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STUDIES ON INFLUENCE OF CO-EXCIPIENTS ON RELEASE RATE OF ACECLOFENAC FROM CARBOPOL CONTROLLED RELEASE MATRIX TABLETS

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ABSTRACT

The aim of the present study was designed to develop model controlled release matrix tablet formulations for aceclofenac. Aceclofenac tablets at different drug to polymer ratios were prepared by the direct compression method using Carbopol 934P. The influence of the proportion of the polymer and several co-excipients like lactose, microcrystalline cellulose, and dibasic calcium phosphate on the release rate of the drug from the tablets was studied. In vitro drug release studies carried out in 0.1 N Hcl was found to occur both by diffusion and swelling-controlled mechanisms exhibiting non- Fickian transport. The drug release was found to follow zero order kinetics. The two co-excipients, lactose and microcrystalline cellulose enhanced the release rate of aceclofenac, while dibasic calcium phosphate exhibited a much slower release of drug from the prepared matrices.

INTRODUCTION

The use of controlled-release technology in the formulation of pharmaceutical products has become increasingly important in the past few years [1]; but for drugs such as NSAIDs a prompt disposition of a fraction of the dose should be reached in the shortest time possible to relieve the symptoms of the disease and then the continuation of the drug effect should be prolonged to optimize the therapy[2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the relief of mild to moderate pain, acute and chronic inflammatory disorders such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac, phenyl acetic acid derivative related to diclofenac, is one of the widely used NSAIDs [1, 2]. The short biological half-life (4 h) and frequent dosing make aceclofenac an ideal candidate for controlled release dosage forms. Its effect lasts only for few hours and needs to be administered 3-4 times a day. Hence, there is every need for formulating a controlled release dosage form for aceclofenac to improve its therapeutic efficacy and patient compliance. Various polymers are used to control the release of drugs from the dosage forms for absorption by the body. Carbopol 934P, synthetic high molecular weight crosslinked polymers of acrylic acid. These carbomers readily hydrate; absorb water with good degree of swelling. Because of their hydrophilic nature and highly crosslinked structure, they are more suitable candidates used in controlled release drug delivery systems.

The objectives of the present investigation were to examine the mechanistic aspects of aceclofenac release kinetics from carbopol 934P controlled release matrix tablets, and to study the influence of co-excipients like microcrystalline cellulose (MCC), lactose and dibasic calcium phosphate (DCP) on release rates of aceclofenac.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Lupin Research Park, Pune, India. Carbopol 934P was obtained as a gift sample from Macleoids Pvt. Ltd., Mumbai. Lactose, Microcrystalline cellulose, and DCP were procured from SD Fine Chem, Mumbai. All the other chemicals and reagents were of analytical grade.

Preparation of Aceclofenac tablets

Matrix tablets of aceclofenac were prepared at different drug to polymer ratios using carbopol 974P by direct compression method. MCC, lactose and DCP were used as diluents and talc and magnesium stearate were used as glidant and lubricant respectively. All the ingredients were passed through 60 mesh sieve separately. Weighed quantity of aceclofenac and all the excipients except lubricants were mixed geometrically with mortar and pestle (Table-1). Finally magnesium stearate and talc were added and mixed. Tablets were compressed on a single punch tablet machine (Cadmach, India) using round flat surface punches of 7.5 mm diameter.

Evaluation of matrix tablets

The prepared matrix tablets were subjected to post compression parameters like hardness, friability, weight variation and uniformity of drug contentS and *In vitro* dissolution studies.

***In vitro* dissolution studies**

In vitro dissolution of aceclofenac tablets was studied in USP XXIII dissolution apparatus (Electrolab) employing a paddle stirrer at 100 rpm. 900 ml of distilled water was used as dissolution medium. The temperature of the dissolution medium was previously warmed to 37±0.5ºC and was maintained throughout the experiment. One tablet was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of a syringe fitted with pre-filter, at known intervals of time (1 hour). The sample was analyzed for drug release by measuring the absorbance at 273 nm using UV-visible spectrophotometer after suitable dilution. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at same temperature. The study was conducted in triplicate.

RESULTS AND DISCUSSION

In the present study, controlled release matrix tablets of aceclofenac were prepared by using carbopol 934P at different drug to polymer ratios viz., 1:0.2, 1:0.4, 1:0.6. And the influence of three co-excipients lactose, MCC and DCP on the release rates of aceclofenac was investigated. The prepared batches (twelve) of tablets were evaluated for hardness, friability, drug content uniformity, weight variation test and *in vitro* drug

release studies. Hardness of the tablets was found to be 5.3 to 5.5 Kg/cm². The friability of all the prepared tablets was found to be in the range of 0.19 to 0.61 (±1%). Drug content was found to be uniform for all the batches of tablets prepared. From the weight variation test, the percent deviation from the average weight was found to be within the prescribed official limits.

From the *in vitro* drug release studies, it was observed that the formulations B1, B2 and B3 containing drug and carbopol 934P prepared at drug-polymer ratio of 1:0.2, 1:0.4 and 1:0.6 released 98.06%, 98.41% and 97.61% of aceclofenac in 8, 11 and 13 hours respectively. During dissolution process it was observed that increase in the amount of carbopol 934P in the tablets resulted in a reduction in the drug release rate. All the tablets showed swelling and the extent of swelling increased with increase in the amount of polymer. Release of drug from carbopol matrices containing lower concentration of carbomer was found to be fast, that could be due to the reason that at low concentration there is a lesser degree of swelling, which may result in the formation of more areas of low microviscosity in the gel structure for the drug to channel through, might have resulted in faster drug release. As the amount of carbopol was increased, it resulted in a reduction in drug release rate may be due to the reduction in regions of low microviscosity and closing of micropores in the swollen state[4, 5]. The swelling of the polymer in distilled water may be due to the ionization of the carboxylic acid group of carbopol 934P might have caused the ionic repulsion of the polymer led to the swelling[6]. The swelling of the tablets could also be due to the hydration of the polymer, which results in a rapid decrease in glass transition temperature to the temperature of the dissolution medium. And there will be a relaxation response of the polymer chains due to the stresses introduced by the presence of the dissolution medium and may result in an increase in the radius of gyration and end-to-end distances of the polymer chains, causing a significant increase in the molecular volume of the hydrated polymer[7].

In formulations B4, B5 and B6 prepared at different drug to polymer ratios containing MCC as co-excipient, exhibited faster drug release as compared to the formulations without MCC (B1, B2 and B3). These formulations have showed a release of 98%, 98.52% and 98.88% of aceclofenac in 6, 7 and 11 hours. The faster drug release observed

for MCC formulations may be due to the disintegration property of MCC that might have resulted in the quick release of drug from matrix tablets. Formulation B7, B8 and B9 containing lactose as coexcipient exhibited higher release rates as compared to same drug-to-polymer ratios without lactose (B1, B2 and B3) and more linear release behaviour was observed with formulation B9 containing higher concentration of carbopol 934P and lower amounts of lactose. Formulations B10, B11 and B12 exhibited a release of 97.79%, 98.96% and 98.70% of drug release in 8, 12 and 13 hours. Much difference was not observed in drug release rates of tablets prepared with DCP as coexcipient when compared to formulation without DCP (B1, B2 and B3). However there was a reduction in the drug release rate in formulation B11 that may be due to the insoluble nature of DCP in the dissolution medium. The comparative effect of co-excipients like lactose, MCC and DCP on the release profile of aceclofenac from the carbomer matrix tablets in terms of dissolution T50 and T90 values, in distilled water. It was observed that formulations containing MCC as coexcipient, exhibited the shortest dissolution time followed by lactose and DCP. The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations. The dissolution data was also subjected to regression analysis according to Higuchi's equation8 as percent cumulative drug release versus square root of time and log cumulative percent drug release versus log time as per korsemeyer's equation[9] in order to determine the mechanism of drug release. The results of linear regression analysis data of aceclofenac is given in table-2.

When the regression coefficient values of zero order and first order plots were compared; it was observed that the 'r' values of zero order plots were in the range of 0.97 to 0.99 indicating drug release from most of the carbopol 934P formulations was found to follow zero order kinetics. It is notable that 'r' values of the linear regressions for Higuchi plots were found to be in the range of 0.98 to 0.99, except for formulation B1, indicating that the data fits the Higuchi model well and the drug release was found to be predominantly controlled by diffusion process. When the slope 'n' values of formulations B1, B2 and B3 in Korsemeyer equation (B1=0.497, B2=0.589, B3=0.619) were compared, it was observed that increasing the amount of carbomer in the tablets led to an increase in the

slope value from 0.497 to 0.619, indicating the drug release by non-Fickian diffusion mechanism. Non-Fickian diffusion is anomalous transport, where diffusion and relaxation occur at comparable rates.

Table-1: Drug-polymer ratios for the preparation of matrix tablets of aceclofenac (for 1 tablet)

Formulation code	Ingredients(mg)						
	Drug	**Carbopol 934P**	**MCC**	**Lactose**	**DCP**	**Magnesium stearate**	**Talc**
B1	100	20	--	--	--	2	2
B2	100	40	--	--	--	2	2
B3	100	60	--	--	--	2	2
B4	100	20	50	--	--	2	2
B5	100	40	40	--	--	2	2
B6	100	60	30	--	--	2	2
B7	100	20	--	50	--	2	2
B8	100	40	--	40	--	2	2
B9	100	60	--	30	--	2	2
B10	100	20	--	--	50	2	2
B11	100	40	--	--	40	2	2
B12	100	60	--	--	30	2	2

Table-2: Regression analysis data of aceclofenac matrix tablets Formulation

Formulation Code	Zero Order 'r'	First Order 'r'	Higuchi Model 'r'
B1	0.9835	0.9032	0.9608
B2	0.970	-0.9628	0.9943
B3	0.9772	-0.9349	0.9931
B4	0.9931	-0.8515	0.9989
B5	0.9791	-0.9079	0.9950
B6	0.9627	-0.9660	0.9878
B7	0.9786	-0.9280	0.9942
B8	0.9975	-0.8962	0.9854
B9	0.9971	0.826	0.9939
B10	0.9969	-0.9322	0.9939
B11	0.9896	-0.8238	0.9857
B12	0.9981	-0.8675	0.9915

CONCLUSION

From the above results, it can be concluded that the release rate of drug from the carbopol 934P matrices depends upon the amount of polymer used. As the amount of polymer was increased, the drug release rate was found to be decreased. Drug release from the matrix tablets was found to occur by both diffusion and swelling-controlled mechanisms exhibiting non-Fickian transport. Among the three co-excipients studied, microcrystalline

cellulose formulations with dissolution T90 values of 5.1, 6.3 and 7.6 hours for B4, B5 and B6 respectively showed substantial enhancement in the drug release rate followed by lactose formulations with dissolution T90 values of 4.9, 7.8 and 11 hours for B7, B8 and B9, whereas DCP formulations with dissolution T90 values of 6.9, 10.8 and 11.8 hours for B10, B11 and B12 exhibited a much slower release of drug from the prepared carbopol matrices.

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