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Solubility Enhancement of Diacerein by Solid Dispersion Technique

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Abstract

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic Effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water (less than 1µg/ml) and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. There are numerous reported methods to enhance aqueous solubility of poorly soluble drug among them solid dispersions is one of the effective and accepted technique in the pharmaceutical industry. Therefore in this study attempt is done to improve the physicochemical properties of diacerein, a poorly water soluble drug, by forming dispersion with sorbitol as water soluble carrier. The solid dispersions of Diacerein: Sorbitol were prepared in ratio 1:0.5, 1:1.5 and 1:2.5 w/w by solvent evaporation and physical triturating method. The formulations were characterized for solubility parameters, drug release studies and drug-carrier interactions by using phase solubility studies, FTIR spectrum, TLC. All the formulations showed marked improvement in the solubility behavior and improve dissolution rate. Formulation containing drug: sorbitol ratio of 1:2.5 w/w showed the best release 96.9% in 60 min as compared to the pure drug i.e. 47 % in 60 min. The interaction studies showed no interaction between the drug and the carrier. It was concluded that Sorbitol as a carrier can be well utilized to improve the solubility of poorly soluble drugs.

***Key Words**: Diacerein, Sorbitol, Solid Dispersion and Solubility.*

Introduction

Discovering a way to increase the solubility of poorly soluble drugs in order to improve their Pharmaceutical and biological availability still remains one of the major technological problems, the current status of scientific development having highly variable oral bioavailability of drugs due to low solubility and dissolution rate in the gastrointestinal absorption of many new drugs. Even though there are many methods intended to solve the problem in which the formulation of solid dispersion is one of the ideal methods to dissolution enhancement.

The solid dispersions as a dispersion of one or more active ingredients in an inert carrier or matrix. Solid dispersion is one of the techniques used to increase the dissolution rate of the lipophilic drugs. Solid dispersion are prepared by the physical triturating, solvent evaporation, fusion method. Solid dispersions are two-component systems which consist of a hydrophilic carrier in which the drug is incorporated. The drug is incorporated in the hydrophilic carrier which may be molecularly dispersed or may occur as Nano crystals or amorphous nanoparticles. Solid dispersions have been explored as potential delivery systems for many poorly water soluble drugs such as Griseofulvin, Indomethacin and Oxazepam. The ability of solid dispersions to afford drug release as fine, dispersed particles has resulted in improvements in dissolution rates of poorly water soluble drugs which have also been reflected in increases in oral bioavailability. [2,3] The enhancement in dissolution rate of the drug can be ascribed to

A. An increasing solubility of the drug because of its amorphous state or small particle size (Kelvin's law) [4-6]
B. An increased surface area available for drug by Conversion of the physicochemical state of the drug, e.g. from crystalline to amorphous. [7]
C. An improvement in wetting of the drug caused by the hydrophilic carrier. [8]

Diacerein is an anti-inflammatory, analgesic drug used in treatment rheumatoid arthritis, osteoarthritis. Diacerein aqueous solubility is 7 to 10 µg /ml at pH 7.0 at 40 ^{o}C. After oral dosing the peak plasma concentration is reported 2.2 hours with even distribution *in vivo* and volume of distribution of 13.2 lit. in humans. Low bio avail ability of Diacerein may be due to its larger volume of distribution and lipophilic nature responsible for low aqueous solubility. The poor solubility and wettability of Diacerein give rise to difficulties in Pharmaceutical formulation meant for oral or parental use, which may lead to variation in bioavailability. [9]

Several highly soluble substances can be use to accelerate the release of poorly hydrosoluble drugs. In our case Sorbitol selected as vehicle for preparation of Diacerein solid dispersions. It has been chosen on the basis of its low toxicity, high aqueous solubility and physiological acceptance. It is hexahydric alcohol isomer of mannitol, white odourless crystalline powder that possess exceptionally high thermal stability (108-110 ^{o}C) and that can be heated up to 250 ^{o}C without any degradation. [8]

MATERIALS AND METHODS

Materials

Diacerein obtained as gift sample from Glenmark research Centre Sinnar. Sorbitol, potassium Dihydrogen phosphate, Sodium hydroxide, ethanol, ethyl acetate, 2- Propranolol are of analytical grade.

Preparation of solid dispersions

A) Physical mixture

Physical mixtures, Diacerein and sorbitol in 1:0.5, 1:1.5,1:2.5 W/W ratios, were prepared by homogeneous blending of previously sieved and weighed quantities in mortar and pestle. The physical mixtures were subsequently stored at room temperature in desiccator over anhydrous $CaCl_2$ until use. [10]

B) Solvent evaporation

Three formulation of solid dispersion containing Diacerein and sorbitol in 1:0.5, 1:1.5, 1: 2.5 w/w ratios were prepared by solvent evaporation method. The drug and carrier were weighed accordingly to the specified drug : carrier ratio. Diacerein and sorbitol were dissolved in ethanol in porcelain dish .The solution was stirred till slurry was formed and allowed to stand overnight. The solvent removed at 60°C until the solid dispersion get dried, pulverized, passed through 44 sieve to get uniform sized particles and stored in a desiccator over anhydrous $CaCl_2$. [11-12]

ESTIMATION OF DIACEREIN

Diacerein was estimated at 258 nm using double bean UV-Visible spectrophotometer (Shimadzu UV-1650). Standard calibration curve of Diacerein was plotted in pH 6.8 phosphate buffer in concentration range 2, 4, 6, 8, 10µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R) -0.9998. The graph obeyed Beer-Lambert's law in the concentration range. [13]

Table 1: Formulation of Diacerein : Sorbitol solid dispersion by different method and different ratio

Sr. no.	Method	Ratio
1	Physical mixture method	1:0.5
2	Physical mixture method	1:1.5
3	Physical mixture method	1:2.5
4	Solvent evaporation method	1 : 0.5
5	Solvent evaporation method	1 : 1.5
6	Solvent evaporation method	1 : 2.5

EVALUATION OF SOLID DISPERSIONS

A) Phase solubility studies

Phase solubility studies were performed according to the method reported by Higuchi and Connors. Solubility studies on pure drug, physical mixture and solid dispersions were conducted in thermostatic shaker bath (Labline, Chennai) for 48 hrs at 37° C ± 5° C, finally the solutions were filtered using whatmann filter paper, suitably diluted and absorbance measured spectrophotometrically (Shimadzu UV-1650), at 258 nm. [2]

All experiments were repeated in triplicate.

B) Assay of the drug content

Known amounts of the drug–Sorbitol binary systems (solvent evaporation and physical mixture) were dissolved in pH 6.8 phosphate buffers and then the drug content was evaluated spectrophotometrically at 258nm, value at which the absorbance of the sorbitol is negligible. The experimental value was the average of three replicates. (Shimadzu UV- 1650). [13]

C) *In-vitro* release

Pure drug and solid dispersion equivalent to 50mg filled in suitable capsule. Dissolution studies of diacerein were performed in 900 ml of pH 6.8 Phosphate buffer solution using the USP I apparatus (basket method) with speed of 50 rpm. At appropriate time intervals, aliquots of 5ml were withdrawn. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The 1 ml of solution was taken and diluted upto 10 ml with phosphate buffer (pH 6.8) and filtered using Whatman filter paper and measured spectrophotometrically (Shimadzu UV-1650) at λ = 258 nm. Experiments were carried out in triplicate. [14, 15]

D) Wettability study

Pure drug and solid dispersion, selected on basis of highest percent dissolution rate, equivalent to 50 mg of diacerein weighed and placed in a Buchner funnel. On the surface of the powder, Methylene blue powder (50mg) was layered uniformly and plunged into a beaker containing water at the same level as that of powder. The time required for wetting the methylene blue powder was taken as the wetting time. [16-17]

E) Permeation study

Pure drug and solid dispersions permeation studies were carried out in a Franz diffusion cell using Egg membrane. At pre-determined time intervals drug diffusion through the membrane were determined spectrophotometrically at λ = 258 nm. [18]

F) Thin layer Chromatography

Thin layer Chromatography analysis was carried out using silica gel GF 254 (0.2 mm) glass plates with a solvent system of 2- Propranolol : ethyl acetate : water (60:30:2 v/v/v) as a mobile phase to study any interaction between the drug and sorbitol. Spots were visualized by exposure to iodine vapors. The *R*f values of pure drug and binary systems were calculated. [19]

G) FTIR spectroscopy

IR spectrum of Pure drug and its solid dispersions, containing drug and Sorbitol in 1:0.5, 1:1.5 and 1:2.5 W/W ratios , were recorded using Jasco FT/IR 4100,infrared spectrophotometer in scanning range 450 to 4000 cm^{-1}, by KBr disc method. [20, 21]

H) Differential Scanning Calorimetric analy*sis*

A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curve of DIA solid dispersions and its physical mixtures representing the rates of heat uptake. About 10 mg of sample was weighed in a standard open aluminum pans, were scanned from 20-300 °C, at a heating rate of 10 °C/minute while being purged with dry nitrogen. [22, 23]

Results and Discussion

A) Solubility studies

The solubility of different concentrations of drug and sorbitol was observed. The solid dispersion prepared with sorbitol 1: 2.5 presented higher dissolution concentration as compared with other formulations 1: 0.5, 1: 1.5. When sorbitol concentration was increased, the solubility was also increased in solvent evaporation and physical mixture method. But maximum solubility was in solvent

evaporation method, 1: 2.5 (drug: sorbitol) (276µg /ml) when compared with pure drug (10µg /ml)

Table 2: Saturation solubility and Phase solubility study of diacerein

Method	1: 0.5 (conc. µg/ml) %w/w	1: 1.5 (conc. µg/ml) % w/w	1 : 2.5 (conc. µg/ml) % w/w
Physical mixture	200	230	245
Solvent evaporation method	220	235	260

B) Drug content analysis

The drug content of different concentrations of drug and sorbitol was estimated spectrophotometrically at 258 nm.

Table 3: % Drug content of Physical Mixture and Solid Dispersion

Method	1: 0.5 Drug: sorbitol (66.66 % w/w)	1: 1.5 drug: sorbitol (40 % w/w)	1 : 2.5 drug: sorbitol (28.5 % w/w)
Physical mixture	97.6	98.9	98.6
Solvent evaporation method	99.5	98.5	99.2

C) In vitro Release studies

The dissolution parameters of the samples and profiles compared with the pure drug is shown in table 4, 5 and Fig.1, 2 respectively.

Table 4: Comparison of dissolution study between drug and solid dispersion (Physical mixture Method)

Time(min)	Cumulative drug release (%) Drug	Drug: sorbitol 1:0.5	Drug: sorbitol 1:1.5	Drug: sorbitol 1: 2.5
5	2	2,8	3.1	3.9
10	6.8	9.2	12.2	18.7
20	12.17	26.2	28	32.4
30	25.2	34.3	42	48
40	34.3	47.8	59	64
50	41.2	62	74	78
60	47	76	82	87

Table 5: Comparison of dissolution study between drug and solid dispersion (Solvent evaporation method)

Time(min)	Drug	Drug:sorbitol 1:0.5	Drug:sorbitol 1:1.5	Drug:sorbitol 1: 2.5
5	2	3.2	3.7	4.6
10	6.8	10.8	22.4	32.4
20	1217	37.8	43.7	68.4
30	25.2	48.6	56.73	81.0
40	34.3	52.2	68.6	90.0
50	41.2	68,8	76	95.4
60	47	81	88	96.9

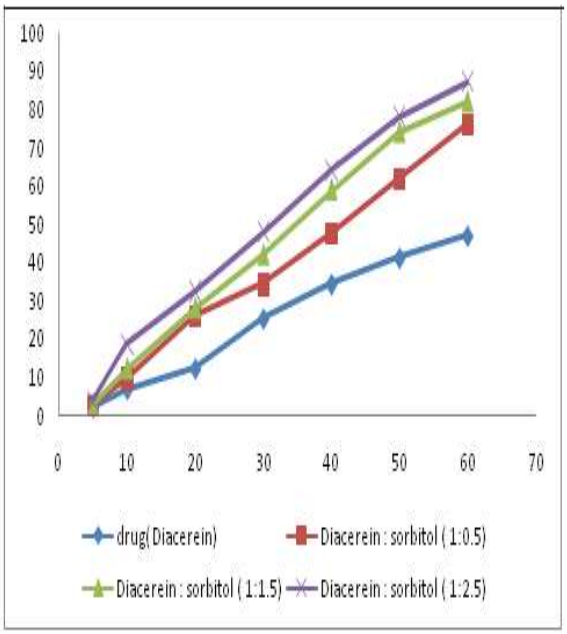

Fig. 1: Comparision of dissolution study between drug and solid dispersion (Physical mixture method)

D) Wettability studies

The wetting time of the pure drug was found to be 85 min which clearly indicates its poor wettability. The wetting time of the selected Samples was found to be much less and the water absorption ratio was higher than for the pure drug. This behavior may be attributed to an increased wettability due to presence of hydrophilic carriers in the samples.

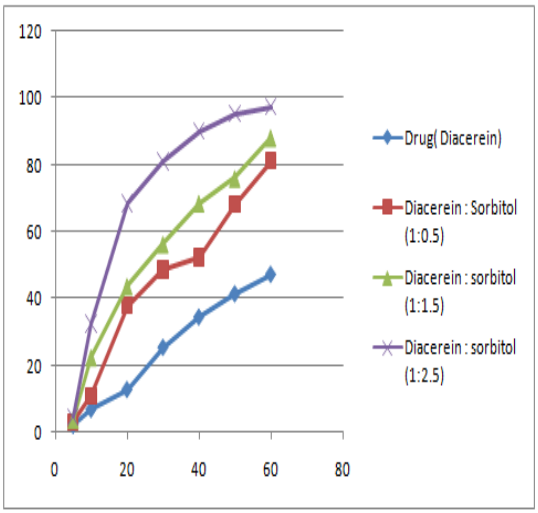

Fig.2: Comparison of dissolution study between drug and solid dispersion (Solvent evaporation method)

E) Permeation studies

It was noted that, the amount of drug that permeated through the membranes was found to be higher than the pure drug ($p>0.05$) these findings can be considered as being evidence for an increased release rate of Diacerein from solid dispersions

F) Thin layer Chromatography

The TLC study indicated *R*f values from 0.62-0.66 for all binary systems, which were almost identical to the *R*f value for pure diacerein. This indicated that there was no chemical interaction between diacerein and sorbitol.

Table 6: Evaluation parameter for formulation

Formulation	Wettability (Min) (Buchner funnel method)	Permeability (mg/ml/hr)	Rf value (TLC)
Pure Drug	85	0.025	0.62
Physical Mixture	57	0.051	0.63
Solvent Evaporation	41	0.061	0.66

G) **FTIR**

FTIR investigations are mainly carried out to examine a Molecular change in the drug due to its interaction with Excipients (carrier)

FTIR spectra of Diacerein, Sorbitol, and Solid Dispersion are shown in Figure 3-7. The principal absorption peaks of Diacerein, were observed at 3,300 cm−1 (O-H, stretch, broad, COOH), 3,050 cm−1 (C-H, stretch, aromatic), 2,955cm−1 (C-H, stretch, aliphatic, sym), 1,770 cm−1 (C=O, stretch, ester), 1,678 cm−1 (C=O, stretch, COOH), 1,693 cm−1 (C=O, stretch, ketone), 1,593 cm−1 (C=C, stretch, aromatic), 1,450 cm−1 (C-O, stretch, COOH), 1,078 cm−1 (C-O, stretch, ester), 760 cm−1 (m substituted benzene), and 704 cm−1 (benzene)

The FTIR spectrum of Sorbitol is characterized by principal absorption peaks at 3333.36 cm−1 (O-H, stretch, broad2930.32 cm−1 (C-H, stretch, aliphatic),1308 cm−1 (in-plane O-H bend) and 1095 cm−1 (C-O stretch) , which consistently appeared in all of the binary systems of diacerein.

All Solid Dispersion systems displayed frequency shifts or the disappearance of characteristic IR bands of either the drug or polymer, indicating alterations in the drug or polymer environment.

There is no effect on principle absorption peaks of diacerein at 3,300, 3,050, 1,678 and 2,955 cm−1 disappeared for all Solid Dispersion. The peak of Sorbitol at 3,485 cm−1 shifted to a lower frequency at 3,445, 3,447, and 3,433 cm−1 in 1:0.5, 1:1.5, and 1:2.5 Solid Dispersion, respectively, revealing its involvement in hydrogen bonding with oxygen in the drug. The peak of Sorbitol at 2,884 cm−1 also shifted to 2,873, 2,886, and 2,872 cm−1 in 1:0.5, 1:1.5, and 1:2.5 Solid Dispersion, respectively, indicating strong physical interaction between the Sorbitol and drug. None of the binary systems of Diacerein-Sorbitol showed any new peaks, indicating the absence of chemical bond formation in those binary systems [24, 25, 26].

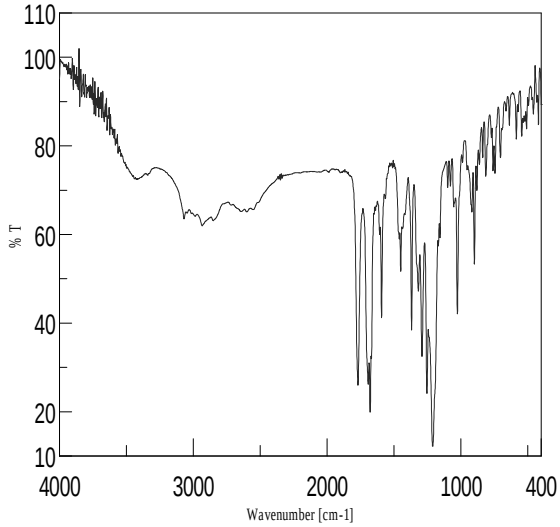

Fig 3: FTIR of Diacerine

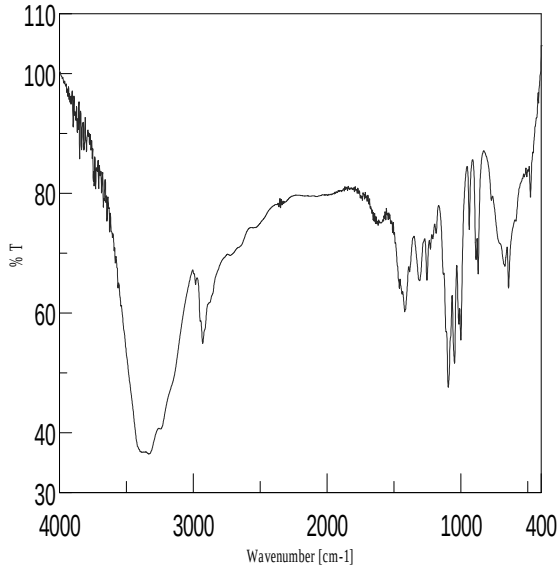

Fig 4: FTIR of sorbitol

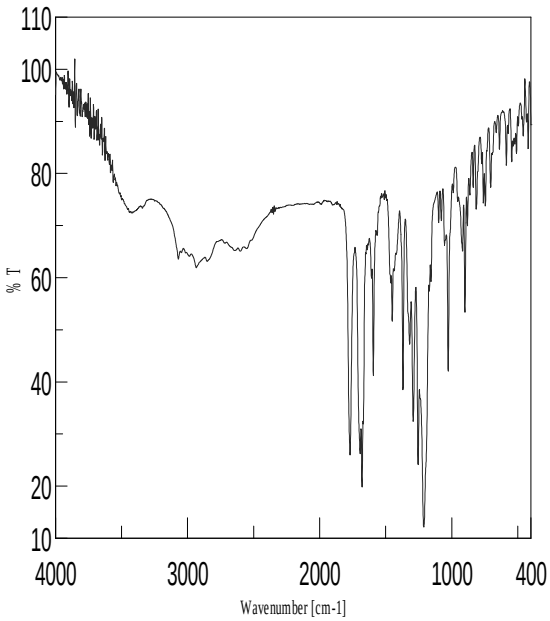

Fig 5: FTIR of Solid dispersion (1:0.5)

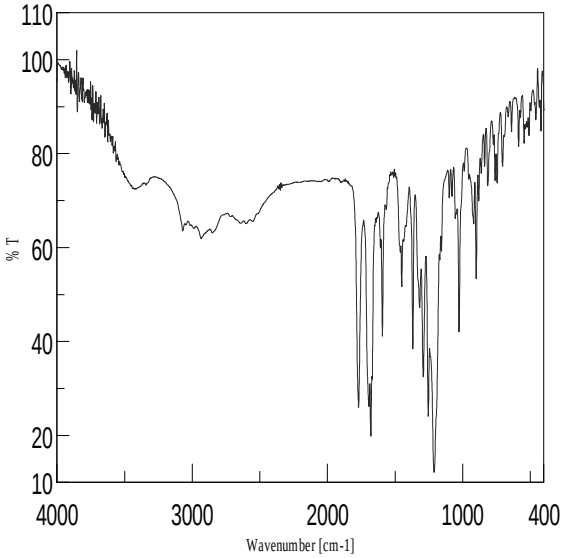

Fig 6: FTIR of solid Dispersion (1:1.5)

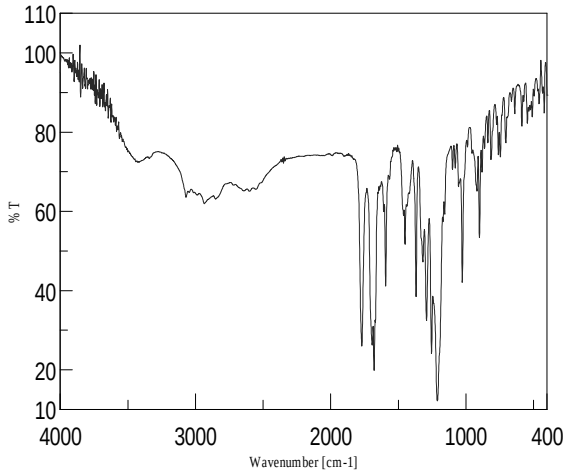

Fig 7: FTIR of solid dispersion (1:2.5)

H) DSC

DSC thermogram of Diacerein and its corresponding binary systems with Sorbitol are shown in Figure 8. As shown in the figure, Diacerein displayed a sharp endothermic T_{max} of 255.12°C, corresponding to the melting point of the crystalline form of Diacerein. In contrast, Sorbitol showed a sharp endothermic at 114.24°C, indicating the melting point of the polymer. A very broad endothermic 252.1°C was observed in the DSC thermogram of 1:0.5 solid dispersion, indicating the presence of some traces of crystalline Diacerein. A significant reduction in the intensity of the sharp peak of Diacerein was noted in 1:1.5 (248.4°C) and 1:2.5 (240.5°C) Solid dispersion. With dispersions, peak temperatures shifted to lower temperatures than with the drug alone, indicating a loss of the characteristic features of Diacerein peaks in these dispersions. This phenomenon might be attributed to complete molecular dispersion and possibly indicate the presence of an amorphous diacerein in these binary systems. In all of the formulations, a decreased melting point peak for diacerein was observed, and this might be attributed to solid solid phase transition or the transfer of heat energy (from sorbitol to drug molecules) released after initial melting of the polymer. The peak for the polymer in all of the binary systems consistently appeared in the range of 112-116 ^{o}C, which indicated the absence of any chemical interaction between the drug and polymer during the thermal process.

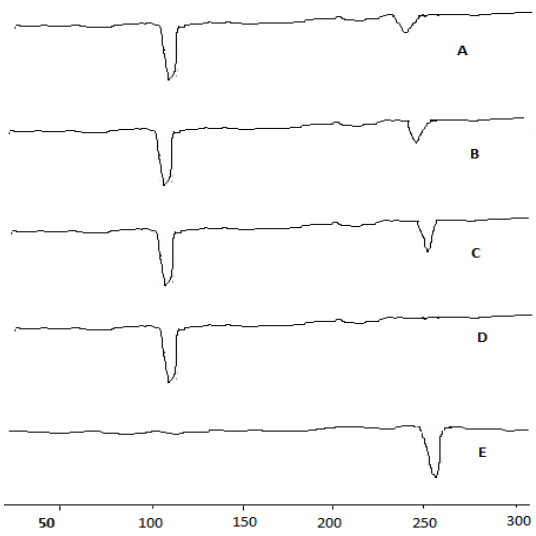

Fig 8: DSC Thermogram of diacerein: sorbitol system A) 1:2.5, (B) 1:1.5, (C) 1:0.5 (D) Sobitol and (E) Diacerein

Conclusion

The study shows that dissolution rate of diacerien can be enhanced to great extent by solid dispersion techniques due to wetting and solubilization phenomena. Analytical method of IR spectrum, DSC and TLC was confirmed the drug carrier interaction or complex and showed that the drug was not degraded. Permeation study shows increase in release rate of drug by solid dispersion method. Increase in dissolution rate with increase in carrier (sorbitol) concentration. A maximum increase in dissolution rates was obtained with the ratio of 1: 2.5 (diacerein : sorbitol) when compared with that of the pure drug and other complexes. The solvent evaporation method is superior than physical mixture method of solid dispersion. Therefore, it can be concluded that the aqueous solubility of poorly soluble drugs (diacerein) can be significantly improved by utilizing the solid dispersion technique, relatively easily.

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