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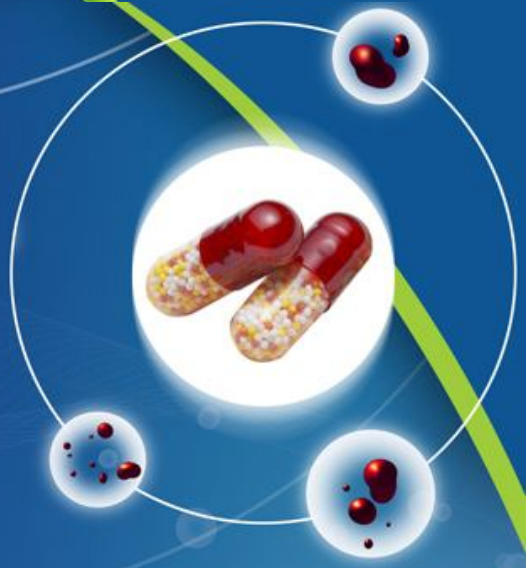

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Research Article

"FORMULATION, CHARACTERIZATION AND OPTIMIZATION OF MOUTH DISSOLVING TABLETS OF DIACEREIN: β-CYCLODEXTRIN SOLID DISPERSION

Gupta Khemchand* and Singhvi Indrajeet

Pacific College of Pharmacy, Udaipur (Rajasthan) -313024.

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ABSTRACT

Diacerein is a poorly water soluble drug and bioavailability from its crystalline form is very low. The purpose of the present investigation was to increase the solubility and dissolution rate of Diacerein by preparing a solid dispersion with β-cyclodextrin (β-CD) using Kneading method. The dissolution profiles of developed formulations in acetate buffer pH 4.5 containing 0.45% SLS were studied. The prepared complexes were characterized by Fourier transform infra red spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). For the preparation of Diacerein mouth dissolving tablets, a 1:2 (Diacerein: β-CD, Batch DK3) solid dispersion was used with L-HPC and croscarmellose sodium as a superdisintegrant. A 3^2 full-factorial design was employed to study the effect of independent variables, the amounts of L-HPC (X_1) and croscarmellose sodium (X_2) on dependent variables disintegration time and percentage friability. FTIR, DSC and PXRD data indicate that Diacerein was in the amorphous form, which explains the faster dissolution rate of the drug from its solid dispersions. Concerning the optimization study, multiple regression analysis reveals that an optimum concentration of croscarmellose sodium and a higher percentage of L-HPC are required for obtaining rapidly mouth dissolving tablets. Accelerated stability studies of mouth dissolving tablets carried out as per ICH guidelines revealed that the tablets were stable.

Key words: *Diacerein, β-cyclodextrin, L-HPC, Croscarmellose sodium, Mouth dissolving tablet, Factorial design (3^2)*

INTRODUCTION

Diacerein (DIA), 9, 10-dihydro-4, 5-bis (acetyl)-9, 10-dioxo-2-anthracene carboxylic acid, is a new anti-inflammatory anthraquinone derivative used mainly as a slow acting disease modifying drug in osteoarthritis, metabolized to active Rhein (Rh) [1, 2]. Rhein is thought to act via inhibition of interleukin-1band proteolytic enzymes, along with which it stimulates the synthesis of cartilage components and modifies the underlying pathological conditions [3, 4].

As it does not inhibit the synthesis of prostaglandins is emerging as better and safe therapeutic agent compared to NSAIDs. Diacerein is sparingly soluble in water (3.197 mg/L) which is the reason for poor dissolution rate, absorption and subsequently low and erratic bioavailability (35–56 %) [3]. Poor aqueous solubility could lead to failure of formulation development in spite of their potential pharmacokinetic activity. Thus, a strategy to improve bioavailability should aim at improving its aqueous solubility and overcoming first pass metabolism.

Innovative drug delivery systems known as melt in mouth or mouth dissolving tablets (MDT) are novel types of tablets that disintegrate/disperse/dissolve in saliva. Their

*Corresponding author
Khemchand Gupta
Pacific College of Pharmacy,
Udaipur (Rajasthan) -313024.
E-mail: khem_pharma@yahoo.co.in

characteristic advantage, such as administration without water anywhere anytime, leads to their suitability for geriatric and pediatric patients. They are also most suitable for drugs that undergo extensive fist pass metabolism. The benefits, in terms of patient compliance, rapid onset of action as the drug goes directly into systemic circulation and good stability, make these tablets popular as a dosage form of choice on the current market. However, a major challenge is to develop mouth-dissolving tablets of poorly soluble drugs[5].

Techniques that have been used to improve dissolution and bioavailability of poorly water-soluble drugs include micronization, use of surfactants and the formation of solid dispersions [6, 7]. Of the various approaches to improve drug solubility, complexation with cyclodextrin is being widely explored. Cyclodextrins are powerful carriers for improving the therapeutic efficacy of drugs with poor aqueous solubility through inclusion complexes.

Full-factorial experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. Factorial design evaluates the influence of various formulation parameters and their interaction with the lowest number of experiments, hence reducing the cost and time of the work[8]. In the present study, independent variables were assigned to the amounts of low- substituted hydroxyl propyl cellulose (X_1) and croscarmellose sodium (X_2) at three different levels, where as dependent variables were assigned to disintegration time and percentage friability. Multiple linear regression analysis of the results gave equations that adequately describe the influence of the independent variables on the selected responses.

Table 1: Abbreviations used to designate different solid dispersion batches

S. No	Batches	Diacerein: β-cyclodextrin ratio
1	DK1	1:1
2	DK2	1:1.5
3	DK3	1:2
4	DK4	1:2.5

The purpose of this study was to improve the solubility and dissolution rate of Diacerein by forming a binary complex with β-cyclodextrin by kneading method and to formulate its mouth dissolving tablets. A 3^2 full factorial design was also used to study the effect of formulation variables on the performance of these tablets.

MATERIALS AND METHODS:

The drug Diacerein was procured as gift sample from Zydus Cadila, Ahmedabad (India), low- substituted hydroxyl propyl cellulose (L-HPC), croscarmellose sodium (CCS) and β-cyclodextrin (β-CD) was procured from Ranbaxy Lab Ltd. Gurgaon (HR). Mannitol and magnesium Stearate was procured from Chem dyes Corpo. Rajkot. All other chemicals were procured locally and were of analytical grade.

Preparation of solid dispersion by kneading method (DK1-DK4)

Inclusion complex of Diacerein with β-cyclodextrin (β-CD) in different molar ratios (1:1, 1:1.5, 1:2 and 1:2.5) was prepared by kneading method. An accurately weighed amount of β-cyclodextrin was taken in glass mortar and kneaded with small amount of water to make slurry. Diacerein was added slowly into the slurry with continuous kneading. Once all the drug was incorporated into the slurry, the thick slurry was then kneaded for 45 min. The slurry was taken into the petri dish and dried at 40 ^{0}C. The dry powder was pulverized and passed through sieve # 100 and stored in dessicator. Different batches of Diacerein: β-CD solid dispersion is shown in table 1.

Characterization of solid dispersions

Estimation of drug content

Solid dispersions of Diacerein were tested for drug content uniformity. Solid dispersion equivalent to 50 mg of drug was weighed and transferred to 50 ml volumetric flask and volume was made up to mark with phosphate buffer pH 6.8. The solution was shaken thoroughly and filtered using Whatman filter

paper no. 41. The filtrate was suitably diluted with phosphate buffer pH 6.8 and analysed against blank solution by spectrophotometrically at 258 nm. This was done in triplicates and the average drug contents were estimated.

In vitro drug release profile

In vitro dissolution test for Diacerein solid dispersions (DKI-DK4) was performed in triplicate using USP dissolution apparatus type II (paddle method). The medium was 900 ml of phosphate pH 6.8 buffers, maintained at 37° C ± 0.5° C. The paddles were rotated at 75 rpm. The solid dispersions equivalent to 50 mg of Diacerein were taken in muslin cloth and tied to the paddle. Sample (5 ml) was withdrawn at different time intervals (5, 10, 15, 30, 45 and 60 minutes) and replaced with the same amount of pH 6.8 buffer to maintain the perfect sink condition. Sample (5 ml) was made up to 10 ml with pH 6.8 buffer (for pure drug: no dilution), filtered and the drug absorbance was measured at wavelength of 258 nm using a double beam spectrophotometer.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectroscopy is one of the most powerful analytical technique which offers the possibility of chemical identification. FTIR spectra of Diacerein, β-cyclodextrin (β-CD) and solid dispersions of Diacerein with β-CD (optimized batch DK3) were recorded using ATR spectrophotometer (Bruker- Alpha E). Samples were scanned from 4000 to 600 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) analysis of the samples (Diacerein, β-cyclodextrin, and solid dispersions of Diacerein with β-CD (optimized batch DK3) was carried out on a DSC-60 (Shimadzu Corporation, Japan). Samples were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10^0C per min over the temperature range of 50 - 300^0C.

Powder X-ray diffraction studies (PXRD)

This technique is extremely reliable to evaluate the changes in the crystalline phase and amorphization of solid drug as a result of excipient or carrier interactions. Crystallinity is indicated by the presence of sharp peaks that are absence in case of amorphous drugs.[9, 10]

The powder X-ray diffraction (XRD) of Diacerein, β-cyclodextrin and solid dispersions of Diacerein with β-CD (optimized batch DK3) was recorded using an X-ray diffractometer (Goniometer PW3050). The scanning rate was 10^0/min and diffraction angle (2θ) was 5-50^0.

Amongst, all the solid dispersion batches (DK1-DK4), the solid dispersion batch DK3 prepared by kneading method at molar ratio of 1:2 (Diacerein: β-CD) showed best in-vitro dissolution results was selected as optimized batch and used for formulating into mouth dissolving tablets.

Preparation of mouth dissolving tablets of diacerein

In the preparation of mouth dissolving tablets (MDTs), the technique of design of experiment (DOE) is used for optimizing the formula. Based on initial trials, levels of L-HPC and croscarmellose sodium were selected. Nine batches of mouth dissolving tablets were prepared from optimized solid dispersion according to 3^2 factorial design and evaluated.

Mouth dissolving tablets were prepared by direct compression method using optimized diacerein: β-CD solid dispersions (Batch DK3), low substituted hydroxyl propyl cellulose (L-HPC), croscarmellose sodium (CCS), mannitol, talc and magnesium stearate. The composition of tablets is shown in the table 2. All the ingredients (except talc and magnesium stearate) were passed through #60 separately, weighed and mixed in geometrical order in a poly bag for 10 minutes. Then lubricant and glidant (# 60) were added and mixed for further 5 minutes. The blend thus obtained was directly compressed using 8 mm flat round punches on a 10-station rotary tablet machine (Ratnakar, Ahmedabad, India). A batch of 50 tablets was prepared for all the designed formulations.

Table 2: Factorial design (3^2) batches of MDTs of Diacerein: β-CD (1:2) solid dispersion

S.No	Ingredients (mg/tab.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Solid dispersion*	151.88								
2	L-HPC	7.5	7.5	7.5	10	10	10	12.5	12.5	12.5
3	CCS	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5
4	Mannitol	80.62	78.12	75.62	78.12	75.62	73.12	75.62	73.12	70.62
5	Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
6	Talc	5	5	5	5	5	5	5	5	5
	Total	250	250	250	250	250	250	250	250	250

* Diacerein: β-CD (1:2, batch DK3) solid dispersion equivalent to 50 mg of Diacerein

Optimization by using 3^2 full factorial design

The statistical experimental design in this study was performed using Design expert® software version 9.0.3 (Stat-Ease, Inc., USA). In order to investigate the factors systematically, a 3^2 factorial design was employed. In this design 2 factors were evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations.[12, 13] The amount of L-HPC (X_1) and the amount of croscarmellose sodium (X_2) were selected as independent variables. The three factorial levels for each independent factors, low, medium and high, were coded as -1, 0 and 1, respectively. The disintegration time (Y_1) and percentage friability (Y_2) were selected as dependent variables. The layout of 3^2 factorial design for factorial batches F1-F9 are shown in table 3.

Table 3: Full factorial design (3^2) layout for mouth dissolving tablets (MDTs) of Diacerein: β-CD (1:2, DK3) solid dispersion

Batch codes	Variable levels in coded Form		Disintegration time (Sec.)*	Friability (%)
	X_1 (mg)	X_2 (mg)		
F1	-1	-1	79±3.60	0.53
F2	-1	0	68±2.64	0.61
F3	-1	1	54±2.0	0.73
F4	0	-1	72±3.46	0.48
F5	0	0	55±1.73	0.56
F6	0	1	47±1.0	0.63
F7	1	-1	56±2.0	0.42
F8	1	0	41±1.0	0.49
F9	1	1	29±1.73	0.55

Coded values	Actual values (mg)	
	X_1	X_2
-1	7.5	2.5
0	10	5
1	12.5	7.5

*Mean ± SD, n=3

X1: Indicates amount of L-HPC (mg), X2: Amount of croscarmellose sodium (mg)

DT: Disintegration time (seconds), F: Friability (%)

Evaluation of mouth dissolving tablets

Weight variation test was carried out as per IP 2010. The hardness of the tablets was measured using a Monsanto hardness tester and friability was measured using a Roche Friabilator. Wetting time and water absorption ratio of mouth dissolving tablets was carried out by using the method given by Bi et al. (1996)[14]. In this method a piece of tissue paper folded twice placed in a petri dish containing 6 ml of water. A tablet is placed on the paper, and the time for complete wetting was measured. The wetted tablet was then weighed and the water absorption ratio was calculated using the equation ($R = 100 (W_b - W_a) / W_a$), Where W_a and W_b are the weights of tablets before and after water absorption respectively. Disintegration test was carried by using the method given by Madgulkar AR et al. (2009)[15]. Drug content was determined by the method given by khemchand et al. (2013)[16].

In vitro drug release studies

In vitro dissolution test for mouth dissolving tablets was performed in triplicate using USP dissolution apparatus type II (paddle method). The medium was 900 ml of phosphate pH 6.8 buffers, maintained at 37° C ± 0.5° C. The paddles were rotated at 75 rpm. Sample (5 ml) was withdrawn at different time intervals (5, 10, 15, 30, 45 and 60 minutes) and replaced with the same amount of pH 6.8 buffer to maintain the perfect sink conditions. Sample (5 ml) was made up to 10 ml with pH 6.8 buffer, filtered and the absorbance was measured at wavelength of 258 nm against blank using a double beam spectrophotometer.

Accelerated stability studies

The stability studies were performed on the most promising mouth dissolving tablet formulation F9 according to ICH (International Conference on Harmonization) guidelines for six months[17]. The study was performed by keeping the prepared tablets in air tight high density polyethylene bottles and placed in a desiccator containing saturated solution of sodium chloride, which gave a relative humidity of 75±5%. The desiccator was placed in a hot air oven maintained at 40±2°C and samples were withdrawn at 30, 90 and 180 days. All the parameters (friability, disintegration time, wetting time, water absorption ratio, drug content and in-vitro drug release) of formulation were measured at predetermined time interval.

RESULTS AND DISCUSSION

Characterization of solid dispersions

Estimation of drug content

The results of estimation of drug content (%) from sold dispersions of Diacerein with β-CD are shown in table 4. The drug content was found to be in the range of 96.37 to 98.76% (DKI- DK4), indicating the acceptability of kneading method for preparation of solid dispersions. Low values of standard deviation in drug content of solid dispersion indicated uniform drug distribution in all the prepared batches.

Table 4: Drug content (%) from solid dispersion batches DK1 to DK4

	DK1	DK2	DK3	DK4
Drug content (%)*	96.37±1.08	97.84±0.92	98.76±0.68	96.88±1.24

*(Mean± S.D.): n=3

In vitro drug release profile

Dissolution studies of pure Diacerein and all prepared solid dispersions were carried out in phosphate buffer pH 6.8. From these data, it is evident that the onset of dissolution of pure Diacerein was very low. The drug released from pure Diacerein (PD) was only 56.11% in 60 minutes during the in vitro dissolution study, suggesting a strong need to enhance the dissolution of Diacerein.

The in vitro dissolution profiles of the pure Diacerein and solid dispersions containing various ratios of Diacerein to β-CD (DK1-DK4) are shown in figure 1. The solid

dispersions prepared by kneading method in the ratios of 1:1, 1:1.5, 1:2 and 1:2.5 (Diacerein: β-CD) were showed 76.34 %, 93.08%, 99.26 % and 91.25 % drug release respectively at the end of 60 minutes. However, the inclusion complex at a molar ratio of 1: 2 (DK3) achieved maximum dissolution rate of the drug. The enhancement of dissolution of Diacerein from the Diacerein-β-CD solid dispersions may be due to several factors such as lack of crystallinity, increased wettability and dispersibility of the drug from dispersion. On further increasing the amount of β-cyclodextrin in solid dispersion i.e. formulations at 1:2.5 ratio (DK4) showed slightly decrease in dissolution rate, this might be due to the higher amount of carrier itself takes time to dissolution.

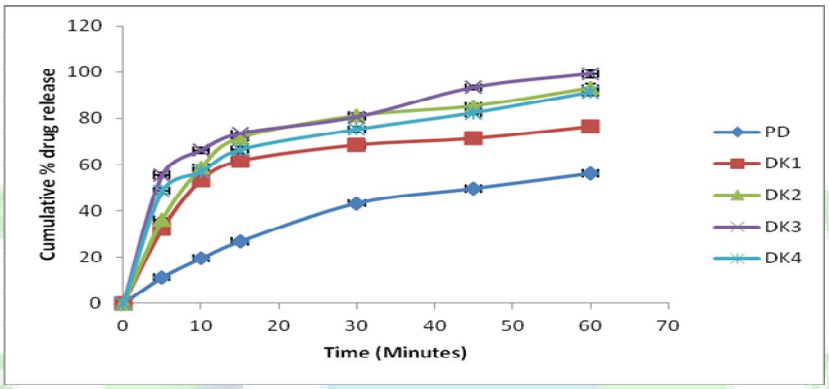
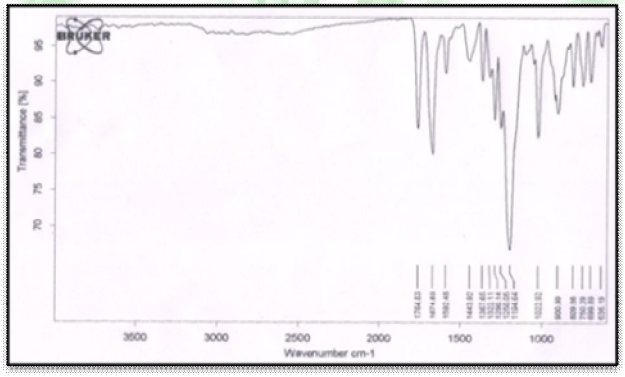


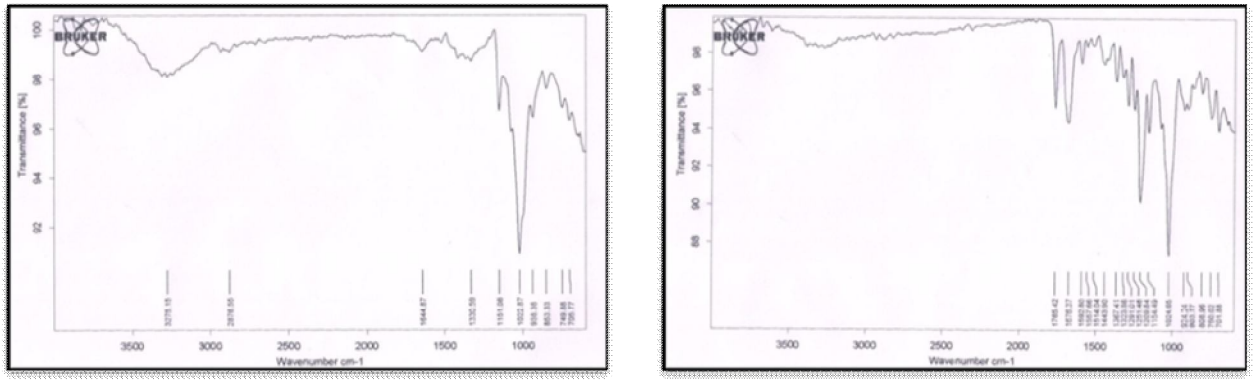
Figure 1: In vitro drug release from Diacerein: β-CD solid dispersion in pH 6.8 Phosphate buffer

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of Diacerein, β-cyclodextrin and solid dispersions of Diacerein with β-CD are shown in figure 2 A, B and C respectively. The IR spectra of Diacerein-β-CD complexes showed considerable differences when compared with those of their corresponding constituents. Upon complexation, a significant shift in the characteristic peaks of the guest molecule, either to higher or lower frequency, disappearance and broadening of the peaks of the guest proves interaction between the drug and β-CD molecules[18]. The principal absorption peaks of Diacerein at 1764.83, 1674.83 and 1194.49 cm^{-1} shifted to a slightly higher frequency at 1765.42, 1676.37 and 1209.84 cm^{-1} respectively and broadening of these peaks were also observed. The observed shifts and broadening of the peaks clearly indicated the presence of host–guest interactions and formation of monomeric drug dispersion as a consequence of the interaction with β-CD, which could result in inclusion of the Diacerein in the hydrophobic cavity of the β-CD. The binary system of Diacerein-β-CD did not show any new peaks, indicating the absence of chemical bond formation in binary system.



A. Diacerein

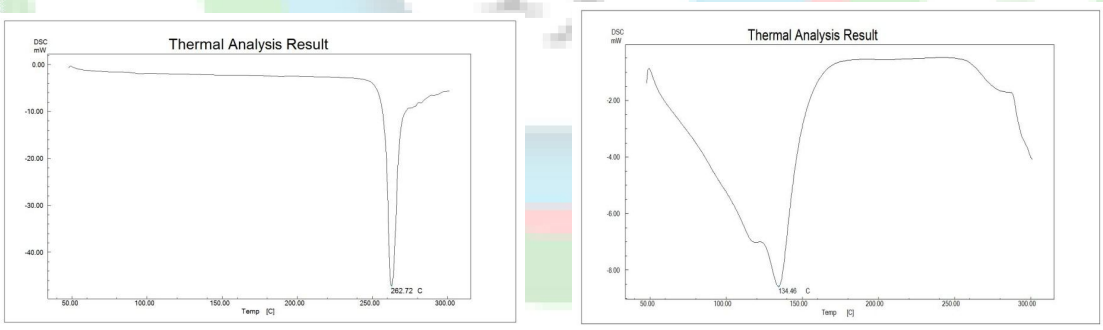


B. β-cyclodextrin **C. Diacerein with β-CD (optimized batch DK3)**

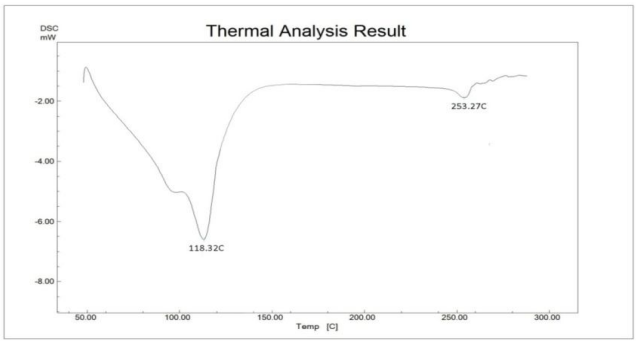
Figure 2: FTIR spectra of Diacerein (A), β-cyclodextrin (B) and solid dispersion of Diacerein with β-CD (C)

Differential Scanning Calorimetry (DSC)

In order to confirm the formation of inclusion complex, thermal behavior of Diacerein and its complex with β-CD was studied using DSC. On formation of inclusion complex, the physical characteristics like boiling, melting and sublimation point either get shifted or disappear within the decomposition range of CD lattice. The thermogram of Diacerein, β-CD and complex with β-CD are shown in the figure 3 A, B & C respectively. Diacerein showed an endothermic peak at 262.72 ºC corresponding to its melting point. Diacerein in its complex with β-CD showed very small peak at 253.27 ºC while another peak at 118.32 ºC was due to loss of water from β-CD molecule. The peak in complex was shifted considerably in comparison of Diacerein which might be due to entrapment of Diacerein in the cavity of β-CD and dispersed in the free state between inclusion complexes.



A. Diacerein **B. β-cyclodextrin**

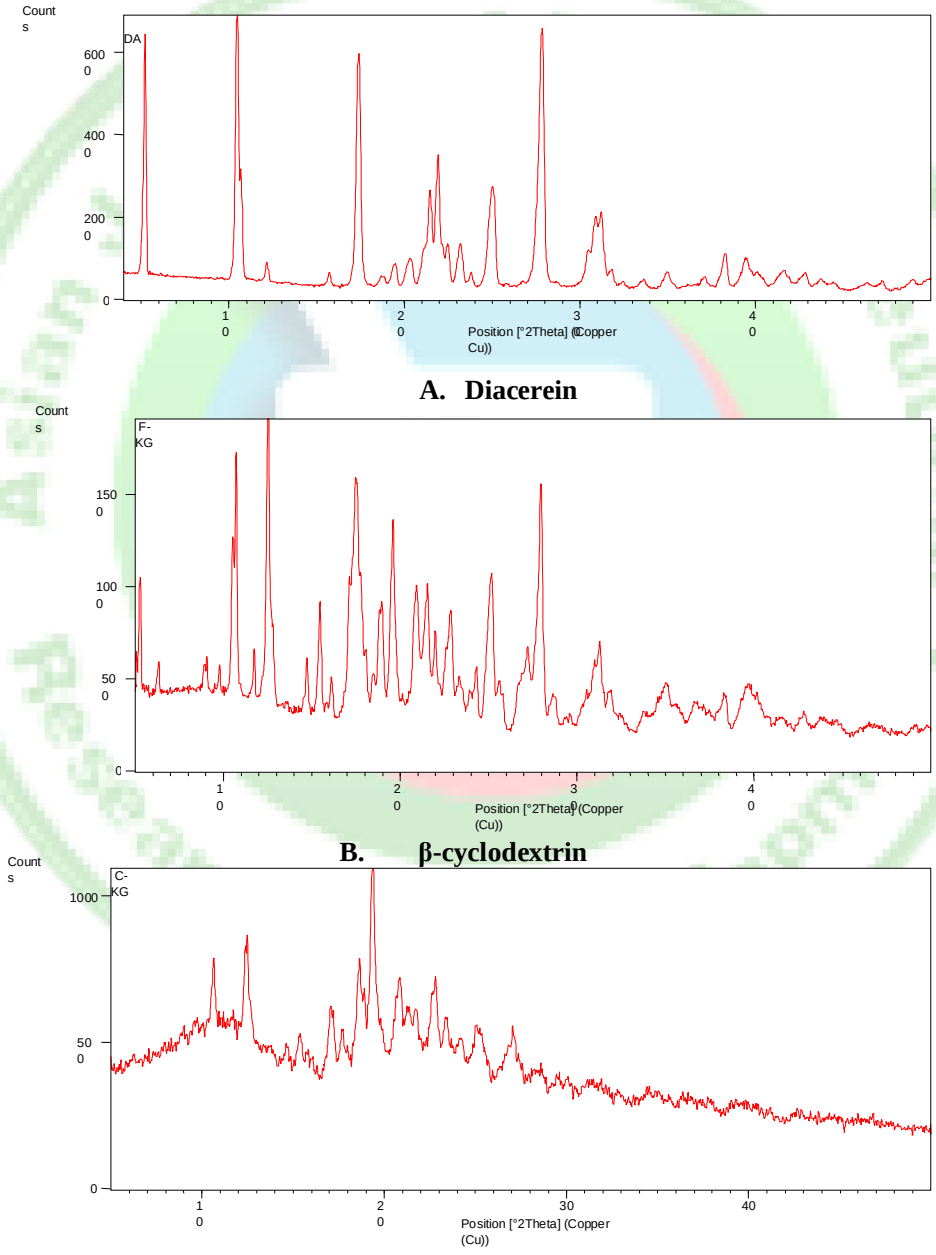


C. Solid dispersion of Diacerein with β-CD (optimized batch DK3)

Figure 3: DSC spectra of Diacerein (A), β-cyclodextrin (B) and Solid dispersion of Diacerein with β-CD (C)

Powder X-ray diffraction studies (PXRD)

The XRD patterns of Diacerein, β-CD and Diacerein–β-CD inclusion complexes are shown in figure 4 A, B & D respectively. The powder X-ray diffraction pattern of pure Diacerein exhibited a series of intense peaks at 2θ value of 10.4°, 17.4°, 15.045°, 25.375°, 27.9°, 32.27°, 37.09° and 41.45° which were indicative of their crystallinity. However, the patterns of β-CD are crystalline in nature with major peaks at 2θ values of 4.75°, 12.7°, 19.7°, 21.1°, 22.8°, 24.3° and 35.9°. The inclusion complexes of Diacerein-β-CD in the ratio of 1:2 prepared by kneaded method have completely diffused diffraction patterns and some peaks were also absent in the complex. These results suggested the amorphization of the drug and formation of amorphous inclusion complexes. These results of PXRD were strongly supported by the above DSC observations.



C. Solid dispersion of Diacerein with β-CD (optimized batch DK3)

Figure 4: X-ray diffraction patterns of Diacerein (A), β-cyclodextrin (B) and solid dispersion of Diacerein with β-CD (C)

Evaluation of mouth dissolving tablets

The data obtained for post-compression parameters such as weight variation test, hardness, wetting time, water absorption ratio and drug content of factorial batches F1- F9 are shown in the table 5. The data obtained for disintegration time and friability are shown in table 3.

Tablets obtained were of uniform weight with acceptable weight variation limits as per IP specification i.e., below 7.5 %. Hardness of tablets was found to be 3.50 to 4.83 kg/cm^2. Water absorption ratio and wetting time were found to be in the range of 56.64 to 74.04 % and 22.67 to 62.33 seconds respectively. Drug content was found to be in the range of 98.22 to 101.08 %, which was within acceptable limits. Friability below 1% was an indication of good mechanical resistance of the tablets. The most important parameter that needs to be optimized in the development of MDTs is the disintegration time of tablets. It was observed that the disintegration time of the tablets decreased from 79 to 29 seconds with increasing in the level of L-HPC and croscarmellose sodium both.

Table 5: Evaluation parameters of mouth dissolving tablets (MDTs) of F1-F9

Batches	Weight variation test (mg)***	Hardness (kg/cm^2)**	Wetting time (sec)*	Water absorption ratio (%)*	Drug content (%)*
F1	249±2.52	3.50±0.55	62.33 ±1.15	56.64±1.16	98.58 ± 0.99
F2	252±2.16	3.66±0.51	53.67 ±0.57	59.26 ±0.71	98.22 ± 1.56
F3	250±2.35	3.66±0.51	40.0 ± 2.0	63.41±2.53	99.29 ± 1.07
F4	251±1.54	4.16±0.41	51.33 ±1.52	60.45±2.14	99.24 ± 2.68
F5	248±1.66	4.50±0.55	37.0 ±1.0	62.74 ±0.67	101.08 ± 0.81
F6	250±0.96	4.66±0.52	32.67 ± 2.08	65.31±1.12	98.90 ± 1.92
F7	249±1.72	4.50±0.55	41.33 ± 1.52	64.39±1.18	99.65 ± 0.84
F8	251±1.14	4.66±0.52	31.0 ± 2.64	68.31±1.96	100.54 ± 1.35
F9	250±0.82	4.83±0.82	22.67 ± 2.51	74.04±1.23	99.09 ± 1.41

(Mean ±S.D), ***n=20, **n=6, *n=3

In vitro drug release studies

Figure 5 and 6 showed the dissolution profiles of Diacerein from mouth dissolving tablets of factorial batches F1-F5 and F6-F9 respectively. The cumulative percentage drug release of formulation batch F1-F9 was found to be in the range of 88.14 to 100.21 % at the end of 60 minutes. The cumulative percentage of the drug released from formulation F9 found by the dissolution test showed the better drug release of 100.21% at the end of 60 minutes indicated good bioavailability of the drug from these formulations. As the amount of L-HPC and CCS increased, drug released was also increased due to the synergistic effect of both superdisintegrant (L-HPC & CCS) since L-HPC acts by swelling action and croscarmellose sodium (CCS) acts by swelling and wicking both. **The formulation batch F9 containing 5 % L-HPC and 3% CCS showed good hardness, least weight variation, shortest wetting and disintegration time, high water absorption ratio and showed 100.21 % drug release in 60 minutes was selected as optimized batch and used for accelerated stability studies**

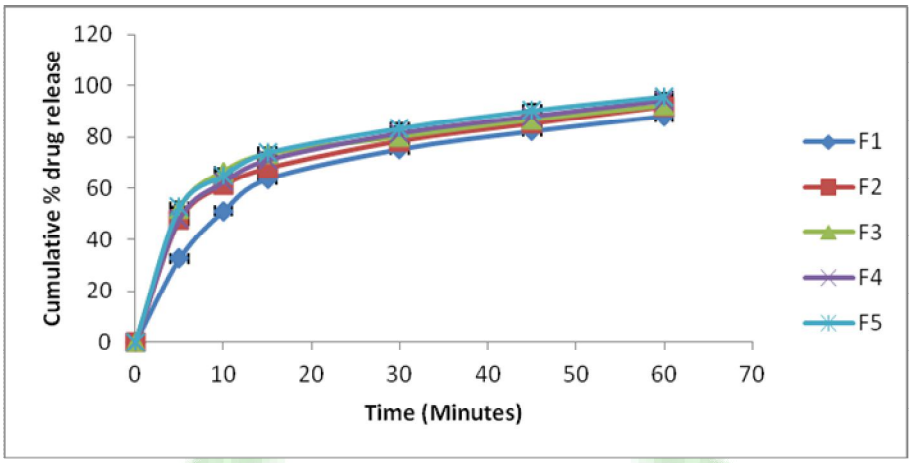


Figure 5: In vitro drug release (%) from Diacerein: β-CD mouth dissolving tablets (F1 to F5)

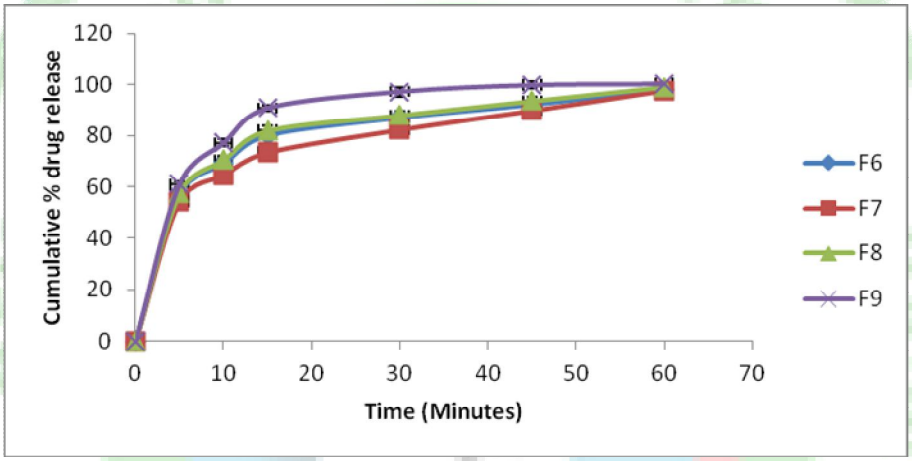


Figure 6: In vitro drug release (%) from Diacerein: β-CD mouth dissolving tablets (F6 to F9)

Optimization by using 3^2 full factorial design

To investigate the factors systematically, a factorial design was employed (Table 3). As shown in equation 1, a statically model incorporating interactive and polynomial terms was used to evaluate the responses.

$Y=b_0 + b_1X_1+b_2X_2+b_{12}X_1X_2+b_1^2X_1^2+ b_2^2X_2^2$ Eq.1

Where Y, is the dependent variables namely disintegration time and percent friability; b_0 is the arithmetic mean response of the 9 runs; and b_1 and b_2 are the estimated coefficients for the independent factors X_1 and X_2, respectively. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms ($X_1^2$and X_2^2) are including investigating nonlinearity.

To optimize the properties of MDTs that contain Diacerein: β-CD solid dispersed drug, three concentration levels of L-HPC (X_1), low (3% w/w), medium (4% w/w) and high (5% w/w) and three concentration levels of CCS (X_2), low (1% w/w), medium (2% w/w) and high (3% w/w) were used in the factorial design experiment.

Based on a 3^2 randomized full factorial design, 9 formulations (F1-F9) were prepared. The design and the results from the 9 experiments are presented in table 3. The disintegration time and percent friability for the 9 batches (F1-F9) showed a wide variation (i.e., 29 -79 seconds and 0.42% - 0.73%

respectively). The data clearly indicated that the disintegration time (Y_1) and percent friability (Y_2) values were strongly dependent on the selected independent variables. The obtained data were analyzed using a Design expert® software version 9.0.3 in order to generate mathematical models for each of the responses. The results of analysis for each response variable were as follows:

Disintegration time (Y_1) = 57 -12.5 X_1 - 12.83X_2- 0.5 X_1 X_2 – 3.5 X_1^2+ 1.5 X_2^2 ------ Eq.2

Friability (Y_2) = 0.55 -0.068 X_1 + 0.080X_2- 0.018X_1 X_2 – 0.001X_1^2+ 0.003X_2^2 ------ Eq.3

Analysis of variance (ANOVA) was performed to evaluate the significance of the quadratic model on the responses and to establish their quantitative effects. Table 6 & 7 summarizes the effects of the model terms and associated p values for all responses. In this case, both the models generated for disintegration time and percent friability were significant. The high values of correlation coefficient for disintegration time and percent friability (0.9937 & 0.9948 respectively) indicate a good fit of model.

In case of the disintegration time (Y_1), X_1 and X_2 are significant model terms. The results of multiple linear regression analysis revealed that on increasing the amount of either L-HPC or CCS, a decrease in disintegration time was observed because both the coefficients X_1 and X_2 bear a negative sign with p value 0.0006 & 0.0006 respectively. The influence of CCS on disintegration time is quite prominent and when higher amount of CCS was used, higher water uptake swelling and deformation of the CCS take place, which gave internal pressure on tablet to disintegrate. It was obvious that in the presence of higher amount of L-HPC, swelling was facilitated. Minimum value of disintegration time was observed at the highest level of both the polymers. The corresponding contour plot of disintegration time is shown in figure 7.

Table 6: Analysis of variance (ANOVA) for response surface quadratic model for MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion (Disintegration time, sec)

Source	Sum of Squares	Degree of Freedom	Mean Square	F-value	p-value Prob > F	
Model	1955.67	5	391.13	95.14	0.0017	Significant
X_1:L-HPC	937.50	1	937.50	228.04	0.0006	
X_2: CCS	988.17	1	988.17	240.36	0.0006	
X_1X_2	1.00	1	1.00	0.24	0.6557	
X_1^2	24.50	1	24.50	5.96	0.0924	
X_2^2	4.50	1	4.50	1.09	0.3723	
Residual	12.33	3	4.11			
Cor Total	1968.00	8				
R^2	0.9937					

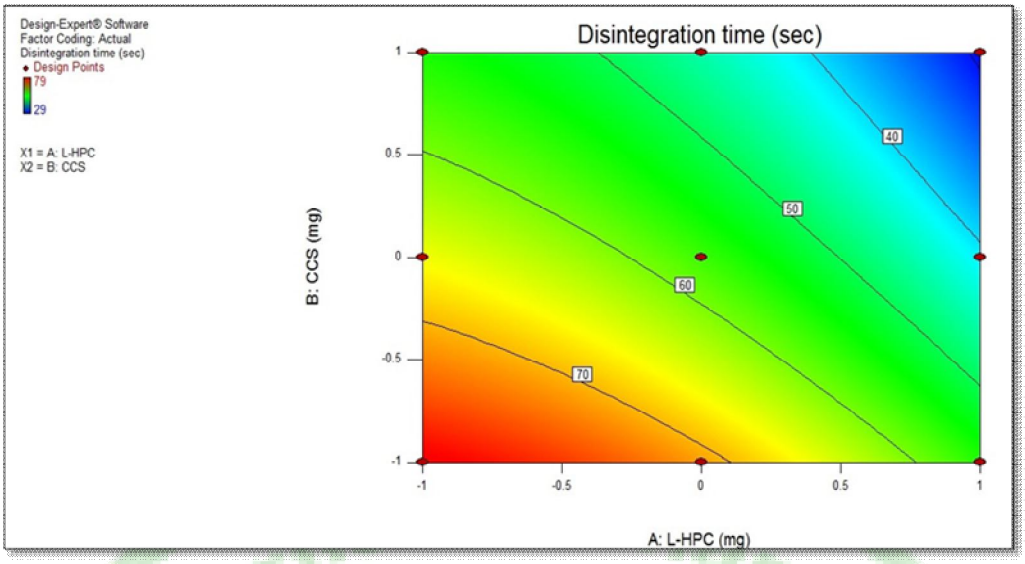


Figure 7: Contour plot of disintegration time for MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion

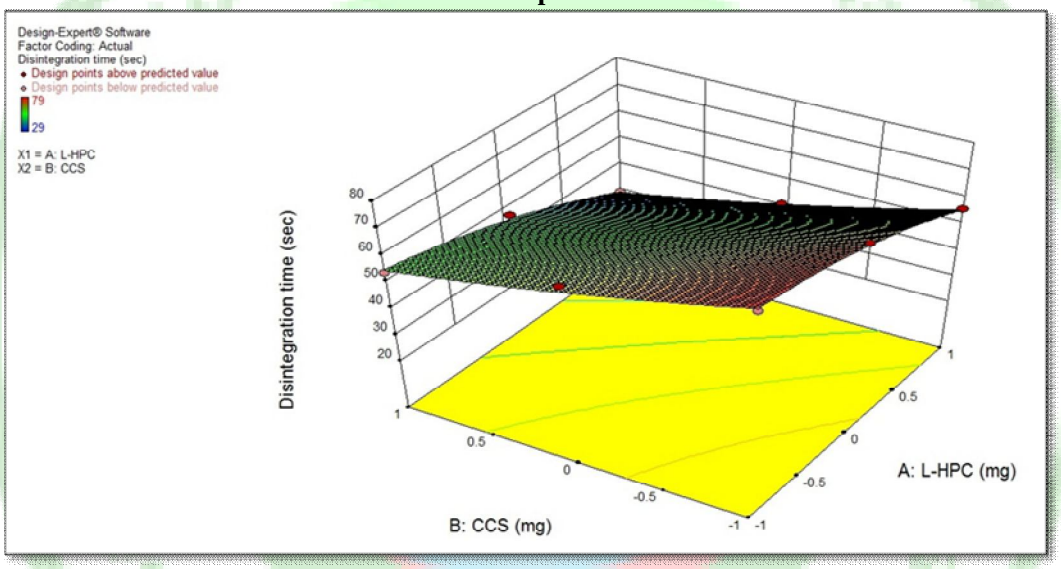


Figure 8: Response surface plot showing the effect of L-HPC and CCS on disintegration time (Y_1) of Diacerein: β-CD MDTs

In case of the friability (Y_2), terms X_1 (L-HPC concentration) and X_2 (CCS concentration) were identified as the most significant factors with p value 0.0006 and 0.0004 respectively, whereas the interactive term X_1X_2 was less significant with p value (0.0483) just below the significant level ($p<0.05$). An increase in the amount of CCS leads to an increase in friability because the coefficient X_2 bear a positive sign. When a higher amount of CCS was used, low compressible tablets were produced, which were mechanically weak. The increase in the amount of L-HPC results in decreased friability values because X_1 bear a negative sign. L-HPC was known to produce mechanically stronger tablets. The polynomial terms X_1^2 and X_2^2 had a very minor quadratic effect on percent friability. The corresponding contour plot of friability is shown in figure 9.

The software was used to generate response surface plots (three dimensional) that simulate the influence of the independent factors on each response individually. The response surface plot for disintegration time and friability are presented in figures 8 and 10 respectively. These plots could provide uninterrupted visual assessment of the change in the response surface as a function of varying the independent factors, individually and simultaneously.

Table 7: Analysis of variance (ANOVA) for response surface quadratic model for MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion (Friability, %)

Source	Sum of Squares	Degree of Freedom	Mean Square	F-value	p-value Prob > F	
Model	0.068	5	0.014	115.09	0.0013	Significant
X_1:L-HPC	0.028	1	0.028	238.25	0.0006	
X_2: CCS	0.038	1	0.038	326.55	0.0004	
X_1X_2	1.225E-003	1	1.225E-003	10.42	0.0483	
X_1^2	5.556E-006	1	5.556E-006	0.047	0.8419	
X_2^2	2.222E-005	1	2.222E-005	0.19	0.6931	
Residual	3.528E-004	3	1.176E-004			
Cor Total	0.068	8				
R^2	0.9948					

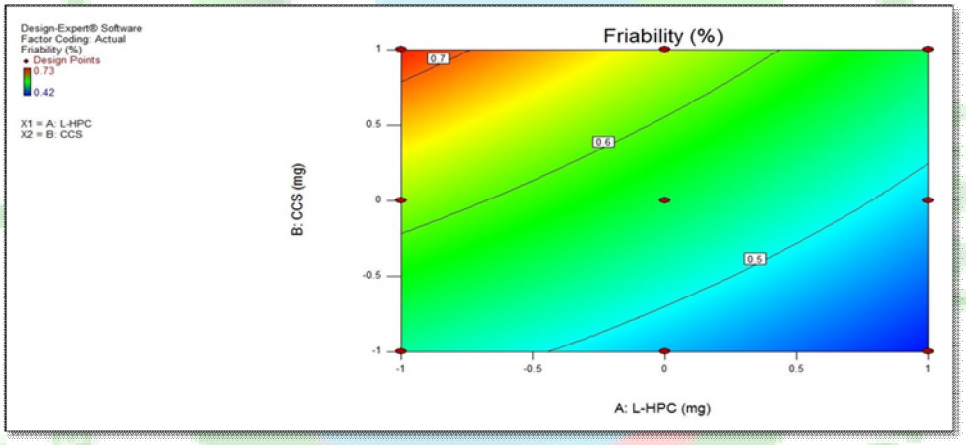


Figure 9: Contour plot of friability for MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion

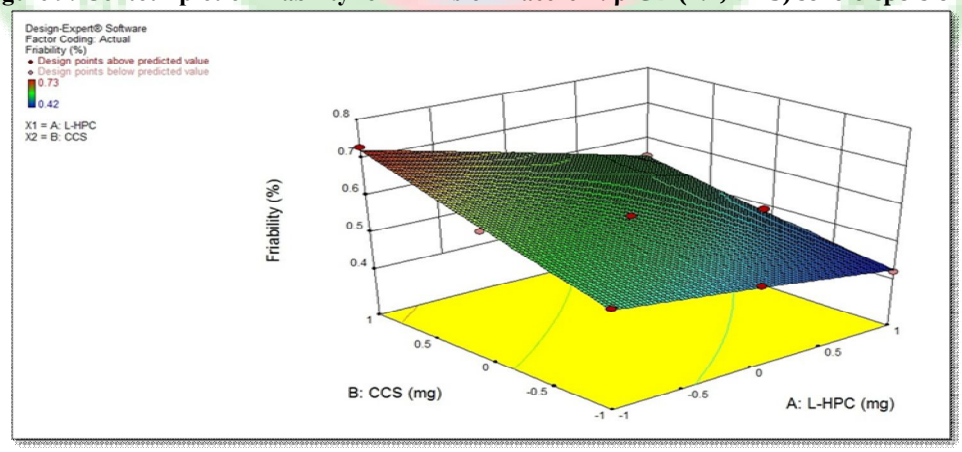


Figure 10: Response surface plot showing the effect of L-HPC and CCS on percent friability (Y_2) of Diacerein: β-CD MDTs

Model validation and optimization of the formulation parameters

Validation of model was done by graphical method (Overlay plot). To validate the regression equations or model, three check

points batches of X_1 = 0.895, X_2 = 0.959, X_1 = 0.968, X_2 = 0.536, and X_1 = 0.249, X_2 = 0.925 were selected and prepared. The composition of the check points formulations, their predicted and experimental values for disintegration time and friability are shown in table 8. The correlation plots between the observed and predicted values of the disintegration time and friability are shown in figure 12 A and B respectively. The overlay plot for disintegration time and friability are shown in figure 11.

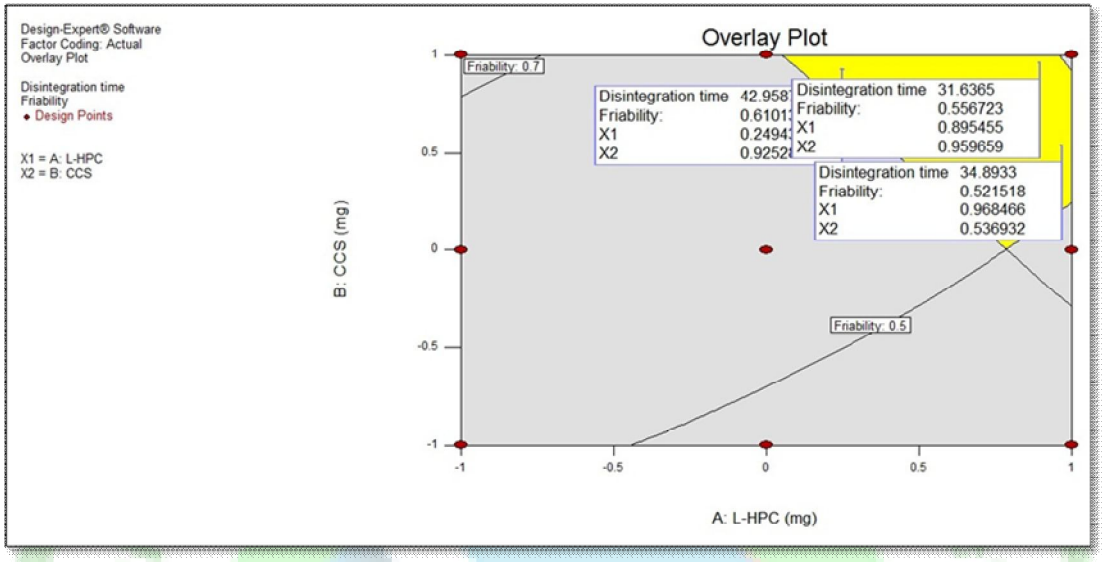


Figure 11: Overlay plot for disintegration time and friability of MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion

Table 8: Observed and predicted responses for check point formulations of MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion

Check Point Formulations	X1	X2	Disintegration time (sec)		Friability (%)	
			Predicted	Observed*	Predicted	Observed
FCP1	0.895	0.959	31.63	30.67±1.15	0.556	0.568
FCP2	0.968	0.536	34.89	35.0±2.0	0.521	0.538
FCP3	0.249	0.925	42.95	42.33±2.51	0.610	0.596

*Mean ± SD, n=3

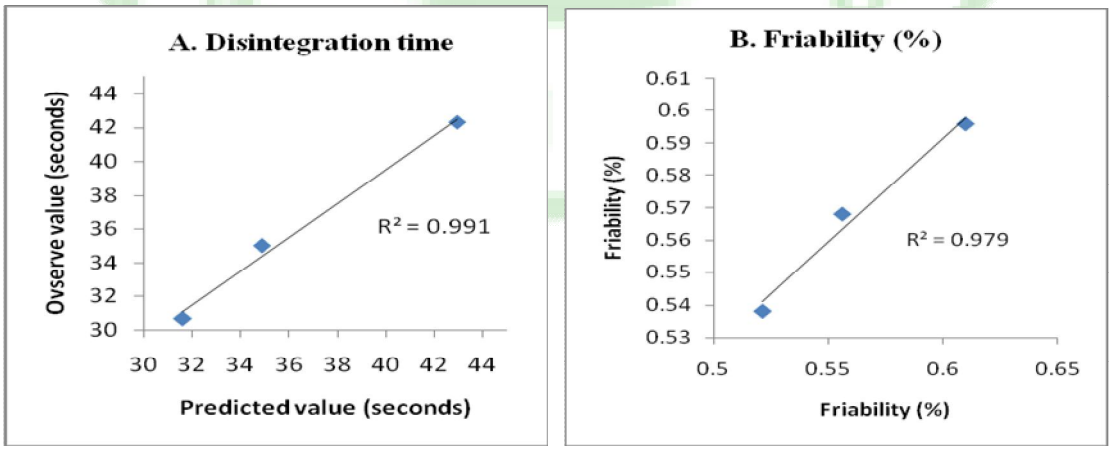


Figure: 12: Linear correlation plots of disintegration time (A) and friability (B) for check points formulations of MDTs of Diacerein: β-CD (1:2, DK3) solid dispersion

Comparison of the magnitudes of the observed responses of three formulations taken as the checkpoints, with those predicted using response surface methodology (RSM), indicated that the observed values of disintegration time and percent friability of the tablets for the check point formulations were in close agreement with the values predicted by the model. The linear correlation plots drawn between the predicted and observed values demonstrated high values of R^2 (0.991 for disintegration time and 0.979 for friability) confirmed the goodness of model.

Accelerated stability studies

No significant variation (1 to 3%) in drug release and other evaluation parameters were observed at accelerated conditions of 45 ± 2º C with 75 ± 5% RH. Therefore, it was concluded that the batch F9 was stable over the chosen temperature and humidity for 6 months. The results are shown in table 9.

Table 9: Accelerated stability studies of the optimized formulation F9 at 40 ± 2 °C/ 75 ± 5 % RH for six months

Parameters	Days			
	0	30	90	180
Friability (%)	0.55	0.55	0.57	0.60
Disintegration time (sec) *	29.0±1.73	29.67±1.73	30.0±2.0	31.33±1.15
Wetting time *	22.67±2.51	23.0±1.0	24.33±0.57	25.67±2.51
Water absorption ratio*	74.04±1.23	74.68±1.48	77.21±2.67	75.35±2.13
Drug content (%)*	99.09±1.41	98.25±0.78	98.12±1.65	97.36±1.18
In vitro drug release in 60 Minutes*	100.21±0.65	99.47±1.56	98.15±2.33	97.30±1.44

*(Mean± S.D.): n=3

CONCLUSION

The present study concluded that β-cyclodextrin is a suitable carrier for the preparation of Diacerein solid dispersions. FTIR and DSC study demonstrated absence of any notable interaction between Diacerein and β-CD. PXRD data showed conversion of Diacerein from crystalline to an amorphous form which is responsible for the enhanced solubility. Experimental design provided a better understanding of the effect of formulation variables on the quality of mouth dissolving tablets containing a solid dispersion of a hydrophobic drug and reveals that an optimum concentration of croscarmellose sodium and a higher percentage of L-HPC are required for obtaining rapidly mouth dissolving tablets. The optimal batch (F9) exhibited a disintegration time of 29 sec, percentage friability of 0.55%, wettability of 22.67 sec and 100.21 % drug release in 60 minutes.

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