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Dispersion of Aceclofenac in Hydroxypropyl Methyl Cellulose, Eudragit Rs 100 and Ethyl Cellulose Polymeric Blend for Sustained Drug Delivery

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ABSTRACT

There are various techniques to control the release rate of the drugs, among which controlling dissolution rate is most popular due to its success and low cost. The use of sustained release dosage forms is increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects. The objectives of the present investigation were to prepare granules of aceclofenac with different polymers and polymer blends by solid dispersion technique and investigate the different tablet evaluation parameters. Solid dispersions were prepared by solvent evaporation technique by using different polymers (Hydroxypropyl methyl cellulose - K4M, Ethyl cellulose, and Eudragit RS-100).Solid state and drug polymer interactions were studied by Fourier transform infra red spectroscopy, Differential scanning calorimetry, X-ray powder diffraction. The pharmaceutical performance was studied by in-vitro dissolution experiments. Studies for the kinetics of the drug release from tablets showed a good fit to zero order kinetics indicating better controlled release of the drug. Significant effect was observed with polymer, concentration of polymer mixture on similarity factor. In stability study there was no significant change in the tablet properties after exposure to 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months.

Keywords: sustained, polymers, solid dispersion, Stability.

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INTRODUCTION

Many problems are associated with conventional multiple-dosing regimen of long-acting therapy, such as systemic accumulation of the drug leading to side effects or toxicities, flip-flop profile of the plasma drug level, and poor patient compliance. Sustained-release drug delivery systems have the potential of solving these problems. So the use of these dosage forms is increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time. Thus the development of sustained drug delivery system is a better alternative for use of multiple-dose regimen and for treatment of diseases those exhibit circadian rhythms such as heart disease, asthma, and rheumatoid arthritis. Several approaches have been used in an attempt to sustain the drug release from dosage forms. The solid dispersion techniques can be used to enhance the dissolution rate of poorly water-soluble drugs as well as to sustain the drug release by choosing appropriate polymers .In recent years much attention on oral sustained drug delivery and effect of formulation and process variables on drug release from tablets of solid dispersion system. Among the polymers polymethacrylate resins, like Eudragit RS100, RL100,HPMCK 4M have been used as film coatings or inert matrices to formulate oral sustained-release delivery systems of nonsteroidal anti-inflammatory drugs. Aceclofenac, 2-[[2-[2-[(2, 6-dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid. The Drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E2 (PGE2) production. In vitro data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole blood assays, with selectivity for Cox-2 being evident. Aceclofenac is rapidly and completely absorbed after oral administration, peak plasma concentrations are reached 1 to 3 hours after an oral dose. The plasma elimination half-life of the drug is approximately 4 hours and thus frequent administration makes it a potential candidate for the design of sustained-release dosage forms. [3]. Aceclofenac is practically insoluble in water[4]. Mutalik S. et al [5] developed ‘once daily’ sustained release tablets of aceclofenac by direct compression using HPMCK4M, also studied Pre-clinical as well as clinical pharmacokinetic studies were conducted for optimized tablets. These tablets exhibited almost similar drug release profile in different dissolution media as that of marketed tablet. For the development of SR dosage form for poorly water-soluble drugs, the low solubility of drug is the most important issue to be improved. In order to overcome the problem, a combination of solid dispersion (SD) and SR techniques is one of the attractive approach [6]. In addition to the improvement of bioavailability, most of recent researches on SD systems have been directed toward their application to the

development of extended-release dosage forms[7-11]. Some previous studies reported on hydroxypropyl methyl cellulose (methocel), eudragit RS 100 and ethyl cellulose based SR solid dispersions[12,13,14]. However no single attempt has been made to prepare solid dispersion based SR formulation of aceclofenac and binary polymeric blend to prepare solid dispersion based SR tablets. The objectives of the present study were to prepare granules of aceclofenac with different polymers and polymer blends by solid dispersion technique, investigate the effect of different polymers and polymer blends on the drug dissolution rate, study the release kinetics by using model dependent and independent methods, compare in vitro drug release profile and release kinetics with marketed formulation and investigate the effect of humidity and temperature on the drug stability

MATERIALS AND METHOD

Aceclofenac was received as gift sample from Ajanta Pharma, Pvt. Ltd. Mumbai. HPMC K4M, Ethyl cellulose and Eudragit RS-100 purchased from Colorcon Asia Pvt. Ltd., Loba Chemie, Mumbai, Degussa, Germany respectively. All other chemicals were analytical grade obtained from Loba Chemie, Mumbai.

Preparation of solid dispersions[15]

Solid dispersions were prepared by solvent evaporation technique. Aceclofenac and different polymers (HPMC K4M, Ethyl cellulose, and Eudragit RS-100) were mixed to get a homogenous mixture. Ethyl alcohol was preheated to about 60^0 C and then gradually added to the drug–polymer mixture to dissolve the blend while continuously heating the mixture on a hotplate and slowly evaporating the solvent. The mixture was then poured on to glass plates and dried in an oven at 60^0C to constant weight. The dried material was then ground, screened and the 0.42–0.84 mm fraction of granules were prepared.

Characterization of solid dispersions

Fourier–transform infrared spectroscopy

FTIR spectra of aceclofenac and prepared solid dispersions were recorded on Shimadzu FTIR 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 450 – 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and the accumulations were 4. Spectra were analyzed by software supplied by Shimadzu.

Differential scanning calorimetry

Differential scanning calorimetric (DSC) analyses of the samples were carried out by using differential scanning calorimeter equipped with computer analyzer (Shimadzu TA –60 differential scanning calorimeter, Shimadzu Corporation, Kyoto, Japan). Samples (of 3-7 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 0-350^{0}C.

X- ray diffraction

The XRD patterns of raw aceclofenac and prepared solid dispersions were recorded using a Philips Analytic X-Ray diffractometer ((Philips PW 1729, Analytical XRD, Holland)) with a copper tube anode over the interval 5–60^0 2q−1. The operation data were as follows: generator tension (voltage) 50 kV; generator current 40 mA; scanning speed 2^0 min−1.

Preparation of Granules from solid dispersion

Prepared solid dispersions were formulated into granules by using microcrystalline cellulose as bulking agent with little alcohol for wetting the mass. This damp mass was then passed through sieve no. 18 and granules retained were dried at 45$^{0\ C}$ for 3 hrs. The dried granules once again passed through series of sieves. Granules were lubricated with Magnesium stearate and evaluated for granular properties like angle of repose, bulkiness, porosity, void volume and percentage compressibility[16, 17].

Compression of granules into tablets

500 mg of granules equivalent to 200mg of aceclofenac were weighed and tablets were compressed on single stroke tablet compression machine (DOLPHINE). Compressed tablets were evaluated for quality control tests official and unofficial in pharmacopeia[18]. First optimization of formulations was done by varying concentrations of polymers ranging alone and in different combinations. Optimized batches for the concentration of the polymer in solid dispersions from the *in vitro* dissolution study formulated into the tablets are shown in table 1.

Table 1: Batches for aceclofenac solid dispersion based tablet formulations

Ingredients	**Formulations (mg)**					
	A	**B**	**C**	**D**	**E**	**F**
Aceclofenac	200	200	200	200	200	200
HPMC (K4M)	40	--	20	20	50	50
Eudragit RS100	--	40	--	20	--	50
Ethyl cellulose	--	--	20	--	50	--
Microcrystalline cellulose	258	258	258	258	198	198
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25
Aerosil	1.0	1.0	1.0	1.0	1.0	1.0

***In vitro* dissolution study**

The *in vitro* drug release of prepared tablets were measured in triplicate by using dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using apparatus USP Type II. Dissolution studies were carried out by using 900mL 0.1 N HCL (2% SLS) (2 hrs). Phosphate buffer (pH6.8) 37 ± 0.5°C at 75 rpm. Samples were withdrawn after 1 hr. for first two hours and after every two hours for remaining time and replaced each time with 5 mL dissolution medium. The solutions were immediately filtered through 0.45 mm membrane filter, diluted and the concentration of aceclofenac determined spectrophotometrically at 274 nm (Shimadzu 1700, Japan). In vitro dissolution profiles of prepared tablets were compared with marketed formulation and similarity-dissimilarity factor were calculated.

Stability study

Stability studies of samples were carried out as per ICH guidelines. The prepared tablet (n=3) were kept in glass vials sealed with rubber plugs for stability studies at 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months in environmental test chamber (HMG INDIA, Mumbai). After 30, 60 and 90 days, the samples were taken out and analyzed for appearance, drug content and dissolution study.

RESULTS AND DISCUSSION

Characterization of solid dispersions

Fourier–transform infrared spectroscopy

The plain aceclofenac showed the characteristic peaks at 1770.81 cm^{-1}, 1716.80 cm^{-1}, 2970.64 cm^{-1}, 2937.85 cm^{-1}, 3319 cm^{-1}, 669.50 cm^{-1} are due to C=0 stretch, OH stretch, CH stretching superimposed on OH stretching, NH stretching and C-Cl respectively. In formulated solid dispersions all corresponding peaks of drug were present along with new additional broad peaks at 3352 cm^{-1} (O-H stretching). This could be indicative of intermolecular hydrogen bonding or this might be due to hydroxyl functional groups of polymers (figure 1). These results indicate the decrease in crystallanity of aceclofenac in solid dispersions with polymers and this is due to aceclofenac molecules interact with polymers through hydrogen bonding and make eutectic mixtures [16]. These results were confirmed further by DSC and PXRD study.

X- ray Diffraction

The PXRD patterns of the pure drug and solid dispersions were compared (figure 2). The PXRD scan of plain aceclofenac showed intense peak at 25.77^0 indicating its crystalline nature. Diffractograms of solid dispersion showed all principal peaks from aceclofenac which were

diffused, broader, fewer and less intense, which suggested the portion of drug has been converted into amorphous form. The X-ray diffraction findings also suggest that some portion of drug still exist in the same crystalline structure of but the relative reduction of diffraction intensity of drug in solid dispersions at specific angles suggests that the drug partially converted into amorphous form.

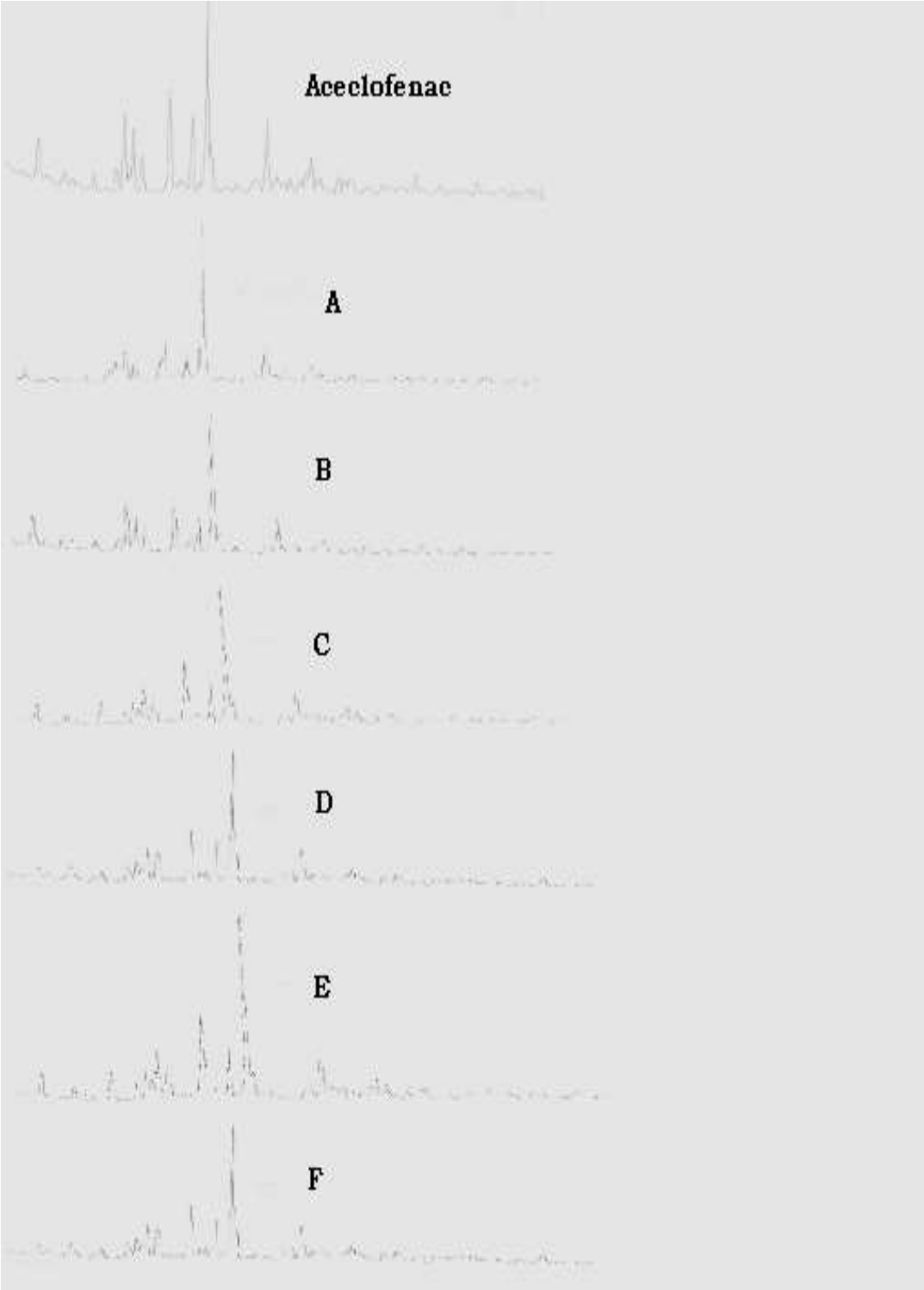

Figure.1: XRPD pattern of pure aceclofenac and prepared solid dispersions.

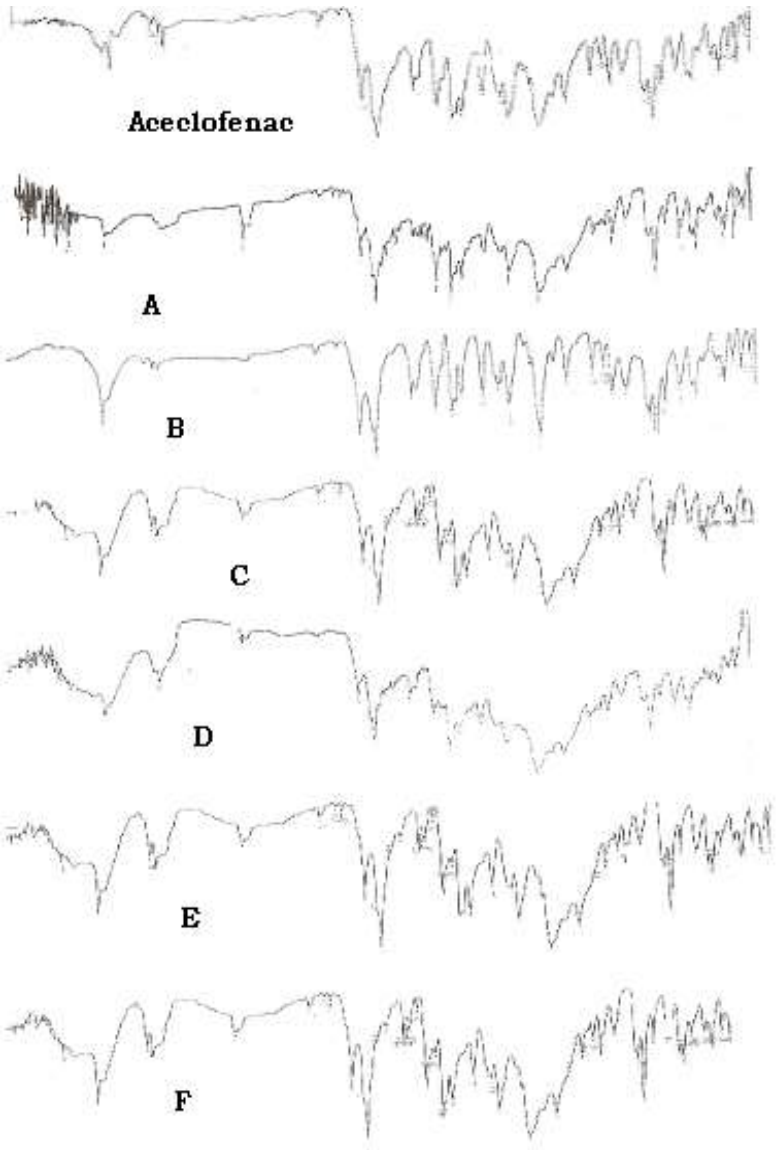

Figure 2: FTIR spectra of aceclofenac and prepared solid dispersions.

Differential scanning calorimetery

Differential scanning calorimetry (DSC) was conducted to indicate the molecular dispersion of aceclofenac into polymers. DSC curves of pure drug and formulations were compared. (figure 3).The pure drug showed a sharp melting endothermic peak around 160^0C corresponding to the melting point of crystalline drug. Two melting endotherms were observed in formulations. The first melting endotherms with reduction in peak areas and melting points. confirming the formation of new phase. Second endotherm in all formulation due to chiral nematic mesophase of glassy aceclofenac. The lowering of melting points, broad and less sharp peaks indicate breaking of bonds, disordered and non randomized structure of molecule. The results of DSC suggest crystalline drug partially converted into amorphous form.

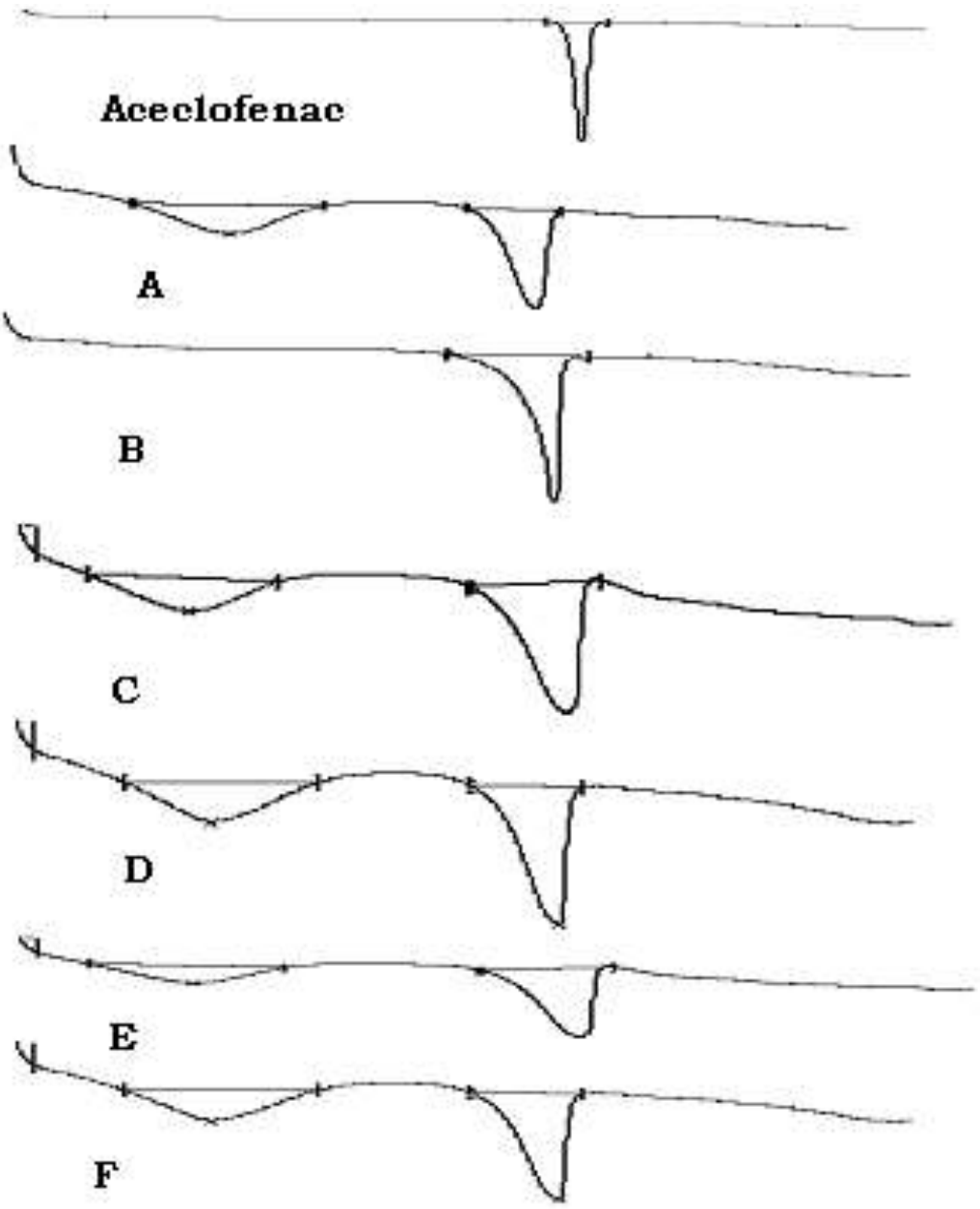

Figure.3: DSC of aceclofenac and prepared solid dispersions.

Micromeritic properties of granules:

The angle of repose is a characteristic of internal friction or cohesion of the particles. If the value of angle of repose is high powder is cohesive and low powder is non cohesive. The angle of repose of prepared granules falls within the range of 25-33^0 indicating good flow properties. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of particle to adhere together. Granules showed the bulk density values of all formulations which were in the range of 0.35-0.5 g/cm^3 indicating good packing capacity and also good compressibility index and ready for compression[16,17] as shown in table 2.

Table 2: Micromeritic properties of granules

Granule properties	Formulations					
	A	**B**	**C**	**D**	**E**	**F**
Angle of repose	25.08	25.64	26.09	22.93	23.33	24.36
Flow rate (gm/sec.)	1.35	1.365	1.34	1.12	1.40	1.3
Bulk Density (gm/cc)	0.393	0.40	0.3910	0.392	0.401	0.393
Bulkiness	2.53	2.50	2.55	2.55	2.49	2.54
Loose Bulk Density	0.339	0.345	0.367	0.335	0.342	0.335
Void Volume(cc)	1.1	1.2	1.1	1.2	1.2	1.2
Porosity (%)	13.75	15	13.8	14.64	14.64	14.6
% compressibility	13.76	13.63	13.9	14.55	14.57	14.76

- **All above results shown are mean values (n = 3)**

Evaluation of tablets

Tablets were prepared by wet granulation (A – G). All the formulations were evaluated for various parameters. The % deviation in weights of tablets was $\pm$ 10 % which is within the range according to Indian pharmacopeia. This shows uniform die fill during tablet compression. The tablets were analyzed for potency. The drug content uniformity was in range of 95-105% showing uniform distribution of drug in matrix. As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during compression process. The hardness of tablet was measured by Erweka hardness tester. The hardness was in range of 8-10 kg/cm^2. In case of disintegration test tablets were not disintegrated in 0.1 N HCL within a period of 2 hrs. Friability was found to be 0.2 – 0.6 %. As friability was below 0.8 % tablets in each formulation can withstand the mechanical shocks[18,19].

***In vitro* dissolution study**

The content of polymer content on drug release as function time was found to be different for a specific set of the polymers. Comparing corresponding release profile for aceclofenac and polymer system, it can be observed that, within 24 hr. study HPMC and eudragit alone in formulation showed 94% and 91% drug release respectively but in combination with themselves and ethyl celluloses showed 78% (C), 85% (D), 75% (E), 84% (F) and marketed formulation (D), showed 94% drug release over 24 hrs (figure 4).

Release kinetics

Model dependent methods

The kinetics of drug release from the tablets was studied by evaluating all the experimentally obtained dissolution data points for zero-order kinetics, first-order kinetics, Higuchi's square root of time equation and Hixson–Crowell's cube root equation. Linear regression was carried out and

the R^2-valuesof the equations are given in Table 3. It was observed that there was no specific trend in the various tablets with respect to the best-fit kinetics. The drug release from the tablets (batch F and C) showed a good linear fit to first-order kinetics As the amount of ethyl cellulose increased and eudragit RS 100 decreased (batches A, B, D, E, G) the drug release showed a corresponding better zero-order kinetic fit, representing greater controlled release.

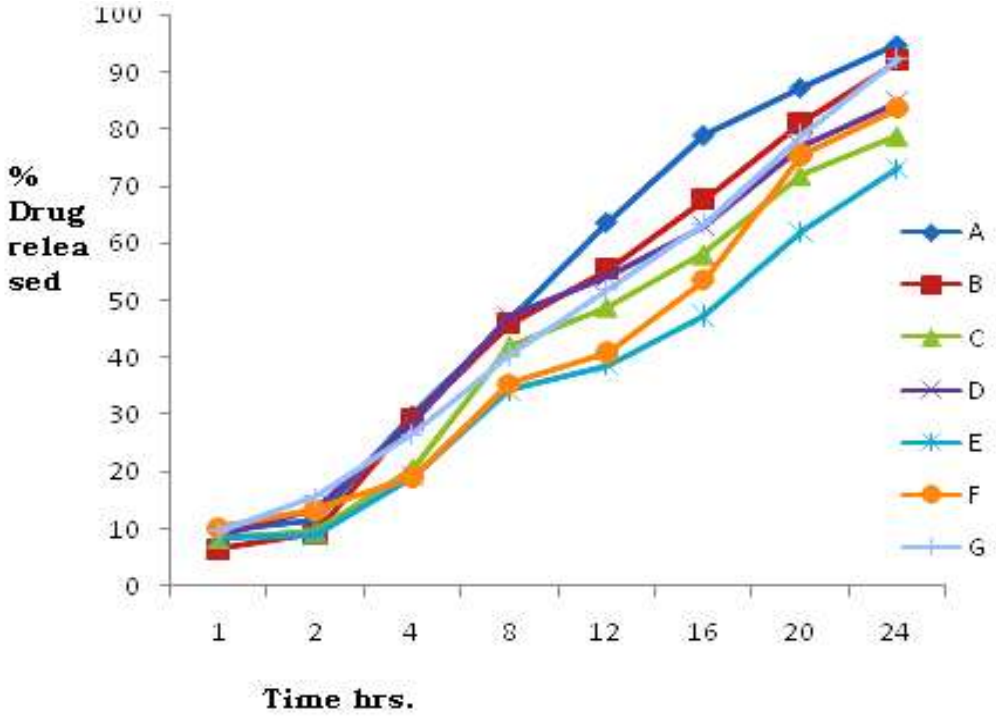

Figure.4: *In vitro* drug release profile

Table 3: R^2-values obtained from linear regression analysis of the dissolution data fitted to various kinetic models.

Formulation	Zero Order	First Order	Higuchi Model	Hixson-Crowell Model
A	0.97	0.96	0.99	0.99
B	0.97	0.92	0.98	0.97
C	0.96	0.96	0.98	0.97
D	0.96	0.94	0.98	0.96
E	0.97	0.94	0.95	0.99
F	0.67	0.90	0.93	0.93
G	0.98	0.88	0.96	0.94

Model Independent Methods

In general, to ensure similarity between the profiles, f_1 should be in the range of 0-10, and f_2 in the range of 50-100. All formulations except formulation B, C, D containing eudragit alone, HPMC-ethyl cellulose, HPMC- eudragit in combination showed similarity with marketed product (Hifenac SR) as shown in table 4.

Table 4: Represents f_1 and f_2 values

Formulation	f_1	f_2
A	15.10	56.15
B	4.15	67.40
C	9.54	63.70
D	2.53	73.09
E	23.99	46.13
F	14.27	56.61

Stability study

In case of stability studies at 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months, there was no significant change in physical appearance, drug content, weight variation, disintegration time and in vitro dissolution was observed with prepared tablet batches and marketed formulation.

CONCLUSION

Application of HPMC, eudragit RS 100 and ethyl cellulose to achieve the controlled release of aceclofenac using the solid dispersion technique was investigated. Aceclofenac partially transformed from crystalline to amorphous state which was confirmed by FTIR, DSC and PXRD. From the dissolution studies, it was seen that as the amount of polymer increased, the drug release rate gradually reduced. Studies for the kinetics of the drug release from tablets showed a good fit to zero order kinetics indicating better controlled release of the drug. There was significant effect was observed with polymer, concentration of polymer mixture on similarity factor. Stability studies showed that there was no significant change in the tablet properties after exposure to 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months. Thus, we can successfully produce a controlled release formulation of acelofenace by using the solid dispersion technique with different polymers.

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