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Dissolution enhancement and formulation of rapid release lornoxicam mini-tablets

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Abstract

The aim was to enhance the dissolution of lornoxicam and to produce mini-tablets with an optimised system to provide a rapid release multiparticulate formulation. Lornoxicam systems were prepared through co-evaporation with either PEG or Pluronic® F-68 and adsorption onto Neusilin® US2 alone or co-adsorption in the presence of different amounts of polysorbate 80. All systems were characterised by FT-IR, DSC, XRD, flowability and dissolution techniques. Mini-tablets were prepared using the system with the optimum dissolution profile and flowability. Tensile strengths, content uniformity and dissolution profiles of the mini-tablets were evaluated. The effects of different excipients and storage conditions on mini-tablet properties were also studied. The optimised rapid release lornoxicam mini-tablets were further evaluated for their in-vivo pharmacokinetic profile.

The co-evaporate of lornoxicam with Pluronic® F-68 showed significantly faster dissolution and superior flowability and was evaluated together with three directly compressible excipients (Cellactose® 80, StarLac® and Emcompress®) for mini-tablet formulation. The formulation with StarLac® provided the optimum results in terms of tensile strength, content uniformity and rapid drug release following a 3 month stability study and was selected for further in vivo evaluation. The pharmacokinetic profile indicated the potential of the mini-tablets achieving rapid release and increased absorption of lornoxicam.
**Abbreviations**

LOR – Lornoxicam

PEG – Polyethylene glycol 6000

PLU – Pluronic® F-68

NEU – NEU® US2

CEL – Cellactose® 80

STA – StarLac®

DCP – Emcompress®
**Introduction**

Lornoxicam (LOR) is a non-steroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties\(^1\) and although structurally related to piroxicam and tenoxicam, LOR is ten-fold more potent\(^2\). Because LOR is used to treat patients with rheumatoid arthritis, osteoarthritis and postoperative management of pain associated with orthopaedic, abdominal, and dental surgeries\(^{1,3,4}\) a rapid onset of action is a desired attribute, but LOR has limited solubility in gastric media which is a rate limiting step for rapid absorption\(^5\). Several techniques have been investigated to enhance the dissolution of poorly soluble compounds, such as; micronization\(^6\), formation of inclusion complexes with cyclodextrins\(^7-9\), micellar solubilisation\(^10,11\) and solid dispersions with hydrophilic macromolecules\(^12-14\). Additionally, adsorption onto compounds with a high surface area (e.g. silicates) can be used successfully to enhance the dissolution and hence the bioavailability of drugs\(^15-18\).

Mini-tablets are compact dosage forms 1.5 - 4 mm in diameter\(^19\) that can be produced by conventional methods, using ordinary reciprocating and rotary tableting machines\(^20\). Mini-tablets can provide dose accuracy, whilst overcoming the stability and storage problems associated with liquid formulations and the swallowing difficulties associated with conventional tablets, which may be encountered by some patients\(^21\). Mini-tablets, like other multiparticulate systems, also offer the advantage of ease of dose adjustment by altering the number of units administered without the need for any formulation or process change\(^22\). Furthermore, because of their uniform size and shape, smooth surface, low porosity and high strength, mini-tablets can maintain their structure and shape in a more reproducible way than other multiparticulate dosage forms such as pellets and granules\(^23\).
The aim of this work was to enhance the dissolution of LOR in gastric media through solid dispersion with polyethylene glycol 6000 (PEG) as an example of a hydrophilic macromolecule, Pluronic® F-68 (PLU) as a non-ionic surfactant and adsorption onto the surface of Neusilin® US2 (NEU), a synthetic amorphous form of magnesium aluminometasilicate. Furthermore, the effect of co-adsorption of LOR onto the surface of NEU in the presence of different amounts of polysorbate 80 was also studied. The LOR systems which showed the optimum dissolution profiles were selected for further characterization and formulation into mini-tablets. Moreover, the effect of different directly compressible excipients on the mechanical properties and in-vitro release of LOR mini-tablets was studied and the stability of the mini-tablets under different storage conditions was evaluated. An in vivo study was also performed in rabbits to estimate the pharmacokinetic parameters for the optimised mini-tablet formulation and to calculate the absolute bioavailability in comparison to intravenous delivery of LOR.

Materials and methods:
LOR was kindly provided by Delta Pharma, (10th of Ramadan City, Cairo, Egypt). PEG was obtained from BDH laboratory suppliers, England. PLU was obtained from BASF, SE Ludwigshafen, Germany. NEU was supplied from Fuji Chemical Industry, Japan. Cellactose® 80 (CEL) and StarLac® (STA), co-processed directly compressible excipients comprising 75% α-lactose monohydrate: 25% cellulose and 85% α-lactose monohydrate: 15% corn starch respectively, were received from Meggle BG excipients and technology, Germany. Emcompress® (DCP), Calcium Hydrogen Phosphate Dihydrate, was obtained from JRS Pharma, Germany. All solvents used in HPLC analysis were of HPLC grade, (Merck, Darmstadt, Germany). All other chemical and analytical reagents were of analytical grades.
and used as received.

**Preparations of LOR solid dispersions and co-adsorbate systems**

Solid dispersions of LOR with PEG, PLU and NEU were prepared by a solvent evaporation technique in order to enhance the dissolution of LOR in gastric fluids. Different weight ratios of LOR: carriers (1:1, 1:3 and 1:5) were prepared. Briefly; accurately weighed amounts from LOR and the investigated carriers were dissolved in chloroform. The solvent was allowed to evaporate in room temperature using magnetic stirrer. After solvent evaporation the powdered mass was dried in vacuum oven at 40°C until a constant weight was reached, ground gently in a mortar using a pestle and the particle size fraction < 200µm was collected through sieving. Powder samples were stored in desiccator for further analysis. Furthermore, co-adsorbate systems of LOR onto the surface of NEU with different amounts of polysorbate 80 in the ratios 1:5:1 and 1:5:3 (LOR: NEU: polysorbate 80) were also prepared using the solvent evaporation technique. Polysorbate 80 was dissolved in chloroform before the calculated amounts of LOR and NEU were added. Powders were collected, dried, sieved and stored in desiccator as previously described. Physical mixtures of LOR with the different carriers were prepared with the same weight ratio for comparisons. A control sample of LOR prepared via solvent evaporation in the absence of any additives was also prepared.

**Physicochemical characterisation of LOR systems**

FT-IR spectra, DSC thermograms and X-ray diffractograms were recorded for pure LOR, PEG, PLU, NEU and their solid systems in the weight ratio of 1:5.

**Fourier-transform infrared spectroscopy**
The spectra were obtained using a Perkin Elmer Spectrum BX Spectrometer, England, fitted with a PIKE technologies MIRacle sampling accessory and using Spectrum v5.0.1 for data processing. The produced spectrum was an average of 16 scans and performed in the scanning range of 4000–550 cm\(^{-1}\) at ambient temperature.

**Differential scanning calorimetry**

Differential scanning calorimetry (DSC) thermograms were obtained using a Perkin Elmer DSC 8000 with Intracooler 2 cooling accessory and Pyris v. 10.1.0.0420 software (Seer Green, UK). The furnace temperature was calibrated using the Perkin Elmer supplied standard reference materials Indium (m.p. = 156.60 °C) and zinc (m.p. = 419.47 °C). Samples, 3-5 mg, were accurately weighed onto aluminum pans and sealed prior to heating at a constant heat rate of 20°C min\(^{-1}\) in a nitrogen atmosphere over a temperature range of 25–250°C.

**Powder X-ray diffraction**

Powder X-ray diffraction (PXRD) patterns were collected by using a Rigaku Miniflex X-ray diffractometer. Samples were finely ground and packed into an aluminum sample holder. Patterns were collected between 5° and 50° 2θ, at increments of 0.02° 2θ, scanning speed 2°min\(^{-1}\), voltage 30KV, current 15 mA using CuK\(\alpha\) (1.54 Å) radiation.

**Powder density**

The bulk and tapped density properties of the optimum LOR systems in terms of superior dissolution, LOR/PLU co-evaporate (1:5 weight ratio) and LOR/NEU/polysorbate 80 co-adsorbate (1:5:3 weight ratio), were determined. Bulk density (\(\rho_B\)) was calculated by
measuring the volume of a known weight of powder mixture in a measuring cylinder. Tapped density ($\rho_T$) was calculated using the volume of the powder after tapping the cylinder 200-250 times, after which there was no further reduction in the volume of powder. Carr’s compressibility index (CI) values and Hausner ratios were determined according to equation 1 and equation 2 respectively.

\[
\text{Carr’s Index (\%)} = \frac{\rho_T - \rho_B}{\rho_T} \times 100
\]

Equation 1

\[
\text{Hausner Ratio} = \frac{\rho_T}{\rho_B}
\]

Equation 2

**Powder mixing**

LOR/PLU co-evaporate mixture (1:5 weight ratio) was mixed with an equal amount of a directly compressible excipient (either CEL, STA or DCP) using a turbula mixer (W.A. Bachofen, Switzerland) for 15 min and subsequently with 1 %w/w magnesium stearate for 5 min. The powder flowability of the formulations was assessed as previously described.

**Production and testing of LOR mini-tablets**

Formulations were compressed into mini-tablets over a range of compression pressures using a Stylcam® 100R rotary press simulator (Medel’Pharm, France) fitted with flat-faced 3 mm tooling at a speed of 20 rpm. Mini-tablet thickness, T (mm) and diameter, D (mm) were measured using a micrometer (Mitutoyo, Japan). Crushing strengths, F (N), were determined using a model 6D tablet tester (Dr. Schleuniger, Germany) and tensile strengths, $\sigma_t$ (MPa) were calculated according to Equation 3 $^{24}$. 

\[
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\]
\[ \sigma_t = \frac{2F}{\pi DT} \]  
\text{Equation 3.}

Compression profiles (pressure vs. strength) were used to characterise each of the LOR mini-tablet formulations and subsequent mini-tablets were produced at compression pressures of 200 – 300 MPa for \textit{in-vitro} dissolution, content uniformity, stability testing and \textit{in vivo} studies.

**Lornoxicam content**

The drug content of LOR from 10 randomly selected mini-tablets in each batch was determined. Briefly, each mini-tablet was grinded, dissolved in 50 mL acetone/PBS 7.4 and filtered (Whatman grade 1 filter paper, 11 μm, (Ø 70 mm), GE Healthcare Life Sciences, UK). Filter compatibility was verified by passing a standard solution of LOR through the filter and determining the concentration of the filtrate. LOR contents were determined as a percentage for each unit using UV/VIS spectrophotometer (Lambda 40, Perkin Elmer, UK) at \( \lambda_{\text{max}} \) of 372nm run via the UV WinLab version 2.80.03 software. The acceptance value (AV) was then calculated according to USP Pharmacopeia 36 (2013) using Equation 4.

\[
\text{AV} = |M + X^-| + ks
\]
\text{Equation 4}

Where M is a reference value; \( X^- \) is a mean of individual contents expressed as a percentage of label claim; k is the acceptability constant (if \( n = 10 \), it will be equal to 2.4) and s is the sample standard deviation.

**In-vitro dissolution**

Dissolution tests on the LOR powder samples and mini-tablets were performed in 0.1 N HCl, (pH 1.2) at 37 ± 0.5 °C using an automated Varian VK 7000 dissolution tester and a Cary 50 UV spectrophotometer at \( \lambda_{\text{max}} \) of 372 nm. Samples (5 mL) were removed from the
dissolution vessels through full flow 35 μm filters (Agilent Technologies, USA) at specified time points and recirculated via peristaltic pump. An additional dissolution test was performed on the LOR/NEU adsorbate (1:5 weight ratio) sample in 0.1 N HCl media containing 12 mg polysorbate 80 to evaluate the effects of the surfactant in drug solubilisation.

**Stability study**

LOR mini-tablets were stored in open amber glass containers at in desiccators at room temperature / 75% RH (saturated solution of NaCl) or 45% RH (saturated solution of K₂CO₃·2H₂O), 40°C/75% RH and at ambient temperature and humidity conditions for 3 months²⁵,²⁶. After the stated time mini-tablets were evaluated for their LOR content, tensile strength and *in-vitro* release. The method for LOR quantification using UV spectrophotometry was validated according to ICH guidelines on Validation of Analytical Procedures²⁷. The wavelength corresponding to the maximum absorbance in PBS of pH 7.4 and 0.1N HCl was found to be 372 nm. Beer's law obeyed over the concentration range of 2-20 μg/mL with correlation coefficient (r²) value of 0.9997 and 0.9992 for PBS of pH 7.4 and 0.1 N HCl, respectively. Intra-day and inter-day precision (%RSD) at different concentration levels were < 2%, indicating that the proposed spectrophotometric method is highly reproducible during one run and between different runs and can be adopted for determination of LOR in mini-tablet formulations. LOD and LOQ were 0.175 and 0.380 μg/mL, respectively in both media signifying the sensitivity of the method. Moreover, the mean recovery was ranged from 99.55% - 100.25%, indicating the accuracy of the method. Also, the obtained results of LOR assay in the presence of different carriers and excipients was found to be in agreement with the label claim indicating absence of interference with
the excipients. The reliability study showed lower value for %RSD at p<0.05 indicating no significant difference between the two UV spectrophotometric instruments used.

**In-vivo study and pharmacokinetic analysis**

An In-vivo study was performed to determine the pharmacokinetics of LOR from mini-tablets produced with the optimal formulation in terms of *in-vitro* release and stability. Furthermore, the absolute bioavailability of LOR in comparison to an aqueous intravenous (IV) injection was estimated. This was performed through administration of single equal doses, 0.75 mg kg\(^{-1}\), of mini-tablet and IV injection to male New Zealand rabbits (2.0-2.5 Kg) using non-blind, two treatment design. Doses were calculated from typical human LOR dose and body surface area in comparison to rabbit. The protocol of the study was approved by the research Ethics Committee in the Faculty of Medicine, Assiut University, Egypt.

**Study design and chromatographic conditions**

Six male rabbits were randomly distributed into two groups of equal numbers. The animals were kept in individual cages under well-defined and standardized conditions (humidity and temperature controlled room) and fed with standard food and water access. Furthermore, the rabbits were cannulated in the right jugular vein prior to study day and allowed to recover and fast overnight for 12 h.\(^{28}\). On the study day, each rabbit in the first group received a LOR mini-tablet (Treatment A). The tablets were placed gently into the mouth of the rabbits and swallowed with the aid of water. Rabbits of the second group received equal doses of LOR through intravenous injection of Xefo\(^\circ\) vial, October Pharm, Egypt (Treatment B). Blood samples (250 µL) were collected immediately after administration of LOR injection in the second group. Moreover, blood samples were also collected at scheduled time
intervals (0.5, 1, 2, 4, 8 and 24 h) from both treatments and treated with heparin to prevent blood clotting. The plasma were obtained via centrifugation (3500 g) for 10 min (Centurion Scientific Ltd, UK), kept in glass tubes and then deep frozen at -25°C. Prior to HPLC analysis, aliquots of plasma (100 μL) or the calibration standards (100 μL of an internal standard solution of piroxicam, 5 μg ml⁻¹) and 100 μL of 5M HCl were added to a glass tube. After brief vortex mixing (Maxi Mix, Thermolyne, USA) 5 ml of diethyl ether was added and the mixture was vortex mixed for 30 s. Each sample was centrifuged (2500 rpm for 10 min), and the organic layer was transferred to a new glass tube and evaporated to dryness under a gentle stream of nitrogen at 40°C. The residue was reconstituted with 500 μL of the mobile phase, (mixture of 20 mM potassium monophosphate-acetonitrile 60:40 v/v, adjusted to pH 3.5 with ortho-phosphoric acid, at a flow rate of 1.2 mL min⁻¹), filtered (0.45 μm glass microfiber/nylon membrane filter (Ø 25 mm), Agilent technologies, USA) and a 20 µL aliquot was injected into the HPLC system. The HPLC system, Knauer, Germany consisted of HPLC pump (Knauer D – 14163), UV detector (Knauer, D – 14163), and integration interface box (Knauer, D – 14163). Chromatographic separation was carried out using Kromasil C-18 column (250 x 4.60 mm, particle size: 10 μm).

**Method validation**

The method was validated according to ICH guidelines on Validation of Analytical Procedures. The detection wavelength, 377 nm, was determined by scanning the maximum absorbance wavelength of LOR and piroxicam in the mobile phase using a UV spectrophotometer (Jenway, Model 6305, UK). The specificity of the method was determined by analysing 15 different blank rabbit plasma samples, to demonstrate lack of chromatographic interference from endogenous plasma components at the retention time.
of both LOR and the internal standard. No significant interfering peak from plasma endogenous compounds was observed at the retention times of LOR and the internal standard which were 3.9 min and 7.8 min respectively. The limit of detection (LOD) and lower limit of quantitation (LLOQ) were determined from the ratio of peak signal and baseline noise and were 40 ng/mL and 50 ng/mL respectively for this method. The linearity of the calibration curve for LOR was assessed over the range of 50 to 3000 ng/mL and was performed after subjecting plasma samples to the sample preparation procedure followed by injection onto the HPLC system. Moreover, the stability of LOR in plasma was studied in three different conditions: frozen plasma (-70.0 ±2.0°C) was kept at room temperature for 6 h before sample preparation (short term stability), freezer stability at -70.0 ±2.0°C for 30 days (long term stability) and three freeze-thaw cycles (stored at -70.0 ±2.0°C between cycles) using QC samples spiked with LOR at low (50 ng/mL) and high (1800 ng/mL) concentrations. A standard curve was constructed by plotting the peak area ratios of LOR and piroxicam against LOR concentrations in plasma. Results were fitted to linear regression analysis. Six replicates of calibration curve were prepared taking each concentration for six times. The regression coefficient ($R^2$) value was used to evaluate the linearity of the calibration curve. The standard curves of LOR in rabbit plasma were linear with a reliable reproducibility over the ranges of 50 to 3000 ng/mL and the regression coefficients ($R^2$) were over 0.9992 from each standard curve of six separate runs. The accuracy and precision was confirmed by analysing six replicates at three QC levels (low, medium and high) and LLOQ on four different days. The intra-day and inter-day accuracy of this bioanalytical method, expressed as the relative standard error, was from 96.22 ±22.3% to 99.72 ±15.4% and from 96.06 ±11.2% to 99.10 ±13.5% respectively for LOR concentration from 50 to 3000 ng/mL. Furthermore, the intra-day and inter-day coefficient of variation ranged from 1.310
±0.22% to 3.215 ±0.87% and from 1.011 ±0.32% to 3.046 ±0.65% respectively. The data confirmed the satisfactory accuracy, precision and reproducibility of the method. Also, it was found that thawing the frozen samples and keeping them at room temperature for 6 h had no effect on quantification and the quality control samples stored at −70°C remained stable for 1 month. Furthermore, the three freeze–thaw cycles of the quality control samples did not appear to affect the quantification, suggesting that human plasma samples containing LOR can be handled under normal laboratory conditions without any significant loss of compound.

**Pharmacokinetic analysis**

The residual method was adapted to estimate the pharmacokinetic parameters of the two treatments for each subject. The maximum drug concentration ($C_{\text{max}}$, µg mL$^{-1}$), the time to reach $C_{\text{max}}$ ($T_{\text{max}}$, h), the absorption rate constant ($K$, h$^{-1}$), the absorption half-life ($t_{1/2a}$, h), the elimination rate constant ($K_e$, h$^{-1}$), elimination half-life ($t_{1/2e}$, h) as well as the mean residence time (MRT$^{(0-\infty)}$, h) were obtained from the LOR plasma concentration time curves. The trapezoidal rule method was employed to calculate the area under curve from zero to 24 hr ($\text{AUC}_{(0-24)}$, µg.h/ml)$^{29}$. Moreover, the area under curve from zero to infinity ($\text{AUC}_{(0-\infty)}$, µg.h ml$^{-1}$) was calculated using Equation 5$^{30}$ and the absolute bioavailability (%) was calculated using Equation 6.

$$\text{AUC}_{(0-\infty)} = \text{AUC}_{(0-t)} + \frac{C_t}{K_e}$$  \hspace{1cm} \text{Equation 5}

Where $C_t$ is the drug plasma concentration observed at time $t$, $K_e$ is the apparent elimination rate constant.
Absolute bioavailability (%) = \frac{\text{AUC} (0-\infty) \text{ mini-tablet}}{\text{AUC} (0-\infty) \text{ IV injection}} \times 100 \quad \text{Equation 6}

**Statistical analysis**

Data were presented as mean ± SD. The linearity of the calibration curve for LOR was validated using the coefficient of determination $R^2$. LOR release, mini-tablet tensile strength and pharmacokinetic data were compared by one-way analysis of variance and post-hoc Tuckey’s test using the Minitab 16 statistical software package (Minitab Inc., USA). A $P$ value of less than 0.05 was considered to be significant.
Results and Discussion

The aim of this study was to enhance the dissolution of LOR in gastric fluids followed by formulation into mini-tablets with the potential to rapidly deliver LOR, providing dose flexibility for patients with swallowing difficulties.

Physicochemical characterisation of LOR solid dispersions and co-adsorbate systems

Fourier-Transform Infrared spectroscopy

Figure 1 represents the FT-IR spectra of pure LOR, PEG, PLU, NEU and their physical mixtures, co-evaporate, adsorbate and co-adsorbate systems. LOR showed a characteristic peak at 3065 cm\(^{-1}\) corresponding to \(-\text{NH}\) stretching vibration. The stretching vibration of carbonyl group in the primary amide showed intense absorption peak 1644 cm\(^{-1}\). Other peaks were observed at 1591 and at 1531 cm\(^{-1}\) and were assigned to bending vibrations of N-H group in the secondary amide. Sulphonyl group showed stretching vibrations bands appeared at 1143, 1379, and at 1323 cm\(^{-1}\). Other prominent peaks appeared at 828.25 cm\(^{-1}\) corresponding to \(-\text{CH}\) aromatic ring bending and heteroaromatics and at 788.22 cm\(^{-1}\) assigned for C-Cl bending vibration. On the other hand, PEG and PLU have nearly the same FT-IR spectrum with absorption bands at 3400 cm\(^{-1}\) O-H stretching vibration, C-O stretching at 1110 cm\(^{-1}\) and 2882 cm\(^{-1}\) C-H stretching vibration\(^{31}\). NEU showed a shallow peak from 3100 to 3600 cm\(^{-1}\) which can be attributed to the bound water molecules. Physical mixtures of LOR and the investigated carriers showed the same characteristic peaks of LOR at the same positions at the different prepared weight ratios and thus give indication about the absence of any interaction in physical mixture. However, in co-evaporate, adsorbate and co-adsorbate systems a complete disappearance of the \(-\text{NH}\) stretching vibration was observed.
at 1:3 and 1:5 weight ratio of the carrier concomitant with appearance of the other LOR peaks but they are reduced in their intensities. In case of co-evaporate of LOR with PEG and Pluronic® (1:5 weight ratio) there was a slight shift in sulphonyl group stretching vibrations to 1146 and 1340 cm\(^{-1}\). Similarly, with NEU adsorbates mixtures (1:3 and 1:5 weight ratio) the sulphonyl group stretching vibrations were shifted to 1335 and 1429 cm\(^{-1}\) and the C-Cl bending vibration was highly reduced in its intensity. Furthermore, co-adsorbate systems displayed a shift of sulphonyl group stretching vibrations to 1431 and 1346 cm\(^{-1}\) and complete disappearance of C-Cl bending vibration. Moreover, the stretching vibration appeared at 2925 cm\(^{-1}\) assigned for \(-\text{CH}_2\) groups of polysorbate 80 becomes clearer at a higher ratio of polysorbate 80 (1:5:3 weight ratio systems, Fig.1, trace K) and the shallow peak at 3390cm\(^{-1}\) becomes broader due to interaction with the \(-\text{OH}\) stretching vibration of polysorbate 80. This FT-IR data referred to the formation of intermolecular hydrogen bond between the -NH group of LOR and \(-\text{OH}\) group of PLU and PEG or Si of SiO2; respectively especially in higher carrier ratios 1:3 and 1:5. The formation of hydrogen bonds between oxicams and PEG 4000\(^{32}\) or Poloxamer 188\(^{33}\) has also been reported. At the same time, the interaction between LOR and NEU could be attributed to an acid-base interaction as LOR is a weak acid and NEU is a basic compound. Similarly, the interaction between Acclofenac and NEU was found to be an acid-base reaction\(^{18}\).

**Differential scanning calorimetry**

The DSC thermograms of pure LOR, PEG, PLU, NEU and their physical mixtures, co-evaporate, adsorbate and co-adsorbate systems are presented in Figure 2. LOR exhibited a single sharp exothermic melting peak at 232.9°C, which is probably due to drug melting and decomposition\(^{34}\). No difference was observed in the DSC thermograms for pure LOR and the
control sample of LOR prepared via solvent evaporation alone (data not shown) confirming the absence of any solvent-mediated conversions. The DSC thermograms of PEG and PLU showed a melting endotherm at 56°C and 62°C, respectively. Furthermore, NEU did not show any melting endotherm over the temperature range studied probably due to the amorphous nature of this carrier.18 The LOR melting exotherm was completely absent from the investigated physical mixtures and solid dispersion (co-evaporate systems) with either PEG or PLU. In the case of the physical mixture, this behaviour could be possibly attributed to the dilution effect of the carrier, especially when present at a high ratio in these samples (1:5 weight ratio), and/or melting of the carrier at a lower temperature causing dissolution of drug crystals in the molten mass of the carrier and the formation of amorphous LOR during the DSC scan. Similar observations have previously been reported35-38. However, in the case of the co-evaporate systems with both PEG and PLU, the disappearance of LOR melting exotherm may be due to the interaction between the drug and the carrier as pointed out from the FT-IR study and thus suggesting possible conversion of crystalline LOR to an amorphous structure within the carrier matrix. Similar behavior was also observed in case of NEU physical mixtures, adsorbates and co-adsorbates. However, the absence of LOR peak in physical mixture could be attributed to the dilution effect (1:5 weight ratio) and interaction between LOR and NEU at the molecular level in case of adsorbate and co-adsorbate systems as observed from FT-IR study. The above finding suggested that the solvent evaporation method induces a certain type of interaction between LOR and the investigated carriers at the molecular level. Similar results were also reported for LOR solid dispersion formation using PVP K30 through solvent evaporation technique39 and co-ground mixture of Acceclofenac with NEU18. To gain further information and evidence about the conversion of LOR from crystalline to amorphous state XRD study was conducted.
**X-ray powder diffractometry**

X-ray powder diffraction patterns of pure LOR, PEG, PLU, NEU and their physical mixtures, co-evaporate, adsorbate and co-adsorbate systems are depicted in Figure 3. LOR showed several sharp high intensity peaks at diffraction angles 2θ of 7.8°, 10.2°, 12.96°, 13.78°, 18.85°, 21.84, 22.87°, 24.6°, 25.35°, 26.90°, 27.95° and 30.44° suggesting its crystalline nature. No difference was observed in the X-ray powder diffraction patterns for pure LOR and the control sample of LOR prepared via solvent evaporation alone (data not shown) confirming the absence of any solvent-mediated conversions. PEG has two characteristic peaks at 2θ values of 19.11° and 23.19°. PLU was also in the crystalline form, having two distinct peaks at 2θ values of 19.18° and 23.21° and a relative broad peak with low intensity between 24° to 27° 2θ. NEU did not show any crystalline peaks, confirming it is an amorphous compound. It was found that physical mixture of the drug with PEG, PLU or NEU showed the characteristic peaks of LOR but they were far lower in their intensity due to the dilution effect of the carrier. This finding revealed that LOR was present in a crystalline state, as evidenced by its diffraction lines, and thereby ruled out the existence of drug–carrier interaction in the physical mixtures. Furthermore, some LOR diffraction peaks were absent from the co-evaporate systems with both carriers while the intense LOR peaks were still detected (Fig. 3). This demonstrated the presence of LOR in ultrafine crystallites within the carrier matrix and is in accordance with previous reports where the interaction between LOR and PVP K30 in a physical mixture and co-evaporate system was studied. Moreover, the diffraction peaks of PLU at 19.1°, 23.3°, and 26° 2θ could still be observed, suggesting that PLU was still present in the crystalline form in both physical mixtures and co-evaporate. This attributed to the presence of PLU in its crystalline state even after recrystallization during solvent removal in the co-evaporation process. On the other hand, the LOR
diffractograms in adsorbates (1:5 weight ratio) and co-adsorbates (1:5:3 weight ratio) showed a complete absence of LOR crystalline peaks. This observation indicates that LOR was entirely converted to the amorphous form. However, the co-adsorbate system (1:5:1 weight ratio) still showed minute LOR diffraction peaks indicating the presence of LOR in a microcrystalline form. So, from the PXRD study, it was clear that LOR physical mixtures with the investigated carriers were still crystalline and the disappearance of LOR melting exotherm observed in DSC was completely due to melting of LOR in the molten mass of the carrier and/or the dilution effect. Furthermore, LOR was present in ultrafine crystallites in the co-evaporate mixture with PEG and PLU despite the complete disappearance of the LOR melting exotherm. Additionally, the complete amorphization of LOR in adsorbate (1:5 weight ratio) and co-adsorbate (1:5:3 weight ratio) systems supported the results of DSC analysis and revealed that adsorption onto the surface of NEU and co-adsorption in the presence of polysorbate 80 can be used successfully to obtain amorphous LOR. It is worth noting that after 3 months refrigerated storage, XRD studies for the LOR PLU co-evaporate and the LOR co-adsorbate (1:5:3 weight ratio) systems were repeated and found to be unchanged in comparison to fresh samples.

In-vitro dissolution

Figure 4 shows the dissolution profiles of LOR alone, physical mixtures, co-evaporate, adsorbate (1:5 weight ratio) and co-adsorbate systems (1:5:1 and 1:5:3 weight ratio). It was clearly evident that LOR dissolved very slowly under the specified dissolution conditions and less than 12 ±1.5% of LOR was dissolved after 1 h in gastric pH conditions. No difference was observed in the dissolution pure LOR and the control sample of LOR prepared via solvent evaporation alone (data not shown) confirming the absence of any solvent-mediated
conversions. However, it was apparent that LOR dissolution was significantly ($P < 0.05$) improved when physically mixed with the carriers in the order: PLU > NEU > PEG, (38.8 ±1.8 > 35.4 ±1.7 > 28.2 ±0.4%) respectively. Moreover, increasing the amount of carrier from 1:1 to 1:5 weight ratios in all of the investigated systems led to enhancement of LOR dissolution. In the case of the co-evaporate mixtures, PLU showed a significantly ($P < 0.05$) higher rate and extent of LOR dissolution after 1 h (90.3 ±1.9%) followed by PEG (63.2 ±0.7%) and finally NEU (40.2 ±0.8%). On the other hand, co-adsorbates with higher amounts of polysorbate 80 (1:5:3 weight ratios) showed almost 100% LOR dissolved after 15 min compared with 63.3 ±0.4% and 27.1 ±0.2% LOR dissolved from the co-adsorbate (1:5:1 weight ratio) and adsorbate mixture respectively. The slight enhancement of LOR dissolution in the case of the physical mixtures with different carriers could be attributed to the decrease in LOR crystallinity and or the effect of carriers. PEG is a hydrophilic carrier and can impart a local solubilisation action in the diffusion layer surrounding the drug particles and increase the drug wettability and subsequent dissolution\textsuperscript{42,43}. Furthermore, PLU is a non-ionic surfactant and can form micelles to aid drug solubilisation\textsuperscript{44}. However, the significantly higher ($P < 0.05$) dissolution of LOR from co-evaporate mixtures with either PEG or PLU compared with physical mixtures and pure LOR were due to the presence of LOR in a molecular dispersion form within the carrier. Additionally, LOR was present in ultrafine crystals with a larger surface area available for dissolution as confirmed from the DSC and XRD studies. NEU is an inert amorphous material consisting of spray-dried agglomerates of magnesium aluminosilicate\textsuperscript{15}, Furthermore, NEU has a high specific surface area (~280 m$^2$/g) and a high adsorption capacity (~3.2 mL/g) making it a good core material for adsorption of a high proportion of drugs\textsuperscript{15}. LOR adsorption onto the surface of NEU, as well as the formation of intermolecular hydrogen bonding between the –NH group of LOR and Si of SiO$_2$
groups of NEU concomitant with conversion of LOR into an amorphous state were responsible for the enhancement of LOR dissolution. As the proportion of NEU increases from 1:1 to 1:5 weight ratio, the effective surface area over which the drug is spread increases accompanied by an enhancement in drug dissolution. Similar results have been presented elsewhere\textsuperscript{15,18} and it has also been reported that the dissolution rate of both meloxicam and piroxicam were enhanced through adsorption onto the surface of Florite\textsuperscript{®} and microcrystalline cellulose\textsuperscript{45,46}. It is also worth noting that the co-evaporate system with either PEG or PLU gave significantly ($P < 0.05$) higher percentage of LOR dissolved compared with LOR adsorbate. This could possibly be attributed to the higher amounts and large specific surface area of NEU as it has been stated that the adsorbent having the larger surface is considered to show the lower dissolution rate\textsuperscript{47,48}. Polysorbate 80 is a non-ionic surfactant and mainly used to enhance the solubility and dissolution of many water insoluble compounds\textsuperscript{11}. LOR co-adsorbate onto NEU in the presence of polysorbate 80 has the ability to give a significant very rapid dissolution. The enhancement of LOR dissolution could be attributed to two different mechanisms; drug solubilisation within the polysorbate micellar core, followed by adsorption onto the surface of NEU. Similar results were reported for enhancement the dissolution of celecoxib using Florite\textsuperscript{®} and polysorbate 80 at the ratio of 1:5:3 (celecoxib: Florite\textsuperscript{®}: polysorbate 80)\textsuperscript{49}. Also, it was reported by other researchers that adsorption of gentamicin and lanzoprazole onto the surface of different adsorbents and in the presence of different types of non-ionic surfactants can enhance the dissolution rate and the oral bioavailability of such drugs \textsuperscript{47,48}. When the dissolution of the LOR/NEU adsorbate (5:1 weigh ratio) was evaluated in media containing additional polysorbate 80 in order to further evaluate the surfactant effects, the amount of LOR dissolved after 1 h increased to $68.5 \pm 3.5\%$ (data not shown) from the previous value of $40.2 \pm 0.8\%$ in the
absence of polysorbate 80. This demonstrated that the presence of polysorbate 80 did enhance the dissolution of LOR through prevention of recrystallization and wetting, but also confirmed the benefit of the co-adsorbate system, where the drug is initially solubilised by the aid of surfactant followed by adsorption into the large surface area of NEU to form ultra-fine deposits. The solubilised drug subsequently dissociates from the surface of NEU on contact with the dissolution media and dissolves rapidly.

**Powder density**

The Carr’s Index and Hausner Ratio values of the two optimum LOR systems and the subsequent formulations with directly compressible excipients are presented in Table 1. The LOR co-adsorbate system displayed very high Carr’s Index values compared with LOR co-evaporate mixture with PLU, which demonstrated far superior flow characteristics. The higher Hausner Ratio of the co-adsorbate formulation also indicated a greater degree of interparticle friction. Although, NEU has good flow and compressibility properties, the addition of polysorbate 80, especially at a higher ratio, is likely to have led to more adhesion and stickiness between the particles which could be responsible for the poor flowability. As the need for improved flowability is exacerbated when manufacturing mini-tablets due to the narrow die orifice, the co-adsorbate system with NEU and polysorbate 80 was not considered for further evaluation in this study, whilst the co-evaporate system with PLU was assessed for its suitability in the formulation of rapid release LOR mini-tablets. Blending of the LOR/PLU co-evaporate system with directly compressible excipients led to a marked reduction in Carr’s index and Hausner ratio (Table 1). The formulation with STA showed superior flowability and the effect of enhancing the powder flow of the LOR/PLU co-evaporate system can be ranked in the following order STA > DCP > CEL.
**Characterisation of LOR mini-tablets**

The mini-tablets manufactured were uniform in their weight (18 ± 1 mg) and thickness (2 ± 0.1 mm) providing a LOR dose of 1.5 ± 0.1 mg per mini-tablet. The prepared LOR mini-tablets complied with US Pharmacopeia 36 requirements in terms of uniformity of drug content, (case I, in which target content per dosage unit (T) < 101.5% can be applied) as the (AV) value for all formulation tested < L1 (%) = 15.

Figure 5 shows the compression profiles for the mini-tablet formulations. Mini-tablets manufactured with all formulations displayed acceptable tensile strengths over a range of compression pressures. Although mini-tablets comprising CEL and DCP displayed superior compression profiles compared to the STA formulation at lower compression pressures, more comparable tensile strength values in the range were obtained at higher compression pressures > 300 MPa. The higher strengths displayed by the mini-tablets comprising CEL at even low compression pressures (~ 100 MPa) is attributable to the compactibility of the excipient. CEL is a co-processed, spray-dried compound formed from 75% α-lactose monohydrate: 25% cellulose and combines the ideal filler and binder properties of its two ingredients, which consolidate by synergistic fragmentation and plastic deformation mechanisms respectively. STA is a co-processed filler-binder consisting of 85% α-lactose monohydrate together with 15% corn starch. The improved flowability and compressibility of STA in comparison to the equivalent physical mixtures of its components is due to the spray-drying process employed during processing. At higher compression pressures (≥ 200 MPa) the tensile strengths of the mini-tablets with CEL and DCP were comparable. DCP consists of aggregates of small primary particles of dicalcium phosphate and its binding properties are insensitive to production speed and the presence of lubricant due to the
mechanism of fragmentation during consolidation and compaction

The dissolution profiles of the LOR mini-tablets at gastric pH are shown in Figure 6. The inclusion of STA and DCP successfully enhanced the extent of LOR released from mini-tablets compared with CEL based formulations, by promoting rapid disintegration and subsequent dissolution. Mini-tablets with DCP provided 91 ±2.5% LOR release after 15 minutes in comparison with the 99 ±0.7% release from those comprising STA (Fig 6). It is the presence of starch that imparts the rapid disintegration properties and leads to the very fast release of the active ingredient, which is the biggest advantage associated with STA. On the other hand the rapid release from mini-tablets comprising DCP is associated with the rapid penetration of liquid into the mini-tablets due to the hydrophilic nature of the excipient. The dissolution profile of mini-tablets with CEL on the other hand was significantly (p < 0.05) lower and provided < 40% LOR release after 15 min due to slow disintegration of the mini-tablets within the dissolution media. The structure of CEL means that cellulose disintegration only begins once the outer layer of lactose has dissolved, resulting in viscous aqueous solutions and further restricting water access to the cellulose nucleus. The compactability of the different LOR/excipient blends may have also contributed to the differences in drug release, particularly as the mini-tablets comprising STA displayed generally lower tensile strengths in comparison to those comprising DCP and CEL over the 200 - 300 MPa range of compression pressures. Overall the rapid LOR release provided by mini-tablets produced with STA, coupled with the superior flowability, good tensile strength, weight and content uniformity would therefore provide optimal properties for further development.
**Stability Studies**

Mini-tablets showed no significant decrease in LOR content after 3 months storage under ambient conditions or at RT/43% RH and RT/75% RH. But LOR content decreased to 92.6% (±4.8), 94.9% (±4.5) and 84.0% (±3.2) for CEL, DCP and STA respectively when stored at 40°C/75% RH due to degradation of the drug.

The fragility of all mini-tablets after 3 months storage at 40°C/75% RH due to the detrimental effects of the high temperature and humidity on their physical stability meant that tensile strength could not be determined. The strength of DCP and STA mini-tablets was slightly lower after 3 months storage at RT/43% RH and RT/75% RH due to the effects of moisture sorption (Table 2). Mini-tablets with CEL, however, increased in strength, probably due to the absorption of moisture leading to greater inter-particulate bonding within the mini-tablets. The hygroscopicity of cellulose powders is dependent on their structural properties, such as surface area, pore volume and crystallinity and moisture sorption during storage under humid conditions leads to water binding to the amorphous fibrils at the surface of microcrystalline cellulose particles. The effects of increased moisture content on the compression properties of microcrystalline cellulose have previously been studied. It is recognised that whilst the low % of water tightly bound within the particles enhances interparticle bonding, higher levels of adsorbed moisture reduces tablet strength through plasticization of the particles and peak tensile strengths for microcrystalline cellulose compacts can exist at intermediate moisture contents. Moisture sorption in CEL is much lower than microcrystalline cellulose alone because lactose covers the cellulose fibres as a result of the co-processing. However, it appears that that sufficient post-compression moisture sorption occurred within mini-tablets comprising CEL when stored at
higher % RH to enhance the interparticle bonding and tensile strength, which in all likelihood led to slower disintegration and further retardation of drug release.

LOR release from mini-tablets with CEL decreased significantly \((P < 0.05)\) after 3 months storage even at ambient conditions (Fig. 7). A decrease was also observed in the rate of LOR release from mini-tablets formulated with STA \((81 \pm 4.4\% \text{ after } 15 \text{ min})\) and more so with DCP \((76 \pm 2.5\% \text{ after } 15 \text{ min})\) following 3 months storage at ambient conditions. A more significant reduction in LOR release rate after storage at higher %RH and/or temperature was seen (Fig 8 & 9) due to the concomitant degradation of the drug. Since no loss in LOR content was observed at ambient conditions, the reduction in drug release can be ascribed to physical changes within the mini-tablets upon exposure to atmospheric conditions over the 3 month period. It is likely that some recrystallization of LOR in the presence of the crystalline excipients within the mini-tablets resulted in the small reduction in release rate. The results indicate that appropriate packaging and storage conditions would be necessary to maintain the stability of the mini-tablets and to ensure that the dissolution enhancement of LOR achieved with the PLU co-evaporate system was maintained. Overall mini-tablets formulated with STA showed the most promising stability profiles, after 3 months storage and were further evaluated for \textit{in vivo} performance.

\textbf{In Vivo study and Pharmacokinetic analysis}

The pharmacokinetic parameters of LOR following oral and intra-venous administration of single doses of 0.75 mg kg\(^{-1}\) of (A) mini-tablets and (B) IV injection into rabbits are shown in Table 3. Moreover, The LOR plasma – concentration time profiles of both treatments are depicted in Fig. 10 and could be best described by a one-compartment model with a first
order absorption and elimination for mini-tablets and a one-compartment IV-Bolus model with first-order elimination for IV injection. The peak plasma concentration of LOR was achieved after 2 h following administration of mini-tablets and the absolute bioavailability, calculated from the $AUC_{(0-\infty)}$ for the oral mini-tablet compared to the IV treatment was found to be 93.90 ±3.9%. A non-significantly higher peak plasma concentration ($C_{\text{max}}$) was found with IV injection compared with mini-tablets ($P > 0.05$) and both treatments showed similar mean residence time (MRT) values. A significantly higher elimination half-life ($t_{1/2e}$) was found for mini-tablets compared to IV injection, ($P < 0.05$). It is also worth noting that the absolute bioavailability and $C_{\text{max}}$ (93.90 ±3.9% and 3.33 ±0.19 µg mL$^{-1}$ respectively) obtained for LOR mini-tablets in the present study are higher than the absolute bioavailability (80.1%) and $C_{\text{max}}$ (1.83 ±0.35 µg mL$^{-1}$) recorded previously from LOR suppositories$^{62}$. Furthermore, the plasma concentrations after 0.5 h (1.5 ± 0.61 µg mL$^{-1}$) and 1 h (3.03 ±0.3 µg mL$^{-1}$) and the $C_{\text{max}}$ achieved from 1.5 mg dose LOR mini-tablets are much higher in comparison to a 4 mg dose from conventional tablets$^{63}$. LOR 8 mg twice daily is currently considered an effective and tolerable alternative NSAID for use as a sole agent or as part of multimodal analgesia in adults$^{64}$ with some formulations providing pain relief after 30 minutes$^{65}$, whilst preoperative 16 mg LOR provides potent pain relief and prevents the need for postoperative rescue analgesia$^{66}$. However, the increased absorption achieved from the lower dose mini-tablets in the present study could provide more dose flexibility and improved therapy for patients. This improvement in absorption may be attributed to the enhancement in dissolution concomitant with the rapid disintegration of the mini-tablets in gastric conditions. The time difference between the rapid dissolution and the $T_{\text{max}}$ is likely to be due to incomplete initial absorption of all the solubilized drug present in the gastric fluid due to ionization of the pyrindo group of LOR (pKa 5.5)$^{5}$. The high drug plasma
concentration obtained after 30 min and the high $C_{max}$ reached 2 hours post-dosing can be attributed to the higher lipophilicity of LOR ($\log P = 1.8$)\textsuperscript{67}. Additionally, the mean residence time of 7.414 ±0.48 h and the significantly ($P < 0.05$) longer elimination half-life of 8.115 ±0.99 h obtained with the mini-tablet formulation could be advantageous controlling the chronic pain associated with inflammatory conditions. Overall, the pharmacokinetic data indicate the potential of the mini-tablet formulation in achieving a high plasma concentration of LOR following rapid release from the dosage form, which could be beneficial in providing effective pre- or post-operative pain relief.

**Conclusion:**

The dissolution of LOR, a potent but insoluble NSAID, was successfully enhanced by producing a solid dispersion system through co-evaporation with PLU or a co-adsorption onto the surface of NEU with polysorbate 80. The LOR co-evaporate system with PLU displayed superior flow properties and was successfully manufactured into mini-tablets with directly compressible excipients. Whilst the mini-tablets comprising CEL showed higher tensile strengths at low compression pressures, incomplete drug release was evident during dissolution testing. Although, mini-tablets with DCP released > 90% of LOR within 15 min, the formulation of the LOR/ PLU co-evaporate system with STA showed superior flow properties together with rapid and complete dissolution of LOR from mini-tablets. Stability studies revealed that although different storage conditions affected the LOR content, *in vitro* release and tensile strength, the optimal mini-tablet formulation with STA showed superior characteristics after 3 months. Overall the *in vivo* pharmacokinetic profile and high absolute bioavailability demonstrate the potential of the formulation and the mini-tablets developed in this study to provide a rapid release multiparticulate formulation of LOR for dose flexibility and improved delivery to patients with swallowing difficulties.
References


FIGURES

Fig. 1: FT-IR spectra of pure LOR, PEG, PLU, NEU and their physical mixtures, co-evaporate, adsorbate and co-adsorbate systems.

(A) pure LOR (B) PEG (C) PLU (D) NEU (E) Physical mixture with PEG (1:5 wt. ratio); (F) Physical mixture with PLU (1:5 wt. ratio); (G) Physical mixture with NEU (1:5 wt. ratio); (H) co-evaporate with PEG (1:5 wt. ratio); (I) co-evaporate with PLU (1:5 wt. ratio); (J) adsorbate with NEU (1:5 wt. ratio); (K) co-adsorbate with NEU/polysorbate 80 (1:5:1 wt. ratios); (L) co-adsorbate with NEU/polysorbate 80 (1:5:3 wt. ratios).
Fig. 2: DSC thermograms of pure LOR, PEG, PLU, NEU and their physical mixtures, co-evaporate, adsorbate and co-adsorbate systems. (A) pure LOR (B) PEG (C) PLU (D) NEU (E) Physical mixture with PEG (1:5 wt. ratio); (F) Physical mixture with PLU (1:5 wt. ratio); (G) Physical mixture with NEU (1:5 wt. ratio); (H) co-evaporate with PEG (1:5 wt. ratio); (I) co-evaporate with PLU (1:5 wt. ratio); (J) adsorbate with NEU (1:5 wt. ratio); (K) co-adsorbate with NEU/polysorbate 80 (1:5:1 wt. ratio); (L) co-adsorbate with NEU/polysorbate 80 (1:5:3 wt. ratio).
Fig. 3: X-ray powder diffraction patterns of pure LOR, PEG, PLU, NEU and their physical mixtures, co-evaporate, adsorbate and co-adsorbate systems.

(A) pure LOR; (B) PEG; (C) PLU; (D) NEU; (E) Physical mixture with PEG (1:5 wt. ratio); (F) Physical mixture with PLU (1:5 wt. ratio); (G) Physical mixture with NEU US2 (1:5 wt. ratio); (H) co-evaporate with PEG (1:5 wt. ratio); (I) co-evaporate with PLU (1:5 wt. ratio); (J) adsorbate with NEU (1:5 wt. ratio); (K) co-adsorbate with NEU/polysorbate 80 (1:5:1 wt. ratios); (L) co-adsorbate with NEU/polysorbate 80 (1:5:3 wt. ratios).
**Fig. 4:** *In vitro* dissolution profiles of LOR alone, physical mixtures, co-evaporate, adsorbate (1:5 weight ratio) and co-adsorbate (1:5:1 and 1:5:3 weight ratio) systems (mean ± SD, n = 3).

**Fig. 5:** The effect of compression pressure on the tensile strength of LOR mini-tablets formulated with different directly compressible excipients.
Fig. 6: *In vitro* dissolution profiles of LOR mini-tablets formulated with different directly compressible excipients (mean ± SD, n = 3).

Fig. 7: *In vitro* dissolution profiles of LOR mini-tablets formulated with CEL after 3 months storage at different temperature and relative humidity conditions (mean ± SD, n = 3).
Fig. 8: *In vitro* dissolution profiles of LOR mini-tablets formulated with STA after 3 months storage at different temperature and relative humidity conditions (mean ± SD, n = 3).

Fig. 9: *In vitro* dissolution profiles of LOR mini-tablets formulated with DCP after 3 months storage at different temperature and relative humidity conditions (mean ± SD, n = 3).
Fig. 10: *In vivo* plasma concentration–time profile for LOR following intravenous and oral administration to rabbits (mean ± SD, n = 3).
### TABLES

Table 1. The % compressibility (Carr’s Index) and Hausner Ratio (H) for Lornoxicam formulations (n=3 ± S.D.)

<table>
<thead>
<tr>
<th>LOR Formulation</th>
<th>Carr’s Index (%)</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-evaporate with PLU (1:5 weight ratio)</td>
<td>27.62 ±4.01</td>
<td>1.38 ±0.07</td>
</tr>
<tr>
<td>Co-adsorbate with NEU and polysorbate 80 (1:5:3 weight ratio)</td>
<td>44.48 ±0.9</td>
<td>1.80 ±0.02</td>
</tr>
<tr>
<td>PLU co-evaporate + CEL</td>
<td>22.38 ±0.21</td>
<td>1.28 ±0.005</td>
</tr>
<tr>
<td>PLU co-evaporate + STA</td>
<td>16.71 ±0.07</td>
<td>1.20 ±0.00</td>
</tr>
<tr>
<td>PLU co-evaporate + DCP</td>
<td>20.92 ±1.2</td>
<td>1.26 ±0.02</td>
</tr>
</tbody>
</table>

Table 2. Tensile strength (MPa) of LOR mini-tablets formulated with different directly compressible excipients after 3 months storage under different conditions (mean ± SD, n = 4). No data could be obtained after storage at 75% RH/ 40°C as mini-tablets were too weak to test.

<table>
<thead>
<tr>
<th></th>
<th>CEL</th>
<th>DCP</th>
<th>STA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambient</strong></td>
<td>1.76 ±0.01</td>
<td>1.20 ±0.05</td>
<td>1.2 ±0.15</td>
</tr>
<tr>
<td><strong>RT/43% RH</strong></td>
<td>1.82 ±0.11</td>
<td>1.17 ±0.10</td>
<td>1.02 ±0.05</td>
</tr>
<tr>
<td><strong>RT/75% RH</strong></td>
<td>1.94 ±0.09</td>
<td>0.77 ±0.11</td>
<td>1.01 ±0.10</td>
</tr>
<tr>
<td><strong>40°C/75% RH</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>
Table 3. Pharmacokinetic parameters of LOR after oral administration of mini-tablet and aqueous IV injection to rabbits (mean ± S.D., n=3 per group)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
<th>$K_a$</th>
<th>$t_{1/2a}$</th>
<th>$K_e$</th>
<th>$t_{1/2e}$</th>
<th>MRT</th>
<th>$\text{AUC}_{(0-24)}$</th>
<th>$\text{AUC}_{(0-\infty)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-tablet (A)</td>
<td>3.33±0.19</td>
<td>2.0±0.0</td>
<td>1.1079±0.96</td>
<td>0.962±0.57</td>
<td>0.0863±0.01</td>
<td>*8.115±0.99</td>
<td>7.414±0.48</td>
<td>19.525±0.88</td>
<td>21.660±0.88</td>
</tr>
<tr>
<td>IV injection (B)</td>
<td>3.72±0.18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.1278±0.04</td>
<td>5.420±1.01</td>
<td>7.50±1.11</td>
<td>21.799±2.13</td>
<td>23.06±1.24</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$: Maximum LOR concentration in plasma (µg ml$^{-1}$); $T_{\text{max}}$: Time to reach the maximum concentration after LOR administration (h); MRT: Mean residence time (h); $K_a$: absorption rate constant (h$^{-1}$); $t_{1/2a}$: absorption half-life (h); $K_e$: Elimination rate constant (h$^{-1}$); $t_{1/2e}$: Elimination half-life (h); $\text{AUC}_{(0-24)}$: The area under LOR plasma concentration time curve from (0-24, µg.hr.ml$^{-1}$); $\text{AUC}_{(0-\infty)}$: The area under LOR plasma concentration time curve from zero to infinity (µg.hr.ml$^{-1}$). * = significantly different compared to IV (p<0.05, ANOVA/Tukey’s).