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Original Research Article

Development and *in-vitro* Evaluation of Once Daily Tablet Dosage Form of Loxoprofen Sodium

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Abstract

Purpose: *To formulate and characterize once daily controlled release tablet of loxoprofen sodium.*
Methods: *Eudragit RS-100, hydroxylpropyl methylcellulose (HPMC) and pectin were used as release retarding polymers. All the formulations were prepared by direct compression method. Various pre-compression studies were carried out to determine Hausner's ratio, Carr's index, angle of repose, bulk density and tapped density Differential scanning calorimetry (DSC) studies and also post-compression studies to evaluate hardness, friability, weight variation, drug content, in-vitro drug release were conducted on the tablets. The drug release data were subjected to kinetic models, including zero order, first order, Hixon Crowell, Higuchi and Korsmeyer-Peppas.*
Results: *Compressibility index (7.6 ± 1.32 - 12.5 ± 1.43%), Hausner's ratio (1.08 ± 0.04 - 1.14 ± 0.03), angle of repose (27.78 ± 0.47 - 30.49 ± 0.46°), hardness (6.25 ± 0.27 - 7.21±0.21 kg/cm2), friability (0.14 ± 0.06 - 0.28 ± 0.0 %), weight variation (249.5 ± 2.09 - 251.35 ± 2.41 mg) and drug content (97.30 ± 0.28 - 103.70 ± 0.31 %) were within generally accepted limits for the pre-and post-compression formulations, respectively. The tablets having the maximum amount of among the three polymers tested as matrix materials, HPMC, represented by F3 tablets, exerted better sustained release properties after 12 h. Release pattern was more of Fickian diffusion followed by Higuchi mechanism.*
Conclusion: *The release of the loxoprofen sodium was optimized up to 12 h.*

Keywords: *Loxoprofen, Sustained release, hydroxypropyl methylcelluose, Pectin, Eudragit, Matrix tablets*

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INTRODUCTION

The oral route is the most convenient route for delivering drugs to systemic circulation. The reasons for preferable use of this route are ease of administration, patient acceptance and flexibility in formulation. Among various oral systems, sustained release delivery systems are designed to release the drug over an extended period of time for maintaining therapeutic drug concentration in the blood. Sustained release dosage forms have different advantages like reduction in dose size, frequency, toxic effects; cost of therapy and enhanced patient compliance [1].

Loxoprofen sodium belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs). It is a pro-drug that is converted into its metabolite after metabolism. Therapeutic activity depends upon its metabolites in systemic circulation. The drug has less gastric irritation and toxicity as compared to other NSAIDs because it is absorbed as free acid. It is a drug of choice in acute pain and rheumatoid etiologies. Daily recommended dose of loxoprofen sodium is 2 to 3 tablets [2,3].

Pectin, hydroxypropyl methylcellulose (HPMC) and Eudragit RS-100 are examples of polymers used in the preparation of sustained release formulations due to their release-controlling, 'burst' effect and release retarding properties respectively. These are biodegradable, biocompatible, easily available polymers that are safe for environment [4,5].

The objective of the present work was to formulate and evaluate matrix tablets of loxoprofen sodium using some polymers in varying concentrations.

EXPERIMENTAL

Materials

Loxoprofen sodium was received as a generous gift from Hilton Pharmaceuticals, Karachi, Pakistan. Eudragit RS-100, HPMC and Pectin polymers were obtained from Neutro Pharmaceuticals, Islamabad, Pakistan. Poly vinyl pyrollidone (PVP), Micro-crystalline cellulose (MCC), avecil, sodium hydroxide (NaOH) and Potassium dihydrogen phosphate were purchased from E-Merck Germany. All chemicals used were of analytical grade.

Computation of sustained release dose component

Total dose (D_t) of the drug for sustained release can be calculated with the help of prompt dose, D_n, and the sustaining dose D_s, i.e.,

$D_t = D_n + D_s$ …….. (1)

When sustained dose (D_s) at time (t) is equal to D_n, Kt the total dose will be low dose is 30 mg

$D_t = D_n + D_nKt$ …… (2)

$D_t = D_n (1 + D_nKt)$ …….. (3)

$D_t = D_n (1+Kt)$ …….. (4)

$D_t = D_n (1 + 0.693 \times T_d/t_{1/2})$ …….. (5)

For loxoprofen sodium, assuming half-life 2 h and D_n is 30 mg. Therefore for 12 hours, the sustained release (T_d), the total dose of drug (D_t) will be 154.74 mg (quantity used was 150 mg/tablet).

Preparation of tablets

Drug and excipients were weighed accurately and individually on electronic weighing balance (Shimadzu, Japan). All ingredients shown in Table 1 were triturated using pestle and mortar for particle size reduction with subsequent mixing in polythene bags for 10 - 15 min. The powder blend was sieved through sieve # 60 having diameter of 250 µm to bring uniformity of contents. Powder blend was compressed into matrix tablets using single punch rotary machine (AR-400 Erweka, Germany) [6].

Table 1: Composition of Loxoprofen Sodium matrix tablets

Formulation	Loxoprofen sodium %	HPMC %	Eudragit %	Pectin %	MCC %
F1	60	10	-	-	22
F2	60	20	-	-	12
F3	60	30	-	-	2
F4	60	-	10	-	22
F5	60	-	20	-	12
F6	60	-	30	-	2
F7	60	-	-	10	22
F8	60	-	-	20	12
F9	60	-	-	30	2

PVP (6 %), Avicel (1 %) and Mg-Sterate (1 %) were used in each formulation

Pre-compression studies

Angle of repose

Power blend of each formulation was evaluated for angle of repose by funnel technique using Eq 6 [7].

Tan ø = h/r …… (6)

where Ɵ = angle of repose, h = height of blend cone, r = radius of base of cone

Angle of repose < 30 ° indicates free flowing powder.

Bulk density

Powder mixture was poured in graduated volume measuring cylinder and bulk volume (Vb) was visually noted. After this powder mass (M) was measured on electronic weighing balance. Bulk density (ρb) was calculated by using equation 7 [7]:

Bulk density (ρb) = M/Vb …… (7)

Tapped density

Measuring cylinder containing known mass (M) of powder contents was tapped for specified number of tapings. Tapped volume (Vt) was noted. Tapped density was calculated by using equation 8 [7]:

Tapped density (ρt) = M/Vt …… (8)

Carr's compressibility index

Free flowing property of powder was confirmed from compressibility index (I). It was calculated by using formula 9 [8]:

Compressibility index (I) = [(Vt – Vb)/Vb] × 100 ….. (9)

Where Vb and Vt are bulk and tapped volume respectively. Carr's index between 13 -19 % confirms good flow and if it is more than 21 % it presents poor flow of powder.

Hausner ratio

It is another parameter for powder flow determination. It is a ratio between two densities i.e. tapped (ρt) and bulk (ρb) densities. It uses equation 10 for its presentation:

Hausner ratio = ρt/ρb …… (10)

Value less than 1.25 is an indicator of good flow of powder while more than 1.25 proves poor flow [9].

Post-compression studies

Twenty tablets were chosen from each formulation and weighed on electronic weighing balance (Shimadzu, AUW220D Japan). Mean weight was calculated and range was established by adding and subtracting ± 5 mg in average weight according to pharmacopoeial limits [9]. The friability of tablets was determined using a Roche friabilator (Pharma Test, Germany). The friabilator was operated at 25 rpm for 4 min. Hardness, thickness and diameters were calculated by digital hardness tester (Pharma Test Germany).

Drug content uniformity assessment

Twenty tablets from each formulation were taken and crushed into powder in pestle and mortar. Amount of the powder equivalent to 60 mg was taken and poured into methanol-water mixture (40:60) for extraction purpose. The extract was diluted up to 900 ml in 1000 ml volumetric flask with extraction mixture of methanol and water (this was the first dilution). The sample was taken, diluted and filtered. Absorbance of the filtered sample was measured at 220 nm using UV-Visible spectrophotometer (Pharma Spec 1700 Shimadzu Japan). Absorbance of pure drug was also calculated as done for reference, and drug release was calculated as shown in Eq 11 [10].

Drug release (%) = (As/Af) x 100 …….. (11)

where As and Af are the absorbance of the sample and reference, respectively.

***In-vitro* drug release studies and kinetic modeling**

USP apparatus –II (Watson Marlo, Stockholm, Sweden), Paddle method was used for dissolution studies. Phosphate buffer of pH 6.8 was used as dissolution medium. All release studies were performed at ambient conditions i.e. 37 ± 2 °C. The speed of the apparatus was kept 50 rpm. Aliquot of 5 ml of the sample was taken at regular and predetermined time intervals and was replaced by fresh phosphate buffer media. Samples were filtered and diluted and their absorbance was noted by using UV- Visible spectrophotometer at 220 nm [3].

Different kinetic models were applied to evaluate the different release pattern of the drug from the matrix tablets. Zero order kinetics ($Q_t = k_o t$), first

order kinetics ($\log Q_t = \log Q_o - k_1 t$), Higuchi model ($Qt = k_H t^{1/2}$) Hixon-Crowell cube root model ($Q_o^{1/3} - Q_1^{1/3} = k_{CH} t$) and Korsmeyer-Peppas model ($M_t/M_\infty = k_{KF} t^n$) were applied to the data. These models were utilized for the prediction of drug release behavior and release kinetics [11].

DSC studies

The DSC studies were conducted on (SDT, Q600 TA USA) mixture of drug and the different polymers were heated in sealed Aluminum pan at a flow rate of 10 °C/min from 0 to 300 °C. Nitrogen flow was kept at 40 ml/min. Sample (4 – 8 mg) was kept in Aluminum pan. Samples were evaluated in triplicate to check reproducibility of results [12].

Similarity index

The similarity and difference factor of dissolution profiles of reference and sample was determined by model independent method (Eq 3).

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad \text{..... (3)}$$

where f_2 is the similarity factor, R_t is amount of reference drug at different time interval and T_t are the percent test drug dissolved at various time [13].

Statistical analysis

Drug release data was subjected to statistical analysis using one-way ANOVA (Dunnet test) at 95 % confidence interval with the aid of Graph Pad Prism (v5).

RESULTS

Pre-compression characteristics

The results of the pre-compression studies are presented in Table 2, and were within generally and/or official limits.

Thermal characteristics

Results of the DSC studies for the various powder blends are presented in Figure 1.

Table 2: Pre-compression results for powder blend (mean ± SD, n = 5)

Formulation	Bulk density (g/mL)	Tap density (g/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose (°)
F1	0.35 ± 0.01	0.40 ± 0.02	12.5 ± 1.43	1.14 ± 0.01	29.61 ± 0.51
F2	0.36 ± 0.02	0.41 ± 0.01	12.1 ± 1.37	1.13 ± 0.02	28.42 ± 0.44
F3	0.36 ± 0.01	0.39 ± 0.00	07.6 ± 1.32	1.08 ± 0.04	28.62 ± 0.48
F4	0.34 ± 0.00	0.39 ± 0.01	12.8 ± 1.38	1.14 ± 0.03	29.59 ± 0.52
F5	0.37 ± 0.00	0.41 ± 0.01	09.8 ± 1.47	1.10 ± 0.01	30.12 ± 0.49
F6	0.35 ± 0.01	0.39 ± 0.00	10.2 ± 1.41	1.11 ± 0.04	27.91 ± 0.53
F7	0.33 ± 0.02	0.37 ± 0.01	10.8 ± 1.48	1.12 ± 0.02	27.78 ± 0.47
F8	0.34 ± 0.02	0.38 ± 0.01	10.5 ± 1.33	1.11 ± 0.03	28.47 ± 0.54
F9	0.36 ± 0.01	0.40 ± 0.02	10.0 ± 1.54	1.11 ± 0.03	30.49 ± 0.46

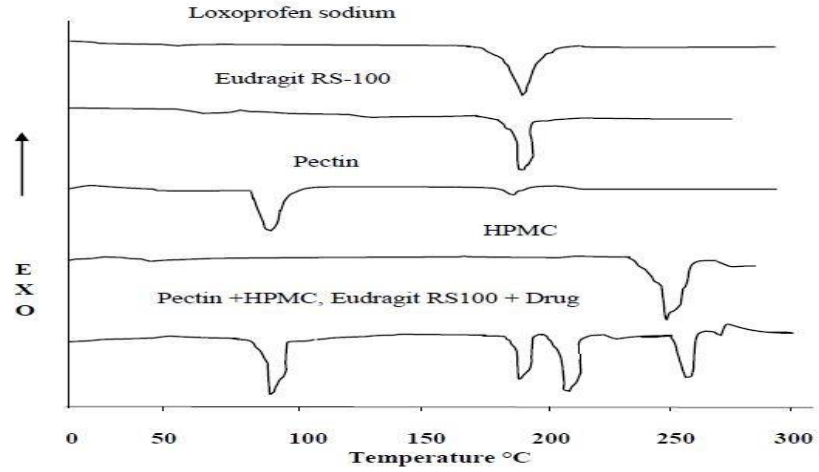

Figure 1: DSC thermograms of powder blend

Post-compression properties

The tablet properties of the formulations, shown in Table 3, are within the acceptance criteria of British Pharmacopoeia.

In-vitro drug release and kinetics

Figure 1 described the percentage drug release from the compressed tablets of loxoprofen sodium. It was observed that formulations F1, F4 and F7 showed more than 91 % drug release in 12 h due to lesser concentrations of the polymers i.e., HPMC, Eudragit and pectin, respectively. In the case of model dependent approaches all formulations followed zero order and Higuchi model. Results of zero, first, Higuchi, Hixson-Crowell are shown in Table 4. F3 formulation had maximum concentration of HPMC was selected as an optimized formulation due to its pre and post compressional results. Similarly, F6 among the Eudragit containing formulations were compared with formulations F4 and F5 and found more similar with F5. In case of pectin containing formulations, F9 was the best formulation and showed more similar results with F8.

F3 released 89 % drug during 12 hr dissolution studies and compared with other formulations considering as reference formulation. Difference factor (f_1) was found to be less than 10 and similarity factor (f_2) was more than 60 % for F5, F6, F8 and F9. F8 was most similar of all these formulation with f_1 = 3.946 and f_2 = 80.54.

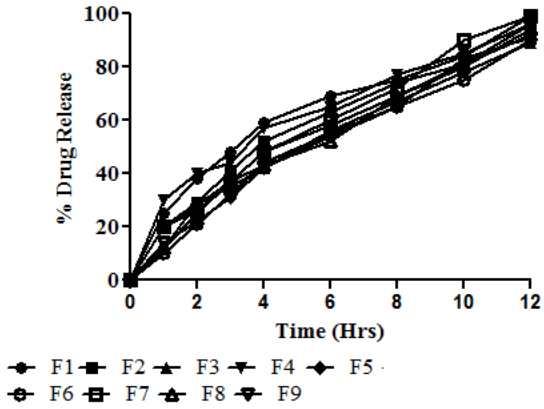

Figure 2: Drug release from matrix tablets of loxoprofen sodium prepared with HPMC (F1 to F3), Eudragit (F4 to F5) and Pectin (F6 to F9)

DISCUSSION

All the pre-compression studies i.e. angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio all were within the pharmacopoeial limits indicating degree of fineness and free flowing characteristics of the powder blend. Bulk density was observed from 0.34 to 0.37 g/dl, tapped density of all the formulations was between 0.37 to 0.41 gm/dl, compressibility index was less than 20 and considered excellent for flow properties.

Table 3: Post-compression characteristics of loxoprofen sodium matrix tablets (mean ± SD)

Formulation	Thickness (mm, n=5)	Hardness (kg, n=10)	Friability (%, n=10)	Weight variation (mg, n=10)	Drug content (%, n=20)
F1	4.01 ± 0.013	6.53 ± 0.23	0.17 ± 0.06	250.95 ± 1.21	98.8 ± 0.15
F2	4.02 ± 0.010	6.68 ± 0.26	0.21 ± 0.07	251.05 ± 2.14	99.9 ± 0.22
F3	4.01 ± 0.014	7.21 ± 0.21	0.14 ± 0.06	250.85 ± 1.54	101.07 ± 0.19
F4	4.01 ± 0.013	6.47 ± 0.28	0.27 ± 0.05	250.45 ± 2.17	103.7 ± 0.31
F5	4.02 ± 0.011	6.62 ± 0.19	0.19 ± 0.08	250.85 ± 2.32	100.9 ± 0.26
F6	4.03 ± 0.012	5.19 ± 0.17	0.18 ± 0.09	249.5 ± 2.09	99.7 ± 0.32
F7	4.02 ± 0.010	6.25 ± 0.27	0.26 ± 0.08	251.35 ± 2.41	97.3 ± 0.28
F8	4.03 ± 0.012	6.65 ± 0.21	0.28 ± 0.07	250.75 ± 2.15	103.1 ± 0.16
F9	4.01 ± 0.011	6.98 ± 0.15	0.18 ± 0.06	250.05 ± 1.99	101.3 ± 0.36

Table 4: Kinetics data (correlation coefficient, R^2) for matrix tablets of loxoprofen sodium

Formulation	Zero order	First order	Hixon Crowell	Higuchi
F1	0.9083	0.7840	0.8751	0.9925
F2	0.9491	0.8943	0.9134	0.9884
F3	0.9684	0.9671	0.8895	0.9781
F4	0.9124	0.9214	0.9493	0.9950
F5	0.9630	0.9494	0.9431	0.9864
F6	0.9632	0.9423	0.8863	0.9639
F7	0.9675	0.8191	0.9534	0.9724
F8	0.9585	0.9069	0.9083	0.9665
F9	0.9553	0.9478	0.9419	0.9609

Angle of repose was more than 25 and also showed excellent characteristics. No drug-polymer interaction was detected by DSC studies. In case of loxoprofen sodium, initially flat curve was obtained but when it came into melting range, sharp exothermic peak was observed that showed its presence as shown in (Figure 1). Similarly, in case of HPMC, pectin and eudragit RS-100 DSC studies were done alone and in combination with drug. All thermograms have not exhibited any change when drug were tested alone or in combination with polymers as there was no shift of peaks with temperature.

In case of post compressional studies the hardness (Kg/cm^2) of the prepared matrix tablets were within the range of 5 to 7 kg. F3 showed maximum hardness value due to the minimum concentration of microcrystalline sodium. Acceptable limits of hardness of all the formulations indicated stability of tablets during storage, transport and handling. Friability of all the formulations (F1-F9) was less than one percent; less value of F3 was observed which may be due to the crystalline nature of the HPMC. Percentage content uniformity of all formulations was within the range of 98 to 103 %. Phosphate buffer of pH 6.8 were selected for dissolution studies for 12 h. All three polymers showed good retardation of the drug up-to 12 h. Due to presence of carboxylic acid group in HPMC maximum controlled was observed at its higher concentration which may be due to complex formulation of the HPMC molecules. Swelling nature of HPMC at higher pH also favors the sustained release behavior of F3 formulations [14]. Decrease in the release of the drug was greatly associated with the concentration of the polymers because increase in the concentrations of the polymers increases the carboxylic acid concentration that may be made more complex mass and decreased the release of the drug. Less polymeric content allow greater penetration of fluid which results in greater release of the drug [15]. Initially, there was less hydration of the polymer that can cause greater initial release but when the polymer gets hydrated it swells and restricts the drug release [16].

Dissolution results were compared with model dependent approaches and it was observed that values of correlations for zero order were in the range of 0.9083 to 0.9675, for first order correlations values were in between 0.7840 to 0.9494. Results revealed that zero order was the best description of Loxoprofen tablets which have time dependent properties. In case of Higuchi model r^2 values were in range of 0.9639 to 0.9925 which was may be due to diffusion based release of the loxoprofen sodium from the compressed formulations. Previous studies have shown that formulations prepared with different concentration of HPMC, eudragit RS100 and pectin followed the Higuchi model and drug release pattern was diffusion controlled [17,18]. HPMC was also used by Hanif *et al* in formulating the intermediate release tablets of Nimesulide 100 mg and found Higuchi dependent release [19]. Similar observations were made in the current studies. When the data was analyzed by Korsmeyer Peppas model, it was observed that as the value of $n < 0.49$ in formulations F1 – F8 they followed Fick's diffusion (case-1 transport) mechanism and F9 followed non-Fickian diffusion pattern because the $n > 0.49$ [20] but overall drug release was governed by diffusion process. F8 was more comparable with reference formulation with f_1 (3.946) and f_2 (80.54) values.

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