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DISSOLUTION ENHANCEMENT OF DIACEREIN USING WATER SOLUBLE CARRIER BY SOLID DISPERSION TECHNOLOGY

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ABSTRACT

Diacerein is generally used in the treatment of Osteoarthritis , this drug comes under the class anthraquinone. The drug is practically insoluble in water and exhibits exceptionally slow and intrinsic dissolution rate with poor bioavailability. In the present study, diacerein and β-cyclodextrin (β-CD) solid dispersions were prepared with a view to study the effect and influence of β-CD on the solubility and dissolution rate of this poorly aqueous soluble drug. Phase solubility profile revealed that the solubility of diacerein was significantly increased in the presence of β-CD and indicating the possible 1:1 stoichiometric inclusion complex with a stability constant of 339.66 M^{-1}. Effect of variable such as drug: Carrier ratios were studied. Physical characterization of the solid dispersion was characterized by Fourier transform infrared spectroscopy (FT-IR), Differential scanning calorimetry (DSC) and X-ray diffraction studies (XRD). These studies revealed that a distinct loss of drug crystallinity in the solid dispersion is ostensibly accounting for enhancement of dissolution rate in distilled water containing 0.1% Tween 80. The scanning electron microscopy (SEM) study revealed that all the binary systems appeared as agglomerates and exhibiting the presence of a homogenous solid phase which could also be responsible for the enhanced dissolution rate in comparison with the pure drug. The drug release from the prepared solid dispersion exhibited a first order kinetics. Solid dispersion of diacerein showed a 7.66 times fold increase in dissolution rate over the pure drug.

Keywords: Diacerein, β-Cyclodextrin, solid dispersion, kneading method, dissolution, release kinetics.

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INTRODUCTION

Poor aqueous soluble drugs are generally associated with certain problems such as slow drug absorption which eventually leading to insufficient and variable bioavailability[1,2]. Slowly soluble drugs may not only be absorbed at a slow rate, they may be incompletely absorbed or in some cases largely unabsorbed following oral administration due to the limitation of its gastrointestinal residence time. Thus, poorly soluble drugs or poorly formulated drug products may result in incomplete absorption. Approximately 40% of the newly discovered drugs are reported to be poorly water soluble[3,4]. In an economic point of view, low oral bioavailability results in wastage of large portion of drug and in turn ultimately adds to cost of drug therapy, especially when the drug is expensive one[5]. Therefore, certain attempts have been made to enhance the drug

solubility of these therapeutic agents to correlate well with enhancement of their bioavailability[6, 7, and 8]. Many techniques have been investigated by researchers to improve the solubility of poorly aqueous soluble drugs, among them solid dispersion technology was proven to be a successful technique, and most widely used [9,10,11, 12,13]. Numerous insoluble drugs have shown to improve their dissolution character upon conversion to solid dispersion[14]. Solid dispersion technology is a well known process used to increase the dissolution kinetics and in turn alters the oral absorption of poorly water soluble drugs using water soluble inert carriers[15, 16]. Various hydrophilic carriers such as sugars, acids, Polyvinyl Pyrrolidone, polyethylene glycol (PEG 4000, 6000), methyl cellulose, and cyclodextrin have been extensively investigated for their improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs. Cyclodextrin are cyclic oligosaccharides consist of (ά-1, 4) - linked ά-D glucopyranose units and contain a somewhat small lipophilic central cavity and a hydrophilic outer surface, that results in enhanced solubility and bioavailability of such compounds. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus in general, they do not permeate lipophilic membranes. In the pharmaceutical industry, Cyclodextrin have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability. Cyclodextrin have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powder. Diacerein is chemically 4, 5 diacetyloxy-9, 10 dioxo anthracene-2-carboxylic acid, slow acting medicine of the class anthraquinone used to treat joint diseases such as osteoarthritis (swelling and pain in the joints).it works by blocking the action of interlukin-1 beta, a protein involved in the inflammation and destruction of cartilage that play a role in the development of symptoms of degenerative joint diseases such osteoarthritis. The major drawback of this drug is its poor aqueous solubility (BCS-II classification) (0.01mg/ml) and its oral bioavailability is 40-50%.It is therefore worthwhile to make a solid dispersion for diacerein to improve its solubility. Hence, in this present investigation, an attempt was made for diacerein by molecular inclusion complexation β-cyclodextrin with an aim to improve its pharmaceutical properties such as aqueous solubility, dissolution properties with a view of increasing its bioavailability and therapeutic efficacy. The characterization of the drug, β-CD and complex was done by using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy FTIR and powder x-ray diffractometry (PX-RD). *In vitro* aqueous solubility and dissolution rate profiles of the complex were performed.

MATERIALS AND METHODS

Diacerein and beta-cyclodextrin was obtained as a gift sample from Guru of cure pharmaceutical, Pondicherry. All other reagents used in the study were of analytical grade.

Preparation of Diacerein β-cyclodextrin solid dispersion by kneading method

A physical mixture of Diacerein and β-cyclodextrin (1:1,1:2,1:3,1:4,1:5,1:6,1:7,1:8,1:9 and 1:10 mol/mol) was triturated in a mortar with a small volume of methanol: water[1:1 vol/vol] solution. The slurry was kneaded for 45 min and dried at 45˚c.The dried mass was pulverized and sieved through 60 and fraction was collected. The prepared powder stored in deccicator for further studies. The prepared solid dispersions were evaluated for their physicochemical parameters such as yield, angle of repose[17] Carr's index [18] moisture uptake, drug content and *in vitro* dissolution studies.

Solid State Studies

Percent Yield

The percentage yield of the solid dispersion was calculated on the basis of dry weight and carrier with respect to the final weight of the inclusion complexes[19]

$$\% \text{ Yield} = \frac{\text{Final weight of the product}}{\text{Dry weight of the drug and carrier}} \times 100 \quad [1]$$

Average Particle Size

The solid dispersion of diacerein were dispersed in liquid paraffin and mounted on slides. A random of 200 particles were measured using a calibrated stage micrometer and eye piece micrometer, their average particle size were calculated[19].

Moisture uptake studies

The moisture uptake/hygroscopicity of the diacerein solid dispersion were assessed by spreading a known mass of the sample (5g) evenly over a clean petriplate having an internal diameter of 10cm at room temperature (20-25˚c).The weight of the sample was observed at 0.25, 0.5, 1, 2, 3, 5, 6 hrs. The experiment was carried out in triplicate and the moisture uptake in percentage was calculated using the formula,

$$\text{Moisture uptake (\%)} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Fourier transforms infrared (FTIR) spectroscopy[19]

FTIR spectral matching approach was employed to detect any possible chemical reaction between drug and polymer. Potassium bromide was used to prepare pellets for all compounds. The pellet was scanned using FTIR-5300 spectrometer (shimadzu, Tokyo, Japan).The scanning range was 4000-400cm^{-1}.

Differential scanning calorimetry[19]

DSC analysis was performed for drug and drug in solid dispersions using DSC Q200, TA instruments, Mumbai, India. The samples (10 mg of diacerein or its equivalent) were heated in a sealed aluminum pans at a rate of 5° C per/min in a temperature range of 10 - 300° C under nitrogen flow of 40 mL/min. An empty aluminum pan was used as reference.

Scanning electron microscopy[19]

The surface morphology of drug and binary systems was determined using a scanning electron microscopy**.** Pure drug (Diacerein) was mounted on a double faced adhesive tape and sputtered with thin gold-palladium layer using sputter coater unit and surface topography was analyzed with a scanning electron microscope(JEOL 457V,Japan)

X-ray powder diffractometry (XRD)

Powder X-ray diffraction (PXRD) patterns were recorded on a Jeol JDX 8030 X-ray diffractometry (Tokyo, Japan) using Ni filtered Cu,K (ά) radiation, a voltage of kV,a current of 30mA and receiving slit of 0.2 in. The samples were analyzed over 2Θ range of 2-40˚c with scan step size of 0.0170 (2Θ) and scan step time of 1s.

Liquid State Studies

Phase solubility study

Accurately weighed each sample (25mg) of Diacerein was transferred to 25ml conical flask containing various concentration of β-cyclodextrin (1, 2, 3, 4, and 5×10^{-4}mM).The flasks were closed with corks and shaken at room temperature up to 72 hrs using rotator shaker. The solutions were filtered through Whatmann no.1 filter paper. The filtrates were diluted suitably with double distilled water and assayed for diacerein at 255nm against double distilled water as blank. The apparent stability was calculated using the formula;

$$Ka= slope/S_0 (1-slope)$$

Estimation of drug content[19]

The content of Diacerein in the formulated solid dispersion was determined by UV spectrophotometer (shimadzu, Japan). An accurately weighed quantity of solid dispersion (10 mg) was dissolved in 0.8ml of methanol and volume was made up to 10ml with double distilled water and the absorbance was measured at 285nm against blank. The drug content was estimated using the formula:

Drug content (mg/ml) = (Absorbance×slope+intercept) × bath volume/1000

Dissolution rate studies[19]

The dissolution studies was carried out using USP (XXII) apparatus (Electro lab, Mumbai, India) following paddle method, freshly prepared double distilled water (900ml) was placed in the dissolution flask and allow to attain a temperature of 37±0.5˚c. The solid dispersion containing a quantity equivalent to 100mg of diacerein was filled in hard gelatin capsule (size 2) and placed in the basket and immersed in the dissolution medium. The basket was rotated at 50rpm for 1hr.Five millilitre of the sample was withdrawn at different time intervals of 0,15,30,45 and 60 min. After each withdrawal, the medium was replaced with equal amount of fresh buffer to maintain the sink conditions. The drug content was estimated by measuring the absorbance at 255nm against blank.

RESULTS AND DISCUSSION

Compatibility study

Compatibility studies of diacerein with selected carrier β-cyclodextrin were done by FTIR spectral matching approach. It was easily understood that there was no appearance and disappearance of peaks. The functional group (c=o) at 1627cm^{-1} {Thiazeto (3, 2-a) quinolone -4one}, C=O at 1813 {1, 3-dioxol-2-one} are not involved in the reaction. Table1. Shows the appearance of band at 1709cm^{-1} (COOH) also exhibited the non reactivity of both the compounds .The phase solubility diagram for the complex formation between diacerein and β-cyclodextrin are presented in Fig.1.The plot showed that the aqueous solubility of the diacerein increases linearity as a function of β-cyclodextrin concentration. The drug apparent stability constant for the drug was found to be 339.66M^{-1}. The FTIR spectrum of Diacerine, β-cyclodextrin, diacerein with β-cyclodextrin are shown in Fig.2A,2B and 2C.

Table 1: Phase solubility studies for Diacerein

Concentration of β-Cyclodextrin (10^{-4} mM)	Absorbance
0	0.258
1	0.372
2	0.392
3	0.404
4	0.408
5	0.430

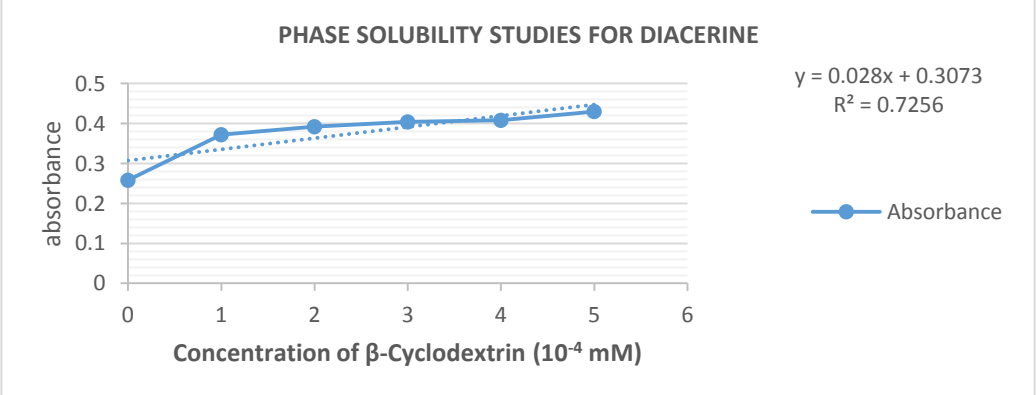

Figure 1: Phase solubility studies for Diacerein

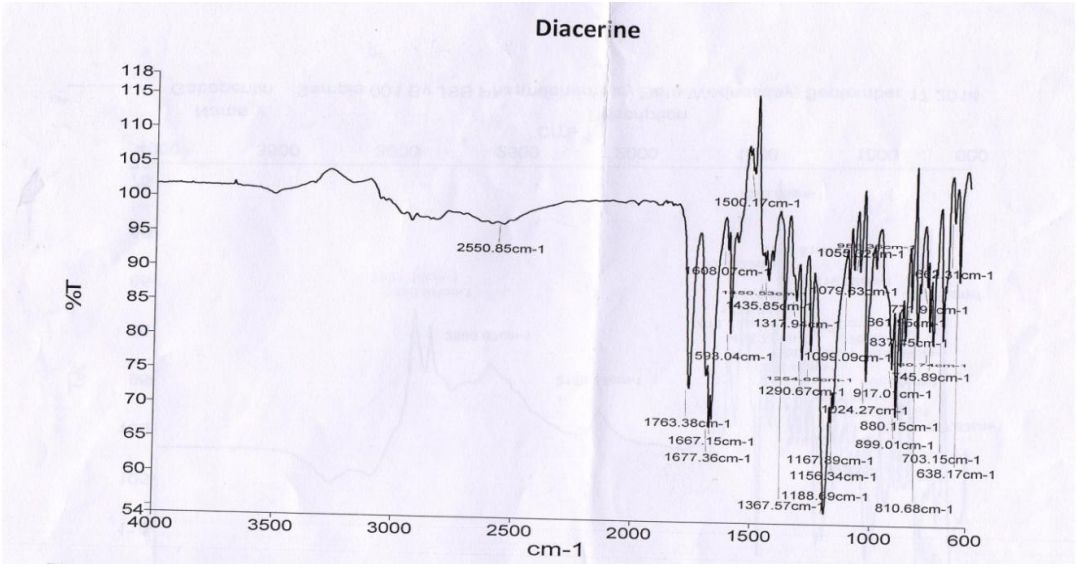

Figure 2A: FTIR spectra of Diacerein

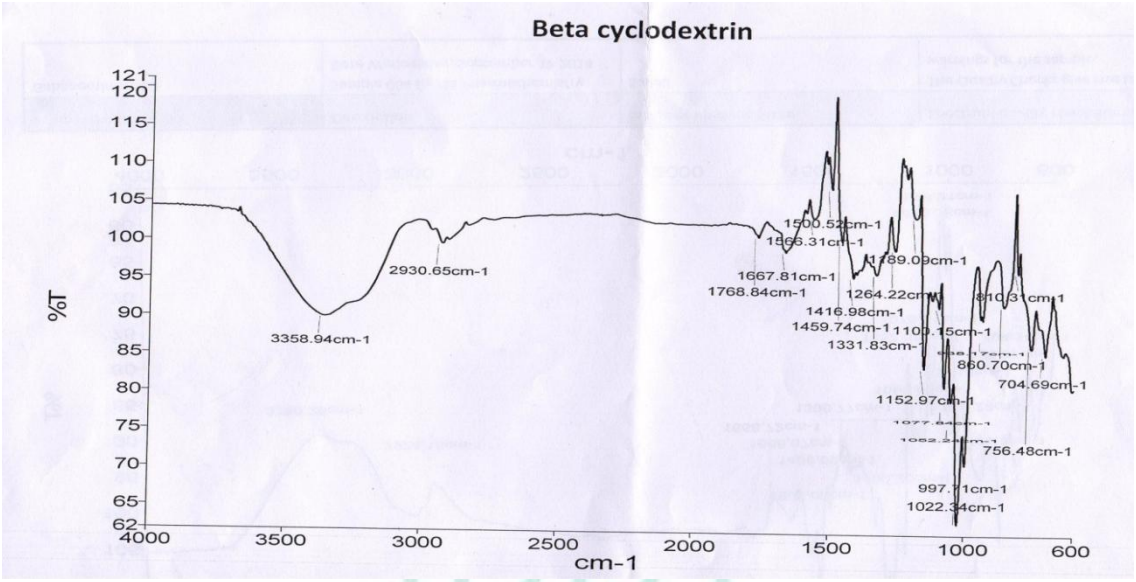

Figure 2B: FTIR spectra of β-cyclodextrin

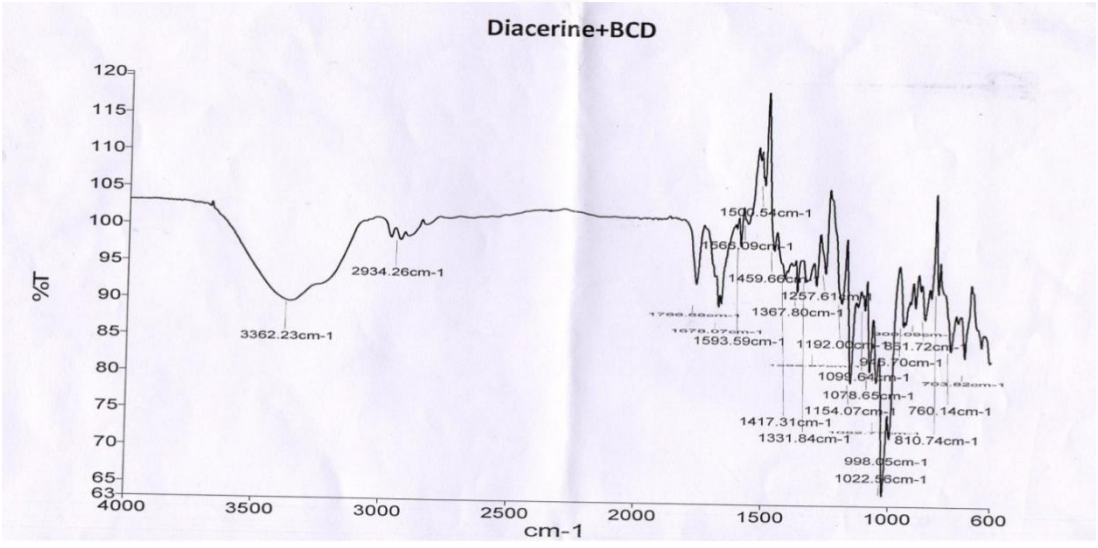

Figure 2C: FTIR spectra of diacerein with β-cyclodextrin

Preparation and evaluation of solid dispersion

Ten batches of solid dispersion were prepared using diacerein as drug, β-cyclodextrin as carrier by kneading method. The prepared solid dispersions was evaluated for average particle size, angle of repose, bulk density, moisture uptake, drug content and in vitro dissolution studies. The angle of repose values was ranged from 22 - 27˚ for kneading mixture. The formulations have shown good flow property. The bulk density value was ranged from 0.80 - 0.88g/cc for kneading mixture. The compressibility values were ranged from 16 -19% for kneading mixture, which was found to be ideal for the formulation of tablets. The moisture uptake values were 6 - 7% for kneading mixture which indicates that the powder was hygroscopic in nature. Table2. Shows the drug content was ranged 96 - 98% for kneading method.

Differential scanning calorimetry study

The DSC studies showed one endothermic peak at 254.97˚c and one exothermic peak at 128.95˚c, which is corresponding to its melting point 250-260˚c. This revealed there was no major shifting of peak in the chemical complex. The thermogram was shown in Fig. 3A, 3B and 3C.

Table 2: Evaluation of solid dispersion of Diacerein

Properties	Kneading Method				
	1:2	1:4	1:6	1:8	1:10
Percentage Yield (%)	98	97	98	97	96
Angle of Repose(^{0})	21	22	22	23	21
Bulk Density(g/cc)	0.82	0.86	0.88	0.84	0.81
Compressibility (%)	17	16	18	19	19
Moisture Uptake (%)	6	7	6	6	6
Drug Content (%)	98	97	98	96	97

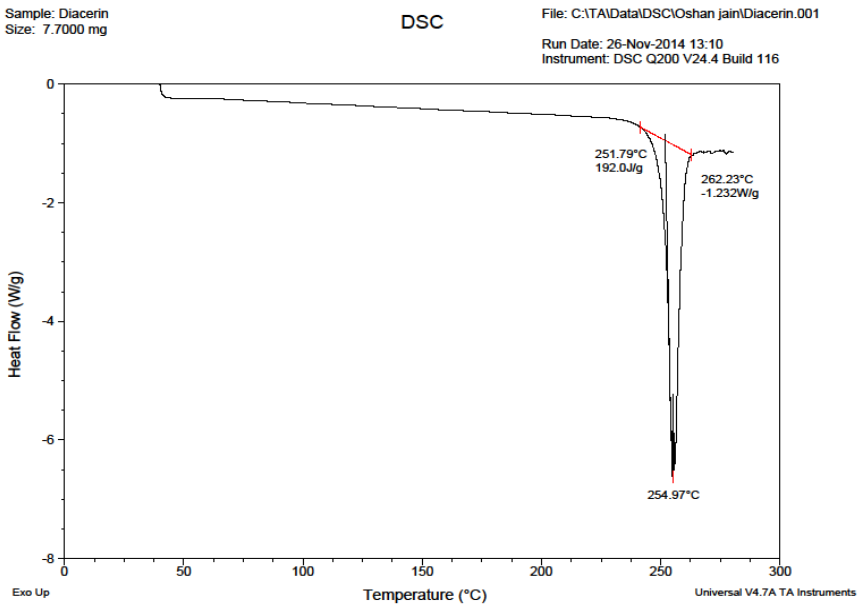

Figure 3A: DSC Thermogram of Diacerein

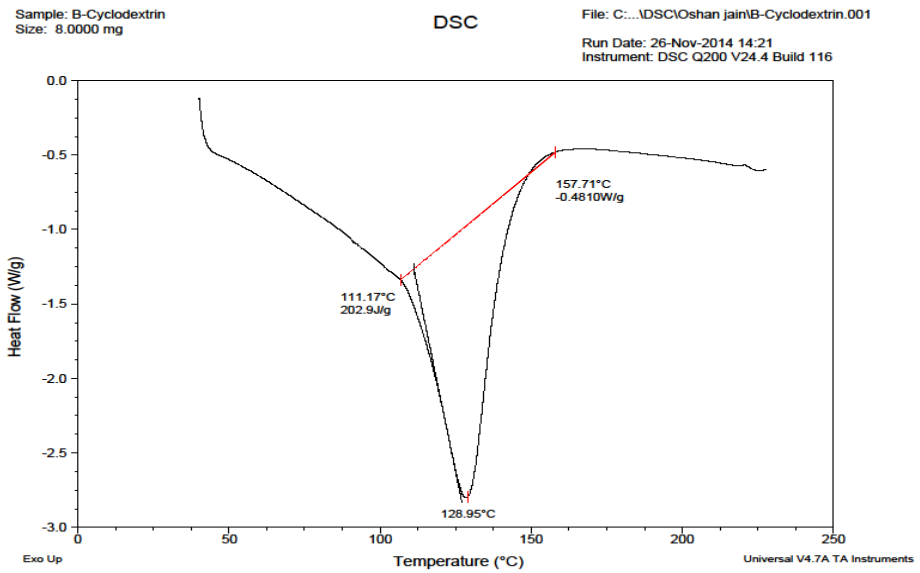

Figure 3B: DSC thermogram of β-cyclodextrin

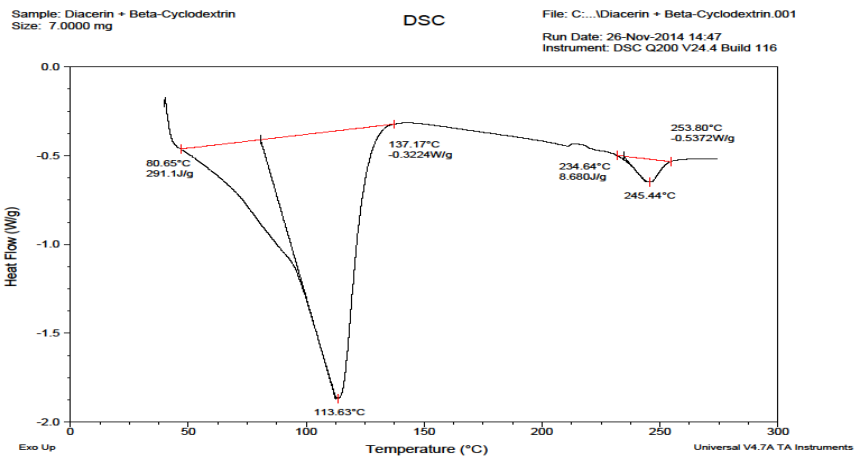

Figure 3C: DSC thermogram of diacerein with β-cyclodextrin

X-RD study

The X-RD spectra of pure diacerein ,β-cyclodextrin (β-CD),and diacerein with β-CD was shown in Fig. 4A,4B and 4C.The diffraction spectrum of solid dispersion vis-a-vis pure drug carrier and mixture indicates the changes produced drug crystal structure as seen from the figure it can be clearly noted that the X-RD pattern of diacerein + β-cyclodextrin become very broaden due to lower crystallinity nature observed at 2Θ (5,10,17,25,27) there are overall amorphous with poor crystalline structure present in the mixture.

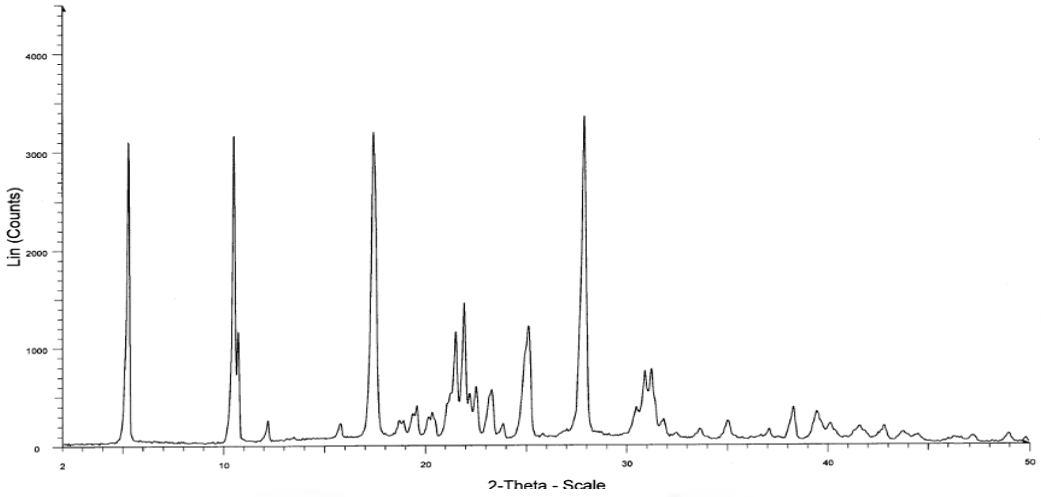

Figure 4A: XRD of diacerein

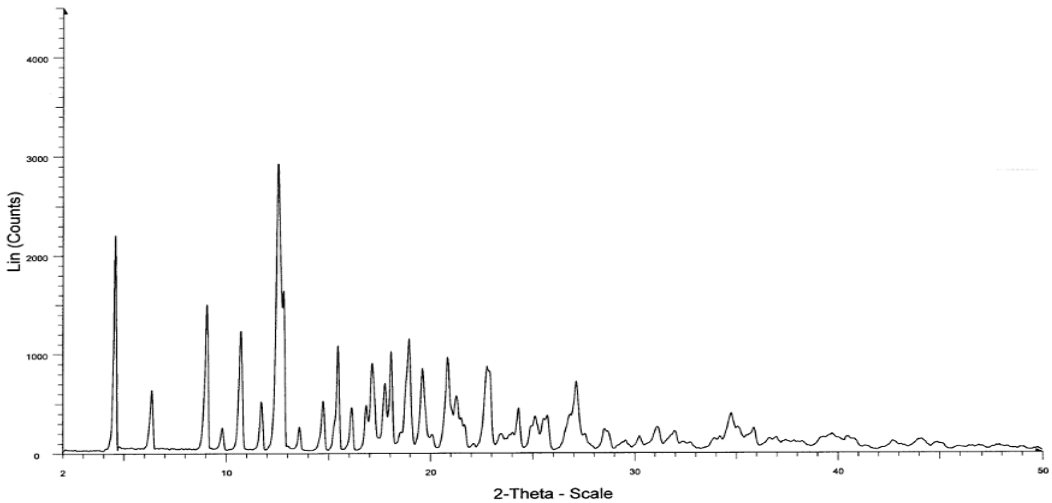

Figure 4B: XRD of β-cyclodextrin

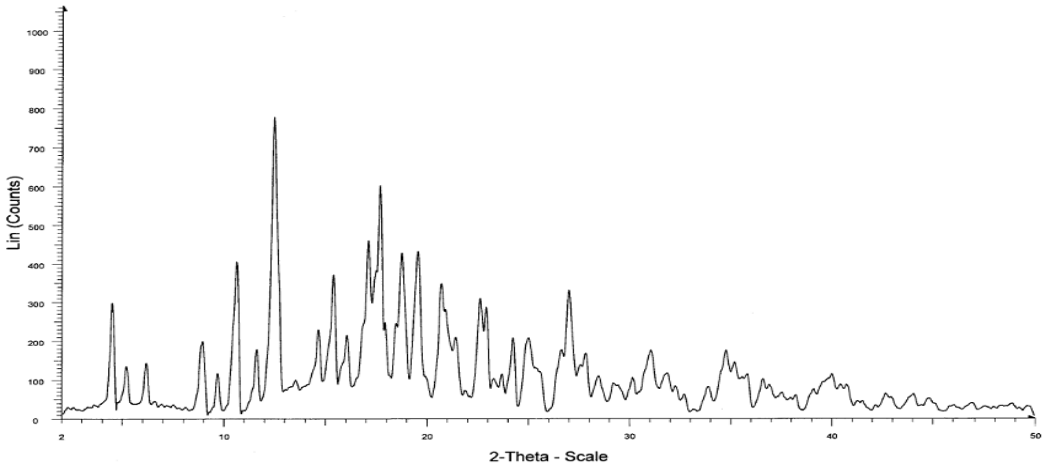

Figure 4C: XRD of diacerein with β-cyclodextrin

In-vitro dissolution studies

The in vitro dissolution studies were carried out using USP (XXII) dissolution apparatus following paddle method for pure drug and solid dispersions using double distilled water maintained at 37±1˚c.The samples was withdrawn at 15, 30, 45 and 60 min. Fig5. Shows the release of drug from the solid dispersion prepared by kneading method, the release of drug from the solid dispersions was 30.14(1:2), 40.47(1:4), 82.17(1:6), 90.13(1:8) at the end of 60 min, where as it was observed that batch and 98.22(1:10) within 30min .The t_{50} values of this batch was 30min. Table 3 showed a pure drug release of 20.12% at the end of 60 min. The solid dispersions improved the dissolution rate to 7.66times fold as to pure drug.

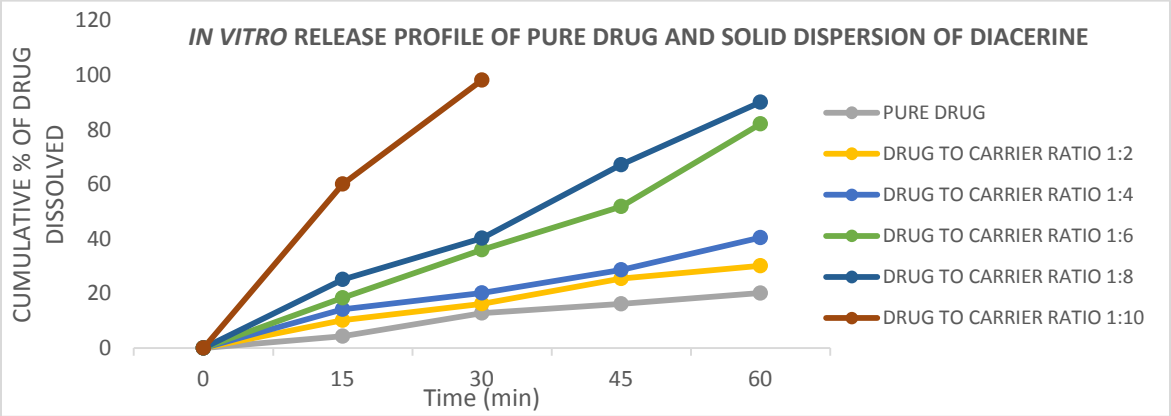

Figure 5: *In vitro* release profile of pure drug and solid dispersion of diacerein for Pure drug and mixture (1:2, 1:4, 1:6, 1:8 and 1:10)

Table 3: *in vitro* dissolutions profile of diacerine solid dispersion

Time (min)	Cumulative % of drug dissolved					
	Pure drug	Drug to carrier ratio				
		1:2	1:4	1:6	1:8	1:10
0	0	0	0	0	0	0
15	4.33	10.17	14.19	18.38	25.14	60.12
30	12.82	16.22	20.17	36.01	40.26	98.22
45	16.17	25.47	28.65	51.89	67.18	-
60	20.12	30.14	40.47	82.17	90.13	-

Scanning electron microscopy study

SEM image of diacerein shows crystalline nature, the SEM images for the binary mixture depicted that the mixture exhibits more agglomerates as compared to the crystalline nature of diacerein, which accounts for the increased solubility of diacerein (Fig.6A, 6B and 6C).

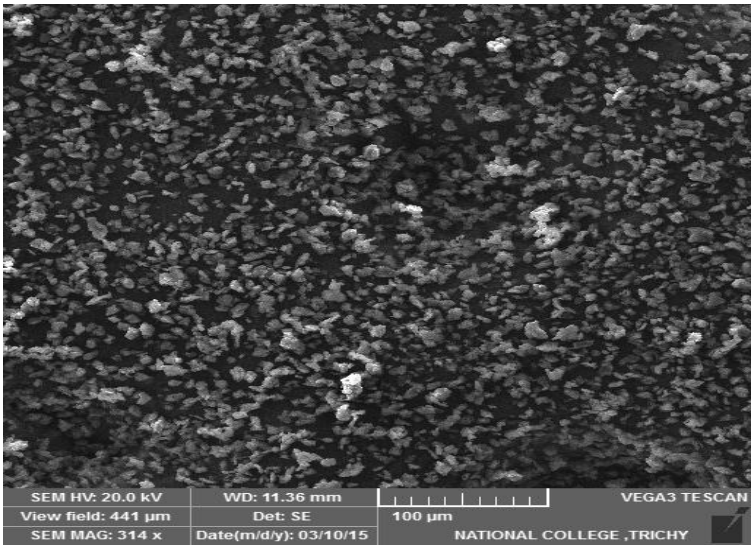

Figure 6A: SEM image of diacerein

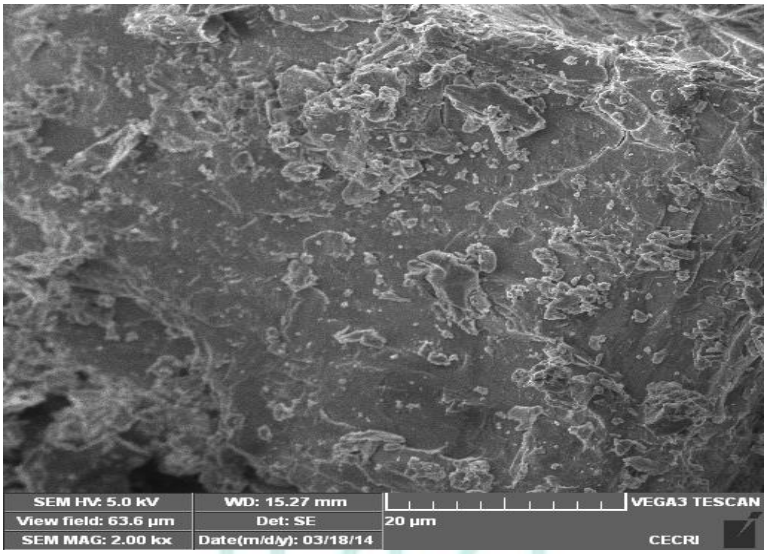

Figure 6B: SEM image of β-cyclodextrin

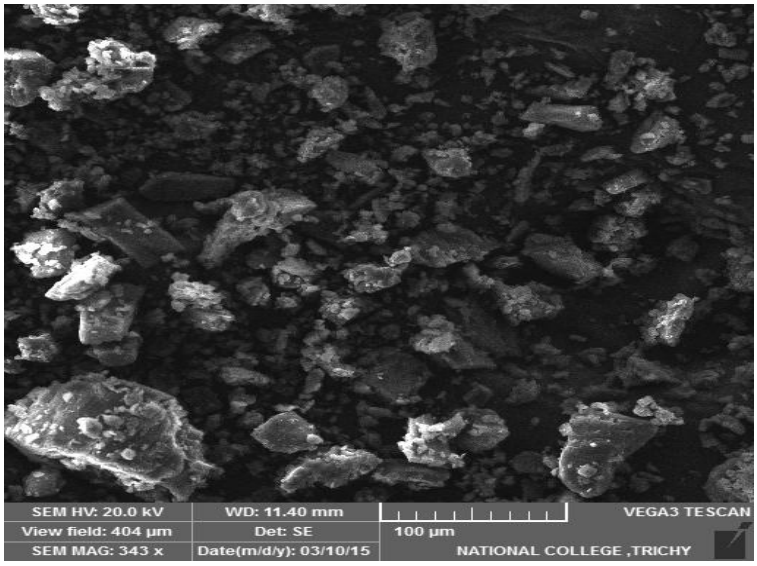

Figure 6C: SEM of diacerein with β-cyclodextrin

CONCLUSION

The objective of the present study was to prepare solid dispersion of diacerein using β-cyclodextrin. Diacerein was selected as drug due to its poor aqueous solubility and β-cyclodextrin used as a carrier. The compatibility studies were also conducted by FTIR method showed that the drug and carrier was found to be compatible and there is no interaction between drug and carrier. The solid dispersion prepared using kneading method was evaluated for average particle size, angle of repose, bulk density, compressibility, and moisture content, drug content and in vitro studies. From the above studies it was concluded that the batch prepared using 1:10 drug polymer ratio by kneading method showed satisfactory in vitro dissolution studies. From the DSC studies it can be concluded that, the chemical complexation was found between drug and carrier. This might be the reason for improving the solubility of drug. The X-RD studies revealed that overall amorphous form with poor crystalline structure present in the mixture which ensures conversion of crystalline to amorphous form. Hence, it can be concluded that solid dispersion complex of drug was giving better dissolution profile as compared to pure drug. This in turn, can reduce the dose of diacerein, reduce adverse effect and improve bioavailability.

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