INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

DISSOLUTION ENHANCEMENT OF ACECLOFENAC SOLID DISPERSION PREPARED WITH HYDROPHILIC CARRIERS BY SOLVENT EVAPORATION METHOD

R. Natarajan*, G. Komala, TR. Ramcy, Swathi Polineni and S. Mohan

Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode – 637 205, Namakkal, India.

ABSTRACT

Aceclofenac is a non-steroidal anti-inflammatory drug having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions of aceclofenac were prepared using PEG6000, polyvinylpyrrolidone and hydroxypropyl methylcellulose to increase its aqueous solubility. Aceclofenac solid dispersions were prepared in 1:1, 1:2 and 1:1:1 ratios of the drug to polymer (by weight). In-vitrorelease profiles of all solid dispersions (F-1 to F-9) were comparatively evaluated and also studied against pure aceclofenac. Solid dispersion of formulation (F7) aceclofenac, PEG6000 and polyvinylpyrrolidone combination prepared in (1:1:1) ratio showed excellent solubility and the dissolution rate was found to be 96.21% was selected as the best formulation in this study. The increase in dissolution rate of the drug may be due to increase 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, FTIR and DSC studies. Absence of significant drug-carrier interaction was confirmed by FTIR and DSC data.

Keywords: Aceclofenac, Solid dispersion, PEG6000, Polyvinylpyrrolidone.

INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development[1]. 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[2].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[3].

In 1961, Sekiguchi and Obi[4] developed a practical method where by many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion[5] involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures[6]. Sekiguchi and Obi[4] suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, Goldberg et al[7] demonstrated that the entire drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, there by forming a solid solution. In either case, once

the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

Aceclofenac (BCS Class II drug) is an orally effective non-steroidal anti-inflammatory drug which possesses remarkable analgesic, antipyretic and anti-inflammation in osteoarthritis and rheumatoid arthritis. It is a weakly acidic drug (pKa= 4–5), practically insoluble in water and acidic pH conditions, but slightly solubility in basic pH conditions. There are certain problems coming with using aceclofenac as traditional oral tablet which includes bioavailability of aceclofenac is highly variable due to its low aqueous solubility and first pass metabolism. An increased solubilty with enhanced dissolution of the drug will improve its bioavailability[8-10]. In order to improve the solubility, dissolution rate and bioavailability of the drug, it was attempted to prepare optimized aceclofenac solid dispersion.

Aceclofenac is practically insoluble in water leading to poor dissolution and variable bioavailability upon oral administration. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of aceclofenac by preparing solid dispersions with various hydrophilic carriers such as polyethylene glycol6000, polyvinyl pyrrolidone and hydroxypropyl methylcellulose. The prepared solid dispersions were evaluated for percentage practical yield, drug content invitro dissolution rate studies, interactions between the drug and polymer using infrared spectra and differential scanning calorimetry studies.

MATERIALS AND METHODS

Aceclofenac was obtained as gift sample from Dr.Reddy's laboratory. Hyderabad, India.

Polyethylene glycol6000 was obtained as gift sample from Yarrow chemicals laboratory. Mumbai, India. Polyvinyl pyrrolidone and hydroxypropyl methylcellulose were obtained as gift sample from Loba chemie pvt.ltd. Mumbai, India. All the chemicals used in the present study were of analytical grade.

Preparation of Solid dispersion[11]

Aceclofenac solid dispersions were prepared by using hydrophilic carriers like PEG6000 polyvinylpyrrolidone and hydroxypropyl methylcellulose in proportions viz. 1:1 (drug:carrier) (50mg: 50mg), 1:2 (drug:carrier) (50mg: 100mg) and 1:1:1 (dug:carrier:carrier) (50mg: 50mg: 50mg) 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 40^0C 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. The formulation code of aceclofenac solid dispersions(Table 1).

Table 1: Formulationof Aceclofenac Solid dispersion

S.No	Formulation code	Composition	Drug : carrier
1	F1	Aceclofenac+ PEG6000	1:1
2	F2	Aceclofenac+ Polyvinylpyrrolidone	1:1
3	F3	Aceclofenac+ Hydroxypropylmethylcellulose	1:1
4	F4	Aceclofenac+ PEG6000	1:2
5	F5	Aceclofenac+ Polyvinylpyrrolidone	1:2
6	F6	Aceclofenac+ Hydroxypropylmethylcellulose	1:2
7	F7	Aceclofenac+PEG6000+ Polyvinylpyrrolidone	1:1:1
8	F8	Aceclofenac+PEG6000+ Hydroxypropylmethylcellulose	1:1:1
9	F9	Aceclofenac+ Polyvinylpyrrolidone Hydroxypropylmethylcellulose	1:1:1

Evaluation of solid dispersion

Solid dispersions obtained from the above method was screened for there solubility. The solid dispersion showed good solubility were further studied for percentage practical yield, drug content, invitro release studies, FTIR and DSC study.

Percentage Practical Yield[12]

Percentage practical yield was calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to

determine practical yield (PY) from the following equation

$$PY\ (\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug+ Carrier)}} \times 100$$

Drug content estimation[13]

Solid dispersions equivalent to 10 mg of aceclofenac were weighed accurately and dissolved in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometer. The Actual Drug Content was calculated using the following equation as follows.

$$\text{Actual amount of drug in Solid dispersion} = \frac{\text{Actual amount of drug in Solid dispersion}}{\text{Theoretical amount of drug in Solid dispersion}} \times 100$$

Determination of phase solubility of Aceclofenac[14]

Drugsolubility studies were performed in triplicate by adding excess amount of aceclofenac to methanol and buffer solutions having different pH (6.8). Solutions containing flasks were kept on a Rotary Shaking Incubator for 24 hrs. After 24 hrs, solutions were analyzed using UV spectrophotometer.

Invitro dissolution study[15]

Invitro release profiles for each solid dispersion as well as pure drug were performed using USP type 2 dissolution apparatus. Sample equivalent to 50mg of aceclofenac was added to900ml phosphate buffer pH 6.8 at 37± 0.5ºC and stirred at 50 rpm. Aliquot of 5ml was withdrawn at time intervals of 10, 20,30,40,50,60,70,80 and 90 min. The withdrawn volume was replaced with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the sample was measured at λmax 275 nm after suitable dilution if necessary, using appropriate blank.

RESULTS AND DISCUSSION

Solid dispersions of aceclofenac were prepared by using carriers like polyethylene glycol6000, polyvinylpyrrolidone and hydroxy propyl methylcellulose. In present wok, nine formulations were prepared and their complete composition (Table1). All the solid dispersions prepared were found to be fine and free flowing powders. The results of Percentage practical yield for all formulations of solid dispersions found to be 89.09 - 95.46 (Table 2). The drug content of the prepared solid dispersions was range of 66.5 to 87.09 (Table 2).

Table 2: % Practical yield andDrug content in all formulation

Formulation code	% Practical yield	Drug content (in %)
F1	92.71±1.0651	76.89±0.7128
F2	89.09±0.291	66.5±0.7071
F3	94.7±0.6420	70.55 ±0.7805
F4	91.08±0.305	67.68±1.2583
F5	90.12±1.307	72.14±1.1185
F6	90.82±0.3614	74.20±1.1145
F7	95.46±0.9799	87.09±3.7390
F8	93.51±0.1937	82.5±2.1210
F9	92.77±0244	78.37±1.4913

Phase solubility study was carried out in order in to ascertain effect of carriers on the solubility characteristics of aceclofenac. Solubility of aceclofenac was increased as the concentration of carriers increased. The solubility of aceclofenac was minimal in methanol and increased approximately eight fold at 0.01%w/v of PEG6000 in methanol. These data indicates that PEG6000 in methanol solubility of aceclofenac was greatly enhanced possibly due to the solvent effect of PEG6000 (Figure 1).

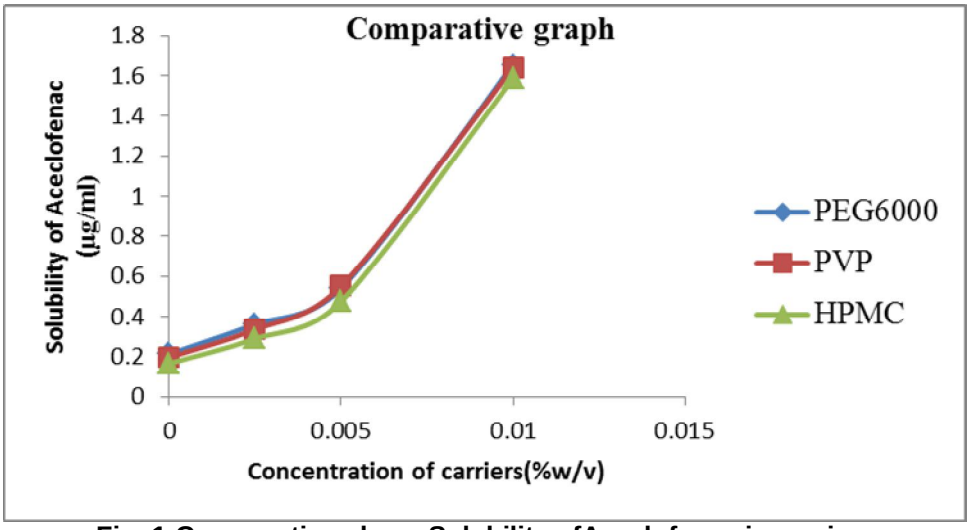

Fig. 1:Comparative phase Solubility ofAceclofenac in carriers

The FTIR spectra exhibited presence of characteristic peaks of pure aceclofenac and drugs in physical mixture and indicate that there was no chemical interaction between the pure drug and physical mixture (Figure 2 and 3) .

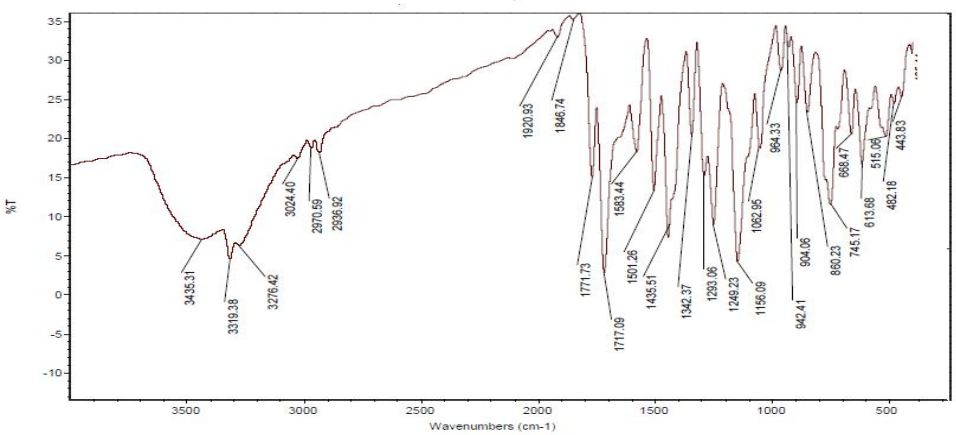

Fig. 2: pure Aceclofenac

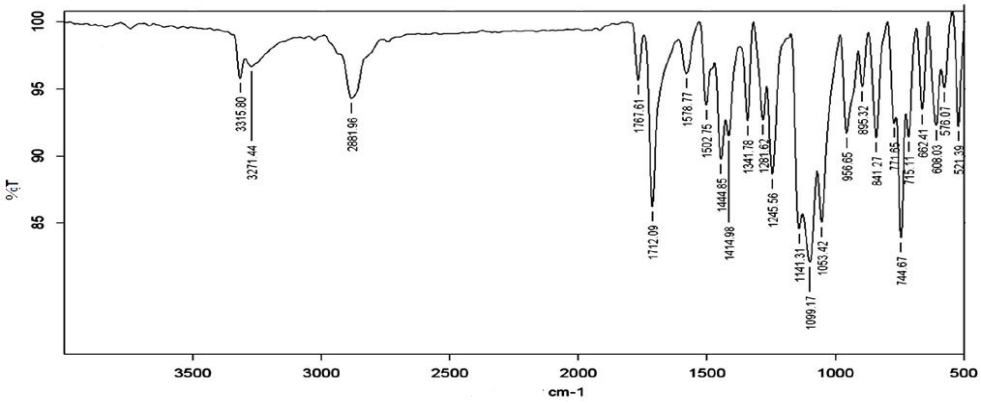

Fig. 3: physical mixture

In the DSC studies of pure aceclofenac showed a sharp endotherm at 152.51^{o}C, PEG6000 at 62.50^{o}C, PVP at 218.76 ^{o}C, Hpmc at 122.8^{o}C and physical mixture at 160^{o}C to its melting point. There was no appreciable change in the melting endotherm of spherical agglomerates compared to that of pure drug (F7 agglomerates =153.27^{0}C) the DSC results also revealed little amorphization of aceclofenac when compared in the form of agglomerates with PEG6000 and PVP combination (Figure 4 and 5).

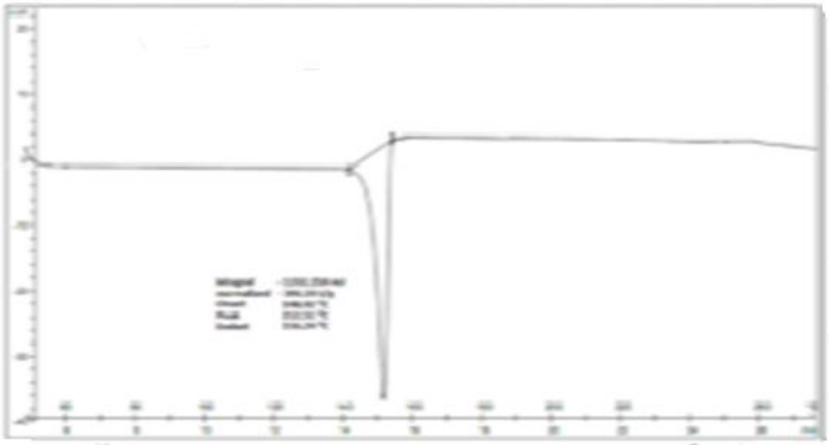

Fig. 4: DSC Thermo gram of pure aceclofenac

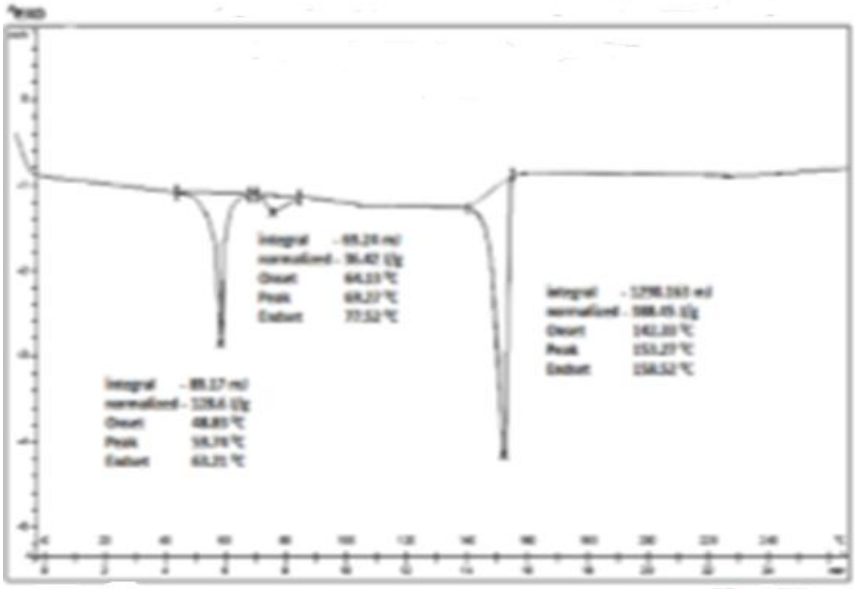

Fig. 5: DSC Thermo gram of f7 formulation

In- vitrorelease studies reveal that there is marked increase in the dissolution rate of aceclofenac from all the solid dispersions when compared to pure aceclofenac itself (Table 3). From the in-vitrodrug release profile, it can be seen that formulation F-7 containing PEG6000 and PVP (1:1:1 ratio of drug: PEG6000: PVP) 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. The increase in dissolution rate is in the order of PEG6000:PVP> PEG6000:HPMC > PVP:HPMC. In the case of solid dispersions of aceclofenac with PEG6000, PVP, and HPMC ratio of 1:1:1, the dissolution rate of drug increased while in the case of those prepared in the ratio of 1:1 and 1:2 the dissolution rate of drug was decreased(Figure 6). This might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. The increase in dissolution rate is in the order of F7 >F8>F9 >F1>F5>F6>F2 >F4>F3. The regression coefficient (r) values for formulations F1 to F9 model that gave higher 'r' value was considered as best fit model (Table 4). The r values were found to be higher in the first order model (0.9804, 0.9805, 0.9569, 0.9656, 0.9805, 0.9865, 0.9850, 0.9849, 0.9557, 0.9837) than those in the zero order model (0.9794,0.9265,0.868,08568,0.9228, 0.9328,0.9252,0.9454,0.8746,0.9277) with all the solid dispersion (pure aceclofenac, F1, F2, F3, F4, F5, F6, F7, F8 and F9

respectively) indicating that the dissolution of aceclofenac as such and from all the solid dispersion followed first order kinetics. Based on 'r' values (greater than 0.9527) it was also observed that all the solid dispersion followed Higuchi matrix suggesting the drug release is by diffusion. Korsemeyar-Peppa's suggest shows that the formulations also appear to release the drug by erosion mechanism and the release is drug dissolution limited. FTIR spectroscopic studies conducted for possible drug: carrier interactions FTIR spectra of pure drug aceclofenac, PEG6000, PVP, HPMC and aceclofenac with its solid dispersion were obtained which shows all the characteristic peaks of aceclofenac and carriers were present in the solid dispersions; thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion.

The solid dispersions of the water- insoluble drug aceclofenac were successfully prepared by solvent evaporation technique using hydrophilic carriers. The in-vitrodissolution test showed a significant increase in thedissolution rate of solid dispersions as compared with pureAceclofenac. Mechanisms involved are solubilization andimproved wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals afterdissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. PEG6000 and PVP combination.

Table 3: In-vitro cumulativepercentage of drug release of f1 to f9 formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
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
20	38.09	50.85	38.23	24.55	40.51	42.77	39.86	48.90	36.53
30	44.03	53.81	39.86	37.81	46.05	45.65	47.15	55.10	44.43
40	52.60	56.40	42.87	40.51	49.78	48.86	55.41	60.86	64.11
50	59.17	57.85	49.22	48.77	58.66	55.15	62.29	69.16	70.01
60	66.42	60.53	55.09	56.39	65.69	59.07	69.96	76.79	75.14
70	73.12	69.43	59.26	61.66	72.24	64.51	77.42	85.33	82.04
80	78.17	73.12	64.71	67.68	79.24	68.77	84.56	90.12	87.30
90	82.22	75.19	69.71	72.14	82.29	76.79	96.21	93.52	91.08

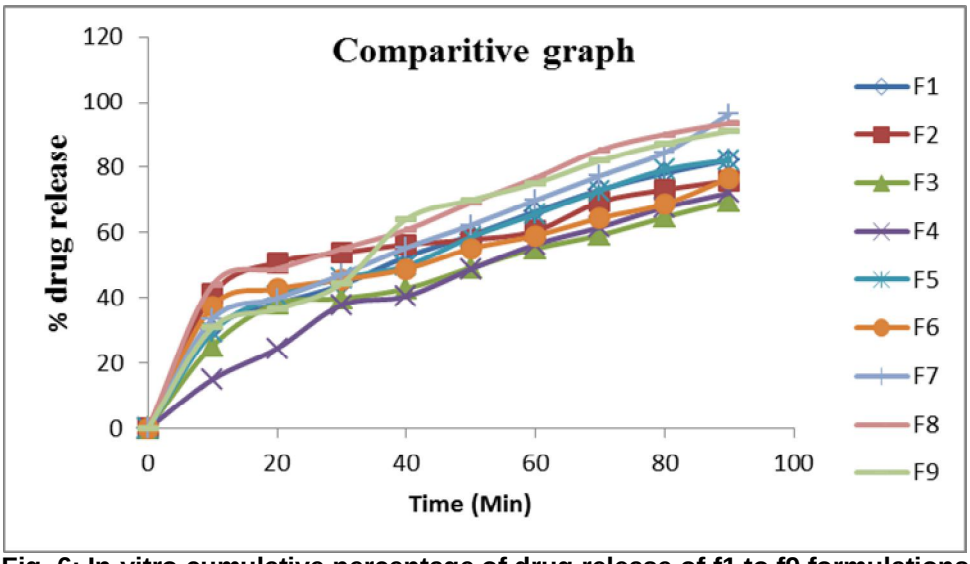

Fig. 6: In-vitro cumulative percentage of drug release of f1 to f9 formulations

Table 4: Kinetics of Aceclofenac Solid dispersions

Formulation code	Zero order ("r"values)	First order ("r" values)	Higuchi ("r" values)	Korsemeyar-Peppas	
				"r" values	"n" values
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
F6	0.8351	0.9810	0.9487	0.9961	0.4304
F7	0.9554	0.9594	0.9834	0.9879	0.3643
F8	0.8746	0.9557	0.969	0.9916	0.347
F9	0.9277	0.9837	0.9708	0.9961	0.4438

CONCLUION

Finally it could be concluded that solid dispersion of aceclofenac using hydrophilic carriers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. This study concluded that the improved solubility as well as drug dissolution of this newly prepared aceclofenac solid dispersion using PEG6000 – PVP combination carrier may be attributed to the improved wettability, and decreased the crystallinity, which can be modulated by appreciates level of hydrophilic carriers.

REFERENCES

1. Jatinder kaur, Geeta Aggarwal, Gurpreet sing and Rana AC. International Journal of Pharmacy and Pharmaceutical Sciences. 2012;4(2):47-53.
2. Leunner C and Dress man J. Eur J Pharm Bio Pharm. 2000;50:47-60.
3. Arora SC, Sharma PK, Raghuveer Irchhaiya and Anurag khatkar. International Journal of Chem Tech Research. 2010;2(2):1156-1162.
4. Sekiguchi K and Obi N. Chem Pharm Bul. 1961;9:866-872.
5. Chiou WL and Riegelman SJ. Pharm Sci. 1971;60:1281-1302.
6. Akiladevi D, Shanmuga Pandiyan P, Jebasing D and Sachinandhan Basak. International Journal of Pharmacy and Pharmaceutical Science. 2011;3(1)187-191.
7. Goldberg AH, Gibaldi M and Kanig JL. J Pharm Sci. 1966;55:482-487.
8. EL-Nabarawi MA, EL-Miligi MF and Khalil IA. International Journal of Pharmacy and Pharmaceutical Sciences. 2012;4(5):554-571.
9. Aggarwal S, Gupta GD and Chaudhary S. International Journal of Pharmaceutical Sciences and Research. 2010;1:1-13.
10. Mohanachandran PS, Sindhumo PG and Kiran TS. International Journal of Comprehensive Pharmacy2010;4:1-10.
11. Ramana B.V, Parameshwari CS, Triveni C, Arundathi T, RathnaPrasanna T. Sch Acad. J Pharm. 2013; 2(2):113-118.
12. Patil SR, RaniKumar M, Patil MSP and Rao VSNM. International Journal of Pharm Tech Research. 2009;1:1198-1204.
13. Anupama Singh, Pramod Kumar Sharma, Jay GopalMeher and RishabhaMalviya. Asian Journal of Pharmaceutical and Clinical Research. 2011;4(1):0974-2441.
14. Bachhav Devidas G, PhatangareKundan E, DeoreLeena P, Nikam. Komal R, PatilUnnatee S and Narmata D. An International Research Journal. 2012;3(3):186-188.
15. Appa Rao B, Shiva lingam MR, Kishore Reddy YV, Somesekhara Rao, Rajesh K and Sunitha N. IJPSDR. 2010;2(2):146-150.