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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF MEFENAMIC ACID USING HYDROPHOBIC 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. Ethyl cellulose (EC), polyvinyl acetate (PVA) and their combination were used as rate controlling polymers. Effects of addition of ethyl cellulose and polyvinyl acetate on in-vitro drug dissolution were studied. Tablets were formulated using total polymer content as 20, 30 and 40 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 24 hours. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. When ethyl cellulose and polyvinyl acetate were used alone as the only retarding polymer, retardation effect increased proportionately as the concentration of polymer increased; however lacked the uniform release profile and desirable physical properties. Combination in the matrix gave both the uniform retardation effect as well as desired physical properties to the formulation. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics.

KEYWORDS: Mefenamic acid , Ethyl cellulose, Polyvinyl Acetate, Release Kinetics.

INTRODUCTION:

Sustained 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 sustained 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]. Ethyl cellulose and polyvinyl acetate can be used as matrix materials. The matrix may be tableted by direct compression.

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[2].

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[3-5].

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.

Therefore, the formulation of MA as sustained release dosage form matrix tablets could be an alternative

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approach to overcome the potential problems in the gastrointestinal tract, in addition to minimizing dosing frequency[6, 7].

The present study is aimed at formulating sustained release matrix tablets of mefenamic acid using hydrophobic polymers viz. ethyl cellulose and polyvinyl acetate.

MATERIALS AND METHOD:

MATERIALS:

Mefenamic acid was obtained as gift sample from Meyer Organics Pvt. Ltd. Thane, Maharashtra. Ethyl Cellulose and polyvinyl acetate was obtained as gift sample from Signet, 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[8] using microcrystalline cellulose as directly compressible vehicle. Ethyl cellulose (EC) and polyvinyl acetate (PVA) were used as retardant material for preparation of tablets[9, 10]. Other excipients were magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant. For preparation of sustained release tablets of mefenamic acid, 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 12.5 mm punches. Tablet compression weight was adjusted to 500 mg. In total, 7 formulations containing different amounts of EC (F1, F2, F3), PVA (F4, F5, F6) and combination of EC& PVA (F7) 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	F7
Mefenamic Acid	250	250	250	250	250	250	250
EC	100	150	200	-	-	-	100
PVA	-	-	-	100	150	200	100
MCC	140	90	40	140	90	40	40
Aerosil	5	5	5	5	5	5	5
Magnesium Stearate	5	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 and 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

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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 formulations (F1-F7).

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.

Firdt 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 hydrophobic polymers namely ethyl cellulose and polyvinyl acetate as rate controlling polymer and effect on in vitro drug dissolution were studied by addition of these polymers at concentrations of 20%, 30% and 40%. Also one formulation was prepared using combination of ethyl cellulose and polyvinyl acetate at 20% each.

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	4.16 ± 0.04	1.13 ± 0.12	68.36 ± 0.93	0.58 ± 0.01
F2	4.08 ± 0.08	1.29 ± 0.16	70.24 ± 1.43	0.55 ± 0.04
F3	4.05 ± 0.06	1.34 ± 0.08	73.51 ± 2.77	0.47 ± 0.03
F4	4.08± 0.04	1.19 ± 0.14	74.15 ± 1.57	0.48 ± 0.03
F5	4.04 ± 0.02	1.33 ± 0.18	76.71 ± 1.46	0.45 ± 0.02
F6	4.17 ± 0.06	1.18 ± 0.09	77.98 ± 2.29	0.44 ± 0.04
F7	4.05 ± 0.05	1.05 ± 0.11	70.23 ± 2.21	0.22 ± 0.03

***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 ± 0.02 mm to 4.17 ± 0.06 mm. The crushing strength of tablets was in the range of 68.36 ± 0.93 N to 77.98 ± 2.29 N. The loss in total weight of the tablets due to friability was less than 0.5% for formulations F3, F4, F5, F6 & F7 and was greater 0.5% for formulations F1& F2. The high value of crushing strength and low friability indicated that the compressibility of mefenamic acid and adjuvant was good for formulations F3, F4, F5, F6 & F7; however compressibility was not good for formulations F1 & F2.

DRUG CONTENT AND IN-VITRO DRUG RELEASE OF TABLETS:

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

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

Formulation code	Drug content (%)	Time required for releasing 50% of drug ($t_{50\%}$) (hrs)	Time required for releasing 80% of drug ($t_{80\%}$) (hrs)
F1	100.24 ± 0.69	8.06 ± 0.12	> 24
F2	99.43 ± 0.76	18.13 ± 0.07	> 24
F3	100.37 ± 1.17	22.16 ± 0.04	> 24
F4	99.16 ± 081	7.07 ± 0.03	16.41 ± 0.17
F5	99.45 ± 0.96	7.22 ± 0.12	18.34 ± 0.13
F6	100.75 ± 1.13	7.95 ± 0.14	19.96 ± 0.04
F7	100.25 ± 1.41	9.81 ± 0.15	20.25 ± 0.18

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

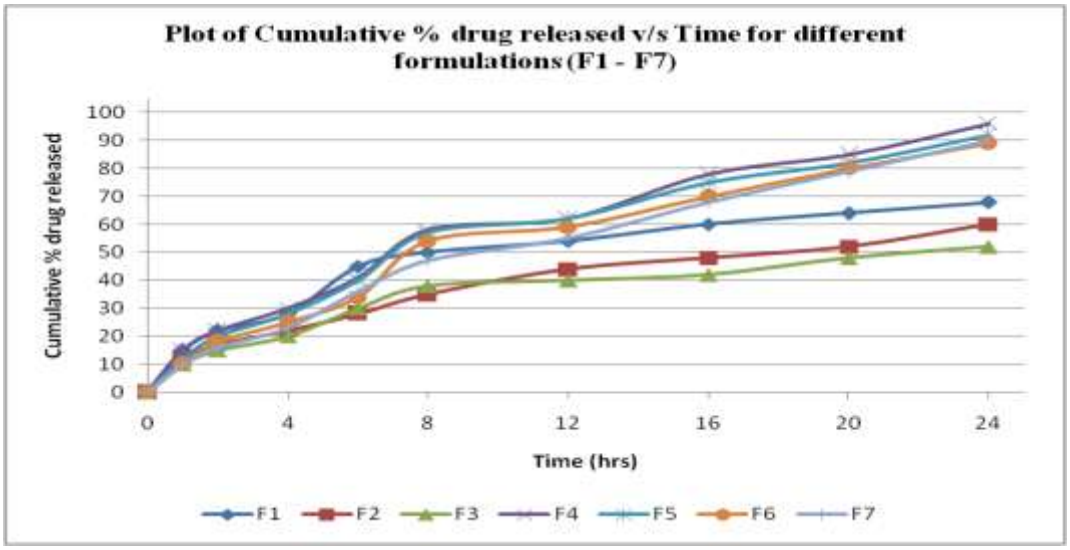

Figure 1: Plot of Cumulative % drug released v/s Time for different formulation (F1-F7)

Drug content was found to be uniform among different formulation of tablets and ranged from 99.16 ± 081% to 100.75 ± 1.13%. In-vitro drug release studies revealed that formulations F1, F2 and F3 containing ethyl cellulose as retarding polymer showed maximum $t_{50\%}$ at 22.16 ± 0.04 hours and maximum $t_{80\%}$ at > 24 hours. In-vitro drug release studies revealed that formulations F4, F5 and F6 containing polyvinyl acetate as retarding polymer showed maximum $t_{50\%}$ at 7.95 ± 0.14 hours and maximum $t_{80\%}$ at 19.96 ± 0.04 hours. For formulation F7 containing combination of ethyl cellulose and polyvinyl acetate $t_{50\%}$ was observed at 9.81 ± 0.15 hours and maximum $t_{80\%}$ at 20.25 ± 0.18 hours. Time at $t_{50\%}$ and $t_{80\%}$ increased as the concentration of polymer increased. Though promising results are observed for $t_{50\%}$ and $t_{80\%}$ for formulations containing ethyl cellulose as retarding polymer, physical characters are not good. Also retardation effect is higher than required. Though promising results are observed for physical characters for formulations containing polyvinyl acetate as retarding polymer, $t_{50\%}$ and $t_{80\%}$ are not good. Also the dissolution profile is not linear. Formulation F7 containing combination of ethyl cellulose and polyvinyl acetate each at 20% (total polymer concentration 40% in formulation) showed good results for physical characters as well as $t_{50\%}$ and $t_{80\%}$. Also release profile is found to be linear. Combination worked in synergy giving desirable results.

KINETICS OF DRUG RELEASE:

There are various applied mathematical models for dissolution data of mefenamic acid controlled release tablet are shown in T**able 4**. All formulations have Korsmeyer - Peppas as best fit kinetic model for drug release and 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.

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Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer - Peppas			Best fit model
				R^2	n	k	
F1	0.862	0.934	0.951	0.966	0.485	1.200	Korsmeyer - Peppas
F2	0.959	0.984	0.992	0.994	0.508	1.069	Korsmeyer - Peppas
F3	0.883	0.924	0.959	0.972	0.522	1.023	Korsmeyer - Peppas
F4	0.959	0.924	0.987	0.989	0.595	1.163	Korsmeyer - Peppas
F5	0.946	0.969	0.987	0.988	0.645	1.095	Korsmeyer - Peppas
F6	0.953	0.976	0.984	0.985	0.686	1.020	Korsmeyer - Peppas
F7	0.978	0.960	0.991	0.993	0.699	0.992	Korsmeyer - Peppas

CONCLUSION:

Results of present research work demonstrate that the combination of hydrophobic polymers was successfully employed for formulation of mefenamic acid sustained release tablets. It is observed that combination of polymers produce a more linear release from matrix tablets with low standard deviation. Ethyl cellulose and polyvinyl acetate in the concentration of 40% to the total polymer concentration is promising concentration for oral controlled release tablets of mefenamic acid and that can give release above 24 hours. 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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