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Solubility and Dissolution enhancement of poorly water soluble drug Aceclofenac by solid dispersion method

Goundla Uday Bhasker Goud[1]*, Uday Kumar Reddy[3], Avadhanam Pranav Kumar[2], Gangi Reddy Sreenivas Reddy[2] and Jakkampudi Sri Venu Prakash[1]

1, Dept. of Industrial Pharmacy, Bharat Institute of Technology, Mangalpally, Hyd, (Telangana) - India
2, Dept. of Pharmaceutics, Bharat Institute of Technology, Mangalpally, Hyd, (Telangana) - India
3, Department of Pharmacy, Gurunanak Institute of Technology, Ibp, Hyd, (Telangana) - India

Abstract

Aceclofenac is a novel non-steroidal anti-inflammatory drug (BCS-class II) 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. So the objective of present work is to improve the solubility and dissolution rate of Aceclofenac using its solid dispersions (SDs) with β-Cyclodextrin. Inclusion complex of Aceclofenac with β-Cyclodextrin was prepared by physical mixture, co-grinding and kneading method at 1:1 w/w ratio. It was clear that kneading method would be the best method for the preparation of inclusion complex of Aceclofenac with β-CD. Hence Kneading method was selected for further study (K1, K2, K3 & K4 in 1:0.5, 1:1, 1:1.5 & 1:2 ratios respectively). Phase solubility study was conducted to evaluate the effect of polymer on aqueous solubility of Aceclofenac. The In vitrodissolution studies were carried in pH 6.8, higher in vitrodissolution of solid dispersions was recorded compared to their corresponding physical mixtures and the pure drug. The prepared solid dispersions were observed that increased in the saturation solubility and dissolution rate of Aceclofenac than that of pure drug. Aceclofenac: β-CD in 1: 2 drug to carrier ratio exhibited the highest drug release (68.13 in 120sec). The FT-IR study and differential scanning calorimetry (DSC) shows that drug was stable in solid dispersions and there were no interactions. It is concluded that dissolution rate was improved by solid dispersion of Aceclofenac-CD prepared as 1:2 ratio showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation.

Key-Words: Solid Dispersions, Aceclofenac, Fusion Technique, Inclusion Complex, Phase Solubility Study, B-Cyclodextrin

Introduction

Aceclofenac is a new generation NSAID used in the treatment of osteoarthritis, rheumatoid arthritis and other joint diseases. It is chemically designated as 2-[(2,6-diclorophenyl) amine] phenyl acetoxy acetic acid). Solid dispersions of aceclofenac were formulated to overcome problems like gastric irritation and other side effects that are frequently experienced with NSAID drug therapy. Aceclofenac is practically insoluble in water leading to poor dissolution[1-3].

Aceclofenac appears to be well tolerated among NSAIDs with a lower incident of gastro intestinal adverse effects[4]. The biopharmaceutical classification system (BCS) divides all drug candidates into four different groups, according to their solubility and permeability.

*** Corresponding Author**
E-mail: gouds.uday04@gmail.com
Mob.: +91 9666883831

Aceclofenac is an example of BCS class II compound (Highly Permeable & Low Soluble); its oral bioavailability is determined by dissolution rate in the gastro intestinal tract. Therefore the improvement of Aceclofenac dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy[5].

Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, complexation, prodrug, addition of solvent or surface active agents and solid dispersions (SD). SD's is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs[6].

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The

drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Transformation of crystalline drug to amorphous drug upon solid dispersion formulation increases the dissolution rate[5]. Solid dispersion techniques have been used to increase the solubility of a poorly water soluble drug[7]. Solid dispersion is a viable and economic method to enhance bioavailability of poorly water soluble drug and also it overcomes the limitations of previous approaches[8]. The present study is aimed at improving the solubility and dissolution rate of poorly water soluble drug Aceclofenac by preparing Solid dispersion with β-CD. The prepared Solid dispersions were evaluated for solubility and in- vitrodissolution rate studies and interactions between the drug and polymer using FTIR spectral studies and DSC[6].

Bio-pharmaceutics classification system for drugs

Class	Solubility	Permeability	Absorption pattern
I	High	High	Well absorbed
II	Low	High	Variable
III	High	Low	Variable
IV	Low	Low	Poorly absorbed

Material and Methods

Aceclofenac from Dishman Pharmaceuticals, Ahmedabad and β-Cyclodextrin from Cadila Pharmaceuticals, Ahmedabad.UV-Vis Spectrophotometer (Shimadzu UV-1800, japan), USP Dissolution Apparatus model, FTIR Instrument (Shimadzu FTIR 8400S spectrometer), Differential Scanning Calorimeter (Shimadzu DSC 60, Japan).

Estimation of aceclofenac

Aceclofenac contents were estimated by UV Spectrophotometric method by measuring the absorbance at 273 nm. The method obeyed Beers law in the concentration range of 2-20 µg/ml (Correlation Coefficient (R^2) = 0.999). When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.90 % and 1.2 % respectively[6,9].

Solubility study

Solubility of Aceclofenac was determined in different media including distilled water, 0.1 N HCL and Phosphate buffer pH 6.8. Excess amount of Aceclofenac was added into three different conical flask containing 100 ml of distilled water, 0 .1 N HCL and phosphate buffer pH 6.8. These solutions were shaken for 48 h at room temp on a magnetic stirrer. After equilibrium, the suspensions were filtered through 0.45 µm Millipore membrane filters. The filtrate was appropriately diluted and the concentration of the Aceclofenac in the filtrate was determined by UV spectrophotometer Shimadzu- 1800, Japan at 276 nm (Table No-1)[10].

Table 1: Results of solubility study

Solution System	Absorbance	Solubility (µg/ml)
Distilled water	0.202	87.5
0.1 N HCL (pH 1.2)	0.082	34.3
Phosphate buffer pH 7.4	0.204	1049.9

Phase solubility studies

Phase solubility study permits to evaluate the affinity between β-CD and Aceclofenac in water. Aceclofenac amount that exceeded its solubility was taken in a screw cap vials containing 20ml of various concentration of β-CD (1-5mm) solution in water. The vial is shaken for 48 hrs in 25^0c. The aliquots were filtered through Whattman filter paper and a portion of sample was analyzed by UV spectrophotometer, no shift in λ-max was confirmed the complex at 273 nm. These procedures were conducted in triplicate. The stability constant Kc was calculated in linear region by the equation Kc = slope / S0 (1-slope). The Kc values indicated that the inclusion complex formed by kneading method were quite stable.

Aceclofenac and β-CD was weighted in 1:1 ratio, the β-CD is kneaded like a paste with small amount of water in mortar. Aceclofenac was dissolved in methanol and added to the above mortar. Several hours of grinding of paste in mortar and result in evaporation of solvent leads the powder. This powder was dried in hot air oven at 40 – 45 ^{0}C and passed through sieve no. 44 and stored in airtight container and the same procedure was repeated for various ratios of drug and β-CD complex (Table no-2).

Table 2: Phase solubility study of Aceclofenac with β-CD

Conc. of carrier	Solubility(µg/ml)
0.25	300.717
0.5	351.263
1.0	424.595
1.5	487.164

Formulation of aceclofenac inclution complex with β-cyclodextrin (β-CD)

Preparation of physical mixture

Weigh the required quantity of Aceclofenac and β-CD as per the ratio shown in the Table No-3. Both were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 84 and stored in a dessicator[10].

Preparation of co-grinding mixture

Weigh the required quantity of Aceclofenac and β-CD as per Table No-3 and pass it through 80 #. The drug

and carrier were mixed in mortar for 5 minutes and stored in glass jar.

Preparation of inclusion complex by kneading method

The required quantity of Drug and β-Cyclodextrin was taken in a mortar and mixed thoroughly; small quantity of water is added while triturating to get slurry like consistency. The triturating is continued for one hour. The slurry was kneaded in glass mortar for 30 min and then completely dried in oven at 60 ^{0}C. The dry product was sieved through # 80 to obtain powder and stored in glass jar (Table 3 & 4).

Table 3: Comparison of Physical mixture, Cogrinding and Kneading method for β-Cyclodextrin

Batch no.	Drug:Carrir Ratio(molar)	Drug (mg)	β-CD (mg)	Method of Preparation
C1	1:1	100	321	Physical
C2	1:1	100	321	Co-grinding
C3	1:1	100	321	Kneading

Table 4: Composition of different batches prepared by kneading method

Batch no	Drug: Carrier Ratio (molar)	Drug (mg)	Carrier (mg)
K1	1:0.5	100	161
K2	1:1	100	321
K3	1:1.5	100	481
K4	1:2	100	641

Solid state characterization

Fourier transforms infrared spectroscopy (FTIR)

FTIR spectral studies were carried out for the pure drug and the solid dispersion to check the compatibility between drug and carrier using SHIMANDZU FTIR-8400S. The spectrum was recorded in the range of 4000-400cm^{-1}. Interaction between the components, if any, was indicated by either producing additional peaks or absence of characteristic peak corresponding to drug and carrier.

Differential calorimetry studies (DSC)

The possibility of any interaction between the drug and the carriers during preparation of Physical mixture, Co-grinded mixture and Kneading method were assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture, Co-grinded mixture and Kneading method using DSC. DSC was performed by Perkin-Elmer 7 series thermal analysis system for the drug (Aceclofenac) and solid dispersion of drug with β-CD. Samples were scanned at 200C to 3000C at a rate of 100C/minute in a N2–(Nitrogen) environment. Interaction between drug and polymer, if any was indicated either by shift in the peak or presence of additional peak of temperature other than those correspondence to the drug and polymer.

***In-Vitro* dissolution studies**

In-vitro Dissolution studies were performed in phosphate buffer (pH 6.8) at 37+0.5oC using USP II rotating paddle apparatus (ELECTROLAB Dissolution tester TDT-08L) at 100 RPM. Pure drug/solid dispersion/inclusion complex (equivalent to 100 mg of Aceclofenac) was subjected to dissolution. 5ml of the samples were withdrawn at time intervals of 10, 20, 30, 40, 60, 90 and 120 minutes. The sample was filtered through Whatman paper (0.7 µ size). The volume of the dissolution fluid was adjusted by replacing 5ml of dissolution medium after each sampling. The absorbance of the solution was measured at 273 nm using dissolution medium as reference standard. The concentration of Aceclofenac was calculated by using standard curve equation.

Results and Discussion

Phase solubility study

Figure No-1,2 shows the solubility profiles of Aceclofenac in pH 6.8 phosphate buffer influenced by carrier material concentration at room temperature. Solubility of Aceclofenac increases with β-Cyclodextrin inclusion complex and this increase in solubility having a linear correlation with conc. Of carrier.β-Cyclodextrin show r^2 value more than 0.95 having AL type of curve.

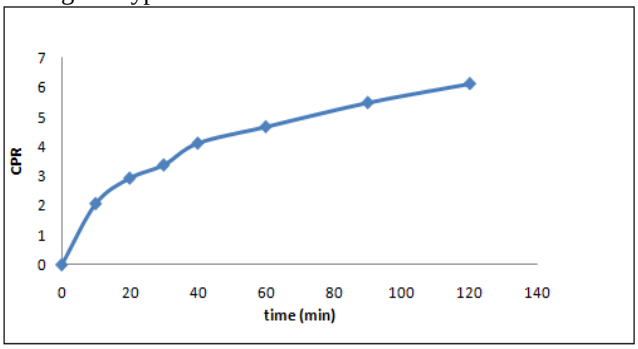

Fig. 1: Dissolution Profile of Pure Aceclofenac

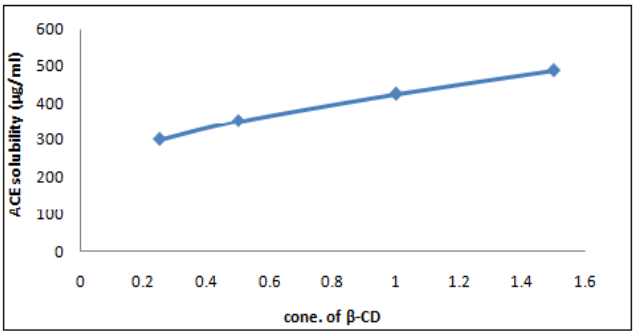

Fig. 2: Phace Solubility Curve Of β-CD.

***In-vitro* drug release of solid dispersion Aceclofenac:β-Cyclodextrin inclusion complex**

The dissolution profile of pure drug is shown in Table No-5 & Fig No-1. The dissolution rate of pure drug is very poor and during 120 minutes a maximum of about 6.1 % of drug was dissolved.

Table 5: Dissolution profile of pure Aceclofenac

Time (min)	Absorbance	Cumulative Percentage Release (CPR)
0	000	0.000
10	0.08	2.065
20	0.102	2.922
30	0.109	3.368
40	0.126	4.101
60	0.140	4.658
90	0.155	5.473
120	0.170	6.111

Fig. No-6 shows the dissolution profile of 1:1 ACE:β-CD inclusion complex prepared by physical mixing, co-grinding and kneading method. From this data it was clearly evident that kneading method gives highest dissolution among the three methods of prepared inclusion complex (Table No-6).

Table 6: Comparative dissolution profile of ACE: β-CD (1:1) molar ratio prepared by physical, co-grinding and kneading methods

S.No	Time (min)	Cumulative Percentage Release (CPR)		
		BatchC1	**BatchC2**	**BatchC3**
1.	0	000	000	000
2.	10	3.80	5.68	6.34
3.	20	8.98	13.36	22.53
4.	30	13.32	19.49	34.64
5.	40	14.87	22.91	40.48
6.	60	21.13	31.55	42.30
7.	90	23.08	34.50	46.42
8.	120	24.11	35.27	48.31

Fig.No-3 to 6 shows the dissolution profile of 1:0.5, 1:1, 1:1.5 and 1:2 molar ratio of ACE: β-CD inclusion complex prepared by kneading method.

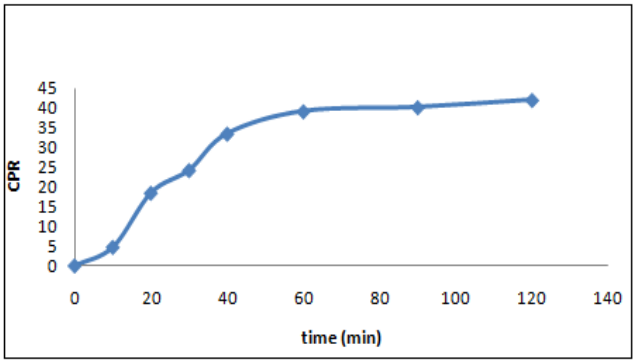

Fig. 3: Dissolution profile of K1

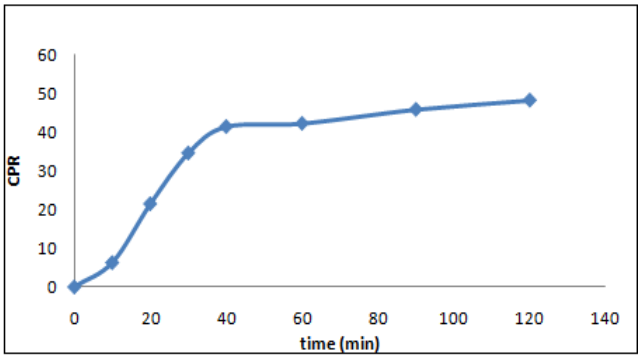

Fig. 4: Dissolution profile of K2

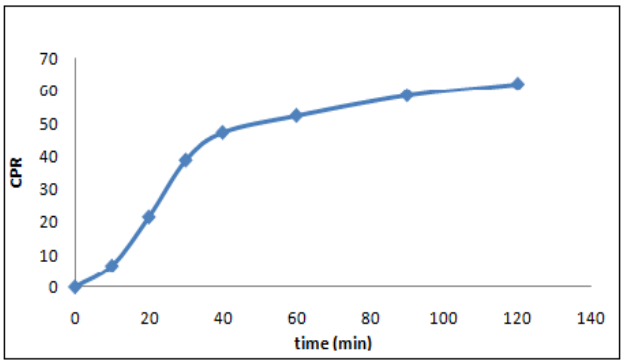

Fig. 5: Dissolution profile of K3

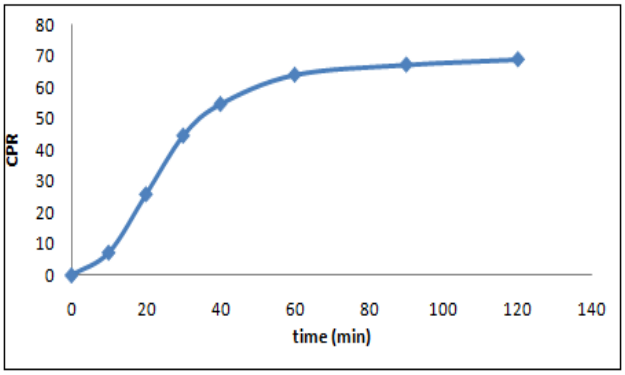

Fig. 6: Dissolution profile of K4

Fig.No-7 & Table No-7 shows the comparative dissolution profile of all the four batches. From Fig No-7, it is observed that as we increase the proportion of β-CD from half molar to two molar the dissolution of drug at 120 minutes increases from 41.95 % to 68.79%.

Table 7: Comparative In-vitro dissolution profile of Batch K1, K2, K3 and K4

Time (min)	K1	K2	K3	K4
0	0.000	0.000	0.000	0.000
10	4.72	6.30	6.69	7.24
20	18.43	21.50	21.60	25.82
30	24.18	34.61	38.80	44.51
40	33.42	41.45	47.19	54.57
60	39.08	42.27	52.33	63.90
90	40.11	45.89	58.61	67.12
120	41.95	48.27	62.16	68.79

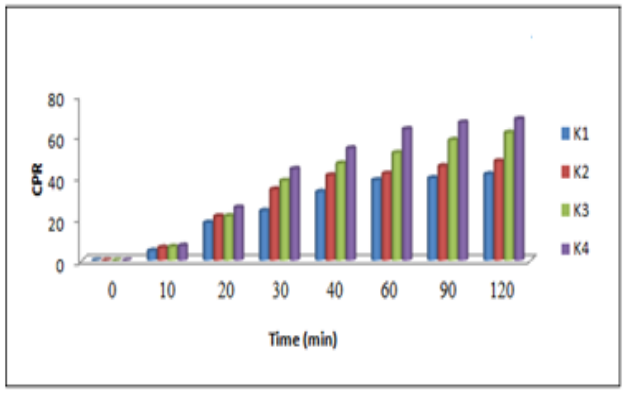

Fig. 7: Comparative dissolution of profile of Aceclofenac:β-CD by kneading method

Solubility study

Solubility of Aceclofenac in distilled water, 0.1 N HCL and Phosphate buffer pH 6.8 are shown in Table No-1. Solubility of Aceclofenac in water, 0.1 N HCL and Phosphate buffer pH 7.5 were found to be 87.5, 34.3 and 1049.9 µg/ml.

FTIR (Fourier Transform Infra-Red Spectroscopy)

The FTIR spectrum of pure Aceclofenac and dispersion are shown in figure No-8 & 9. The spectrum of Aceclofenac are shown characteristic bands at 3319.3 cm-1 (N-H stretching), 2970.2and 2035.5 cm^{-1} (O-H stretching), 1716.5 cm^{-1} (C-O stretching), 1589.2 cm^{-1} (skeleton vibration of aromatic C-C stretching for NH) 1380 cm^{-1} (O-H in plane bending), 1280.6 cm^{-1} (CN aromatic amine), 944 cm^{-1} (O-H out plane bending) and 746 cm^{-1} (out plane bending for N-H).The characteristic bands of β-Cyclodextrin (3305, 1420, 1460 and 1083 cm^{-1}) were also observed. The absence of any significant change in the IR spectrum pattern in the formulation containing the drug and carrier indicate the absence of interaction between the drug and carrier employed for solubility enhancement.

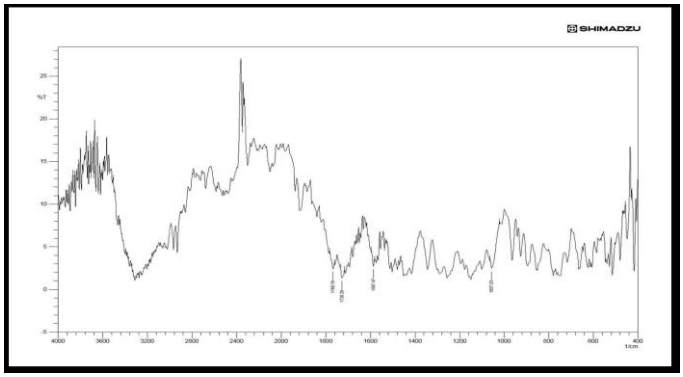

Fig. 8: FTIR spectrum of Aceclofenac

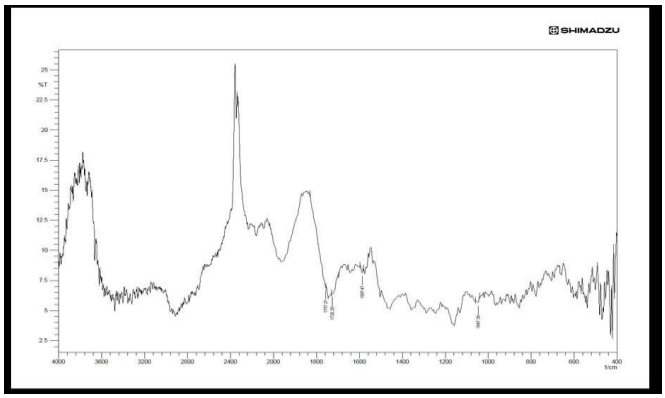

Fig. 9: FTIR spectrum of Aceclofenac with carrier

DSC (Differential ScaningCalorimetry)

The DSC curve obtained for pure Aceclofenac and β-Cyclodextrin in solid dispersion were displayed in the fig No-10 & 11. Pure Aceclofenac exhibit an endothermic peak at 156.110C which represent the melting point of Aceclofenac. DSC curve of β-Cyclodextrin showed a slightly sharp endothermic peak at 107.540C corresponding to the melting point of β-Cyclodextrin.DSC further support that Aceclofenac was compatible with the polymer. There was a noticeable reduction in endothermic peak height and heat of fusion, in physical mixture and in solid dispersion as compared to pure Aceclofenac. These suggest that the physical state of Aceclofenac changed from crystalline to amorphous. It has been that transforming the drug to amorphous or partially

amorphous state leads to a high energy state and high disorder, resulting in enhanced solubility and faster dissolution.

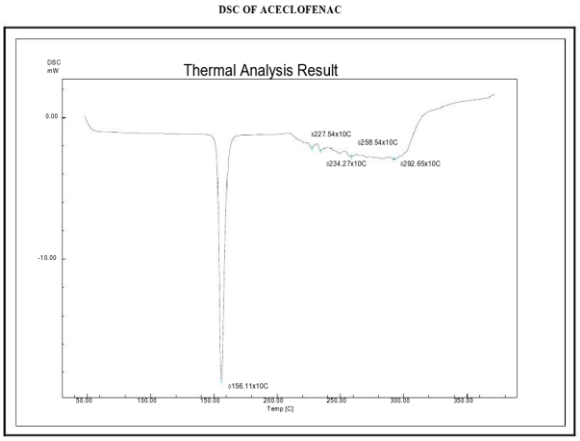

Fig. 10: Thermal Analysis result of Aceclofenac

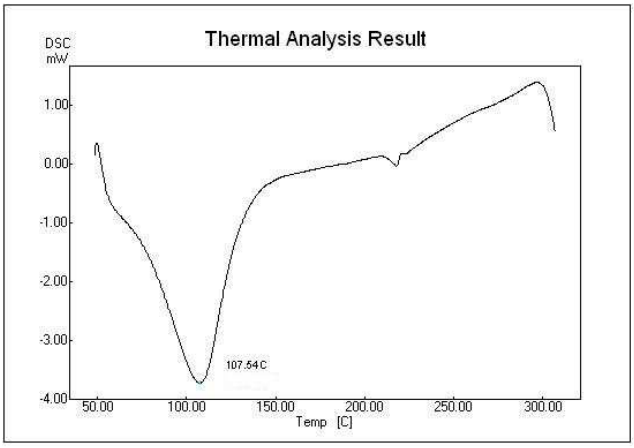

Fig. 11: Thermal Analysis result of β-CD

Conclusion

The present study was performed to improve the dissolution rate and aqueous solubility of Aceclofenac, a poorly soluble drug using β- Cyclodextrin as carrier. Nature and amount of carrier used to play an important role in the enhancement of dissolution rate.

Solid dispersion of drug and carrier were prepared at various ratios (1:0.5, 1:1, 1:1.5, 1:2). Dissolution studies were performed for pure drug, physical mixture, co-grinded mixture, and solid dispersion in phosphate buffer at pH 6.8 using USP dissolution apparatus type-2. From the dissolution data it was shown that, all the solid dispersion (molecular inclusion complex) gave faster dissolution when compared to pure and physical mixture. The Ratio β-CD in 1: 2 drug to carrier ratio exhibited the highest drug release (68.13 in 120sec).

Kneading method > Solvent evaporation > Co-grinding> Melting method> Physical mixture.

The enhancement in the dissolution of Aceclofenac from the solid dispersion system may be due to several factors like lack of crystallization, particle size reduction in interfacial tension between hydrophobic drug and dissolution medium increased wettability and effective surface adsorption of drug on hydrophilic carrier.

Result from FTIR spectroscopy concluded that there is no well-defined interaction between Aceclofenac and carrier employed in the preparation of solid dispersion.

DSC thermo gram of physical mixture and solid dispersion indicated complete miscibility of the drug in the melted carrier. Aceclofenac: β-CD in 1: 2 drug to carrier ratio exhibited the highest drug release (68.13 in 120sec). In conclusion, our studies showed that dissolution rate was improved by solid dispersion of aceclofenac: β-CDpreparedas1:2 ratio showed excellent physicochemical characteristics and was found to be described by dissolution release kinetics and was selected as the best formulation.

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