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Formulation and Evaluation of Solid Dispersion and Inclusion Complex of Poorly Aqueous Soluble Diacerein

Afroze Alam[1], Sabya Sachi Das[2], Afzal Hussain[3]* and Abdul Faruk[4]

[1]*School of Pharmaceutical Sciences, Shoolini University, Solan, India*

[2]*Birla Institute of Technology, Department of Pharmaceutical Sciences and Technology, Mesra, India*

[3]*Faculty of Pharmacy, S. Sinha College Aurangabad-824101, Bihar, India*

[4]*Department of Pharmaceutical Sciences, Hemwati Nandan BahugunaGarhwal University, India*

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***Corresponding author:** Afzal Hussain,Faculty of Pharmacy, S Sinha College, Bihar, India, Tel: +91-6300492526; Email: afzal.pharma@gmail.com

Abstract

The present study was focused on a poorly aqueous soluble drug (diacerein); basic structured anthracene molecule possesses defensive activity against osteoarthritis. The problem with the diacerein is its poor bioavailability (35%) which is due to its poor dissolution profile. The present study efforts to improve the dissolution profile using solubility enhancement techniques. The objective of the study was to improve the solubility of poorly soluble drug diacerein by solid dispersion technique and inclusion complex using the most compatible carriers and technique for the formulation. The prepared solid dispersion and inclusion complex were evaluated for physiochemical characteristics and dissolution efficacy. Thesolid dispersion and inclusion complex were formulated using kneading method with PVP K30 (screened to be the best among different carriers) and β-cyclodextrin respectively. The prepared formulations were characterized by FTIR, SEM, DSC and XRPD. The prepared solid dispersion and inclusion complex were then compressed into conventional tablets which were then coated with acid resistant polymer.

The *in-vitro* dissolution release of drug from solid dispersion and inclusion complex was carried out using USP II dissolution apparatus.Solid dispersion of diacerein prepared with PVP K30 was found to be the most effective in improving the dissolution profile of the drug. The enteric coated tablets showed no drug release in acidic medium resulting in higher bioavailability of the drug. The dissolution profile of diacerein was improved significantly. Dissolution enhancement and acid protection resulted into enhanced oral bioavailability of diacerein.

Keywords: Acid Labile; Bioavailability; Drug Entrapment; Inclusion Complex; Solid Dispersion; Diacerein

Abbrevations: IC: Inclusion Complex; SCF: super critical fluid; SD: Solid dispersion; FTIR: Fourier Transform Infrared; SEM:Scanning Electron Microscopy

Introduction

Poor aqueous solubility of a drug present with numerous challenges in screening of new chemical entities as well as in formulation design and development. To become excellent in terms of bioavailability two essential properties must be the key component of the drug such as it must show high solubility in gastric fluids and it must permeate the biological membrane with ease [1].When delivering an active agent orally, the first rate limiting factor for a drug is to get dissolved in gastric juice to become available in form of aqueous solution at the site of absorption. The second rate limiting factor is the drug permeability across biological membrane that define its bioavailability. Therefore, solubility of a drug is a key determinant of its oral bioavailability and permeability. Acid labile drugs are prone to degrade in gastric environment which is also considered to be a major factor of low bioavailability. Enteric coating is an appropriate approach to overcome the degradation problem [2].

The present study focused on drug "Diacerein" which could be effectively used for the treatment of Osteoarthritis. Diacerein (DCN) or Diacetylrhein (4, 5–diacetoxy-9, 10–dihydro-di-oxo-2 anthracene carboxylic acid) is semisynthetic anthraquinone derivative prodrug developed from its active metabolite "Rhein" having two acetyl groups in order to increase the lipophilicity of the drug [3].Therefore, the drug DCN fall into BCS class II having low solubility and high permeability showed that the drug exhibits dissolution rate limited absorption, leading to a very low bioavailability of 35% and to the very possible reason of acid degradation [4].

Various techniques are employed to enhance the solubility of poorly aqueous soluble drugs such as solid dispersion,particle size reduction, hydrotrophy, co-solvency, pH adjustment, high pressure homogenization, complexation, use of surfactants, spray drying,liquisolid technique, cryogenic technique, salt formation,

inclusion complex (IC), prodrug, precipitation, superdisintegrats, super critical fluid (SCF) technology, sonocrystallization, self-emulsifying drug delivery and nano suspensions[5-9].Among these techniques particle size reduction is considered to be the one of the most commonly used techniques but also leads to the problem of aggregation and agglomeration of particles. Solid dispersion (SD) technique offers a discreet advantage of enhancing the solubility by using various water compatible hydrophilic carriers. The term SD refers to the dispersion of one or more active ingredient in an inert carrier in solid form. SD is a very reliable technique of improving solubility as various mechanism of carrier drug binding is found effective in modifying the reason of insolubility [10].Different techniques to formulate SD's are Fusion method, Solvent evaporation method, Kneading methods, Spray drying method, Lyophilisation, Hot-melt extrusion, Electrostatic spinning method and Supercritical recrystallization method. Based on various mechanism different types of SD are discussed in the Table 1[11-12].

Table 1: Various types of Solid dispersions.

S. No	Solid dispersion type	Matrix*	Drug**
1.	Eutectics	C	C
2	Amorphous precipitations in crystalline matrix	C	A
Solid solutions type			
3	Continuous Solid Solutions	C	M
4	Discontinuous solid solutions	C	M
5	Substitutional solid solutions	C	M
6	Interstitial solid solutions	C	M
7	Glass suspension	A	C
8	Glass suspension	A	A
9	Glass solution	A	M

*A: matrix in the amorphous state, C: matrix in the crystalline state; **: A: drug as amorphous clusters, C: drug in the crystalline state, M: drug molecularly dispersed throughout the matrix

Also, Cyclodextrins are cyclic chained structure of repeating glucopyranose units linked at 1 and 4 positions in an order to form a cavity/void which is hydrophobic from inside and hydrophilic outer surface. The most common cyclodextrins are α-cyclodextrin, β-cyclodextrin (β-CD), and γ-cyclodextrin, which consist of six, seven, and eight glucopyranose units, respectively. The central cavity of the cyclodextrin molecule allows the drugs molecules to entrap in between to form IC without permanent bonding like covalent bonding, thus complexes are readily dissociated [13-14].Thus the entrapment of the drug in the hydrophobic cavity of cyclodextrins is considered to be an efficient approach for enhancing the dissolution profile of poorly aqueous soluble drugs without altering the physiochemical properties of the drug [15].The present work was planned to improve the solubility and dissolution characteristics of the drug diacerein using SD technique and IC formation with β-CD.

Materials

DCN was received as gift sample from Tirupati Medicare Ltd., Distt. Sirmaur, Paonta Sahib, Himachal Pradesh. Instacoat EEN was purchased from Ideal cures Pvt. Ltd. (Provided by Sano cito Therapeutic Inc.). PVP K30 and β-CD were purchased from Himedia laboratories Pvt. Ltd., Mumbai; PEG (4000 and 6000) were purchased from SD fine chem. Ltd., Mumbai; Citric acid was purchased from Qualikem fine chem. Pvt. Ltd., Vadodara; Mannitol, Methanol, sodium chloride, hydrochloric acid and phosphate buffer (mono sodium di hydrogen phosphate and di sodium mono hydrogen phosphate) were purchased from Nice chemical Pvt. Ltd., Kochi; Kerala. All the chemicals and reagents used in the study were of analytical grade.

Methods

Solubility Study of Pure Drug

Solubility studies were carried out in two solvent systems that is 0.1N HCl and Phosphate buffer 6.8 respectively. Both the solvents (30ml) were taken in a conical flask with an excess amount of drug in it. The flasks were shaken for 72hrs in a horizontal water bath shaker maintained at 37 ˚C and 100 strokes per min. The solutions were withdrawn and centrifuged at 5000rpm. The supernatant solution was separated and was analyzed using UV/Vis Spectrophotometer at 257nm [16-17].

Screening of Polymer and Carriers

Different polymers and hydrophilic carriers such as PVP K30, PEG 4000, PEG 6000, Citric acid and Mannitol were blended in a ratio of 1:1 with the drug and their solubility was analyzed using bath shaker in Phosphate buffer 6.8 and the dissolved amount was determined using UV/Vis Spectrophotometer at 257nm[18-19].

Selection of appropriate ratio of Diacerein: polymer and method for preparing Solid Dispersion

To choose the suitable ratio of drug and hydrophilic carrier, different solid dispersions were prepared with drug: polymer in different ratios (1:0.5, 1:1, 1:2, 1:4 and 1:8) employing three different techniques such as kneading, solvent evaporation and hot melt extrusion methods. In kneading method, the drug and the carrier were dissolved in water: ethanol in the ratio of 1:1 and kneaded for 15 min to form paste, then the paste was allowed to stand for 30 min. The paste was dried using lyophilizer and sieved [15,19,20].In solvent evaporation method, the drug was dissolved in a volatile solvent (ethanol) and carrier in aqueous media. The solution were mixed on a magnetic stirrer and sonicated for 15 min. The solution was then filtered, and the filtrate wasallowed to evaporate to collect the residue and the collected residue was sieved [21].Hot melt extrusion method involved melting of the carrier in china dish at controlled temperature of 60 ˚C and then the drug was added with constant stirring. The dispersion was then allowed to cool and sieved [22].

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The prepared SD's were evaluated for appropriate ratio of the carrier and suitable method of preparing SD on the basis of solubility study and physical stability. In physical stability, two parameters were observed which includes, hygroscopicity and stickiness. For solubility studies, 2 mg drug equivalent SD was dissolved in 30 mL of phosphate buffer 6.8 and shaken on horizontal bath shaker maintained at 37 ˚C and 100 strokes per min for 72hrs. The samples were withdrawn and centrifuged at 500rpm and the supernatant was examined using UV/Vis Spectrophotometer at 257nm [16,17,23].

Formulation of diacerein inclusion complex with β-cyclodextrin

Solubility study was carried out to find out the increase in the solubility of DCN with increase in the concentration of carrier. Different molar ratios of DCN: β-CD (1:0.5, 1:1, 1:1.5, 1:2 and 1:2.5) were prepared by kneading method. Molar ratio was selected to formulate IC because complex formation is molecular entrapment of drug in the voids of cyclodextrin. In briefly, the aqueous paste containing dissolved β-CD was kneaded with DCN for 15 min to obtain the equilibrium between the species. After this the solution was frozen and lyophilized for 48hrs [15,24]. The prepared IC's of 1g equivalent of DCN were added to 30mL of phosphate buffer 6.8 and shaken on horizontal bath shaker maintained at 37 ˚C and 100 strokes per min for 72hrs. The samples were withdrawn and centrifuged at 5000rpm and the supernatant was examined using U.V spectrophotometer at 257nm [16,17,23]. The ratio with best solubility will be subjected for further studies.

Characterization of the Prepared Formulations

Fourier transform infrared spectroscopic analysis

Fourier Transform Infrared (FTIR) spectra of moisture free samples of DCN, pure PVP K30, pure β-cyclodextrin, solid dispersion and inclusion complex of DCN in β-cyclodextrin were taken using a FTIR spectrometer (Agilent technologies, Cary 630 FT-IR) and were examined to determine the compatibility between the carriers and drug. Samples were triturated with potassium bromide (KBr) discs (one part of sample to two parts of KBr) and were prepared for analysis. The scanning range was 4,000–400 cm-1 [25].

Powder X-ray Diffraction Analysis

PXRD patterns of all samples were determined X-ray diffraction patterns for pure drug, polymer and SD were recorded using XRPD (X'Pert Pro), at a scan rate of 1˚/min in terms of 2h angle ranging from 10^0C– 60^0C. During sampling the specimen holder was prepared by placing plexiglass on its top surface and the sample was filled in the holder in slightly overfull which was then tapped to compact the powder in the holder. Then the plexiglass cover was lifted off and the specimen holder was placed in diffractometer with Cu Kα filter generated at 45kV voltage and 40mA current over a diffraction angle of 2θ [26].

Differential Scanning Calorimetry Analysis

DSC scans of all samples including pure drug, IC and SD's were recorded using DSC (Mettler Toledo DSC 821). The samples (1mg) were heated at the rate of 10°C/min and was analysed over the range of 20°C – 300°C. DSC was carried out to determine the crystalline or amorphous behaviour of the samples [16].

Scanning Electron Microscopy

Surface morphology of pure drug DCN; carriers; IC and SD were analysed with the help of Scanning Electron Microscopy (SEM) (SEI, QUANTA 450 SEG, Netherland). The samples were placed in a brass specimen stub using double sticky carbon tape and then the samples were electrically conducted by gold coating using a sputter coater. The sample stubs were placed on the mounting holes and readings were taken thereafter [27].

Preparation of tablets

The pure DCN (F1), SD (F2) and IC (F3) were formulated into conventional tablets. The tablet was prepared using microcrystalline cellulose (MCC) and lactose monohydrate as main filler, 10% starch paste as binder, corn starch as disintegrant, magnesium stearate as lubricant and talc as glidant. The formula for the preparation of tablets is shown in Table 2.All the ingredients were mixed accordingly and subjected to modified wet granulation process for the preparation of tablets. The pure DCN, IC and SD were blended respectively with MCC, lactose monohydrate and corn starch (80% of total mass). The blend was granulated using 10% starch paste as binder and passed through sieve no.10 and then dried in hot air oven. The dried mass was then passed through 20 mesh size and blended again with magnesium stearate, corn starch (remaining 20%) and talc. The final granules were compressed into tablets where each tablet contains 50mg of pure DCN [28-29].

Table 2: Ingredients in tablet formulation.

Ingredients	Quantity (mg)		
	F1	F2	F3
DCN	50	-	-
DCN/SD	-	150	-
DCN/IC	-	-	358
MCC	150	150	150
Lactose	100	100	100
Corn starch	50	50	50
Starch paste 10% w/w	q.s	q.s	q.s
Magnesium stearate	10	10	10
Talc	10	10	10

Note: DCN: Please decode all (Abbreviations: DCN: Diacerein; DCN/SD: Diacerein Solid

Dispersion; DCN/IC: Diacerein Inclusion Complex; MCC: Microcrystalline cellulose)

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Coating of prepared tablets

The enteric coating of the prepared tablets was carried out at Sano cito 2 Therapeutic Inc. Instacoat EEN was used as the coating material. The Instacoat EEN coating system was based on methacrylic acid co-polymer Type A and Type B. The enteric coating was performed using spray pan coater (Phoenix Pharmaceutical Vasai) and the pump system (Electrolab, Peristaltic pump V series).

Evaluation of tablets parameters

Uniformity of Weight

Twenty randomly selected tablets of the prepared formulation were weighed (Shimadzu Electronic Balance AY 120) independently and the average weight of the tablets and standard deviation was determined. The tablets were thus scrutinized for their uniformity of weight and were evaluated according to tablet to tablet variations that should be within the limits of the percentage deviation allowed by USP (generally ±10% for tablets weighing 130mg or less, ±7.5% for tablet weighing more than 130–324mg and ±5% for tablet weighing more than 324mg [28].

Friability test

Friability was performed on a batch of ten tablets of each formulation (F1, F2 and F3). Ten tablets were weighed and placed inside the friability test apparatus at 100 rotations in 4 min. Tablets could fall from a height of 15cm for 100 times and then the tablets were weighed again to calculate the weight loss [28-29].Friability was calculated in percentage using formulae given below; where W1 was the initial weight of ten tablets and W2 was the final weight of ten tablets

$$F = \left[(W_1 - W_2) \ / \ W_1\right] x100 \qquad (1)$$

Hardness Test

Randomly selected tablets from the batch of formulation (F1, F2 and F3) were crushed by Monsanto's Hardness tester to find out the crushing strength of tablets. A tablet was placed between the anvils of Monsanto hardness tester and the force (kg/cm2) was recorded.

Disintegration test

The disintegration time was determined using single basket disintegration test apparatus using 0.1N HCl and phosphate buffer 6.8 as dissolution medium alternatively. Five tablets were exposed to test in 0.1N HCl for 2h and after 2hrs, the medium was replaced with phosphate buffer 6.8 maintained at temperature 37 ± 0.5 °C. The time taken by the tablet to disintegrate completely was recorded and results were evaluated for each formulation accordingly[28-29].

In-vitro evaluation of tablets

Both conventional and enteric coated tablets containing 50mg equivalent of pure DCN were evaluated for dissolution profile using USP II type apparatus. The dissolution media used was 0.1N HCl for 2hrs maintained at 37 ± 0.5°C with paddle rotation at 100rpm. The samples aliquots (5ml) were withdrawn at 5, 10, 15, 30, 60, 90 and 120 min and filtered through whatman's filter paper and analysed using UV/Vis spectrophotometer at 257nm. The enteric coated tablets were then withdrawn from 0.1N HCl and further evaluated for 60min in phosphate buffer 6.8 using USP II type dissolution apparatus maintained at 37 ± 0.5°C with paddle rotation at 100rpm. The samples aliquots (5ml) were withdrawn at 120, 125, 130, 140, 150, 160, 170 and 180 min and filtered through whatman's filter paper and analysed using UV/Vis spectrophotometer at 257nm [30-31].

Results and Discussion

Solubility study of pure Diacerein in 0.1 N HCl and Phosphate buffer pH 6.8

The solubility study of pure drug was performed in triplicate (n=3) and found out to be 12.6 ± 0.57µg/ml in phosphate buffer 6.8, while 1.4 ± 2.6µg/ml in 0.1 N HCl. The HCl samples were then subjected to scanning (U.V spectrophotometer) as shown in (Figure 1a& b). Figure 1a showed the absorption maxima in phosphate buffer while in Figure 1b the green line showed the absorption maxima in 0.1N HCl initially and red line showed the absorption maxima of drug in HCl after 30 min. The figures concluded that the drug in HCl was gradually altering molecularly as new peak was appearing causing the decrease in concentration at standard absorption maxima[16,23].

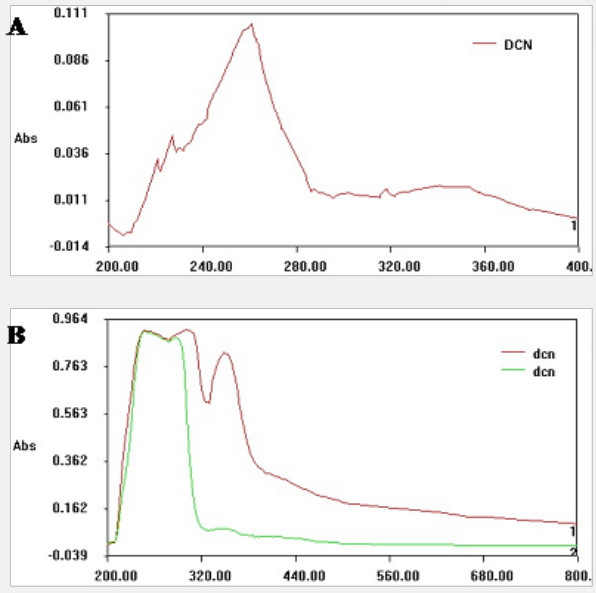

Figure 1: (a) Absorption maxima in phosphate buffer 6.8 and (b) Absorption maxima in 0.1N HCl.

Screening of Polymer

The blended mixture of DCN with different polymers such as PVP K30, PEG (4000, 6000), citric acid and mannitol were prepared and evaluated for their solubility. PVP K30 showed highest increment in solubility of drug (134.2µg/mL) which was 10.65 times higher than the solubility of the pure DCN (12.6µg/mL). The solubility improvement decreases in the order PEG

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600 (10.02 folds), citric acid (8.56 folds), PEG 4000 (7.3 folds) and then mannitol (7.03 folds). Thus based on the results of solubility augmentation of different polymers with DCN, PVP K30 was selected as the polymer to prepare SD [17,21].

Selection of appropriate ratio of Diacerein

PVP K30 and method for preparing Solid Dispersion: SD's were prepared by three different techniques which includes kneading, solvent evaporation and hot melt extrusion method, using five different ratios of DCN: PVP K30 (1:0.5, 1:1, 1:2, 1:4 and 1:8). On the basis of physical stability and solubility, kneading method has shown the best results followed by solvent evaporation and then hot melt extrusion [24]. The solubility of the prepared SD was observed to be increasing significantly with an increase in the polymer concentration, but the SD prepared by kneading method at a ratio of 1:2 showed highest solubility in comparison to other methods as shown in Table 3. The higher concentration of the carrier was not chosen as they may cause to the formation of physically unstable product as observed from the physical stability studies (Table 3).

Table 3: Selection of appropriate ratio of carrier and method for preparing solid dispersion.

Methods	Ratio	Solubility (µg/ml)	Physical stability	
			Hygroscopic	Sticky
Kneading	01:00.5	95.7 ± 0.8	Low	Low
	1:01	148.2 ± 0.3	Low	Medium
	1:02	188.5 ± 0.1	Medium	Medium
	1:04	190.6 ± 7.7	Medium	High
	1:08	193.3 ± 6.2	High	High
Solvent evaporation	01:00.5	88.1 ± 2.9	Low	Low
	1:01	136.7 ± 1.4	Low	Medium
	1:02	170.9 ± 2.6	Medium	Medium
	1:04	186.8 ± 3.4	High	High
	1:08	190.7 ± 4.8	High	High
Hot melt extrusion	01:00.5	76.3 ± 1.2	Low	Low
	1:01	127.5 ± 0.6	Low	Medium
	1:02	161.7 ± 0.9	Medium	Medium
	1:04	181.3 ± 2.5	High	High
	1:08	187.8 ± 0.7	High	High

Development of Inclusion Complex: The IC were prepared by kneading method using different molar ratios of DCN:β-CD (1:0.5, 1:1, 1:1.5, 1:2, 1:2.5 and 1:3). The solubility studies revealed that there is also a progressive increase in solubility with increase in β-CD concentration. However, the instant increase of solubility upto 90.06% was observed in 1 mole of drug and 2 moles of β-CD (1:2). Figure 2(b) shows the improvement in solubility of DCN in presence of β-CD. Therefore, 1:2 molar ratios of DCN and β-CD were selected for further studies [33].

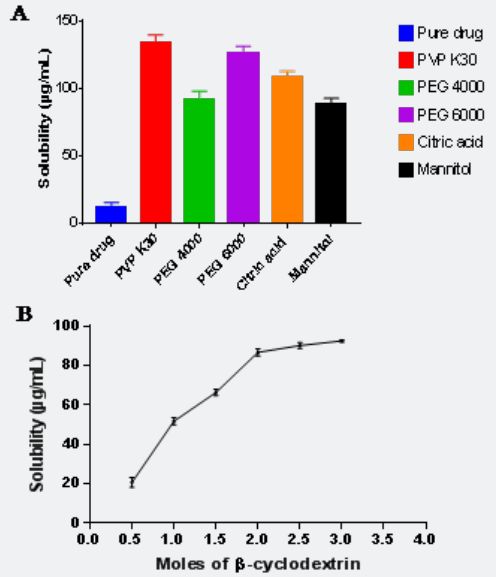

Figure 2: (a) Comparative solubility of physical mixture composed of different Polymers. (b) Solubility studies of Diacerein in β-cyclodextrin.

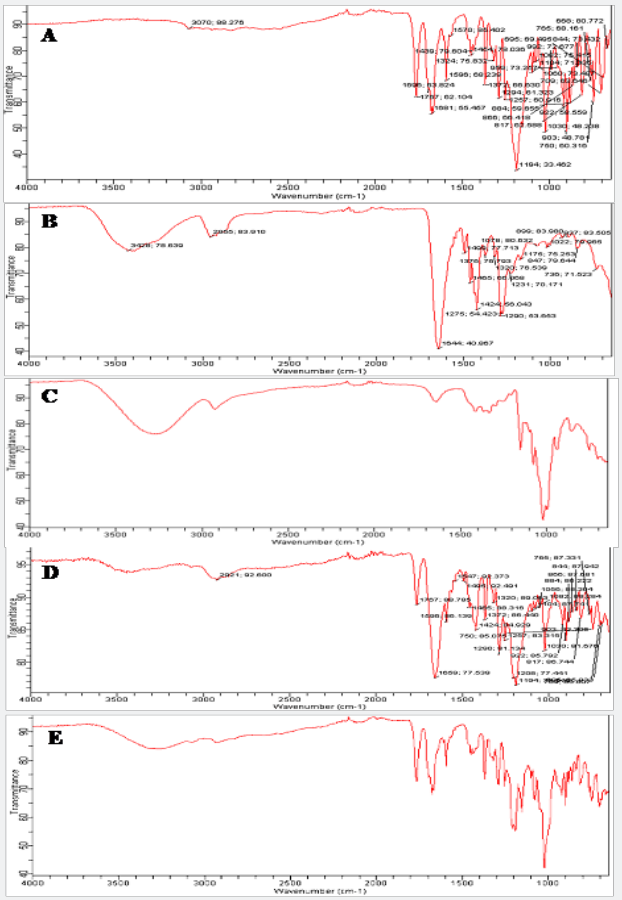

Figure 3: FTIR spectra: (A) pure Diacerein, (B) pure PVP K30, (C) pure β-cyclodextrin, (D) solid dispersion and (E) inclusion complex of Diacerein in β-cyclodextrin.

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Drug-Polymer & Drug-excipient compatibility study: FTIR spectroscopy for pure DCN, excipients, SD and IC was conducted to characterize any possible interaction of drug with excipient. The different FTIR spectra for pure DCN, excipients, SD and IC are shown in(Figure 3A-E).The interpretation of the peaks has revealed the characteristic peaks of DCN at 1194 cm-1of C-O stretching, 1372cm^{-1}of C-O-C stretching and two peaks of C=O stretching at 1681cm-1and 1767cm^{-1} were well observed with no significant changes which confirms the compatibility of drug with PVP K30 and β-CD[25,32].

Surface Morphology by Scanning Electron Microscopy (SEM): The characteristic crystal structure of DCN was observed in the SEM images shown in (Figure 4a-c)shows the SEM images of PVP K30 and pure β-CD indicating their amorphous nature. The SEM images of SD Figure 4dshowed the formation of matrix system in which drug was entrapped. The SEM images of IC Figure 4eshowed the absence of crystalline particles of DCN indicating the entrapment of DCN in β-CD structures[27,33].

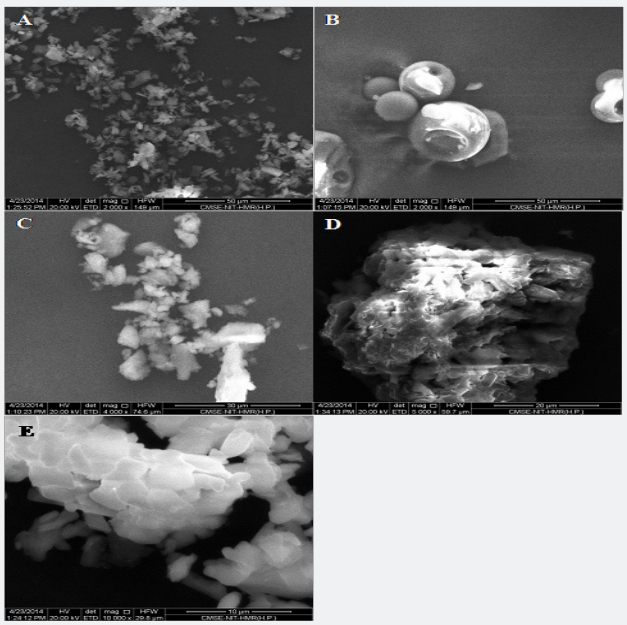

Figure 4: Scanning Electron Microscopic photographs: (A) diacerein, (B) pure PVP K30, (C) pure β-Cyclodextrin, (D) solid dispersion (1:2) and (E) inclusion complex of diacerein in β-cyclodextrin at 5000X magnification.

Differential Scanning Calorimetry (DSC): To approve the formation of SD, thermal behaviour of DCN and its complex with PVP K30 and β-CD was studied using DSC. On formation of SD the physical characteristics like melting, boiling, and sublimation point either gets shifted or fade within the decomposition range of β-CD lattice. The DSC thermogram for pure DCN shows an endothermic peak at 258.15°C corresponding to its melting point Figure 5a. The SD of DCN and PVP K30 shows a peak at 177.75°C which indicates that the characteristic endothermic peak, corresponding to drug melting, was shifted revealing the formation of SD and conversion of crystalline DCN into amorphous form Figure 5b. While in case of the IC the DSC thermogram showed two endothermic peaks at 77.75°C and 243.5°C. The peak at 77.75°C indicate the dehydration of β-CD and the peak of DCN shifted from 258.15°C to 243.5°C indicated the entrapment of DCN in β-CD Figure 5c[16,34].

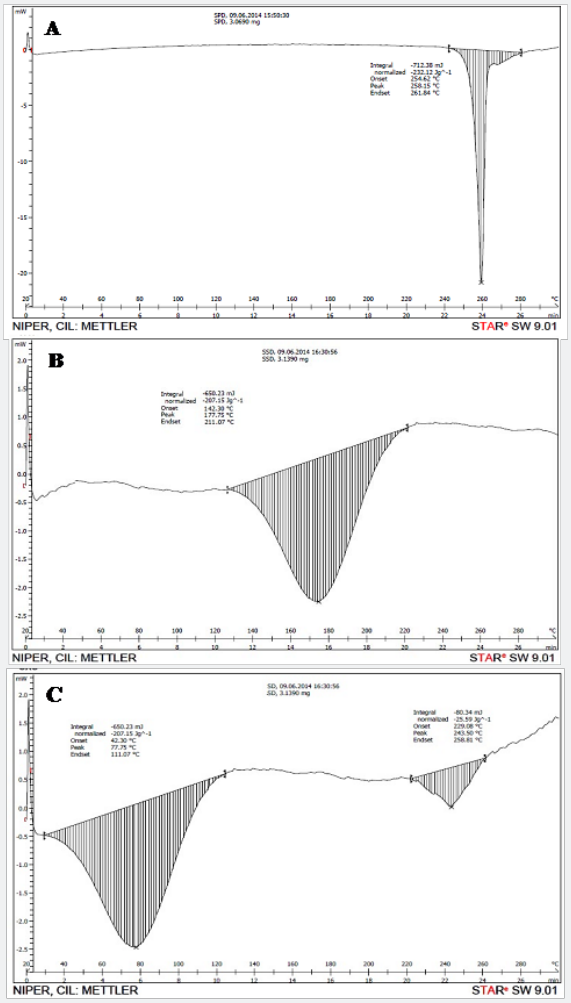

Figure 5: Differential scanning calorimeter thermogram: (a) pure diacerein, (b) solid dispersion, and (c) thermogram of inclusion complex.

X-Ray Powder Diffractometry (XPRD): To associate the degree of crystallinity of pure drug (DCN) and the formulated complex was evaluated by PXRD. On establishment of complex the amorphousness of the drug is amplified and subsequently solubility. The PXRD patterns are shown in the Figure 5. PXRD of DIA Figure 5a showed major diffraction peaks at 2hrs values of 10.63, 12.43, 17.64, 19.42, 22.04, 25.29, 28.16, 31.31 and 49.18 while being amorphous HPb- CD showed no major peaks. From the spectral study decrease in the crystallinity of DIA was observed in its complex with HP-b-CD which was confirmed from the decrease in the intensity of the major peaks. The X-ray diffraction pattern for pure DCN shows distinctive peaks of its crystalline nature are shown in Figure 6, at an intensity of above 8000. The diffraction pattern for pure PVP K30 shows

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irregular peaks with a very low intensity in the region of 1000-1500 indicating its amorphous nature. SD of DCN and PVP K30 were analysed and showed all the principal peaks of pure DCN that are merged with the background diffraction pattern of PVP K30 at lower intensity in the region of 1500-1800. From present structural data of DCN and its complex with β-CD and PVP K30, it can be concluded that SD has been formed with upsurge in amorphousness of DCN in complex[27,35].

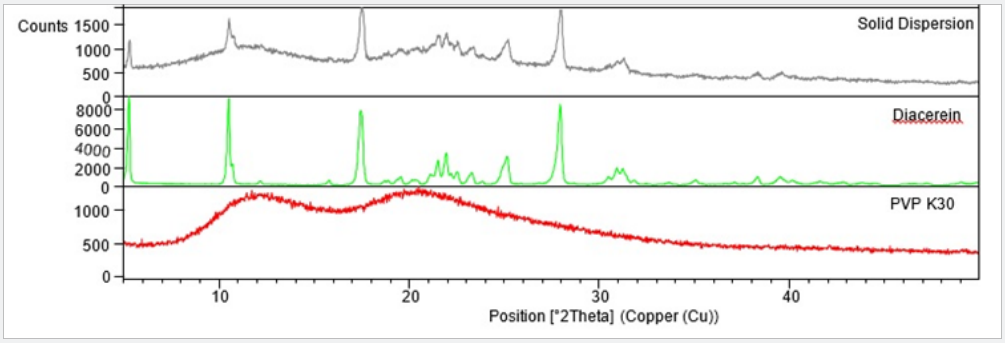

Figure 6: Comparative X-ray diff spectra.

Evaluation of prepared tablets: The prepared F1, F2 and F3 enteric coated tablets were evaluated for friability, weight variation, hardness and disintegration shown in Table 4.The results showed that none of the enteric coated tablet gets disintegrated in 0.1N HCl within 2hrs whereas tablets were disintegrated within 15min in phosphate buffer 6.8 as shown in Table 4. Friability of all the coated tablets were under the I.P limits (not more than 1%). Hardness was optimum for all the formulations. Approximately 6 to 7% of enteric material was coated over each tablet still the weight variation in formulation did not exceed the I.P limit that is average weight ± 5%[19,36].

Table 4: Evaluation of optimized tablets.

Enteric coated tablets	Friability %	Hardness Kg/cm²	Weight variation mg ± %variation	Disintegration(min)	
				0.1N HCl	Phosphate buffer 6.8
F1	0.215	4.9 ± 0.002	395.64 ± 2.52	-	9.45 ± 0.35
F2	0.183	5.2 ± 0.013	500.28 ± 3.45	-	10.05 ± 0.37
F3	0.262	5.1 ± 0.006	720.36 ± 3.92	-	10.55 ± 0.29

***In-vitro* release profile of formulations:** To determine the molecular conversion pattern of the drug in acidic environment, the non-enteric coated tablets (conventional tablets) containing 50mg equivalent of pure DCN, SD and IC were subjected to dissolution studies carried out in 0.1 N HCl for 2hrs. The formulations started the drug release soon after the exposure to gastric environment (0.1 N HCl) and in 15 min SD and IC released drug 45.6% and 41.8% respectively. Pure DCN was dissolved up to 9.4% in 30 min. After, 30 min DCN concentration goes on decreasing in each formulation as well as in pure form due to the molecular conversion of DCN in acidic environment. The results are shown in Figure 7a[35,37].

Enteric coated tablets showed no drug release in acidic environment (0.1N HCl) for first 120min. After the addition of phosphate buffer 6.8 at 120 min, the coated tablets showed no release up to 5 minutes (125 min) but as the coating dissolved, 31.7% of pure DCN was dissolved in 60 min. The SD and IC released 92.5% and 86.8% of the drug respectively in 60 min as shown in Figure7b[38].From the above results it was concluded that the SD formulation was a preferable choice over IC formulation.

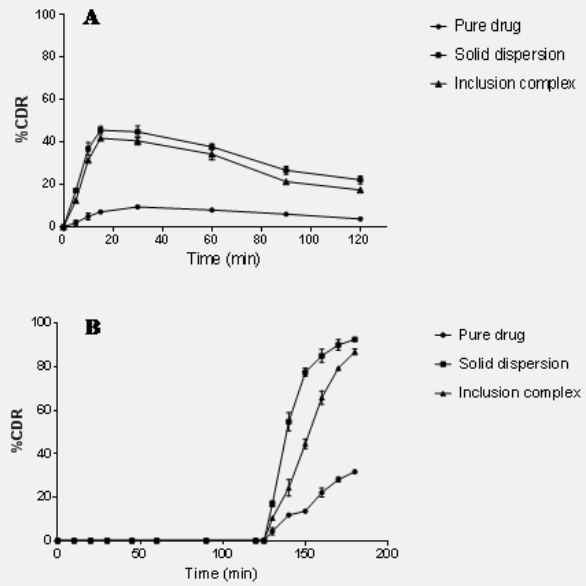

Figure 7: *In vitro* release profile: (a) 0.1N HCl and (b) phosphate buffer pH 6.8.

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Conclusion

From the past investigation, it was concluded that DCN has very poor aqueous solubility. Additionally, as per the literature survey it was revealed that the drug was also reported to have poor bioavailability which may be due to its poor solubility and dissolution. For that reason, SD and IC of DCN were developed to improve its dissolution profile which would expectedly increase its bioavailability. It was found that DCN was degrading in acidic (gastric environment) environment. Thus, acid resistant enteric coated tablets containing 50 mg equivalent DCN were formulated. Further from dissolution study of complexes formulated, DCN-SD formulation was a preferable choice over DCN-IC formulation. Moreover, FTIR and DSC studies demonstrated the absence of any distinguished interface between DCN and SD as well as DCN and PVP K30. PXRD data exhibited conversion of DCN from crystalline to an amorphous form which is accountable for the improved solubility. In vitro drug release of DCN from PVP K30 was superior to that of β-CD. Thus, SD coated with PVP K30 could be a better substitute to improve the aqueous solubility and dissolution rate of DCN. The dissolution profile was improved significantly in phosphate buffer 6.8 and showed that the SD was releases drug more quickly as compare to IC. Thus, conversion of DCN into SD improved the dissolution rate and acid protection coating protected the drug from gastric environment. Hence, it can be finally concluded that the Solid dispersion of DCN can be used for the treatment of osteoarthritis with enhanced solubility and bioavailability as compared to conventional marketed formulations.

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