Malaysian Journal of Pharmaceutical Sciences,
Vol. 7, No. 2, 153–168 (2009)

STUDIES ON THE PREPARATION AND CHARACTERISATION OF β-CYCLODEXTRIN-ACECLOFENAC INCLUSION COMPLEXES

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Aceclofenac/β-cyclodextrin (Ace/β-CD) dispersions were prepared to study the influence of β-CD on the solubility and dissolution rate of this poorly soluble drug. Phase-solubility profile indicated that the solubility of aceclofenac was significantly increased in the presence of β-CD and was classified as A_L-type, indicating the 1:1 stoichiometric inclusion complexes. Physical characterisation of the prepared systems was carried out by differential scanning calorimetry (DSC), X-ray diffractometry (XRD) and IR studies. Solid state characterisation of the drug in the β-CD binary system using XRD, FTIR and DSC revealed distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement of dissolution rate.

Keywords: *Aceclofenac, Dissolution, β-cyclodextrin, Kneading method, Release kinetics*

INTRODUCTION

Poorly water soluble drugs are generally associated with slow drug absorption leading eventually to inadequate and variable bioavailability (Amidon *et al*. 1995; Leuner and Dressman 2000). Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs (Hu, Johnston and Williams 2004; Lipinski 2002). Attempts to enhance drug solubility of these therapeutic agents correlate well with enhancement of their bioavailability (Sekiguchi and Obi 1961; Hye *et al*. 1997). Among them, solid dispersion technology was most widely used (Corrigan 1985; Ford 1986; Craig 1990; Law *et al*. 1992). A number of insoluble drugs has been shown to have improved dissolution character when converted to solid dispersion (Madhusudhan *et al*. 2002).

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Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers (Delahaye *et al.* 1997). The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water soluble drug is increasing (Okimoto *et al.* 1997; Yamada *et al.* 1999). Various hydrophilic carriers such as polyethylene glycol have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs (Margarit, Rodryguez and Cerezo 1994), polyvinylpyrrolidone (Yagi *et al.* 1996) and sugars (Danjo, Nataka and Otsuka 1997).

Cyclodextrins are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central and hydrophilic outer surface. During the past two decades, cyclodextrins and their derivatives have attracted considerable attention in the pharmaceutical field due to their potential in forming complexes with a variety of drug molecules. Cyclodextrins are used to increase the solubility of water insoluble drugs, through inclusion complexation (Chiou and Riegelman 1969, 1971; Narang and Srivastava 1990; Millic -Askrabic *et al.* 1997; Danjo, Nataka and Otsuka 1997). Generally, the small drug molecules and those compounds with lowest water solubility showed an increase in solubility as a function of cyclodextrin concentration. Therefore, cyclodextrins have been used in pharmaceutical preparations in order to increase the stability and bioavailability of poorly water soluble drugs (Moyano *et al*. 1997). Natural cyclodextrins have been used extensively for this purpose. However, they are characterised by a relatively low solubility in water, which limits their application. Hence, chemically modified cyclodextrins are gaining considerable interest to improve the physicochemical properties of cyclodextrin (Arunya and Bragadeesh 1999). Cyclodextrin are known to form an inclusion complex with many drugs of appropriate molecular size and polarity in hydrophobic drug molecules. The resulting complex generally leads to an improvement in some of the properties of drugs in terms of solubility, bioavailability and tolerability.

Aceclofenac is a phenyl acetic acid derivative used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondolytics. The major drawbacks of this drug are its poor aqueous solubility and having an oral bioavailability of only 50% (Merck 2001). To overcome these problems, an increase in the aqueous solubility of

aceclofenac is an important goal. Hence, in this present investigation, inclusion complexation of aceclofenac was tried with the aim to improve its pharmaceutical properties such as aqueous solubility and dissolution properties.

In this study, an attempt was made to improve the solubility and dissolution rate of aceclofenac by complexing with β-cyclodextrin (β-CD). The characterisation of the drug, β-CD and complex was done by using differential scanning calorimetry (DSC), FTIR and X-ray powder diffractometry (XRD). *In vitro* aqueous solubility and dissolution rate studies were performed on the complex.

METHODS

Aceclofenac was obtained as a gift from Alembic Chemical Works, Baroda, India. β-cyclodextrin was obtained from Sigma, USA. All other materials used in the study were of analytical reagent grade.

Preparation Method

Preparation of aceclofenac-β-cyclodextrin solid dispersion (ASD)

A mixture of aceclofenac and β-CD (1:1, 1:2, 1:3, 1:4 and 1:5 w/w) was wetted using a mixture of acetone and water (1:1) and kneaded thoroughly for 30 min in a glass mortar using a pestle (Aftab and Pralhad 2006). The paste formed was dried under vaccum for 24 h. Dried powder was scrapped, crushed, pulverised and passed through sieve no 100 (ASTM-100, 150 μm) and stored in a dessicator for further studies. The solid dispersion were evaluated for its various physicochemical parameters such as yield, angle of repose, bulk density, moisture uptake, drug content and *in vitro* dissolution rate.

Solid State Studies

Fourier transformed infrared (FTIR) spectroscopy

FTIR spectra were recorded on samples prepared by kneading method in different ratio of carrier (w/w) in KBr pellets using Perkin Elmer FT/IR–5300 (Tokyo, Japan). The scanning range was carried out between 450 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential scanning calorimetry (DSC)

DSC analysis was performed using Netzsch DSC 204 (Tokyo, Japan). The samples were heated in a sealed aluminium pan at a rate of 10°C min^{-1} in a range of 30°C to 300°C temperature under nitrogen flow of 40 mL/min.

X-ray powder diffractometry (XRD)

X-ray powder diffraction patterns were recorded on Jeol JDX 8030 X-ray diffractometer (Tokyo, Japan) using Ni-filtered, CuKα radiation, at a voltage of 40°C kV and a 25 mA current. The scanning rate employed was 1° min^{-1} over 10° to 30° diffraction angle (2θ) range.

Liquid State Studies

50 mg of aceclofenac was added to screw capped bottles containing various concentrations of β-CD solution (0.2, 0.4, 0.6, 0.8 and 1 mM $\times$ 10^3). Vials were shaken mechanically at 25 ± 0.5°C for 24 h using rotary flask shaker. After 24 h of shaking, 5 mL of aliquots were withdrawn, filtered (0.45 μm pore size) and spectrophotometrically analysed for drug content at 275 nm (Shimadzu-UV 160A spectrophotometer). Each experiment was performed in triplicate (coefficient of variation, CV<3%) (Higuchi and Connors 1965).

Estimation of Drug Content

Aceclofenac content of the solid dispersion was estimated by UV spectrophotometric method. An accurately weighed quantity of solid

dispersion (100 mg) was extracted with acetone, and the extracts were suitably diluted with phosphate buffer (pH 7.4) (1 mL to 10 mL) and analysed for aceclofenac content by measuring the absorbance at 274 nm. The method obeyed Beer's law in the concentration range of 0–10 μg/mL for its linearity.

Dissolution Rate Studies

Dissolution rate studies were performed in distilled water (pH 6.8) at 37 ± 0.5°C, using USP XXII apparatus (Electrolab, Mumbai, India) with the paddle rotating at 50 rpm. Solid products each containing 100 mg of drug was subjected to dissolution. At fixed time intervals, 5 mL of sample was withdrawn, filtered (0.45 μm pore size) and spectrophotometrically assayed for drug content at 275 nm. 5 mL of fresh buffer was replaced every time to maintain the sink conditions. Each test was performed in triplicate (CV<3%). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time 't' (measured using trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (Khan 1975).

RESULTS AND DISCUSSION

The phase solubility diagram for the complex formation between aceclofenac and β-CD is shown in Figure 1.

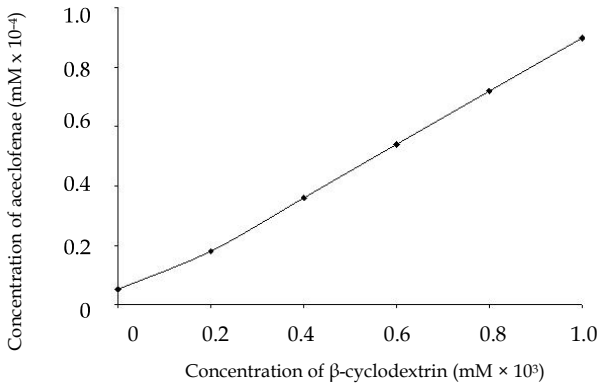

Fig. 1: Phase solubility of aceclofenac and β-cyclodextrin at 25°C.

The aqueous solubility of aceclofenac increased linearly (r = 0.9923) as a function of carrier concentration. The phase solubility diagram showed A_L-type, due to the straight line having a slope less than unity which indicates the formation of the complex. The apparent stability constant, K_C was calculated from the linear plot of the phase solubility diagram according to the equation:

$$K_C = \frac{\text{Slope}}{S_0\,(1-\text{Slope})}$$

where, 'S_0' is the solubility of aceclofenac in the absence of β-CD. The K_C of aceclofenac and β-CD complex was found to be 125.07 mmol, which indicates the formation of stable complex (A_L-type). The FTIR spectra of aceclofenac and its binary systems with β-CD are presented in Figures 2(a), 2(b) and 2(c).

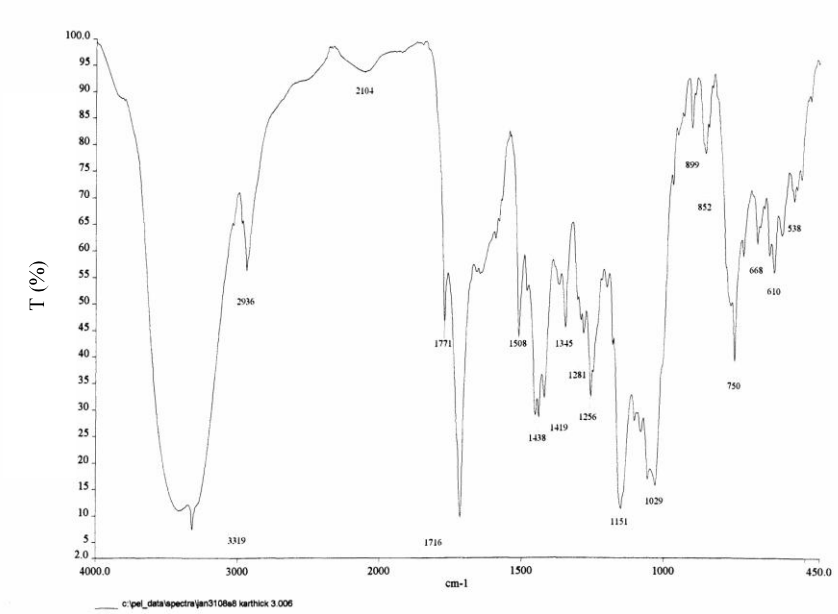

Fig. 2(a): FTIR spectra of aceclofenac.

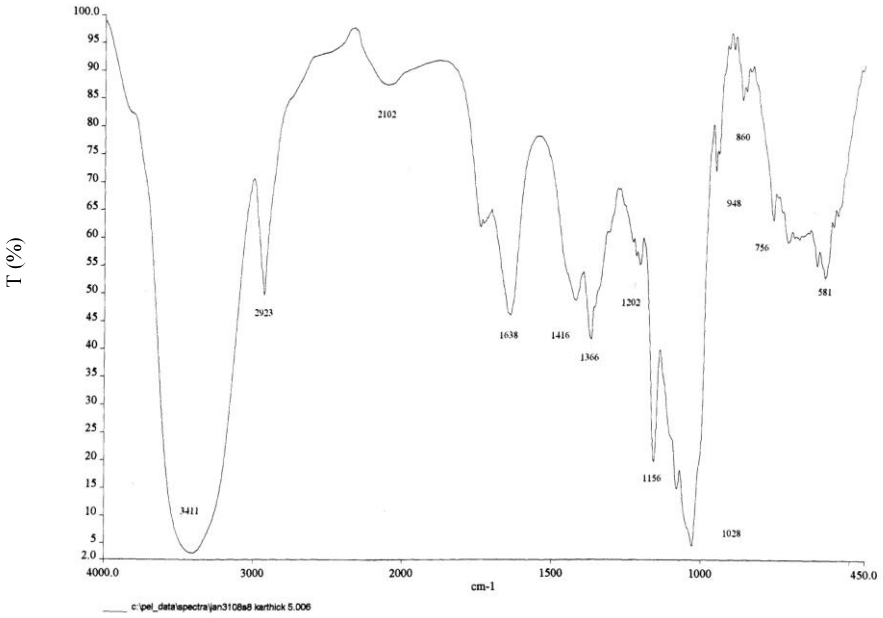

Fig. 2(b): FTIR spectra of β-cyclodextrin.

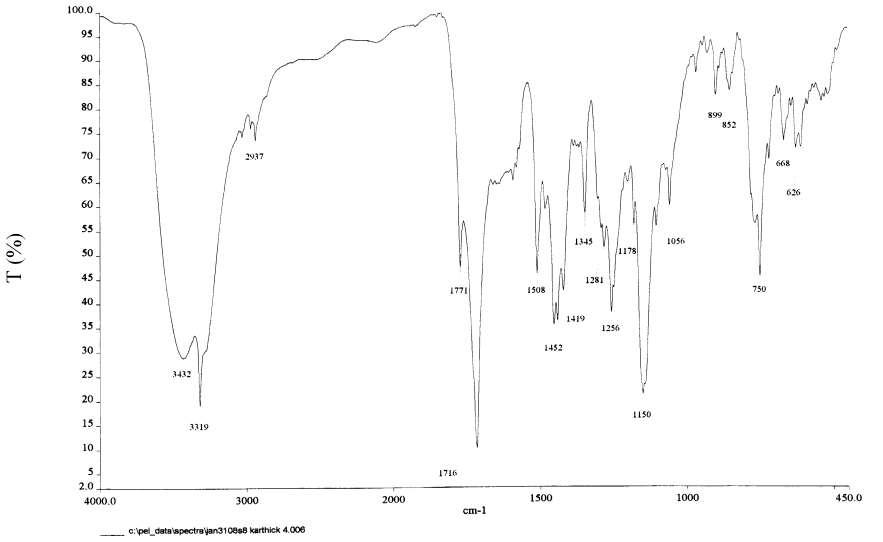

Fig. 2(c): FTIR spectra of aceclofenac and β-cyclodextrin.

Pure drug showed sharp characteristic peaks at 3319, 2936, 1771 and 1508 cm^{-1}. All the above characteristic peaks appeared in the spectra of binary systems at the same wave numbers indicating there was no modification or interaction between drug and carrier. This is also supported by the fact there was no appearance and disappearance of new or existing peaks. Thermal behaviour of pure drug and corresponding drug carrier systems are depicted in Figures 3(a), 3(b) and 3(c). The DSC curve of aceclofenac profiles a sharp exothermic peak (T peak 154.5°C) corresponding to its melting point. However, the characteristic exothermic peak, corresponding to drug was broadened and shifted towards lower temperature, with reduced intensity in the solid dispersions. This could be due to the higher concentration and uniform distribution of drug in the crust of polymer, resulting in the complete miscibility of drug and carrier. Moreover, the data also indicates that there seemed to be no interaction between the components of binary systems. There was no significant difference in DSC pattern of dispersions, which suggests that even the kneading process could not induce the interaction at molecular level and the solid dispersion formed as highly dispersed drug crystals in carrier. The deviation of the baseline from its original position was due to the instrumental error whereby it did not return to its original position before the commencement of melting point of the drug.

The XRD studies revealed that the intense peak was observed in pure aceclofenac at 12.5°, which was broadened in the binary mixture. It revealed the overall amorphous form with poor crystalline structure present in the mixture which ensures conversion of crystalline to amorphous form [Fig. 4(a), 4(b) and 4(c)]. Solid dispersions were found to be fine and free flowing in characteristic. The physicochemical evaluations of the solid dispersions are shown in Table 1.

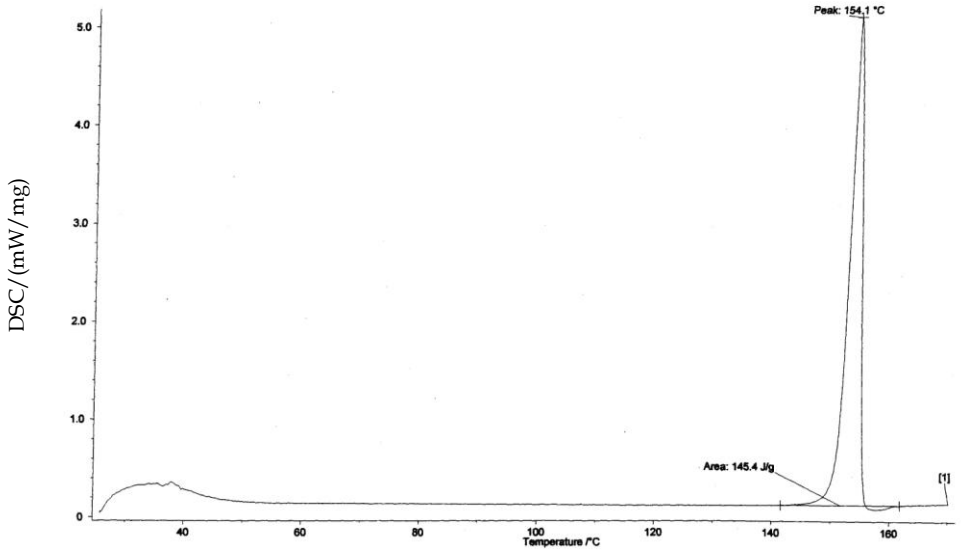

Fig. 3(a): DSC thermogram of aceclofenac.

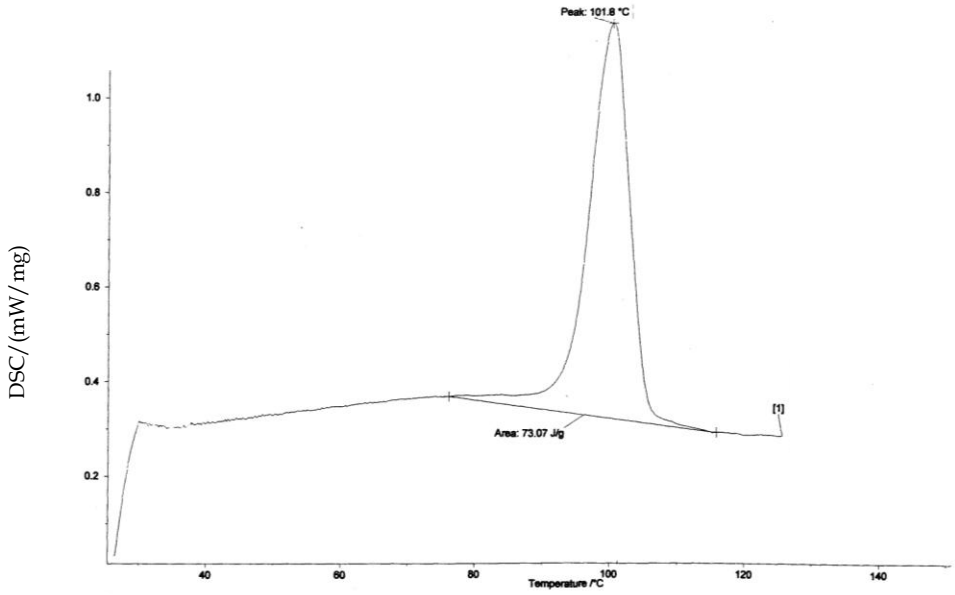

Fig. 3(b): DSC thermogram of β-cyclodextrin.

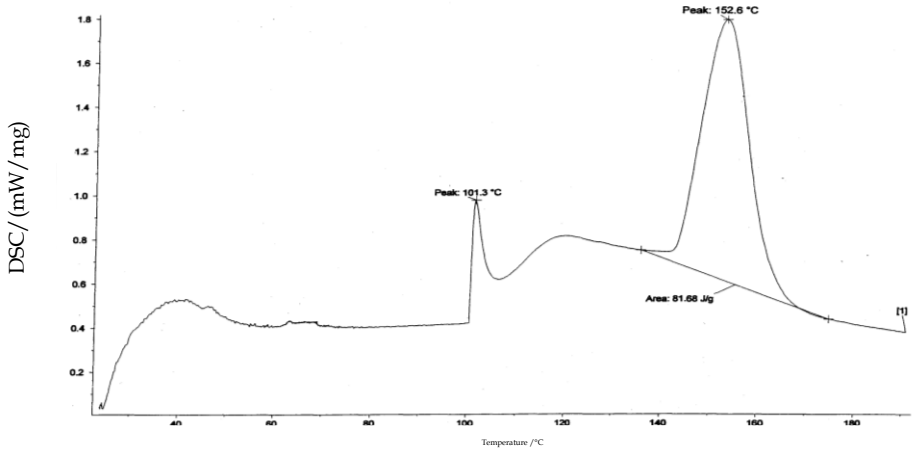

Fig. 3(c): DSC thermogram of aceclofenac and β-cyclodextrin.

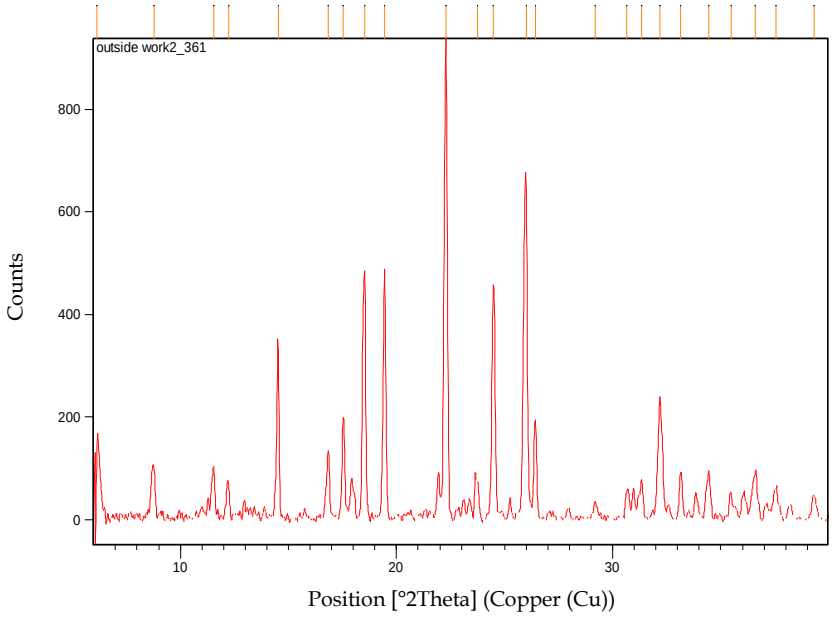

Fig. 4(a): XRD of aceclofenac.

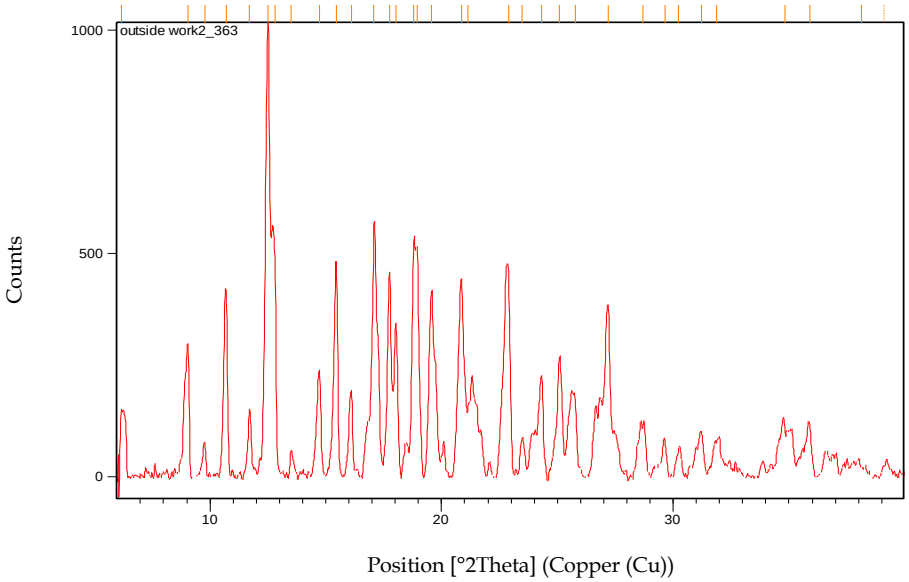

Fig. 4(b): XRD thermogram of β-cyclodextrin.

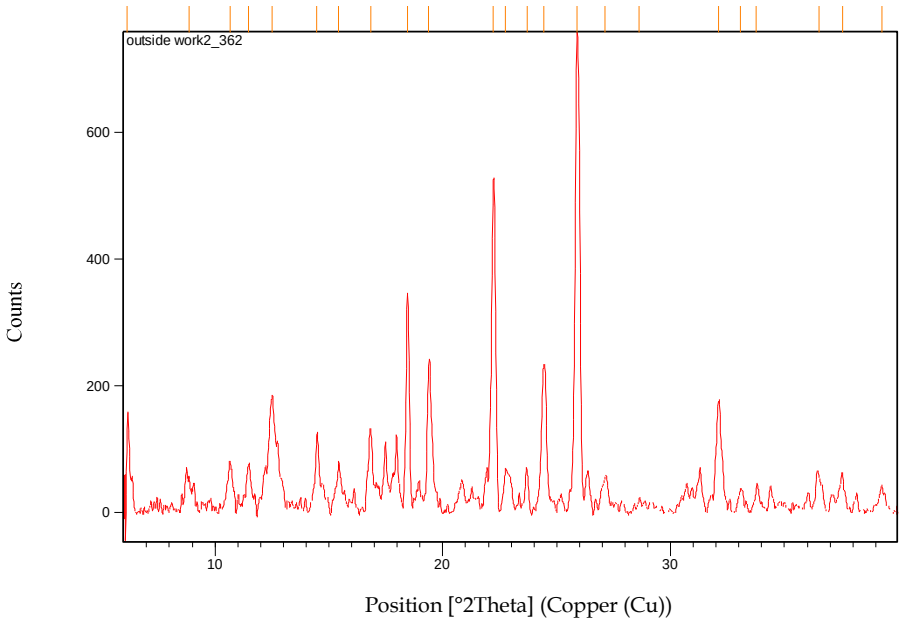

Fig. 4(c): XRD thermogram of aceclofenac and β-cyclodextrin.

Table 1: Physicochemical evaluation of aceclofenac solid dispersions.

S. No	Batch code	Drug: carrier ratio	Yield (%)	Angle of repose (°)	Bulk density (g/cc)	Compressi -bility (%)	Moisture uptake (%)	Drug content (%)	DE_{50} (%)
1	Pure drug	–	–	22±1.4	0.80±0.05	15±0.7	5±0.7	99±1.0	10.23
2	ASD-I	1:1	90.17±1.1	22±1.6	0.81±0.04	16±0.9	6±0.7	94±1.1	22.74
3	ASD-II	1:2	92.76±0.7	22±1.0	0.82±0.05	16±0.7	6±0.9	95±1.4	31.45
4	ASD-III	1:3	94.96±0.8	23±0.8	0.82±0.06	17±1.1	7±0.6	96±1.5	43.33
5	ASD-IV	1:4	95.68±0.9	23±1.3	0.86±0.03	17±1.3	7±0.8	97±1.4	57.96
6	ASD-V	1:5	95.22±0.5	24±1.2	0.88±0.03	18±1.2	7±0.7	97±1.3	74.11

Note: n=3±SD

The release of drug from the solid dispersion were 49.93% (1:1), 64.17% (1:2), 69.74% (1:3), 78.87% (1:4) and 95.66% (1:5) at the end of 60 minutes (Fig. 5). The t_{50} values of the batches prepared using different drug:carrier ratio namely 1:4 and 1:5 were 33 and 28 minutes, respectively. It indicates that the dissolution of 50% drug from the solid dispersion prepared using 1:5 ratio was faster than that of the batch prepared using 1:4 ratio. It reveals that as the drug to carrier concentration increases, an increase in the dissolution rate was observed. The batch prepared in the ratio of 1:5 showed better *in vitro* release and better t_{50} values, when compared with the *in vitro* release of pure drug. The pure drug showed a release of 19.76% at the end of 60 minutes. The solid dispersions increased dissolution rate by 4.50 fold as compared to pure drug. The enhancement of dissolution of aceclofenac from the drug carrier may be due to several factors such as lack of crystallinity, increased wettability and dispersibility. Incorporation of drug with a hydrophilic carrier system offered an increased wetting and reduction in interfacial tension between hydrophobic drug and dissolution medium (Narender Reddy *et al.* 2004). It was observed during the dissolution studies that drug release from the solid dispersions was found to be faster as compared with pure drug. As the proportion of β-CD in solid dispersion increases, an increase in the dissolution rate of the drug was observed. The solid dispersion prepared using 1:5 (drug:carrier) ratio (ASD-IV) achieved maximum dissolution rate of drug. The 'k' values of solid dispersion were found to follow first order kinetics more closely than pure drug (Gopal Rao *et al.* 2005).

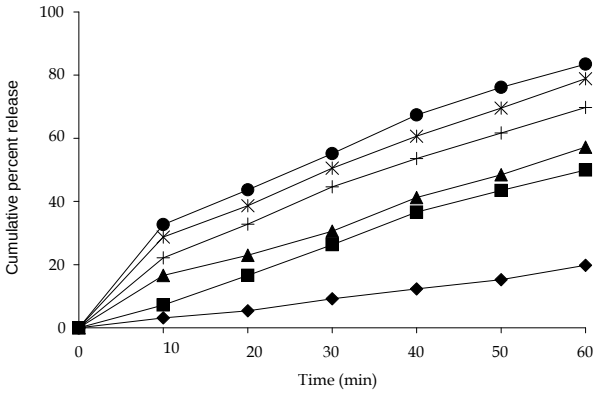

Fig 5: *In vitro* dissolution profiles of solid dispersion containing aceclofenac: bulk drug (♦), ASD-I (■), ASD-II (▲), ASD-III (×), ASD-IV (+) and ASD-V (●). Samples were withdrawn at different time intervals and aceclofenac was determined by UV spectrophotometer.

CONCLUSION

The study shows that the dissolution rate of aceclofenac can be enhanced to a greater extent by solid dispersion technique using an industrially feasible kneading method. The solid dispersion complex of drug gave better dissolution profile as compared to pure drug. This in turn, can lead to a reduction in dose related adverse effects and improved bioavailability.

ACKNOWLEDGEMENT

The authors express their sincere thanks and gratitude to His Holiness Jagadguru Sri Sri Shivaratee Mahaswamigalavaru of Suttur Mutt, Mysore for providing facilities to carry out research work and SAIF, IIT, Chennai for carrying out DSC and FTIR spectra's and CECRI, Karaikudi for XRD studies.

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