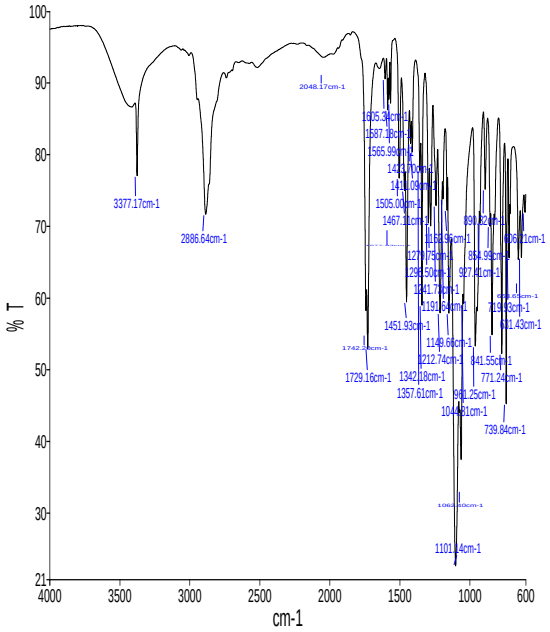

Fig.no.11. IR spectra of Aceclofenac+PEG (1:1)

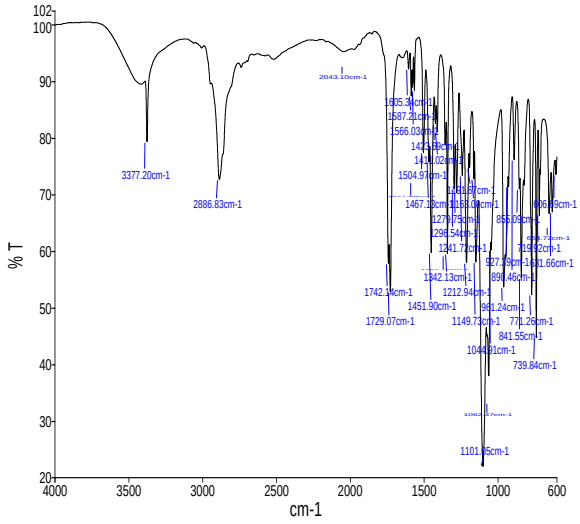

Fig.no.12. IR spectra of Aceclofenac+PEG (1:4)

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.

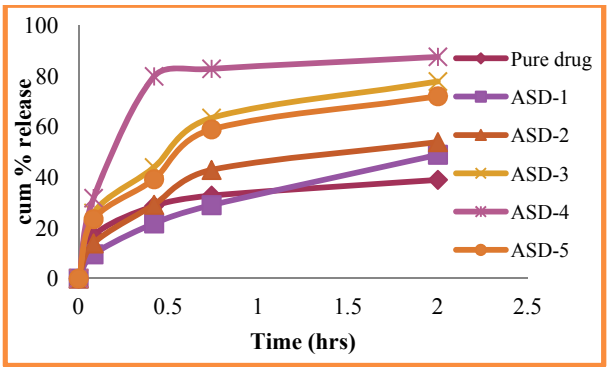

Fig.no.13: *In Vitro* Drug Release of Aceclofenac Solid Dispersions

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

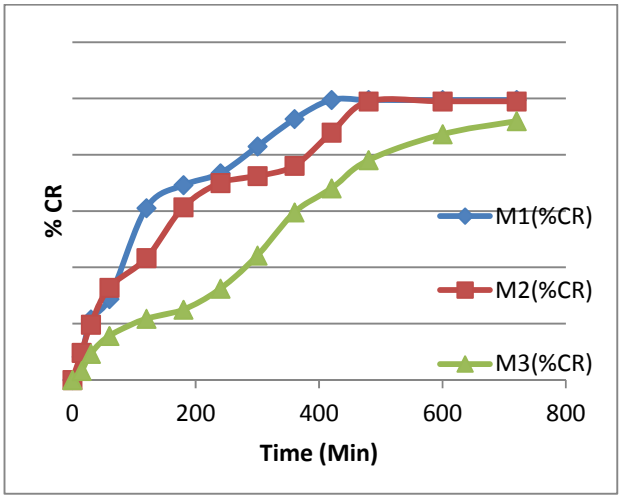

Fig.no.14.In vitro release of aceclofenac pellets

***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

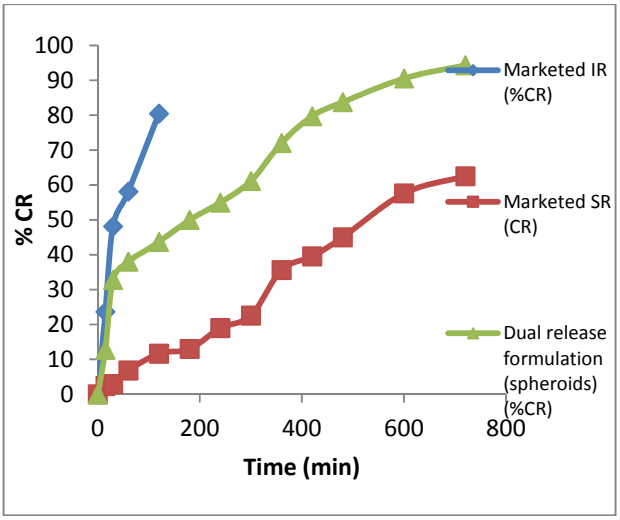

Fig.no.15. Comparative *in vitro* drug release of optimized dual release formulation (Pellets) with marketed formulations

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

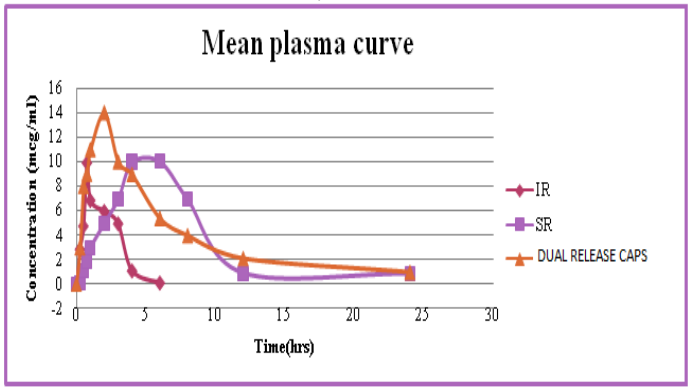

Fig.no.16. Mean plasma concentration curve for developed formulations

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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