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Research Article

Development and Characterization of Diacerein Solid Dispersion through Spray Drying using a novel amphiphillic polymer Soluplus®

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Abstract

In present study, solid dispersion (SD) of diacerein was prepared to enhance its aqueous solubility and dissolution. The SD was prepared by using novel amphiphillic polymer Soluplus® ® which is polyvinylcaprolactam-polyvinyl acetate-polyethylene glycol grafted copolymer with different drug polymer ratios using spray drying technique. The formulation was characterized using differential scanning calorimetry (DSC), X-ray diffraction (XRD), in-vitro dissolution and in-vivo studies. Intrinsic dissolution rate study was performed to find the impact of increased solubility on the dissolution rate. DSC and XRD analysis demonstrated the conversion of diacerein to amorphous form. The FTIR shows the complexation and there were hydrogen bonding interactions. Diacerein solid dispersions with Soluplus® prepared as 1:8 ratio by spray drying technique showed excellent physicochemical characteristics and was found to be described by dissolution kinetics and was selected as the best formulation in the study. The complexation or dispersion efficiency in Soluplus® was twofold that of PEG-6000. Diacerein SD with Soluplus® (1:8 ratio) showed faster drug release as compared to physical mixture marketed formulation. In-vivo study result indicated that SD exhibited significant increase in area under concentration with time (AUC) and maximum concentration.

Keywords: Solid dispersion, Diacerein, Spray drying, Hydrophilic carriers, Soluplus®

1. Introduction

Formulation development of poorly water soluble drug is a major challenge for the formulation scientists. Various techniques can be used to increase the solubility of these drugs such as use of solubilisers, surfactants, formation of inclusion complex and preparation of solid dispersion (SD). Increase in solubility can improve dissolution and in turn the oral bioavailability as well as the therapeutic efficacy and patient compliance.[1] Sekiguchi and Obi (1961) introduced the use of solid dispersion technology to the pharmaceutical industry as a formulation approach to prepare immediate release (IR) oral dosage forms of poorly water soluble drugs.

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The primary reason to develop a SD is to enhance dissolution and improve the oral bioavailability of a poorly water soluble drug. Solid dispersion formulations are not appropriate where a drug has low bioavailability due to either metabolism or poor permeability.[2]

Diacerein is a new anti-inflammatory analgesics and antipyretic drug, developed specially for the treatment of osteoarthritis which is one of the most prevalent degenerative joint disease. Diacerein acts by inhibiting the production of IL-1by human monocytes.[20] So, diacerein is emerging as a better and safer alternative for the treatment of the osteoarthritis, which provides not only symptomatic treatment but also modifies the pathological process. [3-7]

Soluplus® is a novel amphiphilic polymeric solubilizer, which can be better suited in the solid dispersion technology in improving the solubility of poorly soluble drugs. It is a polyvinylcaprolactam-polyvinyl Acetate-polyethylene glycol grafted copolymer with both hydrophilic and lipophilic properties. This unique structure provides ideal interactions with drugs through hydrogen bonding and leverages stability of the system. It is ideal for formulating novel drug substances.[8]

2. Materials and Methods

Materials

Diacerein was received as a kind gift sample from Ami Life Sciences (Gujarat, India). Soluplus® ® was received as gift sample from BASF, India. all the other chemicals used were of analytical grade.

Methods

Preparation of physical mixture:

The physical mixtures of diacerein and hydrophilic carriers Soluplus® prepared by using different proportions of drug and polymers viz. 1:2, 1:4, 1:8. The powders were blended together by geometric proportion method using glass mortar pestle.

Preparation of spray dried dispersion powder:

Diacerein was added slowly to 6:4 solvent mixtures of N, N-dimethylacetamide (DMA) and Methanol under continuous stirring and stirred well till to get a solution. Soluplus® ® was added to the above drug solution and stirred well till to get a solution. The above dispersion was subjected to spray drying using Lab scale spray dryer (Lab-Ultima) Conditions for spray drying are mentioned in Table. Collected spray dried powder was used for further evaluation.

Characterization of solid dispersion

Physical characterization

The organoleptic properties of the solid dispersion, Flow properties:

Angle of repose

The angle of repose of the powder was determined by 'fixed funnel free cone method'

$$\theta = \tan^{-1}\frac{h}{r} \qquad \text{..... (1.1)}$$

h is height between lower tip of funnel and r was radius of the base of heap formed.[22]

Bulk density [22]

Bulk density (gm / mL) = (Weight of samples in gm/volume occupied by sample)

Tapped density [22]

Tapped density (gm/mL) = (Weight of samples in gm / volume occupied by sample)

Carr's Compressibility Index (CI) **……..**(1.2)

$$\text{Carr's Compressibility Index (CI)} = \frac{\text{TBD - LBD}}{\text{TBD}} \times 1000$$

Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. Hausner's ratio = ……. (1.3)

$$\text{Hausner's ratio} = \frac{\text{Loose bulk density}}{\text{Tapped bulk density}}$$

Determination of the saturation solubility of diacerein solid dispersion

Excess quantities of Diacerein were added into each of 5 ml of phosphate buffer (pH 5.8 and 7.0), 0.1N HCl and distilled water contained in glass vials. The solutions were shaken for 24 hrs using orbital incubator shaker (temperature maintained at 25°C). The solutions were filtered through Whatman filter paper No. 41 and the filtrate was diluted properly with respective solutions. The filtrate was analyzed spectrophotometrically at the predetermined λmax (231 nm).

Phase solubility study[9, 10, 11]

According to the method by Higuchi and Connors, Phase solubility study was performed. Diacerein in excess amounts was added to different concentrations of PEG-6000 and Soluplus® ® in glass stoppered flasks. The concentrations used were 0.1%, 0.2%, 0.3, 0.4%, 0.5% and 0.6% w/v in phosphate buffer pH 7 (20 ml) . Flasks were placed in thermostatically controlled shaking water bath for 72 hr at 37^0C. After equilibrium aliquots were withdrawn then passed through a

Millipore filter (0.45 um) then analyzed using a UV visible spectrophotometer at 231 nm. Phase solubility diagrams were obtained by plotting the solubility of diacerein (mole/ml), versus the concentrations of the polymers Soluplus® ® and PEG-6000 used (%w/v).

Drug content estimation[12]

Amount of drug present was determined by taking solid dispersion equivalent to 50 mg of diacerein and carrying out assay method for diacerein as follows: Solid dispersion equivalent to 50 mg of diacerein was dissolved in DMSO and the flask was shaken for 10 min.. 5ml Aliquot withdrawn, adjusted up to 100ml using 1 % w/v sodium lauryl sulphate solution and assayed UV spectrophotometrically at 231 nm. Drug content was then calculated by using calibration curve of pure drug.

FTIR spectral analysis[13, 14]

FTIR studies were done to assess possible interaction among drug and carrier Soluplus® is done by FTIR spectrophotometer. Infrared spectrums of pure drug, physical mixture of ingredients and solid dispersion batches were recorded in the wavelength region of 4000 to 400 cm-1.

Differential scanning calorimetry (DSC)[15]

Thermograms of pure drug, solid dispersion batches were obtained using Differential Scanning Calorimetry instrument (DSC 620, SICKO Nanotechnology, Japan) equipped with an intracooler. The powder samples was hermetically kept in the aluminium pan and heated at constant rate 10ºC/min, over a temperature range of 35°C to 350°C. 27, 28 Powder X-ray diffractometry (XRPD)

To verify the physical state of diacerein in pure state and the changes in the crystallinity of the components of formulation prepared, the PXRD study was carried out by using X ray diffractometer. The samples of pure drug and solid dispersion formulation were analyzed between from 5^0 to 50^0 (2θ).

In vitro Dissolution studies of solid dispersions[16, 17]

The dissolution test was performed in USP type II dissolution apparatus. The solid dispersion containing 50 mg of diacerein were filled into hard gelatin capsules (capsule no. 2). 900 mL of Phosphate buffer solution pH 7.0 at 37 ± 0.5 ^{0}C with paddle speed of 100 rpm. Each sample (5 mL) was withdrawn at 5, 10, 15, 20, 25 and 30, 35, 40, 45 min and filtered through 0.45 µm nylon filter. The amount of drug dissolved determined by UV spectroscopy at λmax of 231 nm.

In vivo absorption study [18, 19]

HPLC analysis of plasma samples for Construction of calibration curve of diacerein. A standard stock solution of diacerein was prepared at a concentration of 100 µg/mL. The diacerein stock standard was diluted with mobile phase to working solutions at concs of 2, 4, 6, 8, 10 and 12 µg/mL. Each plasma matrix (0.5 mL) spiked with varying amounts of diacerein (2 mL) from the stock solutions. Plasma samples centrifuged at 13,000 rpm 20ºC for 5 min.

In vivo absorption studies in male Wistar rats

Male Wistar-strain rats (180–220 g) were housed under normal laboratory conditions at a temperature of 24 ºC, with a controlled 12 h light–dark cycle The experimental procedures were approved by the Institutional Animal ethical committee. The rats were deprived of food but had free access to water 24 h before the day of the experiment. Three groups of rats were used , each group consists 4 rats. First group kept as controlled. Second group administered dissolved aqueous solution of marketed formulation of diacerein. Third group was administered with aqueous solution of diacerein solid-dispersion (SD6) .The equivalent dose of powder which displace 2.5 mg diacerein dose for rat was disperse in distilled water 30 seconds prior to administration.

Pharmacokinetic parameters- Maximum concentration (Cmax) and time to reach maximum concentration (Tmax) are the values obtained directly from concentration time curve. Area under the concentration–time curve (AUC0-a) was also determined.

Results and Discussion

Physical characterization

From the below tables; it was observed that, the θ value for all spray dried batches was found to be in the range of 31-33. The Hausner's ratio of all the batches was not

more than 1.25. There is no significance difference in the flowability of all physical mixing, and spray dried batches. All batches shown passable flow properties.

Saturation solubility of Diacerein in various solvents:

The solid dispersion consists of one or more carriers and drug dispersed with it. The objective of solubility study is to identify good solubilizing capacity for diacerein. The concentration of diacerein in various solvents was determined by UV spectroscopy at room temperature and results are shown in Table 5.

Saturation solubility values of Diacerein in various solvents revealed its poor solubility Similar to the available literature. Maximum saturation solubility observed in phosphate buffer pH 7.0.

Selection of solid dispersion carrier based on phase solubility

Phase solubility study displayed AL type equilibrium phase solubility diagrams for diacerein in both solutions of Soluplus® and PEG-6000, showing that diacerein solubility increases linearly as a function of Soluplus® concentrations and also formed soluble adsorption complexes without any precipitation in the range of carrier concentrations used till 0.6% w/v of the polymer, it shown that reaction became more favorable as concentration of polymer was increased. Due to hydrophilic nature of polymers and surface adsorption of drug on the polymer, solubility of diacerein might be enhanced.

The stability constant was found to be 4.825 mol/ml and 1.909 mol/ml for Soluplus® ® and PEG-6000 respectively. The complexation or dispersion efficiency in Soluplus® ® was twofold that of PEG-6000. In accordance with these results well optimized formation of soluble dispersions established between water soluble polymeric carriers and poorly water soluble drugs.

Evaluation and characterization of prepared solid dispersions

Drug content estimation- Drug content of diacerein solid dispersion batches were determined by UV spectroscopy method. The drug content of different diacerein solid dispersion batches were given in following Table 7.

FTIR-Spectroscopy studies of formulation batches

The FTIR studies of solid dispersion with Soluplus® ® as physical mixture batch PM6 and spray drying batch SD6 was done. The fundamental peak of diacerein at 1764cm-attributable to the (two carboxylic groups of the acetate groups). 1027-cm^{-1} attributable to the acetate group. The formulation batches of solid dispersion with Soluplus® ® shows a retention of characteristic carboxylic functional group at 1735.14 cm-1, 1735cm-1,1734cm-1 respectively with very slight shifting and acetate group at 1023 cm-1,1020cm-1,1026cm-1.

All the formulations of physical mixing and spray drying shows retention of functional group that reveals the formulation is stable and can retain the drug functional ability.

Differential scanning calorimetry (DSC) characterization of solid dispersions

DSC curves of pure drug, physical mixture and spray dried formulation batches were shown in Figure 6.

Pure diacerein show sharp endothermic peak at near about 255.1ºC. The PM6 and SD6 formulation exhibit retained small endothermic peak for diacerein due to dilution by solid carrier. Very small peaks (less heat of absorption) for diacerein were found in solid dispersion batches. It might be explained that crystallization of diacerein was inhibited by Soluplus® ®, in spray dried batches absence of well defined chemical interaction.

Powder X-ray diffractometry (XRPD) characterization

The powder X-ray difractogram o pure Diacerein powder from 5 to 50° 2θ showed numerous distinctive peaks at 2θ degree 5.2, 10.4, 18.2, 20.9, 23.5,26.1, 28.7, 31.3, 30.85, and 31.3 that indicated a high crystallinity. The height of the characteristic peaks of diacerein was remarkably reduced in case of SD6 this indicates that diacerein may have converted to a metastable amorphous form or may have dissolved in the matrix system, or may exist in a microcrystalline form in the matrix system. From these observations, we can deduce that crystalline nature of the drug was still, but the relative reduction of diffraction intensity of diacerein peaks that the quality of the crystals was remarkably reduced.

Dissolution studies of solid dispersions

The vitro dissolution study was performed using USP apparatus II. The in dissolution comparison of optimized solid dispersion formulation batches PM6, and SD6 in dissolution media phosphate buffer pH 7.0. Drug releases from solid dispersion formulations with spray drying by Soluplus® was found to be significantly higher as compared with that of conventional diacerein marketed formulations. Thus, this greater availability of dissolved diacerein from the solid dispersion formulations could lead to higher absorption and bioavailability.

***In vivo* absorption animal study**

Dosing the aqueous suspensions of diacerein marketed formulation resulted in the lowest average diacerein plasma concentrations. However, the AUC_{0-x} (µg h/mL) was 138.8 when diacerein was administered as solid dispersion i.e (SD6) compared with that of the AUC_{0-x} (µg h/mL) obtained for the aqueous diacerein suspension was found to be 48.03. The values of Cmax in solid dispersion (SD6) were found to be 62.14µg/mL while that in marketed formulation of diacerein was found to be 25.95µg/mL. The Tmax observed after dosing of solid dispersion was 2.00 hr while, that of after dosing of aqueous suspension of marketed formulation was 2.5 hr. These results revealed that formulation of diacerein solid dispersion (SD6) results in a significantly increased absorption of diacerein, compared with that from the aqueous suspensions. The improved absorption of diacerein was probably due to the enhanced solubilization. The pharmacokinetic data in male Wistar rats imply that solid dispersion developed in this study could improve dissolution and absorption of diacerein.

Stability Studies

Stability studies of the formulations of Solid Dispersion Batch No- SD 6 kept at 45 ºC ± 2 ºC, 75 ± 5% RH for accelerated condition. The stability data is summarized. The selected formulations were found to be stable under accelerated conditions, with the dissolution, content of diacerein in the range of 96–98% .

Preformulation study of solid dispersion was done with solubility determination.

Potential hydrophilic carriers were screened and selected as Soluplus®, PEG 6000. Solid dispersion by spray drying was successfully done with lab scale spray dryer using Soluplus® as a carrier. Diacerein solid dispersion also prepared by physical mixing method by using carriers Soluplus® and PEG 6000.

Characterization of solid dispersion was done for its physical appearance, spray dried process yield, powder flow properties. Optimization of solid dispersion was done on the basis of saturation solubility, higher drug content, and nature of dispersion and enhanced dissolution rate. SD6 batch found to be optimized.

Characterization of solid dispersion was done with differential scanning calorimetry (DSC) and powder XRD (PXRD); both the study reveals that decrease in the crystallinity of solid dispersion than that of pure drug.

In-vivo absorption study of solid dispersion batch SD6 was done on male wistar rats and compared with aqueous suspension of marketed formulation. The study revealed the higher Cmax and AUC when compared with the marketed formulation.

Accelerated stability testing at 45ºC (75% ±RH) was done for solid dispersion parameters were checked for appearance, dissolution, drug content. The formulations were found to be stable under accelerated conditions.

The present investigation has shown that, it is possible to enhance the solubility, dissolution rate of diacerein and thus improved oral bioavailability by solid dispersion with Soluplus® as a solid carrier.

Conclusion

It could be concluded that the use of novel polymer Soluplus® in solid dispersion formulations can enhance the solubility and dissolution rate of poorly water-soluble drug Diacerein significantly. At high Soluplus® content (1:8) the rate of dissolution enhancement was mostly dependent on the ratio of drug: carrier and the method of dispersion preparation. The spray dried samples exhibited higher dissolution rate than corresponding samples prepared by other methods. It was shown that in spray drying

dispersions with increase in Soluplus® ratio in dispersed, the solubility of Diacerein increased. DSC and XRPD analyses confirmed the presence of amorphous state of Diacerein in dispersed systems. FTIR studies indicated the formation of hydrogen bonding between Diacerein and Soluplus®. The long term stability studies showed that Soluplus® could prevent the recrystallization of Diacerein in dispersed samples. The results of this study showed that spray drying technique and novel hydrophilic polymer Soluplus® is a more suitable carrier to enhance the solubility, dissolution rate and thus improved bioavailability of diacerein in solid dispersion drug delivery system.

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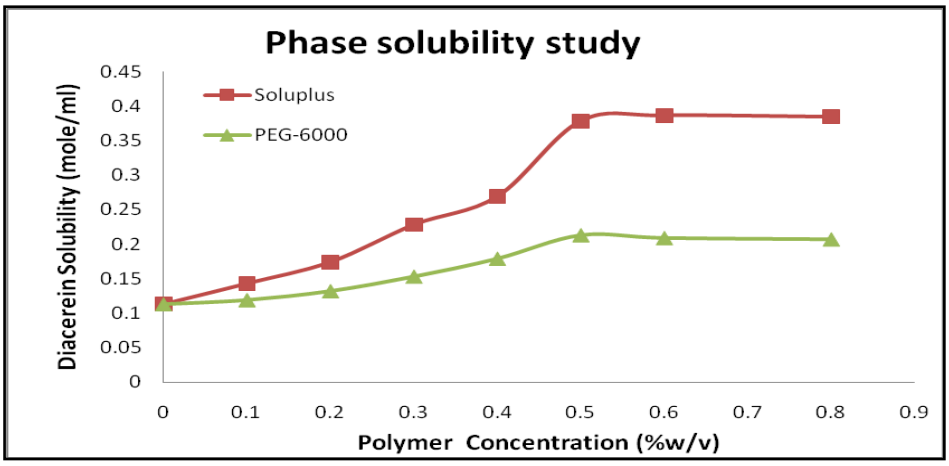

Figure 1: Phase solubility study of diacerein dispersion in Soluplus® and PEG-6000 solutions

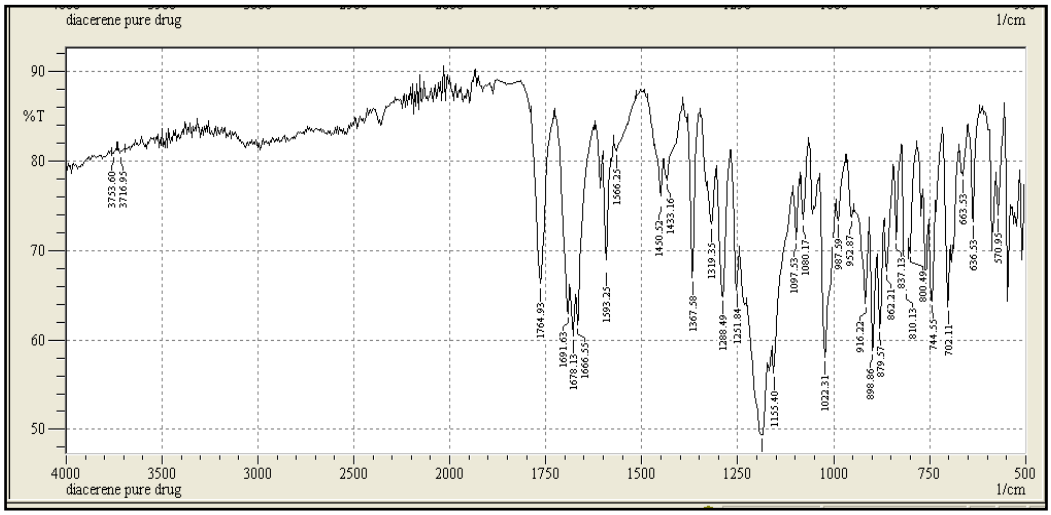

Figure 2: FTIR spectrum of Diacerein pure drug

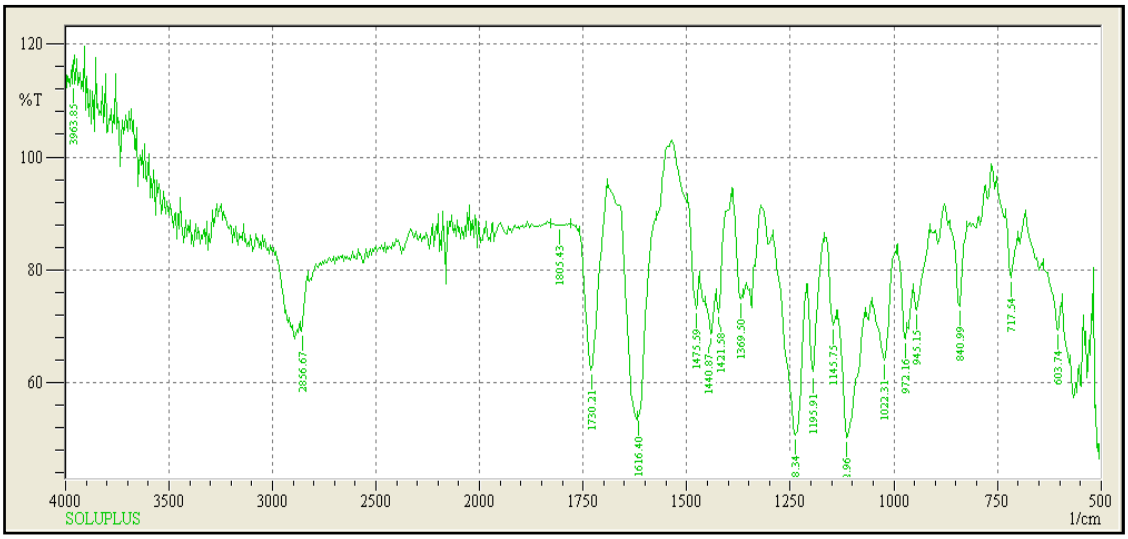

Figure 3: FTIR spectrum of Soluplus®

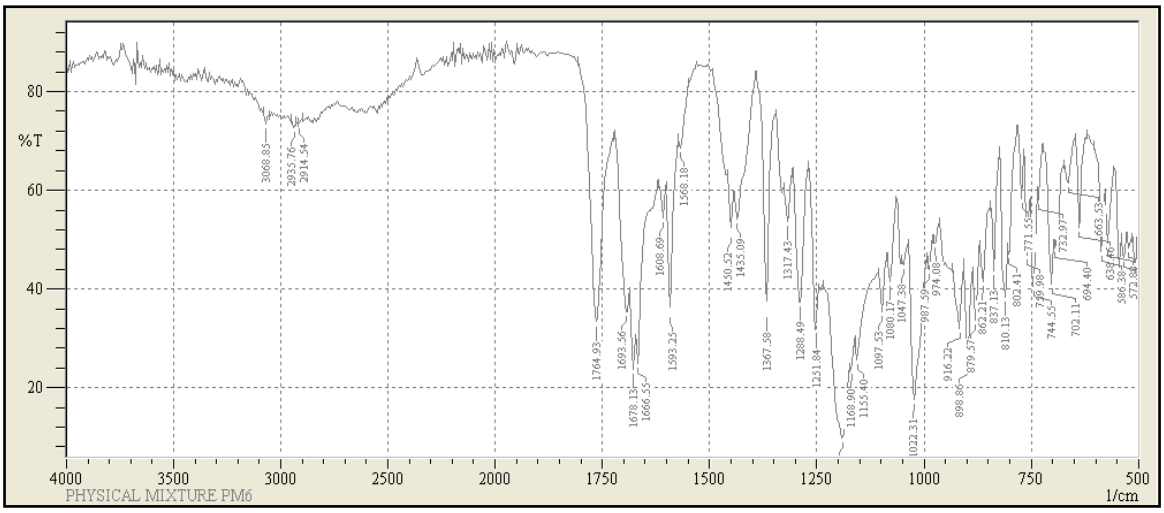

Figure 4: FTIR of Diacerein solid dispersion with Soluplus® by physical mixture- PM6

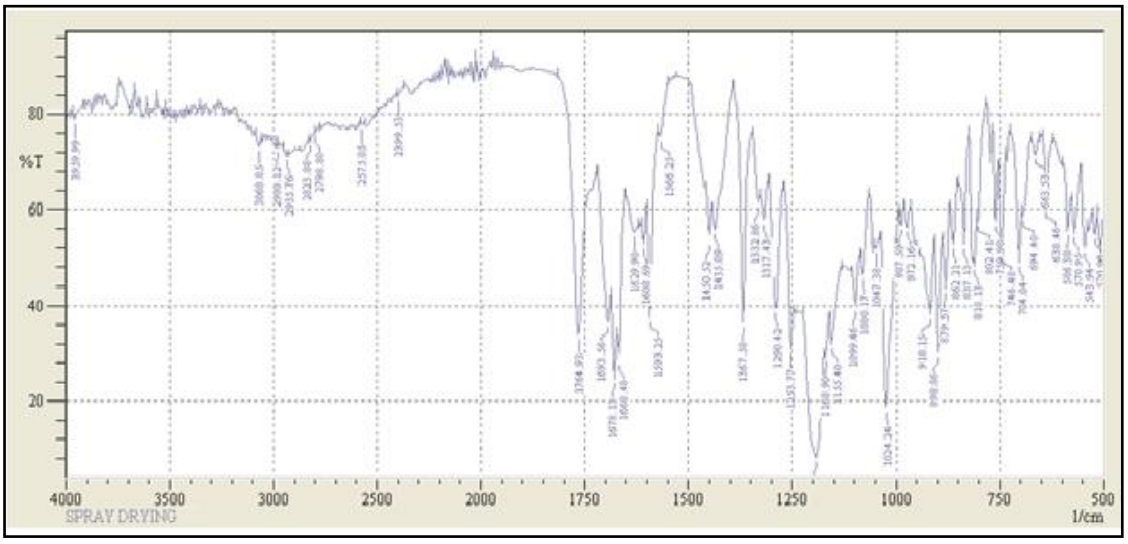

Figure 5: FTIR of Diacerein solid dispersion with Soluplus® by spray drying (SD6)

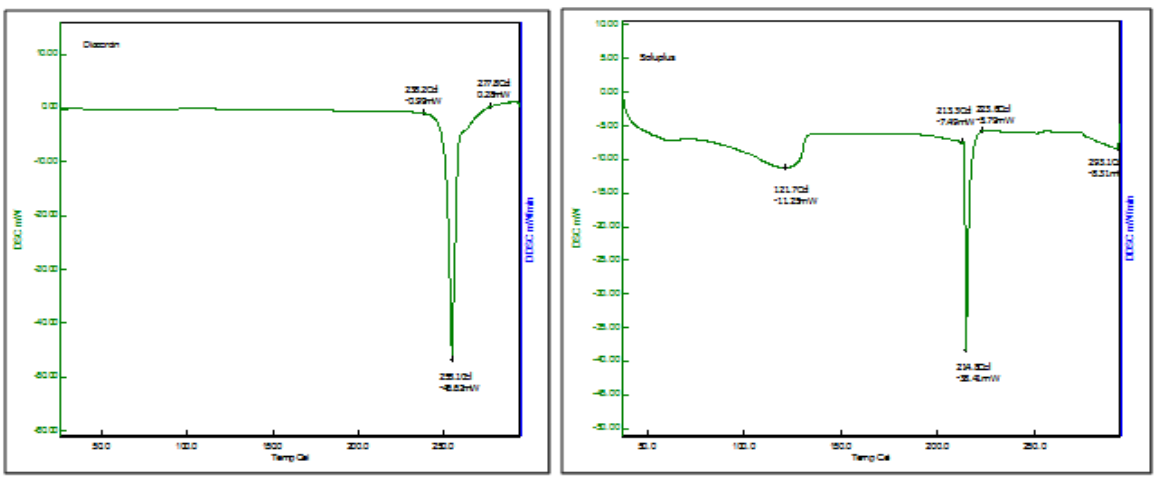

Fig 6.a) DSC Thermogram of Diacerein Fig 6.b) DSC Thermogram of Soluplus®

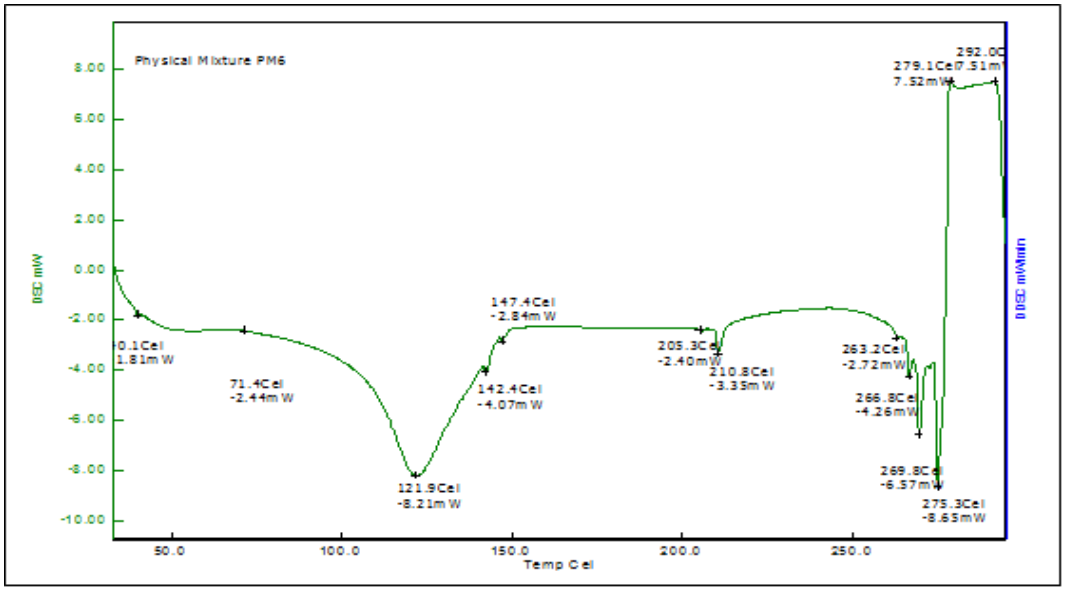

Figure 7: DSC Thermogram of Diacerein Physical Mixture with Soluplus®

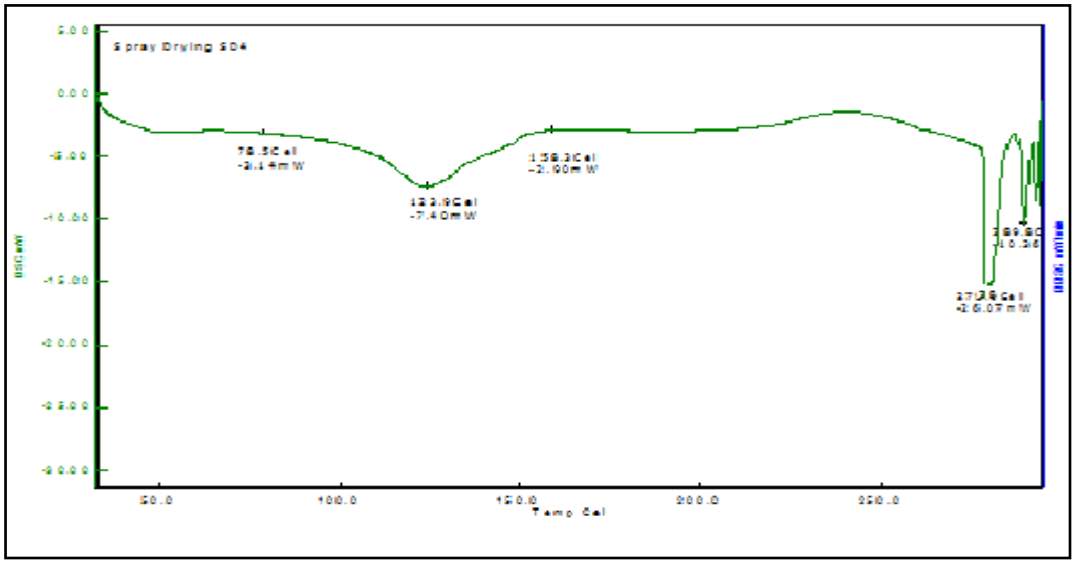

Fig 8: DSC Thermogram of Diacerein Spray Dried dispersion with Soluplus®

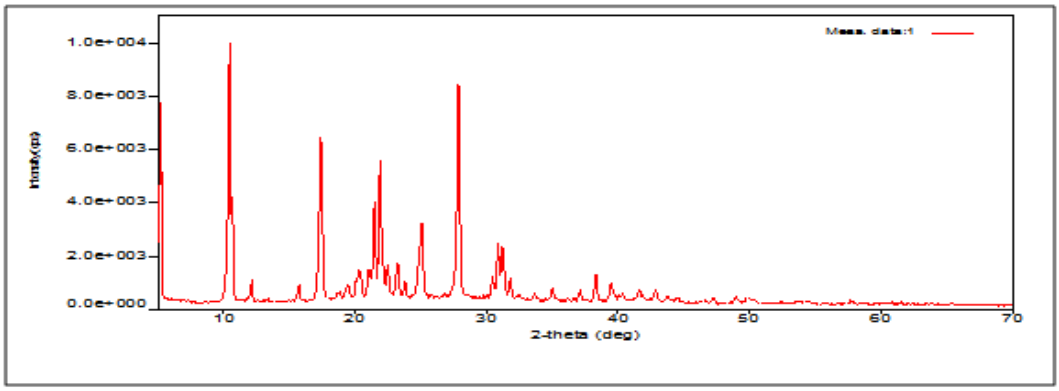

Figure 9: XRPD of Pure drug Diacerein

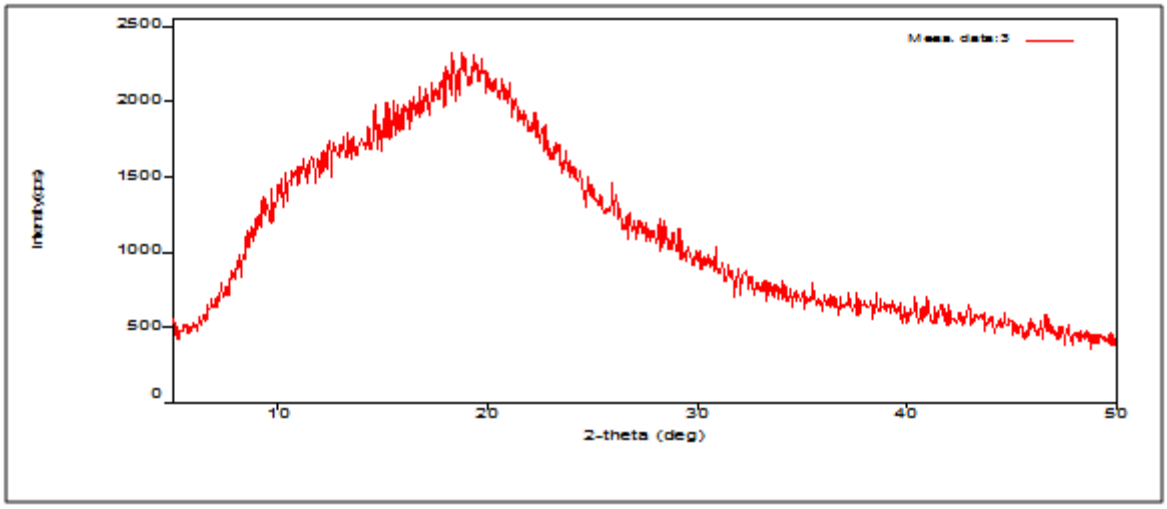

Figure 10: XRPD of Soluplus®

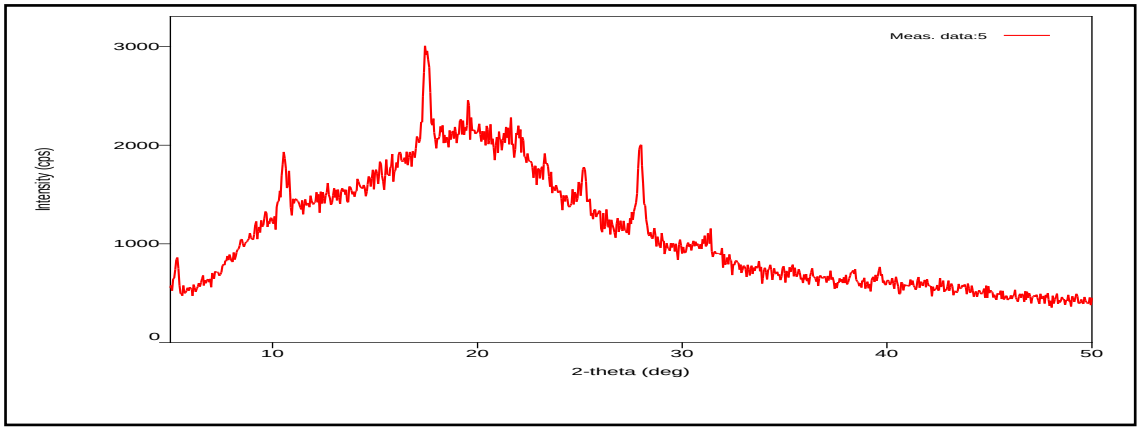

Figure 11: XRPD of Diacerein Physical mixture with Soluplus®

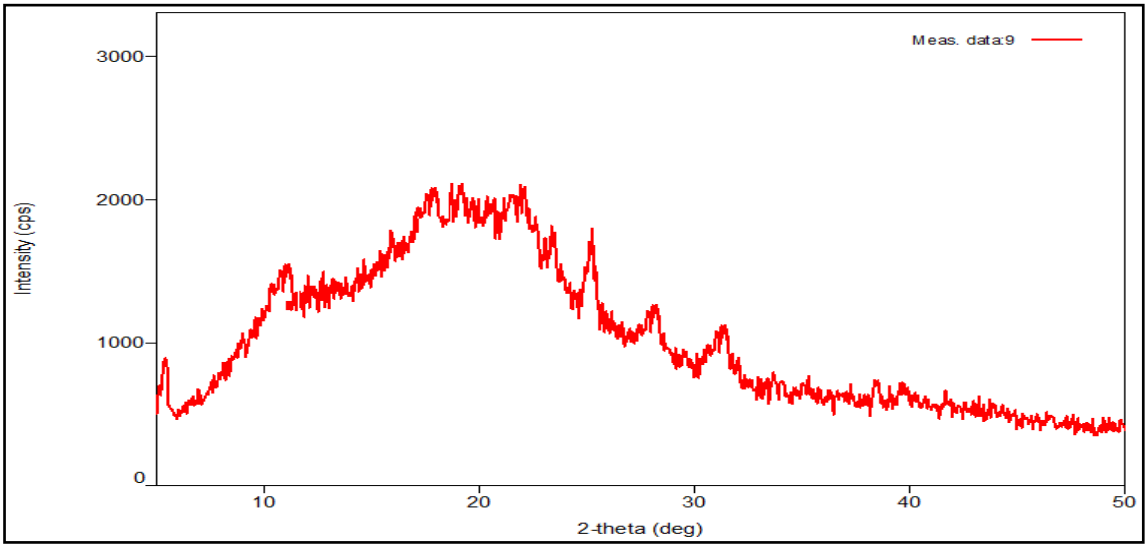

Figure 12: XRPD of Diacerein spray dried solid dispersion with Soluplus®

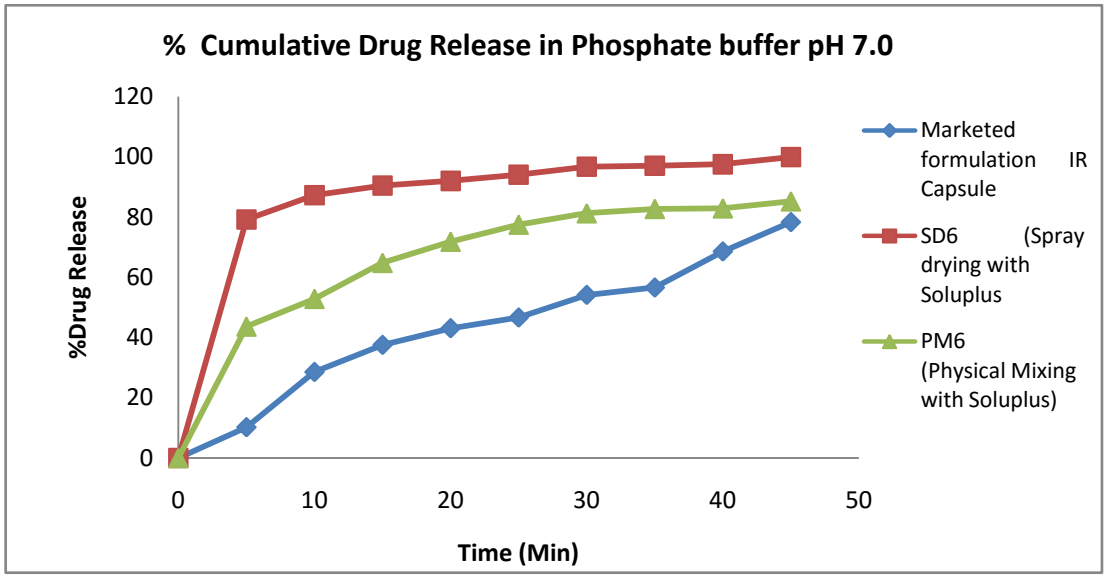

Figure 13: Comparative drug release profile of physical mixture, SD & marketed capsule

Table 1. Physical mixtures batches with Soluplus®

Batch No.	Drug : Polymer	Drug : Polymer Ratio
PM4	DCN : Soluplus®	1 : 2
PM5	DCN :Soluplus®	1 : 4
PM6	DCN : Soluplus®	1 : 8

Table 2. Spray drying solid dispersion batches with Soluplus®

Batch No.	Drug : Polymer	Spray Drying Solvent	Drug : Polymer Ratio
SD4	DCN : Soluplus®	Mixture of N, N-dimethylacetamide (DMA) and Methanol (6:4)	1:2
SD5	DCN : Soluplus®		1:4
SD6	DCN : Soluplus®		1:8

*1 Part is Equivalent to 50 mg of Diacerein

Table 3: Physical characterizations of solid dispersion batches

Batch code	Solid Dispersion Method	Observed Description	Flow properties
PM4, PM5, PM6	Physical Mixing	Light yellow in color, odorless amorphous powder	Passable
SD4, SD5, SD6	Spray Drying	Light yellow in color, odorless amorphous powder	Passable

Table 4: Flow Properties of optimized solid dispersion batches

Sr. No	Batch code	Bulk density	Tapped density	CI	HR	Angle of repose (θ) *
1	PM4	0.2564	0.3225	20.49	1.25	30.09±0.08
2	PM5	0.2541	0.3180	20.09	1.25	30.03±0.09
3	PM6	0.3312	0.4168	20.53	1.25	30.55±0.15
4.	SD4	0.3214	0.4012	19.89	1.24	31.87±0.12
5.	SD5	0.3448	0.4166	17.23	1.20	32.53±0.40
6.	SD6	0.3358	0.4025	16.57	1.19	32.53±0.40

Table 5: Saturation solubility of Diacerein in various solvents

Sr. No.	Type of solvents	Saturation solubility (mg/ml)
1.	Distilled water	0.042 ± 0.06
2.	0.1N HCl (pH 1.2)	0.0014 ± 0.18
3.	Phosphate buffer(pH 5.8)	3.467 ± 0.14
4.	Phosphate buffer (pH 7.0)	3.995 ± 0.20

Table 6: Phase solubility values of Diacerein with Soluplus® and PEG-6000

Soluplus® ® conc. (% w/v)	Diacerein conc. (mole/ml)	PEG 6000 conc. (% w/v)	Diacerein conc. (mole/ml)
0	0.113 ± 0.31	0	0.113 ± 0.29
0.1	0.143 ± 0.17	0.1	0.119 ± 0.33
0.2	0.174 ± 0.12	0.2	0.132 ± 0.18
0.3	0.228 ± 0.19	0.3	0.153 ± 0.21
0.4	0.269 ± 0.23	0.4	0.179 ± 0.26
0.5	0.378 ± 0.25	0.5	0.213 ± 0.35
0.6	0.386 ± 0.34	0.6	0.209 ± 0.27
0.8	0.384 ± 0.24	0.8	0.207 ± 0.23

Table 7: Drug content determination of Diacerein and solid dispersions

Batch No.	Composition(s)	Drug Content (%)*
	DCN Pure	101.85 ± 0.00
	Physical Mixing Method	
PM4	DCN: Soluplus® ® (1:2)	95.75 ± 0.08

To be continued

PM5	DCN: Soluplus® ® (1:4)	97.2 ± 0.00
PM6	DCN: Soluplus® ® (1:8)	97.82 ± 0.02
	Spray Drying Method	
SD4	DCN: Soluplus® ® (1:2)	98.5 ± 0.34
SD5	DCN: Soluplus® ® (1:4)	98.75 ± 0.08
SD6	DCN: Soluplus® ® (1:8)	101.2 ± 0.14

*Represent Mean ± S.D. (n= 3) DCN-Diacerein

Table 8: *In-vitro* dissolution study of solid dispersion batches

Sr. no.	**Time (min)**	**% Cumulative drug release in * (Phosphate buffer 7.0)**		
		Marketed formulation IR Capsule	**SD6** (Spray drying with Soluplus®	**PM6** (Physical Mixing with Soluplus®)
1	0	0	0	0
2	05	10.21±2.495	79.205±1.540	43.65±2.07
3	10	28.56±2.495	87.291±1.5279	52.861±1.527
4	15	37.55±2.991	90.470±1.9312	64.80±1.949
5	20	43.09±2.511	91.03±1.5750	71.85±1.527
6	25	46.64±2.502	93.13±1.0056	77.5±1.526
7	30	54.16±2.515	95.755±1.489	80.28±2.516
8	35	56.61±2.515	95.111±1.550	82.73±1.527
9	40	68.60±2.538	97.552±1.569	82.91±2.51
10	45	77.35±2.999	99.934±1.527	85.25 ±1.51

Source of Support: Nil.

Conflict of Interest: None declared

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