Dissolution Enhancement and Formulation of Rapid-Release Lornoxicam Mini-Tablets

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ABSTRACT: The aim was to enhance the dissolution of lornoxicam (LOR) and to produce mini-tablets with an optimised system to provide a rapid-release multi-particulate formulation. LOR systems were prepared through co-evaporation with either polyethylene glycol 6000 or Pluronic® F-68 (PLU) 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, differential scanning calorimetry, X-ray diffraction, 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 LOR mini-tablets were further evaluated for their *in vivo* pharmacokinetic profile. The co-evaporate of LOR with PLU showed significantly faster dissolution and superior flowability and was evaluated together with three directly compressible excipients (Cellactose® 80, StarLac® (STA) and Emcompress®) for mini-tablet formulation. The formulation with STA 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 LOR. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2470–2483, 2014
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INTRODUCTION

Lornoxicam (LOR) is a non-steroidal anti-inflammatory drug (NSAID), with analgesic and anti-pyretic properties,[1] and although structurally related to piroxicam and tenoxicam, LOR is 10-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 micronisation,[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 multi-particulate 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 multi-particulate 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 characterisation 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

Lornoxicam was kindly provided by Delta Pharma, (10th of Ramadan City, Cairo, Egypt). PEG was obtained from BDH

Abbreviations used: LOR, Lornoxicam; PEG, Polyethylene glycol 6000; PLU, Pluronic® F-68; NEU, Neusilin® US2; CEL, Cellactose® 80; STA, StarLac®; DCP, Emcompress®.

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Laboratory Suppliers (Poole, UK). PLU was obtained from BASF (SE Ludwigshafen, Germany). NEU was supplied from Fuji Chemical Industry (Tokyo, 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 (Wasserburg, Germany). Emcompress® (DCP), calcium hydrogen phosphate dihydrate, was obtained from JRS Pharma (Rosenburg, 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 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 of less than 200 μm 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, differential scanning calorimetry (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.

FT-IR Spectroscopy

The spectra were obtained using a Spectrum BX Spectrometer (Perkin Elmer, Waltham, MA) 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 thermograms were obtained using a Perkin Elmer DSC 8000 with Intracooler 2 cooling accessory and Pyris v. 10.1.0.0420 software. 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 aluminium 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°C–250°C.

Powder X-Ray Diffraction

Powder X-ray diffraction (PXRD) patterns were collected by using a Miniflex X-ray diffractometer (Rigaku, Tokyo, Japan). Samples were finely ground and packed into an aluminium sample holder.

Patterns were collected between 5° and 50° 2θ, at increments of 0.02° 2θ, scanning speed 2° min^{-1}, voltage 30 KV, current 15 mA using CuKα (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 (ρB) was calculated by measuring the volume of a known weight of powder mixture in a measuring cylinder. Tapped density (ρT) 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 values and Hausner ratios were determined according to Eqs. (1) and (2), respectively.

$$\text{Carr's index } (\%) = \frac{\rho T - \rho B}{\rho T} \times 100 \quad (1)$$

$$\text{Hausner ratio} = \frac{\rho T}{\rho B} \quad (2)$$

Powder Mixing

Lornoxicam–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, Muttenz, 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, Beynost, 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, Kanagawa, Japan). Crushing strengths, F (N), were determined using a Dr. Schleuniger model 6D tablet tester (Pharmatron AG, Thun, Switzerland) and tensile strengths, σ_t, (MPa), were calculated according to Eq. (3).[24]

$$\sigma_t = 2F/\pi DT \quad (3)$$

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 *in vitro* dissolution, content uniformity, stability testing and *in vivo* studies.

LOR Content

The drug content of LOR from 10 randomly selected mini-tablets in each batch was determined. Briefly, each mini-tablet