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DESIGN AND EVALUATION OF CR MAFENEMIC ACID TABLETS AND EFFECTS OF CO-EXCIPIENT ON IN-VITRO RELEASE PROFILE

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ABSTRACT

In this study, the controlled release tablets of Mefenamic acid were prepared. The Methocel was used as controlled releasing polymer during dissolution. During study, different drug to polymer ratios were formulated. The directly compressed tablets were prepared from these formulations were subjected to different QC tests. The invitro release pattern was under observation. Moreover, various co-excipients such as starch, methyl cellulose (MC), Carboxy Methyl Cellulose (CMC), Hydroxy Propyl Methyl Cellulose (HPMC) etc were added in the formulations and their effects on the release profile were investigated.

Keywords: Polymers, Controlled Release, Co-Excepients, Tablets, Mefenamic Acid

INTRODUCTION

The phrase Drug delivery reflects the release of drug to into the systemic circulation for diverse pharmacological effects. Controlled drug delivery takes place when a polymer which may be either natural or synthetic in nature is combined with a drug moiety or drug active ingredient in such a way that the active ingredient from the polymer is released in a pre-designed manner. The release of the active ingredient from drug moiety may be constant for a long period of time, it may be triggered by the external environment of the body or other external events or it may be cyclic over a long period of time **[1]**. And in case, the main purpose behind the controlling of the drug delivery is to achieve more

effective therapies and also eliminating the potential for both under dosing and overdosing and to avoid poisons or other harmful adverse effects **[2]**.

Mefenamic acid is a non-steroidal anti-inflammatory drug used to treat pain and inflammation and also for menstrual pain. Mefenamic acid is also suggested in premenstrual migraine headache prophylaxis. Mostly, it is prescribed for oral administration. Its exact mechanism of action is unknown but is suggested to inhibit prostaglandin synthesis. It is chemically 2-(2, 3-dimethylphenyl) amino benzoic acid.

In this study our aim was to design controlled release formulations of Mefenamic acid (100mg) tablets and then qualitative and quantitative evaluation of formulation.

EXPERIMENTAL PLAN

Materials & Chemicals

The Chemical materials used in the research work were of the following origin;

Sodium Hydroxide (Merck, Germany),

Mono basic potassium phosphate (Merck, Germany),

Carboxy Methyl Cellulose (Dow Chemical Co., Midland USA),

Starch (Dow Chemical Co., Midland USA),

Mefenamic Acid (Gift sample from Bio Labs Pharma Islamabad, Pakistan),

Lactose and Magnesium stearate (BDH Chemical Ltd., Pool England),

Methocel K100M Premium EP (Dow Chemical Co., Midland USA)

Instruments

The instruments used during the manufacturing and evaluations of tablet were as follows:

Dissolution Apparatus (Pharma Test),

Electronic Balance Model No, AX-200 (Shimadzu, Japan)

Single Punch Tablet machine (Erweka AR 400, Germany),

UV-Visible spectrophotometer (UVIDEC-1601 Shimadzu, Japan),

Friability Tester (Erweka TA3R, Germany)

Hardness Tester (Erweka Apparatus TB24, Germany)

Mefenemic Acid tablet Formulation

The controlled release tablets of Mefenamic acid (100 mg) were formulated by using 100 mg of active drug and different ratios of controlled release polymer and other necessary excipients. For this research work the formulations used are shown in **Table 1**. In theses formulations starch and magnesium stearate were used as filler and lubricant respectively.

Evaluation of Mixed Powder

The mixed powder of Mefenamic acid-polymer was analyzed for several physical

tests such as angle of repose and compressibility index etc. The angle of repose was observed by funnel method while the compressibility index was determined by cylindrical method. All these tests were carried out as per USP specifications **[3]**.

Preparation of 0.2 M Phosphate Buffer Solution

The 0.2 M phosphate buffer of (pH 7.2) was prepared by dissolving 27.218g of monobasic potassium phosphate (KH_2PO_4) in 1000ml of distilled water to get 0.2M monobasic potassium phosphate solution and prepared 0.2M NaOH by dissolving 8g of NaOH crystals in 1000ml distilled water. Mixed 39.1ml of 0.2M NaOH solution with 50ml of 0.2M monobasic potassium phosphate solution and diluted to 200ml with distilled water.

Preparation of Stock Solution

100ml of Mefenamic acid stock solution was prepared by dissolving 20mg of Mefenamic acid in small amount of phosphate buffer (7.2 pH) in 100ml volumetric flask and then the volume was made to 100ml with phosphate buffer (7.2 pH). Each ml of stock was containing 0.2mg of Mefenamic acid.

Preparation of Tablets

Drug and polymer was taken in mortar and was grind to fine powder than all other excipients were added except lubricant. This mixture was passed through 20 sieve size mesh for three times and then lubricant was added and again passed through the same sieve. The prepared powder was compressed to tablets using single punch tableting machine at an average hardness of 7 kg/cm^2.

Evaluation of Tablets

Hardness of the tablets was determined by hardness tester (Erweka Apparatus TB24, Germany) and dimensional tests were performed using Vernier calliper. The friability of the tablets was determined using Friability tester (Erweka TA3R, Germany).

Dissolution Study

The in-vitro dissolution study was carried on USP apparatus II at 100rpm by using. Phosphate buffer pH 7.2 as dissolution medium, each station of the apparatus containing 900 ml. Samples (5ml) were withdrawn from each station at specific time intervals for the analysis of drug release study. The drug concentration samples were analyzed using UV visible spectrophotometer at 350 nm wavelength.

RESULTS AND DISCUSSION

Physical Characteristics of Mixed Powder and Compressed Tablets

Mefenamic acid-Methocel K100M Premium mixed powder was evaluated using several methods. The angle of repose was determined using funnel method. For the determination of

compressibility index cylindrical method was used. All these tests were performed according to USP specifications. The results of angle of repose and compressibility index shown in **Table 2** reflect that the designed formulations have good flow properties and suitable for compression into tablets.

The results of physical quality control tests applied to the compressed tablets **(Table 3)** also within USP ranges.

Drug Release Studies

The data of dissolution profiles were fitted in several kinetic models and drug release mechanism from tablets were calculated. These kinetic models include:

(i) Zero-order Kinetics

$$W = k_1 t$$

(ii) First-order Kinetics

$$\ln (100 - W) = \ln 100 - k_2 t$$

(iii) Hixon Crowel's Equation (erosion model)

$$(100 - W)^{1/3} = 100^{1/3} - k_3 t$$

(iv) Higuchi's Square of Time Equation (diffusion model)

$$W = k_4 t^{1/2}$$

(v) Power Law Equation (diffusion/relaxation model)

$$M_t / M_\infty = k_5 t^n$$

Where (W) is the percent release of drug at a time t, k_1-k_4 are the release rates constants depending on the kinetic model used in the data. M_t/M_∞ is a fractional release of the drug into the dissolution medium and k_5 is a constant which incorporate geometric and structural characteristic of tablets **[4]**. The parameter (n) is a diffusion exponent that characterizes the release of the drug transport mechanism **[5]**.

The drug release profiles of designed Mefenamic acid CR tablets and that of the reference standard formulation are shown in **Figures 1, 2, 3, 4**. These figures reflect that the drug release rate from all of the test formulations was reduced and the release profiles significantly extended as compared to the reference sample.

Influence of Co-excipients On Release Pattern:

The use of co-excipients in tablet formulations is done to obtain desirable properties. In this regard, the use of several co-excipients like CMC, HPMC and Starch were examined on the release rate of directly compressed CR tablets of Mefenamic acid. Reference drug was taken from the local market. The comparative studies gave difference between different release profiles from the tested and the standard reference formulations. Starch enhances the release of drug from the polymer and the drug was released within 5 hours which was intended to release the drug in 24 hours. **Figure 5** shows Mefenamic acid CR tablets containing MC as co-excipient. In vitro dissolution profile reflects that MC enhances the drug release

from the matrix tablets and the formulations which are intended to release the drug in 24 hours, released the drug in only 4-6 hours. The CMC swells after water absorption and the drug was released from the test tablets containing CMC as co-excipient within 4-5 hours **(Figure 6)** as compared to reference which show drug release profile of 24 hours. HPMC is also a water soluble co-excipient. It also enhances the drug release form formulation having HPMC as a co-excipient and the drug was released within 4-5 hours **(Figure7)**.

Table 1: Formulation of Mefenamic Acid Tablets

Drug	D: P ratio	Polymer	Filler (Lactose)	Lubricant (0.5%)	Co-excipients CMC, HPMC, MC
Mefenamic acid-Methocel CR tablets					
100 mg	10:01	10 mg	89 mg	1 mg	-
100 mg	10:02	20 mg	79 mg	1 mg	-
100 mg	10:03	30 mg	69 mg	1 mg	-
100 mg	10:04	40 mg	59 mg	1 mg	-
Mefenamic acid-Methocel CR tablets with co-excipients					
100 mg	10:04	40 mg	41.3 mg	1 mg	30% of lactose 17.7 mg

Table 2 Results of Physical Test (Angle of Repose and Compressibility Index) of Powder

S. No.	Formulation	Angle of Repose (Deg)	Compressibility Index %
1.	F1	42 ± 3	16 ± 3
2.	F2	42 ± 4	15 ± 4
3.	F3	40 ± 3	17 ± 4
4.	F4	41 ± 4	15 ± 5

Table 3 Physical Properties of Compressed Tablets

S. No.	Formulation	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)
1.	F1	7.7 ± 0.3	2.7 ± 0.4	8 ± 0.5 mm
2.	F2	7.5 ± 0.2	2.5 ± 0.5	8 ± 0.5 mm
3.	F3	7.6 ± 0.3	2.6 ± 0.5	8 ± 0.6 mm
4.	F4	7.7 ± 0.4	2.7 ± 0.4	8 ± 0.6 mm

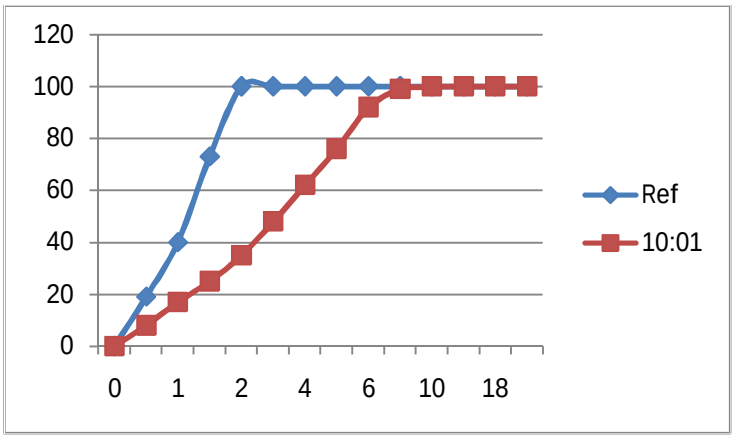

Figure 1: Release Profile of Test Sample (D: P 10:01) and Reference Standard

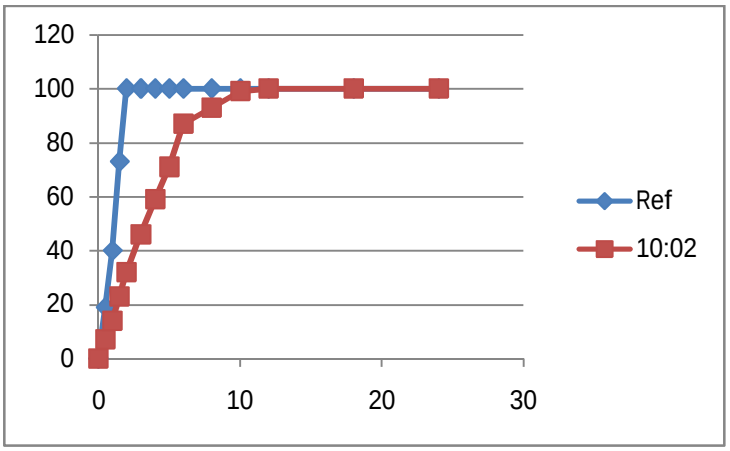

Figure 2: Release Profile of Test Sample (D:P 10:02) and Reference Standard

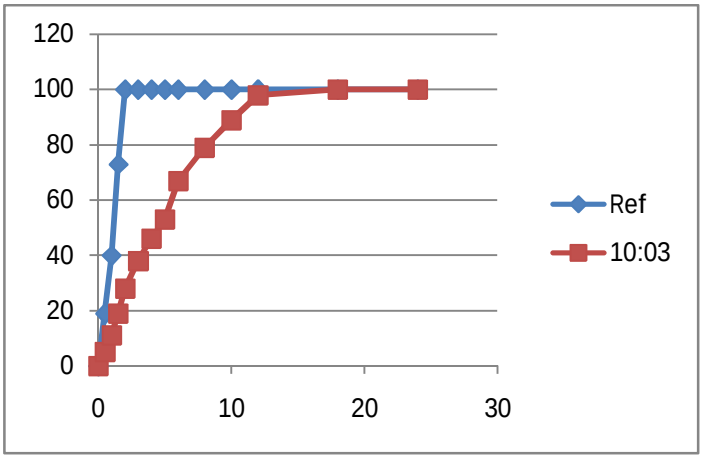

Figure 3: Release profile of Test Sample (D: P= 10:03) and Reference Standard

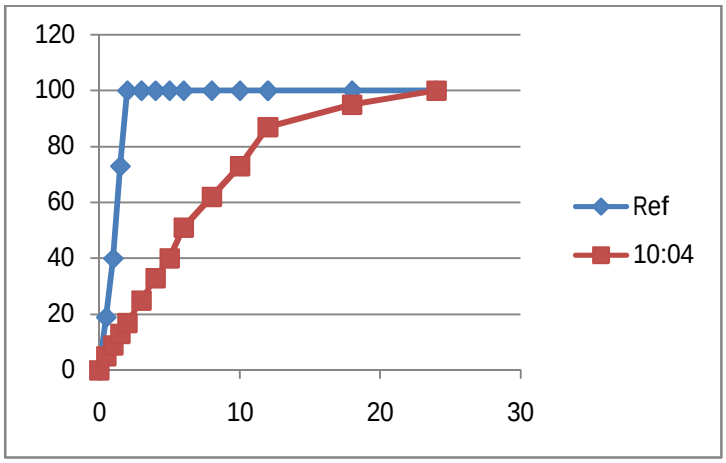

Figure 4: Release Profile of Test Sample (D: P 10:04) and Reference Standard

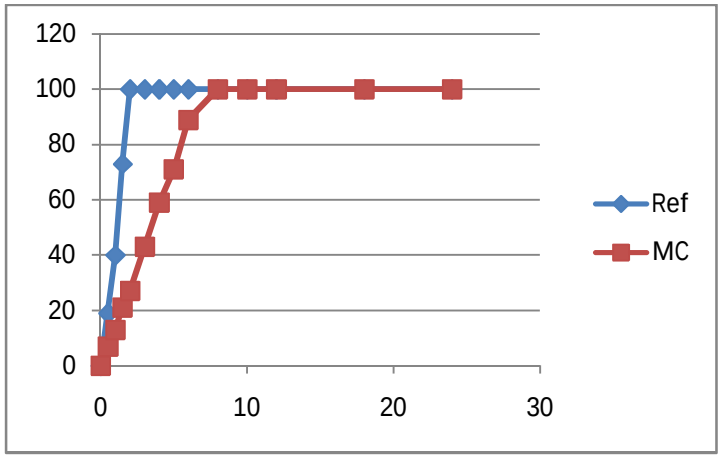

Figure 5: Release Profile of Test Sample with Co-Excipient MC and Reference Standard

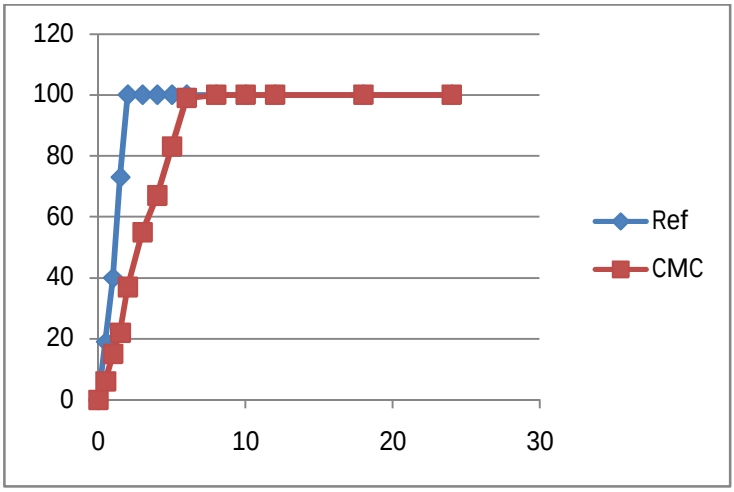

Figure 6: Release Profile of Test Sample with Co-Excipient CMC and Reference Standard

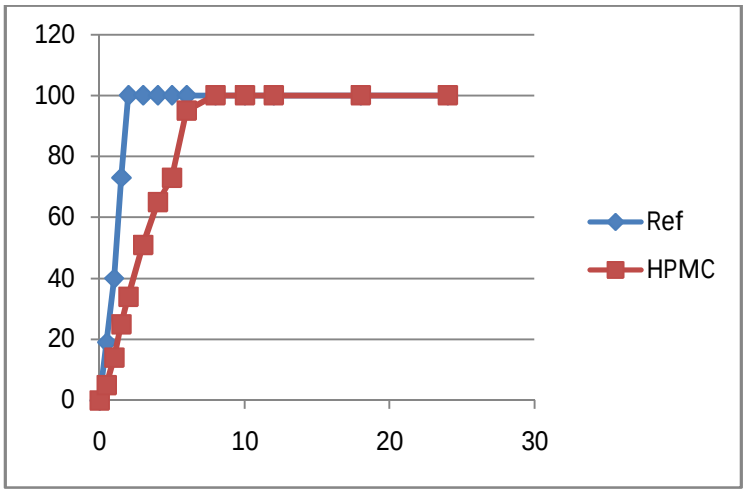

Figure 7: Release Profile of Test Sample with Co-Excipient HPMC and Reference Standard

CONCLUSION

During the dissolution procedure, the swelling of matrix tablets was noticed. This swelling may be due to water uptake by the polymer which results in the swelling of tablet. The leads to a hasty decline in the glass transition temperature of the polymer. In the presence of dissolution medium, the dissolution solvent exerts a stress due to which there take place a relaxation reaction in the polymer chains, which produce increased distances among the polymer chains. In the hydrated polymer, there occurs an increase in the molecular volume of the polymer, which reduces the free volume because due to the presence of microspores, which itself could manifest as a shift in the drug release mechanism. Several other investigators observed the same results during their investigative studies.

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