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Controlled Release Matrix Tablets of Mefenamic Acid Containing Methocel as Matrix Material

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Abstract

Mefenamic acid controlled release tablets with Methocel were prepared at different drug to polymer ratio (D: P) by direct compression method. Aim of the study was to examine the influence of different polymer concentrations and the effect of several co-excipients [CMC, HPMC and MC (Microcrystalline Cellulose)] on the rate of drug release and release mechanism from the CR tablets. Mefenamic acid-Methocel tablets were evaluated for different physico-chemical parameters and in vitro release study of the drug was performed in phosphate buffer pH 7.2 at a constant temperature of 37 ± 0.1°C. In order to investigate the release mechanism of the drug from the tablet 5 different kinetic models were employed to the dissolution data. Factor f_2 applied to the drug release profile from the test CR tablets and were then compared with marketed immediate release Mefenamic acid tablets and were observed to have no resemblance. Different co-excipients in the study were observed to have a splendid enhancing effect on the release rate of Mefenamic acid from CR matrix tablets.

Keywords: Mefenamic acid; Controlled release dosage forms; In-vitro dissolution; mathematical models

Introduction

Day by day the numbers of patients with acute to moderate diseases are highly increasing and these patients are treated with a lot of medicines in their chronic situations for longer durations of time and this can lead to non-compliance. Drugs with short half lives must be taken several times a day so are mainly associated with these types of problems. Controlled drug delivery systems can be used to solve such types of problems [1]. Oral controlled drug delivery systems have gained much attention these days because these systems can deliver the drug at predetermined time and rate thus maintains the therapeutic levels in the plasma for longer durations. These dosage forms reduce the dosing frequency thus has a good compliance [2]. Ideal drug delivery systems should be composed of two basic properties i.e. targeting the drug to specific site of actions and delivering the drug according to the body need for a specific period of time. Controlled drug delivery systems can be used to achieve both of these types of properties that could improve the drugs therapeutic levels and also improves the safety of the drug. The need of cheap medicaments is of very immense interest in controlled drug delivery systems in the recent years [3].

In controlled drug delivery systems and polymeric carriers, several developments like enteric coating, polymeric reservoir devices and osmotic pumps have been done. The matrix system is most widely used in the development of sustain drug delivery systems because of its ease of manufacturing. For development of sustain drug delivery systems several types of natural and synthetic polymers have been investigated, mostly of which are synthetic hydrophilic polymers. These polymers have the ability to extend the release of the drug from the polymeric matrix tablets [4].

Material and Methods

NaOH (Merck, Germany), Mono basic potassium phosphate, CMC, Starch, Mefenamic acid (Bio Labs Pharma Islamabad, Pakistan), Lactose and Magnesium Stearate (BDH Chemical Ltd. , Pool England), Methocel (Dow Chemical Co. , Midland USA), PharmaTest Dissolution Apparatus, Single Punch Tablet machine (Erweka AR 400, Germany), UV-Visible spectrophotometer (UVIDEC-1601 Shimadzu, Japan), Friability Tester (Erweka TA3R, Germany) and Hardness Tester (Erweka Apparatus TB24, Germany).

Formulation and Preparation of Tablets

200mg Mefenamic acid-Methocel tablet, containing Mefenamic acid 100mg was formulated at drug-to-polymer (D: P) ratio of 10:1, 10:2 and 10:3. Lactose was used as excipient and magnesium Stearate (0.5%w/w) as lubricating agent. Formulations are shown in table 1 and 2.

In this investigation study Methocel was used as rate controlling polymer. All the materials were weighed according to table 1 and 2, for Mefenamic acid-Methocel controlled release tablets at different D: P ratios. For the equal distribution of the drug and all the other excipients, Mefenamic acid with Methocel and all other excipients except magnesium stearate (Lubricant) were blended geometrically with pestle and mortar, passed through #16 mesh sieve three times. After this magnesium stearate was added to the mixture and was again passed thrice through the same mesh sieve. The final mixture was compressed into tablets using single punch tablet machine (Erweka AR 400, Germany) using concave punches of 8 mm with a hardness range of 7 kg/cm^2 to 8 kg/cm^2.

To investigate the effect of co-excipients in the release pattern of Mefenamic acid, 30% of lactose was replaced by HPMC, CMC and Starch as shown in the table 2.

In Vitro Drug Release Study

Measurement of drug was performed according to USP method

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D: P Ratio	Mefenamic acid	Methocel	Filler (lactose)	Lubricant (Mg-Stearate)	Co-excipients (HPMC, CMC and Microcrystalline Cellulose)
10:1	100 mg	10 mg	89 mg	1 mg (0.5%)	_____
10:2	100 mg	20 mg	79 mg	1 mg (0.5%)	_____
10:3	100 mg	30 mg	69 mg	1 mg (0.5%)	_____

Table 1: Composition of 200mg Mefenamic acid and Methocel® (10:1, 10:2 and 10:3) controlled-release matrix tablets

Mefenamic acid	Methocel	Filler (lactose)	Lubricant (Mg-Stearate)	Co-excipients (HPMC, CMC and Microcrystalline Cellulose)
100 mg	30 mg	48.3 mg	1 mg (0.5%)	20.7 (30% of lactose)

Table 2: Composition of 200mg Mefenamic acid and Methocel® (10:3) controlled-release matrix tablets containing co-excipients (HPMC and CMC).

1, using 8-station dissolution apparatus Pharma Test Model # PTWS-11/P, TPT (Hainburg, Germany). Each station or flask was filled up to 900ml with 0.2M phosphate buffer (PH 7.2) used as dissolution medium to study the release of the drug from the tablets at 100rpm and 37 ± 0.1°C. At predetermined time intervals, 5ml of samples were taken with the help of syringe and were analyzed spectrophotometically at a detection wave length of 350 nm with the help of UV- Visible Spectrophotometer UV-1601 (Shimadzu, Japan). After each sampling, equal volume of the dissolution medium was added as replacement solution. From the UV absorbance values and a standard Mefenamic acid calibration curve, percentage release was calculated.

Investigation of Drug Release Kinetics

To study the Mefenamic acid release kinetics from each type of matrix tablets, the following mathematical models were fitted to the release data:

1. Zero- order Kinetics Xu GJ & Sunada H 1995 [5]

$W = k_1 t$

2. First- order Kinetics Xu GJ & Sunada H 1995 [5]

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

3. Hixon Crowel's Equation or Erosion Model Xu GJ & Sunada H 1995 [5]

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

4. Higuchi's Square Root of Time Equation Higuchi's 1963 [6]

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

5. Power Law Equation or Diffusion/ Relaxation Model Ritger RL & Peppas NS 1987

$M_t / M_\infty = k_5 t^n$ [7]

Where W shows drug-release in percent at time t and release rate constants are k_1-k_4, depending on used the kinetic model. M_t/M_∞ indicates the fractional drug release into the dissolution medium and the constant k_5 is incorporating structural and geometric properties of tablet. The parameter n is a diffusion-exponent that shows the drug release transport mechanism. Whenever n = 0.5, the drug diffuses from polymeric matrix and is released the with a Quasi-Fickian diffusion mechanism. When n>0.5, then anomalous, a non-Fickian, Case-II or zero- order release kinetic is achieved. When n = 1, a non-Fickian, Case-II or zero- order release kinetics is achieved.

Applying the Similarity (f_2) Factor for Dissolution Equivalency

Recent approach to a similarity factor (f_2) was suggested for comparison of dissolution profiles and was indicated by FDA centre for drug evaluation and research (CDER) and also by European medicines evaluation agency (EMEA) committee for proprietary medicinal products (CPMP) as an assessment criterion of similarity between two *in vitro* dissolution profiles. The f_2 is logarithmic reciprocal square root transformation of sum of squared error and shows a measurement of the similarity in the percent (%) dissolution between the curves [8,9]. similarity factor (f_2) equation is given:

$$f_2 = 50\text{Log}\{[1+1/n\, W_t \Sigma^n_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where n indicates the number of pull points, W_t is an optional weight factor, R_t is the reference profile at time (t) and T_t is the test profile at the same time. When the f_2 value is 100 indicates that the test and reference profiles are similar. When the value of f_2 becomes smaller, the dissimilarity between release profiles increases [10]. The FDA has suggested that two dissolution profiles should be considered identical when f_2 values occur between 50 and 100. Dissolution behavior from test formulations of Methocel® was compared with and also with marketed (Ponstan 250 mg, Parke-Davis reference Conventional Tablets).

Results and Discussions

Mefenamic acid from reference immediate release formulation, and methocel® formulations

Mefenamic acid release profiles from reference immediate release formulation and test Mefenamic acid -Methocel matrices at D: P ratio of 10:1, 10:2 and10:3 are shown in (Figure 1).

Reference immediate release 100mg Mefenamic acid tablets released 100% of the drug after approx. 2 hrs. Methocel formulations at the ratios10:1, 10:2 and10:3 released 100% of the drug at 8, 17 and 23 hrs respectively. It could be clearly observed that Methocel successfully

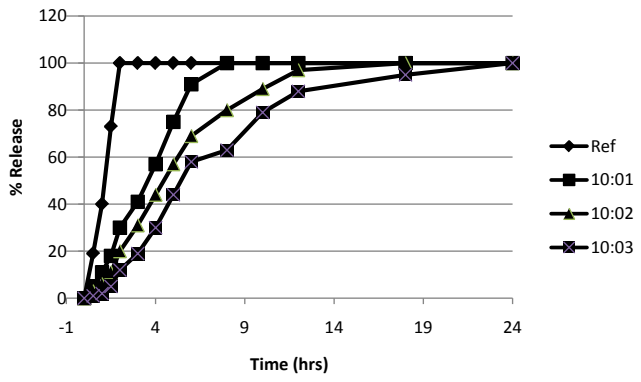

Figure 1: *In vitro* Release of Mefenamic acid in Phosphate Buffer 7.2.

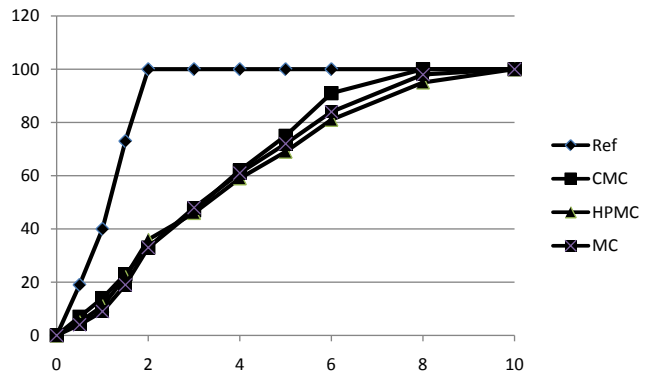

Figure 2: *In vitro* Release of Mefenamic acid containing co-excipients D: P ratio 10:3.

extend the release of the drug during *in vitro* dissolution. It was also observed that the drug prepared with polymer at D:P ratio 10:3 gives more extended release as compared to other two ratios indicating that by increasing of concentration of polymer gives more extended time for drug release and lesser drug release [11]. The addition of co-excipients to the formulations enhanced the drug release rates successfully from the tablets containing Methocel as polymer which could be observed from the figure below. These co-excipients were added to only optimized formulation that is prepared at D:P ratio of 10:3 and thereafter enhance the release of drug by releasing drug in 8 hrs by using CMC, 9 hrs by using HPMC and 9.22 hrs by using MC. These results can prove the findings of certain investigators [11], in the investigative studies of those the drug release was enhanced by using co-excipients in polymeric tablets containing suitable polymers for rate control.

The drug was released during *in vitro* dissolution studies by a specific transport mechanism which was identified by using certain kinetic models. The value of R2 indicates the linearity and optimized constant drug release during in vitro dissolution studies. The value of 'n' which is a diffusion coefficient as mentioned in Korsmeyer Pappas equation represents the transport mechanism. In the given study the value of 'n' for the optimized CR formulations were greater than 0.5 and less than 1, indicating anomalous, non-Fickian diffusion mechanism. In the presenting study, dissolution equivalency factor f2 was applied to the *in vitro* dissolution profiles to find out the similarity between the dissolution profiles of test formulation and a conventional formulation taken as reference standard. This test concludes that the values of f2 were lesser than 50 (range 50-100) indicating difference between the release profiles of the two comparative formulations as the test formulation was a CR formulation and the reference standard was a conventional dosage form.

Conclusion

The results of different parameters revealed that polymer Ethocel is successful in developing controlled release tablets of Mefenamic acid, which gives an optimum nearly constant release during *in vitro* dissolution studies for a long period of time. The several co-excipients used in this study concluded that these can be used for achieving optimum results.

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