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RESEARCH ARTICLE

FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF FLURBIPROFEN USING HYDROXYPROPYL METHYLCELLULOSE

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Abstract

This research work was done to design oral sustained release matrix tablets of flurbiprofen using hydroxypropyl methyl cellulose as the matrix polymer. The tablets were prepared by the wet granulation method using polymers in different combinations; HPMC K4M and HPMC K100 M were selected as the independent variables. Fourier transform infrared spectroscopy studies were performed to check the interactions between polymers and drug. The granules of the tablets evaluated for their physical properties like angle of repose, bulk density, compressibility index, and Hausner ratio were found to be satisfactory. The manufactured tablets were evaluated for in-process and finished product quality control tests including appearance, dimensions, weight variation, hardness, friability, drug content, and *in vitro* drug release. All formulations showed acceptable results and complied with specifications for tested parameters. The results of dissolution studies indicated that formulation containing HPMC K4 M (7.5%) and HPMC K100 M (7.5%) as polymers was the most successful formulation, which was evidenced by similarity (f_2) and dissimilarity (f_1) factors in comparision with theoritical drug release profile. The formulated flurbiprofen tablets followed zero order release kinetics and diffusion was the dominant mechanism of drug release, resulting in regulated and complete release within 24 hours. Formulations were subjected to short term stability studies as per ICH guidelines and were found stable.

Introduction

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug-release profile, they are cost effective and they have broad US Food and Drug Administration acceptance.[1] The hydrophilic polymer matrix system consists of hydrophilic polymer, drug, and other excipients distributed throughout the matrix. This dynamic system is dependent on polymer wetting, hydration, and dissolution for controlled release of drug. At the same time, other soluble excipients or drug substances will also wet, dissolve, and diffuse out of the matrix, whereas insoluble excipients or drug substances will be held in place until the surrounding polymer, excipients, or drug complex erodes or dissolves away.[2]

Hydroxypropyl methylcellulose (HPMC), which is commonly used in hydrophilic matrix drug delivery systems, is mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent.[1] HPMC has been found to be a very versatile material for the formulation of soluble matrix tablets. It is a widely accepted pharmaceutical excipient and is included in all major compendia. Because HPMC is available in a wide range of molecular weights, effective control of gel viscosity is easily provided.[2]

Flurbiprofen is a potent anti-inflammatory, analgesic, and antipyretic agent belonging to the

family of propionates but has not been used as extensively as many of the newer ones, possibly because it requires round the-clock administration due to its shorter half-life (2–6 hours). Thus, a sustained release preparation of flurbiprofen, maintaining plasma concentrations adequately over a 24-hour period will heighten its area of application.[3]

In the present study, the formulation (flur SR) was designed for 24-hour sustained release of flurbiprofen, and the sustained pattern was evaluated by *in vitro* drug release for 24 hours. The drug release data were plotted using various kinetic equations (zero order, first order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics. *In vivo* drug release, biopharmaceutical evaluation, and *in vivo/in vitro* correlations were beyond the scope of this study and will be considered in future work.

Materials and Methods

Materials

HPMC 4000 cps (USP Type-2208) and HPMC 1,00,000 cps (USP Type-2208) was purchased from (Colorcon Asia Pvt. Ltd. Verna, GOA); Flurbiprofen was a gift from sun pharmaceutical Pvt. Ltd. (Aurangabad, India). All other chemicals that is Lactose Monohydrate (Friesland foods, Netherlands), PVP K-30 (Nanhang Industrial Co. Ltd. China), Ethanol (95%) (Ranchem Ltd., Ahmadabad), Sodium Lauryl Sulfate (Nikita chemicals Pvt. Ltd.), Magnesium stearate (Shital Chemicals Ltd. Ahmadabad.), Citric acid (Nikita Chemicals Pvt. Ltd. Nagpur) were used.

Methods

Calculation of the Sustained Dose

The sustained release dose of once a day (24 hours) flurbiprofen tablet was calculated using pharmacokinetic data and was found to be 130 mg and from that theoritical drug release profile was prepared which, help to compare the drug release pattern from the tablet formulation.

Preparation of sustained release matrix tablets

Tablets were formulated according to Table-1. Wet granulation method was employed for formulation. Here, ethanol (95%) was used as granulating fluid[5] because flurbiprofen is freely soluble in ethanol (95%).[4] Here; Drug, polymers and diluent were mixed by geometrically mixing method and then added in plastic bags, shaken for 15 minutes. After that ethanol (95%) was added in blend and then blend was lubricated using magnesium stearate, SLS and further mixed for 5 minutes. After that citric acid was added to the blend and mixed for 5 minutes.[10] The blend was then compressed with RIMEK eight station compression machine to a weight of 600mg.

Evaluation of Tablets

Physical evaluations of tablets

Tablets were evaluated for weight variation (n = 20), thickness (n = 10), hardness (n = 10), and friability (n = 10).

Physical properties of the powder blends

Physical properties of the powder blends like bulk density, tapped density, Carr's index and angle of repose were determined.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra of flurbiprofen, polymers(HPMC K4M,HPMC K100M)and the matrix tablets were obtained using FTIR Spectrophotometer [Model: 8700 S; Shimadzu Scientific Instruments (SSI), Kyoto, Japan] to investigate any interaction between the polymers and the drug in the formulated matrix tablets.

Table 1: Formulation of flurbiprofen tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flurbiprofen	130	130	130	130	130	130	130	130	130
HPMC K4 M	30	30	30	45	45	45	60	60	60
HPMC K100 M	30	45	60	30	45	60	30	45	60
Lactose	335	320	305	320	305	290	305	290	275
PVP K 30	3	3	3	3	3	3	3	3	3
Ethanol (95%)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate	6	6	6	6	6	6	6	6	6
SLS	6	6	6	6	6	6	6	6	6
Citric acid	60	60	60	60	60	60	60	60	60
Total weight	600	600	600	600	600	600	600	600	600

Table 2: Physical properties of the powder-blends of the batches F-I to F-IX

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose(°)	29.33	29.33	29	29	29	29	29	29	29
Bulk density (gm/cm^3)	0.3	0.3	0.29	0.3	0.29	0.29	0.29	0.29	0.28
Tapped density (gm/cm^3)	0.35	0.35	0.34	0.34	0.32	0.33	0.34	0.34	0.35
Carr's index (%)	16.67	16.67	13.33	17.24	12.06	13.79	17.24	15.25	16.67

Drug Release Study

Drug release from six tablets of each formulation, in triplicate, was determined using the USP apparatus II (paddle method), where 900 mL of 0.1 N HCl and phosphate buffer

(pH 6.8) were used as dissolution media maintained at 37°C (5°C) at 100 rpm. The release rates from the tablets were conducted in a dissolution media of 0.1 N HCl for 2 hours and thereafter in phosphate buffer of pH 6.8 for 22 hours. Aliquots of 5 mL were withdrawn at 0, 1, 1, 2, 4, 8, 12, 16, 20 and 24 hours with replacement of 5 mL of the fresh media. All the samples were analyzed directly at 247 nm using an UV-vis 1800 spectrophotometer (Model: U1800; Shimadzu Corporation, Kyoto, Japan). Drug release profiles were drawn using MS-Excel software.

Drug release kinetics

Drug release kinetics is assumed to reflect different release mechanisms of controlled release matrix systems. Therefore, five kinetic models were applied to analyze the drug release data to find the best fitting models. These models are zero-order, first-order,

Higuchi, [4] Hixson–Crowell, [5] and Korsmeyer–Peppas, [6] models.

Swelling behavior:[7] Swelling behavior or water uptake studies of flurbiprofen tablets were studied in phosphate buffer solution, pH 6.8. The matrix tablets were weighed and placed in tared metallic baskets. These baskets were then immersed in 900 ml of 6.8 phosphate buffer solution, pH 6.8 at 100 rpm and 37 $\pm$ 0.5 ^{0}C, At specific time intervals, the basket containing the matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percentage degree of swelling was calculated as follows:

Percentage degree of swelling = [(Ws – WD) / WD] × 100

Results and Discussion

Physical evaluation of tablets

The results for physical evaluation of tablets showed that all batches of tablets were within the limits of USP. The average tablet weight varied between 599 and 601 mg. Hardness varied from 59.99 to 64.66 N. Thickness varied from 3.60 to 3.74 mm. Friability varied between 0.15% and 0.70%.

FTIR spectroscopy

The FTIR spectra (Figure 1, 2, 3, 4) showed no significant differences between pure flurbiprofen, polymers and the sustained release tablets of the flurbiprofen. The main peak remained unchanged and only some peak ratios differed slightly. FTIR spectra of flurbiprofen and sustained release tablets of flurbiprofen showed characteristic broad peak of flurbiprofen in the range of 3050 to 1700 cm^{-1} because of hydrogen bonding. The characteristic peaks of flurbiprofen at 1698 and 2920 cm^{-1} were because of carbonyl and hydroxyl stretching, respectively.

Figure-1: FT-IR spectrum of flurbiprofen

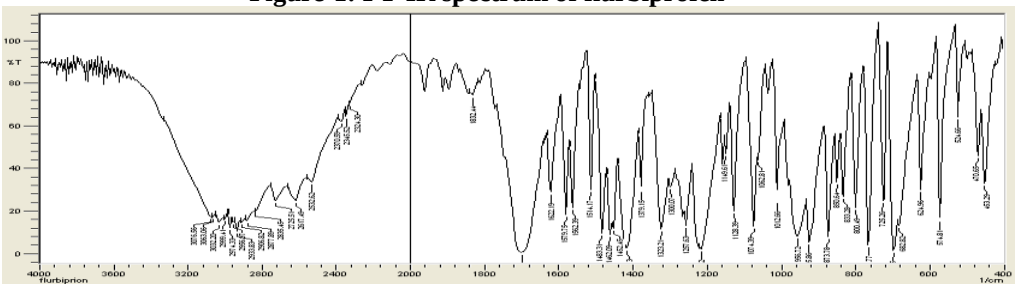


Figure-2: FT-IR spectrum of pure flurbiprofen and HPMC K4 M

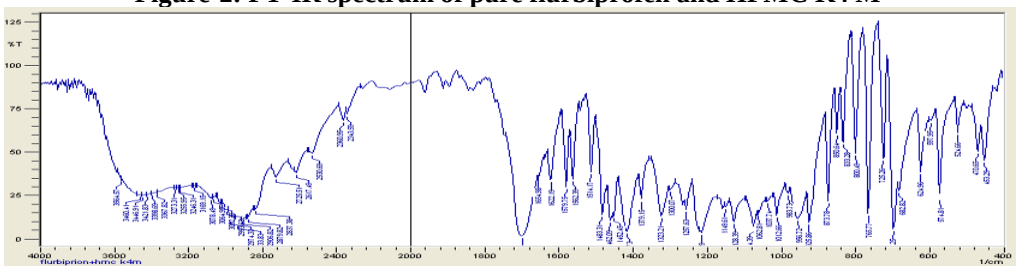


Figure-3: FT-IR spectrum of physical mixture of HPMC K100 M and flurbiprofen

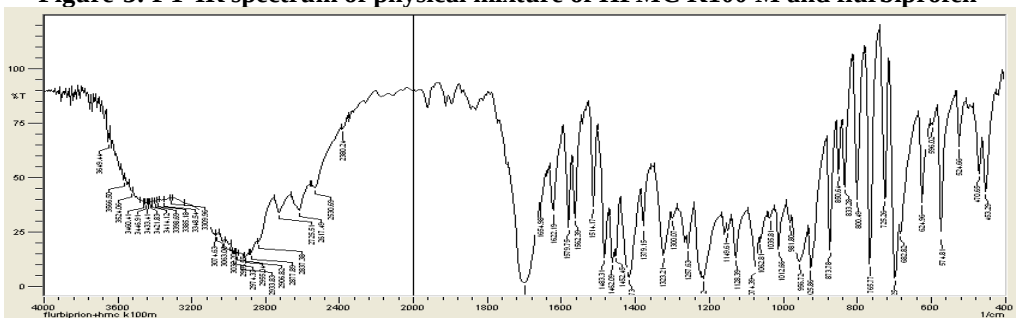
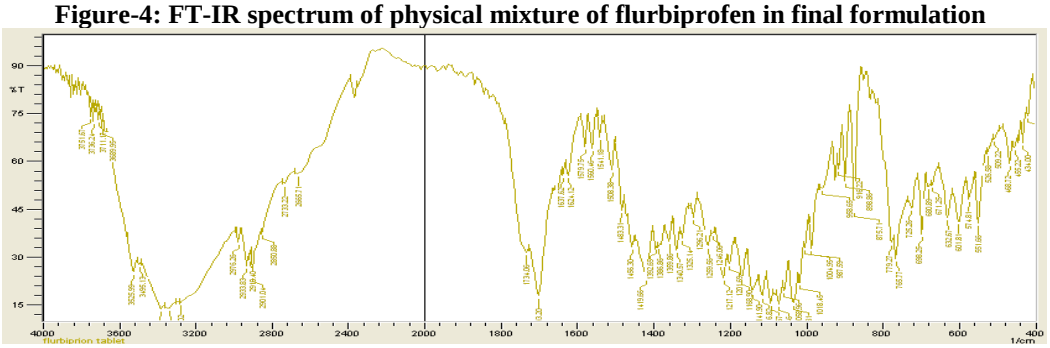


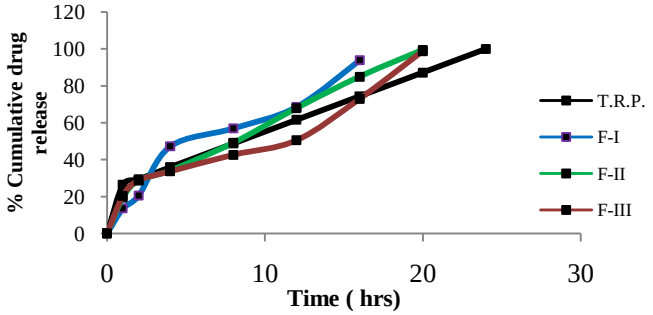
Figure-4: FT-IR spectrum of physical mixture of flurbiprofen in final formulation



Drug release studies

In Figure 5, drug release profiles of formulations F-I, F-II and F-III were prepared according to the experimental design are showed in Table-1. It is clear from Figure 2 that all the formulations showed almost release at pH 1.2 in first 2 hours varying from 13.87% to 20.47% and as the medium of dissolution was changed to phosphate-buffered solution of pH 6.8, the drug release was increased considerably and showed a steady release pattern. The drug release in first 2 hours may be attributed to the low solubility of drug at gastric pH but it is markedly increased by adding citric acid[8] into the formulation. All the formulations were compared with theoritical drug release profile, which help to get idea of proper release pattern.

Figure-5: Dissolution release profile of formulation F-I, F-II and F-III



The dissolution profile comparison carried out using model independent or model dependent method. A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles.

In figure 6 and In figure 7 drug release profiles of formulations F-IV, F-V, F-VI and F-VII, F-VIII,F-IX were prepared according to the experimental design are showed in Table-1.

Figure-6: Dissolution release profile of formulation F-IV, F-V and F-VI

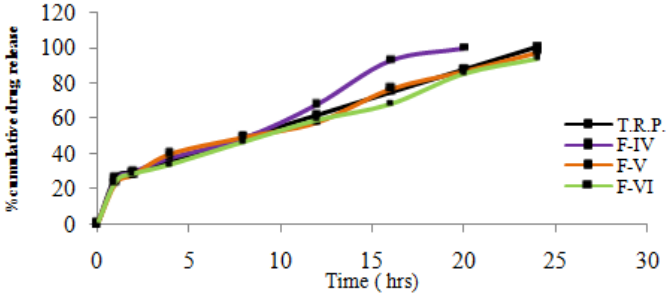
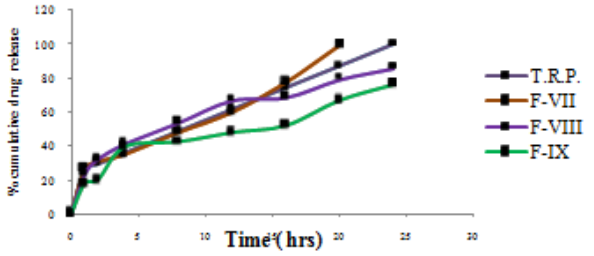


Figure-7: Dissolution release profile of formulation F-VII, F-VIII and F-IX



Drug release profile of F-V formulation mentioned above appears to be closer to the theoretical drug release profile. It is observed that formulations F-V which contain HPMC K4M 45 mg (7.5% of total tablet weight) and HPMC K100M 45 mg (7.5% of total tablet weight) showing good release (97.37± 0.58) in 24 hrs which mimic the theoretical release profile (T.R.P.)[11] The *f1* (Dissimilarity factor) and *f2* (Similarity factor) values of F-V are 4.80 and 79.23 respectively which help to prove that results obtained were in acceptable range.

Drug release kinetics

The zero-order rate describes the systems where the drug release rate is independent of its concentration. Figure 8 shows the cumulative amount of drug release vs. time for zero-order kinetics. The first order which describes the release from systems where the release rate is concentration dependent is illustrated by Figure 9, which shows the log cumulative percent drug remaining vs time. Higuchi's model describes the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. Figure 10 illustrates the Higuchi square root kinetics, showing the cumulative percent drug release Vs the square root of time. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined. It was found that the in vitro drug release of flur SR was best explained by Higuchi's equation, as the plots showed the highest linearity (r^2 = 0.984),followed by zero order (r^2 = 0.990) and first order (r^2 =0.846). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi'skinetics). However, drug release was also found to be very close to zero-order kinetics, indicating that the concentration was nearly independent of drug release.

Figure-8: *In vitro* release profile of flurbiprofen from tablets of F-V fitted in zero order release.

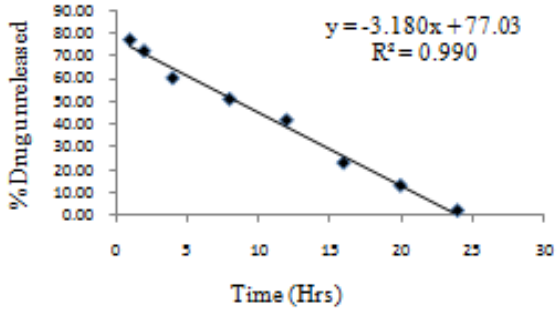


Figure 9: *In vitro* release profile of flurbiprofen from tablets of F-V fitted in first order release

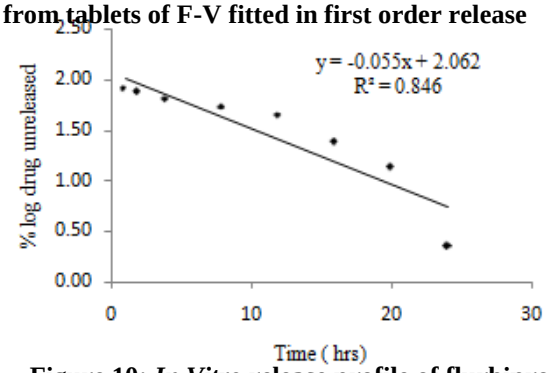


Figure 10: *In Vitro* release profile of flurbiprofen from the tablets of the batch F-VI fitted in Higuchi's plot.

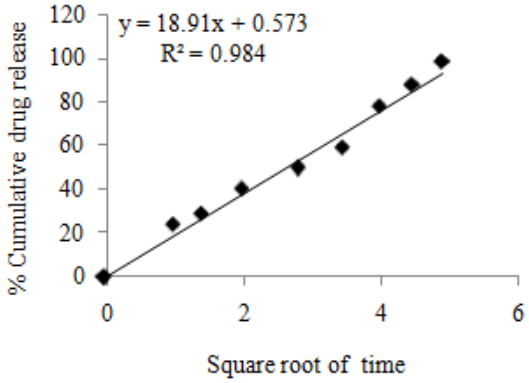
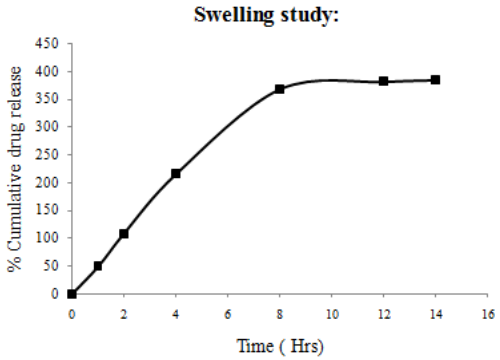


Table-3: Regression equations of *in vitro* release of flurbiprofen from the tablets of F-V

Formulation	*In vitro* release of flurbiprofen from the tablets of F-V		
	Hixon-Crowel model	Higuchi's model	Korsmeyer Peppas model
F-V	y = 0.054x + 0.048 R^2 = 0.946	y = 18.91x + 0.573 R^2 = 0.984	y =- 0.787x + 2.127 R^2 = 0.583

Figure 11: The percentage swelling and water uptake study of tablets of the formulations F-V



HPMC had swollen immediately within 4 hours and complete swelling in 12 hours. About 57% drug was released at the end of 12 hours and erosion process might have initial attributing gradual decrease in %swelling after 12 hours. As described by Siepmann *et al* diffusion of drug significantly depends on water content of the tablet. This may be because the mobility of polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling of the system. From the Figures 11, it can be seen that the swelling of tablet was much faster than the drug release from the tablet (swelling was 400% in 12 hours and 57% drug released).Faster and higher swelling of the tablet led to increase in dimensions of the tablet leading to increase the diffusion pathways and thus decrease in diffusion rates. So, the drug release was found to be high initially and then gradually decreased.

SUMMARY AND CONCLUSIONS

Decreasing the dose frequency of flurbiprofen increases patient compliance; patients prefer to take the drug once daily. It also improves the rate of decreasing the pain and hastens the cure from the indications, and therefore increases compliance. The hydrophilic matrix of HPMC controlled the flurbiprofen drug release effectively for 24 hours; hence, the formulation can be considered as a once-daily sustained-release tablet of flurbiprofen. *In vitro* dissolution studies indicated a sustained-release pattern throughout 24 hours of the study that was comparable to the theoretical release profile. Drug release kinetics indicated that drug release was best explained by Higuchi's equation, as these plots showed the highest linearity (r^2 = 0.984) and a close relationship was also noted with zero-order kinetics (r^2 = 0.990).

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