



Effect of time-dependent polymer on the dissolution rate of flurbiprofen: Formulation and evaluation of colon-specific matrix tablets

Sateesh Kumar Vemula*, Selamu Kebamo, Balisa Mosisa and Biniam Paulos

Department of Pharmacy, College of Medical and Health Sciences, Wollega University, Post Box No: 395, Nekemte, Ethiopia

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ABSTRACT

An effort was made in the present study to prepare flurbiprofen matrix tablets to improve the therapeutic efficacy by increasing therapeutic drug concentrations in lower intestine i.e., site-specific release to colon. The current experiment was aimed to formulate matrix tablets using sodium alginate and HPMC K15M by direct compression method to study the effect of polymer on colon-specific drug release. The prepared matrix tablets were characterized for physical evaluations to indicate tablet uniformity and mechanical integrity. From the evaluations, HPMC matrices were found to be superior in tablet integrity and mechanical strength in comparison to sodium alginate matrices. *In vitro* drug release studies were performed by using USP XXIV Type II dissolution apparatus filled with simulated gastrointestinal fluids. From the *in vitro* dissolution studies, formulation F5 containing 50 mg of HPMC K 15M showed $11.62 \pm 0.78\%$ drug release in 5 h and it was gradually increased to $98.83 \pm 1.02\%$ in 24 h that indicates retardation of drug release in upper gastrointestinal tract and significant amount of drug release was observed in the colon. The accelerated stability studies proved the stability of drug in HPMC matrices. Hence, the development of HPMC K15M matrix tablets was suitable to achieve the colon-specific release of flurbiprofen. Further the efficacy of prepared matrix tablets has to be assessed by pharmacokinetic studies.

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1. Introduction

Flurbiprofen (FLB) is a drug that belongs to non steroidal anti-inflammatory drugs (NSAIDs) used to treat colonic pain and inflammation. Regular administration of NSAIDs like FLB causes the gastric ulceration, bleeding and other gastric problems [1]. Thus the formulation of FLB colon-specific drug delivery is to minimize its adverse symptoms and produce high drug concentrations in the colon and to gain optimal therapeutic effectiveness as well as good patient compliance

[2]. The current study is intended to develop the FLB matrix tablets for colon specific delivery to minimize the drug release in upper gastro intestinal tract (GIT) and to give progressive drug release in colon. Some of the recent research examples reported in literature on colon specific FLB tablets are time-dependent sodium alginate compression coated tablets [3], time-dependent pulsatile tablets [4], controlled release matrix tablets [5].

Oral colon-specific drug delivery has got significant role not only to treat local colonic diseases but also for potential delivery of drugs that are used to treat colonic disorders [6]. Traditionally, colon targeting is achieved with

*Corresponding author at: Department of Pharmacy, College of Medical & Health Sciences, Wollega University, Ethiopia
E-mail: vemulasatish15@gmail.com (SK Vemula)

approaches like prodrug, pH-sensitivity, time-dependent and microbial degradation dependent approaches [7]. Development of colon-specific medication is useful to treat local disorders of colon as well as to improve the delivery of proteins and peptides [8]. Colon targeting is approached by formulating as tablets, capsules, multiparticulates, microspheres and liposomes [9]. Development of matrix tablets is simple and reasonably priced method with conventional tableting facilities and few process variables [10]. To gain colon-specific drug delivery, formulation of matrix tablets is a simple method when compared to other methods. HPMC and sodium alginate are release retardant polymers and widely used as an extended release agents in the pharmaceutical industry. Thus this study aimed to formulate the FLB colonic matrix tablets using sodium alginate and HPMC K15M as controlled release polymers and evaluated the efficacy and suitability of above polymers to gain colon-specific drug release.

2. Materials and Methods

2.1 Materials

Flurbiprofen was gift sample from FDC, Mumbai, India. Sodium alginate and HPMC K15M were gift samples from MSN laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

2.1.1 Preparation of matrix tablets

FLB matrix tablets were prepared using direct compression method. Accurately weighed quantity of FLB and excipients other than glidant and lubricant were passed through 60 mesh sieve and blended in a poly sack for 5-10 min. Then the obtained blend was lubricated with talc and magnesium stearate for 5 min. Finally the resultant powder mixture was converted into tablets using 9 mm round flat punches on rotary tableting machine. The amount of FLB present in each tablet was 100 mg and the final weight was adjusted to 300 mg (Table 1).

Table 1 Formulation of FLB matrix tablets				
Formulation code ^a	FLB (mg)	Sodium alginate (mg)	HPMC K15M (mg)	Total tablet weight (mg)
F1	100	25	-	300
F2	100	50	-	300
F3	100	75	-	300
F4	100	-	25	300
F5	100	-	50	300
F6	100	-	75	300
Tablet thickness (mm)		2.48±0.02		
Tablet diameter (mm)		9.02±0.04		

^aEach compression coat formulation contains 1% Magnesium stearate, 2% Talc and Avicel PH 102 to make up the tablet weight to 300 mg.

2.1.2 Physical evaluation of matrix tablets

The compressed tablets were assessed for weight variation, hardness, friability and drug content. To compute the weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (Shimadzu, Japan) and determined the average weight and deviation. Tablet hardness (n=6) was determined using Monsanto tablet hardness tester. Friability was calculated using ten tablets with the help of Roche friabilator (Electrolab, India).

2.1.3 Determination of drug content uniformity

Drug content uniformity was estimated by crushing randomly picked ten tablets. The drug powder equivalent to 100 mg of FLB was extracted to the drug solution with suitable solvent. To extract the drug solution, drug powder was soaked in 10 ml of ethanol for one hour, filtered and the resultant clear drug solution was added to simulated gastrointestinal fluid and diluted in a suitable manner to gain 10 mg/ml solution. Then the 10 mg/ml drug solution (n=3) were measured for FLB content at 247 nm using UV-Visible spectrophotometer and calculated the drug content uniformity. Similar procedure was used for all the formulations.

2.1.4 In vitro dissolution study

In vitro drug release studies were carried out using USP XXIV Type II dissolution apparatus (Electrolab, TDT-08L) in simulated gastrointestinal fluids at standard conditions i.e., 50 rpm rotation speed and 37 ± 0.5 °C temperature. Initially, the dissolution study was performed using 0.1 N HCl for 2 h, then using pH 5.5 buffer for 2 h and finally in pH 7.4 phosphate buffer up to 24 h. At specific time intervals, 5 ml samples were collected and restored by an equal volume of fresh pre-warmed dissolution medium. Then the collected samples were diluted suitably and determined the FLB content using UV-Visible spectrophotometer at 247 nm. Then the dissolution data was also used to calculate the mean dissolution time (MDT) (the sum of different release fraction periods during dissolution studies divided by the initial loading dose), T10% and T80% (time in hours to take 10% and 80% drug release, respectively) to explain the colon-specific release from prepared tablets [11,12].

2.1.5 Stability studies

According to ICH guidelines, the stability studies were planned to assess the stability of FLB in HPMC matrices. Three replicates of formulation F5 tablets were packed in aluminum coated polyethylene pack and stored at 40 ± 2 °C and 75 ± 5 % RH in the humidity chamber for six months [13]. Specimens were gathered following six months of storage and estimated for the drug content and in vitro dissolution rate [14]. At this point, the data was statistically analyzed using paired t-test to test the significance of difference at level of significance 0.05. Then to prove the stability of dosage form, the

similarity factor (f_2) was calculated by comparing the F5 tablets dissolution data before and after storage.¹² The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

3. Results and Discussion

3.1 Physical evaluation of matrix tablets

Table 2 shows the different physical parameters that evaluated for prepared matrix tablets. The weight variation of the tablets was found in the range of $299.44 \pm$

2.92 mg - 301.82 ± 2.58 mg and all the formulation tablets were fell within the pharmacopoeial limit i.e., average weight $\pm 5\%$. The thickness and diameter of prepared tablets was found as 2.48 ± 0.02 mm and 9.03 ± 0.04 mm respectively. The hardness of the tablets was found as 5-6 kg/cm². All the formulations were found below the 1% friability that indicated the tablet mechanical strength. The tablets were found to contain not less than 98% and not more than 100% of the labeled amount indicating the drug content uniformity. From these results, the prepared tablets complied with Indian pharmacopoeial limits. From the physical characterization, all the tablet formulations were found to be uniform in weight variation, hardness and drug content and within the limits of friability.

Table 2 Physical evaluation of FLB matrix tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm ²)	Friability (%)	Drug content‡ (%)
F1	300.21 ± 2.59	5.2 ± 0.62	0.42	98.72 ± 1.46
F2	301.17 ± 2.46	5.0 ± 0.38	0.48	99.78 ± 1.31
F3	299.44 ± 2.92	5.5 ± 0.41	0.42	99.12 ± 0.28
F4	300.48 ± 2.26	6.5 ± 0.54	0.32	99.14 ± 1.24
F5	300.52 ± 2.12	6.2 ± 0.56	0.36	99.95 ± 1.32
F6	300.52 ± 2.12	6.3 ± 0.42	0.38	98.84 ± 1.41

* All values represent mean \pm standard deviation, n=20

† All values represent mean \pm standard deviation, n=6

‡ All values represent mean \pm standard deviation, n=3

3.1.1 In vitro dissolution study

The percent drug release from formulations F1-F6 containing different levels of sodium alginate and HPMC K15M were shown in Fig. 1. From the in vitro drug release studies, HPMC K15M was superior and gave more satisfactory results than sodium alginate. Among the all formulations, F5 formulation was selected as the best formulation with great respectability and acceptable drug release i.e., $11.62 \pm 0.78\%$ drug release in 5 h and it was progressively increased to $98.83 \pm 1.02\%$ in 24 h. Formulations with high viscosity HPMC 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. But in case of sodium alginate swollen gel, it may lacks the integrity and somewhat easy drug diffusion from matrices that leads to fast dissolution when compared to HPMC matrices. Similar type of results observed in the reported studies of literature i.e., flurbiprofen pulsatile tablets using HPMC

and ketorolac tromethamine compression coated tablets using HPMC K4M [4, 7].

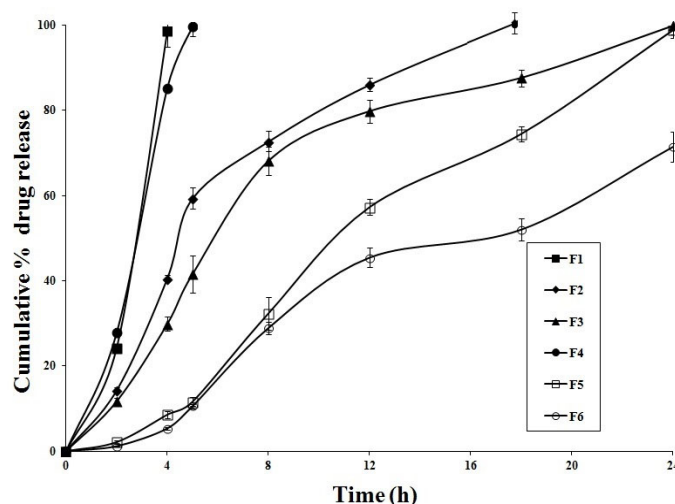


Figure 1 Release profile of FLB from matrix tablets (n=3)

Between the two polymers, HPMC was superior in MDT, T10% and T80% and sodium alginate gave low values. The MDT values of F3 and F5 were found to be 7.83 h and 12.03 h. The T10% and T80% values of optimized formulation (F5) were found to be 4.8 h and 19.6 h respectively (Fig. 2). From the dissolution data, the computed mean dissolution time was increased as increasing the concentration of polymer. It demonstrated the sustained release capacity of polymer and the time

in hours to take 10% and 80% drug release (T10% and T80%) were able to illustrate the colon specific release capability of polymer [7]. Comparable results were observed in flurbiprofen compression coated tablets using HPMC and sodium alginate developed by Vemula *et al.* [3,4]. The above calculated parameters demonstrated that the F5 formulation gave not only 5 h lag time to reach colon but also gave the complete drug release in colon in slow manner in contrast to other formulations.

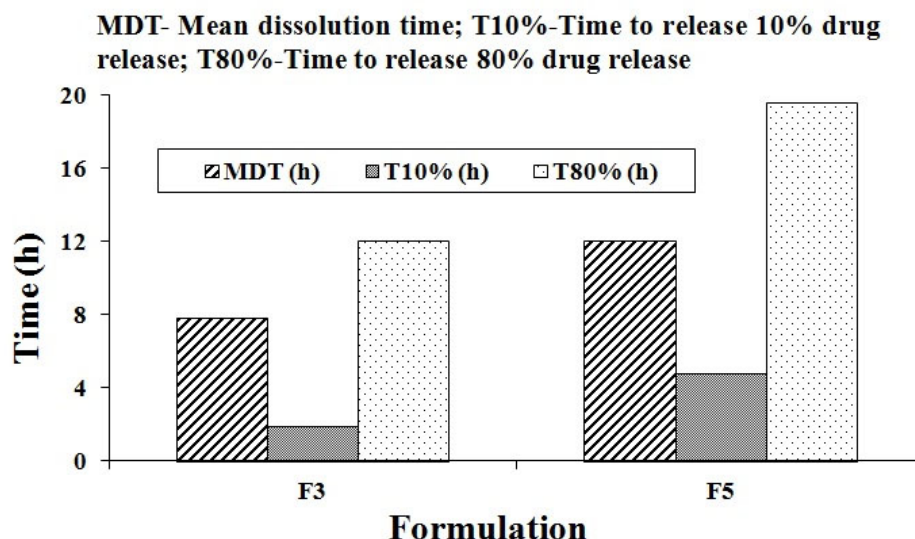


Figure 2 Drug release parameters of FLB matrix tablets

3.1.2 Stability studies

From the stability studies, the tablets were subjected to drug assay and in vitro dissolution studies after storage of six months (Table 3). The stability data of F5 formulation disclosed that there was no significant change in drug content and dissolution rate of tablets before and after storage. The calculated similarity factor ($f_2 = 85.66$) was

found to be more than 50 indicating similarity between the dissolution profile before and after storage [12]. Above all, F5 matrix tablets containing 50 mg of HPMC K15M was considered as the best formulation that gave less than 11% drug release in 5 h and it was progressively increased to 100 % in 24 h, which indicated the colon specific drug release.

Table 3 Stability studies of FLB matrix tablets F5

Time (h)	Before storage	After 6 months	t-test at 0.05 LS	Similarity Factor (f_2)
0	0.00 ± 0.00	0.00 ± 0.00		
2	2.12 ± 0.41	2.08 ± 0.32		
4	8.56 ± 0.78	7.72 ± 0.54		
5	11.62 ± 1.03	10.26 ± 0.98		
8	32.34 ± 2.85	31.02 ± 0.61	Not Significant	85.66
12	57.28 ± 1.94	55.94 ± 1.23		
18	74.48 ± 1.73	72.67 ± 1.58		
24	98.83 ± 1.02	97.56 ± 1.34		
% Assay	99.95 ± 1.32	98.83 ± 1.25	Not Significant	-

4. Conclusion

In the current study, an effort was made to develop the successful colon-specific system of FLB using HPMC matrix tablets to without loss in the upper gastrointestinal tract. From the dissolution studies, F5 HPMC matrix tablets demonstrated considerable amount of colonic drug release with minimum release in lag period of 5h and proved stability of drug in HPMC matrices. In conclusion, development of matrix tablets using HPMC K 15 M as controlled release polymer was a suitable approach for colonic release of FLB.

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