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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF MEFENAMIC ACID USING HYDROPHILIC POLYMERS

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ABSTRACT

Mefenamic acid is a non-steroidal anti-inflammatory drug used to treat pain, including menstrual pain. It has a dose of 250 mg 4 times daily. It has a very short half-life of 2 hours and thus controlling the release would be beneficial. In the present study, mefenamic acid 250 mg controlled release matrices were prepared by direct compression and *in-vitro* drug dissolution studies were performed to find out the drug release rate and patterns. Hydroxypropylmethylcellulose, Hydroxypropylcellulose and Hydroxyethylcellulose were used as rate controlling polymers. Hydroxypropylmethylcellulose was used as primary rate controlling polymer and effects of addition of Hydroxypropyl cellulose and Hydroxyethylcellulose on in-vitro drug dissolution were studied. Tablets were formulated using total polymer content as 30, 35 and 40 percent with 20 percent standard polymer content of Hydroxypropyl methylcellulose in all batches and varying the concentration of Hydroxypropyl cellulose and Hydroxyethylcellulose in the range of 10, 15 and 20 percent. *In-vitro* drug release was carried out using USP Type II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 hours, followed by 900 ml alkaline dissolution medium (pH 7.4) up to 12 hours. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics.

KEYWORDS: Mefenamic acid , Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Hydroxyethyl cellulose, Release Kinetics.

INTRODUCTION:

Controlled release oral dosage forms are in the focus of interest for several reasons. Customer compliance with the trend to simplicity and more comfort of use, the prolonged drug release with more reliable blood levels than those obtained with conventional dosage forms and life-cycle management of existing API's directed the pharmaceutical development towards sustained release formulations. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration[1]. Hydroxypropyl methylcellulose, Hydroxypropyl cellulose and Hydroxyethyl cellulose can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material[2].

Mefenamic acid, an anthranilic acid derivative, is a nonsteroidal anti-inflammatory (NSAI), antipyretic, and analgesic agent that is used for the relief of postoperative and traumatic inflammation and swelling, antiphlogistic and analgesic treatment of rheumatoid arthritis, and antipyretic in acute respiratory tract infection[3].

Mefenamic acid solubility in water is 0.04 mg mL^{-1}. Mefenamic acid is rapidly absorbed after oral administration. Following a single 1 gram oral dose, mean peak plasma levels ranging from 10 to 20 mg mL^{-1} have been reported. Peak plasma levels are attained in 2 to 4 hours and the elimination half-life approximates 2 hours. The short biological half-life of 2 h following oral dosing necessitates frequent administration of the drug in order to maintain the desired steady state levels[4-6].

Moreover, dosage regimens involving conventional oral dosage forms require drug administration three or four times daily to maintain adequate therapeutic effectiveness, with inherent problems associated with patient compliance. In addition, conventional dosage forms do not protect patients against morning joint stiffness common in rheumatoid disease states. Thus the development and clinical use of sustained or controlled release dosage forms of NSAIDs may have several advantages over the use of conventional formulations, such as reduction of side effects, prolongation of drug action and improvement of bioavailability and patient compliance.

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Therefore, the formulation of MA as sustained release dosage form matrix pellets could be an alternative approach to overcome the potential problems in the gastrointestinal tract, in addition to minimizing dosing frequency[7, 8].

The present study is aimed at formulating sustained release matrix tablets of mefenamic acid using hydrophilic polymers viz. hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxyethylcellulose.

MATERIALS AND METHOD:

MATERIALS:

Mefenamic acid was obtained as gift sample from Meyer Organics Pvt. Ltd. Thane, Maharashtra. Hydroxypropyl methylcellulose (HPMC K 4M) was obtained as gift sample from Signet, Mumbai, Maharashtra. Hydroxypropyl cellulose and hydroxyethyl cellulose were obtained as gift sample from International Specialty Products, Mumbai, Maharashtra. Other materials used were of analytical grade and procured from commercial sources.

METHODS:

PREPARATION OF SUSTAINED RELEASE MATRIX TABLETS OF MEFENAMIC ACID:

Controlled release tablets of mefenamic acid were prepared by direct compression method[9] using microcrystalline cellulose as directly compressible vehicle. Hydroxypropylmethylcellulose (HPMC K 4M), Hydroxypropylcellulose and Hydroxyethylcellulose were used as retardant material for preparation of tablets[10]. Other excipients were magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant. For preparation of Controlled release tablets of miglitol, drug and polymer were weighed accurately, all the ingredients were sieved through 40 mesh screen and mixed with other ingredients and the powder mixture was compressed using 16 station rotary tablet compression machine using 5 mm punches. Tablet compression weight was adjusted to 50 mg. In total, 6 formulations containing different amounts of HPC (F1, F2, F3), and HEC (F4, F5, F6) were prepared.

The formula for various formulations attempted have been given in **Table 1**: Composition of sustained release mefenamic acid tablets

Table 1: Composition and physical characters of sustained release mefenamic acid tablets

Ingredient	F1	F2	F3	F4	F5	F6
Mefenamic acid	250	250	250	250	250	250
HPMC K 4M	100	100	100	100	100	100
HPC 2M	50	75	100	--	--	--
HEC 2M	--	--	--	50	75	100
MCC	90	65	40	90	65	40
Aerosil	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5

PHYSICAL CHARACTERIZATION OF FABRICATED TABLETS[11]:

The quality control tests for the tablets, such as hardness, friability, weight variation etc. were determined using reported procedure. The tablet crushing strength was tested by commonly used Dial tablet hardness tester. Friability was determined b y Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated. Weight variation was determined by weighing 20 tablets individually, the weight variation was calculated. Physical characters observed for various batches are given in **Table 2**: Evaluation of Physical characters of mefenamic acid tablets.

ESTIMATION OF DRUG CONTENT[12]:

An UV/Vis spectrophotometric method based on the measurement of absorbance at 285 nm in 0.1 N HCL was used for estimation of mefenamic acid . From each batch of prepared tablets, 10 tablets were collected randomly and powdered. A quantity of powder equivalent to 100 mg of mefenamic acid was transferred into a 100 ml volumetric flask, 60 ml 0.1 N HCL was added and the solution was shaken for 15 to 20 minutes, diluted to volume with 0.1 M HCl, and filtered using a Whatman No. 42 filter paper. First 10 mL portion of filtrate was discarded and subsequent portions were subjected to analysis.The drug content was estimated by measuring the absorbance of both standard and sample solutions at 285 nm using UV/Vis spectrophotometer (Systronic 2201). Results are tabulated in **Table 3**: Drug content In-vitro drug release studies of mefenamic acid tablets.

IN-VITRO RELEASE STUDIES:

The *in-vitro* dissolution studies were performed using USP type 2 dissolution apparatus (paddle) at 50 rpm. The dissolution medium consisted of 1.2 pH medium for first 2 hours and for subsequent 22 hours in phosphate buffer pH 7.4 (900 ml), maintained at 37±0.5 ^{o}C. The release studies were conducted in triplicate. Aliquot of samples (5ml) were withdrawn at specific time intervals and drug content was determined spectrophotometrically at 285 nm. Results are tabulated in **Table 3**: Drug content and In-vitro drug release studies of mefenamic acid tablets.

Results of *in-vitro* dissolution studies are shown graphically in **Figure 1:** Plot of Cumulative % drug released v/s Time for different formulation (F1-F6).

KINETICS OF *IN-VITRO* DRUG RELEASE[13]:

In-vitro release data obtained was treated to zero order rate equation, Higuchi's equation and Korsmeyer-Peppas equation to know precisely the mechanism of drug release from matrix tablet.

Release data obtained is treated with following modes of data treatment.

Zero order equation - Cumulative percentage drug release vs. Time in hours.

First order equation – Log cumulative percentage drug remained vs. Time in hours.

Higuchi's Diffusion equation - Cumulative percentage drug release vs. Square root time. Korsmeyer-Peppas equation - Log cumulative percentage of drug release vs. Log time.

Results are tabulated in **Table 4**: Different kinetic models for mefenamic acid tablets.

RESULTAND DISCUSSION:

In present work an attempt has been made to formulate controlled release matrix tablets of mefenamic acid using three retardants namely hydroxypropyl methylcellulose used as primary rate controlling polymer and effect on in vitro drug dissolution were studied by addition of hydroxypropyl cellulose and hydroxyethyl cellulose different concentrations and combinations.

PHYSICAL CHARACTERIZATION OF TABLETS:

The formulation of tablets was done by using direct compression technique which was found acceptable. All the formulations were prepared according to the formula given in **Table 1**. The prepared matrix tablets were evaluated for various physical properties as indicated in **Table 2.**

Table 2: Evaluation of Physical characters of mefenamic acid tablets

Formulation code	Thickness (mm)**	Weight variation (%)	Hardness (N)**	Friability (%)*
F1	4.13 ± 0.04	0.76 ± 0.08	85.64 ± 3.24	0.15 ± 0.02
F2	4.17 ± 0.02	1.21 ± 0.11	88.15 ± 1.86	0.13 ± 0.01
F3	4.06 ± 0.07	0.85 ± 0.12	90.38 ± 1.42	0.09 ± 0.04
F4	4.04 ± 0.05	0.97 ± 0.09	81.72 ± 3.29	0.19 ± 0.02
F5	4.12 ± 0.06	1.06 ± 0.07	84.68 ± 2.57	0.14 ± 0.03
F6	4.09 ± 0.02	1.31 ± 0.13	86.74 ± 2.19	0.12 ± 0.05

***All the values are expressed as a mean ± SD., n = 3**
**** All the values are expressed as a mean ± SD., n = 6**

The results of evaluation studies can be summarized as follows:

The thickness of the formulations was found to be in the range of 4.04 ± 0.05 mm to 4.17 ± 0.02 mm. The crushing strength of tablets was in the range of 81.72 ± 3.29 N to 90.38 ± 1.42 N. The loss in total weight of the tablets due to friability was less than 0.5% for all the formulations The high value of crushing strength and low friability indicated that the compressibility of mefenamic acid and adjuvant was good.

DRUG CONTENT AND IN-VITRO DRUG RELEASE OF TABLETS:

Drug content and in-vitro drug release studies are indicated in T**able 3**.

Table 3: Drug content and in-vitro drug release studies of mefenamic acid tablets

Formulation code	Drug content (%)	Cumulative % drug release
F1	98.17 ± 1.18	90.26 ± 0.12
F2	99.28 ± 0.83	86.08 ± 0.08
F3	101.34 ± 0.79	74.83± 0.06
F4	98.64 ± 1.43	97.42 ± 0.17

F5	100.43 ± 0.67	94.78 ± 0.21
F6	98.16 ± 0.91	87.61 ± 0.13

All the values are expressed as a mean ± SD, n = 3

Drug content was found to be uniform among different formulation of tablets and ranged from 98.16 ± 0.91% to 101.34 ± 0.79%. In-vitro drug release studies revealed that formulations F1, F2 and F3 containing combination of hydroxypropyl methylcellulose and hydroxypropyl cellulose showed release between 90.26 ± 0.12 and 74.83± 0.06 at the end of 24 hours. Cumulative release decreased as the concentration of polymer increased. Decrease in release indicates rate controlling effect of hydroxypropyl cellulose in addition to hydroxypropyl methylcellulose. Also the standard deviation is low which is usually observed by using single hydroxypropyl methylcellulose in similar concentration. In-vitro drug release studies revealed that formulations F4, F5 and F6 containing combination of hydroxypropyl methylcellulose and hydroxyethylcellulose showed release between 97.42 ± 0.17and 87.61 ± 0.13 at the end of 24 hours. There is no significant decrease in cumulative percent release indicating no additional retarding effect of hydroxyethyl cellulose in addition to hydroxypropyl methylcellulose.

KINETICS OF DRUG RELEASE:

There are various applied mathematical models for dissolution data of miglitol controlled release tablet are shown in T**able 4**. Formulations F1, F2, F3, F5 and F6 have Higuchi as best fit kinetic model for drug release indicating diffusion-controlled process of drug release. Formulation F4 have Korsmeyer - Peppas as best fit kinetic model for drug release which follow anomalous mechanism for drug transport i.e. non-Fickian kinetics indicating deviation of drug release from Fick's law and where drug release is combination of pure diffusion controlled coupled with dissolution controlled drug release.

Table 4:

Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer - Peppas			Best fit model
				R^2	n	k	
F1	0.944	0.982	0.992	0.991	0.565	1.193	Higuchi
F2	0.941	0.971	0.989	0.988	0.509	1.207	Higuchi
F3	0.940	0.988	0.993	0.973	0.493	1.202	Higuchi
F4	0.937	0.988	0.990	0.993	0.540	1.267	Korsmeyer - Peppas
F5	0.959	0.969	0.998	0.996	0.549	1.226	Higuchi
F6	0.955	0.985	0.995	0.981	0.569	1.160	Higuchi

CONCLUSION:

Results of present research work demonstrate that the combination of hydrophilic polymers was successfully employed for formulation of mefenamic acid controlled release tablets. It is observed that combination of polymers produce a more linear release from matrix tablets with low standard deviation. Hydroxypropyl methylcellulose and hydroxypropyl cellulose showed more retardation effect than combination of hydroxypropyl methylcellulose and hydroxyethyl cellulose for oral controlled release tablets of mefenamic acid. In all the formulations, drug release rate is inversely proportional to the concentration of polymer. From this study, it is possible to design promising oral controlled release matrix tablets containing mefenamic acid for the management of pain in various conditions with more efficacy and better patient compliance.

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