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FABRICATION, OPTIMIZATION AND CHARACTERIZATION OF LORNOXICAM BILAYER TABLETS FOR BIPHASIC RELEASE

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Abstract

Lornoxicam is a member of oxicam family and nonsteroidal anti-inflammatory drug (NSAID), possessing short half-life. This study was opted to fabricate, optimize and evaluate lornoxicam bilayer tablets, which exhibit initial burst release of the drug inside the stomach and adhere to the release specifications of sustained release pharmaceuticals. The suggested bilayer tablets consist of two layers i.e. immediate release (IR) and sustained release (SR), in anticipation of initial drug release that begins inside the stomach to quickly relieve the symptoms with persistent action in the intestine to continue extended analgesic efficacy. Various formulations of bilayer tablets were produced using direct compression technique by altering the concentration of polymers, like guar gum, Carbopol 940P and HPMC K4M. The drug excipients compatibility was confirmed by FTIR scans. The formulations displaying the necessary flow characters were subjected to compression after the micromeritic characteristics of powder mixes were assessed. Various physico-chemical characterization tests were evaluated, and the multiple point *in-vitro* drug dissolution was achieved at pH 7.4. *In-vitro* drug release behavior demonstrated a profile of biphasic release, suggesting lornoxicam release from IR layer within 15 min while SR layer maintained drug release control for up to 24 hours. Model dependent as well as independent approaches were put in place to compare

dissolution profiles of formulations. F9 was chosen as the best trial formulation based on controlled release pattern and physico-chemical characterization, including stability determination. The trial lornoxicam bilayer tablet formulations (F1-F9) complied with Fickian diffusion mechanism and zero-order release kinetics (n = 0.364–0.445). *ANOVA* statistical analysis revealed that the cumulative quantity of drug released after 15 min did not change significantly from optimized formulation, however the amount released after 24 h did differ significantly ($p<0.05$). Thus, the outcomes clearly indicated that the natural polymer guar gum was preferred for ensuring a biphasic release profile of lornoxicam.

Keywords: Lornoxicam, direct compression, FTIR analysis, guar gum, biphasic release.

1. Introduction

The administration of active pharmaceutical substances to achieve optimum pharmacological or therapeutic response in humans or animals is termed as drug delivery (1). While considering drug delivery, the oral route is regarded as the most convenient, practical and appropriate approach, with several advantages including self-administration, cost effectiveness, non-invasiveness, safety and enhanced patient compliance (2). The development of dosage forms for the controlled release of oral formulations is of paramount importance in novel drug delivery systems (3). Literature suggests that more than 90% of drugs are meant to be taken orally. This demonstrates the widespread acceptance of this formulation type; hence, the bulk of studies prefer to concentrate on it (4).

Lornoxicam, a non-steroidal anti-inflammatory drug (NSAID), has been used to treat colonic and inflammatory bowel diseases (5). It works by preventing prostaglandins formation, just as other NSAIDs (6). Both tablets for oral usage and injections for intravenous use of lornoxicam are readily available. Drug is often taken in doses of 4 mg TID or 8 mg BID, with 0.2 L/kg volume of distribution (7). After oral administration, it undergoes significant and variable first pass hepatic metabolism with a shorter half-life of 3 to 5 h, as compared to other oxicams. Rapid and complete gastrointestinal absorption characterizes lornoxicam. In about 2 to 2.5 hours, the drug's plasma concentration reaches its peak (8). The plasma concentration of drug increases linearly with the dose and frequency of administration. In plasma, lornoxicam can be found either in its unmodified form or as its inactive hydroxylated metabolite (9). Additionally, lornoxicam is also associated with various gastrointestinal side effects such as ulceration and local gastric irritation.

Tablets have many advantages over other pharmaceutical dosage forms because of their ability to mask taste, improved stability, method of administration, and cost effectiveness (10). Even though immediate release tablets have many benefits, they also have some drawbacks. It may be challenging for elderly people with co-morbidities to take immediate release tablets three or four times per day (11). Based on these factors, a novel oral drug delivery system in the shape of a tablet was suggested, known as bilayer tablet.

Bilayer tablets have been designed to provide controlled drug delivery with preset release patterns (12). The objectives of opting for such dosage form include prevention of chemical incompatibilities between active drug substances by means of physical separation as well as investigation of various drug release patterns i.e. immediate release along with extended release (13). Such type of drug delivery systems is intended to release the drug at two different times and rates (either slow/quick or quick/slow). One portion is designed to achieve a rapid release of the double component drug in order to quickly attain a high serum concentration. The second part is a sustained release layer, which ensures that the drug release takes place over a long time period. Because a quick increase in blood concentration results from drug release from a fast-releasing component, therefore the pharmacokinetic advantage depends on the plasma level. The drug release from sustained layer is responsible to maintain the drug plasma concentration at a steady state level (14). This kind of approach is typically employed when rapid attainment of relief is required, which is then controlled by sustained release phase to prevent repeated administration. According to reports, NSAIDs represent ideal choice for such type of drug delivery systems (15). Utilizing various ethocel and methocel concentrations, Noreen *et al*. successfully developed and assessed sustained release

lornoxicam tablets using the direct compression method (5). Similarly, Tung *et al*. formulated unique biphasic delivery system for lornoxicam by integration of drug nanocrystals into a sustained release matrix based on HPMC (16).

The challenge of drug administration has certainly benefited from polymers application in pharmaceutical as well as medicinal fields. Polymers are termed as sophisticated pharmaceutical excipients which can delay the release of a drug for the desired time period (17). Therefore, the type and quantity of the retardants are key factors in the formulation of controlled release dosage forms (18). Researchers have used a variety of polymers, such as natural, synthetic, semi-synthetic, pH dependent, hydrophilic and hydrophobic, to develop a variety of controlled release products. To develop water soluble matrices, hydrophilic retardants such as natural gums, cellulose esters, sodium carboxymethyl cellulose, and hydroxyl propyl methyl cellulose (HPMC) are widely used. Water insoluble matrices are generally formed from hydrophobic retardants which include stearic acid, ethyl cellulose, glyceryl monostearate and methacrylic resin (19). Taking altogether, the current study was proposed to design, develop and characterize a biphasic delivery system as a bilayer lornoxicam tablet by employing numerous hydrophilic polymers of natural (guar gum), synthetic (carbopol) and semi-synthetic (HPMC) origin.

2. Materials & Methods

2.1. Materials

Lornoxicam was received as a gift by Wilshire Pharma Private Limited, Lahore. Polymers employed were carbopol, guar gum and HPMC K4M (Sigma Aldrich, USA). Starch 1500, microcrystalline cellulose, carboxymethyl cellulose, magnesium stearate and talc (Sigma Aldrich, USA) were used as disintegrant, diluent, binder, lubricant and glidant, respectively. The chemicals were of analytical grade and were used without being further purified.

2.2. Methods

2.2.1. Pre-formulation Studies

2.2.1.1. Solubility Studies

As the drug bioavailability is highly reliant on absorption and dissolution parameters after oral administration, the solubility of the active component plays a significant role in pre-formulation investigations. The particle size, surface area and morphological characteristics are the main factors influencing drug dissolution, hence it is crucial to take solubility into account throughout the pre-formulation process (20).

To ascertain the solubility of lornoxicam in different solvents at varied pH, a saturated solubility experiment was conducted. In this case, an excessive amount of the drug i.e. 1 g was introduced into various selected solvents (10 ml) to obtain saturated drug solutions in closed containers. They were introduced in a shaking water bath at 25 ± 1 ºC for 24 h. After a predetermined time interval, aliquots from the clear supernatants were removed and diluted with distilled water for spectrophotometric analysis at a maximum wavelength of 378 nm (21).

2.2.1.2. FTIR Analysis

The careful excipient selection is crucial for the effectiveness, success and stability of solid dosage forms. Finding suitable excipients that show compatibility with the active drug substance and don't interfere with its stability are the main goals of compatibility studies (22). The samples of pure drug and its physical mixtures with polymers were subjected to FTIR analysis (Spectrum 100, Perkin Elmer, USA) by placing them on KBr discs. Scans were recorded from 4000 – 625 cm^{-1}, and the produced spectra were compared to look for any discernible variations (23).

2.2.1.3. Micromeritical Characteristics

The flow properties of drug, polymer and excipients blend should be within the acceptable official limits in order to produce satisfactory formulations. These characteristics include angle of repose, bulk and tapped densities, compressibility index and Hausner's ratio. Before initiating the formulation

development, these micromeritical parameters should conform to the pharmacopeial standards. The angle of repose was determined by noting the height (h) and radius (r) of powder bulk and fitting in the following equation (24):
Angle of repose (θ) = $\tan^{-1}$ h / r

Bulk and tapped densities are important to calculate compressibility index. Both type of densities were calculated according to following equation by graduated cylinder method (25):
Bulk Density (ρ_{bulk}) = W / V_{bulk}
Tapped Density (ρ_{tapped}) = W / V_{tapped}
Carr's Index = (ρ_{tapped} - ρ_{bulk} / ρ_{tapped}) * 100
Finally Hausner's ratio was obtained by the ratio of taped density to bulk density (26).
Hausner's Ratio = ρ_{tapped} / ρ_{bulk}

2.2.2. Preparation of Lornoxicam Bilayer Tablets

For the formulation of immediate release and controlled release layers, 4 mg and 12 mg of lornoxicam were used, respectively. The formulation of immediate release (IR) layer was accomplished by passing the precisely weighed drug through sieve number 40, together with starch 1500 and CMC as a dry binder. The sieved mixture was put in a plastic bag and stirred for five minutes. The resulting mixture was lubricated using magnesium stearate for 2 minutes that had been processed through a sieve number 60 (27). The formulation of controlled release (CR) layer was achieved by the addition of drug with CR polymers like guar gum, carbopol and HPMC K4M, along with CMC (dry binder) and MCC (diluent). The resultant mixture was then passed through sieve number 40 and thoroughly blended in a plastic bag. Talc and magnesium stearate that had been processed through sieve 60 were used to lubricate the resultant mixture (28). Tables 1 and 2 list the composition of IR and CR layers, respectively:

Table 1. Formulation chart of IR layer of lornoxicam bilayer tablets

Constituents	Quantity / tablet (mg)
Lornoxicam	4
Starch 1500	44
CMC	1.5
Magnesium stearate	0.5
Total	50

Table 2. Formulation chart of CR layer of lornoxicam bilayer tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lornoxicam	12	12	12	12	12	12	12	12	12
Carbopol	60	75	90	-	-	-	-	-	-
HPMC K4M	-	-	-	60	75	90	-	-	-
Guar gum	-	-	-	-	-	-	60	75	90
MCC	70	55	40	70	55	40	70	55	40
CMC	5	5	5	5	5	5	5	5	5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	150	150	150	150	150	150	150	150	150

2.2.3. Bilayer Tablet Compression

Initially, the CR layer blend was introduced into the die, followed by its pre-compression by means of single punch tablet machine (AR 400, Erweka, GMBH, Germany). Then specific quantity of IR layer blend was added to pre-compressed CR layer blend manually and compressed directly to produce bilayer tablets with appropriate hardness of 6-8 $kgcm^{-2}$ (14).

2.2.4. Characterization of Bilayer Tablets

2.2.4.1. Dimensional Specifications

The thickness and diameter of produced batches of bilayer tablets were specified in terms of dimensions. After careful calibration, a vernier caliper (Erweka, Germany) determined the thickness and diameter of the bilayer tablets (29). The results were averaged in the form of mean ± SD.

2.2.4.2. Hardness Test

Bilayer tablets should be strong enough to withstand breaking while being handled normally, but they should also be soft enough to enable appropriate dissolution profile after oral administration. A hardness tester (Erweka, Germany) was used to quantify each tablet's hardness. The experiment was triplicated and averaged (30).

2.2.4.3. Friability

Friability of bilayer tablets was determined by Roche friabilator, according to the pharmacopeial procedure (31). The equation shown below was used to compute the percentage decrease in weight or friability.

Friability (%) = $(W_0 – W / W_0) * 100$

2.2.4.4. Weight Variation Test

For weight uniformity, the randomly selected tablets (20) were individually weighed, mean weight determined, and then the individual weights were compared to the average. The produced bilayer tablets pass the test if no more than two of the individual weights differ by more than 7.5 % from the average weight (200 mg), and no weights differ by more than twice that amount (32).

2.2.4.5. Content Uniformity Test

A validated technique was used to measure the quantity of lornoxicam at 378 nm using a UV spectrophotometer (UV-1601, Shimadzu, Japan) after the appropriate dilutions were produced using pH 7.4 phosphate PBS. Triplicate readings were recorded and shown as mean ± SD (33). The following equation was used to compute the drug content.

Drug Content (%) = Absorbance of sample / Absorbance of standard * 100

2.2.4.6. *In-vitro* Drug Release

Rotating basket method was employed to assess the *in-vitro* drug release profile of compressed bilayer tablets. The tablets were introduced into PBS pH 7.4 (900 ml) as dissolution medium kept at 37 ± 0.5 ºC, and the baskets were allowed for rotation at 50 rpm speed. At specified intervals, aliquots (5 ml) were removed using a syringe equipped with a pre-filter (0.45 μm) and promptly refilled with equal volume of fresh medium kept at the same temperature. Using a UV spectrophotometer (UV-1601, Shimadzu, Japan), the samples were examined for the presence of lornoxicam at 378 nm. The percent drug release was determined through the equation generated from standard calibration curve (34). Triplicate readings were taken and averaged.

2.2.4.7. Kinetic Modeling

The dissolution data was fitted to various well-known release models, including zero-order kinetics, first-order kinetics, Hixon-Crowell model, Higuchi model and Korsemeyer Peppas equations, as part of a model dependent strategy. Using zero or first orders kinetics, drug release order from matrix systems was characterized, and the drug release mechanism was defined using the Higuchi, Hixon-Crowell and Peppas equations (35).

2.2.4.8. Model Independent Approaches

2.2.4.8.1. Difference and Similarity Factors

The total of the vertical distance values between the test and standard values at each point of dissolution time is essentially expressed using the difference factor (f_1). It is determined using the

following equation. The dissolution behavior of two brands is said to be different by a value of f_1 between 0 and 15.

$$f1 = \left\{\left(\sum_{t=1}^{n} \quad Rt\right)\right\} * 100$$

The similarity factor (f_2) is defined as the log reciprocal square root of one plus the mean squared difference in percent drug dissolution between the test and reference products. The following equation may be utilized to compute f_2. In order to measure f_2, it should be close to 100, however a value of f_2 greater than 50 is also acceptable (28).

$$f2 = 50 * log\ log\ [\![1 + \left[\frac{1}{n}\right] \sum_{t=1}^{n} \quad (Rt - Tt)^2]\!]^{-0.5} * 100$$

The F9 formulation, which exhibited outstanding physicochemical features and release characteristics, was chosen as the reference to determine f_1 and f_2 for all formulations because sustained release dosage forms were not readily accessible in the local market.

2.2.4.9. Stability Determination

Lornoxicam bilayer tablets that had been chosen for optimization were subjected to storage at 25 °C and 40 °C, in accordance with ICH guidelines. The stability chamber (Ti-Sc-THH-07-0400 Faisalabad, Pakistan) was employed for this purpose. The percent humidity readings at 25 °C (ambient) and 40°C (accelerated) were 65 % and 75 %, respectively. The matrices had to be heated to 25 °C and 40 °C for this test in order to assess the effects of ambient temperature and accelerated temperature, respectively. Bilayer tablets were exposed to different quality control (QC) tests, like thickness, diameter, hardness, friability, weight variation, content homogeneity and *in-vitro* dissolution, at predetermined intervals of 0, 1, 2, 3 and 6 months (36).

2.2.5. Statistical Analysis

All the tests were conducted in triplicates and findings were shown in the form of mean ± SD. One way ANOVA and student's t-test were used for statistical analysis and p value less than 0.05 was deemed significant.

3. Results & Discussion

3.1. Solubility Experiment

A drug's solubility is essential for ensuring optimal bioavailability. The most frequent challenge in the formulation of new pharmacological moieties is low water solubility. Most medications have either an acidic or a basic nature and have very little water solubility (37). Moreover, lornoxicam has a poor solubility in water. To ascertain the solubility of lornoxicam in different solvents, a saturated solubility experiment was conducted. Figure 1 shows experiments on the solubility of lornoxicam in a variety of solvents, including water, 0.1 N HCl, 0.1 N NaOH, and PBS (pH 6.8, 7.2 and 7.4) maintained at 25 ºC, 37 ºC and 40 ºC. It is evident that lornoxicam is least soluble in water and most soluble in PBS at pH 7.4. These results concurred with those of Hashmat *et al*. who discovered that PBS at pH 7.4 displayed the maximum drug solubility. Also, it has been discovered that, generally speaking, as temperature rises, so does drug solubility; as a result, lornoxicam's solubility in all solvents increased at a higher temperature i.e. 40 ºC. The majority of pharmaceuticals have positive integer values for their heat of solution, which might lead to a better solubility profile whenever the system's temperature is raised. This may be the origin of the heat absorption phenomena (21).

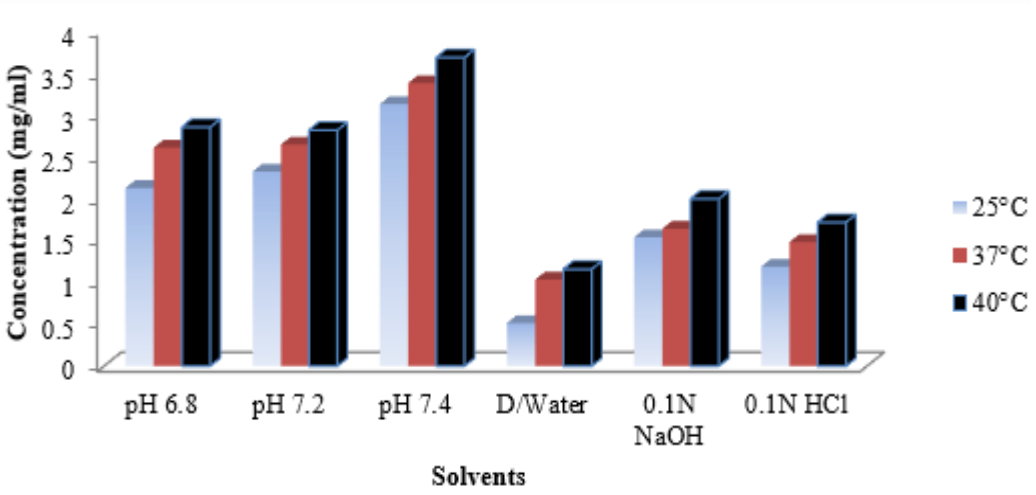

Figure 1. Solubility study of lornoxicam in various solvents carried out at different temperatures.

3.2. Micromeritic Characteristics

Direct powder compression requires better powder flow characteristics and a higher compressibility index than granulation technique, hence excipients for direct compression method must have these qualities. In order to analyze the flow characteristics and compressibility of a powder mass, the micromeritic properties were evaluated. Formulations with acceptable to good flow performance were compressed based on their micromeritic characteristics before further characterization (38).

For lornoxicam trial batches i.e. F1-F9, it was demonstrated that the Hausner's ratio, angles of repose and Carr's index were all less than 1.2, 30° and 15%, respectively, suggesting the free-flowing character of the powder mixes for F1 to F9 trial batches (Table 3). Findings from this analysis were comparable to those from Noreen *et al*., who produced lornoxicam sustained release tablets by means of ethyl cellulose and methyl cellulose as polymers (5).

Table 3. Micromeritic properties of lornoxicam trail formulations (F1-F9) (mean ± SD, n=3)

Formulations	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio
F1	26.3 ± 0.17	12.63 ± 0.25	1.13 ± 0.01
F2	27.9 ± 0.63	11.13 ± 0.12	1.14 ± 0.03
F3	25.8 ± 0.52	12.96 ± 0.66	1.12 ± 0.07
F4	26.9 ± 0.89	13.43 ± 0.41	1.10 ± 0.05
F5	28.3 ± 0.99	14.89 ± 0.21	1.14 ± 0.04
F6	24.7 ± 0.47	13.58 ± 0.09	1.15 ± 0.01
F7	25.9 ± 0.63	12.47 ± 0.52	1.16 ± 0.08
F8	27.1 ± 0.23	11.32 ± 0.14	1.10 ± 0.03
F9	25.3 ± 0.12	14.11 ± 0.31	1.11 ± 0.01

3.3. FTIR Study

The interactions between the active moiety (lornoxicam) and polymers utilized in the formulation of lornoxicam bilayer tablets were examined using FTIR analysis. The pure lornoxicam showed characteristic band peaks at 3062.32 cm^{-1} (N-H stretching), 1645.23 $cm^{-1}$and 1625.02 cm^{-1} (primary amide stretching), 1589.63 cm^{-1} and 1528.58 cm^{-1} (secondary amide stretching), 1375.59 cm^{-1} and 1140.23 cm^{-1} (R-SO_2-R stretching) (39). As with individual FTIR spectra of lornoxicam, the FTIR spectra of the physical drug mixture in combination with polymers displayed all the major representative peaks as detected in those spectra, rejecting the likelihood of any conceivable interaction. The detected peaks agreed with the data of an earlier work conducted by Naseem *et al*. while developing the metronidazole floating effervescent tablets (40). No pharmacological

interaction with the excipients was found when FTIR spectra were examined since no extra peak was found (Figure 2).

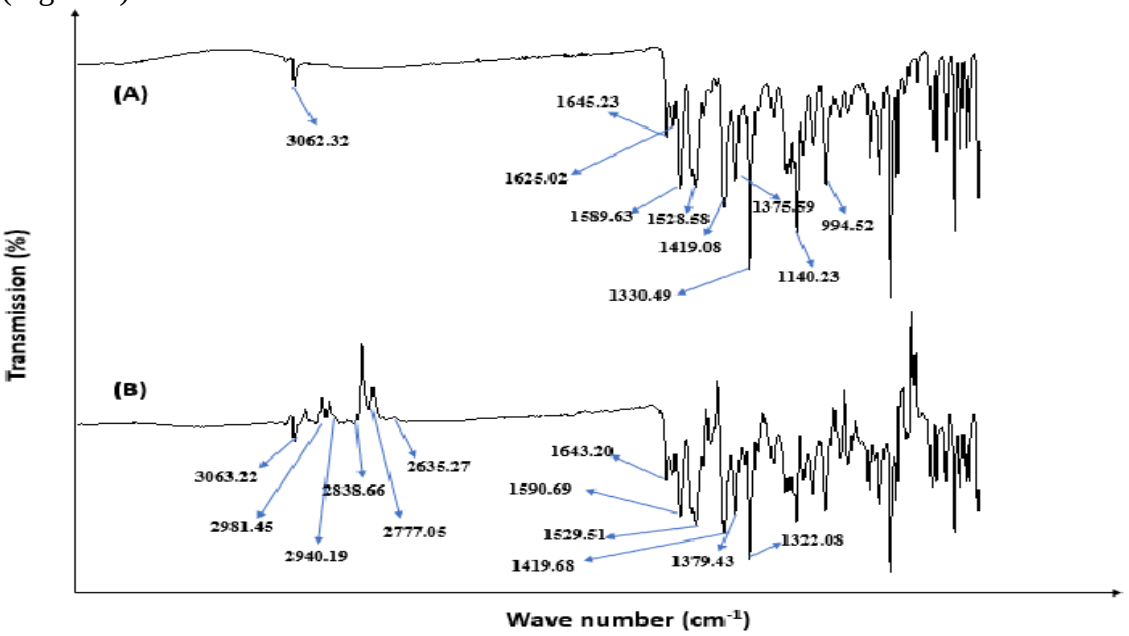

Figure 2. FTIR spectra of (A) lornoxicam and (B) physical drug mixture with polymers

3.4. Post-Compressional Characteristics

The tablet's physical characteristics were deemed to be good. There were no signs of common tablet flaws such capping, chipping, or picking. The features of each batch of bilayer tablet formulations, including hardness, friability, diameter, thickness, weight variation and drug content, are shown in Table 4. The trial formulations' weight variation findings showed minor standard deviation, which was found to be within acceptable limits (7.5 %) due to the drug's outstanding flowability and proper mixing with other formulation excipients (41). The fact that all batches had < 1 % friability shows that tablet surfaces are robust enough to survive mechanical stress or attrition while being stored, transported and up until consumption (42). The tablets were determined to have hardness between 6.5-7.5 $kgcm^{-2}$. It was found that the hardness rose in direct proportion to the polymer content. By entanglement, polymers would likely improve the binding abilities of active moiety and other adjuvants (43).

All testing batches of tablets were determined to have dimensions that were within the limitations, including thickness and diameter. It was discovered that thickness and diameter, measuring 3.5 mm and 6 mm, respectively, remained constant throughout the compression cycle. All batches' drug content was confirmed to be within the acceptable range i.e. 90–110 %. Low standard deviation values for the drug content suggested that the drug was distributed uniformly across all of the produced tablets (44). As a result, it was determined that the lornoxicam bilayer tablets were of high quality and met all approved tablet official compendia.

Nagesh *et al*. demonstrated similar outcomes while preparing lornoxicam bilayer tablets by utilizing excipients such as Kyron 314 and Polyox 303 (45). Our findings also corroborate with those of Pagar *et al*. who formulated lornoxicam sustained release tablets by utilizing ethyl cellulose and HPMC K100M as matrix formers (6).

Table 4. Micromeritic characteristics of various formulation batches of lornoxicam bilayer tablets

F. Code	Hardness (kg/cm^2)*	Friability*	Thickness (mm)*	Diameter (mm)*	Weight Variation (mg) **	Percent Drug Content *
F1	6.2±0.21	0.41±0.01	3.65±0.12	6.24±0.11	203±6.39	95.21±3.96
F2	6.8±0.20	0.78±0.13	3.68±0.23	6.43±0.09	207±5.48	98.09±2.89
F3	7.4±0.15	0.83±0.10	3.52±0.45	6.55±0.42	199±6.47	98.63±6.41
F4	6.1±0.36	0.73±0.34	3.45±0.09	6.14±0.07	201±9.87	96.13±4.59

F5	6.3±0.23	0.95±0.10	3.67±0.10	6.33±0.16	210±6.16	96.71±4.12
F6	6.9±0.39	0.67±0.13	3.70±0.22	6.48±0.52	212±5.87	99.03±3.87
F7	6.5±0.19	0.54±0.21	3.54±0.13	6.74±0.47	214±9.26	98.13±2.99
F8	6.9±0.20	0.62±0.22	3.63±0.41	6.82±0.34	206±9.36	99.01±6.29
F9	7.3±0.17	0.55±0.24	3.87±0.20	6.31±0.19	204±5.22	98.56±5.33

* values shown as mean ± SD, n=10 and ** values shown as mean ± SD, n=20

3.5. *In-vitro* Drug Dissolution

Several retarding polymers (carbopol 934P, HPMC K4M and guar gum) were used in varied concentrations (5 %, 6.25 % and 7.5 % w/w) to develop bilayer tablets. All of the tablets released more than 99 % of the drug. When solid matrices come into contact with aqueous environment, carbopol 934P polymer has a tendency of hydration, generating a thin gel that progressively erodes as the polymer dissolves (46). This is because the polymer can make strong hydrogen bonds with water upon contact. Fresh surfaces are exposed to the dissolving media as the polymer dissolves; however, the gel layer does not begin to restrict the polymer's diffusion until after it has formed (18). The carbopol 934P prepared tablets (F1, F2 and F3) released greater than 99 % of the medication in 4 h, 8 h and 12 h, respectively. More than 99 % of the medication was released after 4, 12 and 16 h, respectively, in the formulations F4, F5 and F6 using HPMC K4M as a retarding polymer. The findings also indicated that additional polymer at the surface caused a gel layer to instantly develop upon contact with the medium, preventing the first burst release of drug (47). This indicates that polymer dissolution has a significant role in controlling drug release for HPMC grades with lower viscosities and/or relatively water insoluble pharmaceuticals (48).

Maximum drug release was seen in 8 h, 16 h and 24 h, respectively, when guar gum was utilized in formulations F7, F8 and F9. Formulation F9 was chosen as an optimized formulation having the largest quantity of rate retarding polymer (guar gum) needed to control drug release for 24 h. The loading dosage of lornoxicam was seen to be released from the IR layer in all formulations during the first 15 minutes of the dissolving trial. Lornoxicam's continued release was monitored for 24 hours. Figure 3 shows the respective dissolution profiles for each formulation. All of the polymers utilized in this study were hydrophilic, but the polymers' tendency to swell explained the variation in percent drug release. The capacity to delay the release of the drug increased in proportion to the polymer's propensity to expand (49). Drug release percentages for all polymers reduced as polymer concentration rose. Guar gum was ranked higher than HPMC K4M and carbopol 934P in terms of the polymers' ability to retard drug release, which also indicates that guar gum had a higher swelling capacity than the other polymers (50).

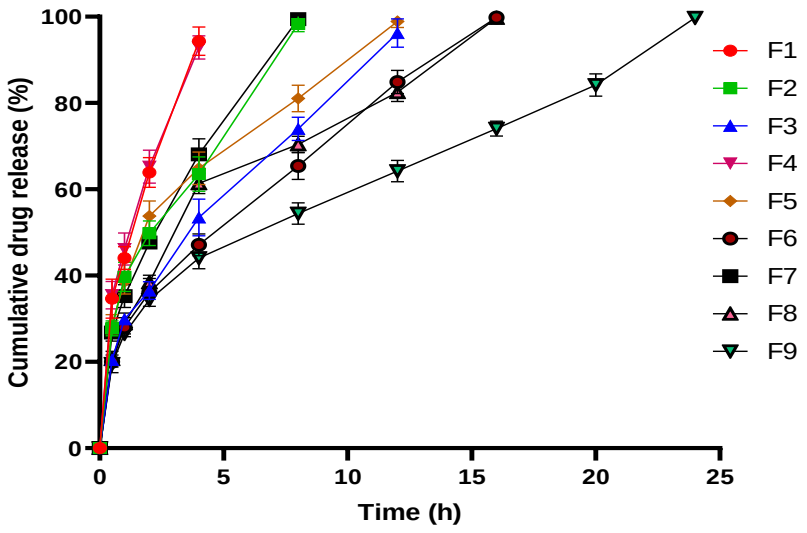

Figure 3. *In-vitro* drug release from bilayer tablet formulations (F1-F9)

3.6. *In-vitro* Drug Release Kinetics

All the formulations (F1- F9) of lornoxicam released the drug. according to zero order kinetics, which was demonstrated by greater 'r' values for the zero order as compared to the first order release. Table 5 displays the rate order values and the 'r' values, which varied from 0.9527 to 0.9942. The results of using the Higuchi model and the Hixon Crowell model to the dissolution data further supported the respective roles of drug diffusion and erosion to drug release. Diffusion usually plays a role in the release of the drug from a matrix tablet containing hydrophilic polymers (51). The 'r' values (0.9572 to 0.9943) were found to be greater than for erosion release, indicating that all formulations (F1 to F9) used a diffusion process. All of the formulations followed the Fickian diffusion process, as evidenced by the fact that the measured diffusion release's "n" value was smaller than 0.5 (52). All formulations from F1 to F9 used a Fickian diffusion mechanism with zero order release. Formulation F9, formulated using guar gum in a drug to polymer ratio of 1:7.5, achieved the desired targeted release over a 24-hour period, is regarded as the best formulation because it has many advantages over synthetic and semi-synthetic polymers like carbopol 934P and HPMC K4M due to the polymer's natural origin. Analysis of variance (ANOVA) revealed that there was no significant difference in drug amount for any of the formulations after 15 minutes, but after 24 hours, the optimized formulation (F9) was significantly different from the other formulations ($p < 0.05$).

Table 5. Fitting of *in-vitro* drug release data to various kinetic models

F. Codes	Zero order		First order		Higuchi model	Hixon Crowell model	Korsemeyer-Peppas model	
	r	K_0	r	K_1	R	r	n	r
F1	0.9527	13.24	0.8650	1.29	0.9932	0.9265	0.4344	0.9913
F2	0.9829	7.89	0.8123	0.45	0.9924	0.8962	0.3757	0.9924
F3	0.9685	7.75	0.8219	0.39	0.9859	0.9299	0.4451	0.9835
F4	0.9536	13.51	0.9034	1.05	0.9943	0.9613	0.4237	0.9683
F5	0.9798	7.89	0.9264	0.29	0.9816	0.8917	0.4136	0.9751
F6	0.9942	5.45	0.8713	0.13	0.9572	0.8166	0.3642	0.9472
F7	0.9847	14.15	0.8900	0.96	0.9897	0.9658	0.4158	0.9695
F8	0.9684	6.80	0.8415	0.21	0.9862	0.9077	0.4356	0.9741
F9	0.9893	4.26	0.8672	0.24	0.9850	0.9672	0.4018	0.9852

3.7. Model Independent Approach

3.7.1. Difference and Similarity Factors

In a model independent study, DD-Solver® software (Microsoft Excel add-in) calculated the difference ($f1$) and similarity ($f2$) factors by comparing formulations to the reference (F9) because of its favorable quality characteristics and release profile. Table 6 contains indexes.

The drug release pattern for formulation F8 was remarkably similar to the reference formulation (F9), with the lowest $f1$ value (7.57) and the highest $f2$ value (95.53). Most sustained release formulations compare dissolution characteristics using the similarity test ($f2$) (53).

Table 6. Difference ($f1$) and similarity ($f2$) factors of various formulation batches of lornoxicam bilayer tablets

Formulation Codes	$f1$	$f2$
F1	24.96	38.45
F2	25.68	33.98
F3	27.99	39.43
F4	14.59	49.92
F5	13.62	47.33
F6	12.99	50.13
F7	10.81	74.63
F8	7.57	95.53

3.8. Stability Studies

During the stability investigation, an optimized lornoxicam loaded bilayer tablet formulation (F9) having guar gum at a drug to polymer ratio of 1:7.5 was used. For this, the formulation was stored for six months at both ambient (25 °C, RH=65%) and accelerated (40 °C, RH=75 %) temperatures. The bilayer tablets were examined at pre-selected time intervals, 0, 1, 2, 3 and 6 months, for hardness, friability, dissolution, content uniformity and weight variation. Tables 7 and 8 demonstrate that tests conducted at the time intervals listed above revealed no significant changes in weight variation, hardness, friability, percent drug content and percent drug release. Similar outcomes were seen following storage at accelerated temperature, and tests done at various time intervals after storage at 0, 1, 2, 3 and 6 months, respectively found no significant changes in weight variation, hardness, drug content, friability, or drug release. It may be stated that lornoxicam bilayer tablets were stable, reliable and reproducible because there is no noticeable difference in the % drug release.

Table 7. Stability testing of optimized (F9) lornoxicam bilayer tablet formulation under ambient conditions (mean ± SD, n=3)

Time points (months)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Drug release (%)
0	7.3±0.22	0.55±0.32	204±0.41	98.56±2.91	99.74±4.36
1	6.9±0.45	0.54±0.02	201±1.54	97.45±3.46	98.47±2.33
2	6.7±1.35	0.68±0.57	199±1.63	95.23±2.31	98.23±4.56
3	6.5±1.40	0.73±0.69	188±1.22	94.51±1.33	97.47±8.42
6	6.2±3.62	0.79±0.03	202±1.61	92.74±4.12	96.10±6.33

Table 8. Stability testing of optimized (F9) lornoxicam bilayer tablet formulation under accelerated conditions (mean ± SD, n=3)

Time points (months)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Drug release (%)
0	7.3±0.22	0.55±0.32	204±0.41	98.56±2.91	99.74±4.36
1	6.8±0.21	0.63±0.01	202±2.58	96.66±4.12	98.56±3.21
2	6.7±2.65	0.68±0.48	200±2.64	95.01±3.22	97.89±4.67
3	6.6±1.52	0.77±0.96	199±1.97	93.32±1.45	96.64±5.26
6	6.4±0.67	0.80±0.47	200±2.01	91.17±2.64	95.22±2.34

4. Conclusion

The sole accessible dosage form of lornoxicam is an immediate release tablet, which does not meet the requirements for treating chronic pain. Neither a controlled release dosage form nor a bilayer dosage form is commercially available. This is accomplished by producing a biphasic release system, in the form of bilayer tablet characterized by an initial rapid release by the immediate release layer, followed by controlled drug release from CR layer of bilayer tablet from the optimized formulation (F9) composed of guar gum, a natural origin polymer utilized in a 1:7.5 ratio of drug and polymer. The guar gum being natural in origin convincingly delayed the release for 24 hours. The type and quantity of polymer in the formulation affects the release of the drug. Its biphasic release overcomes the main drawbacks of controlled release matrix tablets by offering initial burst release (i.e., loading dosage from the IR layer) within 15 min, followed by a sustained release from the controlled release layer over a predetermined length of time. It could be inferred that bilayer tablet approach may be effectively employed to treat chronic painful disorders.

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