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FORMULATION OF FLOATING TABLETS OF MEFENAMIC ACID WITH DIFFERENT GRADES OF HYDROXY PROPYL METHYL CELLULOSE POLYMER AND STUDYING THE RELEASE PROFILES

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ABSTRACT

Hydrodynamically balanced system (HBS) or Floating tablets has gained importance in recent days to improve absorption of drugs especially those that are absorbed from stomach and small intestine. In the present study, an attempt was made to fabricate and evaluate an HBS dosage form of Mefenamic Acid tablet The different viscosity grades of Hydroxypropylmethyl cellulose polymer like HPMC K100, HPMC K4M, HPMC KV600, HPMC K50 was incorpated as hydrophilic swellable polymers for preparing matrix-floating tablets. Sodium bicarbonate was incorporated as a gas-generating agent. The prepared floating tablets were evaluated for the physical parameters like thickness, hardness, friability, drug content, floating lag time, floating time and Invitro dissolution studies. The mechanism of drug release was anomalous type and depends upon the viscosity of polymers, which was mainly concluded as the major controlling factor for the drug release. The results showed that the formulation containing Drug: Hpmc kv600 in the ratio of 1:0.5 is suitable for the formulation of gastroretentive floating tablets of mefenamic acid.

Keywords: *Mefenamic Acid, Hydroxypropylmethylcellulose, buoyancy lag time, Matrix Floating tablet, bioavailability studies, and accelerated stability studies.*

Introduction

HBS dosage form is an attractive gastro-retentive drug delivery system, since it permits control over time and site of drug release. This would be particularly valuable for drugs exhibiting an absorption window in the stomach and small intestine or drugs such as weak bases, which dissolve better in the acid environment of the stomach .In addition, the devices may be useful for local treatment of the stomach disorders[1]. The system reported here is HBS dosage form of Mefenamic acid (NSAID), which is widely used as analgesic, antipyretic especially used in the treatment of the rheumatoid arthritis, osteoarthritis, dysmennorhea, and mild to moderate pain, inflammation, and fever[2]. Mefenamic acid has two distinct metabolites namely hydroxymethyl and a carboxy derivative by cytochrome P450 enzyme. The parent drug and metabolites are also conjugated with glucouronic acid, the other reactive metabolite that binds covalently to renal macromolecules causing irreversible damage and necrosis at higher concentration.[3] This is a major drawback associated with conventional dosage forms which releases the entire drug almost immediately, with peak plasma concentration occurring from 1 to 2 hours after ingestion. HBS dosage form of the drug was formulated to overcome this problem. The system prepared was aimed at providing a sustained release of the drug. Thus, instead of entire dose reaching the small intestine, which is the principal absorption site

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of the drug, as in conventional dosage form, with a limited residence time there, only a limited fraction of the dose would be released in a controlled manner from the formulation retained in the stomach.

Experimental

Materials

The main material used in the study, were mefenamic acid (Maral pharmaceuticals Pvt Ltd, chennai), PVP K-30, HPMC K-100, HPMC KV 600, HPMC K50, HPMC K4M, IPA (Iso propyl Alcohol), PEG 6000, Sodium bicarbonate, Magnesium Stearate, and Talc (S.D fine chemicals Pvt Ltd).

S. No	Ingredients	Amount/ Tablet (mg)
1	Poly Ethylene Glycol 6000	75
2	Sodium Bicarbonate	100
3	PVP K-30	100
4	Lactose	100
5	Magnesium Stearate	12.5
6	Talc	12.5

Table 1: General Formulae for Mefenamic acid floating tablet

Mefenamic acid -250 mg, HPMC of various grades used with drug in the ratios (Drug: Polymer, (1:1, 1:1.5, 1:0.5).

Methods

Prepration of HBS Tablets:

The drug Mefenamic acid, HPMC of various grades, poly ethylene glycol 6000, Sodium bicarbonate, were passed through mesh 40# separately and blended thoroughly. The wet mass was passed through sieve 16# and dried at 65°C for one hour to get the moisture content less than one. The blend was granulated with PVP K-30 in IPA solution. Magnesium Stearate and talc were passed through sieve 40# and blended with dried granules. The lubricated granules were compressed on Cadmach eight punch tablet machine (nomenclature Table-1)

Invitro floatation studies:

Static volume Beaker method was used to study the flotation behavior of the prepared HBS tablet, which was placed in the 100ml beaker containing 0.1N Hcl (pH 1.2). The time required for the HBS tablet to rise to surface of the medium was termed as Lag Time and duration of the tablet constantly floating on the medium was termed as floatation time.[5]

Invitro dissolution studies:

Dissolution studies were carried out in USP dissolution apparatus –II using 900ml of phosphate buffer pH 7.4 .The samples were withdrawn periodically over a period of 24hours .10ml samples were withdrawn and were replaced with fresh dissolution medium. The amount of drug released after every hour was analysed at 276 nm using UV spectrometer. The Invitro dissolution graphs of the best formulations were given in Figure 1.

The compatibility study between ingredients was performed by IR spectral anaysis. The granules were evaluated for its flow properties and compressibility studies by measuring the angle of repose and Carr's index (Table-2). The formulated floating tablets were evaluated for the following physical characters like thickness, hardness, friability, drug content, floating lag time, floating time and dissolution profile. The results were presented in the Table no1. The best formulation was chosen on the basis of and buoyancy lag time, floating time and dissolution profile. The *in-vivo* study using rabbit as animal model was carried out by randomized parallel design. .The animals used in this study was approved and issued by animal ethical committee (protocol approval

No.IAEC/XII/09/CLBMCP/2007-208 dated 10.10.2007).

Results and Discussion

Mefenamic acid raw material passed all the tests for identification and percentage of purity of mefenamic acid was found to be 99.13%. The physical compatibility test between drug and other tablets was carried out at 25-30ºC and 75% R.H for two months. The mixture does not show any visible change, and thus inferring that drug and other components do not have any physical incompatibility. The FTIR and UV scan of the HBS of Mefenamic acid tablets exhibited similar peaks to that of the pure drug. No interactions were detected, hence confirming the suitability of excipients used in the formulation.

The bulk density and tapped density ranged from 0.494 to 519 and 0.521 and 0.676 respectively. The percentage compressibility index was below 30, indicating good flow properties. All the granules (F-I to F-XII) were found to be free flowing and their angles of repose were below 30.

The physical properties of MFA GRS tablets (F-I to F-XII) such as tablet size, hardness, friability and weight variation were determined and results are shown in Table 2 and results are found to be within the limits specified in Pharmacopoeia.

The best formula should posses the minimum lag time (within few minutes) as well as maximum floatation time (more than 12h). Buoyancy lag time and duration of floating were determined using USP dissolution test apparatus and the results were represented in Table 2 and Fig 1 respectively. Buoyancy lag time of tablet F-IX was 24 seconds i.e. less than one minute which is the least value as compared to other tablets .The floating time of F-IX was also found to be 24 hours.

The dissolution studies of the formulations (F-I-to F-XII) were represented in Fig 2. The percentage drug release of the formulation F-II, F-V, F-VIII, F-XI was below 50%. whereas for formulation F-I, F-IV, F-VII, F-X were below 70%. The formulation F-IX showed a constant release of 99% in a sustained manner as similar to zero order kinetics (Figure no 3)

Suitability of HPMC grades in the order of HPMC KV600>HPMC K4M > HPMC K100>HPMC K50, as it was concluded from the dissolution profiles.

An Invivo study was performed for the best formulation F-IX using rabbits as animal model and the Cmax was found to be 29.9mcg/ml and Tmax was found to be 6.1 hr.The optimized MFA GRS F-IX was subjected to stability studies at 40ºC under humidity conditions (75%) for a period of two months. Samples were analysed for colour change appearance, drug content and release characteristics. From the result it was observed that there was no significant change in physiochemical properties as well as in drug release profile.

Batch Code	Thickness (mm)	Hardness (kg/cm^2)	Lag Time (Sec)	Floatation Time (hours)	Percentage Weigh loss	Drug Content Mean ±S.D
F-I	5.94	3.8	01	24	0.037	247.6 ± 2.71
F-II	6.40	4.1	15	24	0.043	247.3 ± 3.11
F-III	4.84	3.1	05	24	0.081	249 ± 1.69
F-IV	6.34	3.4	02	24	0.088	247.7 ± 3.19
F-V	6.63	4.2	41	24	0.049	248.6 ± 2.26
F-VI	4.98	3.2	03	24	0.550	247.9 ± 4.05
F-VII	5.69	3.9	12	24	0.063	248.6 ± 2.38
F-VIII	6.67	4.1	02	24	0.030	249.1 ± 1.22
F-IX	4.99	3.5	08	24	0.029	249.0 ± 1.04
F-X	6.14	4.1	04	24	0.012	251.0 ± 3.06
F-XI	6.93	4.2	07	24	0.079	245.4 ± 8.23
F-XII	4.94	3.8	03	24	0.010	247.4 ± 2.79

Table 2: Physical parameters of HBS Mefenamic acid Tablets

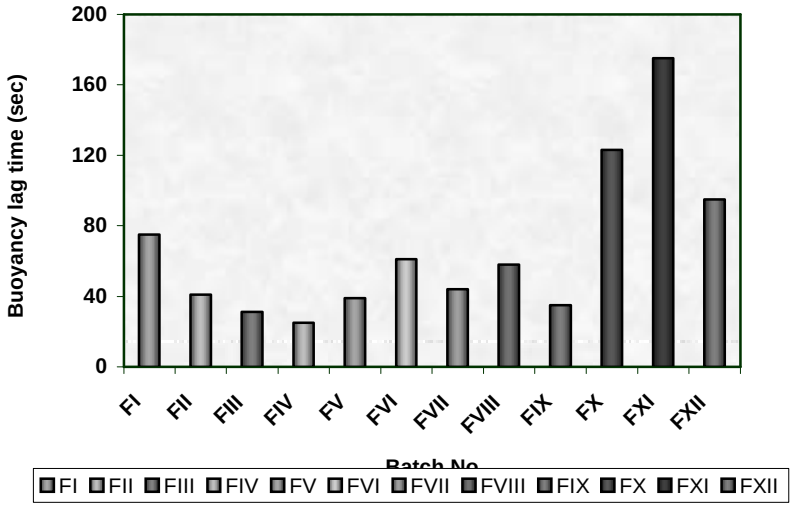

Figure: 1 Buoyancy lag time of Fabricated MFA GRS Tablets (FI-FXII)

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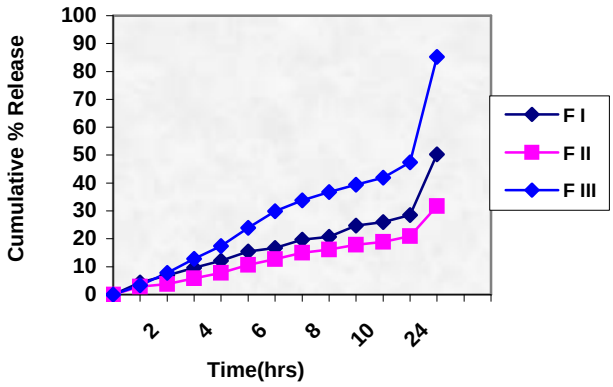

Figure 2a

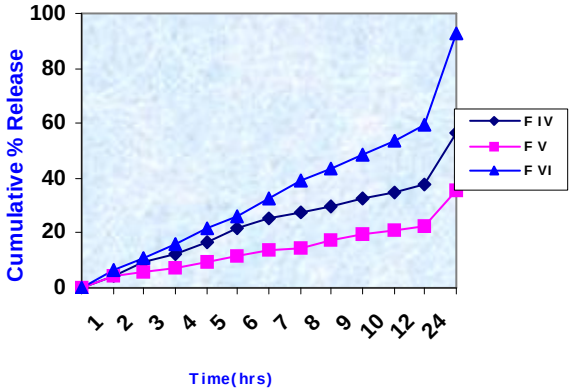

Figure 2b

Fig: 28.

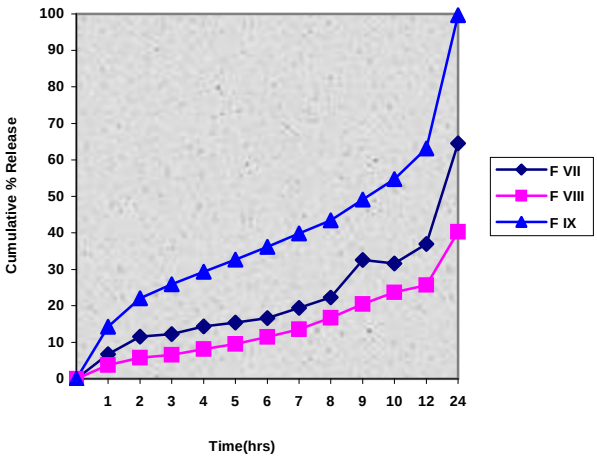

Figure 2c

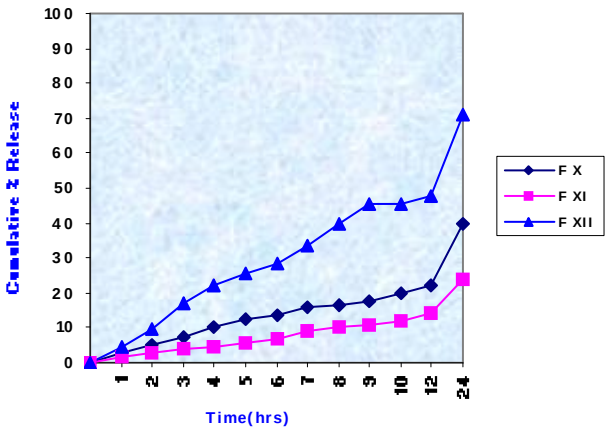

Figure 2d

Figure 2: In-Vitro release profile of MFA GRS Tablets (FI - FXII) in Phosphate Buffer pH 7.4

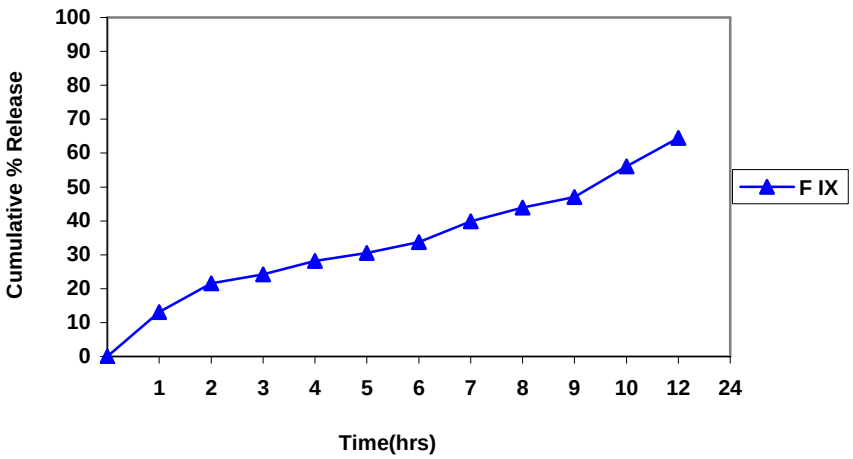

Figure 3: Zero order Kinetics Graphical study of Best Formulation F-IX

Conclusion

It can be concluded that HBS (or) floating tablets of Mefenamic acid (F-IX) with HPMC KV600 in the ratio of 1:0.5 shows desirable characteristics of Invitro floatability of 24 hours and invitro release of 99.65% over a period of 24 hours, with zero order kinetic release and hence F-IX was chosen as best formulation.

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References

1) *Sheth, p.r., and Toussonian, J.,The Hydrodynamically balanced system (HBS™): A novel drug delivery system for oral use . Drug Dev.Ind.Pharm.1984, 10(2):13-319.*

2) *"Drugs for Pain," Med Lett Drugs Ther, 1998, 40(1033):79-84.*

3) *Budoff P W Mefenamic Acid theraphy in dysmennorrhea.J Am Med Ass 1979,241; 2713-2717.*

4) *Patil.JM, Hislakes.RS.,Gide.PS.and Kandam.VI.,Trends in floating drug delivery systems.J. Sci .I res.2006,65,11-12*

5) *Talukder.R., Fassihi.R.and Jain.NK.,A new approach in gastro retentive delivery systems Drug . Dev. Ind. Pharm ,30(4), 405-412*

6) *Baumgartner.s.,Kristel.J.,vreer.F.,vodopivec.P.,an dzorko.B.,Ichikawa.M.,Watanate.s.and Miyake y., A new multiple unit oral floating dosage system preparation and invitro evaluation of floating and sustained-release kinetics. J.Pharm.Sci .1991,80,1062*

7) *Patel VF, Patel NM, Intra gastric floating drug delivery system of cefuroxime axetil: invitro evaluation. Pharm. Sci Tech; 2006,7(1): 12-18*

8) *Whitehead L, Fill JT, Collet JH, Sharma HL, Smith AM. Floating dosage form in vivo study demonstration of prolonged gastric retentive system. J-Controlled Release.1998; 55:3-12.*

9) *Shadab Q,Nadeem I, Mahood A, Muhammad J.Effect of Dehydration on the Pharmacokinetics of Mefenamic Acid.Tr.J.of Med.Sci.1999:29:101-104.*

10) *Mohammad R, Ali A, Fakridin A. High Liquid chromatography method for determination of mefenamic acid in human plasma. Int.J. Pharm.2006; 321(1-2): 167-170.*

11) *Ichikawa M, Watanate S, Miyake Y. A new multiple unit oral floating dosage system preparation and invitro evaluation of floating and sustained-release kinetics. J.Pharm.Sci.1991; 80:10-62*

12) *Desai S, Balton S. Floating drug delivery system invitro in vivo evaluation Pharm.Res.1993; 10:1321-1325.*

13) *Baumgartner S, Kristel J, Vreer F, Vodopivec P. Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm.2001; 95:125-1*

14) *Daves AB, Amin AF, Patel MM.Gastroretentive drug delivery of Ranitidine Hydrochloride. Formulation and invitro Evaluation. Pharm. Sci.Tech.2004; 5(2): article 34.*

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