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PREPARATION OF CONTROLLED-RELEASE TABLETS CONTAINING ACECLOFENAC AND ITS *IN VITRO* STUDIES

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ABSTRACT

The objective of this study was to develop uncoated HPMC matrix tablets, evaluating the relationship and influence of different content levels of microcystalline cellulose (MCC), starch and lactose, in order to achieve a zero-order release of Aceclofenac HPMC matrix tablets of Aceclofenac using microcrystalline cellulose (MCC), starch and lactose were prepared by wet granulation process. The USP paddle method was selected to perform the dissolution profiles carried out in 900 ml 0.1 N HCl, and phosphate buffer. There was no significant difference in drug release between the hydrophilic matrices when the HPMC concentration was modified in low percentage. Release kinetics of Aceclofenac from these swollen matrices was principally regulated by starch (17 percent) or lactose (17 percent), even in the presence of MCC. When starch (8.5 percent) and lactose (8.5 percent) were mixed at lower concentration in a ratio 1:1, MCC (5 percent or 7.5 percent) appeared to control the drug release. The release profile remained unchanged after three months storage of tablets. The best-fit release kinetics was achieved with the zero-order plot, followed by the Higuchi and first-order equations. The data obtained proved that the formulations are useful for a sustained release of Aceclofenac, due to the percentage released after 8 hours is nearly to 70 percent. The release of Aceclofenac was influenced by the presence of MCC, and by the different concentrations of starch and lactose. Compared to conventional tablets, release of the model drug from these HPMC matrix tablets was prolonged; as a result, an oral release dosage form to avoid the gastrointestinal adverse effects was achieved.

Keywords: Aceclofenac, *invitro* studies, HPMC, MCC and USP.

INTRODUCTION

Hydrophilic matrices containing swellable polymers are referred as hydrogel matrices. swellable controlled-release systems or hydrophilic matrix tablets. A number of polymers have been investigated to develop *in situ* gel-forming systems, due to the ability of these hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and corss-linking[1,2,3].

These systems draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Under ideal conditions, a sustained-release formulation maintains therapeutic blood level of a drug for a specific period of time. Oral controlled-release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects[4].

One method of fabricating controlled-release formulations is by the incorporation of the drug in a matrix containing a hydrophilic, rate-controlling polymer[5,6]. Hydroxy-propyl-methyl-cellulose (HPMC) is the polymer most widely used as the gel-forming agent in the formulation of solid, liquid, semisolid and even controlled-release dosage forms.

Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage forms are controlled by the hydration of HPMC, which forms a gel barrier through which the drug diffuses[7,8]. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rate. The importance of the diffusion layer for a swollen HPMC matrix was illustrated in a mathematical model[9]. In addition, the influence of technological variables on drug release from HPMC matrices was reviewed by Vazquez *et al.,* (1992).

Numerous studies have been carried out in order to achieve a desirable release rate of several non-steroidal anti-inflammatory drugs to treat rheumatoid arthritis, and osteoarthrits. Aceclofenac is one of the most useful and potent NSAIDs agent. It takes 1-1.3 hrs to reach its maximum concentration. It is metabolized to 4-Hydroxyaceclofenac, 4-hydroxydiclofenac, 5-hydroxyaceclofenac and diclofenac.

The goal of this study was to develop uncoated HPMC matrix tablets by wet granulation process, evaluating the relationship and influence of co-excipients. Microcrystalline cellulose (MCC) and starch were chosen as release modifiers, and lactose as water-soluble diluent. Another objective of this study was to attempt to achieve a zero-order release of the model drug from these uncoated HPMC matrices.

MATERIAL AND METHODS

Material

Aceclofenac was supplied by Aristo Pharmaceuticals Ltd. India HPMC, were procured from SJCPS, Bhubaneshwar India. MCC, Lactose, PVP (M. wt. 40,000) were purchased from Central Drug House (P) Ltd. India. All other reagents were of analytical and pharmaceutical grade.

Preparation and characterization of matrix tablets

The detailed compositions of HPMC matrix tablet formulations are given in Table-1.

HPMC, at different ratios was blended with the Aceclofenac microcrystalline cellulose (MCC), starch and/or lactose, in a mixer for 5 minutes. Thereafter, the powders were granulated with 10% w/v PVP/EtOH solution, sieved using a Nº14 mesh screen, and the granules obtained dried in a hot air oven at 40ºC for 3 hours. Finally, the granules were dried and sieved using a Nº12 mesh screen before tableting. Tablets of approximately 330mg weight each were prepared from these granules after addition of starch (4%) and magnesium stearate (3.5%). Tablets were compressed using a single punch-tableting machine Industrial Pharma, New Delhi, India with 9mm flat round punches. Three batches were prepared for each formulation. The physical properties of the biopolymeric matrix tablets are given in Table -2. The weight variation of the tablets was evaluated on 20 tablets using an electronic balance. ANAMED Instruments (P) Ltd. India The flow properties were measures by the angle of reposef. Friability was determined using 6 g of tablets in a Roche friabilator for 4 min. at a speed of 25rpm. For each formulation the hardness of 10 tablets was also evaluated using an ERWEKA TBT 28 apparatus (Erweka GmbH, Germany).

Table - 1: Composition (in mg) of 100mg. Aceclofenac matrix tablets

Formulation	HPMC	MCC	Starch	Lactose
T1	148.9	-	56.00	-
T2	131.8	16.5	56.00	-
T3	123.6	24.7	56.00	-
T4	148.9	-	-	56.00
T5	131.8	16.5	-	56.00
T6	123.6	24.7	-	56.00
T7	148.9	-	28.00	28.00
T8	131.8	16.5	28.00	28.00
T9	123.6	24.7	28.00	28.00

The tablet hardness ranged from 7 to 9 Kp. The thickness of the tablets was measured on 10 tablets with a Vernier Caliper, Mitutoyo, Japan.

In vitro Drug Dissolution Studies

Drug release profiles were evaluated in vitro using a dissolution test apparatus (USP Std.) Industrial Pharma, India. The USP method was

Table - 2: Physical properties of Aceclofenac matrix tablets

Tablet	Weight (mg)	Friability (%)	Hardness (kp)	Thickness (mm)
T1	329.6±2.6	0.63±0.1	7.5±1.3	4.12±0.01
T2	331.8±3.3	0.69±0.3	8.2±1.2	4.14±0.02
T3	330.5±2.1	0.35±0.2	8.5±1.3	4.13±0.03
T4	329.1±3.2	0.19±0.2	7.8±1.3	4.12±0.05
T5	330.2±2.6	0.23±0.3	8.7±1.0	4.14±0.03
T6	329.8±1.8	0.08±0.1	7.8±1.3	4.14±0.07
T7	331.9±2.2	0.47±0.2	7.2±1.0	4.13±0.03
T8	329.8±1.6	0.40±0.4	8.3±1.2	4.14±0.02
T9	330.9±2.9	0.08±0.3	8.6±1.3	4.12±0.03

selected to perform the dissolution profiles of Aceclofenac from HPMC. The same test for all the formulations was carried out in 900 mL 0.1 N HCl, and phosphate buffer, (USP XXIV) maintained at 37±0.5ºC at a paddle rotation speed of 50 rpm. Withdrawing 5 mL filtered samples at preselected intervals up to 8 hours monitored progress of the dissolution. The release rates from these hydrophilic polymeric matrices were conducted in a medium of changing pH by starting with a tablet in HCl solution (pH=1,2) for 2 hours. Then, the tablets were immersed into a phosphate buffer (pH=6.8) for 6 hours. The sample solutions were analyzed for Aceclofenac by UV absorbance at 282nm using a Spectrophotometer (UV-Vis, Genesys-2) Cummulative percentage of drug release was calculated and the mean of three determinations was used in data analysis.

Release Kinetics

To study the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations:

Zero-order equation: $Q=Q_o \cdot k_o t$(1)

where Q is the amount of drug release at time t, and k_O is the release rate;

First-order equation: $In\ Q = InQ_o - k_1 t$*(2)*

where k1 is the release rate constant;

Higuchi's equation: $Q=k_2 t^{1/2}$ *(3)*

Where Q is the amount of drug release at time t, and k_2 is the diffusion rate constant.

Stability study

A stability test was conducted by storing tablets in amber bottles at ambient temperature, 40ºC, and 50ºC. The content of Aceclofenac and the dissolution of drug from these matrix tablets were tested monthly for three months. The assay of Aceclofenac and the dissolution study followed the same procedure as previously described.

RESULTS AND DISCUSSION

Physical characterization of the matrix tables

Tablets diameter, friability, thickness, hardness and weight of the formulated tablets are described in Table 2. The weight deviation of the nine matrix tablets was acceptable due to the granule flowability properties. The flow characteristics were improved by adding starch, as a glidant, to the granular mixture. Three different concentration of starch were used (1.5%, 3%, and 4%) and, it was found that optimum concentration of the glidant was 4%. The minimal friability obtained confirmed the suitability of the wet-granulation technology for the preparation of these HPMC matrices.

Influence of pH

It is known that the release rate of drugs from hydrophilic matrices containing HPMC, is affected by changing the pH. Thus, the dissolution rate was investigated at pH 1.2 and 6.8. For all the formulations, the release rate of Aceclofenac was extremely low at acidic pH, since after 2 hours only less than 1% of drug was released, spectrophotometrically observed.

Influence of starch

Starch is water swellable by nature. The presence of starch in an HPMC matrix tablet could modify the release rate, due to the disintegration phenomenon based on the fast water uptake, followed by the HPMC swelling (12). Thus, the comparative influence of the co-excipients starch and MCC as release modifiers was evaluated. Figure 1 shows plot of the cumulative amount of drug released against time for the formulations, T1, T2 and T3.

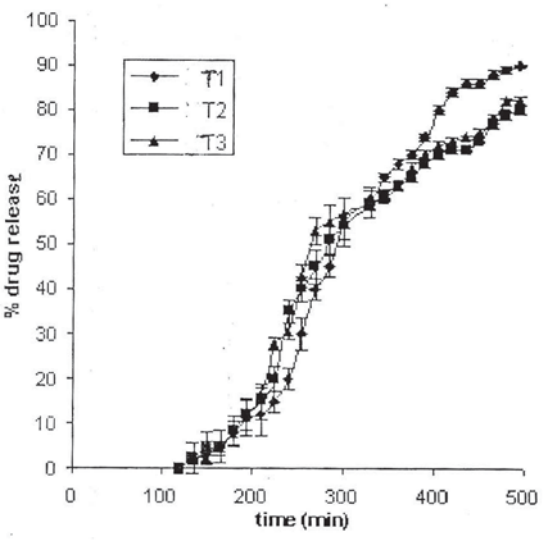

Fig. - 1: Mean (±s.d.) percent of Aceclofenace released from HPMC matrix tablets (n=3), containing 17% of starch in dissolution study at pH=1.2. and pH=6.8

It was observed that the different concentrations of HPMC on the drug release rate were not significant, due to the similar behavior of the three formulations under the same dissolution conditions. In this case, small variations on the HPMC concentration would not affect the profile

release of the model drug, despite of another study where was reported that the increase of HPMC content with the same drug concentration resulted in a decreased release rate of drugs (13). The results obtained herein show clearly that the drug released at 8 h of the batch T1 (0% MCC-17% starch) was slightly higher, compared with the batches T2(5% MCC-17% starch) and T3 (7.5% MCC-17% starch), indicating that MCC did not produce any relevant effect on the drug release rate. We assume, in this particular case, that MCC works as diluent creating the desired bulk as well as giving the right compression characteristics (14). Thus, release rate of Aceclofenac from T1, T2, and T3 would be mainly controlled by the hydration and swelling properties of HPMC and starch, which forms a gel layer that controls the water penetration and drug diffusion.

Influence of lactose

Lactose is the most useful filler used for tablet formulations. It is water-soluble and would modify the drug release for undergoing dissolution. Drug release from the tablets compressed with Aceclofenac, HPMC, lactose and MCC, are shown in Fig. - 2

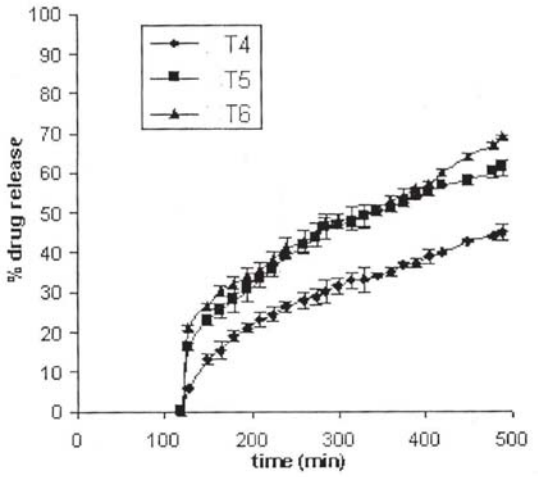

Fig. - 2: Mean (±s.d.) percent of Aceclofenac released from HPMC matrix tablets (n=3), containing 17% of lactose in dissolution study at pH=1.2 and H=6.8.

While the batch T4 (0% MCC-17% lactose), decreased the drug release too much (45% after 8 h), when MCC was incorporated in the formulations T5 (5% MCC-17% lactose), and T6 (7.5% MCC-17% lactose), the release rate was markedly increased upto 70%, compared to a T4 tablet without MCC. In this case, the swelling behavior of MCC allowed further penetration of the aqueous medium, resulting in rapid erosion of the polymer matrices. In addition, lactose in aqueous solution plays a role as important physical barrier, affecting the release kinetics, by reducing the tortuosity of the diffusion pattern of the drug (15). However, if it were mixed with HPMC, the polymer concentration would lead the release rate of the drug. Thus, it was expected that decreasing the HPMC concentration, being constant the lactose concentration could increase the release rate of Aceclofenac as shown in Fig.2

Influence of lactose: starch mixture

The last three batches T7, T8 and T9 were formulated by mixing lactose and starch in a 1:1 ratio, having on mind that each excipient by itself modified the release rate of the drug, in agreement with the results described in Fig.1 and Fig.2. Fig.3 depicts the release profile of T7 (0% MCC-8.5% starch- 8.5% lactose) T8 (5% MCC-8.5% starch 8.5% lactose), and T9 (7.5% MCC-8.5% starch 8.5% lactose)

The percentage of drug released at 8 hr from T8 and T9 matrices was more than 80% and 90%, while the percentage drug release from T7 matrix was less than 70%, clearly showing that in this particular case the presence of MCC plays an important role as a filler as well as a release modifier. (16,17). These tablets containing a 50% less of starch and a 50% less of lactose showed a higher release rate of Aceclofenac compare with the matrix tablets formulated only with starch (T1-T3) or lactose (T4-T6). By this observation, we can conclude that lowering the amount of starch; it was enough to produce the dissolution process on a very good controlled-release rate. Moreover, decreasing the amount of lactose, did not affect the path diffusion of the dug, due to the good release kinetic obtained.

Drug Release Kinetics

In Table 3, the kinetic parameters for Aceclofenac release from these HPMC matrix tablets (T1-T9) are presented.

Dissolution data fit a zero-order kinetics, despite of quite high correlation coefficients were obtained with other kinetic models.

Lot reproducibility and stability test

Three batches of each formulation were prepared and the dissolution rate of Aceclofenac was evaluated under the same conditions. The resulting release profiles of Aceclofenac from these

Table - 3: Kinetic parameters of Aceclofenac release from the matrix tablets

T	A		B		C	
		R^2		R^2		R^2
T1	0.3586	0.9731	3.4521	0.9283	0.0008	0.8945
T2	0.3766	0.9628	4.3654	0.9188	0.0011	0.8836
T3	0.3985	0.9592	5.6589	0.9016	0.0012	0.8741
T4	0.1446	0.9238	4.6833	0.9124	0.0009	0.8966
T5	0.0095	0.9498	5.872	0.8733	0.0012	0.8830
T6	0.1811	0.9159	5.0711	0.7861	0.0048	0.8262
T7	0.4365	0.9939	4.9632	0.8960	0.0009	0.8666
T8	0.4110	0.9911	5.3692	0.8674	0.0011	0.8512
T9	0.3280	0.9752	5.4896	0.8860	0.0012	0.8885

T: matrix tablet; **A:** Zero order equation Ko(%min^{-1})
B: Zero order equation K_H(% min^{½}); **C:** Zero order equation K_1 (% min^{-1})

three different batches of each matrix formulation (T1-T8) showed no significant difference among the release profiles for each set of three batches, indicating that this manufacturing process is reliable and reproducible.

The stability of Aceclofenac in these matrix tablets was evaluated over three months at three different temperatures. There was no physical change in the tablets, moreover, there was insignificant Aceclofenac degradation in the eight

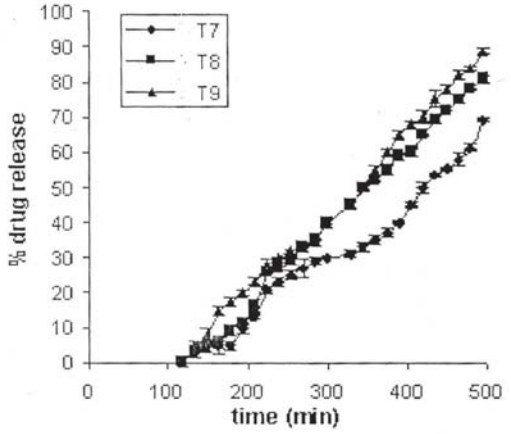

Fig. - 3: Mean (±s.d.) percent of Aceclofenac released from HPMC matrix tablets (n=3), containing 8.5% of starch and 8.5% of lactose in dissolution study at pH=1.2 and pH=6.8

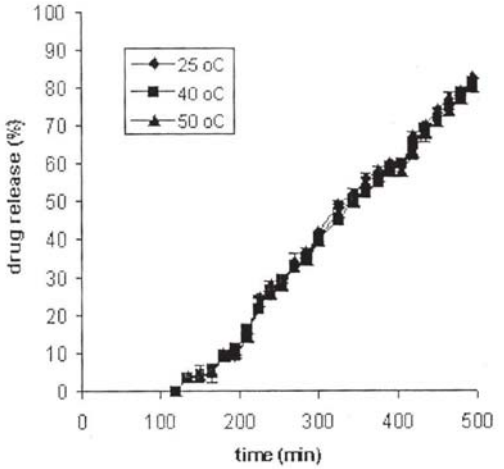

Fig. - 4: Mean (±s.d.) percent of Aceclofenac released from HPMC matrix (n=3), containing 8.5% of starch and 8.5% of lactose stored at 25ºC, 40ºC, and 50ºC.

formulated tablets, suggesting that the drug is stable in the HPMC tablets (Fig.4). Apparently, the drug release from these matrices does not change after storage for this period of time.

CONCLUSION

Aceclofenac release matrices were prepared successfully utilizing HPMC as a carrier. From the technological point of view, the wet granulation method enables the preparation of these matrices. The physical properties described in Table - 2 were found to be optimal for the manufacturing process it was observed that free-flowing powders (a minimum angle of repose f) were obtained by using starch in a 4% concentration as a glidant. There was no significant difference in drug release between the hydrophilic matrices when the HPMC concentration was

modified in low percentage. Drug release from swollen matrices was principally regulated by starch (17%) or lactose (17%), even on the presence of MCC at different levels (5% or 7.5%). However, when starch (8.5%) and lactose (8.5%) were mixed at lower concentration in a ratio 1:1, MCC (5% or 7.5%) appeared to control the drug release from the matrices. Clearly, each of these components was capable of interacting to some extent with each other to control drug release. The best-fit release kinetics with the highest correlation coefficients was achieved with the zero-order plot, followed by the Higuchi and first-order equations, respectively, over 8 h. Compared to conventional tablets, release of Aceclofenac from these release HPMC matrices was prolonged. The data described in Fig. 1,2, and 3 proved that the formulations are useful for a sustained release of Aceclofenac, due to the percentage released after 8 h is nearly to 70%, except the T4 and T5 matrix tablets. The formulations were not affected when subjected to different stability conditions. The release profile remained unchanged after three months storage of tablets.

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