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Formulation of aceclofenac solid dispersion for solubility enhancement

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ABSTRACT

The Aceclofenac is adrug belongs to non-steroidal anti-inflammatory drug (NSAID) which is having anti-inflammatory and analgesic properties, and it is widely used in the treatment of rheumatoidarthritis, osteoarthritis, and ankylosing spondylitis. The most major problems with this drug is its low solubility in biological fluids, which results as poor bioavailability after oral administration. Thats why, solid dispersions (SDs) of aceclofenac were prepared using PEG6000 to increase its aqueous solubility. Aceclofenac SDs wereprepared in 1:1, 1:2, 1:3, 1:4 and 1:5 ratios by kneading method and same ratio taken to prepare SDs prepared by solvent evaporation method too. *In-vitro* release profiles of all SDs (F-1 to F-5 by solvent evaporation method and FM-1 to FM-5 by kneading method) were comparatively evaluated and also studied against pure aceclofenac. Faster dissolution was exhibited by solid dispersion containing (1:5)ratio of drug: PEG6000 prepared by solvent evaporation method. The increase in dissolution rate of the drug may be due toincrease in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity. The prepared solid dispersion was subjected for percentage practical yield, drug content, infrared (IR).

Keywords: Aceclofenac,

INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. There were several ways in which bioavailability of the drug can be enhanced all of which aimed at increasing the surface area of the drugs which includes. Micronization, use of salt form, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation and complexation with cyclodextrins.[1] The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilisation by co solvents and particle size reduction.[1] The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. Lipophilic molecules, especially those belonging to the bio-pharmaceutics classification system (BCS) class II and IV, dissolve slowly, poorly and irregularly, and hence pose serious delivery challenges, like incomplete release from the dosage form, poor bioavailability, increased food effect and high inter-patient variability.[2,3]

MATERIALS AND METHODS

Ingredients Used

Drug Aceclofenac, was kind gift from CIPLA LTD. Mumbai and Polyethylene glycol(PEG6000) was taken from Finar chemicals ltd (Mumbai).

Preformulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.[9] The aceclofenac powder was subjected to preformulation studies for physical tests. (I.P, 2007)

Preparation Of Solid Dispersion By Solvent Evoperation

Aceclofenac solid dispersion were prepared by using hydrophilic carriers like polyethylene glycol (PEG6000) in proportions viz .1:1, 1:2, 1:3, 1:4, 1:5 (drug: carrier), was prepared by solvent evaporation method. Aceclofenac and carriers were dissolved in methanol and mixed with magnetic stirring. Solvent was evaporated at reduced pressure at 40^{o}C in a rotatory evaporation apparatus. Subsequently solid dispersion was stored under vacuum over silica gel for 12hrs at room temperature. After drying the solid dispersion was passed through a 250µm sieve. Sample was stored in a desiccator and used for further investigation[61].

Table 1: Formulation of aceclofenac solid dispersion by solvent evaporation

S.NO	FORMULATION	COMPOSITION	DRUG: CARRIER
1	F1	Aceclofenac+ polyethyleneglycolate(PEG6000)	1:1
2	F2	Aceclofenac+ polyethyleneglycolate(PEG6000)	1:2
3	F3	Aceclofenac+ polyethyleneglycolate(PEG6000)	1:3
4	F4	Aceclofenac+ polyethyleneglycolate(PEG6000)	1:4
5	F5	Aceclofenac+ colate(PEG6000)	1:5

PREPARATION OF SOLID DISPERSION BY KNEADING METHOD

Aceclofenac and carriers were dissolved in methanol, then make paste using a mortar and pestle. Kneading shall be done properly to form uniform mass. Now dry this paste at 45 ^{o}C for 1 hour. Pass the dried mass through 80 mesh sieve and keep it in a desiccator and used for further investigation[63]

Table 2: Formulation of aceclofenac solid dispersion by kneading method

S.NO	FORMULATION	COMPOSITION	DRUG: CARRIER
1	FM1	Aceclofenac+ Polyethyleneglycolate (PEG6000)	1:1
2	FM2	Aceclofenac+ Polyethyleneglycolate (PEG6000)	1:2
3	FM3	Aceclofenac+ Polyethyleneglycolate (PEG6000)	1:3
4	FM4	Aceclofenac+ Polyethyleneglycolate (PEG6000)	1:4
5	FM5	Aceclofenac+ Polyethyleneglycolate (PEG6000)	1:5

Evaluation of Formulations

The prepared formulations of solid dispersions were evaluated for the following Physico chemical characterization

In-vitro dissolution studies

RESULTS AND DISCUSSION

Compatability Study

The FTIR spectra of the pure aceclofenac drug, carriers, physical mixture of drug and carriers and solid dispersion of drug and carrier. The spectra exhibited presence of characteristic peaks of drugs in physical mixture and indicatethat there was no chemical interaction between the drugs.

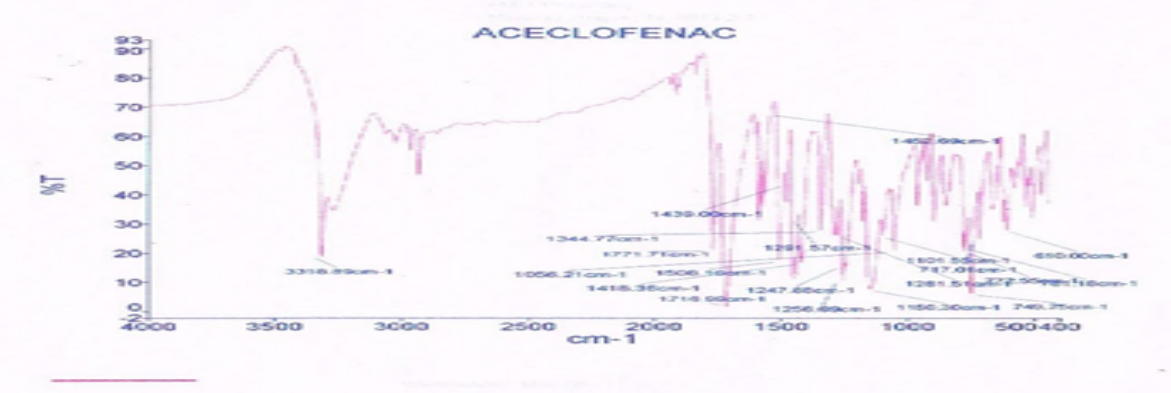

Fig 1: FTIR SPECTRA OF PURE ACECLOFENAC

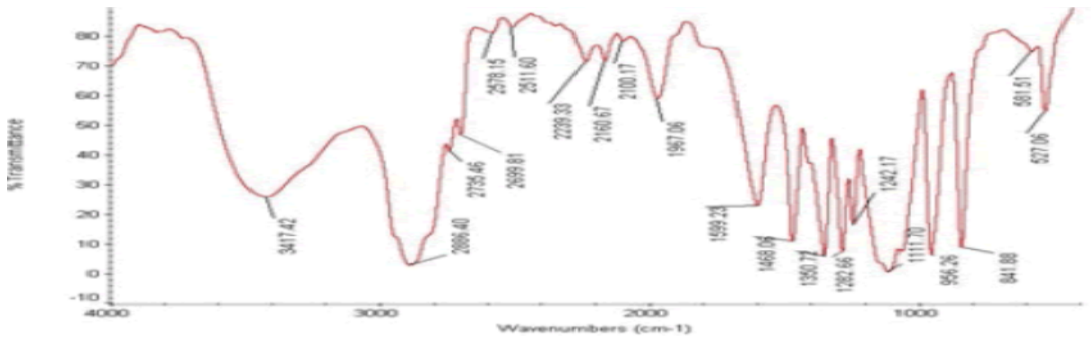

Fig 2: FTIR SPECTRA OF PURE POLYETHYLENE GLYCOL 6000

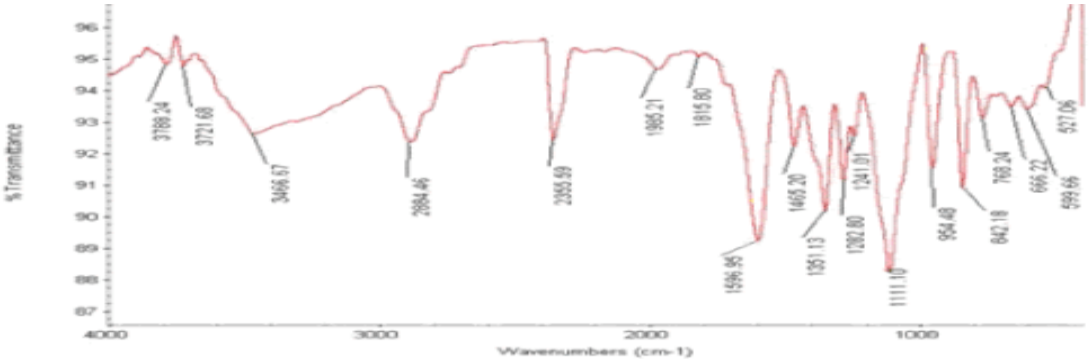

Fig 3: FTIR SPECTRA OF PHYSICAL MIXTURE OF ACECLOFENAC,PEG6000

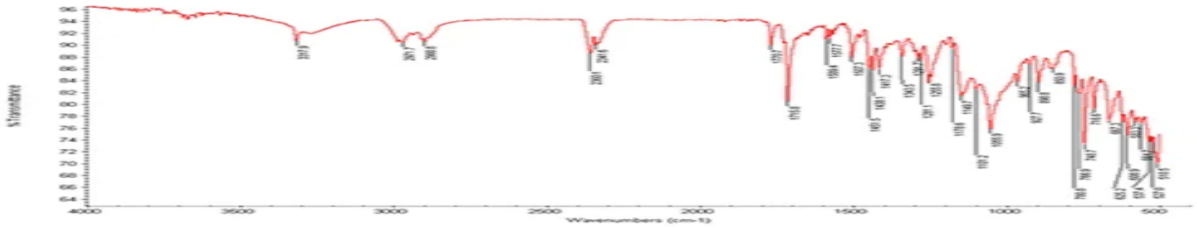

Fig 4: FTIR SPECTRA OF SOLID DISPERSION OF ACECLOOFENAC,PEG6000 BY SOLVENT EVAPORATION METHOD

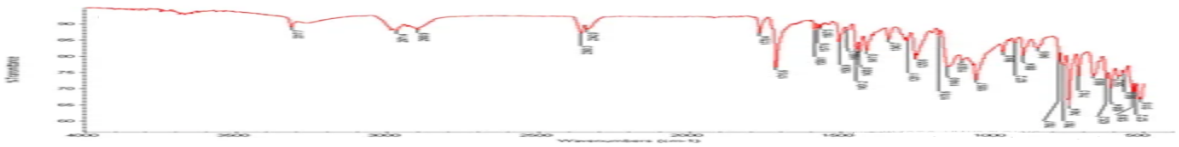

Fig 5: FTIR SPECTRA OF SOLID DISPERSION OF ACECLOOFENAC,PEG6000 BY KNEADING METHOD

Differential Scanning Calorimetry

In the DSC studies of pure aceclofenac showed a sharp endotherm at 152.81ºC, PEG6000 at 61.50ºC and physical mixture at 162ºCto its melting point. There was no appreciable change in the melting endotherm of spherical agglomerates compared to that of pure drug (FM2 agglomerates =153.24^{0}C) the DSC results also revealed little amorphization of aceclofenac when compared in the formof agglomerates with PEG6000.

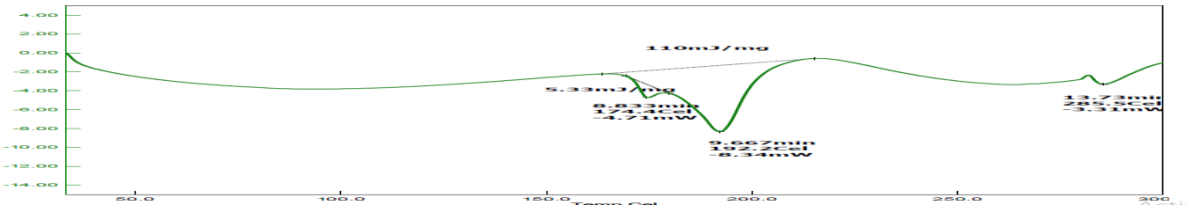

Fig 6: DSC THERMO GRAM OF PURE ACECLOFENAC

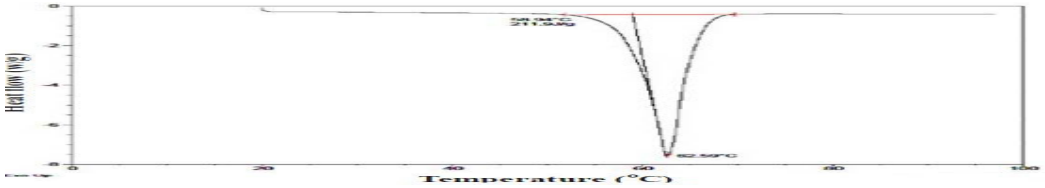

Fig 7: DSC THERMO GRAM OF PURE PEG6000

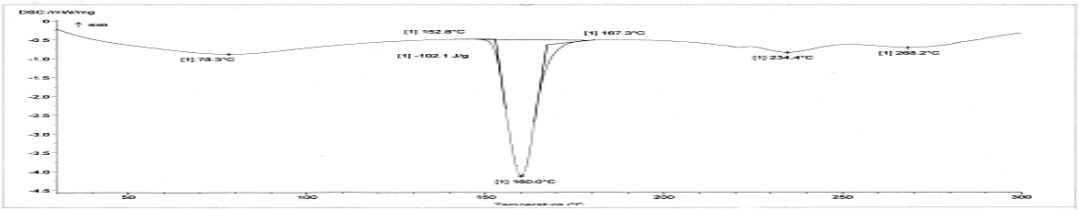

Fig 8: DSC THERMO GRAM OF PHYSICAL MIXTURE

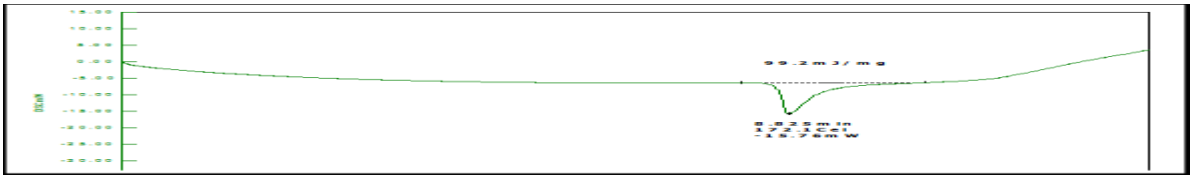

Fig 9: DSC THERMO GRAM OF FM2 FORMULATION

Calibration Curve of Aceclofenac

The calibration curve of aceclofenac was determined in pH 6.8 phosphate buffer by using UV-Visible spectrophotometer at 275 nm. Graph was plotted by taking absorbance (nm) on X-axis verses concentration (µg/ml) on Y-axis and it is follows the Beer's law. The results were shown in table.

Table 3: Calibration curve of aceclofenac

SL. No	Concentration of aceclofenac(µg/ml)	Absorbance at275nm
0	0	0
1	2	0.0556
2	4	0.1048
3	6	0.1563
4	8	0.2018
5	10	0.2625
R^2 value		0.9988

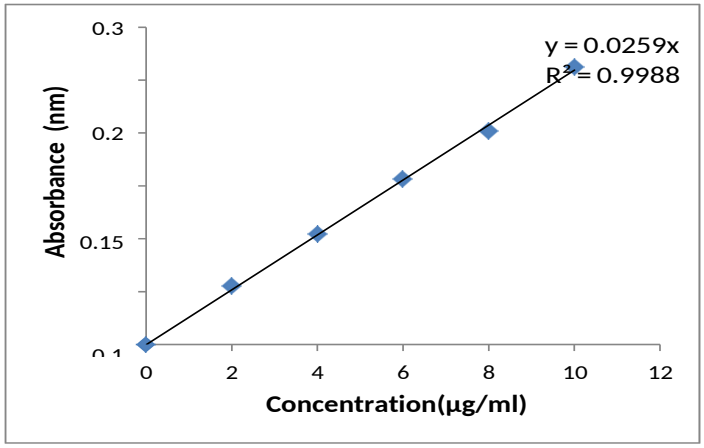

Fig 10: Calibration curve of aceclofenac

Drug Content Estimation

Drug content uniformity of aceclofenac solid dispersion in all the formulations (F1 toF5, FM1 to FM5) were shown from 67.5±0.7076 to 88.09±3.7390 respectively. As shown in table.

Table 4: Drug content of aceclofenac in all formulations

Formulation code	Drug content (in %)
F1	77.89±0.7128
F2	67.5±0.7076
F3	70.55 ±0.7805
F4	69.68±1.2583
F5	82.14±1.1185
FM1	74.20±1.1145
FM2	88.09±3.7390
FM3	86.5±2.121
FM4	77.37±1.4913
FM5	76.14±1.1184

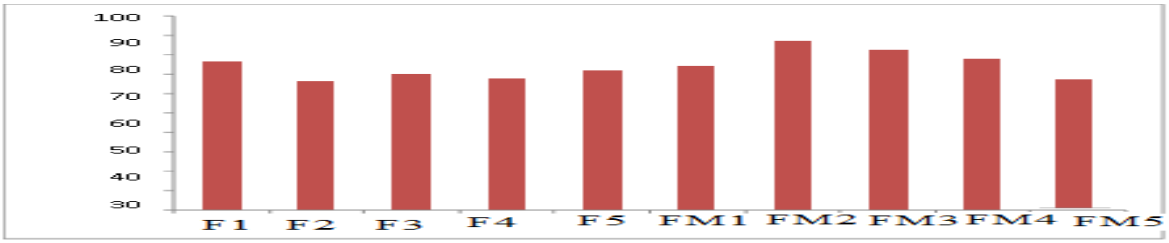

Fig 11: Drug content of aceclofenac in all formulations

Percentage Practical Yield

Percentage practical yield of aceclofenac in all the formulations (F1 toF5, FM1 to FM5) were shown from 87.09±0.290 to 97.46±0.9795 respectively. [63] As shown in table.

Table 5: Drug content of aceclofenac in all formulations

Formulation code	% Practical yield
F1	92.71±1.0651
F2	87.09±0.290

F3	94.7±0.6420
F4	91.08±0.305
F5	90.12±1.307
FM1	90.82±0.3614
FM2	97.46±0.9795
FM3	93.51±0.1937
FM4	92.77±0244
FM5	91.12±1.305

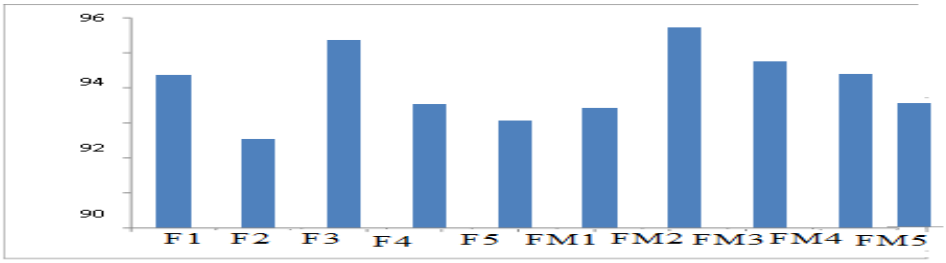

Fig 12: Drug content of aceclofenac in all formulations

Phase Solubility Study

Table 6: Solubility of aceclofenac in PEG6000 solution

Sl.no	Concentration of PEG6000(%w/v)	Solubility of aceclofenac in PEG6000 solution (mg/ml)
1	0	0.2123
2	0.0025	0.3620
3	0.0050	0.5411
4	0.010	1.6538

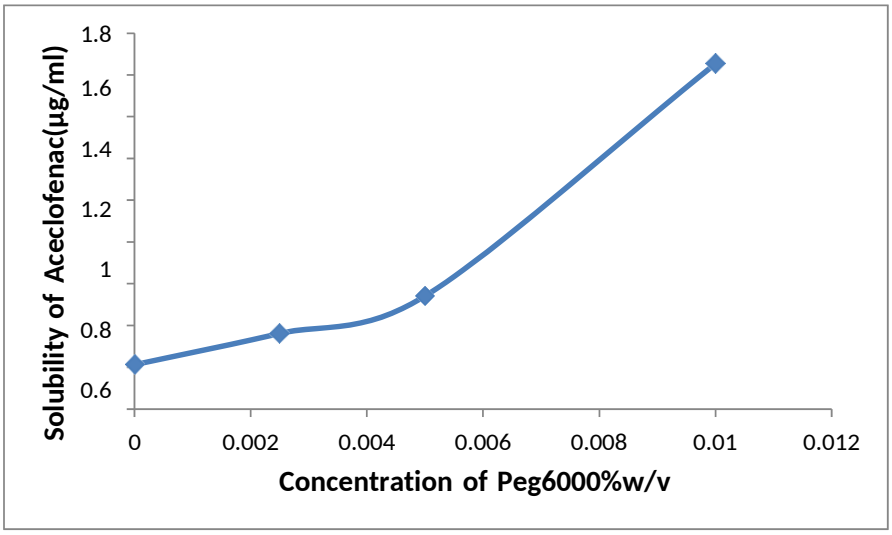

Fig 13: Solubility of aceclofenac in PEG6000 solution

In-Vitro Dissolution Studies

The aceclofenac solid dispersions were prepared by using with hydrophilic carrier PEG6000, in-vitro drug release studies were carried out in trail (n=3) basis for total 10 formulations. The release of aceclofenac solid dispersions was studied in 900 ml

of pH 6.8 phosphate buffer upto 90 min as dissolution medium using USP II (paddle) dissolution apparatus at 50 rpm and 37^0±0.5 ^{0}C. Drug content was determined by UV-Spectrophotometer at 275 nm. Cumulative percentage of drug release was calculated by using an equation obtained from a standard curve. The dissolution studies were performed 3 times for a period of 90 min, where Mean±S.D values were calculated. The results of studies were shown in Tables.

Table 7: In-vitro dissolution profile for solid dispersion F1 formulation

Time (min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.15	29.70	30.90	30.25 ± 0.606
20	38.20	38.15	37.92	38.09±0.1493
30	45.25	44.51	42.35	44.03 ±1.506
40	53.84	52.09	51.89	52.60±1.0727
50	59.57	58.95	59.00	59.17±0.3443
60	67.25	65.70	66.31	66.42±0.7808
70	74.09	72.12	73.15	73.12±0.9853
80	79.23	78.15	77.15	78.17±1.1784
90	84.29	79.13	83.25	82.22±2.7289

Table 8: In-vitro dissolution profile for solid dispersion F2 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	40.08	41.23	42.19	41.16 ±1.0564
20	51.90	50.98	49.67	50.85±1.1206
30	54.01	53.19	54.23	53.81±0.5480
40	57.38	56.29	55.55	56.40±0.9205
50	58.38	57.09	58.09	57.85±0.6767
60	61.38	61.08	59.15	60.53±1.2102
70	70.81	69.15	68.34	69.43±1.2591
80	73.15	72.12	74.09	73.12±0.9853
90	76.39	75.19	76.16	75.91±0.6368

Table 9: In-vitro dissolution profile for solid dispersion F3 formulation

Time (min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	25.30	24.90	25.95	25.38±0.5299
20	37.29	38.51	38.91	38.23±0.8438
30	39.70	40.75	39.15	39.86±0.8129
40	42.78	43.04	42.80	42.87±0.1446
50	49.10	49.81	48.75	49.22±0.5400
60	55.37	55.25	54.65	55.09±0.3857
70	59.43	58.50	59.85	59.26±0.6908
80	64.80	64.34	65.01	64.71±0.3426
90	69.15	69.95	70.03	69.71±0.4866

Table 10: In-vitro dissolution profile for solid dispersion F4 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0

10	14.92	14.70	15.44	15.02±0.3810
20	24.67	24.42	24.55	24.55±0.1245
30	38.66	37.13	37.65	37.81±0.7792
40	41.14	38.88	41.23	40.51±1.4081
50	51.37	46.75	48.20	48.77±2.3599
60	58.54	54.62	56.01	56.39±1.9864
70	62.60	60.48	61.91	61.66±1.0828
80	69.02	66.52	67.50	67.68±1.2583
90	72.37	70.92	73.12	72.14±1.1185

Table 11: In-vitro dissolution profile for solid dispersion F5 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.78	28.35	29.51	29.55± 1.21541
20	41.41	38.88	41.23	40.51±1.4116
30	46.29	45.68	46.17	46.05±0.3231
40	51.02	48.84	49.49	49.78±1.1192
50	60.24	57.52	58.21	58.66±1.4149
60	66.49	64.51	66.07	65.69±1.0432
70	74.14	72.76	71.82	72.90±1.1688
80	80.71	77.45	79.56	79.24±1.16568
90	82.40	81.43	83.04	82.29±0.8078

Table 12: In-vitro dissolution profile for solid dispersion FM1 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	37.30	38.01	37.15	37.48±0.4593
20	42.78	42.10	43.45	42.77±0.6750
30	46.04	44.99	45.94	45.65±0.5795
40	49.10	49.34	48.15	48.86±06293
50	55.37	54.19	55.90	55.15±0.8753
60	59.43	58.19	59.59	59.07±0.7662
70	64.13	64.09	65.32	64.51±0.6988
80	69.17	68.15	68.99	68.77±0.5444
90	76.51	77.41	76.44	76.79±0.5437

Table 13: In-vitro dissolution profile for solid dispersion FM2 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	33.42	34.20	33.06	33.56±0.5827
20	39.70	39.15	40.45	39.86±0.8129
30	47.14	46.50	47.82	47.15±0.6601
40	55.93	56.02	54.29	55.41±0.9738
50	6.70	62.04	63.15	62.29±0.7583
60	69.28	69.32	71.32	69.96±1.1664
70	78.90	77.13	76.23	77.42±0.3584
80	84.24	84.32	85.14	84.56±0.4981
90	97.53	96.25	96.85	96.21±0.6404

Table 14: In-vitro dissolution profile for solid dispersion FM3 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0

10	44.44	42.29	45.37	44.03±1.5828
20	49.23	46.97	50.49	48.90±1.7853
30	55.20	54.32	55.76	55.10±0.7248
40	61.70	60.28	60.60	60.86±0.7413
50	68.94	68.23	70.31	69.16±1.0576
60	76.51	77.41	76.44	76.79±0.5437
70	83.52	87.02	85.46	85.33±0.7578
80	89.80	89.01	91.56	90.12±0.3077
90	93.14	93.67	93.76	93.52±.3384

Table 15: In-vitro dissolution profile for solid dispersion FM4 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.82	31.14	30.77	30.91±0.200
20	36.55	35.98	37.08	36.53±0.550
30	42.91	44.05	43.35	44.43±0.574
40	64.46	64.08	63.80	64.11±0.331
50	70.24	69.63	70.16	70.01±0.331
60	75.22	74.81	75.39	75.14±0.296
70	80.08	79.77	80.29	82.04±0.261
80	86.88	87.30	87.74	87.30±0.430
90	91.09	90.77	91.38	91.08±0.305

Table 16: In-vitro dissolution profile for solid dispersion FM5 formulation

Time(min)	Trail 1	Trail 2	Trail3	Mean ± SD
0	0	0	0	0
10	30.78	28.35	29.51	29.55± 1.21541
20	41.41	38.88	41.23	40.51±1.4116
30	46.29	45.68	46.17	46.05±0.3231
40	51.02	48.84	49.49	49.78±1.1192
50	60.24	57.52	58.21	58.66±1.4149
60	66.49	64.51	66.07	65.69±1.0432
70	74.14	72.76	71.82	72.90±1.1688
80	80.71	77.45	79.56	79.24±1.16568
90	82.40	81.43	83.04	82.29±0.8078

Table 17: In-vitro cumulative percentage of drug release of F1 to FM5 formulations

Time (min)	F1	F2	F3	F4	F5	FM1	FM2	FM3	FM4	FM5
0	0	0	0	0	0	0	0	0	0	0
10	30.25	41.16	25.38	15.02	29.55	37.48	33.56	44.03	30.91	29.55
20	38.09	50.85	38.23	24.55	40.51	42.77	39.86	48.90	36.53	40.51
30	44.03	53.81	39.86	37.81	46.05	45.65	47.15	55.10	44.43	46.05
40	52.60	56.40	42.87	40.51	49.78	48.86	55.41	60.86	64.11	49.78
50	59.17	57.85	49.22	48.77	58.66	55.15	62.29	69.16	70.01	58.66
60	66.42	60.53	55.09	56.39	65.69	59.07	69.96	76.79	75.14	65.69
70	73.12	69.43	59.26	61.66	72.24	64.51	77.42	85.33	82.04	72.24
80	78.17	73.12	64.71	67.68	79.24	68.77	84.56	90.12	87.30	79.24
90	82.22	75.19	69.71	72.14	82.29	76.79	96.21	93.52	91.08	82.29

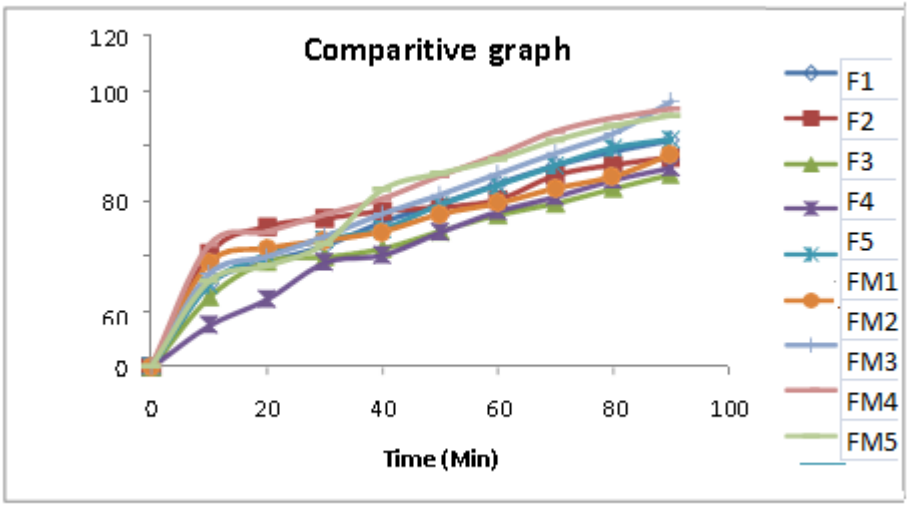

Fig 14: comparative graph for all formulations

Table 18: Kinetics of aceclofenac solid dispersions

Formulation code	Zero order ("r"values)	First order ("r" values)	Higuchi ("r" values)	Korsemeyar-Peppas	
				("r" values) values	"n"
Pure drug	0.9265	0.9728	0.9341	0.9819	0.2579
F1	0.9733	0.9879	0.9895	0.9972	0.3649
F2	0.768	0.9069	0.9316	0.9639	0.424
F3	0.8568	0.9656	0.9758	0.9987	0.3918
F4	0.9694	0.9882	0.9838	0.9932	0.3318
F5	0.9228	0.9805	0.9833	0.9932	0.3318
FM1	0.8351	0.9810	0.9487	0.9961	0.4304
FM2	0.9554	0.9594	0.9834	0.9879	0.3643
FM3	0.8746	0.9557	0.969	0.9916	0.347
FM4	0.9277	0.9837	0.9708	0.9961	0.4438
FM5	0.9228	0.9805	0.9833	0.9932	0.3318

CONCLUSION

In- vitro release studies reveal that there is marked increase in the dissolution rate of aceclofenac from all the solid dispersions when compared to pure aceclofenac itself. From the in-vitro drug release profile, it can be seen that formulation FM2 containing PEG6000 prepared by solvent evaporation shows higher dissolution rate compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier.

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