Sustained Release Floating Tablets of Mefenamic Acid: An Effervescent Gastro Retentive Approach

Kruthi Gurudev, *B. V. Basavaraj, S. Bharath, R. Deveswaran

Faculty of Pharmacy, M. S. Ramaiah University of Applied Sciences, Bangalore 560 054

*Contact Author e-mail: bvbasu@rediffmail.com

ABSTRACT

The present research work was concerned with the development of effervescent floating matrix tablets of mefenamic acid. Matrix tablets were prepared by wet granulation method by using synthetic swelling polymers like HPMC K4M, HPMC K15M and HPMC K100M for ascertaining the best possible polymer. Sodium bicarbonate and citric acid was incorporated as gas-generating agent. The prepared tablets were evaluated in terms of their pre-compression and post-compression parameters. The formulations were optimised for different viscosity grades of HPMC and its concentration using central composite design by taking HPMC K4M, HPMC K15M and HPMC K100M as independent variables and floating lag time, floating time and 90% drug release as dependent variables respectively. Pre-compression and post-compression studies of preliminary trials and initial optimised formulations were within the specified limits. The final optimised formulations containing HPMC K4M (OFT1) showed floating lag time of 46 sec, floating time of 24 h and maximum drug release of 95.08 % when compared to the formulations containing HPMC K15M (OFT2) and HPMC K100M (OFT3) with floating lag time of 68 sec and 120 sec, floating time of 24 h and drug release of 92.04 % and 81.14 %. Respectively.The results of pre-compression and post-compression parameters of final optimised were within the specified limits. The accelerated stability studies of the final optimised formulations indicated no appreciable change in drug content and in vitro drug release rates of the formulations. Thus, it can be concluded that with increase in polymer concentration and increased viscosity grade of HPMC the drug release of mefenamic acid can be sustained by promoting extended gastric residence and buoyancy.

Keywords: Sustained Release, Mefenamic acid, Floating lag time, Floating time

1. INTRODUCTION

In recent years, considerable attention has been focused on the development of new drug delivery systems. The word “new” or “novel” in the relation to drug delivery systems is a search for something out of necessity. They provide a prompt release of drug but in order to achieve as well as maintain the drug concentration within the therapeutically achieved range, it is often necessary to administer it several times a day, resulting in significant fluctuations in drug levels [1].The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. An appropriately designed sustained or controlled release drug delivery system can be a major advance toward solving the problems associated with the existing drug delivery systems [2].

Oral delivery of drug is by far the most preferable route of drug delivery due to several advantages. Various attempts have been made to develop gastro retentive delivery systems (GRDDS), encompassing a variety of systems and devices benefitting drugs that have a narrow window of absorption in the stomach and upper GI tract and even drugs that have shorter half life [3].

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastro residence time (GRT) for a prolonged period of time. Effervescent FDDS when reached to the stomach, CO_2 is liberated by the acidity of gastric contents and is entrapped in the jellified hydrocolloid. The CO_2 generating components such as sodium bicarbonate, calcium carbonate, citric acid and tartaric acid mixtures may be used [4].

Mefenamic acid, an anthranilic acid derivative, is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is widely used as analgesic, antipyretic, especially used in the treatment of rheumatoid arthritis, and osteoarthritis, Similar to other NSAIDs, mefenamic acid inhibits prostaglandin synthetase [5]. .Mefenamic acid is having a half-life of 2 h and undergoes first pass metabolism with the need for intermittent dosings. Hence, the present work was aimed at the formulation and evaluation of sustained release floating tablet of mefenamic acid by effervescence to enhance the therapeutic effectiveness of mefenamic acid.

2. MATERIALS AND METHODS

Mefenamic acid was procured from Strides ArcoLab Ltd, Bangalore, HPMC K4M, K15M, K100M from Yarrow Chem Products, Mumbai, Sodium bicarbonate from Qualigens Fine Chemicals, Mumbai, Citric acid from Rankem, New Delhi, Lactose from Merck Specialities Private Limited, Mumbai.

3. PREFORMULATION STUDIES

3.1 Drug – polymer compatibility studies

a. FTIR Study

The spectra were recorded for pure drug, polymer and the physical mixture of drug and polymer in the ratio 1:1 at the

scanning range of 400 – 4000 cm-1using FTIR – 8400 S, spectrophotometer (Shimadzu, Japan).

b. Differential Scanning Calorimetry

Samples of about 5 mg were placed in 50 µl perforated aluminium pans and sealed. Heat runs for each sample were set from 5 to 3000C /min, using nitrogen as purging gas. The apparatus was indium – cyclohexane calibrated.

3.2 Formulation of Mefenamic acid floating tablet

Floating tablets of mefenamic acid were prepared by wet granulation technique using varying concentrations of different grades of polymers with citric acid and sodium bicarbonate as effervescent agents (Table 1).Weighed quantities of drug and polymer were mixed homogenously using mortar and pestle. PVP–K30 (5% w/v) solution in isopropyl alcohol was granulating agent. Granules were prepared by passing wet coherent mass through a BSS#12 sieve. The obtained granules were dried at room temperature. The dried granules were sieved through BSS#16 and lubricated with magnesium stearate and talc. Lubricated granules were compressed into tablets using ten station single rotary punching machine (Rimek RSB-4 mini press) to obtain tablets of desired specifications [5].

Table 1. Preliminary trials for floating tablets of mefenamic acid with HPMC K4M, HPMC K15M and HPMC K100M polymers

Ingredients	Quantity (mg)						
	F1	F2	F3	F4	F5	F6	F7
Mefenamic acid	250	250	250	250	250	250	250
HPMC K4M	100	200	300	-	-	-	-
HPMC K15M	-	-	-	100	200	300	-
HPMC K100M	-	-	-	-	-	-	100
$NaHCO_3$	50	50	50	50	50	50	50
Citric acid	25	25	25	25	25	25	25
Mg stearate	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10
Lactose	210	110	10	210	110	10	210
Total weight	650	650	650	650	650	650	650

4. OPTIMIZATION STUDIES

Formulations were developed following a central composite design after results obtained through preliminary trials. The Design Expert Software (Version 8.0.1, Stat – Ease Inc., Minneapolis, USA) suggested fifteen (15) model formulations. Concentration of HPMC K4M, HPMC K15M and HPMC K100M were considered as independent variables (Table 2). Floating lag time, floating time and 90% drug release were considered as dependent variables.

Table 2. Maximum and minimum levels of independent variables given in the design

Ingredients	Units	Level	
		Low	High
HPMC K4M	Mg	100	300
HPMC K15M	Mg	100	300
HPMC K100M	Mg	100	300

5. EVALUATION

5.1 Pre compression parameters

The granules were subjected to several analyses for determining its suitability for further development into tablets.

5.2 Post compression parameters

The prepared tablets were tested for weight variation, drug content uniformity, friability (Koshiash Industries, Mumbai) thickness and hardness (Monsanto tablet hardness tester, Secor India Laboratory Instruments, Delhi).

5.3 Drug content

A quantity of powdered tablet equal to 250 mg of mefenamic acid was dissolved in 0.1 N HCl in 100 ml volumetric flask. The sample solution was further diluted and the absorbance was measured at 285 nm using 0.1 N HCl as blank and the % drug content was estimated.

5.4 In- vitro buoyancy determination

The floating lag time (FLT; time period between placing the tablet in the dissolution medium and tablet floating) and floating duration of the tablets (FD were determined by visual observation of tablets placed in a 100 ml beaker containing 0.1 N HCl [6].

5.5 Swelling Index studies

The extent of swelling can be measured in terms of % weight gain by the tablet. Swelling studies were carried out for formulations and from each formulae, one tablet was weighed and individually (designated as Wo) and placed separately in petri dish containing 15 ml of 0.1 N HCl. At regular 1 h time intervals until 5 h, the tablets were removed from petri dish and the excess surface liquid was removed carefully using tissue paper. The swollen tablets were then reweighed and swelling index (SI) was calculated using formula [7].

5.6 In- vitro drug release

A Sample (5ml) of the solution was withdrawn from the dissolution apparatus at regular time intervals and each time fresh media was replaced in same amount to maintain sink condition. Sample absorbance was measured at 285 nm by using UV/Visible Spectrophotometer (UV-1600). Cumulative

percentage of drug release was calculated using the equation obtained from a standard curve.

5.7 Mechanism of drug release:

The different mathematical model was applied for describing the kinetics of drug release process from tablets. The kinetics of mefenamic acid was determined from tablets formulations finding the best fit release data to Zero order, first order, Hixon crowell, Higuchi, Kors-meyer peppas plots.

5.8 Stability studies

Accelerated stability studies were performed for all the optimized formulations (OFT1, OFT2& OFT3) as per ICH guidelines. The formulations were stored at 40 ± 2 ºC/ 75 ± 5 % RH for 6 months. At an interval of 2, 4 and 6 months, the samples were withdrawn and tablet evaluation tests were conducted. There was no appreciable change in the drug content and invitro drug release rates of the formulations.

6. RESULTS AND DISCUSSION

6.1 Drug – polymer compatibility studies

The IR spectra of physical drug-polymer blend (Fig. 1) showed neither significant nor disappearance of characteristic peaks when compared with IR spectrum of pure sample suggesting that there was no interaction between drug and polymers and drug was stable without undergoing any physical change.

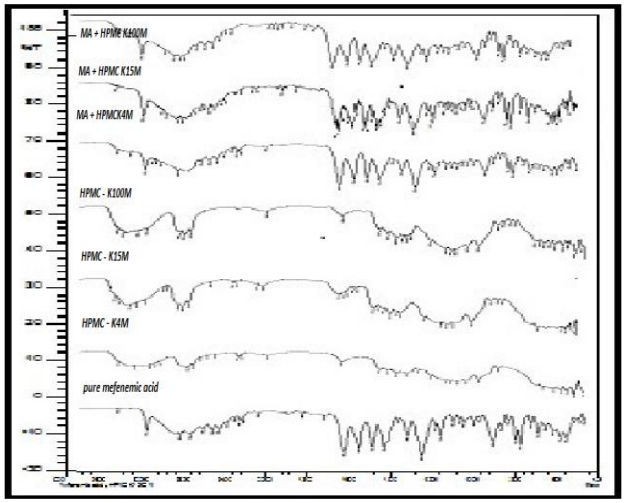

Fig. 1 FTIR spectras of mefenamic, HPMC 4M.K15M, K100M and physical mixtures of drug and polymers from bottom to top

DSC studies revealed that drug polymer blends; mefenamic acid + HPMC K4M, mefenamic acid + HPMC K15M, mefenamic acid + HPMC K100M exhibited endothermic peaks at 219.110C, 222.330C and 217.320C respectively indicating that the melting point of mefenamic acid was not significantly affected with the polymers.. The additional peaks might be due to the presence of water or entrapped moisture. Thus the drug was found to be stable without any physical deformation.

The formulation of floating tablets were developed using mefenamic acid with HPMC K4M, HPMC K15M, HPMC K 100M alone and with effervescent agents sodium bicarbonate and citric acid by non – aqueous wet granulation method (Table 1). The tablets were found to be physically intact and fit for handling.

6.2 Evaluation studies

All the parameters were within the acceptable limits for powder blend as well as for granules with good flow properties without much deviation while compressing the formulations ranging from F1 to F7. The official and unofficial tests carried out on these formulations showed compliance with the specified guidelines.

Optimisation was carried out by using central composite design by taking HPMC K4M, HPMC K15M and HPMC K100M as independent variables and floating lag time, floating time and 90% drug release as dependent variables respectively. Maximum and minimum levels of independent variables given in the design are shown in Table 2. Fifteen formulations were developed i.e. five formulations each using HPMC K4M, HPMC K15M and HPMC K100M as per the runs given in the optimisation. Fifteen formulations were prepared as per the runs given in the optimization design.. The model term for all the formulations and responses were found to be significant for HPMC K4M, HPMC K15M and HPMC K100M. Optimization was carried out by fixing the target for the three responses. The solutions obtained from optimization results with high desirability were selected as the optimized formulations for the preparation of floating tablets of mefenamic acid to obtain desired floating lag time, floating time and drug release coded as OFT1, OFT2 and OFT3. All the values of pre and post compression evaluation of optimization trials (five each for each polymer) indicated that they were with in the prescribed and acceptable limit.

The evaluation of the final three optimized formulations OFT1, OFT2 and OFT3 (Table 3) for the three dependable responses viz., floating lag time, floating time and 90% drug release were found to be in close proximity of the predicted values by the optimization design.

The final tablets were found to exhibit shorter floating lag time (ranging from 45 to 120 sec) due to presence of sodium bicarbonate and citric acid. Decrease in the citric acid level increased in the floating lag time and tablets were found to float for longer duration. They exhibited good floatation over a period of 24 hours without much physical problems.

Swelling index was studied for 5 h in 0.1 N HCl and the results of swelling. The initial increase and subsequent decrease in swelling was probably due to the erosion of surface layer of tablet and the order of swelling was found to 55, 63 and 64%. Photograph of swelling index for optimized formulation OFT1 is shown in the Fig. 2.

In vitro drug release studies of optimized formulations showed prominent upto 90% within 10 h ranging from 95, 92 and 81% (Table 3) and Fig. 3**.**

From this, the release of drug can be sustained with high concentration and high viscosity grade of the polymer as HPMC K 100M, a hydrophilic polymer upon contact with

aqueous fluid is able to form a quite viscous gel, and hence retard the drug release from hydrophilic matrix.

Table 3. Optimised formulations OFT1, OFT2 and OFT3 (Predicted v/s Actual)

Obs	Formulation-code	Qty (mg)	Floating lag time (sec)	Floating time (h)	90% Drug release
Predicted values	OFT1 (HPMC K4M)	145	45	24	92
Actual values			**46**	**24**	**95**
Predicted values	OFT2 (HPMC K15M)	110	70	24	92
Actual values			**68**	**24**	**92**
Predicted values	OFT3 (HPMC K100M)	206	115	23	79
Actual values			**120**	**24**	**81**

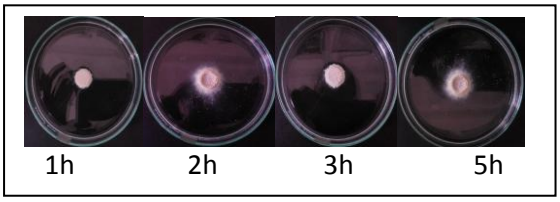

Fig. 2 Photographs of swelling index for optimized formulation OFT1

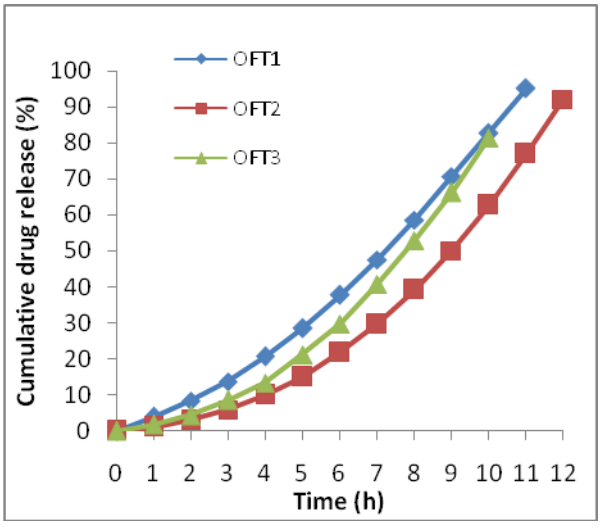

Fig. 3 The comparative in vitro release profile of optimized formulations

The best fit model shown by optimised formulation was by Matrix, Peppas and Zero –order and mechanism of drug release was by non-fickian and supercase transport II.

The stability studies indicated that there was no appreciable change in the drug content and invitro drug release rates of the formulations.

7. CONCLUSION

- Floating tablets of mefenamic acid was prepared by non-aqueous wet granulation method by using different hydrophilic polymers like HPMC K4M, HPMC K15M and HPMC K100M.
- A central composite design was preferred by taking HPMC K4M, HPMC K15M and HPMC K100M as independent variables and floating lag time, floating time and 90% drug release as dependent variables respectively. The end results were found to be on par with the predicted values.
- As the polymer concentration was increased with increased viscosity grade, the percentage drug release got decreased resulting in a sustained drug release pattern over a period of more than 12 h due to enhanced floatation, low density and effervescence.

REFERENCES

[1] Chien Y.W., (1992) Concepts and System Design for Rate-Controlled Drug Delivery in Novel Drug Delivery Systems, New York: Marcel Dekker Inc.

[2] Longer M.A., Robinson J.R., (1995) Remington: The Science and Practice of Industrial Pharmacy, Eastern Pennsylvania: Mack Publication Company.

[3] Christian V.G., Gajjar V., (2011) A Review on Floating Drug Delivery System as a Part of GRDDS, IJPRD., 3(6), pp. 233-241.

[4] Mathur P., Saroha K., (2010) Floating Drug Delivery System: An Innovative Acceptable Approach in Gastroretentive Drug Delivery, Arch Apl Sci Res., 2(2), pp. 257-270.

[5] Ramanathan G., Kavitha K., (2010) Formulation of Floating Tablets of Mefenamic Acid With Different Grades of Hydroxy Propyl Methyl Cellulose Polymer and Studying the Release Profiles, Int J Drug Dev Res., 2(3), pp. 599-604.

[6] Aphale Sanjivani, Shinde Swapnila, (2011) Development and Evaluation of Hollow Microspheres of Clarithromycin as a Gastroretentive Drug Delivery System Using Eudragit Polymers, IJPBS., 2(3), pp. 344-358.

[7] Devendra K.B., Peeyush B., (2009) Development and Characterisation of Floating Tablets of Captopril Using Natural Polymers, Pharma Res., 1, pp. 213-222.