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Formulation and Development of Dual Release Multiparticulate System for Aceclofenac

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Abstract

The objective of present work was to prepare a dual release drug delivery systems comprising fast and delayed release pattern using solid dispersion and pellets of the aceclofenac to achieve a desired *in vitro* and *in vivo* profile. Aceclofenac solid dispersions were prepared by solvent evaporation method using PEG 6000 as carrier at different ratios. The prepared solid dispersion was evaluated for percentage yield, drug content and *in vitro* characterization**.** Based on *In vitro* release studies ASD-4(1:4 ratios) batch is chosen as optimized batch and incorporated into dual release capsules of aceclofenac. Aceclofenac pellets were prepared using different concentrations of HPMC by extrusion spheronization technique**.** Based on *In vitro* release studies M3 (15%HPMC) batch is chosen as optimized batch and incorporated into dual release capsules of aceclofenac. The dual release dosage forms were constructed incorporating the optimized batch of solid dispersion (ASD4) with either pellets (M3). The dual released capsules showed a biphasic *in vitro* release pattern with initial burst release and sustained release following the quasi-Fickian diffusion-based release mechanism. Bioavailability studies for the optimized dual release formulation were carried out to assess the pharmacokinetic parameters. The peak plasma concentration (C_{max}) was achieved in 2h . The C_{max} of dual release spheroids was found to be greater than that of IR and SR dosage forms indicating that higher plasma concentration could be achieved quicker (2h and 3h spheroids) than the SR formulation (6h). Thus the absorption lag time associated with SR formulations could be minimized using these formulations. Further, there was significant increase in AUC $_{0-\alpha}$ in case of dual release spheroids indicating the enhanced absorption of poorly water soluble aceclofenac.

Key Words: ***Aceclofenac, Solid dispersion, Pellets, In Vitro drug release, Pharmacokinetic studies***

INTRODUCTION

Oral administration is recognized to be the predominant route of drug delivery. More than 50% of drug delivery systems (DDSs) available in the market are oral DDSs. These dosage forms are easy to administer and increase the patient compliance. However, the development process of such systems is precluded by several physiological difficulties. In fact, orally administered dosage forms are exposed to wide range of highly variable conditions during their transit throughout the gastrointestinal tract. Food ingestion and type of meal caloric content volume, viscosity and physical state influence the gastric physiology and thus affecting the dissolution of the active drug from dosage forms(DFs) (Goole, et al. 2008). Oral controlled release drug delivery systems are broadly classified into two types;

1) Single unit dosage forms (SUDFs) such as tablets and capsules.
2) Multiple unit dosage forms (MUDFs) such as granules, pellets and mini tablets.

The concept of the multiple unit dosage form was initially introduced in the early 1950s. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics.These MUDFs have numerous advantages over SUDFs. MUDFs are less dependent on gastric emptying and on nutritional state as these are sufficiently small to be evacuated through the pylorus during the digestive phase. Hence, have less effect on release of the active drug. Additionally owing to the reproducibility of transit times and high degree of dispersion in the digestive tract, multi particulate systems show less variance and also more stable plasma profile and little risk of local side effects (Stefanie Siepe, et al. 2008).The formulation of MUDFs is a common strategy to control the release of a drug as shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFs. Among the various types of multiple unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages (Carla M.Lopes, et al. 2006). Traditionally, the word pellets has been used to describe a variety of systematically produced geometrically defined agglomerates obtained from diverse starting materials using different processing condition. Pelletization is an agglomeration process that converts fine powders or granules of bulk drug and excipients into small, free flowing, spherical or semi spherical units referred to as pellets. These pellets usually range in size from 0.5-1.5mm (Manuel Efentakis, et al. 2000).

MATERIALS & METHODS

Aceclofenac was kindly provided by Karnataka Antibiotics, Bangalore. Hydroxy propyl methyl cellulose K100M was kindly provided by Colorcon Asia, Mumbai. Poly ethylene glycol 6000, Aerosil, Potassium dihydrogen phosphate, Sodium hydroxide, Triethylamine, Ortho phosphoric acid were kindly provided by S.D. Fine Chemicals, Mumbai.

Avicel PH 102, Potassium bromide (IR grade) were kindly provided by Signet Chemicals, Mumbai.

Solubility studies

The solubility of pure aceclofenac in phosphate buffer of pH 6.8 and distilled water was determined by the excess quantity of aceclofenac was added to 10 ml of each of the above mentioned solutions in screw capped glass vials. The vials were placed a shaking water bath maintained at a speed of 50 strokes per min. at 37 ^{0}C until equilibrium. Then, the solutions were filtered and the amount of drug dissolved in each medium was determined by means of UV spectroscopy.

COMPATIBILITY OF ACECLOFENAC WITH USED ADDITIVES

Differential scanning calorimetry (DSC)

DSC analysis was performed using Shimadzu differential scanning calorimeter. Samples (3-4 mg) were placed in aluminum pan and heated at a rate of 10°C/min, with indium in the reference pan, in an atmosphere of nitrogen to a temperature of 200°C. The DSC studies were performed for the drug, polymer and for the solid dispersion.

Infrared spectroscopy

IR spectra of pure aceclofenac, PEG 6000 and aceclofenac with its solid dispersion were obtained by a Perkin-Elmer Fourier transform infrared spectrophotometer using KBr pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The scanning range used was 4000 to 400cm-1.

FORMULATION OF ACECLOFENAC SOLID DISPERSION (ASD)

Formulation variables with different ratios of the selected carriers

Aceclofenac solid dispersions were prepared by solvent evaporation method using PEG 6000 as carrier at different ratios. The drug and carrier was dissolved in a mixture of dichloromethane and methanol (1:1 v/v) and triturated in dry mortar until the solvent evaporated. The resultant solid dispersion was scraped out with a spatula, pulverized in a mortar and pestle and stored in an air tight container for further analysis. The compositions of different batches are shown in Table.1.

Table.no.1.The compositions of different batches of solid dispersion

S.No.	Code of solid dispersion	Drug to carrier ratio
1	ASD – 1	1:1
2	ASD – 2	1:2
3	ASD – 3	1:3
4	ASD – 4	1:4
5	ASD – 5	1:5

FORMULATION OF ACECLOFENAC PELLETS

Formulation of aceclofenac pellets using different ratios of selected polymers

The required quantity of MCC as spheronization enhancer, HPMC (Table.2**)** as polymeric material and aceclofenac were weighed. To this mixture, sufficient quantity of isopropyl alcohol as granulating agent was added to get a wet mass. The solid blend was passed through the extruder to form the extrudates. The formed extrudates were introduced into the spheronizer to get spherical pellets by varying different spheronization speed as shown in Table.2.Preparation of aceclofenac pellets using different concentrations of HPMC by extrusion spheronization technique based on the shape of the pellets formed with narrow range were selected for further evaluation (Michael, et al.2004).

PREPARATION OF DUAL RELEASE DOSAGE FORM

Dual release dosage forms were constructed incorporating the optimized batch of solid dispersion (ASD4) pellets (M3). The amount of pellets equivalent to 200mg of aceclofenac(Sustained release) and amount of solid dispersion equivalent to 100mg of aceclofenac(Immediate release) were filled in gelatin capsule (size 2) the prepared dual release dosage form were evaluated for *in vitro* and *in vivo* experiments.

Table.No.2: Optimization of pellatization technique using HPMC, MCC pH 101

DRUG:HPMC:MCC PH 101	Isopropyl alcohol Content (ml)	Spheronization speed (rpm)	Residence time (Min)	Pellet description
M1(20:5:75)	15	1000	15	Rod shaped
		1500		Rod shaped
		2000		Rod shaped
		2200		Rod and dumb bell Shaped
		2500		Pellets with narrow range
M2(20:10:70)	15	1000	50	Rod shaped
		1500		Rod shaped
		2000		Rod and dumb bell Shaped
		2200		Rod and dumb bell Shaped
		2500		Pellets with narrow range
M3(20:15:65)	11	1000	60	Rod shaped
		1500		Rod shaped
		2000		Rod and dumb bell
		2200		Rod and dumb bell
		2500		Pellets with narrow range

Invitro evaluation of aceclofenac solid dispersion (Babu, et al. 2008)

Drug content

The solid dispersion formulation equivalent to 10 mg of aceclofenac was weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 273 nm by UV spectrophotometer. The actual drug content was calculated using the following formula,

$$\text{Drug content (\%)} = \frac{\text{Actual amount of drug in solid dispersion}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

***In vitro* drug release studies of aceclofanac solid disperssions**

In vitro release profile of solid dispersion and pure drug were performed using USP XXII type 2 dissolution apparatus (TDP-06P, Electro lab, Mumbai, India). Sample equivalent to 100 mg of aceclofenac was filled in to capsules and subjected to *in vitro* drug release of aceclofenac using at pH 6.8 phosphate buffer was carried out at 37± 0.5ºC with a stirring speed of 50 rpm. Aliquot of 5ml was withdrawn at predetermined time intervals of 0, 5, 10, 15, 20, 30, 45, 60 and 90 min. The withdrawn volume was replaced with the same volume of dissolution medium to maintain the sink condition. The absorbance of the samples was measured at 273 nm using UV spectrophotometer (Ramana, et al. 2006).

In vitro Evaluation of the prepared pellets

The prepared tablets were tested for Size distribution analysis, bulk density, True density, Porosity, Angle of repose, Carr's consolidation index, Friability, Drug content uniformity test.

***In vitro* dissolution studies for pellets**

A quantity of pellets which theoretically contain a drug content of 200mg of aceclofenac was filled in the capsules and subjected to *in vitro* dissolution study using USP XXII model type II (paddle). 900ml of phosphate buffer pH 6.8 was transferred to each jar and placed them in a test assembly which is maintained at 37°C. The medium was stirred at 50 rpm. 5ml of samples were withdrawn at different time intervals up to 720 minutes (0,15,30,60,120,180,240,300,360,420,480,600 and 720). Equal quantity of fresh medium was replaced after each sampling. The sample was diluted to 10 times and absorbance was measured at 273 nm.

Release kinetics

Release kinetics studies were done to assess the kinetics of drug release from prepared dual release drug delivery systems using models such as *zero order kinetics* (cumulative percentage amount of drug release versus time), *First order kinetics* (log cumulative percentage of drug remaining to release versus time), *Higuchi* (fraction of drug release, Mt/Mi, versus square root of time) and *Korsmeyer-Peppas* (log fraction of drug released, log Mt/Mi, versus log time) were applied. The most suited model for drug release was predicted on the basis of regression coefficient i.e. nearer the value of regression coefficient towards 1, greater the suitability of best fitted release mechanism (Peppas , et al. 1987.

***In vivo* studies**

A comparative bioavailability studies on the optimized dual release formulations were carried out in a New Zealand albino rabbits, weighing 2.5-3.0 kg .The permission was obtained from the *Committee for the Purpose of Control and Supervision of Experiments on animals (CPCSE) / Institutional Animals Ethics Committee (IAEC) proposal no JSSCP/IAEC/Ph.D/Ph.Ceutics//01/2012-2013.*The animals were divided into 5 groups each containing three rabbits .The animals were kept in environmentally controlled animal house, of J.S.S.College of Pharmacy, for one week before the experiment with free access to water and other feeds necessary to them. The animals were fasted over night prior to experiment, but were allowed free access to water. The dose of aceclofenac for rabbits were calculated on the basis of body surface area ratio of rabbits with respect to human. The pellets and mini tablets are administered to the animals with 5ml of water through esophageal tube.

Table.no.3.Grouping of animals

GROUP 1	Control
GROUP 2	Marketed Aceclofenac(Immediate Release) Formulation
GROUP 3	Marketed Aceclofenac(Sustained Release) Formulation
GROUP 4	In House Dual Release Aceclofenac Mini Matrix Tablets
GROUP 5	In House Dual Release Aceclofenac Spheroids

Blood samples (2ml) were directly withdrawn from the ear vein (in heparinised Riavials) at different time intervals of 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 18.0 and 24.0 hours after oral administration. The collected samples were centrifuged at 2500 rpm for 10 min to separate the plasma. The separated plasma were collected in Ependorf tubes and stored in a deep freezer until the sample is analyzed by HPLC method. The pharmacokinetic parameters like $C_{max,}$ $t_{max,}$ $(AUC)_{0\text{-}t}$, $(AUC)_{0\text{-}\alpha}$, K_e $T_{1/2}$ was determined for each group.

Chromatographic conditions

The plasma samples were analyzed for aceclofenac using a modified HPLC method . The mobile phase consisted of Acetonitrile: Phosphate buffer (60:40 v/v), adjusted to pH 3.5 with glacial acetic acid. The pump was gradient pump with drug run time of 7.9min (IS). The stationary phase was, Hibar C_{18} (250 x 4.6 mm i.d., 5µ) and the flow rate was adjusted at 1 ml/min with the sample volume 20 µl using Rheodyne 7725i injector. The detector was PDA detector (Model SPD-10 A, Shimadzu, Japan) and the detection wavelength was 28

RESULTS AND DISCUSSION

Solubility studies

The solubility of ACE in water was found to be 3.8µg/ml, and hence, aceclofenac can be considered as a practically insoluble drug. The drug is also available in crystalline form. According to observations obtained from the solubility

analysis of solid dispersion of drug and carrier, there were significant changes in the solubility of drug as compared to that of pure drug in distilled water and PBS pH 6.8(Table.3). Enhanced solubility of aceclofenac from solid dispersion could be related to the surface activity, wetting effect which may lead to reduced agglomeration and hence increased surface area, and solubilizing effect of PEG 6000(Leunner, et al.2000).

Table.no.4. Solubility of aceclofenac in pH6.8 buffer and water

Formulation Code	Drug: carrier Ratio	Phosphate buffer saline pH 6.8 (µg/ml)	Water (µg/ml)
ASD-1	1:1	30.3	20.3
ASD-2	1:2	49.9	32.9
ASD-3	1:3	61.2	45.2
ASD-4	1:4	74.3	55.3
ASD-5	1:5	72.0	54.2
Pure Drug		--	3.8

Differential scanning calorimetry

The DSC thermo gram of drug exhibited an endothermic peak at 153.75 ^{O}C, which corresponds to the melting Point of aceclofenac. The carrier PEG 6000 showed an endothermic peak at 63.40 ^{O} C which corresponds to the melting point of PEG 6000.There was endothermic peak observed for solid dispersions prepared using drug: carrier ratio, 1:4 at 56.96^{o}C which corresponds to the melting of PEG 6000. The intensity of endothermic peak of drug (aceclofenac) in solid dispersion was much lower than pure drug suggesting that the drug has been converted from its original crystalline form to semi crystalline where most of part of the drug is in amorphous state. It gives an idea that most of aceclofenac is in dissolved state in melted PEG 6000.

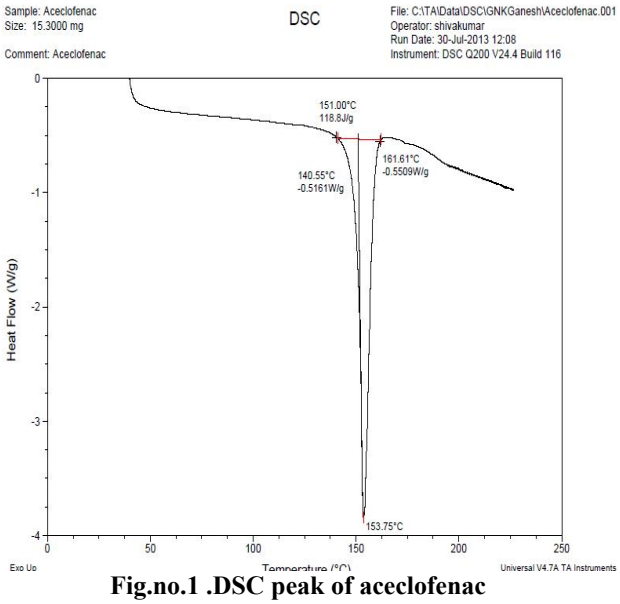

Fig.no.1 .DSC peak of aceclofenac

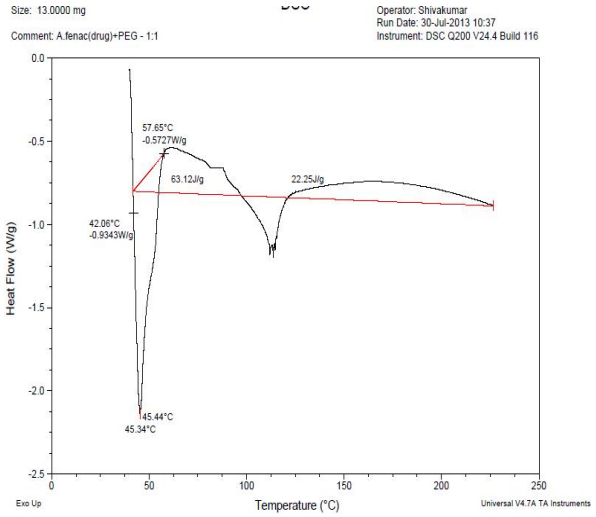

Fig.no.2.DSC Peak of aceclofenac+ PEG (1:1)

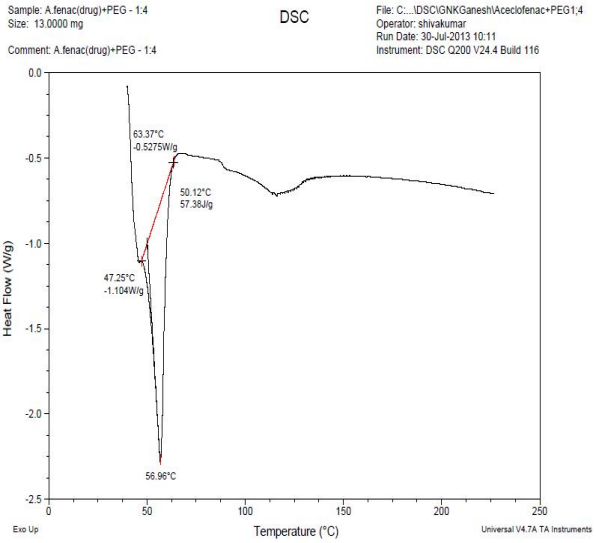

Fig.no.3. DSC peak of aceclofenac+PEG (1:4)

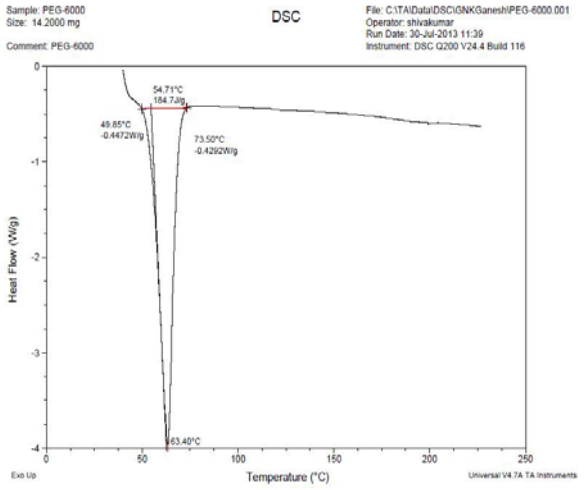

Fig.no.4.DSC peak of PEG

Infrared spectroscopy

The FTIR spectra of the drug with polymer and excipients (HPMC, MCC, and PEG6000) showed there was no major shifting, loss or appearance of functional peaks between the spectra of drug, excipients and physical mixture of drug and excipients. This confirms that the drug and excipients were compatible with each other without any chemical interaction.

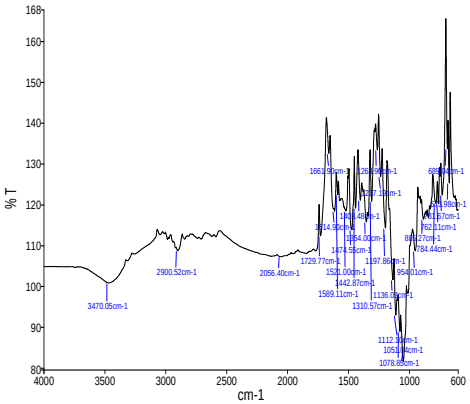

Fig.no.5.IR Spectra of HPMC K 100

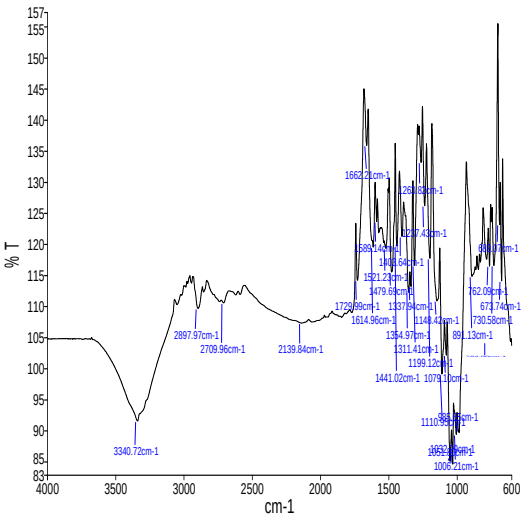

Fig.no.6.IR spectra for MCC 101

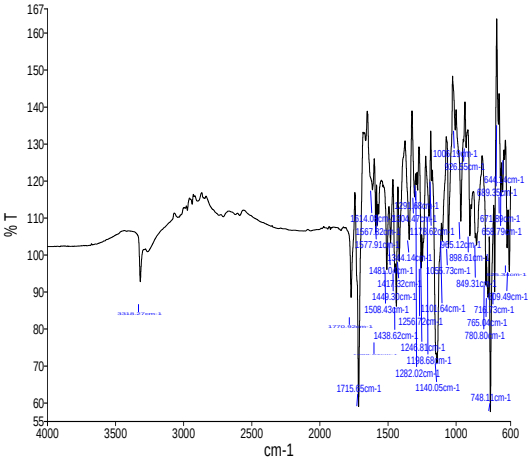

Fig.no.7. IR Spectra of Aceclofenac

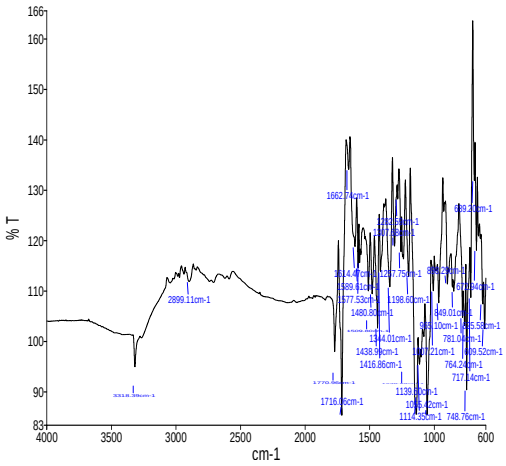

Fig.no.8. IR spectra of HPMC+MCC+Aceclofenac

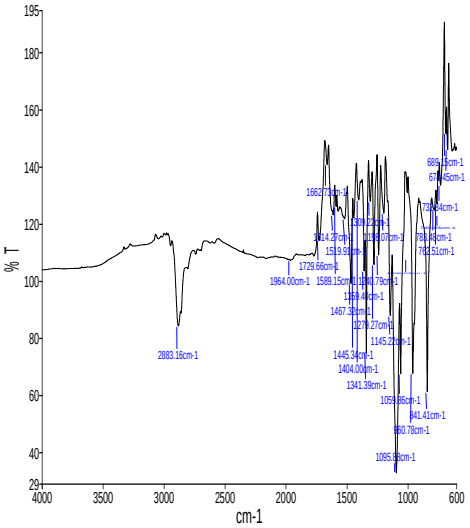

Fig.no.9. IR spectra of PEG 6000

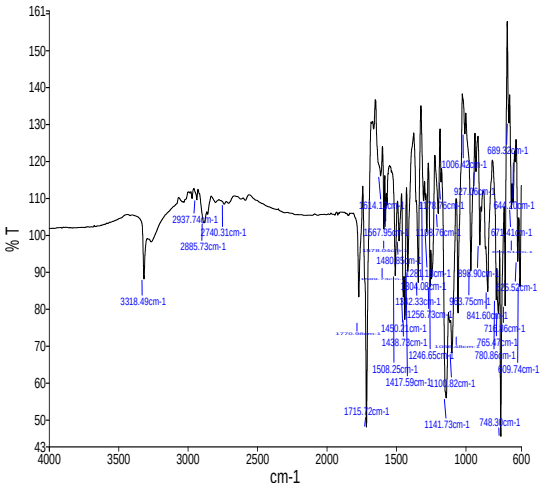

Fig.no.10. IR Spectra of PEG+Aceclofenac Physical mixture

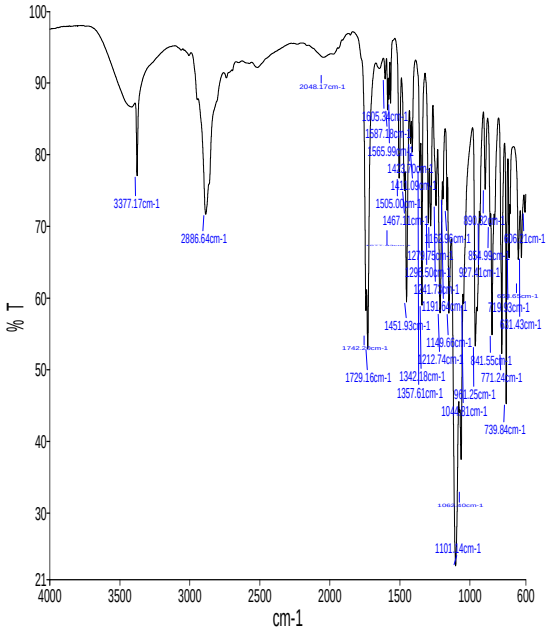

Fig.no.11. IR spectra of Aceclofenac+PEG (1:1)

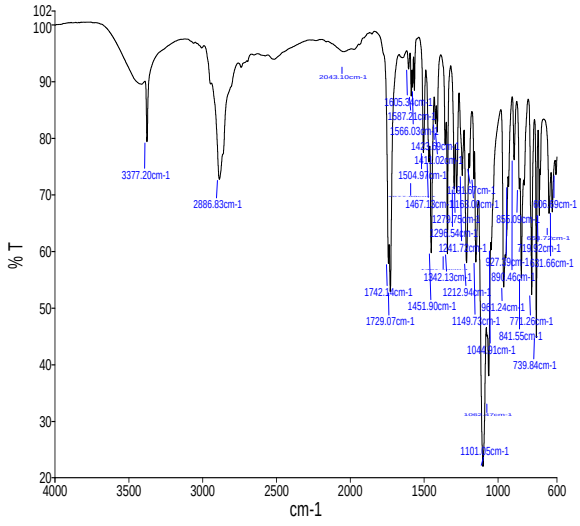

Fig.no.12. IR spectra of Aceclofenac+PEG (1:4)

Drug content of solid dispersions

Percentage drug content of various solid dispersion formulations i.e. ASD1, ASD2, ASD3, ASD4,and ASD5 were found to be 98.5%, 99.1%, 98.7%, 98.5%, and 97.2%, respectively. The percentage drug content was found to be 95±5% for all the solid dispersion formulations.

***In vitro* drug release of aceclofenac solid dispersion**

The drug release behavior of aceclofenac from various solid dispersion formulations and pure drug in PBS (pH 6.8) was examined in comparison with the intact drug by plotting the percentage of drug released against time as shown in figure.2. The drug release from different solid dispersion formulations prepared by solvent evaporation method followed the order: ASD4 > ASD5 > ASD3 > ASD2 > ASD1. It is evident that the rate of dissolution of pure drug is very low, only 38.98 % of the drug being dissolved within 2 h. Dispersion of the drug in the hydrophilic carrier's considerably enhanced drug release compared to the pure drug. This could be due to the effect of molecular dispersion of drug in PEG, and the decreased crystallinity of aceclofenac existing in Solid dispersion.

The dissolution rate of the solid dispersion formulations was higher compared to pure aceclofenac. From the *in vitro* drug release profile for different Solid dispersion formulation, it is evident that amongst the Solid dispersion formulated, there was increase in dissolution up to the ratio 1:4, but after this there is no significant increase in the release of the drug. This might be due to complete dispersion of drug with PEG 6000 at 1:4 ratio.

Further, as the concentration of the polymer increased, a decrease in drug release was observed. This might be due to formation of viscous boundary layer around the drug particles, leading to decrease in the drug release rate. Hence, formulation ASD 4 was selected for further studies to prepare dual release formulation.

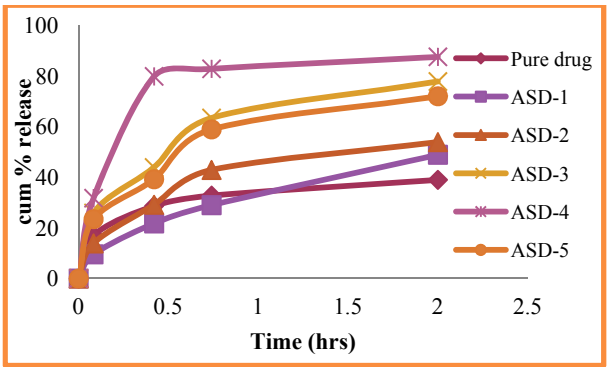

Fig.no.13: *In Vitro* Drug Release of Aceclofenac Solid Dispersions

Invitro evaluation of pellets

Particle size determination of aceclofenac pellets

The developed spheroids of aceclofenac had exhibited satisfactory particle size and the data showed in Table.5**.**

Table.no.5.Interpretation of Compatability studies of drug with excepients

S.No	Functional Group	Vibration in Cm^{-1} of Aceclofenac	Vibration In Cm^{-1} of Aceclofenac +PEG
1	Carboxylic acid	3300- 3480	3377.17
2	Keto group	1715	1729.16, 1742.20
3	Aromatic	1450-1600	1451.93, 1587.18
4	Alkyl halides	600-800	631.43, 739.48
5	c-o	1050-1150	1101.14
6	Alknaes	-	2886.64

Table.no.6. Particle size and size distribution of aceclofenac pellets

Sieve No	Avg. opening size(mm)	Arithmetic mean size opening(mm)	Wt of pellets retained	% of Wt of pellets retained	Wt size	%Wt undersize	%Wt oversize
16	1.0	1.0	2.5	7.2	7.2	92.8	7.2
22	0.710	0.855	11.5	33.33	28.49	59.47	40.53
25	0.600	0.655	13.5	39.13	25.63	20.34	79.66
60	0.250	0.425	7	20.28	8.619	0.06	99.94
Avg. particle size = 0.6993 mm			34.5		69.93		

Determination of physicochemical and flow characteristics

The developed pellets of aceclofenac had exhibited good flow properties and pharmacotechnical parameters. All the results were well within the range, the drug content was found to be nearly 100% (Table.6**)**.

Table.no.7. Physiochemical properties of pellets formulated with (Drug: HPMC: MCC pH101)

Properties	(Drug: HPMC: MCC Ph101)		
	M1	M2	M3
Average Particle size(mm)	0.6996	0.6993	0.6995
Bulk density(g/cc)	0.502	0.498	0.501
True density(g/cc)	0.5311	0.5315	0.05318
Carr's Index	4.7832	4.7801	4.6981
Angle of repose(degrees)	24.38	23.33	28.91
Porosity	0.0599	0.0595	0.0587
Friability	1.4	1.5	1.7
Drug content (% label claim)	97.3	98.1	98.8

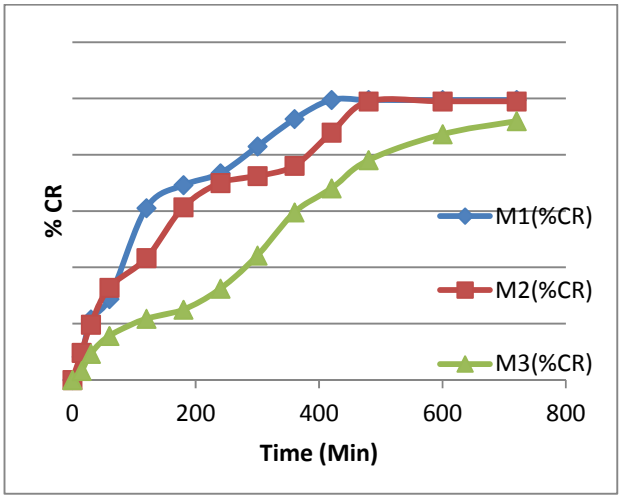

Fig.no.14.In vitro release of aceclofenac pellets

***In vitro* drug release of aceclofenac pellets**

It was found that the drug release from the three batches of aceclofenac pellets was sustained over a period of time. However, it was found that the drug release from the spheroids containing 5 % and 10 % concentration of polymer had initial burst release of about 20 % at 30 minutes when compared to the spheroids containing 15 % HPMC (Table.6). It was also found that the maximum of nearly 100 % drug release occurred within 7 h and 8 h for M1 and M2 respectively. The amount of drug release from M3 batch was found to be about 92 % over a period of 12 hours. Hence, M3 batch was chosen as optimized batch to prepare the dual release capsules of aceclofenac.

Table.no.8. *In vitro* drug release of aceclofenac pellets

Time(min)	M1(%CR)	M2(%CR)	M3(%CR)
0	0	0	0
15	8.24±0.2	9.65±1.1	3.23±1.9
30	21.54±0.3	19.65±1.2	9.30±1.7
60	28.76±0.4	32.76±1.4	15.65±1.5
120	61.07±0.5	43.32±1.6	21.76±1.3
180	69.24±0.6	61.36±1.8	24.98±1.1
240	73.456±0.7	69.98±1.3	32.45±1.8
300	82.98±0.8	72.45±1.5	44.21±1.6
360	92.72±0.6	76.09±1.7	59.54±1.4
420	99.48±0.7	87.89±1.9	68.07±1.2
480	--	98.95±0.9	78.12±1.0
600	--	--	87.32±0.9
720	--	--	91.98±0.7

Mean±SD, n=3

Evaluation of dual release dosage form using optimized batches

Table.no.9.Comparative *in vitro* drug release of optimized dual release formulation (Pellets) with marketed formulations

Time (min)	Marketed IR (% CR)	Marketed SR (% CR)	Dual release formulation (spheroids) (% CR)	Dual release formulation (spheroids) (Amount CR)
0	0	0	0	0
15	23.64±0.6	2.39±0.9	12.74±1.9	38.22
30	48.124±0.7	2.95±1.0	32.81±1.8	98.45
60	58.11±0.8	6.84±1.1	38.04±1.7	114.12
120	80.46±0.9	11.66±1.2	43.69±1.6	131.08
180	----	13.01±1.3	49.98±1.5	149.96
240	----	18.98±1.4	54.96±1.4	164.90
300	---	22.58±1.5	61.14±1.3	183.42
360	----	35.63±1.6	72.02±1.2	216.08
420	----	39.55±1.7	79.71±1.1	239.15
480	----	45.02±1.8	83.75±1.0	251.25
600	---	57.60±1.9	90.54±1.1	271.64
720	---	62.52±1.8	94.32±1.2	282.97

Mean±SD, n=3

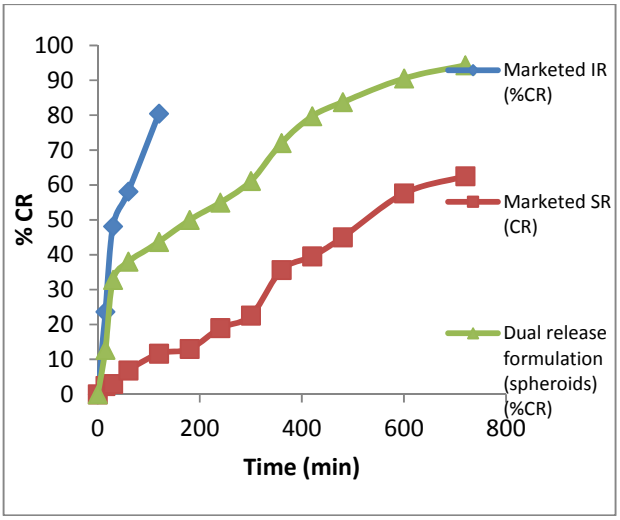

Fig.no.15. Comparative *in vitro* drug release of optimized dual release formulation (Pellets) with marketed formulations

Release kinetics

The release models were plotted and regression coefficient values were shown in Table.9.It was observed that the developed dual release matrix tablets and pellets follow first order kinetics obeying fickian diffusion.

Table.no.10. Regression co-efficient of zero order, first order, higuchi and peppa's

Name of the formulation	Zero order	First order	Higuchi	Peppa's	
				R2	N
Dual release Pellets	0.9434	0.9784	0.9892	0.9875	0.371766

Bioavailability studies

Bioavailability studies for the optimized dual release formulations were carried out to assess the pharmacokinetic parameters (Table.8) .The peak plasma concentration (C_{max}) was achieved in 2h for spheroids.The C_{max} of dual release spheroids (13.9783 µg/ml) was found to be greater than that of IR (9.9461 µg/ml) and SR (10.0123 µg/ml) dosage forms indicating that higher plasma concentration could be achieved quicker (2h spheroids) than the SR formulation (6h). Thus the absorption lag time associated with SR formulations could be minimized using these formulations. Further, there was significant increase in AUC $_{0-\alpha}$ in case of dual release spheroids (192.689 µg/ml/h) than the IR (77.2675 µg/ml/h) and SR (117.6524 µg/ml/h) indicating the enhanced absorption of poorly water soluble aceclofenac which may be attributed to enhanced solubility by solid dispersion technique and greater surface area of multiparticulate dosage forms. There was no significant variation in Ke and $t_{1/2}$ for spheroids (0.119164 h^{-1} and 5.81677 h),when compared with marketed SR formulation (0.1333 h^{-1} and 5.199896 h). This indicated that the developed formulations did not change intrinsic pharmacokinetic parameters such as K_e and $t_{1/2}$.

Table.no.11.Pharmacokinetic parameters for optimized dual release spheroids formulation

PK Parameters	Marketed IR tablet	Marketed SR tablet	Dual release spheroids
Cmax (µg/ml)	9.9461±1.1	10.0123±0.8	13.9783 ±0.5
Tmax(h)	0.75±0.97	6 ±1.01	2 ±0.82
AUC_{0-t}(µg/ml/h)	65.4147 ±5.1	102.5415±10.6	175.38551 ±15.2
k (h^{-1})	0.140377±0.02	0.1333±0.01	0.119164±0.03
$t_{½}$ (h)	4.251607±0.51	5.19989 ±0.42	5.81677± 0.37
$AUC_{0-\alpha}$(µg/ml/h)	77.2675±0.97	117.6524±1.23	192.689±2.44

Mean±SD, n=3

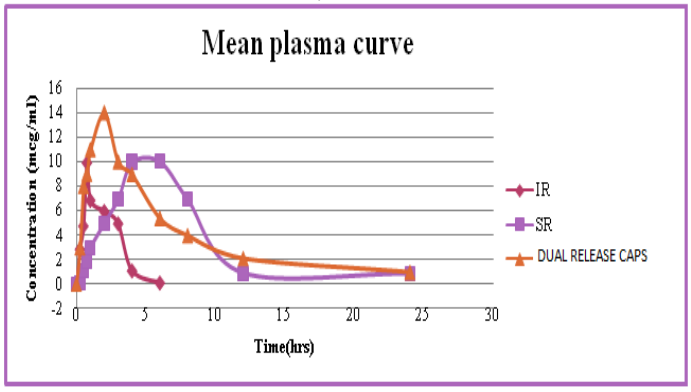

Fig.no.16. Mean plasma concentration curve for developed formulations

CONCLUSION

The developed dual release system was able to deliver a first fraction of the dose in short time and deliver a second fraction at a sustained rate for a longer period of time to overcome significant variation in drug concentration in the plasma and to improve the patient compliance for aceclofenac.

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