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Research Article

COLON SPECIFIC CONTROLLED RELEASE MATRIX TABLETS OF FLURBIPROFEN: DEVELOPMENT AND CHARACTERIZATION

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ABSTRACT

Development of oral colon-specific drug delivery systems is for treatment of local diseases associated with colon and for potential delivery of proteins and peptides. The aim of present study is to formulate hydroxypropyl methylcellulose matrix tablets of flurbiprofen for colon delivery based on controlled release mechanism. Flurbiprofen matrix tablets were prepared by using direct compression method and characterized for weight variation, hardness, friability and assay. In-vitro drug release behavior was studied in different pH media. The optimized formulation showed negligible drug release in the initial lag period (5 hrs) followed by controlled release for up to 24 hrs which clearly indicates that the drug is delivered in colon. Differential scanning calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) studies were carried out to understand the drug-polymer compatibility and revealed that there was no possible interaction between them. Thus developed controlled release matrix tablets may be suitable to localize the flurbiprofen in colon to treat inflammation.

Keywords:

INTRODUCTION

Oral administration of different dosage forms is the most commonly used method due to greater flexibility in design of dosage form and high patient acceptance, but the gastrointestinal tract presents several formidable barriers to drug delivery[1]. In oral colon-specific drug delivery system, colon has a large amount of lymphoma tissue (facilitates direct absorption in to the blood), negligible brush boarder membrane activity, and much less pancreatic enzymatic activity as compared with the small intestine[2]. Colon-specific drug delivery by oral route has gained increased importance from last two decades, to treat local diseases associated with colon and for potential delivery of proteins and peptides[3]. The traditional approaches for colon targeting are prodrug formulation, pH-sensitive drug delivery, time-dependent systems and microbial degradation methods to formulate different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes[4].

Formulation of matrix tablets is inexpensive method and easy to manufacture with conventional tableting facilities and less processing variables[5]. To achieve colon delivery, preparation of matrix tablets is simple method when compared to other methods like tablets coated with different polymers and chemical conjugation of drug. Hydroxypropyl methylcellulose (HPMC) is a synthetic retardant that is widely used as an extended release agent in the pharmaceutical industry[6]. It shows good swelling and gel-forming properties and its controlled release mechanism is applied to formulate FLB-HPMC colon specific matrix tablets.

Flurbiprofen (FLB), a non steroidal anti-inflammatory drug was efficient to treat inflammation and pain related to colon. FLB has a plasma half-life of 3–6 h and its administration rate is frequent due to its short half-life[7]. The frequent intake of NSAIDS like FLB leads to gastric ulceration, bleeding and other gastric complications[8]. Hence the development of colonic delivery of FLB is to reduce its side effects and achieve high local drug concentration at the afflicted site in the colon, hence optimal therapeutic effectiveness and good patient compliance[9]. The objective of the present study is to formulate FLB-HPMC matrix tablets that could provide a controlled delivery of FLB to the colonic region for the treatment of inflammation related to colon.

MATERIALS AND METHODS

Materials

Flurbiprofen was gift sample from FDC Limited, Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4M), MCC (Avicel PH 101) was gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Methods

Preparation of Matrix Tablets

Matrix tablets using HPMC was prepared by direct compression method. FLB, HPMC and excipients other than glidant and lubricant were accurately weighed, passed through 60-mesh sieve and mixed in a poly bag for 5-10 minutes. The obtained blend was lubricated with talc and magnesium stearate for another 5 minutes and the resultant mixture was directly compressed into tablets with 9 mm round flat punches using 16-station rotary tabletting machine (Cadmach, Ahmedabad, India). The final weight of the tablet was adjusted to 300 mg. The compositions of matrix tablets are given in Table 1.

Table 1.composition of flb-hpmc matrix tablets

Formulation	Viscosity grade	HPMC Content (% 0f Drug)
A1	K4M	20
A2	K4M	40
A3	K4M	60
A4	K4M	80
A5	K4M	100
B1	E50	40
B2	K100	40
B3	K4M	40
B4	K15M	40
B5	K100M	40

Powder characterization

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped) and compressibility index. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$Tan\ \theta = h/r \quad [1]$$

In which, θ is angle of repose, h is height of the cone and r is radius of the cone base. Angle of repose less than 30^0 shows the free flowing of the material. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas:

$$Carr's\ Index = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100 \quad [2]$$

In which, ρ_b is bulk density and ρ_{tap} is tapped density.

Evaluation of Physical Parameters

The designed formulations were studied for their physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an Electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India) for 4 min at 25 rpm.

Determination of drug content

For estimation of drug content, ten tablets were crushed, and the aliquot of powder equivalent to 100 mg of drug was extracted in methanol/phosphate buffer pH 7.4 (1:9), suitably diluted using phosphate buffer pH 7.4 and determined by UV-Visible spectrophotometer (Systronics 2202, Ahmedabad, India) at 247nm. The drug concentration was calculated from the calibration curve.

In Vitro Dissolution Study

The release of FLB from matrix tablets was carried out using USP XXIV Type II (paddle method) dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 50 rpm, and a temperature of 37±0.5°C. In order to simulate the gastrointestinal transit conditions, the tablets were subjected to different dissolution media. Initially, the drug release was carried out for 2 hrs in 0.1 N HCl, 2 hrs in buffer pH 5.5 and finally in phosphate buffer pH 7.4 up to 24 hrs. The samples were filtered, by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed spectrophotometrically at 247 nm.

In Vitro Release Kinetics

Cumulative percentage drug release was plotted as a function of time. The data was fitted to zero order, first order and Higuchi models to explain the pattern and the release mechanism from the formulations[10]. Koresmeyer–Peppas model is one of the mathematical expressions, used to understand the mechanism of drug release from these formulations[11]. The Koresmeyer–Peppas equation is as follows;

$$M_t / M_\alpha = Kt^n \quad [3]$$

In which, M_t / M_α is the fractional amount of drug released at time t, K is a kinetic rate constant, and n is the diffusional exponent that characterizes the mechanism of drug release. The values of the coefficient were calculated using linear regression analysis between log M_t / M_α and log t data obtained from drug release studies. The value of n was obtained as slope of the regression equation, and K was calculated as antilog of the intercept value[12].

If the value of n for a cylinder is <0.45 it suggests the Fickian release (diffusion controlled), for n is >0.45 and <0.89 it is non-Fickian release (diffusion and polymer relaxation), 0.89 for case II release (only relaxation and swelling), and for >0.89 it suggests super case II release (relaxation and erosion) for swellable systems. For cylindrical systems like tablets, the n values of 0.45 and 0.89 represent pure diffusion or erosion controlled release, respectively[13, 14]. The mean dissolution time (MDT) is defined as the sum of different release fraction periods (release areas) during dissolution studies divided by the initial loading dose and is calculated by the following equation[15]:

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad [4]$$

Where i is the dissolution sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and i-1, and ΔM is the amount of drug dissolved between i and i-1.

Drug- Polymer Interaction Studies

To study the possible interaction between FLB and HPMC, DSC study was carried out on pure dug and optimized formulation (A2) and the thermograms were obtained using DSC (Perkin-Elmer, Shelton, U.S). The analyses were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrrolytic effects at a standard heating rate of 15ºC/minute over a temperature range of 50ºC - 350ºC. The infrared spectra of FLB and optimized formulation (A2) recorded between 400 to 4000 cm^{-1} on FTIR to detect the drug-excipient interactions. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (Perkin Elmer FT-IR, Perkin Elmer Inst. USA). The resultant spectra were compared for any possible changes in the peaks of the spectra.

RESULTS AND DISCUSSION

Powder characterization

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), compressibility index and their values were shown in Table 1.The apparent and tapped bulk density values ranged from 0.312 to 0.365 and 0.384 to 0.469 respectively. The results of angle of repose and % Carr's index ranged from 27.12±1.13 to 32.12±1.84 and 18.75 to 22.17 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture[16].

Evaluation of Physical Parameters

The physical properties of FLB-HPMC matrix tablets are given in Table 2. In weight variation test, the pharmacopoeial limit for the tablets of not more than 5% of the average weight. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per official requirements (Indian Pharmacopoeia, 1996). The hardness of the tablets was found to be in the range of 5.0-5.6 kg/cm^2. Another measure of tablets strength is friability. Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. The tablets were found to contain 95.8±1.74 to103.2±0.35% of the labeled amount indicating uniformity of drug content. The physical properties like weight variation, thickness, hardness and friability of all formulations were complied with pharmacopoeial standards, so all the tablets were with acceptable physical characteristics.

Table 2: characterization of powder mixture

Formulation	Angle of Repose*	Bulk density	Tapped Bulk density	% Carr's Index
A1	29.12±1.24	0.321	0.402	20.149
A2	31.23±1.32	0.332	0.412	19.417
A3	30.35±1.35	0.312	0.386	19.170
A4	29.56±1.46	0.323	0.398	18.844
A5	27.12±1.13	0.325	0.405	19.753
B1	30.35±1.35	0.365	0.469	22.174
B2	32.12±1.84	0.344	0.436	21.100
B3	30.65±1.35	0.332	0.412	19.417
B4	29.56±1.86	0.315	0.402	21.641
B5	32.12±1.23	0.312	0.384	18.750

In Vitro Dissolution Study

The cumulative mean percent of FLB released from matrix tablets containing varying amounts of HPMC K4M (from A2 to A5) was found to vary from 19.16±1.02 to10.28 ±2.86 after 5 h of testing in simulated gastric and intestinal fluids and the percent drug release was increased gradually after 5 hrs and it was found to be 101.6±2.14 to 48.62±1.36 in 24 hrs (Figure 1). This indicates that a minimal amount of the drug (<20%) is released in the physiological environment of stomach and small intestine and maximum drug release (>80%) was observed in colonic region. From the above formulations, the optimized formula A2 showed the 19% drug release in the initial lag period (5 hrs) followed by 101% drug release for 24 hrs in a controlled manner. Thus the formulation A2 was considered better among other formulations to produce colon specific drug delivery of FLB. The drug delivery systems targeted to the colon should not only protect the drug from being released in the

physiological environment of stomach and small intestine, but also release the drug in colon[17].

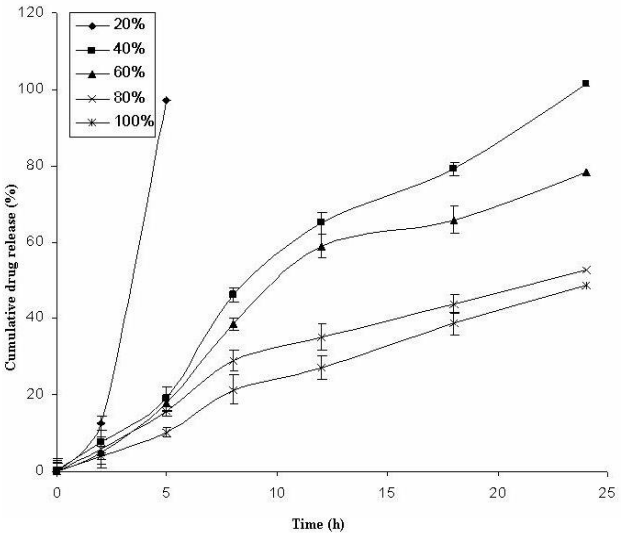

Figure 1: Release profile of Flurbiprofen from matrix tables prepared by using different percentages of HPMC K4M

Figure 2 shows the release profiles of FLB from the HPMC matrix tablets of different viscosity grades. Formulations with HPMC of high viscosity formed swollen gel matrix with substantial integrity and the drug release was in a controlled manner which could be due to the better control of water and drug diffusion. In comparison with low viscosity grades of HPMC, the tablet lacks strength and was eroded quickly after swelling. In the present investigation, HPMC K4M in comparison to HPMC K15M and 100M showed negligible drug release in the initial lag period and followed by controlled release for 24 hrs, which is normal residence time of solid dosage form in the colon [18, 19].

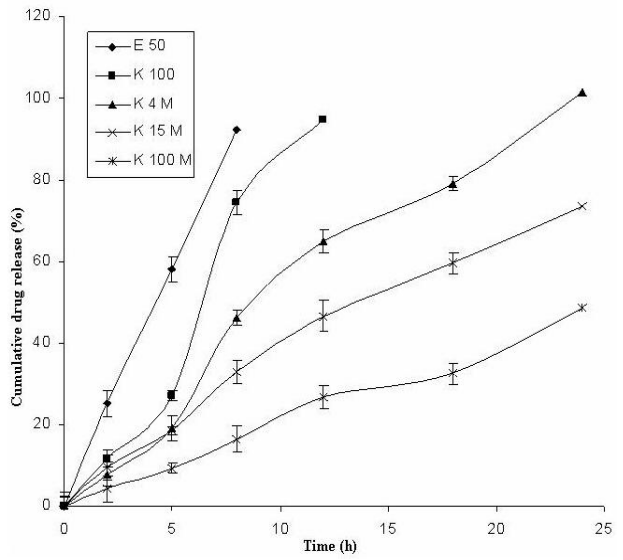

Figure 2 : Release profile of Flurbiprofen from matrix tables prepared by using different viscosity grades of HPMC

The drug release kinetics studies revealed high correlation coefficient values for zero order than first order indicating that the drug release from matrix tablets followed zero order profile. The high regression value of Higuchi model ensured that the release of drug from matrix tablets followed diffusion mechanism. The values of K, and r^2 (correlation coefficient of the regression analysis) of zero order, first order and Higuchi models of designed formulations are given in Table 4.

TABLE 3 : PHYSICAL PROPERTIES OF FLB-HPMC MATRIX TABLETS

Formulation	Weight variation* (mg)	Hardness** (Kg/cm²)	Friability (%)	Drug content *** (%)
A1	299.1 ± 4.51	5.0±0.61	0.40	99.2±1.76
A2	299.15 ± 2.99	5.2±0.35	0.33	95.9±0.61
A3	299.2 ± 3.91	5.1±0.42	0.45	96.6±0.28
A4	299.0 ± 3.72	5.0±0.25	0.38	95.8±1.74
A5	299.4 ± 5.09	5.4±0.64	0.54	103.2±0.35
B1	300.35 ± 3.16	5.0±0.86	0.58	97.2±0.28
B2	300.47± 2.83	5.6±0.52	0.26	99.9±0.70
B3	300.85± 2.91	5.5±0.62	0.32	98.0±0.76
B4	300.2 ± 2.48	5.3±0.28	0.48	98.2±0.70
B5	300.25± 3.34	5.2±0.46	0.46	97.1±0.70

* All values represent mean ± standard deviation, n=20
** All values represent mean ± standard deviation, n=6
*** All values represent mean ± standard deviation, n=3

TABLE 4: RELEASE KINETICS OF FLB-HPMC MATRIX TABLETS

Formulation	Zero order		First order		Higuchi model	
	K_0 (mg/hr)	r^2	K_1 (hr^{-1})	r^2	K (mg/$hr^{-1/2}$)	r^2
A1	-	-	-	-	-	-
A2	4.339	0.992	0.069	0.722	21.79	0.923
A3	3.437	0.937	0.068	0.701	17.78	0.931
A4	2.191	0.949	0.058	0.673	11.45	0.964
A5	2.057	0.988	0.061	0.761	10.38	0.935
B1	11.47	0.999	0.220	0.759	31.61	0.930
B2	8.414	0.961	0.150	0.810	27.96	0.841
B3	4.339	0.992	0.069	0.722	21.79	0.923
B4	3.068	0.981	0.067	0.669	15.71	0.955
B5	1.973	0.989	0.059	0.789	9.80	0.906

The n values calculated for different formulations were found in the range of 1.151to 1.419, indicating a supercase-II transport. The MDT was higher for formulations with high viscosity HPMC grades compared to low viscosity grades of HPMC, indicating better controlled release. The values of K, n, r^2, and MDT from the dissolution data of designed formulations are given in Table 5.

Table 5 : release kinetics of flb-hpmc matrix tablets

Formulation	n	K	r^2	MDT (hrs)
A1	-	-	-	-
A2	1.362	1.795	0.948	10.78
A3	1.419	1.738	0.944	9.62
A4	1.179	1.749	0.932	9.58
A5	1.184	1.389	0.973	11.04
B1	2.021	2.094	0.848	3.93
B2	1.741	1.702	0.931	6.08
B3	1.362	1.794	0.948	10.78
B4	1.224	2.051	0.909	10.35
B5	1.151	1.374	0.976	12.27

Drug - Polymer Interaction Studies

DSC studies were performed to understand the nature of the drug in the formulated tablets. Thermograms of the pure drug and optimized formulation (A2) are shown in Figure 3. A sharp

endothermic peak corresponding to the melting point of FLB was found at 116°C. An endothermic peak corresponding to the melting point of FLB in optimized formulation was observed at 115.4°C. Thermogram of the optimized formulation did not show any significant shift in the endothermic peak, indicating that there was no physical change in drug in the HPMC matrices.

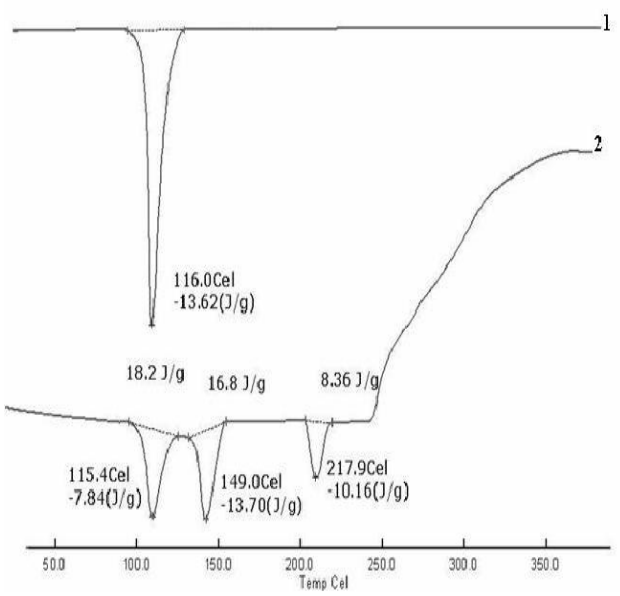

Figure 3: DSC thermograms of 1) Flurbiprofen 2) Optimized formulation (FLB-HPMC matrix tablet)

The IR spectral analysis of FLB alone showed that the principal peaks were observed at wave numbers of 1701.22, 1415.75, 1217.06, 923.9, 765.7and 696.23 cm^{-1}. In the IR spectra of the optimized formulation (A2) were 1701.22, 1419.61, 1217.06, 925.83, 765.7and 696.23 cm^{-1} wave numbers were observed (Figure 4). However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. These results suggest that there is no interaction between the drug and polymers used in the present study.

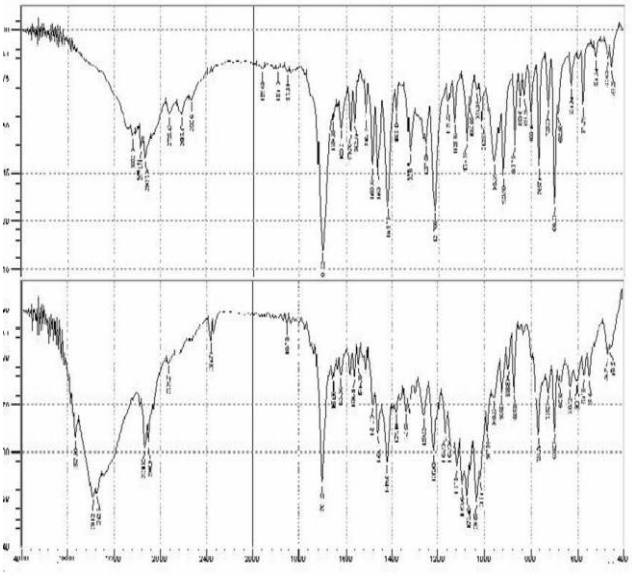

Figure 4 : Fourier transform infrared spectra of 1) Flurbiprofen 2) Optimized formulation (FLB-HPMC matrix tablet)

CONCLUSION

An attempt was made to develop matrix type colon drug delivery system of FLB with acceptable physical characteristics. HPMC matrix tablets are capable of protecting the drug from being released in the upper region of GI system, i.e. stomach and small intestine. Based on in vitro drug release studies, A2 formulation showed the significant level of drug release in the colon. The drug release from above formulation followed zero order profile and the mechanism of drug release from matrix tablets followed supercase II transport. DSC and FTIR spectral studies showed that there is no interaction between the drug and excipients. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans. In conclusion, development of HPMC matrix tablets is a good approach to localize the flurbiprofen in colon to treat inflammation.

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