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# Innovation of novel sustained release compression-coated tablets for lornoxicam: formulation and in vitro investigations

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**Abstract**

*Objective*: The objective of this study was to modify the release characteristics of lornoxicam, a highly potent nonsteroidal anti-inflammatory drug, by preparing compression-coated tablets (CCTs) that provide complete drug release that starts in the stomach to rapidly alleviate the painful symptoms and continues in the intestine to maintain prolonged analgesic effect as well as meets the reported sustained release specifications. *Methods*: Each of the prepared CCTs was composed of a sustained release tablet core and an immediate release coat layer. Amorphous, well-characterized, freeze-dried solid dispersion of lornoxicam with polyvinylpyrrolidone K-30 was employed in the coat layer to attain an initial rapid dissolution of lornoxicam in the stomach, assuring rapid onset of analgesic effect. Compritol® ATO 888, a lipophilic matrix-forming material, was included in the core tablets to sustain lornoxicam release. Lactose was also incorporated into these core tablets to ensure complete release of lornoxicam in a time period comparable to the gastrointestinal residence time. *Results*: All the prepared CCTs showed acceptable physical properties that complied with compendial requirements. On the basis of in vitro drug release studies, performed in simulated gastric and intestinal fluids in sequence to mimic the gastrointestinal transit, CCTs belonging to formulations F3 CCTs and F4 CCTs were able to show the desired release profile. *Conclusion*: This study demonstrated the possibility of modulating lornoxicam release using CCTs to meet the reported sustained release specifications.

**Key words:** *Compression-coated tablets; Compritol® ATO 888; lactose; lornoxicam; polyvinylpyrrolidone K-30; solid dispersion; sustained release*

## Introduction

In many therapies, an initial burst of drug release followed by prolonged release over a defined period of time is required for successful treatment. This biphasic release pattern is used primarily when maximum relief needs to be achieved as quickly as possible and is followed by a sustained release phase to avoid repeated drug administration. Suitable candidate drugs for this type of administration include antihypertensive, antihistaminic, antiallergic agents, and nonsteroidal anti-inflammatory drugs (NSAIDs)[1]. Compression-coated tablets (CCTs) represent a promising approach to achieve biphasic release pattern. Each of these tablets is composed of a sustained release core tablet, which is coated by compression over the whole surface with a fast-disintegrating coat layer. Both the core tablet and the outer coat layer contain the drug. From manufacturing viewpoint, the CCTs are extremely acceptable to industry because they are prepared using conventional manufacturing methods[2].

Lornoxicam, also known as chlortenoxicam, is a member of the oxicam group of NSAIDs with extremely potent anti-inflammatory and analgesic activities[3]. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis[4,5]. Moreover, it showed great efficacy in various clinical trials in the management of perioperative

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and postoperative pain associated with gynecological, orthopedic, abdominal, and dental surgeries[3–6]. Like all other NSAIDs, lornoxicam mechanism of action is based on decreasing prostaglandin synthesis by inhibition of cyclooxygenase enzymes[7]. However, lornoxicam has a relatively superior gastrointestinal (GI) tolerability when compared with other NSAIDs[8,9], which is advantageous in terms of fewer side effects. Although lornoxicam shows considerable therapeutic effects, its usefulness is limited by its short duration of action because of its rapid elimination[10,11]. Hence, it requires repeated daily administration to achieve long-lasting and constant pain relief. Added to that, lornoxicam shows a distinct pH-dependent solubility characterized by poor solubility in low pH conditions present in the stomach[10].

Preparation of solid dispersions (SDs) using water-soluble polymeric carriers is an effective method for improving the dissolution characteristics of poorly soluble drugs in gastric conditions[12,13]. Among different polymeric carriers present, polyvinylpyrrolidone K-30 (PVP K-30) was chosen in this study as it is well tolerated physiologically, readily soluble in water, and has been extensively used to increase the dissolution and oral absorption of poorly soluble drugs[14–17]. Besides, the stability of aged SDs prepared with PVP K-30 was reported to be high[12,18]. On the other hand, Compritol® ATO 888, glyceryl behenate, was selected as lipophilic matrix-forming agent, because of its chemical inertness against other materials, ease of manufacturing with high reproducibility without special instrumentation, low production cost[19] as well as its wide application as a sustained release excipient[20,21].

To ensure rapid analgesic effect of lornoxicam after its oral administration and reduce the frequency of its administration, we have designed and characterized a novel oral delivery system for lornoxicam in form of CCTs. These tablets are composed of sustained release tablet cores, containing lornoxicam and Compritol ATO 888, coated over their whole surface with fast-disintegrating layer containing the SD of lornoxicam with PVP K-30. The proposed CCTs are expected to promptly release lornoxicam from their coat layer in the stomach with the aim of reaching high serum concentration in a short period of time, thus ensuring rapid palliative effect for the painful symptoms. This action is then pursued by an extended release phase of lornoxicam from the core tablets for 8 hours to maintain its effective plasma level for prolonged period of time, avoiding repetitive drug administration and improving patients' compliance.

In this work, preliminary experiments were carried out to prepare SDs of lornoxicam with PVP K-30 using different preparation techniques. The attained SDs were characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), and Fourier-transform infrared spectroscopy (FTIR). In vitro drug-dissolution studies for the prepared SDs were carried out in 0.1 N HCl, to choose the SD with superior dissolution characteristics, to be incorporated into the fast-release coat layer present in lornoxicam CCTs. On the other hand, the sustained release cores were prepared using Compritol ATO 888 in concentration ranging from 1% (w/w) to 10% (w/w), and their in vitro release studies were performed. Additionally, lactose was added to selected core tablets to tailor lornoxicam release to suit with humans' GI residence time. The prepared core tablets, with appropriate sustainment of lornoxicam release, were coated with lornoxicam SD mixed with selected excipients to form CCTs containing a net of 8 mg lornoxicam distributed between the core and the coat layer. Finally, the pharmaco-technical properties, namely weight variation, content uniformity, thickness, friability, and in vitro release were evaluated for the prepared CCTs.

## Materials and methods

### *Materials*

Lornoxicam (chlortenoxicam), kindly provided by Delta Pharma, 10th of Ramadan City, Cairo, Egypt. Compritol 888 ATO (glyceryl behenate) was generously donated by Gattefossé, Saint Priest, France. Lactose monohydrate, Avicel PH 102 (microcrystalline cellulose), and Ac-Di-Sol (crosscarmellose sodium) were purchased from FMC Corp. (Philadelphia, PA, USA). Polyvinylpyrrolidone K-30 (PVP K-30) was supplied from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All other chemicals and solvents were of analytical grade and were used as received.

### *Determination of the saturated solubility of lornoxicam in media with different pH values*

The saturated solubility of lornoxicam in 0.1 N HCl of pH 1.2, in deionized water of pH 5.1, and in phosphate buffer of pH 6.8, was determined. Excess amounts of lornoxicam were added to 20 mL of the above-mentioned media in screw-capped glass vials. Next, these vials were sonicated in an ultrasonic water bath (Model 275 T, Crest Ultrasonics Corp., Trenton, NJ, USA) for 1 hour then were shaken for 7 days at 25 ± 0.5°C using a thermostatically controlled shaking water bath (Model 1083, GLF Corp., Burgwedel, Germany) maintained at a speed of 50 strokes per minute. Following that, the suspension in each vial was withdrawn through 0.45-μm Millipore filter and the amount of lornoxicam dissolved in each medium was determined spectrophotometrically (1601-PC Double beam spectrophotometer,

Shimadzu, Kyoto, Japan) using the regression equation of a standard curve developed in the same medium. Each experiment was carried out in triplicate.

### *Preparation of SDs of lornoxicam with PVP K-30*

Aiming to improve the dissolution behavior of lornoxicam in gastric conditions, SDs of lornoxicam with PVP K-30 were prepared at different weight ratios, namely 1:1, 1:3, and 1:5, respectively, using solvent evaporation method and freeze-drying method as following:

#### Solvent evaporation method

Accurately weighed amounts of lornoxicam and PVP K-30 were dissolved in the least quantity of methylene chloride. Then, the solvent was evaporated under continuous stirring using a magnetic stirrer at room temperature. The obtained dried mass was crushed, dried in an oven at 40°C until constant weight, ground gently in a mortar by means of a pestle, and the particle size fraction <250 μm obtained by sieving was used throughout the study. The prepared samples were kept in a desiccator until the next experiments[12].

#### Freeze-drying method

Accurately weighed amount of lornoxicam and PVP K-30 were dissolved in the least quantity of 25% aqueous ammonia solution and distilled water, 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 hours at −50°C using a Novalyphe freeze-dryer (Novalyphe-NL 500; Savant Instruments Corp., Holbrook, NY, USA). The obtained mass was grounded gently with a mortar and pestle, sieved, and the particle size fraction <250 μm was used throughout the study. The samples were stored in a desiccator until use[12].

Physical mixtures of lornoxicam and PVP K-30 (<250 μm) were prepared at the same weight ratios as in the prepared SDs for comparative purpose.

### *Physicochemical characterization of lornoxicam–PVP K-30 solid systems*

DSC thermograms, X-ray diffractograms, and FTIR spectra were recorded for pure lornoxicam, pure PVP K-30, and their solid systems prepared by using different techniques in weight ratio of 1:5 (drug to PVP K-30).

#### Differential scanning calorimetry

DSC analysis was performed using a Shimadzu differential scanning calorimeter (DSC-50, Shimadzu, Kyoto, 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., Sunnyvale, CA, USA). The samples were irradiated with Ni-filtered Cu $K_\alpha$ radiation, at 45 kV voltage and 40 mA current. The scanning rate employed was 2°/min over a diffraction angle of $2\theta$ and range of 4–60°.

#### Fourier-transform infrared spectroscopy

The FTIR spectra were recorded using a Bruker FTIR spectrophotometer (Model 22; Bruker, Coventry, UK) according to the KBr disc 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 4000–400 $cm^{-1}$ at ambient temperature.

### *In vitro dissolution studies for lornoxicam–PVP K-30 solid systems*

Preliminary dissolution tests in gastric conditions were performed using a USP Dissolution Tester, Apparatus II (VK 7000 Dissolution Testing Station; Vankel Industries, Inc., Edison, NJ, USA), with the intention of selecting the SD characterized by superior dissolution properties to be incorporated into the coat layer in the proposed CCTs. Physical mixtures of lornoxicam with PVP K-30, and their SDs prepared using solvent evaporation and freeze-dried methods, equivalent to 8 mg of lornoxicam were placed in USP dissolution vessel containing 400 mL of 0.1 N HCl. The dissolution study was carried out at 37 ± 0.5°C, and the stirring shaft was adjusted to rotate at a speed of 100 rpm. At appropriate time intervals, samples from the dissolution medium were withdrawn through a 0.45-μm membrane filter and replaced with an equivalent amount of the fresh dissolution medium. Concentrations of lornoxicam, in the withdrawn samples, were determined spectrophotometrically (1601-PC Double beam spectrophotometer, Shimadzu, Kyoto, Japan) at $\lambda_{max}$ value of 372 nm using the regression equation of a standard curve developed in the same medium. The dissolution studies were conducted in triplicates and the mean values were plotted versus time. Lornoxicam dissolution profiles were evaluated on the basis of the dissolution efficiency parameter at 60 minutes ($DE_{60}$, %), 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[22].

Two-sided unpaired Student's *t*-test was performed between the $DE_{60}$ of each prepared solid system and that of pure lornoxicam, in order to test the significance of the formulation on the dissolution of the drug at $P \leq 0.05$. Moreover, the calculated $DE_{60}$ of the prepared solid systems were statistically analyzed using two-way ANOVA to test the significance of the effects of the preparation method, and weight ratio at $P \leq 0.05$ using StatView® software version 4.75 (Abacus Concepts Inc., Berkeley, CA, USA). Multiple comparisons were then performed between different preparation methods and weight ratios at 95% confidence level according to Scheffé test using SPSS® software, version 10 (SPSS Inc., Chicago, IL, USA). Differences were considered significant at $P \leq 0.05$.

### *Preparation of sustained release core tablets*

Core tablets containing 8 mg lornoxicam were prepared by direct compression. The detailed composition of the prepared core matrix tablets are presented in Tables 1 and 2. Accurately weighed amount of lornoxicam was mixed thoroughly with the required amount of Compritol ATO 888 in a glass mortar using a pestle for 30 minutes. Then, the calculated amount of diluents, either Avicel PH 102 alone or mixtures of Avicel PH 102 and lactose monohydrate present in different weight ratios, were added to the above mixture and blended together for another 30 minutes. The resultant powder blends were compressed into 50-mg core tablets using a single-punch tablet machine equipped with 7 mm round, flat, and plain punches. The force of compression was adjusted so that hardness of all the prepared core tablets ranged from 4 to 5 kg (HDT-300, Logan Instruments Corp., Somerset, NJ, USA).

**Table 1.** The composition of lornoxicam core tablets prepared using different percentage of Compritol® ATO 888.

| | Composition | | |
|---|---|---|---|
| Code of formulation | Lornoxicam (mg) | Compritol® ATO 888 (%, w/w) | Avicel PH 102 up to (mg) |
| F1 | 8 | 1 | 50 |
| F2 | 8 | 3 | 50 |
| F3 | 8 | 5 | 50 |
| F4 | 8 | 7 | 50 |
| F5 | 8 | 10 | 50 |

**Table 2.** The composition of lornoxicam core tablets prepared using 3% Compritol® ATO 888 and different ratios of lactose to Avicel PH 102.

| | Composition | | | |
|---|---|---|---|---|
| Code of formulation | Lornoxicam (mg) | Compritol® ATO 888 (%, w/w) | Filler ratio (lactose : Avicel PH 102) | Filler up to (mg) |
| F2a | 8 | 3 | 3:1 | 50 |
| F2b | 8 | 3 | 2:1 | 50 |
| F2c | 8 | 3 | 1:1 | 50 |
| F2d | 8 | 3 | 1:2 | 50 |
| F2e | 8 | 3 | 1:3 | 50 |

### *In vitro drug release studies for the prepared core tablets*

The release of lornoxicam from the prepared core tablets was performed using the USP Dissolution Tester, Apparatus II (Rotating paddle) at a rotation of 100 rpm. Studies were carried out in 400 mL of 0.1 N HCl maintained at 37 ± 0.5°C for a period of 2 hours followed by release in phosphate buffer of pH 6.8 achieved by adding 200 mL of 0.2 M tri-sodium orthophosphate solution, preheated to 37 ± 0.5°C, for another 6 hours[23]. Aliquots from the release medium were withdrawn through Millipore filter membrane of 0.45-µm pore size at predetermined time intervals. Concentrations of lornoxicam in the withdrawn samples were determined spectrophotometrically by measuring their absorbances using an UV spectroscopy (1601-PC Double beam spectrophotometer, Shimadzu, Kyoto, Japan) at $\lambda_{max}$ values of 372 and 376.8 nm when 0.1 N HCl and phosphate buffer of pH 6.8 were used as release medium, respectively. All the withdrawn samples were replenished with equal volumes of same release medium to keep the release volume constant. The release studies were conducted in triplicates and the mean values were plotted versus time.

### *Preparation of CCTs*

CCTs, each containing 8 mg of lornoxicam and weighing 200 mg, were prepared by direct compression[2,24]. The detailed composition of these tablets is presented in Table 3. The sustained release core tablets, weighing 50 mg, were prepared beforehand by direct compression as described earlier. The die of the tableting machine was first filled manually with half of the coat layer powder (75 mg) to make a powder bed, on the center of which the core tablet was carefully placed. Then, the remaining half of the coat powder (75 mg) was added to cover the core tablet and compressed using a single-punch tablet machine equipped with 9 mm round, flat, and plain punches. The force of compression was adjusted so that hardness of all the prepared tablets ranged from 4 to 5 kg (HDT-300, Logan Instruments Corp.).

### *Physical characterization of the prepared CCTs*

#### Tablet weight variation

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

**Table 3.** The composition of the investigated compression-coated tablets (CCTs).

| | Composition of lornoxicam CCTs[a] | | | | | |
|---|---|---|---|---|---|---|
| | Composition of the core tablets (50 mg) | | | Composition of the coat layer (150 mg) | | |
| Code of formulation | Lornoxicam (mg) | Compritol® (w/w, %) | Lactose : Avicel PH 102[b] | Lornoxicam[3] (mg) | Ac-Di-Sol (mg) (%) | Avicel PH 102 up to (mg) |
| F1 CCTs | 1 | 3 | 1:2 | 7 | 10 | 150 |
| F2 CCTs | 2 | 3 | 1:2 | 6 | 10 | 150 |
| F3 CCTs | 3 | 3 | 1:2 | 5 | 10 | 150 |
| F4 CCTs | 4 | 3 | 1:2 | 4 | 10 | 150 |
| F5 CCTs | 5 | 3 | 1:2 | 3 | 10 | 150 |
| F6 CCTs | 6 | 3 | 1:2 | 2 | 10 | 150 |
| F7 CCTs | 7 | 3 | 1:2 | 1 | 10 | 150 |

[a]Average weight of 200 mg and contains a total of 8 mg lornoxicam/tablet. [b]Added up to 50 mg. [c]Present in the form of freeze-dried solid dispersion of lornoxicam with PVP K-30 in 1:5 weight ratio equivalent to the tabulated amount of lornoxicam.

**Tablet thickness**

The thickness of 10 randomly selected CCTs was determined using a vernier caliper (For-bro Engineers, Mumbai, India). The results are expressed as mean values of 10 determinations.

**Drug content uniformity**

Ten CCTs were weighed individually, crushed, and the drug was extracted in phosphate buffer of pH 6.8. The solution was filtered through a cellulose acetate membrane (0.45 μm) and the drug content was determined spectrophotometrically by measuring their absorbances using UV spectroscopy (1601-PC Double beam spectrophotometer, Shimadzu) at $\lambda_{max}$ value of 376.8 nm after suitable dilution.

**Tablet friability**

According to the BP Specifications[25], a sample of 20 tablets was placed in the drum of a tablet friability test apparatus (FAB-2, Logan Instruments Corp, Somerset, NJ, USA). The drum was adjusted to rotate 100 times in 4 minutes then the tablets were removed from the drum, dedusted, and accurately weighed. The percent weight loss was calculated.

***Morphological examination of the prepared CCTs***

Morphological examination of longitudinal and horizontal cross-sections of selected CCTs was carried out using an electron microscope equipped with 60× lens. The tested core tablets were colored red using Sudan III dye to aid better visualization and distinction between the core tablet and the coat layer present in the investigated CCTs after compression[26].

***In vitro drug release studies***

In vitro drug release studies for the prepared CCTs were performed using the same procedures presented formerly for the prepared core tablets.

## Results and discussion

***Saturated solubility of lornoxicam in media with different pH values***

The saturated solubility of lornoxicam in media with different pH values is compiled in Table 4. Lornoxicam is a weak acid with p$K_a$ value of 5.5[10] and is present in an anionic form at pH > 6[3]. It is clearly evident from Table 4 that lornoxicam is poorly soluble in aqueous media, particularly in media with pH value lower than its p$K_a$ value and shows higher solubility in media with pH value above its p$K_a$ value, i.e., pH 6.8. This pH-dependent solubility is probably attributed to the presence of lornoxicam molecules uncharged at lower pH values, whereas at higher pH values lornoxicam molecules are negatively charged.

***Physicochemical characterization of lornoxicam–PVP K-30 solid systems***

**Differential scanning calorimetry**

Figure 1(I) presents the DSC thermograms of pure lornoxicam, pure PVP K-30, and their physical mixture and SDs prepared by solvent evaporation method and freeze-drying method. The DSC thermogram of lornoxicam exhibited a single sharp exothermic peak at 232.9°C, which is probably due to drug melting and decomposition[27]. However, the DSC thermogram of PVP K-30 showed a broad endotherm over the temperature range from 50°C to 100°C, which is typically present

**Table 4.** Saturated solubility of lornoxicam in media with different pH values at 25 ± 0.5°C (mean ± SD, $n = 3$).

| Media tested | Mean drug solubility (mg/mL) ± SD |
|---|---|
| 0.1 N HCl (pH 1.2) | 0.006 ± 0.002 |
| Deionized water (pH 5.1) | 0.021 ± 0.009 |
| Phosphate buffer (pH 6.8) | 0.305 ± 0.083 |

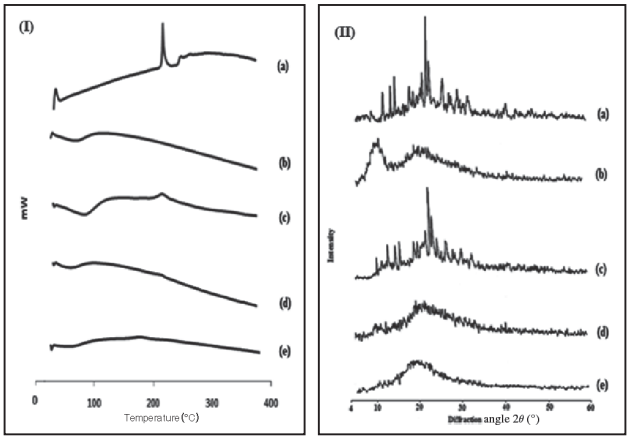


**Figure 1.** DSC thermograms (I) and X-ray diffraction patterns (II) of lornoxicam–PVP K-30 solid systems: (a) pure lornoxicam; (b) pure PVP K-30; (c) physical mixture 1:5; (d) solvent-evaporated product 1:5; (e) freeze-dried product 1:5.

in amorphous hydrated substances and is attributed to the loss of residual moisture present in PVP K-30. Similar results have been reported by several authors[16,28].

The DSC thermogram of the investigated physical mixture exhibited the characteristic exothermic peak of lornoxicam, indicating the absence of interaction between the two components present in the physical mixture[12,29]. However, the intensity of the drug exothermic peak was noticeably decreased. This was attributed to the great dilution of the drug caused by the presence of very high ratio of PVP K-30 to drug (5:1). However, the DSC pattern of SD prepared by solvent evaporation method showed an obvious decrease in peak's intensity, which was hardly apparent, when compared with the peak present in DSC thermogram of the corresponding physical mixture. The above finding suggested that the solvent evaporation method induces a certain type of interaction between lornoxicam and PVP K-30 at the molecular level[12]. Complete disappearance of lornoxicam exothermic peak was evident in the thermogram of SD prepared by freeze-drying method suggesting that lornoxicam was present in an amorphous state inside PVP K-30 matrix. This finding is in complete agreement with the work of Kalaiselvan et al.[30], who attributed that the complete disappearance of drug characteristic peaks to the amorphous precipitation of the drug and/or its better solubilization in the carrier. Also, similar effect was reported for meloxicam SDs prepared with PVP K-30 by freeze-drying method[12].

### X-ray powder diffractometry

Figure 1(II) shows the XRD patterns of pure lornoxicam, PVP K-30, and their physical mixture and SDs prepared by solvent evaporation and freeze-drying methods. The diffraction pattern of lornoxicam powder revealed several sharp high-intensity peaks at diffraction angles $2\theta$ of 7.8°, 10.2°, 12.2°, 14.5°, 18.2°, 22.2°, and 24.5°, suggesting that it existed as a crystalline material. However, the diffraction spectrum of PVP K-30 appeared as a halo structure verifying its amorphous nature[12,18].

The diffraction patterns of the investigated physical mixture of lornoxicam and PVP K-30 showed the presence of lornoxicam characteristic diffraction peaks. This finding 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 the physical mixtures. However, the observed slight attenuation of lornoxicam diffraction peaks was due to its dilution by the high carrier ratio[31]. A marked decrease in lornoxicam crystalline character was observed in the SD prepared by solvent evaporation method evidenced by the noticeable decrease in number and intensities of peaks present in its X-ray diffractogram when compared with the corresponding physical mixture. On the other hand, the diffractogram of the prepared freeze-dried SD revealed a typical diffuse pattern and showed a complete absence of lornoxicam crystalline peaks. This observation indicates that lornoxicam was entirely converted to amorphous form or a microcrystalline form during the freeze-drying process. Moreover, it supported the results of DSC analysis and confirmed the formation of an amorphous SD when freeze-drying technique was adopted for the SD preparation. The present findings are in complete agreement with the reports presented by several research groups investigating other drugs[12,18].

### Fourier-transform infrared spectroscopy

Figure 2 presents the FTIR spectra of pure lornoxicam, pure PVP K-30, and their physical mixture and SDs prepared by solvent evaporation and freeze-drying methods. The FTIR spectrum of lornoxicam showed a characteristic peak at 3090 $cm^{-1}$ corresponding to –NH stretching vibration. Intense absorption peak was found at 1642 $cm^{-1}$ because of the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1597 and at 1559 $cm^{-1}$ and were assigned to bending vibrations of N−H group in the secondary amide. The stretching vibrations of the O=S=O group appeared at 1157, 1387, and at 1336 $cm^{-1}$. Other prominent peaks appeared at 827.94 $cm^{-1}$ corresponding to −CH aromatic ring bending and heteroaromatics and at 766.8 $cm^{-1}$ because of C−Cl bending vibration. On the other hand, the FTIR spectra of pure PVP K-30 illustrated an intense broad absorption band between 3100 and 3700 $cm^{-1}$ corresponding to the OH− stretching vibrations of absorbed water and confirming the broad endotherm detected in the DSC experiments. Another large band occurred between 2700 and 2900 $cm^{-1}$, which might be assigned to the C−H stretching

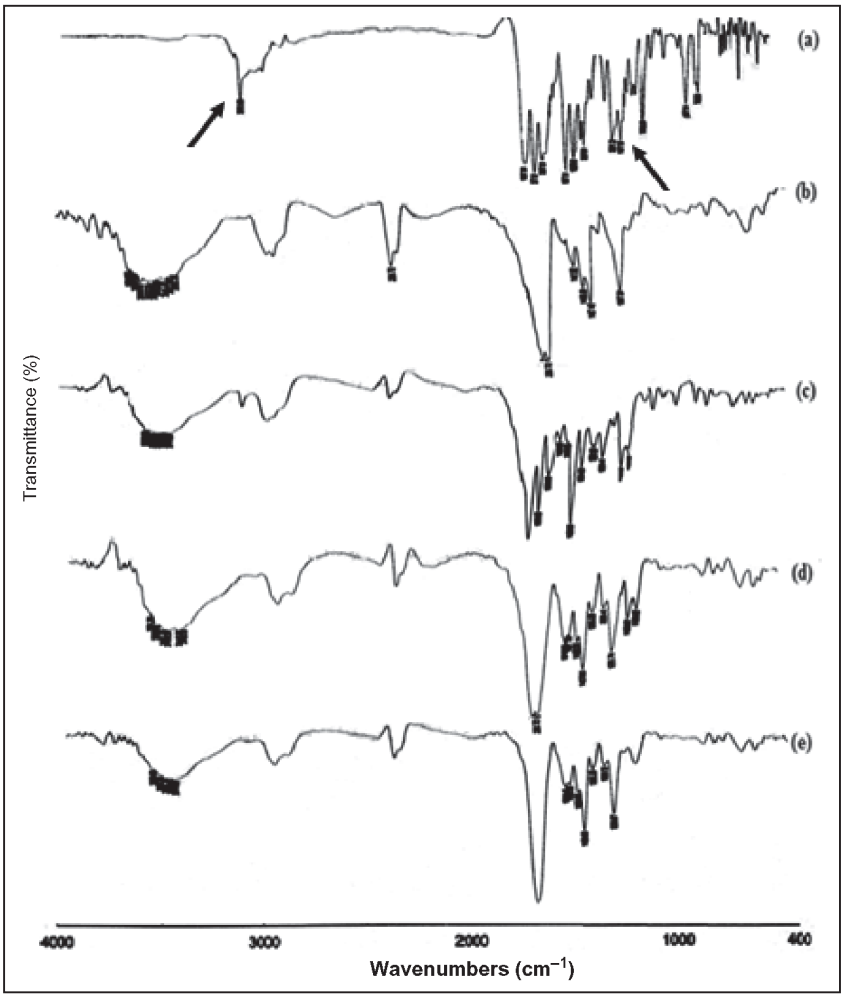


**Figure 2.** FTIR spectra of lornoxicam–PVP K-30 solid systems: (a) pure lornoxicam; (b) pure PVP K-30; (c) physical mixture 1:5; (d) solvent-evaporated product 1:5; (e) freeze-dried product 1:5.

vibration. An intense absorption band was found at 1674 cm$^{-1}$ because of the stretching vibration of C=O group, another sharp band was found at 1287 cm$^{-1}$ because of C−N group. Other characteristic peaks in PVP K-30 spectra at 1427, 1460, 1497, and 2360 cm$^{-1}$ were also evident. Similar observations have been reported in the literature[15,16,32,33].

In our study, the −NH stretching vibration at 3090 cm$^{-1}$, and the sulfonyl group vibration at 1157 cm$^{-1}$ of lornoxicam were the main characteristic peaks used to assess the drug–PVP K-30 interactions (indicated by the black arrows in Figure 2), because of the absence of overlapping between these peaks and PVP K-30 peaks.

The FTIR spectrum of the investigated physical mixture did not show any significant changes with respect to the FTIR spectra of the pure components, in particular, the characteristic peaks of lornoxicam. Moreover, it represented the summation of lornoxicam and PVP K-30 spectrum and this reflects the absence of interaction between lornoxicam and PVP K-30 after physical mixing. This result was in good agreement with that observed by Thybo et al.[18] and Tantishaiyakul et al.[34] regarding the FTIR spectra of the physical mixtures of tolfenamic acid and piroxicam with PVP K-30, respectively. Concerning the FTIR spectrum of SD prepared by solvent evaporation technique, it showed the characteristic intense peak of lornoxicam present at 1157 cm$^{-1}$ because of sulfonyl stretching. Conversely, the −NH stretching band present at 3090 cm$^{-1}$ completely disappeared, suggesting partial interaction of the drug with PVP K-30 molecules[33]. It was clearly evident that lornoxicam peaks present at 3090 and at 1157 cm$^{-1}$ totally disappeared in the FTIR spectrum of freeze-dried system. This observation might be attributed to the substantial difference in the intermolecular hydrogen-bonding networks present in this SD as a consequence of drug amorphization. According to Tantishaiyakul et al.[34], the intermolecular hydrogen bonding occurring

in amorphous SDs might be stronger than those present in crystalline drugs; therefore the stretching vibrations might be weakened resulting in broadening or complete disappearance of drug characteristic peaks. Added to that, Thybo et al.[18] reported that the absence of the −NH peak of tolfenamic acid in the IR spectra of its SDs may be the outcome of the involvement of the −NH group of tolfenamic acid in hydrogen bonding with PVP K-30 and/or the presence of tolfenamic acid in the amorphous state.

Taking into consideration the above results together with that obtained from the DSC and X-ray studies, they all supported the complete transformation of the crystalline drug to an amorphous state and the existence of strong interaction between the drug and PVP K-30 when freeze-drying method was used.

### *In vitro dissolution studies for lornoxicam–PVP K-30 solid systems*

Figure 3 illustrates the dissolution profiles of lornoxicam solid systems with PVP K-30 in 0.1 N HCl. It was clearly evident that lornoxicam dissolved very slowly under the specified dissolution conditions and less than 10% of lornoxicam was dissolved after 2 hours of the dissolution study. However, it was apparent that lornoxicam dissolution was slightly improved when physically mixed with PVP K-30 because of the local solubilization action of PVP K-30 in the diffusion layer surrounding the drug particles[35,36]. Moreover, Varma and Pandi[37] reported that the presence of PVP K-30 reduces the interfacial tension between the insoluble drug particles and the dissolution medium, facilitating its wettability, and thus, the drug's dissolution.

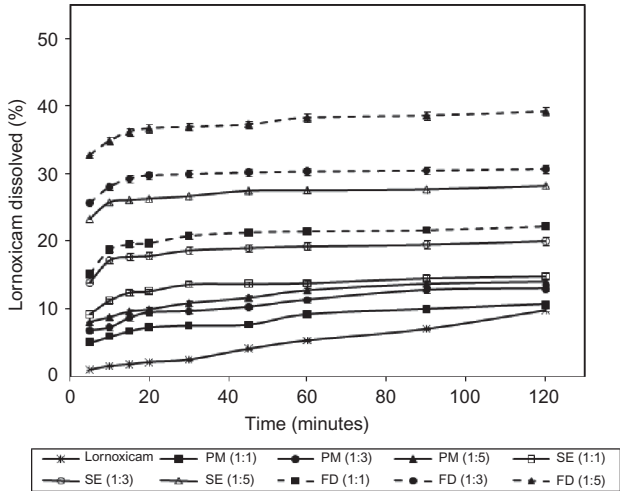


**Figure 3.** Dissolution profiles of lornoxicam from lornoxicam–PVP K-30 solid systems performed in 0.1 N HCl maintained at 37 ± 0.5°C (mean ± SD, $n = 3$).

Regarding the SDs prepared by solvent evaporation method, they showed a greater enhancement in lornoxicam dissolution when compared with the corresponding physical mixtures. This observed increment is probably attributed to the decrease in the crystallinity of the drug in the presence of PVP K-30 as a consequence of the solvent evaporation technique[12], as evidenced by the presented results of DSC and XRD studies. On the other hand, the freeze-dried SDs showed marked increase in lornoxicam dissolution compared with the corresponding physical mixtures and SDs prepared using the solvent evaporation technique. This finding was accredited mainly to the presence of the drug in high energetic amorphous state accompanied by complete disappearance in its crystallinity as confirmed by DSC and XRD studies. This outcome is in good agreement with that reported by other authors concerning the effectiveness of the freeze-drying method in preparing SDs[12,35].

Table 5 presents the dissolution efficiency data calculated based on 60 minutes ($DE_{60}$). As can be seen for all the studied solid systems, the drug $DE_{60}$ was improved by increasing the PVP K-30 weight ratio. Overall, the rank order of improvement in $DE_{60}$ of lornoxicam from solid systems prepared using different techniques was as follows: 1:5 > 1:3 > 1:1 (drug to PVP K-30). Sekikawa et al.[38] pointed out that higher ratio of PVP K-30 is able to form a polymer net upon the drug crystal surface or among its molecules, resulting in optimum orientation and stronger interaction between drug and PVP K-30. This, in turn, enhances the surface hydrophilicity of the SD particles and reduces their agglomeration after exposure to the dissolution medium. In addition to that, PVP K-30 inhibits crystal growth by hindering the association of the drug molecules to form crystal nucleus. This inhibitory effect on drug recrystallization is associated with high proportion of PVP K-30[34,35].

**Table 5.** Dissolution efficiency ($DE_{60}$, %) of lornoxicam from its solid systems with PVP K-30 prepared using different preparation techniques (mean ± SD, $n = 3$).

| Solid systems | $DE_{60}$ (%) |
|---|---|
| Lornoxicam | 2.91 ± 0.06 |
| Lornoxicam–PVP K-30 (1:1) PM | 7.03 ± 0.06 |
| Lornoxicam–PVP K-30 (1:3) PM | 9.07 ± 0.62 |
| Lornoxicam–PVP K-30 (1:5) PM | 10.18 ± 0.66 |
| Lornoxicam–PVP K-30 (1:1) SE | 12.29 ± 0.46 |
| Lornoxicam–PVP K-30 (1:3) SE | 17.34 ± 0.66 |
| Lornoxicam–PVP K-30 (1:5) SE | 25.34 ± 0.75 |
| Lornoxicam–PVP K-30 (1:1) FD | 19.21 ± 1.87 |
| Lornoxicam–PVP K-30 (1:3) FD | 28.13 ± 0.56 |
| Lornoxicam–PVP K-30 (1:5) FD | 34.91 ± 1.61 |

PM, physical mixture; SE, solvent-evaporated product; FD, freeze-dried product.

The results of the two-sided unpaired Student's *t*-test applied on the $DE_{60}$ data of each of the prepared solid systems and pure lornoxicam revealed that all the prepared solid systems showed significant enhancement in dissolution compared with pure drug at $P \leq 0.05$. Moreover, the results of the two-way ANOVA performed on the $DE_{60}$ data for the prepared lornoxicam–PVP K-30 solid systems revealed the presence of significant differences among the different preparation methods (physical mixing, solvent evaporation, freeze-drying) and weight ratios (1:1, 1:3, and 1:5, drug to PVP K-30) at $P \leq 0.05$ ($F$-values = 557.038 and 180.823 for preparation method and weight ratio, respectively). The computed $F$-values indicated that the effect of the preparation method is more statistically significant on the dissolution enhancement of the drug compared with the effect of molar ratio. Multiple comparisons between different preparation methods at each weight ratio according to Scheffé test revealed that the freeze-drying technique exhibited the most significant effect on the dissolution enhancement of lornoxicam compared with the other methods at $P \leq 0.05$. In addition, multiple comparisons between the different molar ratios for the freeze-dried products according to Scheffé test revealed that the weight ratio of 1:5 (drug to PVP K-30) exhibited the most significant improvement on the dissolution efficiency compared with the other weight ratios investigated at $P \leq 0.05$. These results confirmed that the freeze-dried systems prepared at a weight ratio of 1:5 (drug to PVP K-30) showed the most superior and significant effect on the dissolution pattern of lornoxicam. Accordingly, this freeze-dried system was chosen for coating the lipophilic core tablets of the investigated CCTs.

### *In vitro drug release studies for the prepared core tablets*

Figure 4 illustrates the in vitro release profiles of lornoxicam from the prepared core tablets. 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 pH 1.2 for 2 hours followed by phosphate buffer of pH 6.8 for the sequential 6 hours[39]. Moreover, the release sampling duration lasted 8 hours as the total GI transit time of dosage forms after oral administration in humans is reported to be approximately 8 hours[40].

Because of its distinct pH-dependent solubility, lornoxicam showed an extremely slow dissolution in acidic pH attributed to its weak acidic nature. In fact, less than 10% of the drug was dissolved after 2 hours. However, complete drug dissolution was displayed when the pH of the release medium was changed to 6.8.

It is quite noticeable that the release of lornoxicam from core tablets containing 1% Compritol ATO 888 was retarded only for 6 hours, after which these tablets disintegrated and the drug completely dissolved into the dissolution medium. On the other hand, there was a striking decrease in the extent of lornoxicam release from the inspected core tablets when Compritol ATO 888 percentage exceeded 1% and these tablets were able to retain their shape without disintegration during the whole release study. However, their surfaces showed slight erosion accompanied by the formation of many pores and cracks from which lornoxicam slowly diffused. It was reported that the release of drugs from lipophilic matrix tablets occurred progressively through a diffusion-controlled leaching process through the diffusion channels of pores and cracks formed on the tablets' surfaces[41]. Li et al.[42] reported that compressed matrices prepared using Compritol ATO 888 are highly hydrophobic, and hence they impede the rate of permeation of dissolution fluid into them, leading to effective retardation on the drug release, and as indeed was found to be the case. Obviously, none of the prepared core tablets were able to sustain lornoxicam release for 8 hours, which represent the approximate GI residence time for oral dosage forms[40]. Therefore, core tablets belonging to formulation F2, which were able to sustain lornoxicam release and contained the least concentration of Compritol ATO 888 (3%, w/w), were selected to be exposed to further modifications to ensure that most of their lornoxicam content is released in a time period comparable with the reported GI residence time.

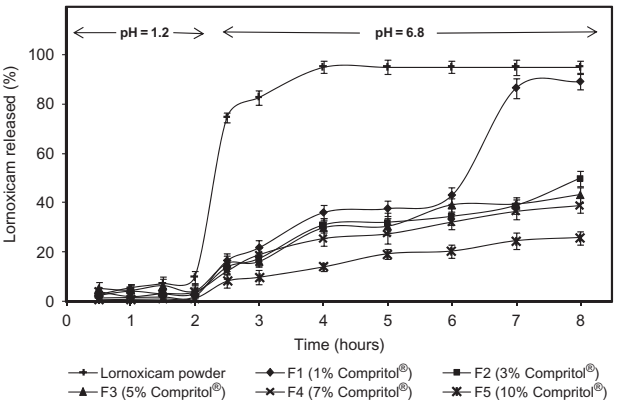


**Figure 4.** In vitro release profiles of lornoxicam from core tablets containing different percentage of Compritol® ATO 888 performed in 0.1 N HCl of pH 1.2 for 2 hours and in phosphate buffer of pH 6.8 for the subsequent 6 hours at 37 ± 0.5°C (mean ± SD, $n = 3$).

El-Malah et al.[43] along with Huang and coworkers[44] reported that lactose can be regarded as a channeling agent that is able to adjust drug release from sustained release matrices by modifying their internal geometry during dissolution process. Accordingly, in order to efficiently tailor lornoxicam release to suit the GI residence time, different ratios of lactose to Avicel PH 102 were added to core tablets containing 3% Compritol ATO

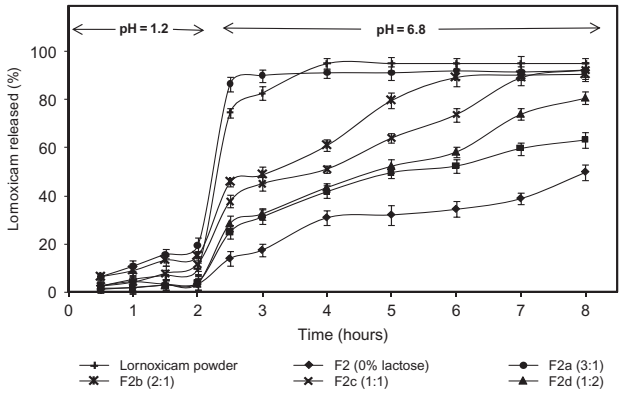


**Figure 5.** Effect of incorporating lactose on the release profiles of lornoxicam from core tablets containing 3% of Compritol® ATO 888 performed in 0.1 N HCl of pH 1.2 for 2 hours and in phosphate buffer of pH 6.8 for the subsequent 6 hours at 37 ± 0.5°C (mean ± SD, $n$ = 3). The values present between brackets represent the weight ratio of lactose to Avicel PH 102.

888, to ensure the complete release of lornoxicam from them in nearly 8 hours. The obtained release profiles are shown in Figure 5.

It is clearly evident that lornoxicam release from these core tablets was dependent on the ratio of lactose to Avicel PH 102 present in them. Core tablets belonging to formulation F2a, containing lactose to Avicel PH 102 in 3:1 weight ratio, showed no sustainment effect on lornoxicam release. Actually, they showed complete tablet disintegration within 30 minutes, and complete drug release after 2 hours when the pH of the release medium was changed from 1.2 to 6.8. This was attributed to the good aqueous solubility of lactose; upon contact with the release medium, lactose rapidly dissolved and diffused out of the core tablets, thereby increasing the porosity of the matrix systems, allowing their rapid disintegration[42,45]. On the other hand, core tablets belonging to formulation F2b, containing lactose to Avicel PH 102 in 2:1 weight ratio, had a tendency to sustain lornoxicam release up to 5 hours, after which these core tablets completely disintegrated. As expected, further sustainment of lornoxicam release was achieved by decreasing the ratio of lactose to Avicel PH 102 in the prepared core tablets. This finding fits well with those of other studies[43,44].

The target release profile parameters for sustained release products were reported as follows[46</rref]: after 2 hours 20–50% of the drug is released, and 45–75% of the drug is released after 4 hours, and 75–105% of the drug is released after 8 hours. Among all the investigated core tablets, only those belonging to formulation F2d, prepared using 3% Compritol ATO 888 and the ratio of lactose to Avicel PH 102 present in them is 1:2, met the release specification of sustained release products at 4 and 8 hours, as they released 43.47% and 80.73% of their drug content at those times, respectively. But unfortunately, they failed to meet the release requirement set after 2 hours as they released only 3.52% of their lornoxicam content at that time. Consequently, additional modification was executed to optimize lornoxicam release from core tablets belonging to formulation F2d with the aim of meeting the reported sustained release requirements together with ensuring burst release of lornoxicam in the stomach.

### *Preparation of CCTs*

Table 3 represents a compilation of the composition of the investigated CCTs. All the prepared CCTs contained a total of 8-mg lornoxicam distributed between the core and the coat layer. The powder used to enrobe the sustained release core was formulated to achieve rapid disintegration followed by rapid dissolution of lornoxicam. In light of the previous results presented in our study, the coat layer contained lornoxicam–PVP K-30 freeze-dried SD, in weight ratio 1:5 (drug to PVP K-30), to improve the low solubility of lornoxicam in acidic medium and to ensure its rapid release and absorption in the stomach to attain its analgesic effect. Avicel PH 102 was used as a diluent because of its superior compression properties[26]. Ac-Di-Sol was used as a superdisintegrant to achieve immediate disintegration of the coat layer when exposed to the dissolution media allowing rapid release of the drug[26]. The core tablets were composed of 3% of Compritol ATO 888, and lactose to Avicel PH 102 in weight ratio of 1:2.

### *Physical characterization of the prepared CCTs*

All CCTs prepared in this study met the pharmacopeial requirements for weight variation and drug uniformity. The tablet thickness was in the range of 2.4–2.6 mm. Moreover, the percentage friability for all the CCTs formulations was below 1%, indicating that the friability was within the compendial limits (data not shown).

### *Morphological examination of the prepared CCTs*

Figure 6 illustrates a photograph showing the horizontal and longitudinal cross-sections of selected CCTs. Obviously, the core tablet was centralized and completely surrounded by the coat layer. Moreover, it tended to keep its integrity and did not fragment during the compression process.

### *In vitro drug release studies*

Figure 7 presents the release profiles of lornoxicam from the prepared CCTs containing different proportions of lornoxicam fractioned between the sustained

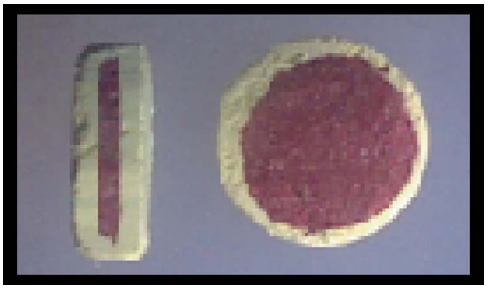

**Figure 6.** Photograph of longitudinal and horizontal cross-sections in selected compression-coated tablets (CCTs) of lornoxicam showing a fast-release outer coat and an inner sustained release lipophilic core.

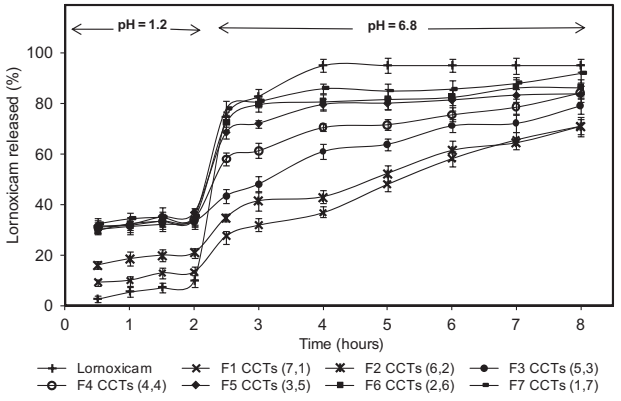


**Figure 7.** In vitro release profiles of lornoxicam from compression-coated tablets (CCTs) composed of a fast-release coat and a sustained release lipophilic core performed in 0.1 N HCl of pH 1.2 for 2 hours and in phosphate buffer of pH 6.8 for the subsequent 6 hours at 37 ± 0.5°C (mean ± SD, $n = 3$). The values present between brackets represent the amount (mg) of lornoxicam in core tablet and coat layer, respectively.

release core and an immediate release coat. Obviously, CCTs belonging to formulations, F1 CCTs, F2 CCTs, F3 CCTs, and F4 CCTs were able to sustain the release of lornoxicam. However, tablets belonging to formulation F5 CCTs, F6 CCTs, and F7 CCTs failed in this regard. This may be attributed to the presence of higher amount of lornoxicam (in form of freeze-dried SD) in the immediate release coat than that present in the lipophilic slow release core that is able to sustain lornoxicam release.

It is interesting to note that the extent of lornoxicam released after the first 2 hours of dissolution, from CCTs belonging to formulation F1 CCTs, F2 CCTs, and F3 CCTs increased proportionally with the increase in amount of lornoxicam freeze-dried SD present in the coat layer of these tablets. However, further increase in the amount of lornoxicam SD in the coat layer (>3 mg), as depicted in formulations F4 CCTs, F5 CCTs, F6 CCTs, and F7 CCTs, did not simultaneously lead to an increase

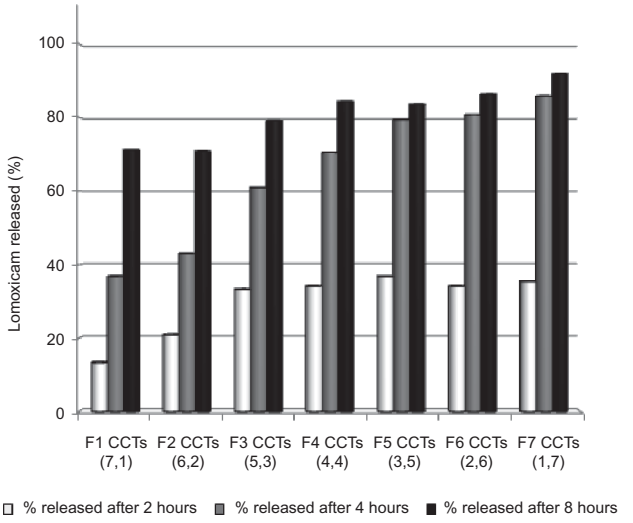


**Figure 8.** The percentages of lornoxicam released after 2, 4, and 8 hours from compression-coated tablets (CCTs) composed of a fast-release coat and a sustained release lipophilic core performed in 0.1 N HCl of pH 1.2 for 2 hours and in phosphate buffer of pH 6.8 for the subsequent 6 hours at 37 ± 0.5°C. The values present between brackets represent the amount (mg) of lornoxicam in core tablet and coat layer, respectively.

in the extent of lornoxicam release and they showed nearly the same extent of lornoxicam release during the first 2 hours.

For assessment and comparison to the release specifications for sustained release products, the percentage of drug released from the investigated CCTs after 2, 4, and 8 hours were extracted directly from the release data and are graphically depicted in Figure 8. It is clearly evident that CCTs belonging to formulation F3 CCTs and F4 CCTs exhibited sustained release profiles that agreed with the release requirements of sustained release products. Tablets belonging to formulation F3 CCTs released approximately 33.21%, 60.98%, and 79.13% and those belonging to formulation F4 CCTs released approximately 34.13%, 70.54%, and 84.39% at 2, 4, and 8 hours, respectively. Moreover, these CCTs illustrated a burst release of lornoxicam as they released more than 30% of their drug content after only 30 minutes, so they are expected to overcome the disadvantages associated with the delayed dissolution of lornoxicam in acidic conditions.

## Conclusions

In this study, the proposed sustained release CCTs 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 hours.

The CCT formulations were composed of a sustained release core tablets prepared using 3% of Compritol ATO 888, and lactose to Avicel PH 102 in weight ratio of 1:2. The coat layer, however, contained lornoxicam–PVP K-30 freeze-dried SD in weight ratio 1:5, which was proven to be advantageous in the context of enhancing lornoxicam dissolution characteristics in acidic medium. Furthermore, the presented CCTs met the pharmacopeial requirements for tablets and were manufactured using currently applicable pharmaceutical technologies. The in vitro drug release studies revealed that CCTs formulations belonging to F3 CCTs and F4 CCTs were able to reach the preset goal. In conclusion, the adopted formulation strategy could be of great potential as an effective approach to tailor the release patterns of drugs to accomplish the desired drug release profile, according to their pharmacokinetics and therapeutic needs.

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## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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