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Preformulation, Development and In-Vitro Study of Bilayer Tablets of Lornoxicam

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ABSTRACT

This work aims at designing, developing and characterizing a biphasic delivery dosage form of lornoxicam, a highly potent nonsteroidal anti-inflammatory drug with a short half-life, as a bilayered tablet in which the fast release pattern is achieved by a fast release layer and controlled release is achieved by a sustained release layer. Thus, lornoxicam is released in a soluble form in the stomach with the aim of reaching high serum concentration in a short period of time, ensuring rapid relief for the symptoms followed by an extended release of lornoxicam for more than 8 hs to avoid its repetitive administration and improve patients' compliance as well as minimize the incidence of its side effects. Solid dispersions of lornoxicam with acrysol and poloxamer 407 present in 1:2, 1:6 and 1:10 (drug/carrier) ratios as well as soluplus in 1:1, 1:2 and 1:3 (drug/carrier) ratios were prepared and employed in the fast-release layer to enhance the dissolution of lornoxicam in the stomach and assure rapid onset of its analgesic effect. Polyox 205 LEO, Polyox 1105, carbopol 71G and Suglet as polymer were incorporated in different ratios in sustained release layer as release retardant materials.

INTRODUCTION

Lornoxicam is a nonsteroidal anti-inflammatory drug (NSAIDs) of the oxicam class. It has analgesic, anti-inflammatory and antipyretic properties [1]. It is widely used for the symptomatic treatment of pain and inflammation in patient with osteo-arthritis and rheumatoid arthritis. Moreover, it showed great efficacy in various clinical trials in the management of pre-operative and post-operative 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 hs[2,3].

Bilayer tablets have been developed to achieve controlled delivery of different drugs with predefined release profiles. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation and to enable the development of different drug release profiles (immediate release with extended release)[4]. Bilayer tablet or Biphasic drug delivery systems are designed to release the drug at two different rates or at two different time periods *i.e.* they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst release of drug followed by a constant rate (ideally) of release over a defined period of time. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a controlled release phase to avoid repeated administration[5]. It is reported that the NSAIDs are suitable candidate drugs for this type of administration [6].

The aim of this study was to develop and characterize a biphasic delivery dosage form of lornoxicam as a bilayered tablet in which the fast release effect is achieved by a fast release layer and the controlled release effect is achieved by a sustained release layer prepared.

MATERIALS AND METHODS

Materials

Lornoxicam was kindly provided by Hikma Pharm. 6th October, Cairo Egypt. Acrysol was supplied by Corel PharmaChem, India. Carbopol 71G was supplied by Lubrizol Corporation, Ohio, USA. Poloxamer 407 was supplied by E.P.I.C.O, Egypt. Polyox 205, Polyox 1105 and Suglet were purchased from ColorconLimted, Dartford Kent, UK. Soluplus and KollidonCl were supplied by BASF SE, Ludwigshafen, Germany. Lactopress was obtained from DFE PharmaGmBH& Co. KG, Goch, Germany. Avicel PH 102 was kindly supplied by the El-MehanComponay, Egypt. Magnesium stearate was kindly provided by Alexandria Company for Pharmaceutical Industries, Alexandria, Egypt. The other ingredients were of analytical grade and were used as received.Xefo® was used as a marketed lornoxicam tablet as a reference product.

Phase-Solubility Study

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors,1965[7]. An excess amount of lornoxicam was added to the aqueous solutions of

(acrysol, poloxamer 407 and soluplus) in water containing increasing concentrations of polymer (010% w/v). The vials were sealed and shaken at 37±0.5 °C for 48 hs in a shaking water bath (Gallen Kamp, England) and the samples were filtered using 0.45 µm filter paper. The filtrate was suitably diluted and the concentration in the solution was determined spectrophoto metrically at λ_{max} of 377nm [8].

Phase solubility diagrams were obtained by plotting the concentration of solubilized lornoxicam versus the concentrations of the polymer used. The apparent stability constants (Ks) were estimated from the straight line of the phase solubility diagrams according to the following equation[7]:

$Ks = slope / S_o(1\text{-}slope)$

Where S_o represents the drug solubility in the absence of polymer (the intercept of the phase solubility diagram).

Preparation of the Solid Dispersions (SD) of Lornoxicam

To improve the dissolution behavior of lornoxicam in gastric conditions, solid dispersions of lornoxicam with acrysol, soluplus and poloxamer 407 (SD1-SD9) were prepared at three different ratios namely 1:1, 1:2 and 1:3 (drug:soluplus) while ratios of 1:2, 1:6 and 1:10 were used for both drug with acrysol and poloxamer. Physical mixtures in the same ratios (PM1-PM9) were also prepared for comparison purpose where lornoxicam and polymer were triturated smoothly in a mortar, passed through sieve no.60 and placed in a desiccator for further study [9].

Solid dispersions of lornoxicam with acrysol were prepared by fusion method. The accurately weighed amount of acrysol was melted on heated water bath and then drug was dispersed in the molten solution. The mixtures were stirred repeatedly, cooled after 10 min by placing the porcelain dish for 15 min in an ice bath. Solid mass obtained was crushed, mixed and passed through sieve no.60. The resulting solid dispersions were stored in a desiccator until use [10].

Table 1 : Formulation of lornoxicam solid dispersions using various carriers.

Formulation code	Lornoxicam (mg)	Acrysol (mg)	Poloxamer 407 (mg)	Soluplus (mg)
SD1	4	8		
SD2	4	24		
SD3	4	40		
SD4	4		8	
SD5	4	24		
SD6	4		40	
SD7	4			4
SD8	4			8
SD9	4			12

Solid dispersions of lornoxicam with poloxamer and soluplus were prepared by solvent evaporation method. The weighed amounts of lornoxicam and carrier (poloxamer 407, soluplus) were dissolved in a minimum amount of methanol. Then, the organic solvent was removed by evaporation at 40° C for 24 hs. The dried mass was crushed, mixed and passed through sieve no. 60. The samples were kept in a desiccator until use [11,12].

Physicochemical Characterization of Lornoxicam Solid Systems and Compatibility with the Used Polymers

For fast release layer, FTIR spectra and DSC thermograms were recorded for lornoxicam, acrysol, soluplus and poloxamer 407, their physical mixtures and their solid dispersions prepared using different techniques in 1:1 (drug/carrier) ratio. Also, Samples of drug, each sustained release polymers used namely (Polyox 205 LEO, Polyox 1105, carbopol 71G and Suglet) and their physical mixtures were used to determine their compatibility using (FTIR) spectroscopy and DSC.

In vitro Dissolution Studies for Lornoxicam Solid Systems

In vitro dissolution tests under simulated gastric conditions for prepared solid dispersions and their corresponding physical mixtures were performed using (USP) dissolution apparatus II (DA6D, Bombay- 400-069, India) at 100 rpm [13]. A sample of each solid system equivalent to 4 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 time intervals, samples from the dissolution medium were withdrawn and filtered, and concentrations of lornoxicam were determined spectrophoto metrically at 370 nm. 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 (DE60, 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:

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

where y is the drug percentage dissolved at time t [13].

Preparation of Lornoxicam Bilayer Tablets

In order to prepare lornoxicam bilayer tablets, both fast and sustained layers, were initially prepared separately to gain insight into the dissolution profile of each layer with the aim of selecting the best formulations of each, that could be combined together to provide bilayer tablets with suitable release pattern characterized by an initial burst drug release.

Precompression Studies of the Prepared Blend to be Compressed into a Tablet

Prior to the compression of the formulation blends into tablets, flow properties of the powders were determined to check its suitability for compression.

Angle of repose (AR), compressibility Index (CI) and Hausner's ratio (HR) were used to characterize flow properties of the blends.

Formulation of the Fast-Release Layer

Table (2) shows the composition of fast release tablet

formulations. SD3, SD6 and SD9 were selected, based on their superior dissolution properties in 0.1 N HCl, to be incorporated into the fast-release tablets. Lactopress was added as diluent and kollidonCl was added as tablet superdisintegrant. Tablet formulations were mixed thoroughly 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 using a single-punch tableting machine (First medicine machinery, Factory of Donghai branch, Shanghai, China) into 125 mg tablets.

Formulation of the Sustained Release Layer

Twelve sustained release tablet formulations each containing 4 mg lornoxicam, were prepared by direct compression using Tablet Compression Machine with flat-faced single punch. They were prepared using different sustained release polymers namely, polyox 1105, polyox 205 LEO, carbopol 71G, suglets. Avicel PH 102 was added as diluent. Tablet formulations were mixed thoroughly in a glass mortar with the help of a pestle for 30 min. 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 using a single-punch tableting machine into 125 mg tablets. The detailed composition of the sustained release tablet formulations are represented in table (3).

Table 2 : Composition of lornoxicam fast release tablet formulations.

Formulation code	Solid dispersion equivalent to 4 mg lornoxicam	KollidonCl (mg)	Magnesium stearate (mg)	Lactopress (mg)
FSD3	SD3 (Lor:acrysol 1:10)	12.5	1.25	67.25
FSD6	SD6 (Lor:polox 1:10)	12.5	1.25	67.25
FSD9	SD9 (Lor:soluplus 1:3)	12.5	1.25	95.25

In vitro Drug Dissolution Studies for the Fast Release Formulations

The dissolution behavior of the tablets was examined using the same conditions used for lornoxicam solid systems. Studies were carried out in 400 mL of 0.1 N HCl maintained at 37±0.5°C for a period of 2 hs followed by dissolution in phosphate buffer of pH 6.8 for another 6 hs. Aliquots from the dissolution 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. Dissolution studies were carried out in triplicate and the mean values were plotted versus time.

Formulation of Lornoxicam Bilayer Tablets

Table (4) shows the detailed composition of lornoxicam bilayer tablet formulations composed of sustained release and fast release layers. The bilayer tablets were prepared by two techniques. In the bilayer technique (F1-F9), tablets were prepared by direct compression using a single-punch tableting machine. The die was initially filled with the weighed amount of sustained release portion and lightly compressed, then the fast release portion was added directly, and then recompressed together to combine them. The total weight of each bilayer tablet was adjusted to 250 mg containing 8 mg of lornoxicam fractioned between the two layers.

Table 3 : Composition of lornoxicam sustained release tablet formulations

Formula	Lornoxicam(mg)	Polyox 1105 (mg)	Polyox 205 LEO (mg)	Carbopol 71G (mg)	Suglet (mg)	Magnesium stearate (mg)	Avicel PH 102 (mg)
FS1	4	24	---	---	----	1.25	95.75
FS2		32	---	---	----		87.75
FS3		40	---	---	----		79.75
FS4		48	---	---	----		71.75
FS5		---	24	---	----		95.75
FS6		---	32	---	----		87.75
FS7		---	40	---	----		79.75
FS8		---	48	---	----		71.75
FS9		---	---	16	8		95.75
FS10		---	---	21.4	10.6		87.75
FS11		---	---	26.6	13.3		79.85
FS12		---	---	32	16		71.75

In the press coating technique (F10-F18), tablets were prepared by sandwiching a sustained release layer (core tablet) between two fast release layers. All the ingredients of sustained release layer were accurately weighed, directly compressed using a single punch tableting machine equipped with 8 mm punch. The fast release layer was accurately weighed. Half of the weighed amount of the fast releasing powder was put into the die (10 mm punch) manually forming a powder bed, on the center of which a core tablet was placed. Then the other half of the powder was added to cover the core tablet. Then double layer tablet were compressed manually [15].

Characterization of Bilayer Tablets

Uniformity of Weight

The uniformity of weight was tested for each batch according to **USP 2012**[14]. For the test, 20 tablets were weighed individually to the nearest 0.1 mg using an electronic balance (Mettler, J 100, Switzerland), and the average weight and standard deviation were calculated.

Uniformity of Thickness

The thickness of 10 tablets from each formula was measured using Tablet Thickness Apparatus, Planimeter, (India). The mean thickness and standard deviation were calculated.

Table 4 : Composition of bilayer tablets *F1-F9 were formulated by bilayer technique and F10-F18 were formulated by press coating technique as sustained core and fast coat.

Ingredients in mg	F1, F10	F2, F11	F3, F12	F4, F13	F5, F14	F6, F15	F7, F16	F8, F17	F9, F18
	Fast release components								
SD equivalent to 4mg lornoxicam	SD3			SD6			SD9		
KollidonCl (mg)	12.5								
Magnesium stearate (mg)	1.25								
Lactopress (mg)	67.25								
Total weight (mg)	125								
	Sustained release components								
Lornoxicam (mg)	4								
Polyox 1105 (mg)	40	---	---	40	---	---	40	---	---
Polyox 205 LEO (mg)	---	40	---	---	40	---	---	40	---
Carbopol 71G (mg)	---	---	32	---	---	32	---	---	32
Suglet (mg)	---	---	16	---	---	16	---	---	16
Magnesium stearate (mg)	1.25								
Avicel PH 102 (mg)	79.75	79.75	71.75	79.75	79.75	71.75	79.75	79.75	71.75
Total weight (mg)	125								

Hardness Test

The tablet hardness was measured by tablet hardness tester (pharma test, Type PTB301, Germany). The hardness was measured in terms of Kg/cm^2. The mean hardness and standard deviation were calculated[16].

Friability Test

Ten tablets were randomly selected, and brushed to free them from adhering dust. They were accurately weighed and placed in the drum of the tablet friability test apparatus (FT-2D, Bombay, India) which was rotated at 100 rpm for a period of four minutes. At the end of rotation period, the tablets were removed from the drum, carefully brushed to free them from adhering dust, and reweighed. The loss in weight in terms of percent (% F) was taken as a measure of tablet friability [17].

$$\%F = \left[\frac{W_1 - W_2}{W_1}\right] \times 100$$

Where F is the loss in weight in terms of percent, W_1 is the weight of each tablet before rotation and W_2 is the weight of each tablet after rotation.

Content Uniformity

Ten bilayer tablets were weighed individually and crushed, and the drug was extracted in phosphate buffer of pH 6.8. The solution was filtered and the drug content was determined spectrophotometrically at λ_{max} 376 nm after suitable dilution [13].

Disintegration Test for Fast Release Layer

The disintegration time was determined by using USP Tablet disintegration test apparatus (VEEGO, Model VTD-3D, India) using 900 ml of distilled water. Time taken by tablets (Sec) for complete disintegration of the tablets until no mass remaining in apparatus was measured [16].

In vitro Drug Dissolution Studies for Lornoxicam Bilayer Tablets

In vitro drug dissolution studies of lornoxicam from the bilayer tablets were performed using the same method used for the sustained release tablet formulations.

RESULTS

Phase-Solubility Study

Lornoxicam aqueous solubility was observed to be 0.02 mg/ml. Phase solubility diagrams of lornoxicam with acrysol, soluplus and poloxamer are shown in Fig. (1). Phase solubility showed an increase in drug solubility with increasing carrier concentration. Solubility of lornoxicam showed 65, 75 and 90 fold increase in presence of 10% w/v of acrysol, soluplus and poloxamer. The values of the stability constants (Ks) calculated from the equation of Higuchi and Connors were found to be 1.75, 3.63 and 2.35 for acrysol, poloxamer and soluplus respectively.

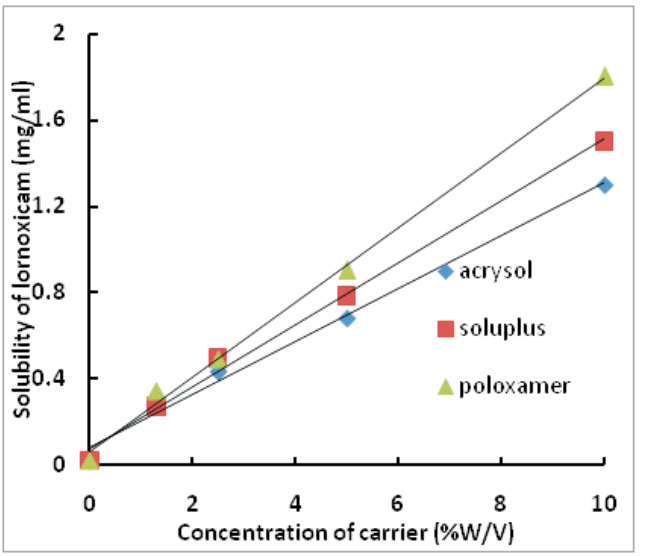

Fig. 1: Phase solubility diagrams of lornoxicam with acrysol, soluplus and poloxamer in distilled water

Physicochemical Characterization of Lornoxicam Solid Systems and Compatibility with the Used Polymers

Fourier Transform Infrared Spectroscopy (FTIR)

Figure 2 shows the FTIR spectra of individual components and their solid systems prepared by different techniques at 1:1 (drug/carrier) ratio. FTIR spectra of physical mixtures of drug and sustained release polymers are illustrated in figure 3.

Differential Scanning Calorimetry (DSC)

Figure 4 shows DSC thermogramsoflornoxicam solid systems in 1:1 (drug/carrier) ratio and DSC thermograms of physical mixture of lornoxicam and sustained release polymers are represented in figure 5.

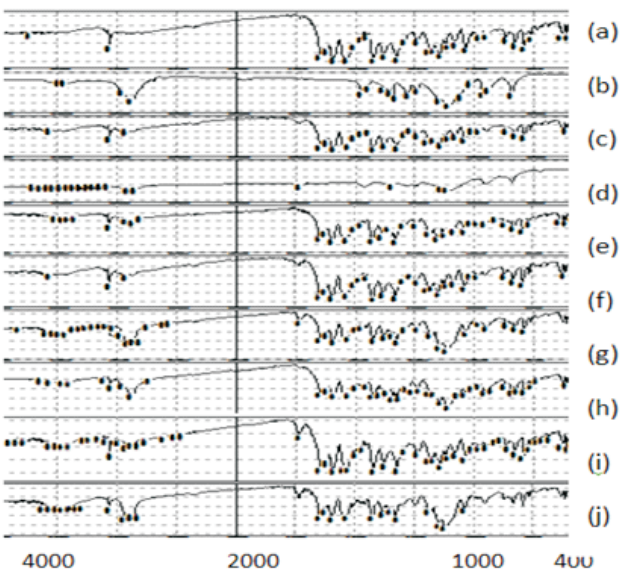

Fig. 2: FTIR spectra of lornoxicam solid systems in 1:1 (drug/carrier) ratio: (a) lornoxicam powder; (b) poloxamer; (c) soluplus; (d) acrysol; (e) lornoxicam poloxamer physical mixture; (f) lornoxicam soluplus physical mixture; (g) lornoxicam acrysol physical mixture; (h) lornoxicam polxamer solid dispersion; (i) lornoxicam soluplus solid dispersion; (j) lornoxicam acrysol solid dispersion.

In vitro dissolution Studies for Lornoxicam Solid Dispersions

The dissolution of pure lornoxicam was the slowest as compared to tested SDs and corresponding physical mixtures. SD6 (Lor:polox 1:10) gave high percent drug dissolved (99.45%) after 2 hr. Similarly, SD3 (Lor:acrysol 1:10) showed a percent drug dissolved of (94.85%). SD9 (Lor:soluplus 1:3) gave the highest percent drug dissolved (100%) after 2 hr (Figures 6-8). Dissolution efficiency (%) of lornoxicam solid systems with acrysol, soluplus and poloxamer 407 are represented in Table 5.

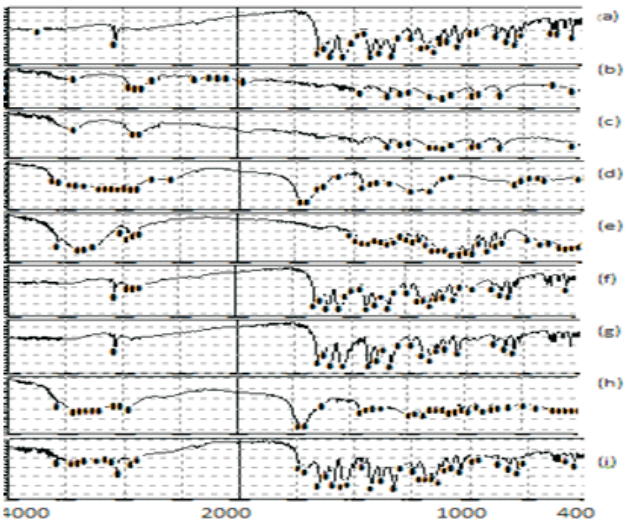

Fig. 3: FTIR spectra of (a) lornoxicam, (b) polyox 1105, (c) polyox 205LEO, (d) carbopol 71 G, (e) suglet, (f) lornoxicam/ polyox 1105 physical mixture, (g) lornoxicam/ polyox 205LEO physical mixture, (h) carbopol 71 G/ suglet physical mixture, (i) lornoxicam/ (carbopol/suglet) physical mixture.

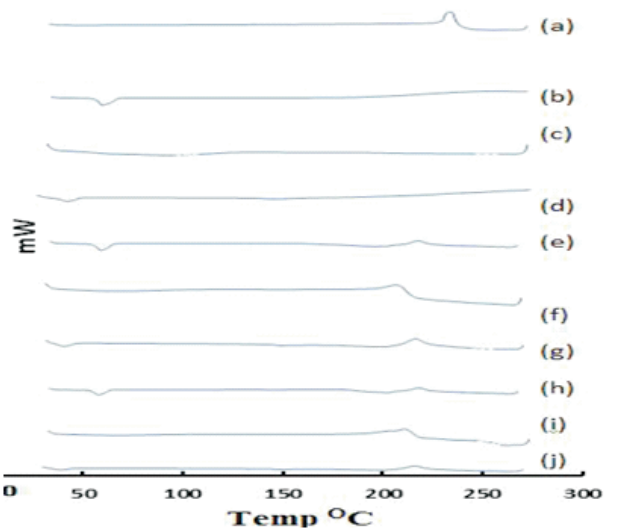

Figure 4: DSC thermogramsof lornoxicam solid systems in 1:1 (drug/carrier) ratio: (a) lornoxicam powder; (b) poloxamer; (c) soluplus; (d) acrysol; (e) lornoxicam poloxamer physical mixture; (f) lornoxicam soluplus physical mixture; (g) lornoxicam acrysol physical mixture; (h) lornoxicam polxamer solid dispersion; (i) lornoxicam soluplus solid dispersion; (j) lornoxicam acrysol solid dispersion.

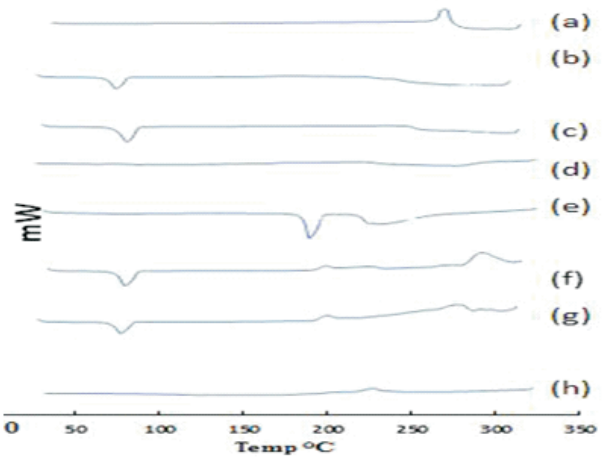

Fig. 5: DSC thermograms of (a) lornoxicam, (b) polyox 1105, (c) polyox 205LEO, (d) carbopol 71 G, (e) suglet, (f) lornoxicam/ polyox 1105 physical mixture, (g) lornoxicam/ polyox 205LEO physical mixture, (h) lornoxicam/ (carbopol/suglet) physical mixture.

Precompression Studies of the Prepared Blend:

Fast release powder blend showed excellent to good flow properties while sustained release powder blend showed good to passable flow properties.

In vitro Drug Dissolution Studies for the Fast Release Layer Tablets

FSD9 containing lornoxicam:soluplus solid dispersions gave the highest dissolution (98.95%) after 2 hours followed by FSD6 containing lornoxicam: poloxamer solid dispersions (96.2%) and FSD3 containing lornoxicam: acrysol solid dispersions (91.2%) (Figure 9).

In vitro Drug Dissolution Studies for the Sustained Release Layer Tablets

Figures (10-12) show the *in vitro* dissolution data of lornoxicam from the prepared sustained release tablets containing different ratios and different polymers compared to lornoxicam powder. Drug was dissolved too quickly in case of FS1, FS5 and FS9. Upon increasing polymer concentration (1:8 and 1:10 drug: polymer), the drug dissolution was decreased. It was found that on further increase of polyox concentration (from 1:10 to 1:12 drug: polymer), the drug dissolution was increased in case of polyox 1105 and polyox 205 LEO. Drug dissolution from carbopol/ suglets combination was decreased with increasing the polymer ratio. FS3and FS7 having drug: polymer ratio of 1:10 and FS12 having drug: polymer ratio of 1:12 gave the highest sustained effect.

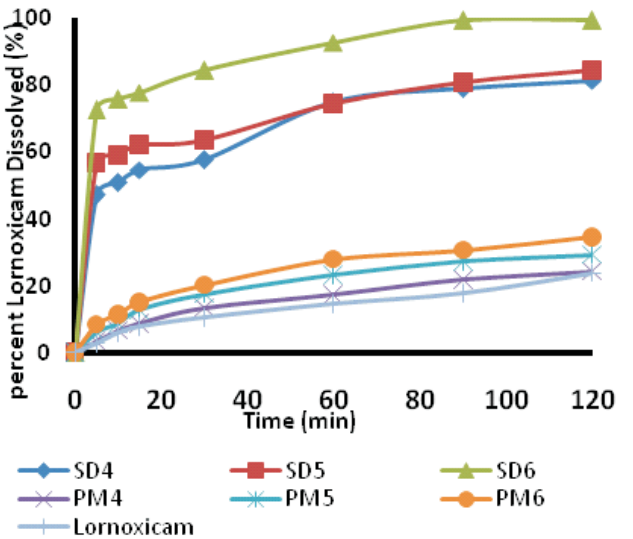

Fig. 7: Dissolution profiles of lornoxicam solid dispersions and physical mixtures with poloxamer 407 compared to pure lornoxicam powder at 0.1N HCl.

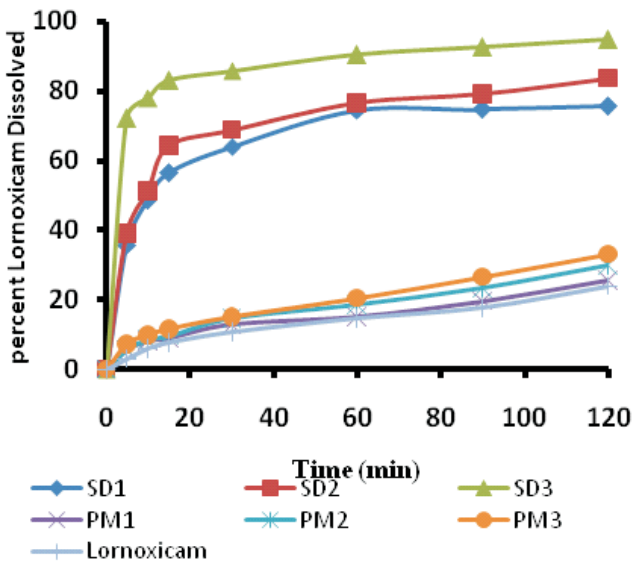

Fig. (6): Dissolution profiles of lornoxicam solid dispersions and physical mixtures with acrysol compared to pure lornoxicam powder at 0.1N HCl.

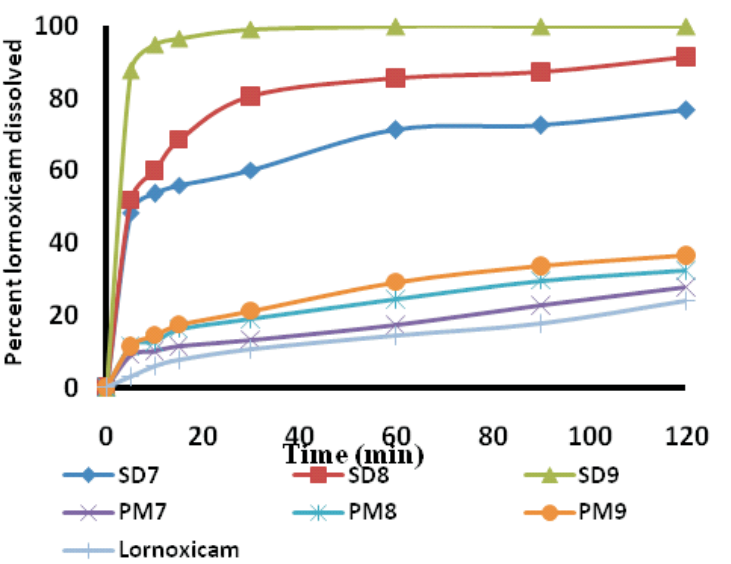

Fig. 8: Dissolution profile of lornoxicam solid dispersions and physical mixtures with soluplus compared to pure lornoxicam powder at 0.1N HCl.

Table 5 : Dissolution efficiency (%) of lornoxicam solid systems with acrysol, soluplus and poloxamer 407.

Solid system formulations	DE_{60}, %	Solid system formulations	DE_{60}, %
PM1 (Lor:acrysol 1:2)	10.89	SD1 (Lor:acrysol 1:2)	57.6
PM2 (Lor:acrysol 1:6)	12.53	SD2 (Lor:acrysol 1:6)	61.55
PM3 (Lor:acrysol1:10)	13.75	SD3 (Lor:acrysol 1:10)	78.06
PM4 (Lor:polox 1:2)	11.57	SD4 (Lor:polox 1:2)	55.5
PM5 (Lor:polox 1:6)	15.47	SD5 (Lor:polox 1:6)	60.06
PM6 (Lor:polox 1:10)	18.41	SD6 (Lor:polox 1:10)	76.41
PM7 (Lor:soluplus 1:1)	12.48	SD7 (Lor:soluplus 1:1)	56.28
PM8 (Lor:soluplus 1:2)	17.48	SD8(Lor:soluplus 1:2)	69.9
PM9 (Lor:soluplus 1:3)	19.91	SD9 (Lor:soluplus 1:3)	89.86

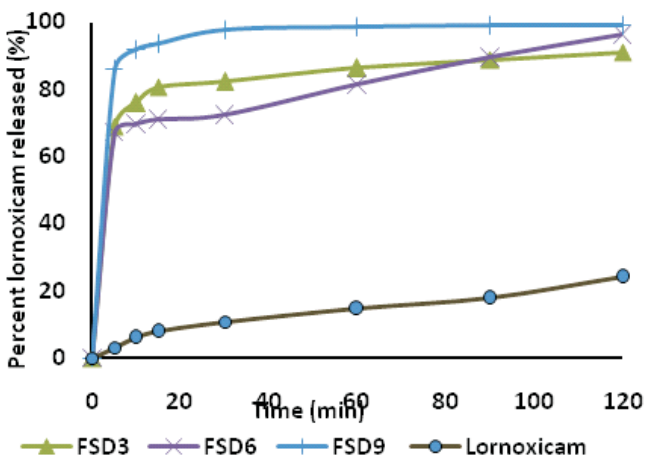

Fig. 9: *In vitro* release profile of lornoxicam fast release tablets in 0.1 N HCl at 37±0.5°C.

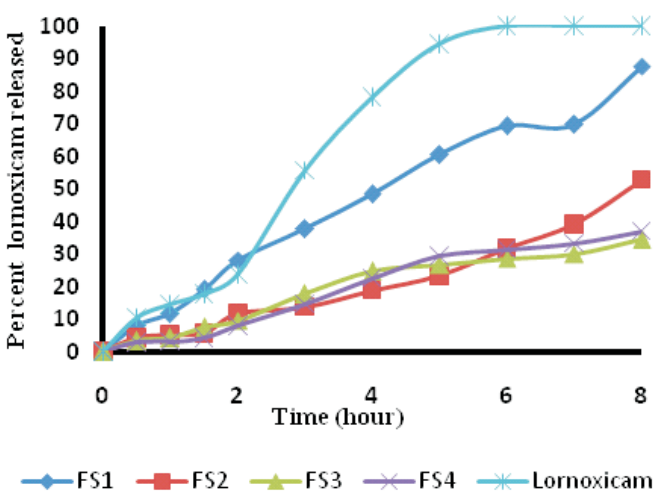

Fig. 10: In vitro release profile of lornoxicam sustained release tablets containing Polyox 1105.

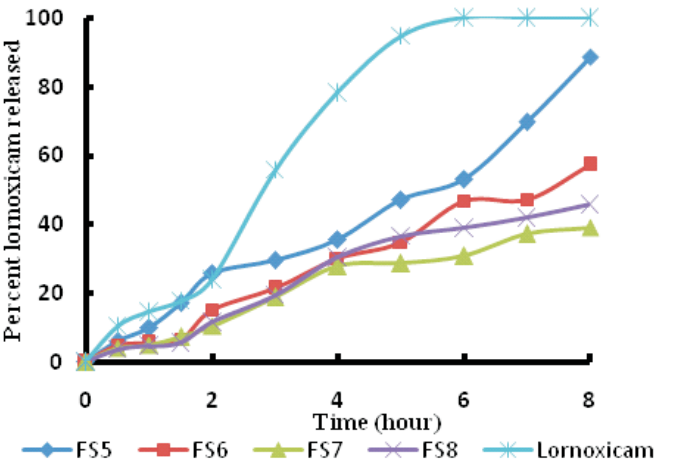

Fig. 11: In vitro release profile of lornoxicam sustained release tablets containing Polyox 205 LEO.

Characterization of Bilayer Tablets

The average weight of the prepared tablets varied from 243.6 mg to 257.4 mg. The average thickness values ranged between 2.89 mm and 3.58 mm. Tablets showed hardness values ranged from 6.12 Kg/cm^2 to 8.43 Kg/cm^2. The drug content of lornoxicam bilayer tablets was ranged between (97.88- 103.55 %). The mean percent loss of weight ranged from 0.229 % to 0.987 %. The percentage friability for tested bilayer tablets was below 1%. Disintegration time for fast release layer was ranged between 2.33 and 4.06 seconds.

In vitro Drug Dissolution Studies for the Bilayer Tablets

All prepared tablet formulations showed burst dissolution of more than 20% of their lornoxicam content in 0.1 N HCl during the first 30 min of the dissolution study. The percent dissolved after 30 min ranged from 24.36% and 37.99%. F8 containing soluplus solid dispersion gave the highest dissolution 37.99% which was higher than marketed formulation (Xefo) 33.35%. More than 30% of the drug (31.32% and 45.34%) in 2 hs was dissolved which is equivalent to 62.64% to 90.68% of the fast release part. After this, the sustained portion starts to dissolve the

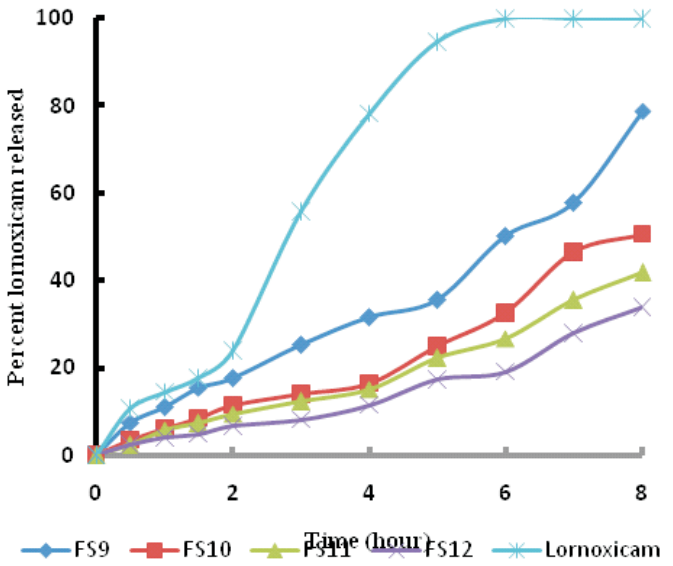

Fig. 12: *In vitro* release profile of lornoxicam sustained release tablets containing Carbopol 71G: Suglet (2:1).

drug in a controlled manner ending up with 66.77% to 89.37% dissolution in 8 hs (Figures 13-14).

DISCUSSION

Phase-Solubility Study

Lornoxicam aqueous solubility was observed to be 0.02 mg/ml; therefore, lornoxicam could be defined as practically insoluble drug [18]. Phase solubility showed an increase in drug solubility with increasing carrier concentration. Solubility of lornoxicam showed 65, 75 and 90 fold increase in presence of 10% w/v of acrysol, soluplus and poloxamer, indicating excellent affinity between lornoxicam and carriers to form a molecular dispersion. The values of the stability constants (Ks) calculated from the equation of Higuchi and Connors were found to be 1.75, 3.63 and 2.35 for acrysol, poloxamer and soluplus respectively. Phase solubility showed an increase in drug solubility with increasing carrier concentration, with coefficient of determination r^2 value equal to 0.992, 0.994 and 0.996 for acrysol, poloxamer and soluplus, respectively. The diagrams were classified as A_N-type phase diagram[7].

Physicochemical Characterization of Lornoxicam Solid Systems and Compatibility with the Used Polymers

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectrum of lornoxicam showed a characteristic peak at 3066 cm^{-1} corresponding to NH stretching vibration. Intense absorption peak was found at 1647 cm^{-1} due to the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1593 and 1539 cm^{-1} and were assigned to bending vibrations of the NH group in the secondary amide. The stretching vibrations of the O=S=O group appeared at 1145, 1381, and 1327 cm^{-1}. Other prominent peaks appeared at 829 cm^{-1} corresponding to CH aromatic ring bending and heteroaromatics and at 765 cm^{-1} due to the CCl bending vibration [2]. Poloxamer 407 showed intense broad absorption bands at 34913452 cm^{-1} (free OH stretching vibration), 2887 cm^{1}(C-H stretch aliphatic), 1467 cm^{-1} (C-H bend), 1342 cm^{1} (in-plane O-H bend) and 1112 cm^{1} (C-O stretching). Soluplus showed peaks at 3448 cm^{-1} (O-H

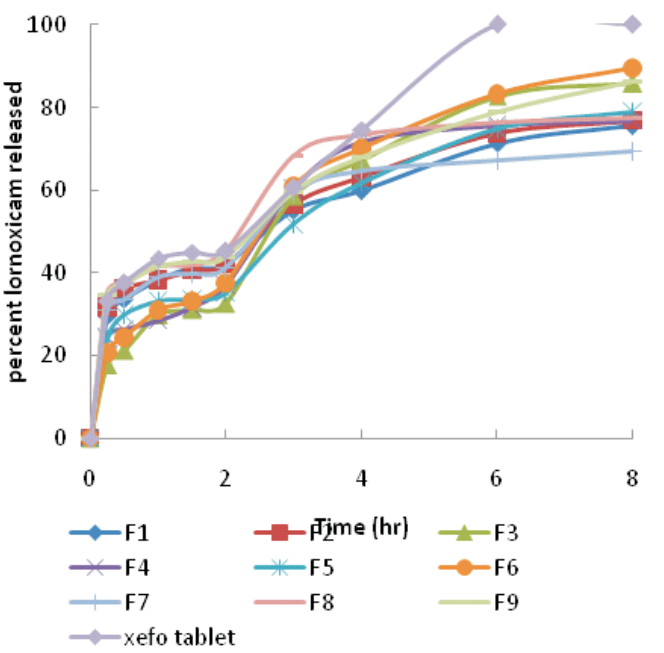

Fig. 13: *In vitro* release profile of lornoxicam form bilayer tablet formulations (F1-F9) compared to commercial product.

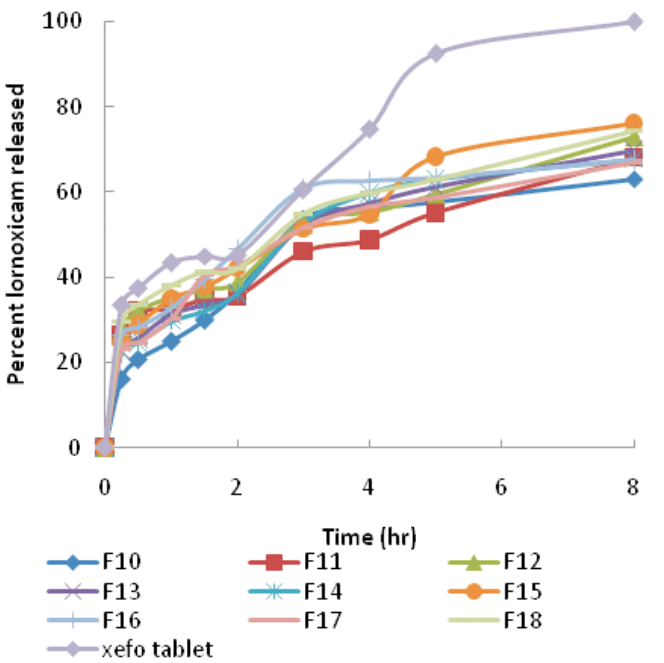

Fig. 14: *In vitro* release profile of lornoxicam form press-coated tablet (core and coat) formulations (F10-18) compared to commercial product.

stretching), 2929 cm^{-1} (aromatic C-H stretching), 1735 cm^{-1}, 1635 cm^{-1} (C-O stretching), and 1477 cm^{-1} (C-O-C Stretching) [19]. Acrysol showed peaks at 3342 cm^{1} (O-H stretching), 2922cm^{1}, 2860cm^{1} (aliphatic C-H stretching vibrations), 1734cm^{1} (C=O stretching vibrations) [20, 21]. Solid dispersions did not show any new peaks, indicating the absence of chemical bond formation in these binary systems [22]. The solid dispersions showed all peaks of lornoxicam (pure) and carriers. These results indicate that there is no chemical interaction between drug and carriers when formed as solid dispersions and predict stability of drug in its solid

dispersions [23, 24].

FTIR spectra of physical mixtures of drug and sustained release polymers showed the characteristic peaks of lornoxicam suggesting absence of interaction between the drug and polymers [25].

Differential Scanning Calorimetry (DSC)

The DSC thermogram of lornoxicam was a typical of crystalline substance, exhibiting a sharp exothermic peak at 232.1°C corresponding to its melting point and decomposition [26]. Poloxamer showed a sharp endotherm at 55.80°C indicating the melting point, followed by a broad exotherm at 254.16°C indicating recrystallization or transfer of heat (energy) to surrounding molecules gained in the melting process [22] The DSC thermograms of acrysol showed two endothermic peaks at 39.74 and 144.09 ^{O}C. The DSC thermograms of soluplus showed broad endothermic peaks at 88.33 °C and 250.48 °C [19]. Solid dispersions showed reduction in the intensity of the sharp peak of lornoxicam and shifting to lower melting point was noted in 1:1 solid dispersion due to molecular dispersion and possibly indicating the presence of an amorphous lornoxicam in the solid dispersions[22].

DSC thermograms showed absence of any chemical interaction between the drug and sustained release polymers during the thermal process.

In vitro Dissolution Studies for Lornoxicam Solid Dispersions

The dissolution of pure lornoxicam was the slowest as compared to tested SDs and corresponding physical mixtures. Lornoxicam has a low pKa value (pKa= 4.7) so it is less soluble in acidic pH.Lornoxicam dissolution was enhanced when physically mixed with carrier and percent drug dissolved increased with increasing carrier ratio. This is possibly due to the close contact of the drug with the hydrophilic carrier, brought about by the mixing process and high surfactant properties of carrier resulting in increased wettability and dispersibility of the drug [27].

Results obtained from lornoxicampoloxamer solid dispersions showed that the percent of drug dissolved from the formulations were increased as the ratio of poloxamer 407 was increased where SD6 (Lor:polox 1:10) gave the highest percent drug dissolved (99.45%) after 2 hr.

This increase in drug dissolution from poloxamer solid dispersion may be due to the molecular and colloidal dispersion of drug in hydrophilic polymer matrix of poloxamer. Poloxamer copolymers exist in solution as monomers but self-assemble into micelles. In addition, the greater hydrophilicity and surface properties of poloxamer increased wettability, dispersibility, and reduced particle size of the drug which might contribute to the enhanced dissolution of lornoxicam [22, 28]. Improvement in the dissolution of the drug from acrysol solid dispersions may be due to its entrapment within the molten polymer during the melting (fusion technique) process. This improvement could be also attributed to the solubilizing and emulsifying nature of the polymer by modifying the polarity of dissolution medium and wetting the surface of solute (drug) by lowering the contact angle between the solute and dissolution medium. SD3 (Lor:acrysol 1:10) showed a percent drug dissolved of (94.85%). The rapid dissolution of lornoxicam from soluplus solid dispersion could be explained by dispersion of drug particles in the polymer matrix as a result of the proper miscibility of the drug with the caprolactam (hydrophobic) part of the polymer. As the drug-polymer came in contact with water, the ethylene glycol (hydrophilic) part of the polymer hydrated rapidly into solution, solubilizing the dispersed drug particles as well. Also, the reduction in particle size increases the surface/volume ratio and the surface interactions, thus resulting in proper drug-polymer miscibility and enhancement of the dissolution rate [19]. SD9 (Lor:soluplus 1:3) gave the highest percent drug dissolved (100%) after 2 hr.

In vitro Drug Dissolution Studies for the Fast Release Layer Tablets

It is worth noting that kollidonCl was used as a superdisintegrant in these tablet formulations. It absorbs a huge amount of water causing immediate disintegration when exposed to the dissolution media, thus enhance rapid dissolution of the drug [29]. It is quite clear that the prepared fast release tablet formulations, containing lornoxicam solid dispersions have shown manifested improvement in drug dissolution properties in acidic conditions when compared to lornoxicam powder similar to that obtained from solid dispersions dissolutions. FSD9 containing lornoxicam:soluplus solid dispersions gave the highest dissolution (98.95%) after 2 hours followed by FSD6 containing lornoxicam:poloxamer solid dispersions (96.2%) and FSD3 containing lornoxicam: acrysol solid dispersions (91.2%).

In vitro Drug Dissolution Studies for the Sustained Release Layer Tablets

To simulate the conditions that exist in human GI tract as the tablet transits from stomach to intestine, the dissolution studies were performed in 0.1 N HCl of pH1.2 for 2 hs followed by phosphate buffer of pH 6.8 for the sequential 6 hs*[30]*. Moreover, the dissolution sampling duration lasted 8 hs as the total GI transit time of dosage forms after oral administration in humans is reported to be approximately 8 hs [31].

Due to its acidic nature, lornoxicam showed slow dissolution in acidic pH. However, complete drug dissolution was displayed when the pH of the medium was changed to 6.8. Polymer concentration was too low in case of FS1, FS5 and FS9 a complete gel layer may not form resulting in a significant amount of drug being dissolved too quickly and failed to sustain lornoxicam dissolution [32]. In tested formulations, polyox hydrate rapidly and form a gelatinous barrier layer around the wetted tablet when it comes in contact with aqueous solvent. Drug dissolution occured by diffusion through gel layer or gradual erosion of gel, exposing fresh surfaces containing drug to the dissolution medium *[33]*. Higher proportion of polymer matrix reduces the rate of drug dissolution, since a larger amount of polymer increases the degree of swelling, resulting in an increase in the drug diffusional path and consequent delay in the dissolution rate. It was found that on further increase of polyox concentration (from 1:10 to 1:12 drug: polymer), the drug dissolution was increased in case of polyox 1105 and polyox 205 LEO. This indicated that there is a threshold level for retardation of drug dissolution rate that is achievable, beyond which, an increase in polyox level does not result in further decrease in lornoxicam dissolution rate. Drug dissolution from carbopol matrices was medium-dependent due to the anionic nature of carbopol. At low pH (the first 2 hrs.), the dissolution of the drug was fast because the polymer is not fully swollen and the drug is dissolved faster, before formation of the complete gel layer. Suglet (sugar spheres for sustained or extended release) has low or no drug release in 0.1 N HCl and rapid release in phosphate buffer of pH 6.8 *[34]*. The

combination of carbopol/ suglets resulted in retardation of drug dissolution in pH 1.2. At pH 6.8 (after pH change of the dissolution medium, after 2 hrs.), the carboxylic groups of carbopol were ionized and repel each other causing maximum swelling, resulting in fewer and smaller regions of microviscosity. The rapid gel formation acts as a barrier for the dissolution of the drug thus, prolonging the dissolution**.** FS3and FS7 having drug: polymer ratio of 1:10 and FS12 having drug: polymer ratio of 1:12 gave the highest sustained effect.

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The target dissolution profile parameters for sustained release products were reported as follows [35]: after 2 h, 2045% of the drug is dissolved; after 4 h, 4575% of the drug is dissolved; and finally, after 8 h, 75105% of the drug is dissolved. It was found that F1, F2, F3, F4, F5, F6, F8, F9 and F15 exhibited release profiles that fulfilled the abovementioned release requirements.

CONCLUSION

From the results obtained, the proposed bilayer tablets of 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. F1, F2, F3, F4, F5, F6, F8, F9 and F15 showed acceptable physical properties and achieved the required *in vitro* release pattern that meets the purpose set for this study.

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