require less regulatory testing and offer advantages such as better dilution potential, improved machinability, and reduced sensitivity to lubricants [13–15]. However, co-processed excipients are associated with certain drawbacks. One of the major limitations is that they are made of a fixed ratio of individual constituents, and during formulation, this may not be a desirable choice for the dose and characteristics of the API [16]. Additionally, these excipients in many cases do not have an official monograph; consequently, they are not recognised by pharmacopoeias. This results in a longer time for regulatory approval, which makes them a less attractive choice for pharmaceutical companies [17]. Therefore, additional characterization such as physicochemical, performance, and compatibility studies is often required to support the safety and quality of a new drug product. Scaling up CPEs from laboratory to commercial manufacturing presents a major challenge, as it demands strict process control to maintain consistency in terms of quality and performance.

Lactose-based CPEs are among the most widely adopted in the pharmaceutical industry for direct compression tablet production. Examples include MicroceLac® 100 (≈90% α-lactose monohydrate + ≈10% microcrystalline cellulose), StarLac® (≈85% lactose monohydrate + ≈15% maize starch), and SuperTab® 40LL (≈75% spray-dried lactose + ≈25% microcrystalline cellulose/lactitol). MicroceLac® 100 integrates brittle and plastic deformation mechanisms to enhance binding and flow [18]; StarLac® improves flow and compressibility while promoting rapid disintegration [19]; and SuperTab® 40LL provides excellent flowability and lubricant insensitivity suitable for high-speed tableting [20].

Despite their increasing use, there is a lack of systematic, comparative data to guide excipient selection. Many studies focus on a single co-processed excipient (CPE) or compare only two, often under varying APIs, compression conditions, or analytical protocols, which limits the ability to directly compare results across studies. Moreover, investigations are frequently restricted to a single model API, typically at low drug loadings, providing little insight into how CPEs perform with drugs of differing solubility and mechanical properties.

To address this limitation, model APIs were selected to represent a wide range of aqueous solubilities and mechanical characteristics. According to the British and European Pharmacopoeias, paracetamol is classified as sparingly soluble in water and is known to exhibit poor flowability and low compressibility. Theophylline is a crystalline powder classified as very slightly soluble in water. Promethazine hydrochloride is freely soluble in water, while hydrocortisone is a hydrophobic drug classified as practically insoluble in water. These drugs therefore provide a representative spectrum of solubility behaviour relevant to direct compression formulation challenges.

The present study addresses this gap by providing a direct, head-to-head comparison of three commonly used lactose-based CPEs StarLac®, SuperTab® 40LL, and MicroceLac® 100 using a unified experimental framework. Four model APIs with distinct properties were incorporated at 20% and 30% loadings to evaluate excipient performance across realistic formulation conditions. The study integrates assessment of flowability, compressibility, compactibility, tabletability, friability, disintegration, and dissolution.

By systematically evaluating these excipients under comparable conditions, this work provides practical data to support rational excipient selection for DC tablet formulations and informs Quality-by-Design (QbD) development strategies for oral solid dosage forms.

Materials and Methods

Materials

The model drugs promethazine hydrochloride, acetaminophen (paracetamol; USP grade, 98.0–102.0%), hydrocortisone (≥98%, HPLC), and anhydrous theophylline (>99%) and reagents such as sodium hydroxide (NaOH) and potassium dihydrogen phosphate (KH_2PO_4) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The directly compressible excipient SuperTab® 40LL was supplied by DFE Pharma (Goch, Germany), while other co-processed excipients, StarLac®, and MicroceLac® 100, were obtained from MEGGLE GmbH (Wasserburg, Germany) and sodium stearyl fumarate (PRUV®) from JRS Pharma (Rosenborg,

Germany). All materials were used as received without further modification.

The APIs were chosen to represent a range of physicochemical properties related to direct compression method, including differences in dose, solubility, particle characteristics, and deformation behaviour. The CPEs were selected due to their widespread industrial use in direct compression and their differing compositions and manufacturing approaches. These CPEs combine brittle and plastically deforming components, offering varied mechanical performance and drug–excipient interaction profiles.

True Density

A helium pycnometer (Multipycnometer™, Quantachrome, Florida, USA) was used to measure the true density (ρ) of the CPEs based on the gas displacement method. Helium gas penetration into pores and interparticulate spaces enables accurate determination of true volume, ensuring high reliability and reproducibility [21]. All measurements were conducted in triplicate ($n=3$) in accordance with the British Pharmacopoeia, and results are reported as mean ± standard deviation.

The true density of the samples was calculated using the following equation (Eq. 1):

True density calculation

$$\text{True Density}\,(\rho) = \frac{\text{Sample Weight}}{\text{Sample Volume}} \tag{1}$$

where the sample volume V_s is given by:

$$V_S = V_C + \frac{v_r}{1 - \frac{P_1}{P_2}}$$

Here, V_s represents the sample volume, V_c is the volume of the empty sample chamber, V_r is the reference volume, P_1 is the pressure in the sample chamber, and P_2 represents the reduced pressure measured after the gas expands to fill both the sample and reference chambers. The values of V_c and V_r were obtained from prior calibration.

The true density values were subsequently applied to calculate the solid fraction of the CPEs by Eqs. 2 and 3.

Solid fraction

$$Solid\ Fraction = \frac{\text{Tablet Density}}{\text{True Density}} \tag{2}$$

Tablet density

$$Tablet\ Density = \frac{\text{Weight}}{\text{Volume}} \tag{3}$$

Tablet Volume

$$\text{Tablet Volume} = \pi r^2 T \tag{3}$$

- r = tablet radius (mm)
- T = tablet thickness (mm)

Powder Preparation for Direct Compression

For formulation preparation, the CPEs were combined with the model drugs at two drug loading levels (20 and 30%w/w) and 1%w/w sodium stearyl fumarate (SSF) as a lubricant (Table 1). API concentrations of 20 and 30 wt% were selected to represent moderate and relatively high drug loading levels commonly encountered in immediate-release tablet formulations prepared by direct compression. The powder components were homogeneously blended in a TURBULA® shaker-mixer (Type T2 C, Willy A. Bachofen AG, Basel, Switzerland). The procedure was performed in two steps: first, the drug and CPE were mixed for 5 min; then, SSF was added and blending continued for an additional 2 min.

For hydrocortisone and paracetamol formulations, a slightly modified procedure was followed. Due to agglomerate formation, the initial blend (after the first 5 min) was passed through a 500 µm sieve to break up and remove agglomerates. The sieved powder was subsequently remixed for a further 5 min before adding the lubricant.

Flowability

A TD1 Tap Density Tester (SOTAX Corporation, Massachusetts, USA) was utilised to evaluate the flow properties of the CPEs, both alone and in combination with the model drugs. This analysis followed Methods 1 and 2 as described in the British and European Pharmacopoeias (Ph. Eur. 2.9.34). Flowability was assessed by determining the bulk density (ρ_bulk), tapped density (ρ_tapped), Carr's compressibility index (CI), and Hausner ratio (HR). Each measurement was repeated three times ($n=3$) using new samples each time, and results are reported as mean ± standard deviation with temperature and relative humidity controlled at 25 °C and 40%, respectively.

Preparation of Tablets

All powder blends, including excipient-only mixtures and those containing the four model drugs, were processed into tablets using direct compression method. A Riva Minipress MII single-punch tablet press (Riva, Hampshire, UK) equipped with 10 mm round flat punches was employed for tablet preparation. Formulations containing only excipients were compressed under forces ranging from 900 to 10,000 N.

Table 1 Composition of formulated powder blends used in direct compression

Blend ID	Excipient type	Excipient % (w/w)	Drug model	Drug % (w/w)	Lubricant (SSF) %
C1	StarLac®	99%	-	-	1%
C2	MicroceLac® 100	99%	-	-	1%
C3	SuperTab® 40LL	99%	-	-	1%
C4	StarLac®	79%	Paracetamol	20%	1%
C5	MicroceLac® 100	79%	Paracetamol	20%	1%
C6	SuperTab® 40LL	79%	Paracetamol	20%	1%
C7	StarLac®	69%	Paracetamol	30%	1%
C8	MicroceLac® 100	69%	Paracetamol	30%	1%
C9	SuperTab® 40LL	69%	Paracetamol	30%	1%
C10	StarLac®	79%	Hydrocortisone	20%	1%
C11	MicroceLac® 100	79%	Hydrocortisone	20%	1%
C12	SuperTab® 40LL	79%	Hydrocortisone	20%	1%
C13	StarLac®	69%	Hydrocortisone	30%	1%
C14	MicroceLac® 100	69%	Hydrocortisone	30%	1%
C15	SuperTab® 40LL	69%	Hydrocortisone	30%	1%
C16	StarLac®	79%	Theophylline	20%	1%
C17	MicroceLac® 100	79%	Theophylline	20%	1%
C18	SuperTab® 40LL	79%	Theophylline	20%	1%
C19	StarLac®	69%	Theophylline	30%	1%
C20	MicroceLac® 100	69%	Theophylline	30%	1%
C21	SuperTab® 40LL	69%	Theophylline	30%	1%
C22	StarLac®	79%	Promethazine	20%	1%
C23	MicroceLac® 100	79%	Promethazine	20%	1%
C24	SuperTab® 40LL	79%	Promethazine	20%	1%
C25	StarLac®	69%	Promethazine	30%	1%
C26	MicroceLac® 100	69%	Promethazine	30%	1%
C27	SuperTab® 40LL	69%	Promethazine	30%	1%

Blends C1–C3 consisted of a single CPE combined with SSF. Blends C4–C27 included a model drug at either 20% or 30% w/w together with one of the three CPEs (StarLac®, SuperTab® 40LL, or MicroceLac® 100). All formulations contained 1% w/w SSF as a lubricant

In the case of blends with active pharmaceutical ingredients (APIs), compression was applied at the optimal forces determined from preliminary trials to achieve satisfactory mechanical strength (Table 2). The optimal compression forces were determined from tabletability profiles obtained during preliminary trials in which each co-processed excipient (CPE) was compressed alone. Tabletability graphs, which relate tensile strength to compression pressure or force, were used to evaluate the evolution of tablet strength with increasing compaction. For each formulation, the optimal compression force was selected within the region where tensile strength increased progressively with applied force, indicating effective interparticulate bonding, while tablets maintained structural integrity without visible defects such as capping or lamination. Compression forces beyond this region were avoided, as further increases did not yield substantial improvements in tensile strength.

Table 2 Applied compression forces for co-processed excipient (CPE) formulations with model APIs

StarLac® + API compression force (*N*)	MicroceLac®100 + API compression force (*N*)	SuperTab® 40LL + API compression force (*N*)
7500 ± 500	7000 ± 500	8000 ± 500

The table presents the nominal compression forces (in newtons) applied to StarLac®, MicroceLac® 100, and SuperTab® 40LL combined with model APIs during direct compression. Each excipient-API formulation was subjected to forces that fluctuated approximately ± 500 N around the nominal value to generate compressibility profiles for subsequent analysis

Fifty tablets with weight about 300 mg were prepared from each batch and stored in sealed containers under ambient conditions for friability, disintegration, and dissolution testing. This sample size was selected to ensure sufficient numbers for mechanical and performance testing, including tensile strength, friability, disintegration, and dissolution. The chosen batch size is commonly accepted practice in tablet formulation studies, providing a balance between experimental reproducibility and material availability. Mechanical characterisation (compressibility and compactibility testing) was initiated 15 min after tablet compression. All formulations were tested using the same post-compression time interval to ensure consistency across batches.

Evaluation of Tablet Physical Characteristics and Compression Performance

For physical characterisation, ten tablets from each batch were randomly chosen. An analytical balance (XS204, 0.01 mg precision; Mettler Toledo Inc., Ohio, USA) was used to measure tablet weight, a digital Vernier caliper (LUPO 150 mm Stainless Steel; LUPO Ltd., Northampton, UK) recorded thickness, and tablet hardness was evaluated using a hardness tester (MT50; SOTAX Group, Aesch, Switzerland). Tablet thickness was measured once for each tablet using a LUPO 150 mm Vernier caliper with a precision of ± 0.01 mm. The recorded measurements were

used to determine the compression behaviour of the tablets through calculations of tablet volume (Eq. 4), tensile strength (Eq. 5), an compaction pressure (Eq. 6).

Tensile Strength (σ)

$$\sigma = \frac{2p}{\pi DT} \tag{5}$$

Tensile strength (σ) was calculated to assess the mechanical integrity of the tablets. It was determined using six tablets per formulation ($n=6$), and mean values ± standard deviation were reported. This parameter reflects the tablet's ability to withstand fracture or breakage during handling. In the equation, **p** represents the crushing strength measured in newtons (N), **D** is the tablet diameter (mm), and **T** is the tablet thickness (mm). By relating the breaking force to the tablet's dimensions, this equation provides an estimate of the internal bonding strength within the compact.

Compression Pressure (MPa)

$$\text{Compression Pressure} = \frac{\text{Compression Force (N)}}{\text{Punch Surface Area } (mm^2)} \tag{6}$$

Compression profiles were generated using the recorded parameters as outlined below:

- **Tabletability**: tensile strength plotted against compression pressure.
- **Compressibility**: solid fraction plotted against compression pressure.
- **Compactibility**: tensile strength plotted against solid fraction.

Friability

Using an analytical balance (HR-120, A&D Company, Tokyo, Japan), about 6.5 g of tablets (corresponding to the minimum weight requirement) were accurately weighed for each test then loaded into a FT 2 friability tester (SOTAX Group, Aesch, Switzerland). Tablets were randomly selected from each batch to ensure representative sampling. The test was carried out following the British Pharmacopoeia method for 4 min at 25 rpm (equivalent to 100 rotations). After testing, the tablets were collected, any loose dust removed and reweighed to determine the percentage weight loss. Equation 7 was applied to calculate the friability percentage.

% friability

$$\%\text{friability} = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \tag{7}$$

Disintegration Test

A manual two-station tablet disintegration tester (DT2, Sotax, Aesch, Switzerland) was used to evaluate disintegration according to Ph. Eur. method 2.9.1. Six tablets ($n=6$) with minimum size 2.12 mm were placed individually in the basket rack tubes and immersed in 800 mL of distilled water at 37 °C. Complete disintegration was performed once and defined as the absence of any remaining tablet pieces larger than 2.0 ± 0.2 mm, in accordance with Ph. Eur.

Dissolution Test

Tablets formulated with co-processed excipients and model drugs were evaluated for dissolution using a paddle apparatus (DIS 600i, Copley Scientific, Nottingham, UK) according to Ph. Eur. 2.9.3, with the test run at 50 rpm for 45 min. Dissolution studies were carried out once for each formulation using six tablets tested in parallel ($n=6$). For theophylline, promethazine, and hydrocortisone tablets, 900 mL of distilled water dissolution medium maintained at 37 ± 0.5 °C, while paracetamol tablets were tested using 0.05 M potassium phosphate buffer (KH_2PO_4/NaOH, pH 5.8). Following the test, samples were taken from the vessels, and a UV-Visible spectrophotometer (Genesys 6, Thermo Electron Corporation, New York, USA) was used to measure their absorbance without prior filtration. The detection wavelengths were 248 nm for hydrocortisone, 257 nm for paracetamol, 224 nm for promethazine, and 272 nm for theophylline. Analyte quantification was performed using external standard calibration, with calibration curves constructed from serial dilutions of reference standards to correlate instrument response with concentration. The cumulative percentage of drug released at each sampling interval was calculated from the measured concentrations and reported relative to the initial drug content of the dosage form, following predefined analytical procedures and quality-control criteria. The quality control of the tablets was ensured according to Ph. Eur. specifications for dissolution and drug content. Quality-control criteria included verification of dissolution apparatus suitability, maintenance of test temperature and rotation speed in accordance with Ph. Eur. 2.9.3, confirmation of sink conditions, and validation of the UV–Vis analytical method in terms of linearity, precision, and specificity (Ph. Eur. 2.2.25). The analytical methods were validated following ICH Q2(R2) guidelines for linearity, accuracy, precision, and specificity. Furthermore, the dissolution procedures used are consistent with the methods described in the relevant pharmacopoeial monographs for each drug substance investigated.

Preparation of Calibration Standards and Serial Dilutions

Stock solutions were prepared by accurately weighing theophylline, hydrocortisone, paracetamol, and promethazine on an electronic balance, then dissolving each in the designated solvent to the target volume. Specifically, promethazine (63.8 mg) in 100 mL distilled water with sonication; paracetamol (58.4 mg) was dissolved in 500 mL phosphate buffer with sonication; theophylline (32.2 mg) in 1000 mL distilled water; and hydrocortisone (51.7 mg) in 500 mL distilled water with sonication.

Serial dilutions were prepared by transferring measured aliquots of each stock into 25 mL volumetric flasks and making up to volume with distilled water. For paracetamol, hydrocortisone, and promethazine, aliquots of 10, 7.5, 5, 2.5, and 1 mL were used; for theophylline, aliquots of 20, 15, 10, 5, and 1 mL were used. UV absorbance of each solution was measured using a spectrophotometer, and calibration curves were constructed and covered the whole concentrations for all samples that was taken from dissolution vessels. The UV–Vis spectrophotometric method used for API quantification was evaluated for linearity over the concentration ranges relevant to each API. The correlation coefficients (R^2) obtained were 0.998 for promethazine, 0.9954 for theophylline, 0.9952 for hydrocortisone, and 0.9951 for paracetamol, indicating good linearity for all APIs.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics (version 30.0.0.0 (172), IBM Corp., USA). Three-way analysis of variance (ANOVA) was employed to investigate the effects of excipient type (StarLac®, SuperTab® 40LL, and MicroceLac® 100), API type, and drug loading level (20% and 30%) on tablet tensile strength and dissolution performance (% drug released at 45 min). All factors were treated as fixed effects, and a full factorial model was applied to evaluate main effects as well as two-way and three-way interactions. When statistically significant differences were detected, Tukey's HSD post-hoc test was used for pairwise comparisons. Statistical significance was defined as $p < 0.05$.

Results and Discussion

True Density

The true density values of the investigated lactose-based excipients are presented in Table 3. SuperTab® 40LL exhibited the highest true density (1.673 g/cm³), followed by MicroceLac® 100 (1.645 g/cm³) and StarLac® (1.627 g/cm³). The observed differences can be attributed to variations in composition and co-processing techniques, particularly the presence of binder components and differences in particle packing at the solid-state level. These density variations may influence downstream processing behavior, including powder flow, compressibility, and tablet porosity, and should therefore be considered when selecting excipients for direct compression formulations.

Table 3 True density of co-processed excipients (mean ± SD, $n = 3$)

Excipient	True density (g/cm³)
StarLac®	1.627 ± 0.024
MicroceLac® 100	1.645 ± 0.042
SuperTab® 40LL	1.673 ± 0.047

Flowability

As presented in Table 4, when CPEs evaluated alone, in the absence of API, StarLac® and SuperTab® 40LL exhibited superior flow characteristics compared with MicroceLac® 100. The observed differences in flowability are likely influenced by several physicochemical factors, including particle size, morphology, surface area, moisture content, and bulk density [22]. The presence of microcrystalline cellulose (MCC) in MicroceLac® 100 may account for its fair flowability, as MCC generally exhibits inferior flow properties compared with lactose [22]. An inverse relationship between the Hausner ratio and particle sphericity has been documented, with increased sphericity resulting in a decreased Hausner ratio [23]. The more spherical and smoother particles of StarLac® compared with MicroceLac® 100 are believed to enhance its flow characteristics [19]. Additionally, MicroceLac® 100 typically exhibits a broader range of particle size distribution, with higher proportion of coarse particles [24], which may further influence its flow performance. It should be noted that sieving during the powder preparation process could potentially alter the particle size distribution, which may affect flow characteristics. SuperTab® 40LL consists of anhydrous lactose and lactitol monohydrate known for their improved flow properties [25, 26]. The combination of these two components results in a co-processed excipient with enhanced functional characteristics, including improved flow, which is typical of agglomerated products [27]. The findings of the present study are consistent with previously published data. Özalp et al. [28] reported that StarLac® demonstrates good flowability, in line with the results observed here. Similarly, Bowles et al. [29] described MicroceLac® 100 as exhibiting fair flowability, and another study [30] classified its flow as fair to passable. In contrast, Dominik et al. [31] found that StarLac® shows excellent flowability, whereas MicroceLac® 100 was characterised as having good flowability, further supporting

Table 4 Summary of hausner ratio, compressibility index, and flow properties british pharmacopoeia scale (BP) for powder blends containing model APIs at 20% and 30% loadings with co-processed excipients. Values represent mean ± standard deviation of three (n = 3) independent measurements

API	MicroceLac® 100			StarLac®			SuperTab® 40LL		
	Hausner Ratio	Carr's Index (%)	Flowability (BP Scale)	Hausner Ratio	Carr's Index (%)	Flowability (BP Scale)	Hausner Ratio	Carr's Index (%)	Flowability (BP Scale)
Neat CPE (no API)	1.2 ± 0.00	16.67 ± 0.00	Fair	1.14 ± 0.004	12.33 ± 0.29	Good	1.14 ± 0.029	12.82 ± 2.28	Good
20% Paracetamol	1.39 ± 0.00	28.39 ± 0.00	Poor	1.36 ± 0.018	26.92 ± 0.62	Poor	1.28 ± 0.033	19.03 ± 1.53	Passable
30% Paracetamol	1.38 ± 0.069	27.83 ± 3.03	Poor	1.37 ± 0.030	26.84 ± 1.39	Poor	1.60 ± 0.050	37.78 ± 1.91	Very poor
20% Promethazine	1.25 ± 0.033	20.00 ± 2.89	Fair	1.2 ± 0.000	16.67 ± 2.89	Fair	1.17 ± 0.005	14.76 ± 0.36	Good
30% Promethazine	1.34 ± 0.043	24.96 ± 2.89	Passable	1.2 ± 0.022	16.67 ± 1.65	Fair	1.33 ± 0.035	24.96 ± 2.27	Passable
20% Theophylline	1.21 ± 0.027	17.78 ± 2.31	Fair	1.23 ± 0.033	18.67 ± 2.89	Fair	1.18 ± 0.033	18.67 ± 2.31	Fair
30% Theophylline	1.25 ± 0.00	20.15 ± 0.00	Fair	1.25 ± 0.042	20.00 ± 3.12	Fair	1.19 ± 0.029	18.89 ± 1.53	Fair
20% Hydrocortisone	1.47 ± 0.011	32.32 ± 0.62	Very poor	1.37 ± 0.018	27.28 ± 0.87	Poor	1.29 ± 0.036	22.67 ± 2.31	Passable
30% Hydrocortisone	1.49 ± 0.040	33.27 ± 1.73	Very poor	1.42 ± 0.062	29.72 ± 2.79	Poor	1.42 ± 0.000	30.00 ± 0.000	Poor

the comparative trends observed in this study. The differences observed between the present study and the findings reported by Dominik et al. [29] may be attributed to several factors. Minor variations in the proportion of fine or coarse particles, or differences in environmental humidity during testing, may have contributed to the slightly lower flow rating for MicroceLac® 100 observed here. Additionally, differences in measurement techniques or equipment calibration could also account for discrepancies between studies.

As indicated in Table 3, CPEs incorporating hydrocortisone or paracetamol did not achieve pharmacopeial flowability requirements across all tested concentrations. SuperTab® 40LL was the only excipient to demonstrate adequate flowability when combined with 20% paracetamol or 20% hydrocortisone. Poor flow performance in paracetamol-containing mixtures can be attributed to the prismatic shape of paracetamol particles and their relatively high mass-to-surface area ratio, which negatively affects flow behaviour [32]. The lowest flowability values among all API–excipient combinations were observed in the 30% hydrocortisone formulations. In these formulations, MicroceLac® 100 showed very poor flowability, whereas SuperTab® 40LL and StarLac® exhibited poor flowability. The observed reduction in flow performance can be explained by the adhesive nature of hydrocortisone, affected by its particle morphology and size, along with interparticulate forces including Van der Waals and electrostatic interactions [33]. Among the four model drugs evaluated, formulations containing 20% promethazine exhibited the best flow characteristics, likely due to the interaction between drug and excipient or advantageous particle properties of the mixtures. Previous studies have reported that promethazine powder possesses good inherent flowability, supporting this observation [34].

Tablet Compression Profiles

Tabletability

Figure 1 presents the tabletability profiles of the CPEs, illustrating the influence of compression pressure on tablet tensile strength. The highest tensile strength was observed for SuperTab® 40LL, whereas the lowest values were recorded for StarLac®. MicroceLac® 100 showed intermediate performance, with tensile strength values higher than those of StarLac®, which is consistent with the findings reported by Dominik et al. [31]. In general, the tensile strength of all excipients increased as compression pressure increased; nevertheless, a reduction was noted for StarLac® at 132.42 MPa, suggesting a reduction in compactibility at higher pressures [35].

This behaviour can be explained by the fact that StarLac® comprises maize starch, a plastic material with high elasticity [31]. The higher pressure stores more elastic energy in viscoelastic components (starch), and release on decompression can create internal flaws (microcracks) that lower measured tensile strength [36]. Moreover, Starch needs higher compression pressures and longer dwell times to form bonds, and the elastic deformation of its particles can lead to a reduction in tensile strength. SuperTab® 40LL, composed mainly of anhydrous lactose and lactitol monohydrate, exhibited the most favourable tabletability properties among the evaluated CPEs. Its superior performance can be attributed to the combined deformation mechanisms of fragmentation and plastic deformation, which enhance the formation of interparticulate bonding sites during compression [37, 38]. The high proportion of anhydrous lactose (approximately 95%) likely plays a key role, given its superior tabletability relative to other lactose forms [39]. Lactose primarily undergoes consolidation through fragmentation,

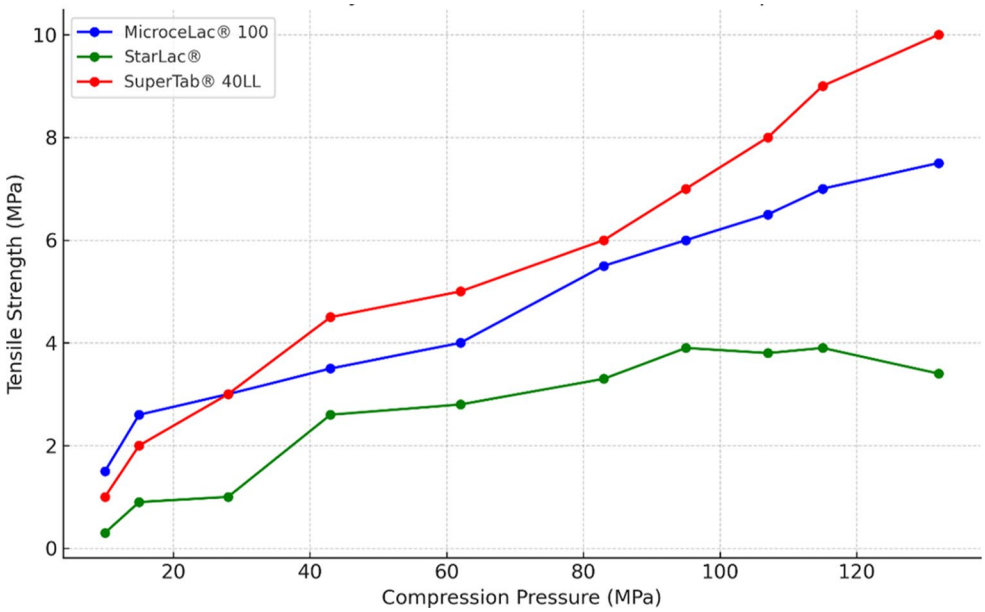

Fig. 1 Tabletability profiles showing tensile strength versus compaction pressure for SuperTab® 40LL, StarLac®, and MicroceLac® 100 prepared by direct compression

with the degree of fragmentation increasing as particle size increases [40]. Owing to its agglomerated anhydrous lactose composition and larger particle size, SuperTab® 40LL exhibits a greater tendency toward fragmentation during compression, resulting in enhanced tabletability. Furthermore, the strength of the interparticulate bonds formed during compression likely contributed to the reduced elastic recovery during decompression, further improving tablet integrity [41]. According to Vromans et al. [39], the superior binding properties of anhydrous lactose-based co-processed excipients are largely influenced by morphological characteristics, such as crystallinity, which are determined by manufacturing conditions. By comparison, StarLac® demonstrated the lowest tabletability among the CPEs. This can be attributed to its high lactose monohydrate content, which is known to exhibit relatively low tabletability compared with other lactose types [39]. Additionally, the starch component in StarLac® shows more pronounced elastic behaviour during compression compared with cellulose [31], which negatively affects tablet strength. Nevertheless, the combination of starch and lactose in StarLac® produced a synergistic effect that improves tabletability compared with lactose alone [42]. However, achieving acceptable hardness with StarLac® compacts typically requires the application of higher compression pressures [31]. The combination of plastically deforming MCC with brittle lactose in MicroceLac® 100 contributes to its improved tabletability. MCC is well known for its excellent binding properties, which contribute to high tensile strength and enhanced compactibility. However, it is highly sensitive to lubricants such as SSF, often leading to softer tablets with reduced tensile strength [22]. The inclusion of lactose, which is less lubricant-sensitive, helps to mitigate this effect by preventing the lubricant from fully coating the MCC particles and thereby reducing lubricant sensitivity [22, 43].

Compressibility

Figure 2 shows the compressibility profiles of the CPEs alone without APIs. Although differences exist between the curves, they generally follow similar trends. All CPEs exhibited minimal risk of overcompression, as their solid fraction values were below 0.9 at compression pressures below 140 MPa. Additionally, all formulations exhibited a gradual increase in solid fraction at compression pressures below 40 MPa, consistent with the findings of Dominik et al. [31], who observed that the solid fraction of StarLac® rises in response to higher compression pressure. Compared to their physical mixtures, all three CPEs showed plastic deformation and particle fragmentation, which improve compressibility. According to Mužíková and Vajglová [43] MicroceLac® 100 possesses markedly higher compressibility than a physical mixture of microcrystalline cellulose (MCC) PH-102 and spray-dried lactose. This enhanced performance may be attributed to the co-processing method, which promotes improved particle bonding and uniformity, rather than the presence of MCC alone, which is one of the most compressible fillers for direct compression [44]. A compaction pressure of approximately 100 MPa is sufficient to produce pore-free MCC compacts, reflecting its high plasticity and the plasticising effect of residual moisture. Among lactose-based co-processed excipients, MicroceLac® 100 has been shown to form tablets with the highest pycnometric density, exhibiting minimal further increase beyond a certain compression pressure [31]. The compressibility of StarLac® is primarily governed by the

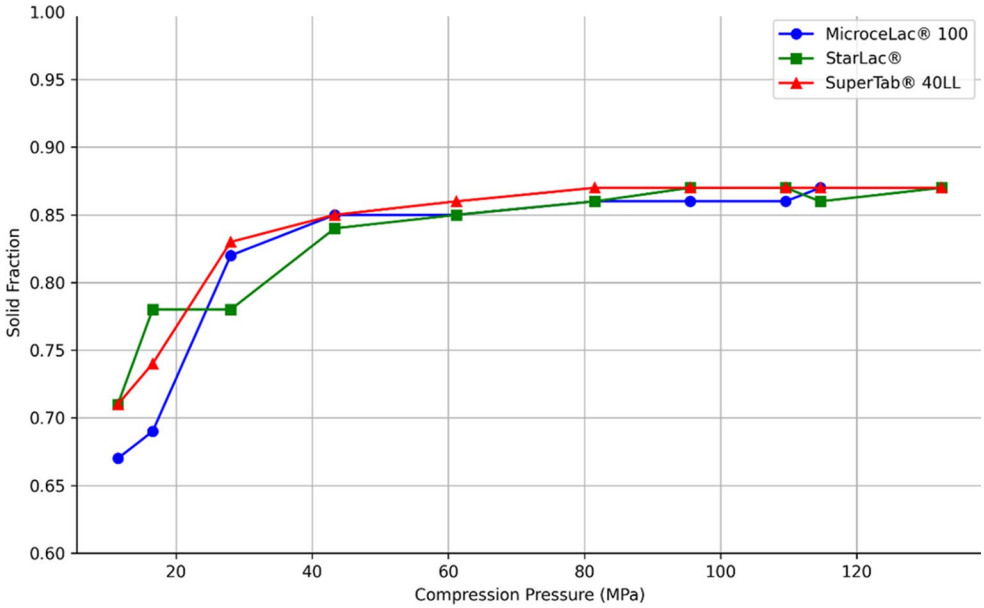

Fig. 2 Compressibility profiles for co-processed excipients (SuperTab® 40LL, StarLac®, and MicroceLac® 100). Solid fraction values were calculated based on true density, tablet thickness, diameter, and mass

fragmentation behaviour of lactose rather than the elastic response of starch in comparison with MicroceLac® 100. The higher compressibility of StarLac® can be explained by its dominant lactose fragmentation mechanism during compaction. According to the literature, the combination of a high proportion of brittle lactose and the viscoelastic properties of starch results in superior compressibility relative to plain lactose used for direct compression [17]. Brittle lactose fractures under pressure, creating fresh surfaces that enhance interparticle contact and bonding. The viscoelastic starch phase supports particle rearrangement and energy dissipation at low pressures, but its elastic recovery plays a secondary role. In contrast, MicroceLac® 100 relies more on plastic deformation than fragmentation. Therefore, the synergistic combination of lactose fragmentation and starch viscoelasticity in StarLac® results in more efficient densification and superior compressibility compared with plain lactose for direct compression.

SuperTab® 40LL also exhibited a favourable compressibility profile, which can be explained by its composition of anhydrous β-lactose and lactitol monohydrate. The combination of these two components has been demonstrated to enhance compressibility of the tablet [43]. Analysis of the compressibility profile of SuperTab® 40LL reveals a dual compression mechanism, where lactitol's plasticity and elasticity enable stress absorption and the formation of new bonding sites among the particles [45]

Compactibility

As shown in Fig. 3 for the compactibility profiles, all CPEs showed a progressive increase in tensile strength (σ) along with increasing solid fraction. The compactibility ranking of the excipients was as follows: MicroceLac® 100 > SuperTab® 40LL > StarLac®. The superior compactibility of MicroceLac® 100 resulted from a combined consolidation mechanism, whereby lactose undergoes fragmentation while MCC deforms plastically, which together improve particle bonding and densification [10, 46]. The high compactibility of MCC is related to its physicomechanical characteristics, including interparticulate bonding through solid bridge formation, mechanical interlocking, low bulk density, rod-shaped particle structure, and extensive surface area [46]. In the case of lactose, fragmentation produces smaller fragments that occupy the interparticulate voids, leading to tighter packing and denser compacts [46]. SuperTab® 40LL displayed superior compactibility compared to StarLac®, which can be explained by differences in their compositions. It has been reported in previous studies that the agglomerated anhydrous β-lactose, which represents the major constituent of SuperTab® 40LL, shows higher compactibility than α-lactose monohydrate [47, 48]. By contrast, StarLac® consists of a mainly brittle component (lactose) and a plastic–elastic component (starch) which exhibits both plasticity and elasticity; this combination is less advantageous for producing strong compacts. Literature reports have consistently reported that StarLac® demonstrates low mechanical strength, primarily attributed to the viscoelastic behaviour of starch and the high content of brittle lactose, both of which require extended dwell time and greater compression pressure for effective interparticle bond formation [31]. Although SuperTab® 40LL has the highest tensile strength in the tabletability profiles (Fig. 1), the compactibility profiles (Fig. 3) showed a different ranking. SuperTab® exhibited lower compactibility, while MicroceLac® 100 has the highest compactibility. This

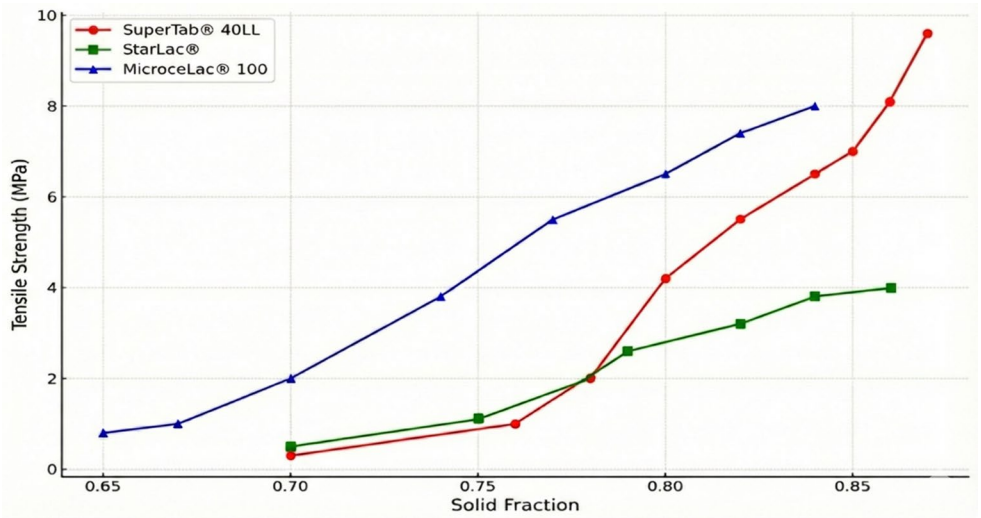

Fig. 3 Relationship between tensile strength and solid fraction (compactibility profile) for tablets produced using SuperTab® 40LL, MicroceLac® 100, and StarLac®

reflects the fundamental difference between tabletability and compactibility. Tabletability describes the ability of a material to develop tensile strength as a function of applied compression pressure. Compactibility is defined as the ability of a powder to form tablets with a specified strength under the influence of densification, expressed as an increase in solid fraction. The high tabletability observed for SuperTab® 40LL indicates efficient bond formation under compression. However, the comparatively lower compactibility suggests that tablet strength is not primarily caused by densification but rather by the nature and strength of interparticulate bonding. The superior compactibility of MicroceLac® 100 can be attributed to the synergistic consolidation mechanisms of plastic deformation of MCC and fragmentation of lactose, which promote efficient particle rearrangement and interparticulate bonding at higher solid fractions.

Tensile Strength

The tensile strength values of various CPEs combined with different APIs are presented in Fig. 4. Among the three excipients, StarLac® exhibited the lowest tensile strength, which can be attributed to its composition of lactose and starch, collectively resulting in weaker mechanical integrity. Conversely, MicroceLac® 100 exhibited the highest tensile strength overall, except in formulations containing 30% theophylline and 20% paracetamol, where SuperTab® 40LL produced greater tensile strength. Overall, SuperTab® 40LL exhibited moderate compactibility, with tensile strength results closely matching those of MicroceLac® 100 in most instances. The observed increase in tensile strength with the inclusion of microcrystalline cellulose (MCC) can be attributed to enhanced particle deformation and densification

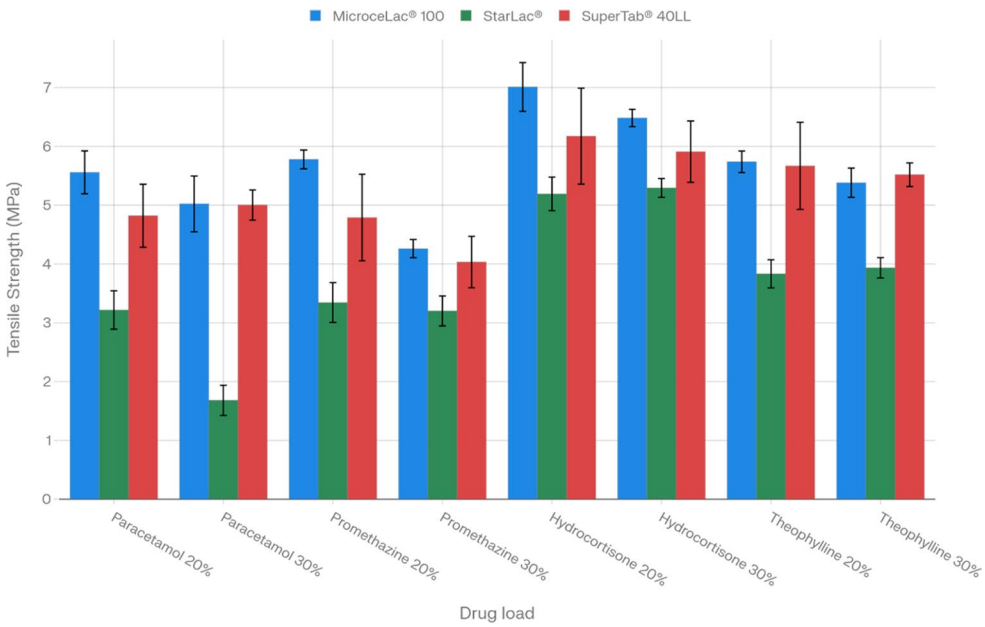

Fig. 4 Bars show mean tensile strength and error bars indicate variability (mean ± SD) of tablets ($n = 6$) formulated with the co-processed excipients using various APIs (promethazine, paracetamol, theophylline, and hydrocortisone) at two different drug loadings: 20% and 30%

during compaction. Compression promotes closer particle packing, produces more inter-particle contact sites, and facilitates the development of solid bonds, leading to tablets with higher mechanical strength [49]. Across the four APIs tested, hydrocortisone-containing tablets (20% and 30%) exhibited the highest tensile strengths for all CPEs. In contrast, MicroceLac® 100 and SuperTab® 40LL formulations containing 30% promethazine, as well as StarLac® formulations containing 30% paracetamol, exhibited the lowest tensile strength. The tensile strength remained largely unaffected by minor changes in CPE concentration, suggesting that other factors predominantly dictate tablet mechanical strength. Specifically, particle–particle interactions within the excipient blend (contact forces, friction, and bonding during compression) and the applied compression pressure.Using formulation-specific optimal compression forces ensured that each tablet achieved adequate mechanical strength; however, this approach may influence direct comparability between formulations, as the applied compression forces differed slightly among CPEs. Consequently, observed differences in tensile strength may reflect a combination of intrinsic excipient properties and the specific compression conditions employed. Therefore, comparisons across formulations should be interpreted with consideration of both excipient characteristics and compression-force effects. MicroceLac® 100 consistently produced tablets with the highest mechanical strength across multiple APIs, indicating its suitability for formulating challenging compounds. StarLac®, in contrast, is less suitable for applications requiring high tensile strength unless higher compaction pressures are applied. SuperTab® 40LL provided intermediate performance, suggesting that lactose-based excipients can be improved (e.g., via lactitol co-processing) but still do not fully match the mechanical performance of MCC-containing excipients. Across APIs, tensile strength followed the trend hydrocortisone > theophylline > paracetamol > promethazine, indicating that lower API solubility and higher cohesiveness enhance tablet strength. Hydrocortisone-containing tablets, in particular, achieved high tensile strength regardless of excipient type, highlighting the significant contribution of drug properties such as compressibility and particle cohesion. Although CPE concentration had a minor to moderate effect on tensile strength, particle interactions and compression pressure remained the predominant factors. Overall, tablet tensile strength is determined by a combination of excipient characteristics, CPE concentration, and API properties, particularly solubility and plasticity.

Three-way ANOVA revealed statistically significant main effects of excipient type ($F = 522.6$, $p < 0.001$), API ($F = 261.0$, $p < 0.001$), and drug loading ($F = 71.4$, $p < 0.001$) on tablet tensile strength. Significant two-way interactions were observed between excipient and API, excipient and drug loading, and API and drug loading ($p < 0.001$). A statistically significant three-way interaction between excipient, API, and drug loading was also detected ($F = 11.4$, $p < 0.001$), indicating that the influence of excipient on tensile strength was dependent on both API type and drug concentration.

Tukey's HSD post-hoc analysis demonstrated significant differences in tensile strength between all excipient pairs ($p < 0.001$). Tablets prepared with MicroceLac® 100 exhibited significantly higher tensile strength than those formulated with SuperTab® 40LL (mean difference = 0.39 MPa) and StarLac® (mean difference = 1.96 MPa). SuperTab® 40LL also produced significantly stronger tablets than StarLac® (mean difference = 1.57 MPa).

Friability

The friability results presented in Fig. 5 indicate that all co-processed excipients (CPEs) met the pharmacopeial requirement, achieving values below 0.5%, except for one distinct case. Tablets containing 30% paracetamol formulated with StarLac® failed the friability test, showing a friability value of 13.12%. This may be attributed to drug–excipient interactions at higher API loading and variations in particle packing within the CPE. Changes in API content (especially at high drug loadings) can affect tablet mechanical properties such as hardness and porosity, which in turn influence friability. This explains why tablets with 20% paracetamol passed the friability test, whereas those with 30% paracetamol failed when formulated with StarLac®. The elevated friability of StarLac® and SuperTab® which contain higher lactose concentrations compared to MicroceLac® 100 can be explained by the brittle deformation of lactose, which results in weaker compacts when subjected to compression [10]. Similar observations have been reported in the literature. For example, Gong and Sun [50] noted that lactose negatively affects tablet mechanical properties because of its brittle nature, and Paul and Sun [51] showed that formulations containing a higher proportion of lactose experienced greater weight loss during friability testing than those with higher MCC content. Notably, StarLac® formulations with 20% paracetamol showed a friability value of 0.20%, successfully complying with the pharmacopeial limit. Vandy et al. [52] indicated that paracetamol tablets generally display low friability, with friability values for different brands ranging from 0.09% to 0.77%, indicating their suitability for handling and packaging. Among the tested APIs, StarLac® showed the lowest friability with 20% promethazine (0.13%). SuperTab® 40LL exhibited consistently low friability across different paracetamol concentrations, with values of 0.20% for both 20% and 30% paracetamol. Across all tested drugs and concentrations, MicroceLac®

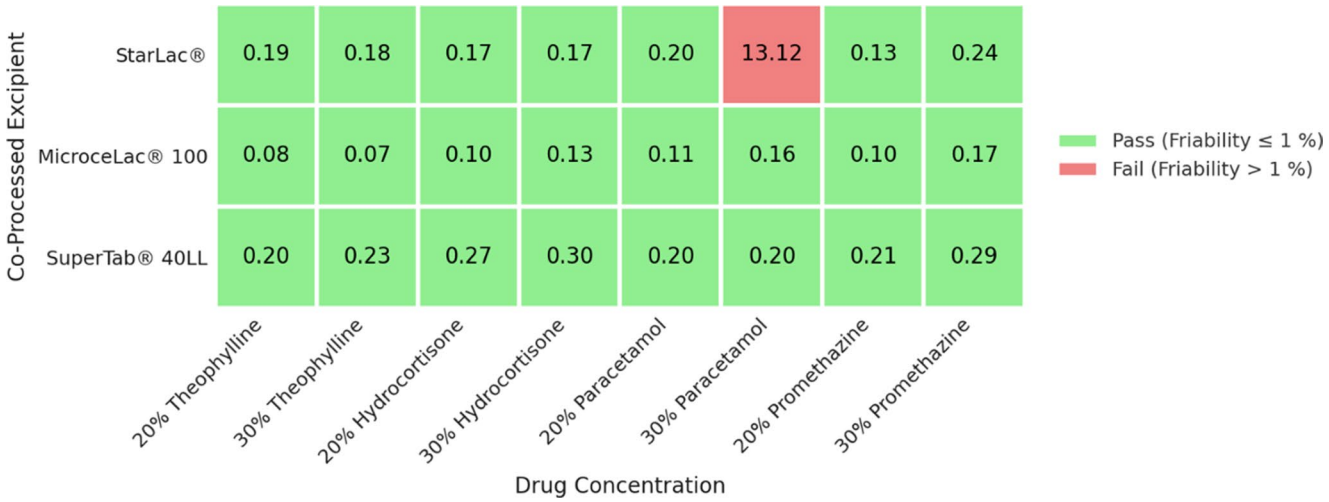

Fig. 5 Heatmap illustrating the friability percentage of formulations containing different APIs (promethazine, paracetamol, hydrocortisone, and theophylline) at 20% and 30% loadings, with CPEs (SuperTab® 40LL, MicroceLac® 100, and StarLac®). Green cells represent formulations that complied with the British Pharmacopoeia friability limit (≤1%), while red cells indicate non-compliance (>1%), as observed in the formulation containing StarLac® with 30% paracetamol

100 exhibited the lowest friability values compared to the other CPEs. The presence of MCC in MicroceLac® 100 contributes to its low friability, as higher MCC content generally leads to lowers friability by promoting plastic deformation and the development of strong interparticle bonds [46]. These observations are supported by previous studies. Dominik et al. [31] reported that StarLac® exhibits higher friability than MicroceLac® 100, primarily due to its high lactose content (~85%) and the presence of maize starch, which, being plastic and highly elastic, produces weaker interparticle connections. Conversely, Akin-Ajani et al. [30] linked the low friability of MicroceLac® 100 to its favorable particle shape and smaller particle size, both of which enhance interparticle bonding and packing density. Additionally, Narayan and Hancock [53] noted that surface roughness contributes to friability by increasing interparticle friction, which is associated with elevated friability in formulated tablets.

Disintegration

The disintegration times for tablets containing the CPEs and model APIs are shown in Fig. 6. Among the CPEs, StarLac® exhibited the fastest disintegration: all StarLac® formulations passed the disintegration test except those containing 20% and 30% hydrocortisone. These formulations also exhibited the highest tensile strength (Fig. 4), indicating that they were mechanically stronger and more compact than other tablets. The combination of high tensile strength and the cohesive nature of hydrocortisone likely contributed

Fig. 6 Disintegration-time heatmap for 20% and 30% drug-load tablets with StarLac®, SuperTab® 40LL, and MicroceLac® 100: Green cells in the heatmap represent formulations that meet the British Pharmacopoeia (BP 2025, monograph 2.9.1) disintegration requirement of 15 min or less (≤15 min), signifying a pass, while red cells indicate failure to meet this criterion (disintegration time>15 min). All disintegration times are reported in minutes

to slower disintegration, highlighting the drug- and concentration-dependent effects of StarLac® on tablet performance. StarLac® tablets containing 20% theophylline and 20% paracetamol showed the shortest disintegration times, disintegrating within 1.0 min. This behaviour aligns with previous reports describing StarLac® as a fast-disintegrating excipient [10, 19]. Dominik et al. [31] reported that orally dispersible tablets containing StarLac® disintegrated more rapidly than those containing MicroceLac® 100. The rapid disintegration performance of StarLac® can be attributed to its composition, as it contains starch, which functions as a disintegrant. Starch enhances water penetration, promotes tablet softening and swelling, and consequently disrupts the compact structure upon hydration [42, 54–56]. Additionally, the type of lactose used influences disintegration time, with anhydrous lactose promoting rapid disintegration when compared to lactose monohydrate 90 M, even when particle size is comparable [10]. In contrast, MicroceLac® 100 failed to pass the disintegration test all tested APIs primarily due to the presence of MCC [9]. A higher MCC content produces denser compacts with fewer pores, thereby reducing water penetration and delaying disintegration. Furthermore, wetting and dissolution may be hindered by the presence of physically entrapped, deformed MCC particles [2]. However, MCC can also enhance disintegration under certain conditions. Mužíková and Vajglová [43] reported that MCC absorbs water through a capillary network, causing swelling that generates forces to facilitate tablet disintegration. Similarly, Alamdari et al. [57] demonstrated that MCC increases tablet porosity, allowing more efficient water penetration and faster disintegration. Variability in disintegration times between different MCCs has been linked to differences in lubricant sensitivity and source [22, 43, 57]. Differences in API type, concentration, and formulation excipients also significantly influence disintegration behaviour [29, 30]. SuperTab® 40LL also failed the disintegration test for most formulations, except those containing 20% and 30% promethazine and 20% paracetamol. As shown in Fig. 6, formulations containing SuperTab® 40LL with 20% and 30% promethazine, as well as 20% paracetamol, exhibited the fastest disintegration. In contrast, hydrocortisone at both 30% and 20% loadings was the only API that consistently did not pass the disintegration test across all CPEs. It is worth noting that for all CPEs, formulations containing hydrocortisone exhibited the highest tensile strength compared with other APIs, which explain the influence of drug properties on tablet hardness. Overall, the data indicate that disintegration time decreases with increasing API solubility. Based on literature solubility data, the APIs used can be ranked as follows: promethazine > paracetamol > theophylline > hydrocortisone. This ranking correlates well with the observed disintegration and dissolution results. Tablets containing more soluble APIs generally exhibited faster disintegration and higher dissolution rates, as solubility facilitates water penetration into the tablet matrix [53]. Conversely, hydrocortisone, the least soluble API, showed slower disintegration and lower dissolution. While increasing drug concentration generally slightly increased disintegration time, an exception was observed with promethazine in SuperTab® 40LL, where higher concentrations slightly reduced disintegration time.

Dissolution

Figure 7 presents the dissolution profiles of tablets containing the four APIs formulated with the three CPEs, with the 75% drug release threshold indicated by a red dashed line. Total drug release values are shown to slightly exceed 100%. This may result from analytical variability in UV–Vis spectrophotometry, minor absorbance by excipients at the measurement wavelength, or small differences in tablet content uniformity, where certain tablets contain slightly higher amounts of the API. StarLac® fulfilled the dissolution specifications for tablets formulated with 20% and 30% theophylline, paracetamol and promethazine, indicating its superior performance. This finding aligns with Hauschild et al. [58], who reported that StarLac® facilitates faster drug release than other excipient formulations. The observed rapid dissolution is a consequence of its high water uptake and hydration efficiency [19] and particle morphology. StarLac® has a predominantly spherical particle structure, which may contribute to reduced compressibility, more rapid disintegration, and increased dissolution [59]Conversely, the lowest dissolution rates were observed for MicroceLac® 100, which failed the dissolution test for all tested drugs and loadings. This is likely due to its relatively high tensile strength, with lower porosity, restricting water penetration and consequently slowing dissolution. According to Akin-Ajani et al. and Lara Garcia et al. [30, 60] MicroceLac® 100 often exhibits higher dissolution than alternative CPEs; however, the lower dissolution rates observed here may reflect the influence of API type, experimental conditions, batch variability, particle size, compaction force, or interactions between API and excipient. The dissolution rate of SuperTab® 40LL was slightly higher than that of StarLac® for tablets containing 20% paracetamol, whereas StarLac®-containing formulations exhibited the highest dissolution among all excipients and APIs tested. Despite its performance at lower drug loadings, SuperTab® 40LL did not satisfy dissolution standards for 30% theophylline and 30% paracetamol tablets, yielding drug dissolution rates of roughly 74% and 65%, respectively. Tablets of 20% theophylline and 20% paracetamol showed the highest dissolution, complied with BP standards when tablets were prepared

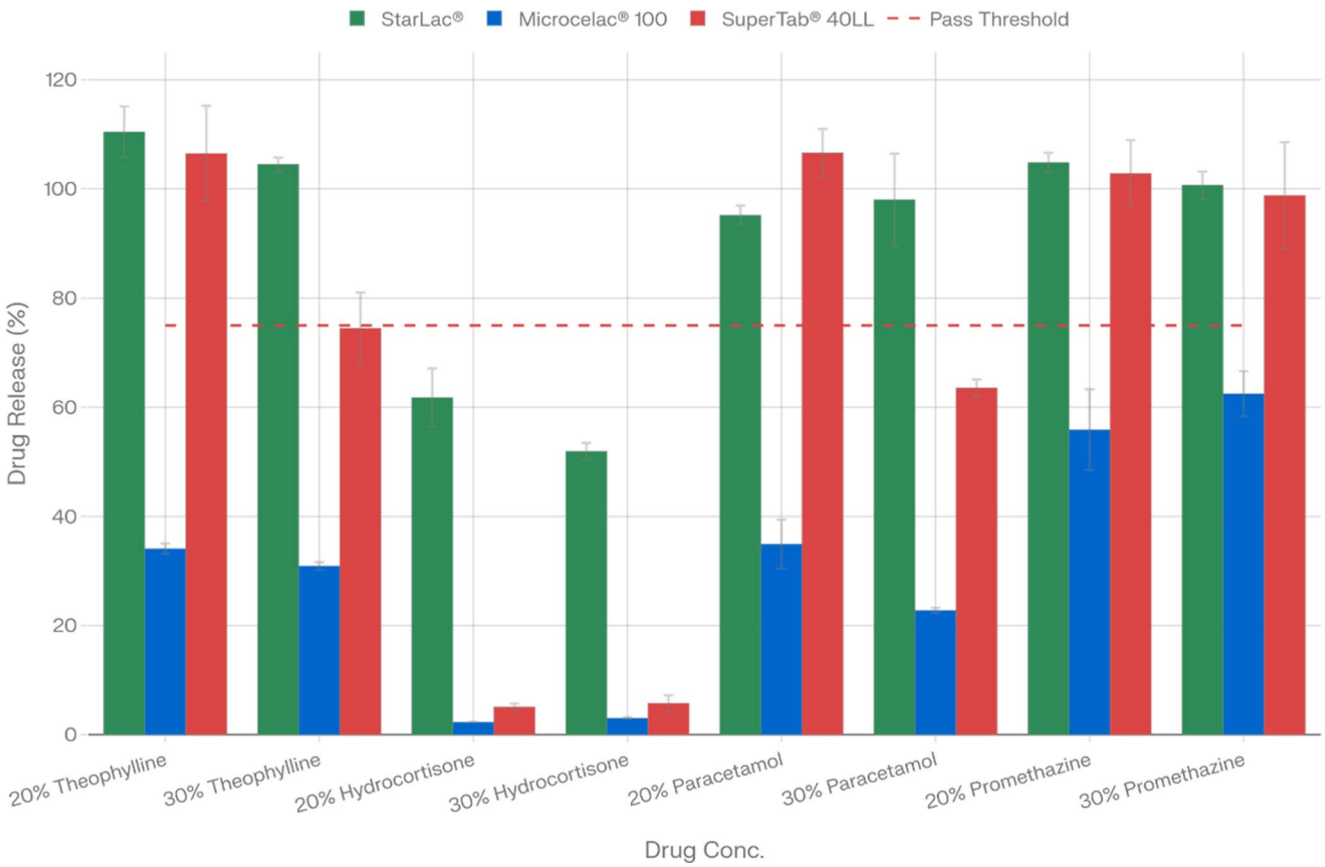

Fig. 7 Drug release percentages (%) for immediate-release tablet formulations of MicroceLac® 100, StarLac®, and SuperTab® 40LL, formulated with promethazine, paracetamol, hydrocortisone, and theophylline at 20% and 30% API concentrations, were measured at 45 min. Bars show mean drug release and error bars indicate variability (mean ± SD) of tablets of tablets ($n = 6$). The red dashed line denotes the British Pharmacopoeia (BP) threshold of 75% drug release for immediate-release tablets

using StarLac® or SuperTab® 40LL. In contrast, 20% and 30% hydrocortisone tablets exhibited the lowest dissolution rates, with none of the CPEs achieving satisfactory release, likely attributable to the hydrophobic nature of hydrocortisone, which restricts water ingress. It is worth mentioning, when interpreting the dissolution results, the relationship between the API doses investigated in this study and those commonly used in marketed products, particularly for hydrocortisone. In the present study, API loadings of 20% and 30% corresponded to doses of 60 mg and 90 mg, respectively, which are reasonable doses for paracetamol, theophylline, and promethazine, whereas commercially available hydrocortisone tablets typically contain a maximum dose of 20 mg. At these relatively high doses, saturation of the dissolution medium is likely to occur, which may have limited the extent of drug release and contributed to the generally low dissolution profiles observed across all co-processed excipients. Consequently, the dissolution behaviour under these conditions is predominantly solubility-limited rather than formulation-limited. Nevertheless, despite these challenging conditions, StarLac®-based formulations consistently exhibited superior dissolution performance. This may be attributed to the presence of starch in StarLac®, which promotes rapid tablet disintegration and enhances wettability, thereby facilitating drug release even when dissolution is constrained by API solubility. Promethazine tablets with StarLac® and SuperTab® at both 20% and 30% successfully met the dissolution criteria, consistent with the drug's hydrophilic nature. This indicates that the formulations allowed adequate water penetration and rapid disintegration, overcoming potential limitations from tablet hardness or compaction. Overall, the dissolution results closely mirrored the disintegration behaviour, confirming that disintegration was a key determinant of drug release. Formulations that disintegrated rapidly—particularly those prepared with StarLac® and, at lower drug loadings, SuperTab® 40LL—exhibited higher dissolution, whereas formulations with poor disintegration, notably those containing MicroceLac® 100 or hydrocortisone, showed limited drug release. The overall dissolution performance across APIs followed the order theophylline ≈ promethazine hydrochloride > paracetamol >> hydrocortisone, highlighting the

combined influence of API solubility, excipient wettability, and tablet microstructure.

The results also highlight clear differences in excipient dilution capacity. StarLac® demonstrated a high dilution capacity, maintaining acceptable disintegration and dissolution performance even at 30% API loading across multiple drugs. SuperTab® 40LL showed moderate dilution capacity, with satisfactory performance at 20% API loading but reduced dissolution at higher drug contents. In contrast, MicroceLac® 100 exhibited low dilution capacity, failing to maintain adequate tablet performance even at lower API loadings. These findings underscore the importance of excipient selection in high drug-load formulations and provide practical guidance for formulation development involving APIs with varying solubility.

Three-way ANOVA of dissolution data (% drug released at 45 min) revealed statistically significant effects of excipient type ($F = 1327.7$, $p < 0.001$), API ($F = 863.7$, $p < 0.001$), and drug loading ($F = 72.8$, $p < 0.001$). Significant two-way interactions were observed between excipient and API, excipient and drug loading, and API and drug loading ($p < 0.001$). A significant three-way interaction between excipient, API, and drug loading was also detected ($F = 14.9$, $p < 0.001$), indicating that dissolution behaviour was highly formulation-dependent. StarLac® exhibited significantly higher overall dissolution compared with SuperTab® 40LL and MicroceLac® 100, although excipient effects depended on API type and drug loading.

Tukey's HSD post-hoc analysis demonstrated significant differences in dissolution performance between all excipient pairs ($p < 0.001$). Tablets formulated with StarLac® showed significantly higher drug release compared with SuperTab® 40LL (mean difference = 21.3%) and MicroceLac® 100 (mean difference = 61.7%). SuperTab® 40LL also exhibited significantly higher dissolution than MicroceLac® 100 (mean difference = 40.4%).

Limitations

This study is subjected to several limitations, which also offer opportunities for future investigation. These limitations primarily stemmed from time restrictions, a relatively small sample size, limited access to advanced instrumentation, and financial constraints. Additionally, data for neat APIs were not included, which limits the ability to fully interpret the influence of co-processed excipients on tablet performance. Only four APIs were examined at two concentration levels, which limits the generalisability of the findings. Future research should therefore consider evaluating a wider variety of drugs with different physicochemical properties across multiple drug loadings. In this work, 1% sodium stearyl fumarate was used as the sole lubricant, and no disintegrants were incorporated. Exploring different lubricants and introducing various disintegrants—such as crospovidone, low-substituted hydroxypropyl cellulose (L-HPC), or higher levels of sodium starch glycolate (SSG)—would offer a more comprehensive understanding of excipient functionality. Additionally, advanced analytical tools including SEM, XRPD, DSC, DVS, and laser diffraction could be employed in future studies to better characterise particle morphology, solid-state properties, and interactions between excipients and APIs. Wettability and contact angle measurements were not included in this investigation; incorporating these techniques in future work would help clarify the role of interfacial properties on dissolution and disintegration behaviour. Furthermore, a single-punch press employing gravity-fed die filling was used for tablet production, which does not replicate industrial manufacturing conditions. Future studies should use rotary presses to assess the effects of feed-frame behaviour, compression rate, and process scalability. Finally, stability testing under accelerated conditions, along with evaluation of performance characteristics such as ejection force, sticking, capping, and lamination, is recommended to achieve a more comprehensive understanding of tablet robustness and manufacturability.

Conclusion

This study investigated the behaviour of three CPEs in direct compression tablet formulations using four models APIs at two concentration levels. Choosing the most appropriate CPE is inherently challenging, as each excipient possesses unique characteristics that address different formulation requirements. With respect to flow properties, SuperTab® 40LL showed performance comparable to StarLac® and was significantly superior to MicroceLac® 100. Increasing the proportion of excipient consistently enhanced powder flow across all formulations. MicroceLac® 100 displayed the highest mechanical strength and compactibility, making it particularly advantageous for formulations that require robust tablets. All formulations complied with pharmacopeial friability limits, with the exception of StarLac® combined with 30% paracetamol. StarLac® was identified as the most effective CPE for promoting rapid tablet disintegration and drug release. Conversely, across all APIs, MicroceLac® 100 failed disintegration tests and showed the poorest dissolution performance at both levels of drug loading. In summary, StarLac® is best suited for formulations targeting fast disintegration and dissolution, SuperTab® 40LL offers superior flow enhancement, and MicroceLac® 100 provides excellent mechanical strength. The behaviour of

the co-processed excipients was influenced by API type and concentration, along with key processing variables. These results contribute to the development of a structured comparative framework for evaluating CPEs, enabling formulators to select excipients that match specific formulation objectives. Such an approach can help accelerate product development, enhance tablet quality, and align with Quality by Design (QbD) principles in pharmaceutical manufacturing.

Author Contributions Dr. Matthew Roberts – Study conception and design, validation, and verification of results. Zaid Al-Dujaili – Data collection, analysis, interpretation of results, and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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Data Availability All data generated or analysed during this study are included in this published article and its supplementary materials.

Declarations

Competing interests The authors declare no competing interests.

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