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Research Article

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Improvement of dissolution rate of diacerein using liquisolid technique

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ABSTRACT

The aim of this study to investigate the use of liquisolid technique in improving the dissolution profiles of diacerein in a solid dosage form. This study was designed to improve the dissolution rate of diacerein using liquisolid technique. The liquisolid systems were formulated with PEG 400 as non-volatile liquid vehicle at three different drug concentrations, 40, 45 and 50 % W/W using two different carrier/coating ratio (5 and 10). The empirical method as introduced by spireas and Bolton was applied (1999) strictly to calculate the amounts of carrier and coating materials required to prepare diacerein liquisolid capsules. Quality control tests i.e. disintegration test, drug content and in vitro dissolution test were performed to evaluate each batch of prepared capsules. In vitro dissolution profiles of the liquisolid formulation were studied and compared with conventional formulation. DSC, FTIR and XRD were used to investigate physicochemical interaction between diacerein and the excipients. It was found that liquisolid capsules formulated with PEG 400 at lower drug concentration (40% W/W) produced high dissolution profile than conventional formulation. DSC and XRD revealed that drug particles in liquisolid formulations were completely solubilized and available in the molecularly dispersed state. In conclusion, the liquid vehicle used within diacerein liquisolid formulations enhanced drug dissolution rate.

Keywords: Diacerein, Liquisolid, PEG 400, Liquisolid capsule, Dissolution

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INTRODUCTION

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs [1]. One of the most promising approaches for release enhancement is the liquisolid technique [2].

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics. Liquisolid solid system is acceptably flowing and compressible powdered forms of liquid medications [3-9].

Due to the rapidly aging population today, osteoarthritis is now considered a major public health issue in most developed countries. Up to 10% of the world population suffers from osteoarthritis, and it has been estimated that more than 50% of those aged over 50 years are affected [10]. Diacerein, a purified compound with anthraquinonic structure, has been shown to inhibit *in vitro* and *in vivo* the production and activity of IL-1 and the secretion of metalloproteases, without affecting prostaglandin synthesis. In several animal models, diacerein has shown beneficial effects on cartilage by preventing or reducing the macroscopic and microscopic lesions of the joint tissue. Further, in several clinical trials of 2–6 months duration, diacerein significantly reduced pain and functional impairment in patients with hip or knee osteoarthritis compared with placebo [11]. Diacerein is very sparingly soluble in water (0.01 mg/ml). The poor solubility and wettability of diacerein give rise to difficulties in pharmaceutical formulation meant for oral or parenteral use, which may lead to variation in bioavailability [12]. The poor aqueous solubility and hence limited dissolution of diacerein mean that only 35-56% of the drug reaches the systemic circulation [13].

Poor bioavailability of a drug often results in a limited therapeutic response. Therefore, the aim of the current research work is to improve the dissolution rate of diacerein via liquisolid technique and consequently improvement of the bioavailability.

EXPERIMENTAL SECTION

Diacerein was kindly gifted by AMI life sciences, Gujarat, Avicel PH 102, Aerosil was gifted by (FMC biopolymers, USA), Propylene glycol (Loba chemie), Kolliphor EL (BASF - Germany), Tween 80 (RFCL Ltd), PEG 400 (Merck), Sodium starch glycolate (Rouquette -Germany), Magnesium stearate (Otto Kemi), Talc (SD fine chem).

Saturation solubility studies

The solubility of diacerein in water, phosphate buffer pH 6.8 with 0.03% SLS and four liquid vehicles attempted to prepare the liquisolid systems, namely tween 80, kolliphor EL, propylene glycol and PEG 400 were studied by preparing saturated solutions of the drug in these solvents and analyzing their drug content spectrophotometrically. Diacerein was mixed in 5ml screw capped vials with such amounts of each of the above solvents in order to produce systems containing an excess of drug. The mixtures were shaken on a mechanical shaker for 24 hours and then settled for another 2 hours. The screw capped vials were centrifuged at 2500 rpm for 15 min and kept for further settling of undissolved particles thereby obtaining a clear supernatant. After centrifugation, accurately measured quantities of the filtered supernatant solutions were further diluted with phosphate buffer pH 6.8 with 0.03% SLS and analyzed spectrophotometrically at 258 nm for their drug content.

Preparation of diacerein liquisolid formulation and conventional capsules [14]

Diacerein liquisolid formulation were prepared at three different drug concentration viz. 40, 45 and 50% (w/w) in PEG 400 containing Avicel PH 102 as carrier and aerosil as coating material at two different carrier/coat ratio (R) of 5 and 10. The drug liquid system was prepared by mixing the previously weighed drug (50mg/capsule) and PEG 400 in beaker, and then the dispersion was sonicated until a homogenous mixture was formed. The resulting liquid medication was incorporated onto the calculated amount of the carrier material Avicel PH 102 (Q) with mixing. The resulting slurry was then blended with the calculated amount of the coating material aerosil (q) using standard mixing process according to spireas [15, 16] to form simple mixture. Conventional capsules of diacerein also prepared by the procedure as mentioned above. The resultant mixture was encapsulated in the empty gelatin capsule (size 0). The composition of each formulation is demonstrated in Table 1.

Table 1: Formulation of liquisolid systems

Formulation code	Drug concentration in liquid medication (% w/w)	R	L_f	Drug	Liquid Vehicle (mg)	Avicel PH 102 (mg)	Aerosil 200 (mg)	Unit dose (mg)
DA1	40	5	0.657	50	75	190.26	38.05	374.70
DA2	40	10	0.331	50	75	377.64	37.76	573.12
DA3	45	5	0.657	50	61.11	169.12	33.82	333.06
DA4	45	10	0.331	50	61.11	335.68	33.57	509.18
DA5	50	5	0.657	50	50	152.21	30.44	299.76
DA6	50	10	0.331	50	50	302.11	30.21	458.49
Conventional capsule	-	10	-	50	-	377.64	37.76	498.11

Precompresssion studies of prepared liquisolid powder systems

Angle of repose (θ):

The frictional forces in a loose powder can be measured by the angle of repose. It is defined as maximum angle possible between the freely sliding surface of a pile of powder and the horizontal plane.

$$\theta = \tan^{-1}(h/r) \quad (1)$$

Where h = height of pile, r = radius of the base of the pile, θ = angle of repose.

Compressibility index (CI %):

The compressibility index of the powder blend was determined by carr's compressibility index. The formula for carr's index is as follows

$$\text{Carr's index (\%)} = [(\text{Tapped density} - \text{Bulk density}) \times 100]/ \text{Tapped density} \quad (2)$$

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula [17]

$$\text{Hausner's ratio} = \text{Tapped density}/ \text{Bulk density} \quad (3)$$

Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy helps to determine any chemical interaction between drug and excipients used in the formulation. The FTIR spectra for diacerein, and physical mixtures were obtained using JASCO FTIR- 4100 spectrophotometer in the range of 4000-400 cm^{-1}.

Differential scanning calorimetry (DSC)

It was performed using differential scanning calorimeter (Model NETZSCHSTA 449F3 STA449F3A-1100-M) in order to assess the thermotropic properties and thermal behaviours of the drug (Diacerein), and optimized liquisolid system prepared. Samples of diacerein (3.022 mg) and optimized formulation (3.88 mg) were weighed and transferred into the equipment for analysis in sealed hermetically aluminium pans. The instrument was calibrated with indium before running the samples. Thermal behavior of the samples was investigated at a scanning rate 10.0 K/min, from 30° C to 500° C.

X-ray diffraction studies (XRD)

X-ray diffraction patterns were determined for diacerein, Avicel PH 102, Aerosil and liquisolid system prepared. The X-ray powder diffraction was obtained using PAN ANALYTICAL x-ray diffractometer. The samples were exposed to Cu-Kα radiation (45 kV × 30 mA), the results were then obtained as peak height (intensity) versus 2θ.

Post Compression Parameters

Disintegration time

The disintegration time of tablet was determined using disintegration apparatus in phosphate buffer pH 6.8 with 0.03% SLS as disintegration medium maintained at 37^0C. When all the six capsules are completely disintegrated, the time was noted.

Drug content

Drug content was calculated by dissolving liquisolid powders equivalent to 50mg drug into 50 ml measuring cylinder containing phosphate buffer pH 6.8 with 0.03% of SLS and then sonicated for 15 min followed by filtered through the whatman filter paper. It was then diluted suitably with phosphate buffer pH 6.8 with 0.03% SLS. The absorbance of both standard and sample preparation after appropriate dilution were measured in UV spectrophotometer at 258 nm using phosphate buffer pH 6.8 with 0.03% SLS.

***In vitro* drug release**

The dissolution study of different formulations was determined using a USP- type I (basket type) apparatus under sink condition. The dissolution medium was 900 ml phosphate buffer pH 6.8 with 0.03% SLS at 37 ± 0.5°C at 50 rpm, to simulate *in vivo* conditions. The formulation prepared was subjected to dissolution tests for 1 hr. Sample

(5ml) was withdrawn at predetermined time intervals, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. The sample was suitably diluted with phosphate buffer pH 6.8 with 0.03% SLS and drug content in the dissolution sample was determined by UV spectrophotometer at 258nm.

RESULTS AND DISCUSSION

Solubility studies

Solubility data of pure drug diacerein in various liquid vehicles is shown in Table 2. Diacerein appears to be more soluble in PEG 400 than other vehicles. The solubility is an important tool in liquisolid systems, as higher solubility of drug in liquid vehicle can lead to higher dissolution rates since the drug will be more molecularly dispersed and more surface of drug will be exposed to the dissolution media. Solubility of diacerein was significantly increased in presence of PEG 400 i.e. 44.325 mg/ml. As shown in Fig. 1 the saturation solubility of diacerein increases in the order of water < Phosphate buffer pH 6.8 with 0.03% SLS < Tween 80 < Kolliphor EL < PEG 400. So PEG 400 was selected as a non-volatile solvent in preparation of liquisolid system.

Table 2: Solubility data of diacerein in various liquid vehicles

Solvent	Solubility (mg/ml)
Water	0.2928
Phosphate buffer pH 6.8 + 0.03% SLS	1.5345
Kolliphor EL	12.180
Tween 80	3.783
PEG 400	44.325
PG	2.031

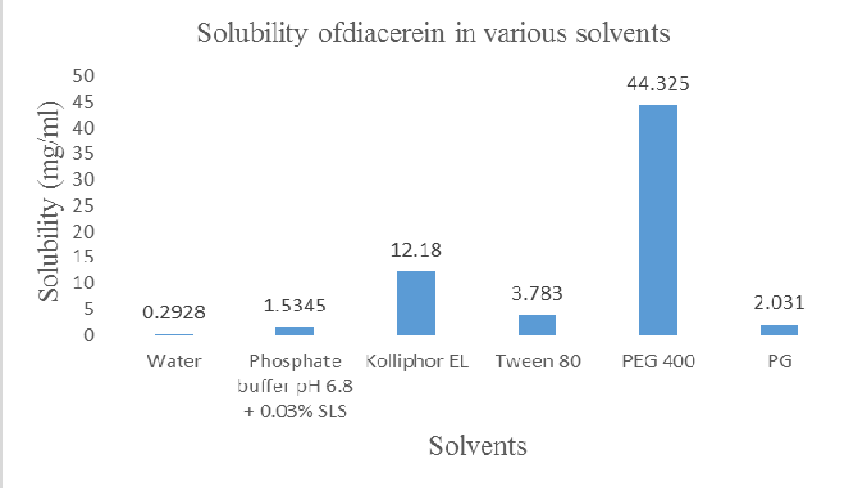


Fig. 1 Solubility of diacerein in various Solvents

Precompression studies

Powder flow properties are crucial in handling and processing operations such as flow from hopper confirms uniformity of both capsule weight and drug content.

Table 3: Flow parameters of liquisolid formulation

Formulation code	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
DA1	25.94	14.81	1.17
DA2	24.44	14.29	1.11
DA3	29.76	12.50	1.14
DA4	26.02	15.79	1.19
DA5	27.76	22.22	1.29
DA6	25.20	6.67	1.07

The flow properties of the granules are vital for the performance of the capsules. Hence the flow the properties of the liquisolid powders were analysed before filling into the empty gelatin capsules. The powder flowability can be measured by evaluating parameters such as the angle of repose, compressibility index and hausner's ratio. The results of various flow parameters are shown in Table 3.Carr's index (CI %) is commonly used parameter for evaluation of powder flow properties, hence reflecting the magnitude of interparticulate interactions within the powder mass. Generally, CI below 15% indicates good flow, whereas values above 25% suggest poor flowability [18]. The flow properties of the prepared liquisolid powders were evaluated using CI% and the results for DA1, DA2, DA3, DA4, DA5 and DA6 were 14.81%, 14.29%, 12.50%, 15.79%, 22.22% and 6.67%, respectively, all have CI below 25%, which indicate adequate flow properties. The powder has a good flowability when the hausner's ratio is lower than 1.25, while it indicates poor flowability when the value exceeds 1.25. The results obtained for evaluation of hausner's ratio is given in the Table 3. Except DA5 remaining formulae shows within the aforementioned range. In general angle of repose is characteristic of the internal frictional forces of the particles. Angle of repose will be high if the particles are cohesive. Values of angle of repose $\leq 30°$ indicate free flow and angles $\geq 40°$ indicate poor flow [19]. Diacerein liquisolid powders (DA2-DA6) showed angle of repose values are within the $\leq 30°$ hence all formulations shows a good flow property.

Post compression studies

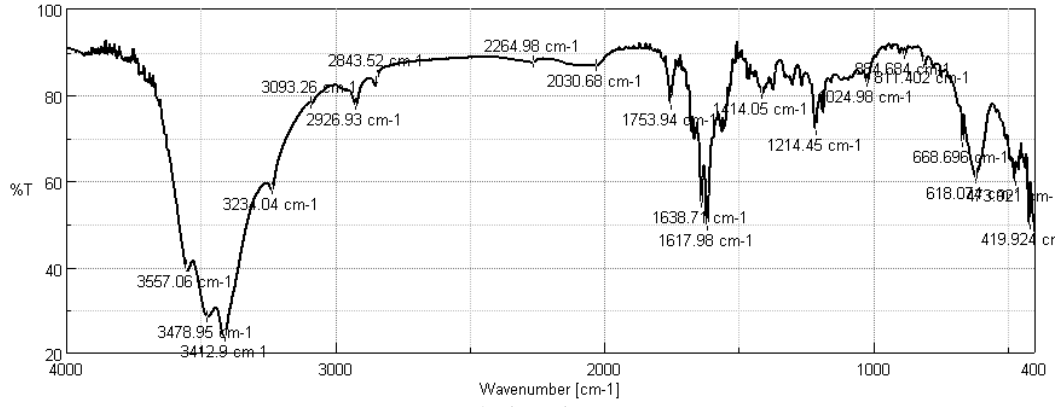
The disintegration time test revealed that the all liquisolid formulae disintegrated in less than 5min and the values ranged between 125.40 min to 208.80 min intended for immediate drug release. Drug content values of all liquisolid formulae were ranged between 98.12 – 99.46% (Table .4).

Table 4: Evaluation of post-compression parameters of diacerein formulations

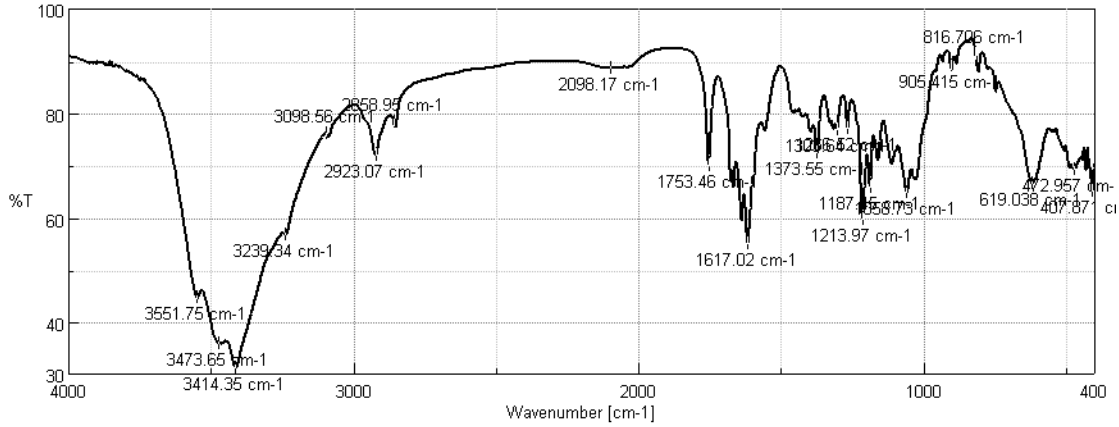
Formulation code	Disintegration time (sec)	Drug content (%)
DA1	128.04	98.12
DA2	208.80	99.46
DA3	125.40	99.38
DA4	133.20	98.57
DA5	145.68	99.22
DA6	136.80	98.91

Fourier transform infrared spectroscopy (FTIR)

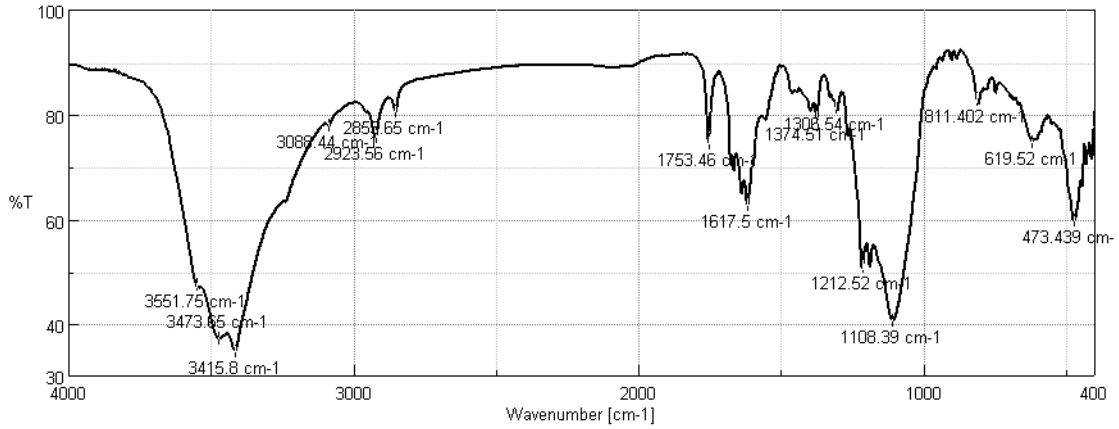
Samples of diacerein, Avicel PH 102, Aerosil, sodium starch glycolate, magnesium stearate, and talc as physical mixtures were subjected to FTIR spectroscopic analysis and their spectra are shown in Fig. 2. FTIR analyses provide information on physicochemical properties of substances with respect to compatibility [20]. IR spectrum of diacerein exhibits characteristic peaks at 2926 cm $^{-1}$ (asymmetric CH_2 stretching), 2843 cm $^{-1}$ (symmetric CH_2 stretching), 1753 cm $^{-1}$ C=O (stretching of ester), 1638 cm $^{-1}$ C=O (stretching of ketone), 1413 cm $^{-1}$ (C-O-H in plane bend), 3053 cm $^{-1}$ (C-H aromatic stretching), 3557 cm $^{-1}$ [OH stretching phenolic (ketoenol)] 3300-2500 cm $^{-1}$ (OH stretching of COOH). All characteristic relevant peaks are observed in all formulation. It clearly indicates that there was no interaction found between diacerein with other excipients.



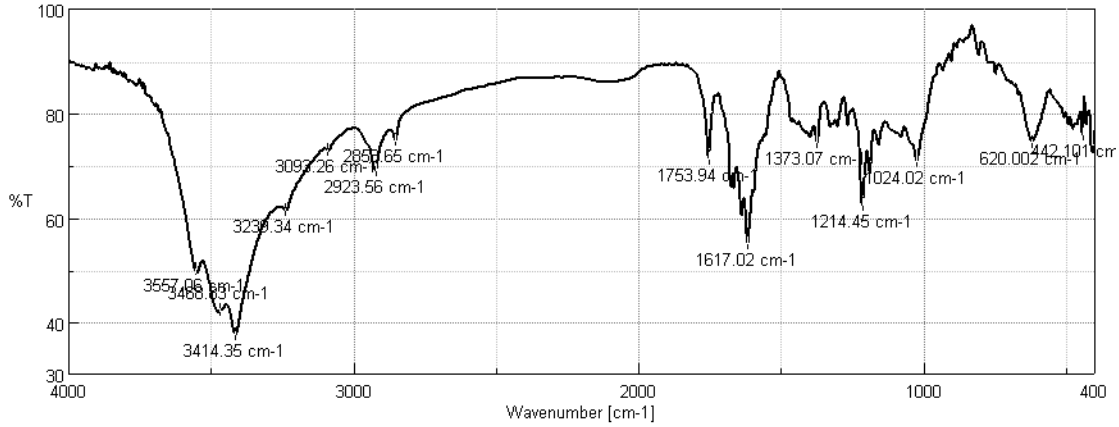
a) Diacerein



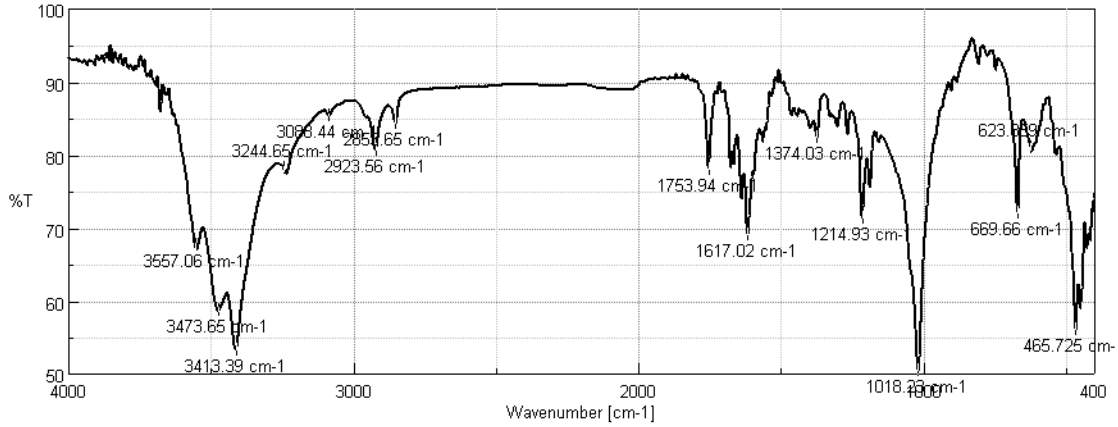
b) Diacerein with Microcrystalline cellulose PH102



C) Diacerein with Aerosil



d) Diacerein with sodium starch glycolate

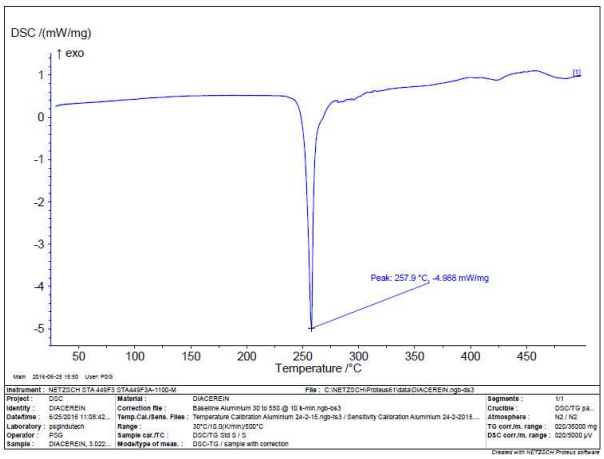


e) Diacerein with talc

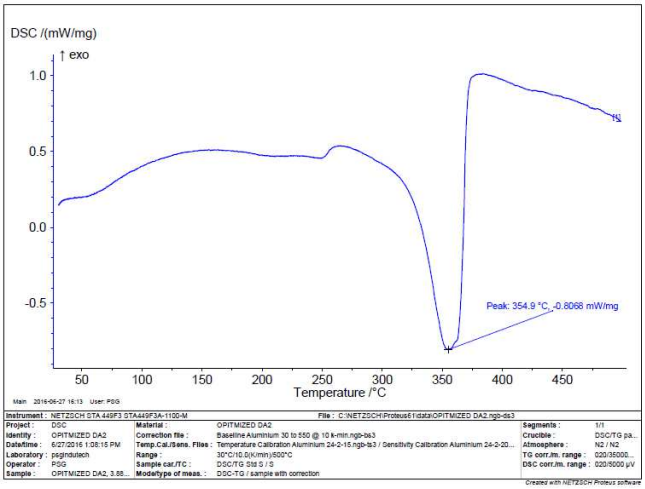
Fig. 2 FTIR spectra of Diacerein (a), Physical mixtures – Diacerein with Microcrystalline cellulose PH102 (b), Physical mixtures - Diacerein with Aerosil (c), Physical mixtures- Diacerein with sodium starch glycolate (d) and Physical mixtures - Diacerein with talc (e)

Differential scanning calorimetry (DSC)

The pure Diacerein showed a sharp endothermic crystalline peak at 257.9° C and it indicates the high crystallinity of diacerein. Such sharp endothermic peak signifies that diacerein used was in pure crystalline state. On the other hand, liquisolid system (b) thermogram displayed complete disappearance of characteristic peak of diacerein; a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e. the drug was molecularly dispersed within the liquisolid matrix. Such disappearance of the drug peak in formulation of the liquisolid system was in agreement with Mura et al who declared that the complete suppression of all drug thermal features, undoubtedly indicate the formation of an amorphous solid solution.



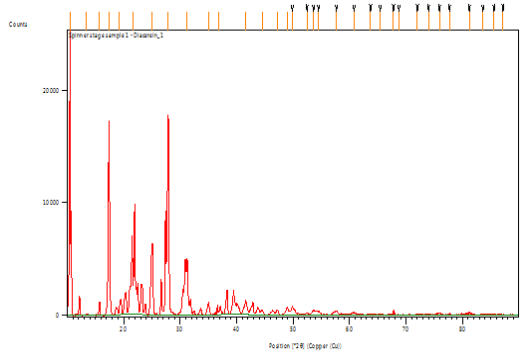
a) DSC thermogram of diacerein



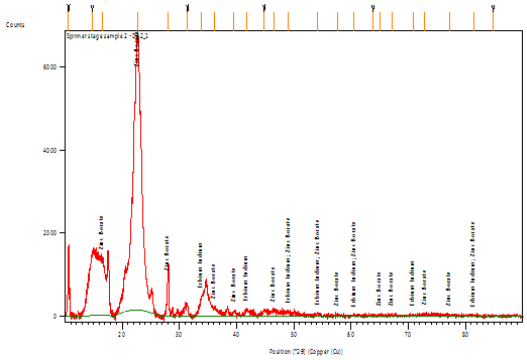
b) DSC thermogram of optimized formulation DA2

Fig. 3 DSC thermogram of diacerein (a), Optimized liquisolid formulation DA2 (b)

X-ray powder diffractometry (XRD)



a. XRD diffractogram of diacerein



b. XRD diffractogram of optimized formulation DA2

Fig. 4 X-ray diffractogram of Diacerein (a) and Optimized liquisolid formulation DA2 (b)

Numerous sharp intense peaks were observed between 4 to 40 theta positions. The characteristic peaks at 4, 6, 14,22,26,28,32,34,36, and 40 C. It indicates the crystallinity of diacerein. In the formulation spectra it can be notice that the all the characteristic peaks are found to broadened at the base, number of peaks reduced it clearly indicates that the crystallinity has been reduced in the formulation.

***In vitro* dissolution studies**

The dissolution profiles of the prepared liquisolid systems and the dissolution profile of the diacerein conventional capsules, are presented in Fig. 5, Fig. 6 respectively.

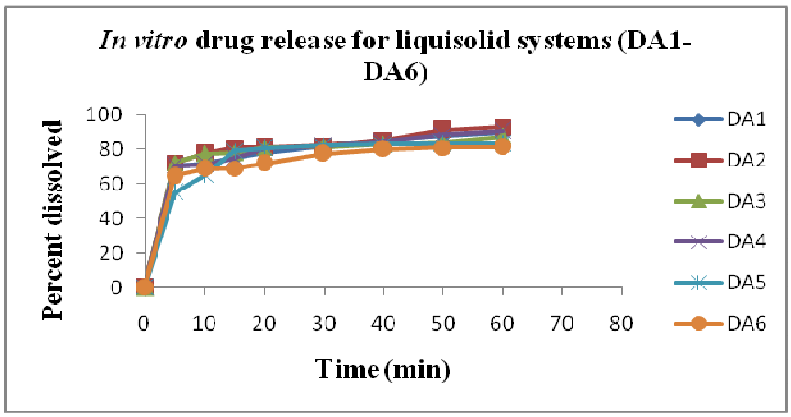


Fig. 5 *In vitro* drug release for liquisolid systems (DA1-DA6)

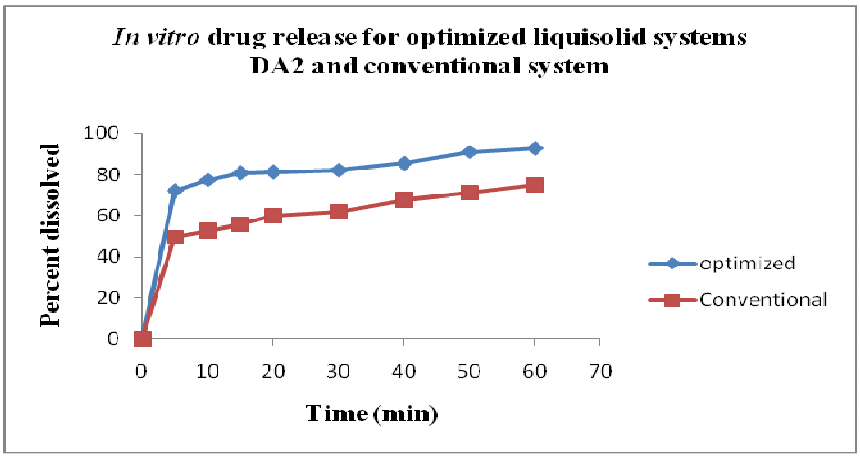


Fig. 6 *In vitro* drug release for optimized liquisolid systems DA2 and conventional system

Table 5: Percentages of diacerein dissolved after 10 min and 10min dissolution rates from the conventional capsules of diacerein and formulations

Formulation code	$Q_{10\%}$	DR (µg/min)
DA1	73.34	1466.80
DA2	77.30	1546
DA3	72.10	1442
DA4	71.07	1421.40
DA5	64.93	1298.60
DA6	68.69	1373.80
Conventional capsule	52.94	1058.80

It was apparent that formula DA2 has the highest dissolution pattern in both the rate and the extent of drug dissolved. The percentage of diacerein dissolved from DA2 reached 92.71% after only 60 min, while conventional formulation had a maximum diacerein content (75.14%) dissolved after 60 min. The percent of drug dissolved from each formula after 10min (Q_{10}) and the drug release (D_R) were taken as a measure of the extent and the rate of drug dissolved from the prepared capsules respectively as presented in Table 5. The results in the table clearly affirm that the liquisolid capsules DA2 had the highest percentage of drug dissolved in 10 min it dissolved 77.30% of its diacerein content during first 10min. As well, it is clear from the table that DA2 had the highest diacerein dissolution

rate of all the formulae. In Fig. 7 shows comparison of the 10 min dissolution rate of optimized liquisolid formulations (DA2) and conventional capsules.

Another formulation parameter that may be optimized is the ratio of carrier to coating material (*R*). An increase in the *R*-value results in an enhanced release rate if microcrystalline cellulose and colloidal silica are used as carrier and coating materials, respectively. Liquisolid compacts with high *R*-values contain high amounts of microcrystalline cellulose, low quantities of colloidal silica, and low liquid/powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release. In contrast, if high amounts of colloidal silica are used, which means that the *R*-value is low, the liquisolid compact is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus decreased release rates [21-22]. Moreover, as colloidal silica is a hydrophobic material high amounts of it can cause retardation of drug release.

Moreover, it was previously established that the higher dissolution rates displayed by liquisolid systems, in comparison with conventional capsules may also imply enhanced oral bioavailability due to increased wetting properties and surface of drug available for dissolution. Therefore, they proved that the liquisolid technique can be promising alternative for the formulation of water insoluble drugs.

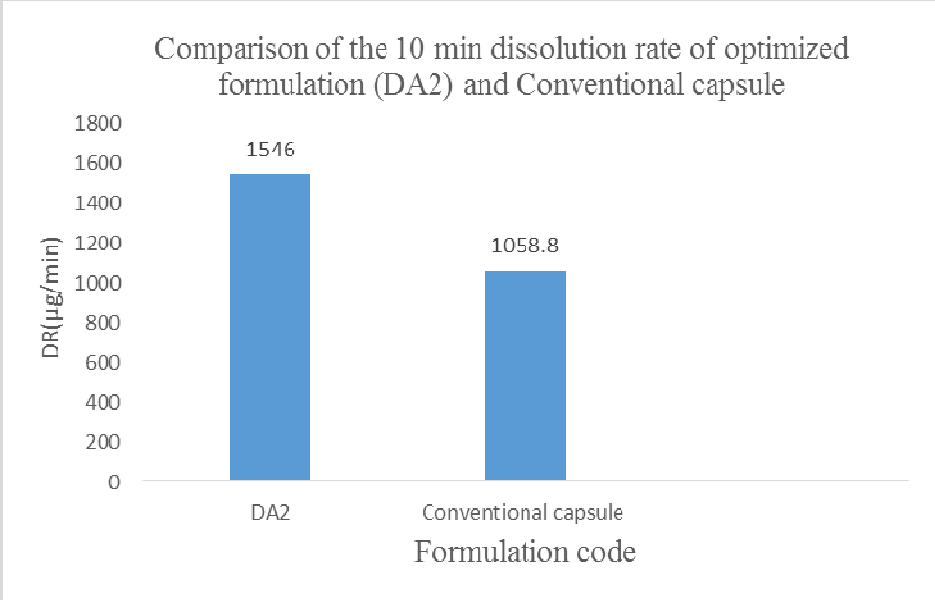


Fig. 7 The comparison of the 10 min dissolution rate of diacerein showed by liquisolid formulations containing PEG 400 (DA 1 and DA 6) and conventional capsules

CONCLUSION

In the present work six formulations of diacerein capsules were successfully developed by using liquisolid technique. Dissolution of diacerein capsules were improved by liquisolid technique thereby to enhances the bioavailability of diacerein. From the results it was concluded that, percent drug release was decreased with increase in the concentrations of diacerein. It has been shown that the solubility of the drug in the liquid medication of the liquisolid compacts is directly proportional to their diacerein dissolution rates.

From the *in-vitro* drug release studies the optimized formulation DA2 showed 92.71% drug release in the 60 min whereas the conventional capsules showed 75.14 in 60 min. Thus the formulation DA2 was considered as better formulations among the other formulations to produce fast release of the diacerein. The percent drug release in 10 min ($Q_{10\%}$) and dissolution rate (DR) for optimized formulation was 77.30% and 1546 µg/min respectively. These were very much higher compared to conventional tablet (52.94 % and 1058.80 µg/min). The improvement in the

dissolution characteristics of liquisolid systems due to changes the properties of diacerein particles in a non-volatile liquid vehicle which in turn increase the wetting properties and surface area of drug particles and hence improve the dissolution profile and might be oral bioavailability.

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