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Research Article

Formulation and Evaluation of Controlled Release Matrix Tablet with Solid Dispersion Granules of Aceclofenac

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ABSTRACT

The goal of this study is to develop once daily controlled release matrix tablet of aceclofenac by applying solid dispersion technique for improving solubility. The matrix tablets of aceclofenac solid dispersion granules were prepared by direct compression method using selected hydrophilic polymers like hydroxylmethyl cellulose (HPMC) and Carbopol 934(CP). Preformulation and micromeritic studies were carried out. The matrix tablets were evaluated for their physicochemical properties, *in vitro* drug release and stability studies. Formulation containing 25% HPMC (F1) has complete release of 24 hrs as well as CP containing formulations showed concentration dependent rate of drug release. To achieve complete drug release, solid dispersion of aceclofenac was prepared using mannitol and dicalcium phosphate (DCP). Dissolution profile of matrix tablet containing solid dispersion with mannitol/ DCP has shown increase in the release rate compared to matrix tablets alone. Solid dispersion using mannitol was found effective with matrix tablets of CP as compared to matrix tablet of HPMC. From this study, it was clarified that solid dispersion granules was one of the promising controlled release system applying solid dispersion technique for the poorly water soluble drug.

INTRODUCTION

Aceclofenac is one of the emerging NSAID molecules for arthritis treatment. It is a newer derivative of diclofenac and has less gastric complications.[1, 2, 3] The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired. Controlled release dosage form delivers the drug at a constant rate over an extended period of time. The short biological half-life (about 4 hrs) and dosing frequency more than once per day make aceclofenac an ideal candidate for controlled release. The development of oral controlled release dosage forms has attracted much attention in the recent years and hydrophilic matrix tablets are among the most widely used of the numerous controlled releases dosage forms currently available. The most important variable in hydrophilic matrix systems is the rate at which the drug substance is released. The release of drug is controlled by the formation of a hydrogel layer around the matrix following exposure to aqueous fluid. [4, 5, 6]

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Matrix tablets composed of drug and release retarding materials offer the simplest approach in designing controlled release system. Among a variety of hydrophilic polymers, HPMC[7] are widely used materials in the pharmaceutical industry mainly because of its non-toxicity, high water-solubility and swellability, insensitivity to the pH of the biological medium and ease of production. Carbopol (CP-934), the polymers of acrylic acid has been extensively used in the formulation of various dosage forms e.g. swellable tablets, buccal tablets, chewable tablets, effervescent tablets, suppositories and gels forms to modify the drug release due to their gel forming characteristics. The gel layer formed around the tablet core acts almost like the rate controlling membrane. [8]

The present study was aimed to prepare once-daily controlled release matrix tablets of aceclofenac using hydrophilic polymers as release retarding materials by direct compression method and evaluated with respect to various *in-vitro* tests.

MATERIAL AND METHODS

Materials:

Aceclofenac was obtained as gift sample from Rantus Pharmaceuticals Pvt. Ltd, Hyderabad. Hydroxypropyl methyl cellulose K100M, Carbopol-934, Dicalcium phosphate and directly compressible Mannitol were obtained from the Redson pharmaceuticals Pvt. Ltd, Ahmadabad. Magnesium stearate and Talc were

obtained from the S.D. Fine Chem., Mumbai. All other chemicals used were of pharmaceutical grade.

Preparation of matrix tablets:
Matrix tablets of aceclofenac were prepared by employing various polymers like HPMC K100M and CP-934 by direct compression method using 8 mm flat-faced punch of 10 station Rimek compression machine. For the preparation of matrix tablets, the active ingredient was uniformly mixed with polymer (s) using a Poly bag for 15 min; magnesium stearate and talc were added to the above blend as flow promoters. In all the formulations, concentration of aceclofenac was kept constant at 200 mg and the polymers HPMC K100M and CP-934 were used in different ratios like 25, 37.5 and 50% w/w with respect to drug. The formulae of different matrix tablets of aceclofenac are given in the Table 1.

Table 1: Formulae of different matrix tablet formulations of aceclofenac

Ingredients (mg/ tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	200	200	200	200	200	200	200	200
HPMC	50	75	100	50	-	-	-	-
CP-934	-	-	-	-	50	75	100	75
Mannitol	100	100	100	-	100	100	100	-
DCP	-	-	-	100	-	-	-	100
Magnesium Stearate	3.5	3.75	4	3.5	3.5	3.75	4	3.75
Talc	3.5	3.75	4	3.5	3.5	3.75	4	3.75

Solid dispersion using mannitol [9]**:**
Solid dispersion of aceclofenac was prepared by solvent evaporation method using mannitol and drug in 2:1 ratio. To the methanolic solution of carrier, weighed amount of aceclofenac was added and solvent was evaporated at 50°C. The solidified mass after complete evaporation of the solvent was crushed, pulverized and passed through mesh # 80.

Solid dispersion using DCP [10]**:**
Solid dispersions of aceclofenac were prepared by solvent deposition method with 2:1 ratio of carrier and drug. The solid dispersions were prepared by dissolving aceclofenac in dichloromethane to obtain a clear solution. The excipient was then added to the solution and dispersed. The solvent was removed by evaporation at 40° C while mixing the contents. The mass obtained was powdered and passed through mesh # 100.

Preparation of matrix tablets containing solid dispersion:
The solid dispersion of mannitol/DCP equivalent to 200 mg of aceclofenac was blended with different polymers like HPMC K100M and CP-934 for 10 min using mortar and pestle. Further this mixture was blended with flow promoters like magnesium stearate & talc and finally compressed using 8 mm flat-faced punch of 10 station Rimek compression machine. The formulae of different matrix tablets of aceclofenac containing solid dispersion are given in Table 2.

Table 2: Formulae of different matrix tablets containing aceclofenac solid dispersion

Ingredients (mg/ tablet)	F9	F10	F11	F12
SDM*	302	-	300	-
SDD*	-	306	-	301
HPMC	75	75	-	-
CP-934	-	-	100	100
Magnesium stearate	3.75	3.75	4	4
Talc	3.75	3.75	4	4

SDM* and SDD* indicates the solid dispersion of aceclofenac with mannitol and DCP respectively equivalent to 200 mg of aceclofenac.

Solubility study of aceclofenac:
An excess quantity of aceclofenac was added to 10 ml of different solvents like water, 0.1 N HCl, phosphate buffer of pH 6.8 and phosphate buffer of pH 7.4 in a shaking water bath at room temperature for 24 hrs. The solutions were then filtered through Whatman filter paper (No. 41) and the filtrate was suitably diluted and analyzed spectrophotometrically at 274 nm. The result of aceclofenac solubility in various media is shown in the Table 3**.**

Table 3: Aceclofenac solubility aspects

Solvents	Solubility (mg/ml)
Water	0.18
0.1 N HCl	0.045
Phosphate buffer of pH 6.8	9.585
Phosphate buffer of pH 7.4	6.714

Evaluation of tablets:
The matrix tablet of aceclofenac, prepared with and without solid dispersions by direct compression techniques, were evaluated for preformulation and post-formulation parameters such as, angle of repose, compressibility (%), hausner's ratio and hardness, friability, weight variation, thickness, drug content the obtained results were tabulated in Table 4 and 5 respectively.

Table 4: Evaluation of preformulation parameters

Formulation	Angle of repose (θ)	Compressibility (%)	Hausner's ratio
F1	25.71 ± 0.23	15.80 ± 0.33	1.18 ± 0.01
F2	23.40 ± 0.22	12.66 ± 0.62	1.14 ± 0.04
F3	26.12 ± 0.26	14.89 ± 0.39	1.16 ± 0.02
F4	26.52 ± 0.24	13.64 ± 0.43	1.15 ± 0.02
F5	27.79 ± 0.19	13.91 ± 0.27	1.16 ± 0.03
F6	26.58 ± 0.16	14.31 ± 0.41	1.16 ± 0.04
F7	30.11 ± 0.21	15.50 ± 0.32	1.17 ± 0.01
F8	27.33 ± 0.14	13.50 ± 0.49	1.15 ± 0.03
F9	25.85 ± 0.20	12.27 ± 0.38	1.13 ± 0.04
F10	27.17 ± 0.17	12.86 ± 0.36	1.14 ± 0.06
F11	26.55 ± 0.14	12.26 ± 0.20	1.13 ± 0.03
F12	24.72 ± 0.18	13.41 ± 0.27	1.13 ± 0.01

All values are expressed as mean ± SD

Table 5: Evaluation of postformulation parameters

Formulation	Hardness test*	Friability**	Weight variation***	Thickness**	Drug content*
	(kg/cm2)	(%)	(%)	(mm)	(%)
F1	5.5 ± 0.33	0.82 ± 0.01	2.83 ± 0.34	6.23 ± 0.03	99.67 ± 0.33
F2	6.1 ± 0.55	0.54 ± 0.02	2.11 ± 0.19	6.42 ± 0.01	99.12 ± 0.65
F3	5.3 ± 0.64	0.67 ± 0.01	1.47 ± 0.37	6.79 ± 0.04	99.74 ± 0.42
F4	5.7 ± 0.46	0.62 ± 0.05	1.18 ± 0.34	6.22 ± 0.01	98.34 ± 0.37
F5	5.5 ± 0.30	0.66 ± 0.03	2.53 ± 0.48	6.14 ± 0.06	99.67 ± 0.21
F6	5.9 ± 0.28	0.47 ± 0.06	2.39 ± 0.65	6.32 ± 0.02	99.37 ± 0.16
F7	6.3 ± 0.35	0.41 ± 0.01	2.82 ± 0.16	6.13 ± 0.01	99.76 ± 0.38
F8	6.2 ± 033	0.48 ± 0.04	1.18 ± 0.57	6.15 ± 0.03	99.45 ± 0.64
F9	5.4 ± 0.21	0.72 ± 0.02	1.59 ± 0.34	6.79 ± 0.06	99.34 ± 0.38
F10	5.3 ± 0.54	0.68 ± 0.01	1.42 ± 0.67	6.70 ± 0.04	98.26 ± 0.41
F11	5.9 ± 0.32	0.54 ± 0.03	1.67 ± 0.49	6.13 ± 0.01	98.86 ± 0.18
F12	6.2 ± 0.61	0.49 ± 0.05	1.93 ± 0.71	6.14 ± 0.05	99.18 ± 0.45

Table 6: Physicochemical data after stability study

Formulation	Hardness test* (kg/cm^2)	Friability** (%)	Weight variation*** (%)	Thickness** (mm)	Drug content* (%)
F1	5.4 ± 0.41	0.64 ± 0.02	1.15 ± 0.47	6.23 ± 0.04	99.29 ± 0.63
F6	6.1 ± 0.37	0.44 ± 0.04	1.16 ± 0.51	6.16 ± 0.02	99.47 ± 0.18
F11	5.7 ± 0.23	0.41 ± 0.05	1.19 ± 0.32	6.13 ± 0.04	97.51 ± 0.45
F12	5.9 ± 0.12	0.36 ± 0.06	1.06 ± 0.52	6.14 ± 0.05	98.86 ± 0.18

All values are expressed as mean **±** SD**, ***n=5, **n=10, ***n=20.

***In vitro* release studies:**

In vitro drug release studies for the prepared matrix tablets were conducted for a period of 24 hours using a basket dissolution apparatus (Electro lab, Mumbai.) at 37±0.5°C and 75 rpm speed using phosphate buffer of pH 6.8 as dissolution medium. At predetermined interval of time, 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 274 nm for aceclofenac by a UV-Visible spectrophotometer. The amount of drug present in the samples was determined.

DSC study:

The differential scanning colorimetery study of the pure drug and solid dispersion of mannitol as well as dicalcium phosphate was carried out by differential scanning colorimeter (NETZSCH, DSC 200PC, Japan).

Stability studies [11]**:**

The stability study of the formulations F1, F6 and F11, F12 was carried out according to ICH guidelines at 40±2°C/75±5%RH for one month by storing the samples in stability chamber (Lab-care, Mumbai). The result of stability study was shown in Table 6.

RESULTS AND DISCUSSION

The result of aceclofenac solubility in various media is shown in the Table 3. The solubility of aceclofenac was very poor in water and 0.1 N HCl (0.18 and 0.045 mg/ml respectively). At lower pH, the solubility was less and as the pH increases from acidic to 6.8, the solubility was drastically increased. However phosphate buffer of pH 6.8 may be suitable for dissolution studies as sufficient solubility (9.585 mg/ml) was observed. The results of micrometric properties of formulations in which angle of repose, compressibility (%) and hausner's ratio were found in the range of 23.40±0.22° to 30.11±0.21°, 12.26±0.20% to 15.80±0.33% and 1.13±0.01 to 1.18±0.01 respectively (Table 4). The results of post formulation parameters of matrix tablets such as hardness, friability (%), wt. variation, thickness and drug content were found 5.3±0.64 to 6.3±0.35 kg/cm^2, 0.41±0.01 to 0.82±0.01 (%), 1.18±0.57 to 2.83±0.34 (%) and 98.26±0.41 to 99.74±0.42 (%) respectively in Table 5. All tablets complied with pharmacopieal specifications for all the post formulation parameters. The results indicated that the tablets did not show any physical changes (hardness, friability) during the study period and the drug content was found about 97% at the end of 30 days for selected formulation (Table 6). This indicates that tablets are fairly stable at accelerated storage condition.

The thermograms obtained from DSC study enables us the quantitative detection of all processes in which energy are required or produced. In the present study, the thermogram of pure drug showed melting endotherm peak at 153°c. The endothermic peak of mannitol at 168°c and the endothermic peak of DCP obtained at 98°. Aceclofenac: mannitol solid dispersion

thermogram showed that the melting of mannitol endotherm peak at 166°c and exhibit small broaden endothermic peak of aceclofenac at 153°c. It indicates that there is some percentage of aceclofenac crystalinity in solid dispersion prepared by mannitol. The melting endothermic peak of pure mannitol at higher temperature than melting endothermic peak of aceclofenac because of that there may be a possibility of dissolution of drug into mannitol and observed semi-crystalinity of aceclofenac in mannitol based solid dispersion.[12] Aceclofenac: dicalcium phosphate solid dispersion thermogram showed that the melting of dicalcium phosphate endotherm peak at 96°c and exhibit shortened broad endothermic peak of aceclofenac at 153°c, indicates the traces of drug crystalinity in the solid dispersion. [13] The comparative study of DSC thermogram revealed that there is no any appreciable change in the nature of the melting endotherms suggesting that the drug has not lost its characteristic properties even in its solid dispersion form as there is no interaction of the drug with the polymer used for the study. The generated thermogrames of pure drug, mannitol, DCP, solid dispersion of mannitol and DCP were shown in the Fig 1.

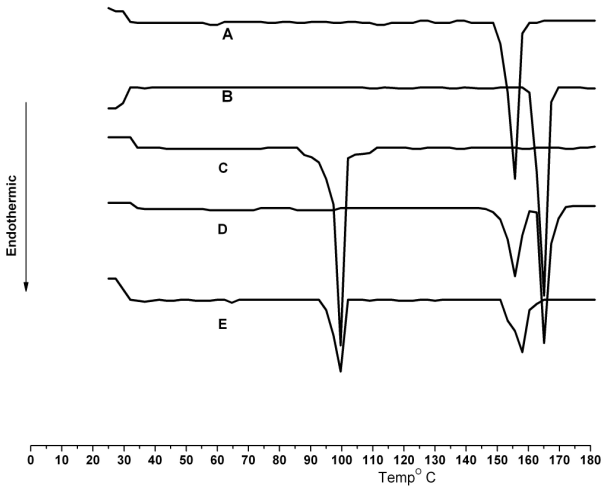

Figure 1: DSC thermogrames of pure drug (A), mannitol (B), DCP (C), solid dispersion of mannitol (D), solid dispersion of DCP (E).

Tablet F1, F2 and F3 containing different concentration like 25, 37.5 and 50% w/w with respect to drug showed that the cumulative drug release of 98.88, 85.97 and 74.42% at the end of 24 hrs. Fig 2 shows the release profile of aceclofenac from of HPMC matrices. It was observed that as the polymer level was increased, the polymer gel formed is more likely to be resistance to drug diffusion and gel erosion. Formulation F1 showed complete release at the end of 24 hrs and was selected for further studies. The *in vitro* release studies of CP matrix tables showed that the cumulative drug release was in the order of F5 (25% CP) > F6 (37.5% CP) > F7 (50% CP) as shown in Fig. 2. Tablet of F6 containing 37.5% of CP resulted controlled and complete release at the end of 24 hrs as compared to F5 and F7 formulations. The release profile of tablet F6 was found complete at the end of 24 hrs and was subjected for further studies.

The solid dispersions of aceclofenac were incorporated in the matrix formulations that showed incomplete release at the end of 24 hrs. The increment in the dissolution rate of different solid dispersion formulation was found to be in the order of F12 (99.21%) >F11 (98.43%) >F10 (94.48%) >F9 (92.92%) irrespective of polymers used. Solid dispersion using mannitol was found effective with matrix tablets of CP as compared to matrix tablet of HPMC. The release profile of solid dispersion containing matrix tablets is shown in the Fig 3.

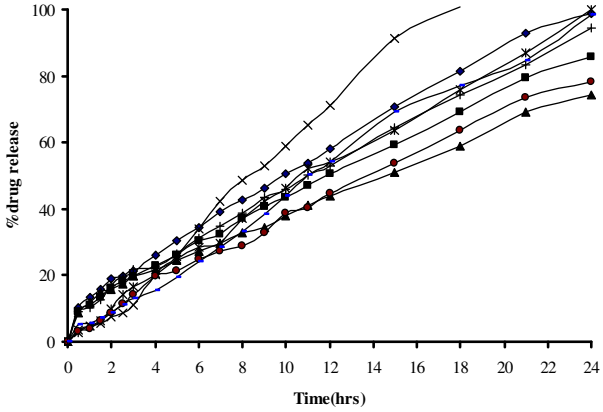

Figure 2: Comparative dissolution profile of aceclofenac from HPMC and CP934 formulations. Formulation F1 (♦), F2 (■), F3 (▲), F4 (+) containing HPMC and F5 (×), F6 (◊), F7 (○), F8 (-) containing CP- 934

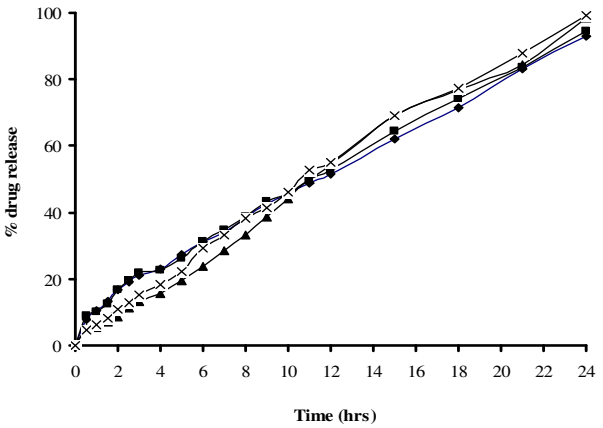

Figure 3: Comparative dissolution profile of solid dispersions of SDD and SDM formulations. Formulation F9 (-♦-) and F11 (-▲-) SDM formulation and formulation F10 (-■-) and F12 (-Δ-) SDD formulation

CONCLUSION:

In the present study it can be concluded that the release was inversely proportional to the polymer concentration irrespective of polymer used and the nature of diluent has no effect on the release rate. The matrix tablet of aceclofenac prepared by solid dispersion with mannitol as well as DCP having higher release rate than that of plain matrix tablet. Solid dispersion using mannitol was found effective with matrix tablets of CP as compared to matrix tablet of HPMC.

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