Research Article

Design and *In Vitro* Evaluation of Novel Sustained-Release Double-Layer Tablets of Lornoxicam: Utility of Cyclodextrin and Xanthan Gum Combination

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Abstract. The objective of the present study was to develop new directly compressed, double-layer tablets (DLTs) of lornoxicam, a highly potent nonsteroidal anti-inflammatory drug with short half-life, that are characterized by initial burst drug release in the stomach and comply with the release requirements of sustained-release products. Each of the proposed DLTs is composed of a fast-release layer and a sustained-release layer, anticipating rapid drug release that starts in the stomach to rapidly alleviate the symptoms and continues in the intestine to maintain protracted analgesic effect. An amorphous, freeze-dried inclusion complex of lornoxicam with hydroxypropyl-β-cyclodextrin, present in 1:2 (drug/cyclodextrin) molar ratio, was employed in the fast-release layer to enhance the dissolution of lornoxicam in the stomach and assure rapid onset of its analgesic effect. Xanthan gum (XG), a hydrophilic matrix-forming agent, was integrated in the sustained-release layer to provide appropriate sustainment of drug release. The weight ratios between the sustained-release layer and fast-release layer present in DLTs were adjusted to reach optimal formulations. DLTs composed of sustained-release layer (40% XG) to fast-release layer in 2:1 weight ratio and those composed of sustained-release layer (50% XG) to fast-release layer in 1:1 weight ratio showed the desired release profile. The drug contained in the fast-release layer showed an initial burst drug release of more than 30% of its drug content during the first 30 min of the release study followed by gradual release of the drug for a period of 8 h.

KEY WORDS: cyclodextrins; double-layer tablets; lornoxicam; sustained release; xanthan gum.

INTRODUCTION

Lornoxicam, also known as chlortenoxicam (1), is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs) with extremely potent anti-inflammatory and analgesic activities (2). Lornoxicam is commercially available in the form of conventional immediate-release tablets (4 and 8 mg), rapid-release tablets (8 mg), and parenteral formulations (4 mg/ml) for intravenous and intramuscular use (2). It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis (3). Moreover, it showed great efficacy in various clinical trials in the management of perioperative and postoperative pain associated with gynecological, orthopedic, abdominal, and dental surgeries (2). However, lornoxicam's usefulness is limited due to its short half-life that ranges from 3 to 5 h (4,5). Added to that, lornoxicam shows a distinct pH-dependent solubility characterized by very poor solubility in acidic conditions present in the stomach (5). Thus, it remains in contact with the stomach wall for a long period which might lead to local irritation and ulceration (6).

The layered tablet concept has been utilized to develop controlled-release formulations (7–12). Such a tablet is considered as a biphasic delivery system that is designed to release the drug at two different rates and is usually composed of a fast-release layer combined with single (7–10) or double sustained-release layers (11,12). Generally, conventional controlled-release dosage forms delay the release of drugs and do not provide a rapid onset of action after oral administration (13,14). Hence, the layered tablets offer a pharmacokinetic advantage over conventional controlled-release dosage forms as the drug is quickly released from the fast-release layer leading to rapid rise of drug plasma concentration followed by continuation of drug release from the sustained-release layer (14). This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained-release phase to avoid repeated drug administration. It is reported that the NSAIDs are suitable candidate drugs for this type of administration (13,14).

Accordingly, the current study was undertaken to modify the release pattern of lornoxicam through its incorporation in an oral dosage form that is able to promptly release lornoxicam in a soluble form in the stomach with the aim of reaching high serum concentration in a short period of time, ensuring rapid palliative effect for the symptoms. This action is then followed by an extended release of lornoxicam for more than 8 h to avoid its repetitive administration and

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improve patients' compliance as well as minimize the incidence of its side effects. To accomplish the goal stated above, double-layer tablets (DLTs) composed of a sustained-release layer combined with a fast-release layer were manufactured by direct compression using conventional tableting facilities in a simple and easy-to-scale-up formulation strategy.

Cyclodextrins (CDs) are a group of cyclic oligosaccharides, which have been investigated to improve the solubility and dissolution rate of various poorly soluble drugs (15–20). Moreover, CDs have been successfully employed to modify the release pattern of drugs in several modified-release formulations (8–10). In addition, it has been reported that the local gastric irritation/ulceration associated with the oral use of NSAIDs is extensively reduced by averting their direct contact with the stomach wall through their entrapment and inclusion in the hydrophobic cavity of CDs (21). According to the aforementioned reasons (8–10,15–21), both natural parent β-cyclodextrin (β-CD) and its chemically modified derivative, hydroxypropyl-β-cyclodextrin (HP-β-CD), were investigated for their suitability to be included in the fast-release layer of the DLTs. Xanthan gum (XG) was chosen as the candidate matrix-forming material to obtain suitable slow release of the drug from the sustained-release layer present in the prepared DLTs due to its biocompatibility, inertness (22), as well as its wide application as a sustained-release excipient (22–24).

In order to reach the goal of this study, solid systems of lornoxicam with either β-CD or HP-β-CD were prepared using different techniques, aiming to improve lornoxicam dissolution properties in acidic medium, as a primary step in development of DLTs. The interaction between lornoxicam and the two CDs was investigated in solution state using phase solubility and in solid state using differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR). Preliminary *in vitro* drug dissolution studies for the prepared solid systems were carried out in 0.1 N HCl to choose the solid system with superior dissolution characteristics to be incorporated into the fast-release layer present in the proposed DLTs. Matrix tablets containing different concentrations of XG ranging from 10% (*w/w*) to 50% (*w/w*) were initially prepared by direct compression. Subsequently, their *in vitro* release behavior was investigated to select suitable concentrations of XG, which are capable of sustaining lornoxicam release, to be employed in the sustained-release layer of the designed DLTs. Finally, DLTs composed of different ratios of sustained-release layer to fast-release layer were prepared by direct compression and their physical properties and *in vitro* release behavior in simulated gastric and intestinal fluids used in sequence were evaluated.

MATERIAL AND METHODS

Materials

Lornoxicam was kindly provided by Delta Pharma, 10th of Ramadan City, Cairo, Egypt. XG was supplied by Fluka Biochemika, Saint-Quentin-Fallavier, France. β-CD (MW= 1,135 Da) and HP-β-CD (average degree of substitution=0.8 and MW=1,460 Da) were purchased from Sigma-Aldrich, GmbH, Germany. Avicel PH 102 (microcrystalline cellulose) and Ac-Di-Sol (crosscarmellose sodium) were purchased

from FMC Corp., Philadelphia, Pennsylvania, USA. Magnesium stearate was obtained from Prolab, Paris, France. All other chemicals and solvents were of analytical grade and were used as received.

Phase Solubility Studies

The effects of β-CD and HP-β-CD on the solubility of lornoxicam were investigated according to the phase solubility technique established by Higuchi and Connors (25). Excess amounts of lornoxicam were added to 25 mL of either distilled water or aqueous solutions containing increasing concentrations of CDs, ranging from 2 to 20 mM, in a series of glass-stoppered vials. The suspensions were shaken at $25\pm 0.5°C$ for 7 days. Aliquots were withdrawn through a Millipore filter (0.45 μm pore size) and concentrations of lornoxicam were analyzed spectrophotometrically (1601-PC double beam spectrophotometer, Shimadzu, Japan) at λ_{max} 380 nm. Each experiment was carried out in triplicate.

Phase solubility diagrams were obtained by plotting the molar concentration of solubilized lornoxicam *versus* the molar concentrations of the CDs used. The apparent stability constants (K_s) were estimated from the straight line of the phase solubility diagrams according to the following equation of Higuchi and Connors (25):

$$K_s = slope/S_o(1 - slope)$$

where S_o represents the drug solubility in the absence of CDs (the intercept of the phase solubility diagram).

The complexation efficiency (CE), which reflects the solubilizing power of the CDs towards the drug, was calculated according to the following equation (26):

$$CE = [drug - CD]/[CD] = slope/1 - slope$$

where $[drug-CD]$ is the concentration of the drug–CD complex and $[CD]$ is the concentration of the free CD.

Preparation of Solid Systems of Lornoxicam with CDs

Aiming to improve the dissolution behavior of lornoxicam in gastric conditions, solid systems of lornoxicam with β-CD and HP-β-CD were prepared at two molar ratios, namely, 1:1 and 1:2 (drug/CD), using the kneading and freeze-drying methods. Physical mixtures were also prepared in the same molar ratios for comparison.

Physical Mixtures

Physical mixtures of lornoxicam and CDs were prepared by thoroughly mixing the two components in a mortar for 30 min.

Kneading Method

The calculated amounts of lornoxicam and CD were accurately weighed, transferred to a glass mortar, and triturated with a small volume of water/ethanol (1:1 volume ratio). The slurry obtained was kneaded for 30 min and then dried under vacuum at room temperature in the presence of calcium chloride as a dehydrating agent. Water/ethanol (1:1

volume ratio) was used as a wetting agent to achieve better interaction of lornoxicam with CDs during the kneading process (27).

Freeze-Drying Method

Appropriate quantities of CD and lornoxicam were dissolved in distilled water and 25% aqueous ammonia solution, respectively. The resultant solutions were mixed together by stirring to obtain a clear solution. The latter was frozen at −20°C and subsequently freeze-dried for 24 h at −50°C using a Novalyphe freeze dryer (Novalyphe-NL 500; Savant Instruments Corp., USA).

Physicochemical Characterization of Lornoxicam–CD Solid Systems

DSC thermograms, X-ray diffractograms, and FTIR spectra were recorded for lornoxicam, CDs, and their solid systems prepared by using different techniques in 1:2 (drug/ CD) molar ratio.

Differential Scanning Calorimetry

DSC analysis was performed using a Shimadzu differential scanning calorimeter (DSC-50, Shimadzu, Japan). The apparatus was calibrated with purified indium (99.9%). Samples (3–4 mg) were placed in flat-bottomed aluminum pan and heated at a constant rate of 10°C/min in an atmosphere of nitrogen in a temperature range of 20–400°C.

X-ray Diffractometry

The X-ray diffraction patterns were recorded at room temperature using a Scintag diffractometer (XGEN-4000, Scintag Corp., USA). The samples were irradiated with Ni-filtered Cu Kα radiation at 45 kV voltage and 40 mA current. The scanning rate employed was 2°/min over a diffraction angle of 2θ and range of 4–60°.

Fourier Transform Infrared Spectroscopy

The FTIR spectra were recorded using a Bruker FTIR spectrophotometer (Model 22, Bruker, UK) using the KBr disk technique. The smoothing of the spectra and the baseline correlation procedures were applied. The spectra were saved using a Lotus123 computer program. The FTIR measurements were performed in the scanning range of 4,000–400 cm^{-1} at ambient temperature.

In Vitro Dissolution Studies for Lornoxicam–CD Solid Systems

Preliminary dissolution tests under gastric conditions, intended for selecting the solid system with superior dissolution properties to be incorporated into the fast-release layer of DLTs, were performed using the United States Pharmacopeia (USP) dissolution apparatus II at 100 rpm (27). A sample equivalent to 8 mg of lornoxicam was placed in the dissolution vessel containing 400 mL of 0.1 N HCl maintained at 37±0.5°C. At appropriate intervals, samples from the

dissolution medium were withdrawn and filtered, and concentrations of lornoxicam were determined spectrophotometrically. The dissolution studies were conducted in triplicate and the mean values were plotted *versus* time. Additionally, lornoxicam dissolution profiles were evaluated on the basis of the dissolution efficiency parameter at 60 min (DE$_{60}$, in percent), calculated from the area under the dissolution curves, and expressed as a percent of the area of the rectangle described by 100% dissolution in the same time according to the following equation (28):

$$DE = \frac{\int_0^t y \times dt}{y100 \times t} \times 100$$

where y is the drug percentage dissolved at time t.

The DE$_{60}$ data of the investigated solid systems were analyzed using two-way analysis of variance (ANOVA) to test the significance of the effects of the preparation method, CD type, and molar ratio at $p \leq 0.05$ using StatView® software version 4.75 (Abacus Concepts Inc., Berkeley, USA). Multiple comparisons between different preparation methods, molar ratios, and CD types were then performed according to Scheffé's test using SPSS® software, version 7.5 (SPSS Inc., Chicago, USA) at $p \leq 0.05$ (15).

Preparation of Lornoxicam DLTs

In order to prepare lornoxicam DLTs, fast and sustained-release single-layer tablet formulations were initially prepared to gain insight into the dissolution profile of each layer separately with the aim of selecting the best formulations of each that could be combined together to provide DLTs with suitable release pattern characterized by an initial burst drug release in 0.1 N HCl followed by extended drug release profile for 8 h.

Formulation of the Fast-Release Layer

Table I presents the composition of the fast-release tablet formulation. Lornoxicam–HP-β-CD freeze-dried product in 1:2 (drug/CD) molar ratio was selected, based on its superior dissolution properties in 0.1 N HCl, to be incorporated into the fast-release tablets. Avicel PH 102 and Ac-Di-Sol were added as tablets diluent and superdisintegrant, respectively (29). They were mixed thoroughly with the lornoxicam–HP-β-CD freeze-dried product in a glass mortar with the help of a pestle for 30 min. Then, 1% (*w/w*) magnesium stearate was added as a lubricant to the powder blend and mixed for an additional 30 min. The resultant powder blend was compressed under constant pressure using a single-punch tableting machine into 200 mg tablets, each containing a total of 8 mg lornoxicam. The dissolution behavior of the tablets was examined using the same conditions used for lornoxicam–CD solid systems.

Formulation of the Sustained-Release Layer

Single-layer sustained-release tablet formulations were prepared using 10% to 50% (*w/w*) XG, lornoxicam, and Avicel PH 102 by mixing for 30 min in a glass mortar using a

Table I. Composition of Lornoxicam Fast-Release Tablet Formulations

Composition	Amounts (mg)
Lornoxicam freeze-dried product[a]	70.81
Ac-Di-Sol	20
Avicel PH 102	107.19
Magnesium stearate	2

[a] Lornoxicam–HP-β-CD freeze-dried product in 1:2 (drug/CD) molar ratio equivalent to 8 mg lornoxicam

pestle. Then, 1% (w/w) magnesium stearate was added to the powder blend and mixed for an additional 30 min. All of the prepared powder blends were compressed under constant pressure using a single-punch tableting machine into 200 mg tablets, each containing 8 mg lornoxicam. The detailed composition of the sustained-release tablet formulations are presented in Table II.

In Vitro Drug Release Studies for the Sustained-Release Formulations

The release of lornoxicam from the prepared sustained-release tablets was performed using USP dissolution apparatus II at 100 rpm (30,31). Studies were carried out in 400 mL of 0.1 N HCl maintained at $37\pm0.5°C$ for a period of 2 h followed by release in phosphate buffer of pH6.8 achieved by adding 200 mL of 0.2 M trisodium orthophosphate solution for another 6 h (32). Aliquots from the release medium were withdrawn and filtered, and concentrations of lornoxicam were determined spectrophotometrically. The withdrawn samples were replaced with equal volumes of media to maintain constant volumes. Release studies were carried out in triplicate and the mean values were plotted *versus* time.

Formulation of Lornoxicam DLTs

Table III provides the detailed composition of lornoxicam DLT formulations composed of different ratios of sustained-release to fast-release layer. The DLTs were prepared by direct compression using a single-punch tableting machine where its die was initially filled with the weighed amount of sustained-release portion and lightly compressed, then the fast-release portion was added directly onto the obtained compressed tablet, and then recompressed together to combine them (7,8). The total weight of each DLT was adjusted to 200 mg containing 8 mg of lornoxicam fractioned between the two layers.

Physical Tests for the Prepared DLTs

Tablet Weight Variation

Twenty DLTs were randomly selected and accurately weighed using an electronic balance (Sartorius GmbH, Gottingen, Germany). The results are expressed as mean values of 20 determinations.

Drug Content Uniformity

Ten DLTs were weighed individually and crushed, and the drug was extracted in phosphate buffer of pH6.8. The solution was filtered through a Millipore filter (0.45 μm pore size) and the drug content was determined spectrophotometrically at λ_{max} 376.8 nm after suitable dilution.

Tablet Friability

According to the BP specifications (33), a sample of 20 DLTs was placed in the drum of a tablet friability test apparatus (FAB-2, Logan Instruments Corp., NJ, USA). The drum was adjusted to rotate 100 times in 4 min then the tablets were removed from the drum, dedusted, and accurately weighed. The percent weight loss was calculated.

In Vitro Drug Release Studies for Lornoxicam DLTs

In vitro drug release studies of the DLTs were performed using the same method used for the sustained-release tablet formulations.

RESULTS AND DISCUSSION

Phase Solubility Studies

The phase solubility diagrams of lornoxicam with β-CD and HP-β-CD in distilled water performed at $25\pm0.5°C$ are shown in Fig. 1. It is apparent that the solubility of lornoxicam increased as the concentrations of CDs increased. The values of the stability constants (K_s) calculated from the equation of Higuchi and Connors (25) were found to be 56.027 and 218.426 M^{-1} for β-CD and HP-β-CD, respectively. The coefficient of determination (r^2) values of the phase solubility diagrams with both CDs were <0.990 (0.9703 and 0.9828 for β-CD and HP-β-CD, respectively); therefore, these diagrams were classified as Ap-type phase diagrams (34). Such positive deviations from linearity suggest the formation of higher-order inclusion complexes between lornoxicam and CDs attributed to the formation of complex aggregates that could solubilize additional amount of the guest

Table II. Composition of Lornoxicam Sustained-Release Tablet Formulations

Formulations	Composition			
	Lornoxicam (mg)	XG (% w/w)	Magnesium stearate (%)	Avicel PH 102 up to (mg)
F X1	8	10	1	200
F X2	8	20	1	200
F X3	8	30	1	200
F X4	8	40	1	200
F X5	8	50	1	200

XG Xanthan Gum

Table III. Composition of Lornoxicam DLT Formulations and Their Physical Characterization

Formulations[a]	% Xanthan Gum in sustained-release layer	Sustained-release layer: fast-release layer	Average weight (mg) ± SD	Average drug content (%) ± SD	Friability (%)
F 1		2:1	200.87±2.44	99.45±1.77	0.78
F 2	40	1:1	198.93±2.80	99.45±1.06	0.57
F 3		1:2	203.03±1.93	101.3±1.98	0.21
F 4		2:1	201.70±2.62	99.35±1.63	1.39
F 5	50	1:1	199.83±1.40	98.5±2.26	0.82
F 6		1:2	201.17±2.46	97.75±2.62	0.53

[a] Total amount of lornoxicam in each DLT is 8 mg
DLT Double-layer Tablet

molecules through non-inclusion complexation or formation of micelle-like structures (35).The calculated CE values revealed that the solubilizing power of CDs towards the drug follows the order: HP-β-CD (0.00742) > β-CD (0.00205). The calculated higher values of K_s and CE obtained for HP-β-CD compared to β-CD indicate that lornoxicam interacts more strongly with HP-β-CD and this may be attributed to the better wetting ability and greater solubilizing power of HP-β-CD towards the drug. Similar results were observed in literature for tadalafil (15), efavirenz (17), and valdecoxib (36) when solubilized with both β-CD and HP-β-CD.

## Physicochemical Characterization of Lornoxicam–CD Solid Systems

Differential Scanning Calorimetry

DSC was performed for lornoxicam, CDs, and their solid systems prepared by different techniques at a molar ratio of 1:2 (drug/CD; figures not shown). The DSC thermogram of lornoxicam was typical of a crystalline substance, exhibiting a sharp exothermic peak at 232.9°C corresponding to its melting and decomposition (1). The thermograms of the physical mixtures of lornoxicam with either β-CD or HP-β-CD showed the existence of the drug exothermic peak which could indicate the absence of interaction between lornoxicam and CDs. However, a marked reduction in lornoxicam peak intensity was observed in the aforementioned systems and could be attributed to the low drug to CD molar ratio (1:2) (15). On the other hand, the drug-melting exotherm was recorded in the kneaded systems prepared using either β-CD or HP-β-CD, but with noticeable broadening and reduction in intensity which could be ascribed to increase in the drug–CD interaction as a consequence of the more drastic mechanical treatment during kneading compared to physical mixing (37). The drug exothermic peak completely disappeared in the DSC thermograms of the freeze-dried systems prepared using either β-CD or HP-β-CD. This could indicate complete drug amorphization and/or its interaction with the carrier caused by the supply of thermal energy during the DSC scan process (38). Therefore, X-ray powder diffractometry was considered in conjunction with DSC analysis to reach a definite conclusion.
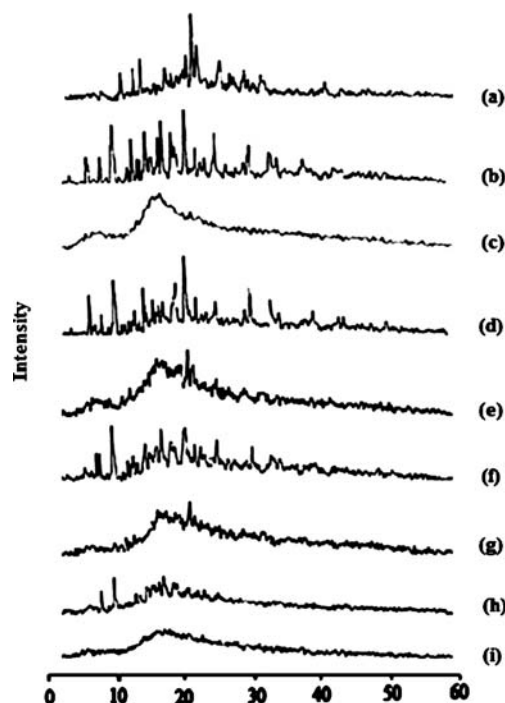
X-ray Powder Diffractometry

Figure 2 presents the XRD patterns for individual components and their solid systems prepared by different techniques at 1:2 (drug/CD) molar ratio. The diffraction pattern of lornoxicam powder revealed several sharp high-intensity peaks at diffraction angles 2θ of 7.8°, 10.2°, 12.2°, 14.5°, 18.2°, 22.2°, and 24.5°, suggesting that it existed as a crystalline material. β-CD showed a crystalline diffractogram, while a diffuse halo pattern was recorded for HP-β-CD (15). Generally, the diffraction patterns of the investigated physical mixtures correspond to the superposition of those of the individual components and revealed that lornoxicam was present in a crystalline state, as evidenced by its diffraction lines, and thereby ruled out the existence of drug–carrier interaction in these physical mixtures. However, slight decrease in lornoxicam crystalline character was observed in the diffractograms of the kneaded systems evidenced by the noticeable decrease in the number and intensities of peaks present in their X-ray diffractogram when compared to the corresponding physical mixtures. This finding might be attributed to the reduction in the drug particle size during the kneading process (39) and/or the presence of an interaction between the drug and CD during the drying process (37). The diffractogram of lornoxicam–β-CD freeze-dried system showed the presence some lornoxicam peaks, which suggest the presence of free crystalline drug, although great reduction in their number and intensities were observed (15). On the other hand, the diffractogram of freeze-dried system prepared using HP-β-CD showed a typical diffuse pattern indicating the complete conversion of lornoxicam to amorphous form (40).
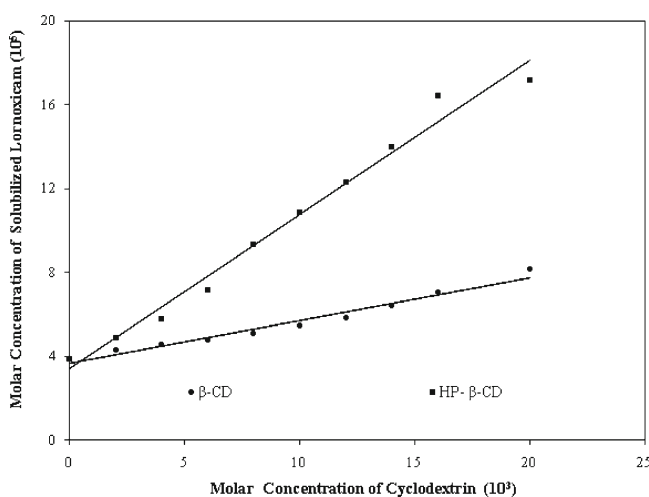
Fig. 1. Phase solubility diagrams of lornoxicam with different CDs in distilled water at 25±0.5°C

Fig. 2. X-ray diffraction patterns of lornoxicam–CD solid systems in 1:2 (drug/CD) molar ratio: *a* lornoxicam powder; *b* pure β-CD; *c* pure HP-β-CD; *d* physical mixture of lornoxicam with β-CD; *e* physical mixture of lornoxicam with HP-β-CD; *f* kneaded product of lornoxicam with β-CD; *g* kneaded product of lornoxicam with HP-β-CD; *h* freeze-dried product of lornoxicam with β-CD; *i* freeze-dried product of lornoxicam with HP-β-CD

Fourier Transform Infrared Spectroscopy

Figure 3 presents the FTIR spectra of individual components and their solid systems prepared by different techniques at 1:2 (drug/CD) molar ratio. The FTIR spectrum of lornoxicam showed a characteristic peak at 3,090 cm^{-1} corresponding to –NH stretching vibration. Intense absorption peak was found at 1,642 cm^{-1} due to the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1,597 and 1,559 cm^{-1} and were assigned to bending vibrations of the N–H group in the secondary amide. The stretching vibrations of the O=S=O group appeared at 1,157, 1,387, and 1,336 cm^{-1}. Other prominent peaks appeared at 827.94 cm^{-1} corresponding to –CH aromatic ring bending and heteroaromatics and at 766.8 cm^{-1} due to the C–Cl bending vibration. The FTIR spectra of the investigated CDs illustrated intense broad absorption bands at 3,800–3,100 cm^{-1} corresponding to the free –OH stretching vibration. The vibration of the –CH and –CH$_2$ groups appeared in the region 2,950–2,600 cm^{-1}. A shorter band appeared in the region 1,500–1,200 cm^{-1} that could be ascribed to the hydrated bonds within CD molecules. Another large band assigned to the C–O–C stretching vibration occurred between 1,200 and 1,030 cm^{-1} (15,18). The three intense peaks due to carbonyl stretching of lornoxicam at 1,642 cm^{-1} and the N–H bending present at 1,597 and 1,559 cm^{-1} were the main characteristic bands used to assess the drug–CDs interactions (indicated by the black

arrow in Fig. 3) due to absence of overlapping between those peaks and CD peaks.

The FTIR spectra of the investigated physical mixtures did not show any significant shifts with respect to the FTIR spectra of the components and, in particular, the characteristic carbonyl stretching and the N–H bending of lornoxicam. Likewise, there was no shift in the characteristic stretching band of lornoxicam in the spectrum of its kneaded product with β-CD. However, the same band was diminished in the case of the lornoxicam–HP-β-CD kneaded product when compared to the corresponding physical mixture, suggesting partial interaction of the drug with the HP-β-CD molecule. On the other hand, the lornoxicam characteristic carbonyl stretching band and amide bands were highly broadened and diminished in the FTIR spectra of both freeze-dried products. This might indicate the inclusion of lornoxicam in the hydrophobic cavity of the carrier (15,36). Taking into account the above results together with that obtained from the DSC and X-ray studies, they all supported an almost complete transformation of the crystalline drug to an amorphous state and the existence of strong interaction between the drug and HP-β-CD when the freeze-drying method was used.

***In Vitro* Dissolution Studies for Lornoxicam–CD Solid Systems**

Figure 4 illustrates the dissolution profiles of the lornoxicam–CD solid systems in 0.1 N HCl and Table IV represents a compilation of their dissolution efficiency data calculated based on 60 min (DE$_{60}$). Actually, lornoxicam dissolved very slowly under the specified dissolution conditions and less than 10% of lornoxicam was dissolved after
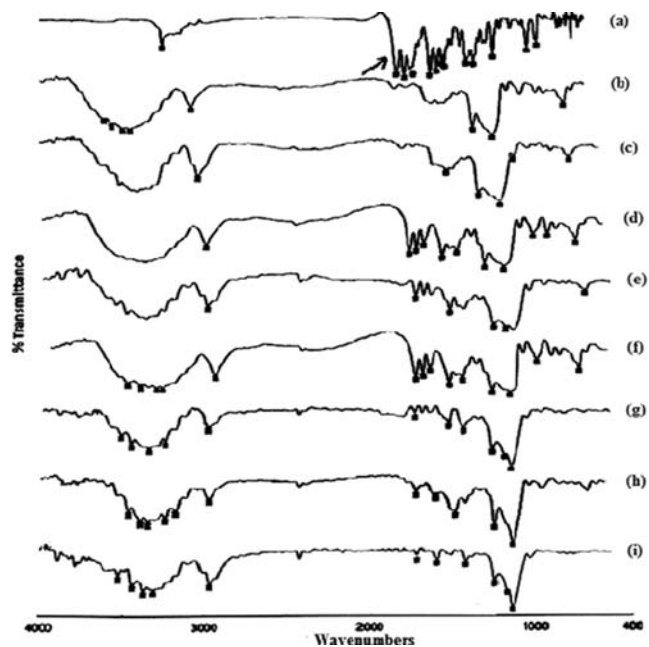
Fig. 3. FTIR spectra of lornoxicam–CD solid systems in 1:2 (drug/CD) molar ratio: *a* lornoxicam powder; *b* pure β-CD; *c* pure HP-β-CD; *d* physical mixture of lornoxicam with β-CD; *e* physical mixture of lornoxicam with HP-β-CD; *f* kneaded product of lornoxicam with β-CD; *g* kneaded product of lornoxicam with HP-β-CD; *h* freeze-dried product of lornoxicam with β-CD; *i* freeze-dried product of lornoxicam with HP-β-CD

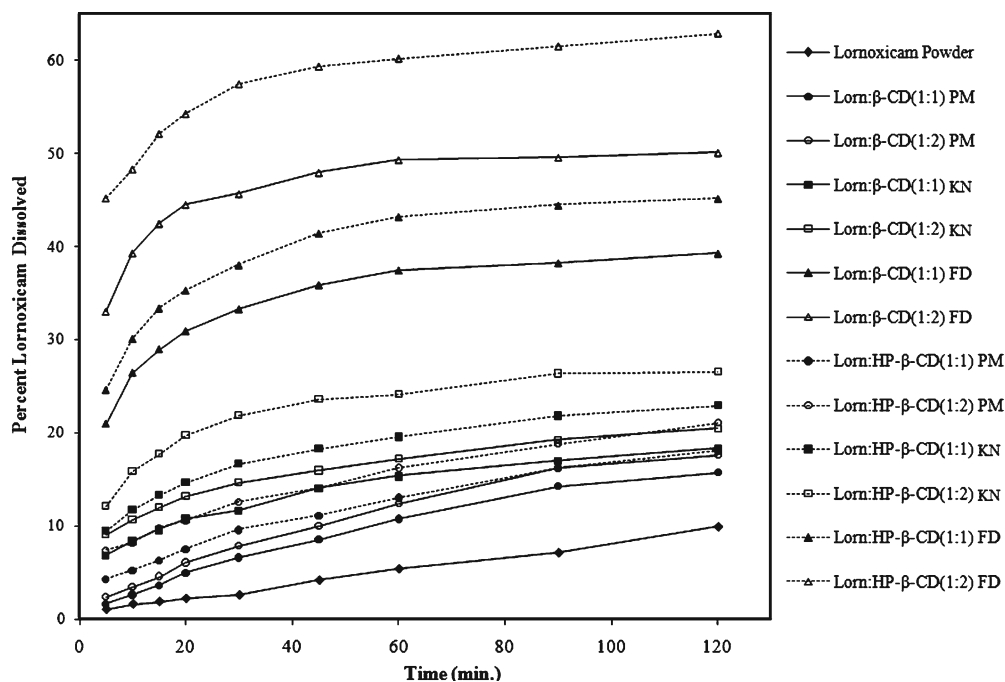**Fig. 4.** Dissolution profiles of lornoxicam from its solid systems with β-CD and HP-β-CD in 0.1 N HCl at 37±0.5°C (*Lorn* lornoxicam, *PM* physical mixture, *KN* kneaded product, *FD* freeze-dried product)

2 h. Generally, lornoxicam dissolution was improved from all of the investigated solid systems and this improvement depended on the preparation method, drug to CD molar ratio, and type of CD used.

It is quite evident that the preparation method affected lornoxicam dissolution from the investigated solid systems (15). Lornoxicam dissolution was enhanced when physically mixed with CDs due to local solubilization action of the carrier operating in the aqueous microenvironment surrounding the drug (40). The kneaded products showed slight increment in lornoxicam dissolution compared to the corresponding physical mixtures probably due to the increase in drug–carrier contact surface as a consequence of the more drastic mechanical treatment during the kneading process (37). However, the freeze-dried solid systems showed marked increase in lornoxicam dissolution compared with the other preparation methods primarily due to the formation of soluble inclusion complexes of the drug with CDs accompanied by reduction of its crystallinity following complexation as reported in the literature (15,17).

In addition, it was obvious that lornoxicam dissolution was enhanced on increasing the molar ratio of CD in the investigated solid systems. Physical mixtures showed the least effect for the molar ratio since the observed enhancement in dissolution is mainly due to the wetting effect of the CDs (40). Conversely, the most pronounced effect for the molar ratio was observed for the freeze-dried products due to better dispersion and/or inclusion of the drug with increasing CD molar ratio during preparation.

The effect of the CD type was also obvious on the dissolution of lornoxicam where the solid systems prepared using HP-β-CD showed superior enhancement in lornoxicam dissolution compared with those prepared using the parent β-CD, especially on using the freeze-dried technique (17). This

Table IV. Dissolution Efficiency of Lornoxicam From its Solid Systems with β-CD and HP-β-CD Prepared Using Different Preparation Techniques

Solid system	Dissolution efficiency (DE_{60}, %)[a]
Lornoxicam–β-CD (1:1) physical mixture	6.13±0.57
Lornoxicam–β-CD (1:2) physical mixture	7.31±0.54
Lornoxicam–β-CD (1:1) kneaded product	11.25±0.49
Lornoxicam–β-CD (1:2) kneaded product	13.50±1.69
Lornoxicam–β-CD (1:1) freeze-dried product	30.79±0.60
Lornoxicam–β-CD (1:2) freeze-dried product	42.77±0.51
Lornoxicam–HP-β-CD (1:1) physical mixture	8.67±0.19
Lornoxicam–HP-β-CD (1:2) physical mixture	11.62±0.12
Lornoxicam–HP-β-CD (1:1) kneaded product	15.19±0.68
Lornoxicam–HP-β-CD (1:2) kneaded product	19.77±0.65
Lornoxicam–HP-β-CD (1:1) freeze-dried product	35.42±0.71
Lornoxicam–HP-β-CD (1:2) freeze-dried product	53.17±0.44

[a] Calculated from the area under the dissolution curve after 60 min

could be explained on the basis of greater water solubility, better wetting ability, and higher complexing power of HP-β-CD towards the drug in the solid state (20) and also reflects the inability of the parent CD to promote true inclusion complexation with lornoxicam (15). The previous findings are in perfect agreement with the calculated values of K_s and CE obtained for lornoxicam with the investigated CDs.

The results of the two-way ANOVA performed on the DE_{60} data revealed the presence of significant differences among the two CD types, preparation methods, and molar ratios at $p \leq 0.05$. The computed F values indicated that the dissolution of lornoxicam from its solid systems was dependent mostly on the preparation method followed by the molar ratio and finally the CD type. Multiple comparisons between the different preparation methods for each CD type at each molar ratio according to Scheffé's test revealed that the freeze-drying technique exhibited the most significant effect on the dissolution enhancement of lornoxicam compared to the other methods at $p \leq 0.05$. In addition, multiple comparisons between the two molar ratios employed in the freeze-dried products of each CD according to Scheffé's test revealed that the molar ratio of 1:2 (drug/CD) exhibited the most significant improvement on the dissolution efficiency compared to the other molar ratio for both CDs at $p \leq 0.05$. These results confirmed that the freeze-dried systems prepared at 1:2 (drug/CD) molar ratio showed the most superior and significant enhancement effect on the dissolution pattern of lornoxicam. Therefore, the DE_{60} of these systems were statistically compared using Scheffé's test to separate the effect of different CDs at $p \leq 0.05$. The results showed significant difference between β-CD and HP-β-CD. Accordingly, the freeze-dried system lornoxicam–HP-β-CD, prepared at 1:2 (drug/CD) molar ratio, was chosen for further incorporation into the tablet formulations.

In Vitro Drug Release Studies for the Fast-Release and Sustained-Release Tablets

Figure 5 presents the dissolution profile of lornoxicam from the prepared fast-release tablets in comparison to the dissolution profile of lornoxicam in 0.1 N HCl. It is worth noting that Ac-Di-Sol was used as a superdisintegrant in these tablet formulations to cause their immediate disintegration when exposed to the dissolution media, thus enhance rapid release of the drug (29). It is quite clear that the prepared fast-release tablet formulation, containing lornoxicam–HP-β-
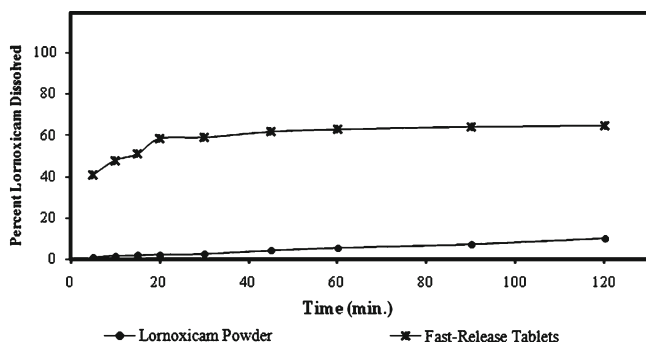

Fig. 5. Dissolution profiles of lornoxicam from fast-release tablets containing lornoxicam–HP-β-CD freeze-dried product in 1:2 (drug/CD) molar ratio in comparison with lornoxicam powder performed in 0.1 N HCl at 37±0.5°C

CD freeze-dried complex in 1:2 (drug/CD) molar ratio, has shown manifested improvement in drug dissolution properties in acidic conditions when compared to lornoxicam. This can be ascribed to the decrease in crystallinity of lornoxicam as a result of its complexation with HP-β-CD during the freeze-drying process as evidenced from its physicochemical characterization described previously. Furthermore, the observed enhancement of lornoxicam dissolution behavior in gastric conditions as well as its entrapment within the HP-β-CD cavity at the molecular level is expected to prevent its direct contact with the stomach wall and thus reduce its local irritation and side effects (21).

Figure 6 illustrates the *in vitro* release profiles of lornoxicam from the prepared sustained-release tablets containing different percentages of XG. To simulate the conditions that exist in human GI tract as the tablet transits from stomach to intestine, the release studies were performed in 0.1 N HCl of pH1.2 for 2 h followed by phosphate buffer of pH6.8 for the sequential 6 h (41). Moreover, the release sampling duration lasted 8 h as the total GI transit time of dosage forms after oral administration in humans is reported to be approximately 8 h (42).

Due to its distinct pH-dependent solubility, lornoxicam showed an extremely slow dissolution in acidic pH; in fact, less than 10% of the drug was dissolved after 2 h. However, complete drug dissolution was displayed when the pH of the release medium was changed to 6.8. Tablets belonging to formulation F X1, F X2, and F X3 that contained 10%, 20%, and 30% of XG, respectively, failed to sustain lornoxicam release. This was generally attributed to their extensive disintegration at the beginning of the dissolution test that prevented the formation of a continuous gel layer, which is reported to be responsible for the modulation of the drug release process (14,43). On the other hand, matrix tablets containing higher percentages of XG, namely, F X4 and F X5 that contained 40% and 50% of XG, respectively, were able to keep their integrity and showed a good control on lornoxicam release. The extent of lornoxicam release from these tablets, after the 8-h dissolution period, was 75.63% and 47.77%, respectively. As expected, the extent of lornoxicam release from these tablet formulations was inversely related to the percentage of XG present in the tablet formulation. This observation is in complete concurrence with literature findings and is probably due to the formation of a highly viscous thick gel layer, on the surface of the tablets, characterized by slower erosion rate when XG is present in higher concentration (24). Moreover, it is reported that the entanglement density of the polymer increases when present in higher concentrations, resulting in more convoluted drug diffusion path, which consequently retard the release of the drug out of the tablets (44). In view of the abovementioned results, only formulations F X4 and F X5 that were able to sustain lornoxicam release and contained 40% and 50% of XG, respectively, were selected for preparing the sustained-release layers present in the proposed DLTs.

Preparation and Physical Characterization of Lornoxicam DLTs

Table III represents a compilation of the compositions of the prepared DLTs containing different ratios of sustained-
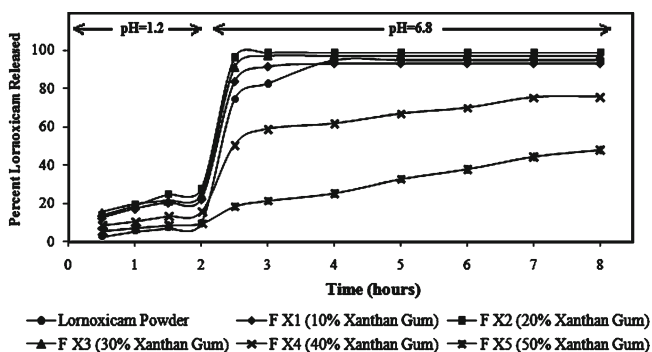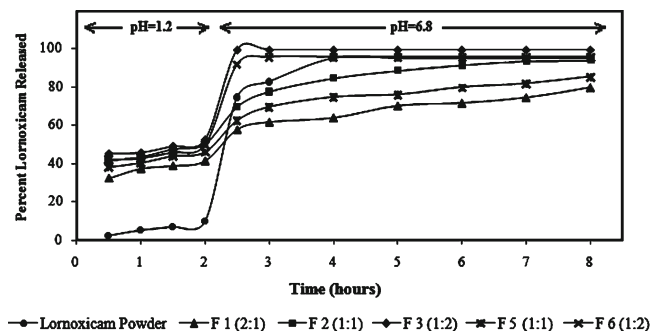
Fig. 6. *In vitro* release profiles of lornoxicam from matrix tablets containing different percentages of XG performed in 0.1 N HCl of pH1.2 for 2 h and phosphate buffer of pH6.8 for the subsequent 6 h at 37±0.5°C

release to fast-release layers. In light of the previous results presented in our study, the fast-release layer contained the freeze-dried inclusion complex of lornoxicam with HP-β-CD in 1:2 (drug/CD) molar ratio to attain an initial rapid release of lornoxicam in the stomach. However, the sustained-release layer contained lornoxicam embedded in hydrophilic matrix containing XG in concentration of either 40% or 50% (*w/w*).

The comparison of the physical properties of the prepared DLT formulations is shown in Table III. The average weight of the formulations ranged from 198.93 to 203.03 mg. Drug content uniformity results were found to be good among formulations of DLTs, and the percentage of drug content was more than 98.5%. The percentage friability for DLTs belonging to formulations F 1, F 2, F 3, F 5, and F 6 was below 1%, indicating that their friability was within the compendial limits (33). Conversely, DLTs belonging to formulation F 4 were very friable and exceeded the acceptable friability limits, so were excluded from further *in vitro* drug release studies.

In Vitro Drug Release Studies for Lornoxicam DLT

Figure 7 presents the release profiles of lornoxicam from the prepared DLTs composed of different ratios of sustained-release to fast-release layer. All of the prepared DLT formulations showed burst release of more than 30% of their lornoxicam content in 0.1 N HCl during the first 30 min of the

release study. This was attributed to the prompt disintegration of the fast-release layer, followed by the rapid dissolution of the incorporated lornoxicam–HP-β-CD freeze-dried complex. It is interesting to note that, after the pH of the release medium was changed to 6.8, clearly different release profiles were attained from the investigated DLTs.

It is evident that DLTs belonging to formulation F 3 and F 6 failed to sustain the release of lornoxicam due to the lower ratio of sustained-release to fast-release layer (1:2) employed in these tablets. However, those belonging to formulations F 1, F 2, and F 5 succeeded in this regard and were able to sustain the release of lornoxicam. Although DLTs belonging to formulation F 1 and F 2 contained the same percentage of XG (40%) in the sustained-release layers, they showed different dissolution profiles; the extent of dissolution of lornoxicam after 8 h was 79% and 93%, respectively. This observation is likely due to the difference in the weight ratio of the sustained-release to fast-release layer present in these tablets. DLTs belonging to formulation F 2 and F 5 containing the same weight ratio of sustained-release to fast-release layer (1:1) showed distinct dissolution profiles due to the difference in the concentration of XG present in the sustained-release layer. Conclusively, from inspecting all of the release profiles of the prepared DLTs, it is clearly manifested that they show a wide range of release profiles by varying the concentration of XG in the sustained-release layer as well as varying the weight ratio of the two layers (sustained and fast) present in DLTs in order to obtain the desirable *in vitro* release profile.

The target release profile parameters for sustained-release products were reported as follows (45): after 2 h, 20–50% of the drug is released; after 4 h, 45–75% of the drug is released; and finally, after 8 h, 75–105% of the drug is released. For assessment and comparison with these release specifications, the percent of drug released from the prepared DLT formulations after 2, 4, and 8 h were extracted directly from the release data and were graphically depicted in Fig. 8. It is evident that DLTs belonging to formulation F 1 [sustained-release layer (40% XG)/fast-release layer, 2:1] and F 5 [sustained-release layer (50% XG)/fast-release layer,
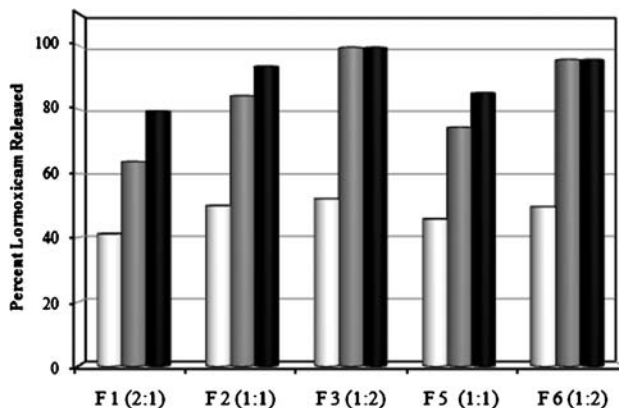

Fig. 7. *In vitro* release profiles of lornoxicam from the prepared DLTs performed in 0.1 N HCl of pH1.2 for 2 h and in phosphate buffer of pH6.8 for the subsequent 6 h at 37±0.5°C. The *values present between parentheses* represent the weight ratio of sustained-release to fast-release layer

Fig. 8. The percentage of lornoxicam released after 2, 4, and 8 h from the prepared DLTs performed in 0.1 N HCl of pH1.2 for 2 h and in phosphate buffer of pH6.8 for the subsequent 6 h at 37±0.5°C. The *values present between parentheses* represent the weight ratio of sustained-release to fast-release layer

1:1] exhibited release profiles that fulfilled the abovementioned release requirements; tablets belonging to formulation F 1 released approximately 41.11%, 63.69%, and 79.45% and those belonging to formulation F 5 released approximately 45.81%, 74.52%, and 85.19% at 2, 4, and 8 h, respectively. As can be seen, these DLTs also illustrated a burst release of more than 30% their drug content during the first 30 min of the release study, so they are expected to overcome the disadvantages associated with the delayed dissolution of lornoxicam in acidic conditions. For these reasons, further ulcerogenic and *in vivo* studies for DLTs belonging to formulation F 1 and F 5 are currently under investigation in order to assess their therapeutic effectiveness in comparison with immediate-release formulations.

CONCLUSION

In the present study, the proposed DLTs for lornoxicam were confirmed to be a successful tool for providing the desired drug release pattern characterized by initial burst release of lornoxicam in acidic conditions followed by its prolonged release for 8 h. These tablets were composed of sustained-release layer, prepared using 40% or 50% of XG, and fast-release layer containing lornoxicam–HP-β-CD freeze-dried complex in 1:2 (drug/CD) molar ratio which was proven to be advantageous in the context of enhancing lornoxicam dissolution characteristics in acidic medium. DLTs, examined for drug release in simulated gastric and intestinal fluids used in sequence to mimic the GI transit, revealed different release patterns depending on the percentage of XG present in the sustained-release layer and the weight ratio of the sustained-release to fast-release layer. DLTs belonging to formulations F 1 [sustained-release layer (40% XG)/fast-release layer, 2:1] and F 5 [sustained-release layer (50% XG)/fast-release layer, 1:1] showed acceptable physical properties and elicited the required *in vitro* release pattern that coincides with the purpose set for this study. In conclusion, it can be reasonably hypothesized that the adopted formulation strategy to obtain the desirable modulation of drug release profile, according to its pharmacokinetics and therapeutic needs, was achieved by the proposed DLTs. Further *in vivo* studies are ongoing to assess the improvement in therapeutic efficiency and gastric tolerance of the proposed DLTs compared to immediate-release formulations.

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