RESEARCH PAPER

Functionality improvement of Diacerein by Crystallo-co-agglomeration using a Quality by Design approach and Central Composite Design

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ABSTRACT

The aim of present work was to improve physicochemical properties of model drug Diacerein by crystallo-co-agglomeration (CCA) in the presence of different polymers and excipients. Identification of Quality Target Product Profile and Critical Quality Attributes were done using Risk assessment. CCA was formulated by applying Central composite design. CCA was further studied for its topographical, micromeritic, mechanical, compressional, and dissolution properties. Prepared CCA showed improvement in flow and packability with rich drug content (92.28%). Heckel parameters indicated greater plastic deformation and tensile strength compared to the pure drug. CCA showed negligible elastic recovery (0.7745%) compared to the pure drug (4.0324%). Dissolution of the drug was increased to 2.69-folds compared to the pure drug after 60 min. The amount of directly compressible diluents could be minimized in tablet formulation, which was a considerable improvement in the properties of the drug for making directly compressible form. The study highlights an improvement of processing characteristics of Diacerein by CCA using an integrated approach of QbD.

KEYWORDS: Diacerein, Crystallo-co-agglomeration, Central composite design, Quality by design, physicomechanical parameters,

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1. INTRODUCTION

Majority of active pharmaceutical ingredients (APIs) available on the market belong to the BCS Class II category. The industry is facing a lot of manufacturing issues for APIs which show poor dissolution. It has also been observed that the majority of APIs having poor dissolution profiles have also shown poor flow property and compressibility.

It is very difficult to prepare solid oral dosage form with such kinds of APIs. Industry personal has to control various process and material parameters. Due to the fundamental property defects like poor physicochemical and poor mechanical properties, variability in process increases. Quality by design (QbD) has been developed as a systematic approach for the development of a robust pharmaceutical product. It is a process to identify critical parameters involved with efficacy and safety (critical quality attributes, CQA) as well as process and materials (critical process parameters, CPP and critical material attributes, CMA) used in the manufacturing. Drugs with poor compressibility and flowability are not suitable for direct compression. In recent times, particle engineering/design techniques are widely used in pharmaceutical industries to modify primary (particle shape, size, crystal habit, crystal form, density, porosity dust generation, etc.) as well as secondary (flowability, compressibility, compactibility, consolidation, reduced adhesion of

formulation to the processing equipment, reduction in air entrapment during processing, etc.) properties of pharmaceuticals [1]. Especially, improvement in the efficiency of the manufacturing process and high degree of particle functionality can be achieved by these techniques. Novel techniques like pelletization [2], fluidized bed granulation , spray drying [3], spray congealing, melt solidification [4], [5], [6], melt sonocrystallization [7], co-crystallization [8], spherical crystallization (SC) [9], [10], crystallo-co-agglomeration (CCA), etc.[11], [12], [13] have been considered as a value addition to existing ones. Simultaneous improvement in the extent and rate of dissolution of poorly soluble drugs along with its mechanical properties is highly desirable which can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy [14]. Physical modification focuses on particle size reduction or generation of amorphous states. [15], [16]

Table: 1 Quality target product profile elements

QTPP Elements	Target	Justification
Dosage form	Tablet	Most common oral dosage form
Dosage design	Flat faced and Uncoated tablet	Easy for swallow. Patient compliance
Route of administration	Oral	Most convenient route for administration
Dosage strength	50-100 mg	Pharmaceutical equivalence requirement : same strength
Drug Product Quality Attributes	Physical attributes	Pharmaceutical equivalent requirement. Must meet the compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).
	Identification	
	Assay	
	Mean diameter	
	Angle of repose	
	Crushing strength	
	%yield	

Crystallo-co-agglomerates (CCA) are the crystals of drug aggregate in the form of small spherical particles along with excipients and solvents that were used to develop an intermediate material with improved micromeritic and mechanical properties.

In this study, CCA of model drug Diacerein (DIA) are prepared using various excipients. A concept of QbD are applied in the present study to explore its practical application in designing CCA followed by directly compressible tablets for beginners.

Diacerein (DIA), chemically known as 4, 5-diacetyloxy-9,10- dioxoanthracene-2-carboxylic acid, is approved for the treatment of osteoarthritis, has mild anti-inflammatory, antipyretic, analgesic activities, and is metabolized to the diacetyl precursor Rhein.[17], [18], [19] The molecular weight of DIA is 368.3 g/mol, and the LogP is 2.4. It exists as a yellow crystalline material with a melting point of 255.2 °C. On the basis of its aqueous solubility, it is classified as a BCS II drug (~3.197 mg/L) which limits its oral absorption (35−56%). [20] Additionally, DIA shows poor processing characteristics concerning flowability, tabletability, manufacturability, and compressibility, further leading to difficulties in the development of pharmaceutical oral solid forms.[21]

2. MATERIALS AND METHODS

DIA was a kind gift from Ami Lifesciences Pvt. Ltd. (Baroda, India). Purified Talc was purchased from S. D. Fine Chem Limited, Mumbai, India. Hydroxy propyl methyl cellulose E50 LV IP was procured from S. D. Fine chems Ltd. Mumbai, India. Polyethylene glycol 400 NF (PEG) and polyvinyl pyrrolidone K30 IP (PVP K30) were purchased from Merck Pvt. Limited, Mumbai, India, and Sisco Research Laboratories Pvt. Ltd., Mumbai, India, respectively. All other chemicals used were of analytical grade (Merck Pvt. Limited, Mumbai, India) and double-distilled water was utilized throughout the study.

2.1. Significant QTPP and CQAs

Initially, adopting an FbD-based approach of CCA development the QTPP was set-up involving a potential review of the quality features of the drug product capable of enhancing the physic-mechanical properties of Diacerein for achieving maximal therapeutic effects [22]. The role of various elements of QTPP in developing CCA has clearly been discussed in Table 1. Similarly, Tables 2 and 3 illustrate the potential CQAs, CMAs, and CPPs affecting the performance of the CCA formulations along with suitable justification(s) for each of them, respectively.

2.2. Risk assessment

A risk assessment plan was conducted to identify the possible relations among drug and excipients with various unit operations, and estimating the probability of risk(s) or failure(s), if any [22]. The Ishikawa fish-bone diagram was constructed to organize the risk analysis operation for determining the causes and sub-causes affecting the CQAs of drug product. Figure 1 describes the resultant fish-bone diagram depicting the effect of key material attributes and/or processing parameters for the development of CCA of Diacerein. Moreover, the prioritization exercise was carried out for selecting the factors with high risk by structuring the risk estimation matrix (REM) depicting the potential risk(s) associated with each of the material attribute(s) and/or process parameter(s) on the potential CQAs explicatively by assigning low, medium, and high values to each of them.

Table 2. Critical quality attributes for CCA and their justification.

Critical Quality Attributes (CQA)				
Quality attributes of the drug products		**Target**	**Is it CQA?**	**Justification**
Physical Attributes	**Appearance**	Colour and shape will acceptable by patients	No	Colour, shape and appearance having not direct effect on safety, efficacy and economy
	Odor	Not unpleasant odor	No	Not acceptable odor having not direct effect on safety and efficacy
	Mean size	Diameter of agglomerates effect on compression	Yes	Having specific effect on direct compression and directly effect of product quality and economy
Angle of repose		Agglomerates must having Angle of repose below 25ɵ	Yes	Having specific effect in experimentation for ease of flow of material and ease to flow through hopper
Crushing Strength		Agglomerates must having 40-55 gm crushing strength range	Yes	Having an effect on tablet compression
% Yield		Yield needed more for tablet preparation	Yes	Having effect on economy and quality of product

Table 3. Critical process parameters (CPP) and Critical material attributes (CMA) for CCA and their justification.

Critical process parameters (CPP) and Critical material attributes (CMA)			
Process parameter &material attributes of the drug products	**Target**	**Is it Critical?**	**Justification**
Agitation Speed	Appropriate, effect on quality attributes	Yes	Require in range, because it will provide sphericity
ml of DCM	Appropriate, Effect in quantity of product	Yes	Require, because of recrystallization of drug
Concentration of Polymers PVP K30	Appropriate concentration	Yes	Provide enlargement of the particle
Concentration of Polymers Talc	Appropriate concentration	Yes	Provide seeding in to the system
Concentration of Polymers HPMC E50 LV	Appropriate concentration	Yes	Provide binding strength to the crystals

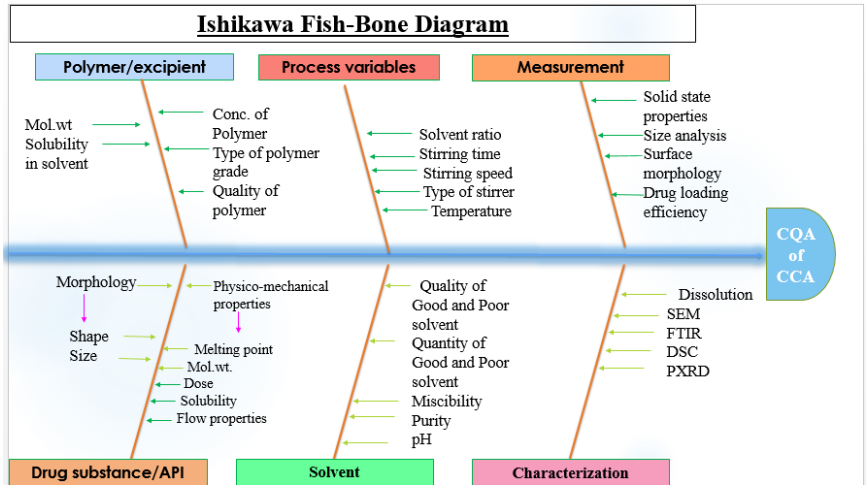


Figure 1. Ishikawa fish-bone diagram.

2.3. Selection of solvent system

The solubility study of Diacerein was carried out to select good solvent and poor solvent for drug [23]. A range of solvents from highly polar to non-polar nature were selected and solubility of pure drug was checked. About 5ml of each solvent was taken and an excess amount of drug was added in it. These saturated solutions were then kept for 24 h in Cryostatic constant temperature reciprocating shaker bath (Tempo Instrument Pvt. Ltd., Mumbai, India) at the temperature of 25 ±1 ºC with continuous shaking at 100 RPM. The saturated solutions were then filtered using 0.45 micron whatman filter paper (previously soaked with individual solvents) and amount of drug dissolved in particular solvent was measured at 280 nm using UV–Visible Spectrophotometer (Pharmspec 1800, Shimadzu, Japan). The study was in triplicate in the same manner to obtain reproducible results.

2.4. Preparation of agglomerates (CCA)

On the basis of solubility study, good and poor solvents were identified and selected for the preparation of CCA. A crystallization protocol was designed in which the drug and/or single or combination of excipients in different ratios were dissolved in good solvent and added drop wise to the bad solvent which was being stirred by using four blade mechanical stirrers (Remi Motors Ltd., Mumbai, India) [23], [24]. Here, the good solvent also acted as a bridging liquid. The stirring was continued for some time. The stirring was stopped when the overall mixture appeared clear at the top and the particles settled down. The agglomerates generated were filtered and dried at room temperature. The surface moisture was removed by storing the samples in the desiccators containing self-indicating silica crystals for 1–2 weeks and stored in an air tight screw cap glass bottle.

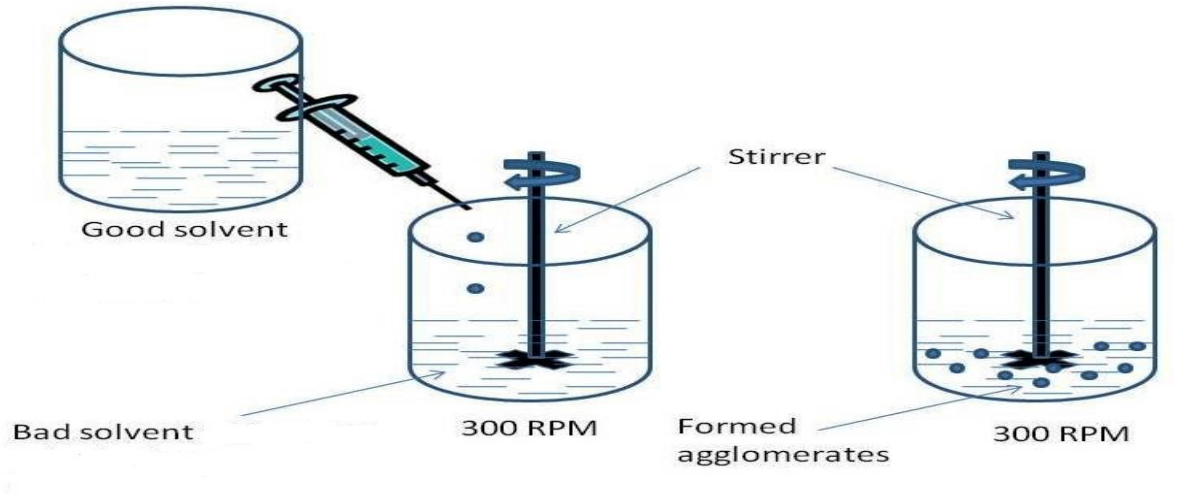


Figure 2 Steps for preparing Crystallo-co-agglomerates

2.5. Packability and flow parameters

For the rheological characterization of the prepared samples, angle of repose, Carr's index, and Hausner's ratio were measured. Angle of repose was determined using fixed funnel method. Percentage compressibility (Carr's Index) and Hausner's ratio were calculated after tapping of fixed amount of sample using Electrolab tap density tester (USP). Angle of repose (a) of the powder material was calculated using the following formula:

$$\alpha=\tan^{-1}(h/r)\ldots\ldots. \text{ (Eq.-1)}$$

Where, h is the height of the pile and r is the radius of thepile.

The bulk density (qb) was the quotient of weight to the volume of the sample at zero tap. Tapped density (qt) was determined as the quotient of weight of the sample to the volume after tapping a measuring cylinder for 500 times from a height of 2 inch. Carr's Index (percentage compressibility— CI) was calculated as one hundred times the ratio of the difference between tapped density and bulk density to the tapped density:

$$CI\ (\%) = (\rho t - \rho b/\rho t)\ x100\ldots\ldots. \text{ (Eq.-2)}$$

Hausner's ratio (HR) was calculated using measured values of bulk density and tapped density as follows:

$$HR= \rho t/ \rho b\ldots\ldots. \text{ (Eq.-3)}$$

Packability parameters like a (compressibility, or amount of densification due to tapping), 1/b (cohesiveness, or how fast/easily the final packing state was achieved), and K (Kuno's constant was determined directly putting the values of densities) were calculated using Kawakita and Kuno's equations at taps 10, 30, 50, 100, 200, and 300.The values of "a" and "b" were calculated from the slope and intercept of the linear plot of N/C Vs N, respectively.

2.6. Kawakita equation

$$n/C= (1/ab) + (n/a)\ldots\ldots.\text{(Eq.-4)}$$

Here, where, Y = n/C, Slope = n/a and Intercept = 1/ab, Where, C= (V0-Vn)/V0

2.7. Kuno's equation:

$$\ln(\rho t- \rho n)= -Kn+\ln(\rho t- \rho 0)\ldots\ldots.\text{(Eq.-5)}$$

Where, n is number of tapping

V0 and Vn are initial volume and volume after 'n' no. of taps ρ0, ρn and ρt are the initial density, density at 'n' taps and density at infinite taps respectively.

a, b and K are the constants representing flowability and packability of powder under mechanical force.

The smaller values of parameters 'a' and '1/b' in Kawakita equation for the samples indicated higher packability of the sample compared to pure drug. Higher values of parameter 'K' in Kuno's equation for sample, was an indication of marked improvement in compressibility and packability attributed to the much higher rate of their packing processes than that of pure drug due to sphericity of particles [25]

2.8. Capillary melting point

The sample was filled in one end sealed capillary and melting range was determined on digital melting point apparatus (accuracy ± 0.1°C).

2.9. Microscopic determination and surface topography

Shape and size of the samples were observed under the optical microscope with 10X magnification and photomicrographs were taken using CCD camera for comparing morphological changes in prepared samples compared to pure drug. The preliminary observation of the shape and surface of the prepared samples was done and the batches for the further study were selected.

2.10. Drug loading efficiency and % yield

Drug loading efficiency is the ratio of experimentally measured drug content to the theoretical value, expressed as percentage (%) [26]. Accurately weighed quantity of prepared samples were dissolved in little quantity of a suitable solvent in which it was easily soluble and made the volume to 50 ml in a volumetric flask. These solutions were appropriately diluted and drug content was determined by UV spectrophotometer using the same solvent as blank. The experimental drug content was calculated using calibration equation. The % yield of sample was calculated using equation-6.

$$\%Yield= (\text{total weight of sample/total weight of drug and polymer})\ x100\ldots\ldots. \text{ (Eq.-6)}$$

2.11. Micromeritic study

Size analysis was performed using optical microscopy method. The size and size distribution of particles were counted using eye piece micrometer which was previously calibrated using stage micrometer. Particle size was determined by taking longest dimension of the particle for a minimum of 100 particles. Mean aspect ratio (AR), defined as the ratio of length (longest dimension from edge to edge of a particle oriented parallel to the ocular scale) to the width (the longest dimension of the particle measured at right angles of the length) of the particle, was calculated. The size of 300 randomly selected particles from prepared batch was measured and appropriate geometric mean diameter (dg) was calculated.

2.12. Sphericity determination

Shape factor (SF) and circularity factor (CF) for the prepared sample were obtained from the area (A) and perimeter (P') of the particle[27]. The photomicrographs of the particles were taken at 40X using CCD camera and tracings of the enlarged photomicrographs were used for the measurement of area and perimeter. The shape factor and circularity factor were calculated using equation7 and 8 respectively.

Shape Factor, P= (P''/P')……. (Eq.-7)

Where P'' = 2π (A/π) ½

Circularity Factor, S= (P') 2 / 4лA……. (Eq.-8)

2.13. Crushing strength

The crushing strength of the prepared sample was determined by mercury load cell method using 10 ml hypodermic glass syringe. The particle was placed inside the syringe and mercury was added through hollow syringe tube. The total weight of tube with mercury, at the stage where particle broke, gave the measure of crushing strength of that particle.

2.14. Heckel Plot

Accurately weighed quantity of prepared samples was compressed at the constant compression at different pressures [28]. The punch and die were lubricated using 1 % w/v dispersion of magnesium stearate in acetone. Compression behavior of the samples was expressed as parameters of Heckel equation Plot of ln [1/ (1-D)] versus P was drawn and values of K, A and σ0 were obtained. Heckel parameter was calculated using Equation-9.

ln (1/1-D)=Kp+A…….(Eq.-9)

Where, D is relative density of compacts i.e. ratio of compact density to true density of powder, P is the applied pressure, K is the slope of Heckel plot; K = 1/Py. Py is the mean yield pressure. The constant A expresses the densification at low pressure. σ0 is yield strength, σ0 = 1/ 3K.

Here, density of prepared compacts for heckel parameter was calculated from volume of compacts and mass of compacts.

2.15. Tensile Strength measurement

After determination of diameter and thickness of compacts prepared for the study of heckel parameters, the compacts were subjected to relaxation for 24 hours. Then the compacts were subjected to tensile strength measurement in which the force required to break the compacts (P) was measured using Monsanto hardness tester [23]. The tensile strength (T, Kg) of the compacts was calculated using the following equation. The tensile strength was calculated using equation-10.

T=2F/лdt……. (Eq,-10)

Where, d and t are the diameter and thickness (cm) of the compacts respectively. F is force (Kg/cm2) required to break compacts.

2.16. Elastic recovery

The compacts prepared for the heckel plot study and tensile strength determination were used for the elastic recovery test. The thickness of the compacts was measured immediately after ejection (Hc) and after the 24 h relaxation period (He). Elastic recovery was calculated using the equation [29]. The elastic recovery was calculated using equation-11.

%ER= [(He-Hc)/Hc] x100……. (Eq.-11)

2.17. Differential scanning Calorimetry [30]

Thermograms of the pure drug and prepared samples were performed using DSC 60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of drug and prepared samples. The instrument comprised of calorimeter (DSC 60), flow controller (FCL60), thermal analyzer (TA 60WS) and operating software (TA 60). The samples were heated in hermetically sealed aluminum pans under air atmosphere. Empty aluminum pan was used as a reference.

2.18. Fourier transform infra-red (FT-IR) spectroscopy

Infrared spectra of pure drug and prepared samples were recorded using infrared spectrophotometer (FTIR 8400 spectrophotometer, Shimadzu, Japan). The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The spectrum was recorded.

2.19. Powder x-ray diffractometry

The x-ray powder diffraction patterns of pure drug and optimized samples were recorded using PAN analytical diffractometer system (X pert pro PW 30-40/60) with a copper target and scintillation counter detector (voltage 40 kV; current 30 mA; scanning speed 0.05°/sec). The sample holder was non-rotating and temperature of acquisition was room temperature. The diffraction pattern was analyzed in a specific 2ɵ range.[28]

2.20. Scanning electron microscopy

The shape and surface morphology were observed using scanning electron microscope (JEOL, JSM 5610 LV). The samples were observed at various magnifications to have an idea about the effect of various additives on surface treatment (morphology) and particle size.

2.21. Moisture content

Moisture content of agglomerates was measured in Hot air oven (Janki Impex Pvt. Ltd., Ahmedabad,

India). Agglomerates (5 g) were placed in the heating chamber of the instrument and heated constantly at 105 ℃ for 4 h. The percent reduction in the weight of agglomerates due to moisture loss was measured by measuring the weight of the agglomerates after heating. Difference in weight of agglomerates before and after the treatment was a measure of percentage moisture content in agglomerates. The study was performed in triplicate.

2.22. Preparation of dosage form and its evaluations

Preparation of directly compressible tablets of Diacerein and prepared samples

Formulation excipients were selected on the basis of preliminary tests which demonstrated no interference of these excipients at the λmax of API. Tablets containing equivalent amount of API were made by direct compression using different formulation excipients of directly compressible type. Samples used for tableting were having similar size range of particles. The material for each tablet was weighed (containing equivalent amount of API), introduced manually into the die and compressed in tablet machine. The compaction surfaces were lubricated with 2% w/w magnesium stearate in acetone before compaction. The blend was compressed on an eight-station rotary tablet machine (Karnawati Engineering Ltd., India) to obtain tablets of required hardness and thickness. The tablets were studied in three replicates. The compacts were ejected and stored in screw-capped bottles for 24 h before using, to allow for possible hardening and elastic recovery. Compacts were also taken for in-process and finished product evaluation tests. The same technique was applied for preparation of tablets of API as well as tablets of control batch.

2.23. Evaluation parameters for prepared directly compressible tablets

2.23.1. Thickness and diameter of the tablets

The thickness and diameter of individual tablet was measured with a vernier caliper (Mitutoyo), which permitted accurate measurements. The study was conducted for 20 tablets and average result was considered.

2.23.2. Weight variation test of the tablets

The USP has provided limits for the average weight of uncoated compressed tablets. Twenty tablets were weighed individually and the average weight was calculated.

2.23.3. Tablet friability test

Tablet friability was measured by using Roche friabilator (Electrolab, Mumbai). Ten tablets were weighed and placed in the apparatus where they were exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, tablets were weighed and compared with the initial weight. The loss due to abrasion was a measure of the tablet friability. Tablet friability was calculated using Equation-12.

Friability= (Wf-Wi/Wf) x100……. (Eq.-12)

Where, W_f was Final weight and W_i was initial weight.

2.23.4. Tablet hardness test

Tablet hardness was measured using Pfizer hardness tester. The instrument measured the force required to break the tablet when force generated by a coil spring was applied diametrally to the tablet. The test was done for three tablets from each samples and average was considered.

2.23.5. Tablet disintegration test

The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 # screen. The disintegration test was carried out using the tablet disintegration tester (Electrolab, Mumbai) which consisted of a basket rack holding 6 plastic tubes, opened at the top and bottom, the bottom of the tube was covered by a 10 # screen. The basket was immersed in one liter beaker containing distilled water held at 37 ± 1 ºC. As the basket was moved up and down, tablets kept in the tubes were started disintegrating. The time required for disintegration of tablet was measured in accordance with the United States Pharmacopoeia 29.

2.23.6. *In-vitro* Dissolution study

A USP dissolution test apparatus were used to monitor the dissolution profiles to evaluate the influence of process and excipients on drug release. The dissolution medium was equilibrated to 37 ± 0.5 °C. Peddles/ baskets were rotated at predetermined RPM. From the dissolution flask, 5 ml samples were withdrawn at selected time intervals and the concentrations of API in the samples were determined by UV spectrophotometer at λmax of drug by diluting with suitable solvent using same media as blank. The mass of API dissolved was calculated from the concentration after correcting for the change in volume of the dissolution medium. Concentration of drug was calculated by fitting value of absorbance read in the linear regression equation for the calibration curve of drug at its λmax. All determinations were performed in triplicate.

3. RESULTS AND DISCUSSION

3.1. Risk assessment

Figure 1 depicts the Ishikawa fish-bone diagram for the CCA shows a cause-and-effect relationship among the probable factors influencing the drug product CQAs. Tables 1–3 illustrate the risk assessment

matrix suggested for identifying the QTPP and also risk associated with each material attributes and/or process parameters. Rational justification of various risk(s) for each of the material attributes and process parameters corresponding to the respective CQAs is enlisted in these matrixes.

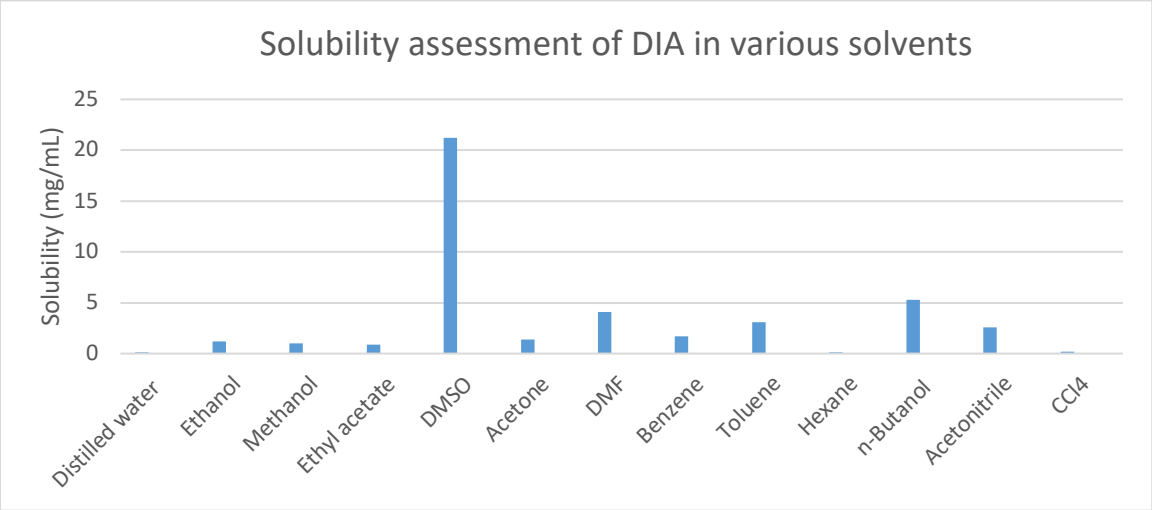


Figure 3 Solubility assessment of DIA in various solvents

From figure 3, it was observed that Diacerein exhibited good solubility in DMSO. At the same time, it showed poor solubility in distilled water. Hence, former were selected as good solvents and later were selected as poor solvents for the maximum recrystallization of drug. The drug was dissolved in good solvent (DMSO) and added drop wise to the bad solvent (water) which was being stirred by using four blade mechanical stirrers. The amount of good solvent was 10 ml and poor solvent was 300 ml and this ratio was kept constant in all the trials. Excipients used in the preparation of agglomerates were PVP K30, PEG 6000, Eudragit RL100, HPMC E50 LV, HPMC K4M, Purified talc, etc., which were co dissolved either in good or poor solvents alone or in combinations.

The study revealed poor or negligible agglomeration in absence of additives (control batch). Preliminary trials were conducted with various excipients in various concentrations ranging from 0.2% to 2.0% w/v of the saturated solution of drug in DMSO-distilled water system. In most of the cases, agglomerates could not be formed. The solution of drug excipients in DMSO as good solvent was added drop wise into poor solvent like water with constant stirring started little agglomeration. The combinations of various excipients were also used where the concentration of one was kept constant (which gave good results at that particular concentration) while varying concentration of second excipient. The agglomerates obtained in preliminary trials were subjected to the evaluation of angle of repose, Carr's index, Hausner's ratio, Kawakita, shape factor, circularity factor, and crushing strength (data not shown as preliminary trials). Some batches were rejected during preliminary trials. Although the presence of excipient improved the flow of the co-agglomerates as compared to pure drug and control batch, significant results were not found with all the additives. Various combinations of the additives were also tried and not all but some of them produced co-agglomerates with remarkable improvement in micromeritic and mechanical properties.

Moreover, agglomerates were also prepared at various stirring speed ranging from 100 to 500RPM on mechanical stirrer (Remi Laboratory Instruments, Mumbai, India). All the batches were evaluated based on the crushing strength of agglomerates (Table 4). The results revealed that at 100, no agglomerates were formed. Produced shear energy might not be sufficient for the formation of CCA. Probably low stirring speed was not sufficient to generate a centrifugal effect over the recrystallized drug-excipient mixture in the solution [31]. At 200 RPM, agglomerates showed poor crushing strength. Good results with sufficient crushing strength were obtained in case of 300 RPM. Above that, again there was a reduction in crushing strength. It might be due to unwanted higher impact energy of collision was generated by stirrer. Moreover, it might cause destruction of forming agglomerates [32]. Hence, 300RPM was kept as constant for the entire preparation.

Table 4 Optimization of speed of rotor in CCA formation.

Sr. no.	RPM	CCA formation	Crushing strength ± S.D.[a]
1	100	Only Fines generated	NA
2	200	CCA formed with bigger size	34.20 ± 1.246
3	300	CCA formed	51.56 ± 1.039
4	400	CCA formed	43.28 ± 1.358
5	500	CCA formed and starts breaking	40.31 ± 1.227

3.2. Central composite design

Here, in this experiment 2 factors were selected HPMC Concentration (%) (X1) and ml of water (X2), and accordingly 4 responses were selected. In this concentration of polymers and solvent were now fixed means talc (2 %) and PVPK30 (1 %) and Dimethyl Sulfoxide (DMSO) (10ml) for all batches.

Particle size (mm) (Y1), % yield (Y2), Shape factor (Y3) and circularity factor (Y4) were selected as responses.

Table: 5 Design matrix of Central composite design with response

Batches	**X1 (%)**	**X2 (ml)**	**X1 (%)**	**X2 (ml)**	**Y1 (mm) Mean ±SD***	**Y2 (%) Mean ±SD***	**Y3 Mean ±SD***	**Y4 Mean ±SD***
1	-1	-1	0.2	200	0.847±0.12	52.47±0.74	1.17±1.27	0.872±0.38
2	1	-1	0.6	200	0.627±0.43	61.28±0.10	1.048±1.08	1.04±0.62
3	-1	1	0.2	300	1.02±0.27	84.15±0.85	0.991±0.47	0.627±0.35
4	1	1	0.6	300	0.458±0.17	62.18±1.73	0.998±0.59	1.257±0.24
5	0	0	0.4	250	0.732±0.63	82.12±1.95	0.997±0.23	0.989±0.19
6	0	0	0.4	250	0.727±0.21	82.49±1.73	0.994±0.14	0.990±0.71
7	-1.414	0	0.1282	250	1.01±0.95	92.15±0.49	1.09±0.82	0.982±1.82
8	1.414	0	0.8484	250	0.33±1.18	61.27±1.27	0.992±0.63	1.43±1.20
9	0	-1.414	0.4	160	0.715±0.29	69.12±0.83	1.052±0.45	0.999±1.48
10	0	1.414	0.4	424	0.628±0.34	76.28±0.13	1.012±1.37	0.73±0.77
11	0	0	0.4	250	0.723±0.57	85.29±0.49	0.999±0.98	0.981±0.69
12	0	0	0.4	250	0.719±0.91	85.24±17	0.998±0.67	0.982±0.93

* Each reading is mean ±S.D of three readings

3.3. Statistical analysis of design batches:

3.3.1. Regression analysis: Regression coefficient and p-value of full model as calculated for mean diameter, %yield, shape factor and circularity factor. P-value less than 0.05 indicated that the factor is significant. Values obtained from analysis is shown in table 6.

Table: 6 Regression co-efficient and their p-value of CCD design variables

Response	Mean diameter (Y1)	p-value
β0	0.7245	1.46^{-10}

β1	-0.2179	6.07^{-10}
β2	-0.014	0.362

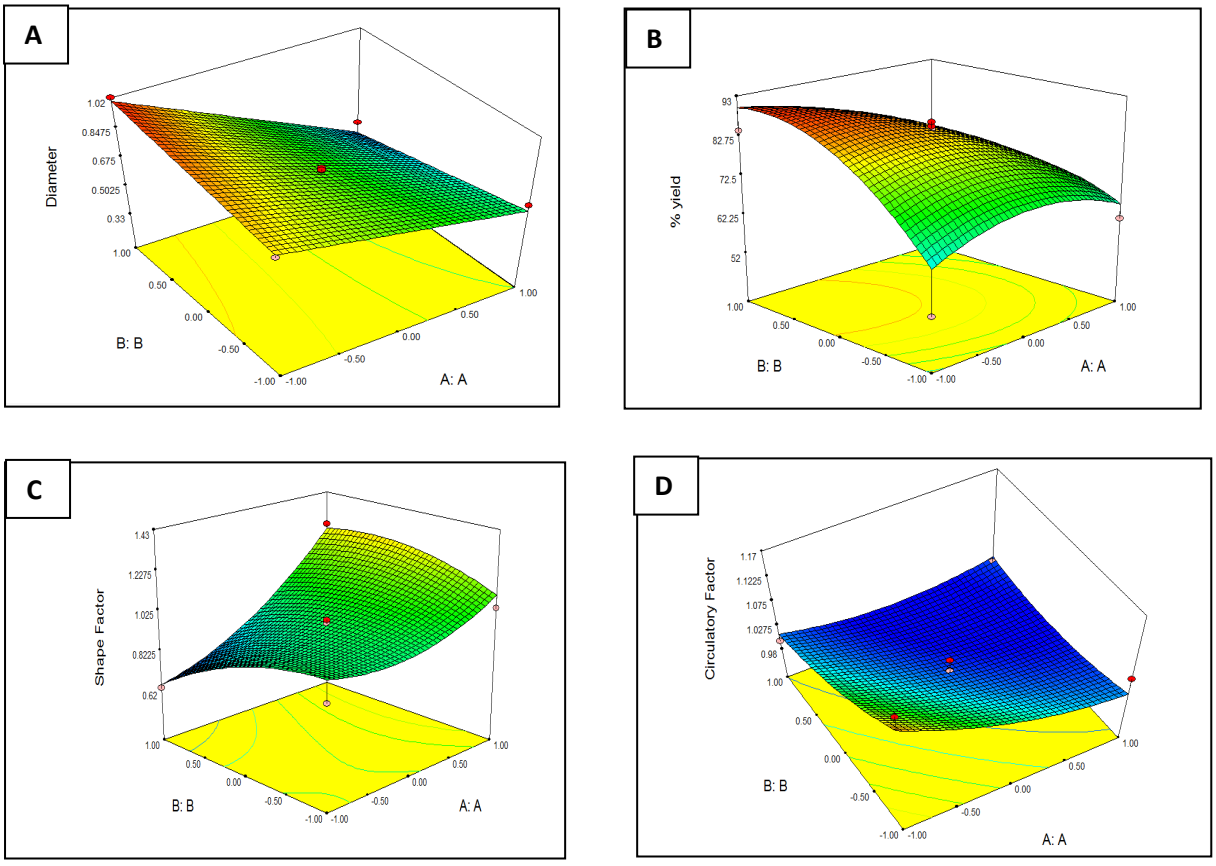
Response	% yield (Y2)	p-value
β0	84.825	1.55^{-09}
β1	-7.103	0.019
β2	5.33	0.05

Response	Shape factor (Y3)	p-value
β0	0.975	3.65^{-10}
β1	0.178	5.85^{-05}
β2	-0.051	0.05

Response	Circularity factor (Y4)	p-value
β0	1.001	8.27^{-14}
β1	-0.032	0.004
β2	-0.034	0.003

From the regression analysis as shown in table, R2 value for mean size, %yield, shape factor and circularity factor is 0.964, 0.813, 0.928, and 0.864 respectively.

3.3.2. 3D Surface of central composite design



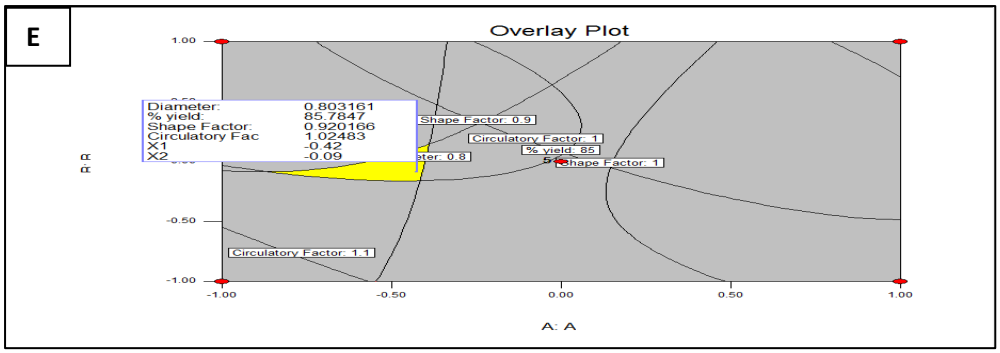


Figure 4 3D plots for mean diameter (A), %yield (B), shape factor (C), circularity factor (D), and overlay plot (E),

Figure 4(A) 3D Surface of mean diameter in central composite design when increase the concentration of HPMC mean diameter was decreases. And when we decrease the concentration of HPMC mean diameter was increase and increase the ml of water the mean diameter also decrease. Figure 4(B) 3D Surface of %yield when increase the ml of water the %yield increases and when we decreases the concentration of HPMC the %yield increases. Figure 4(C) 3D Surface of shape factor when increase the concentration of HPMC the shape factor increases and when we decreases the ml of water the shape factor increases. Figure 4(D) 3D Surface of circularity factor when increase the concentration of HPMC the circularity factor increases and when we decreases the ml of water the circularity factor increases (not drastically).

Figure 4(E) Overlay plot the yellow region shows that in this experimental area predefine response limit will give good result practically. In this put a flag point which shows the possibility of responses according to factors. In that X1 and X2 value shows the value of response and that response value put into the linier regression equation, which give the theoretical values and accordingly do the practical with same factor and measure the response which give the response value.

$Y= \beta0+B1X1+B2X2+B3X3……+BnXn$

Where, Y=Responses, β0=Intercept, B1= X-variable 1, B2= X-variable 2, X1= Factor 1 value in yellow region, X2= Factor 2 value in yellow region

Table: 7 Theoretical and practical value of experiment

	Theoretical value	**Practical value**
Mean diameter	0.8118	0.806
% yield	85.82	85.80
Shape factor	0.9255	0.921
Circularity factor	1.022	1.020

The error was found by using mean error equation

e= Theoretical value- practical value x 100 / Theoretical value

Table: 8 Error into the practical work

	Error (e)
Mean diameter	0.714
% yield	0.023
Shape factor	0.486

Circularity factor	0.195

On the basis of theoretic and practical value here find the error into the experiment. In this all responses were below then 1, it means very small error in practical work. By using design and statistics on the basis of possibilities the design reduce the experimental efforts in the way of cost and time, so by this approach quality of product is increased and by this approach reduced waste of time as well as money.

3.4. Evaluation parameters of agglomerates by destructive parameters

3.4.1. Drug loading efficiency

Drug loading efficiency of prepared agglomerates was obtained by dissolving them into 1.2 pH phosphate buffer and evaluating spectrophotometrically at 258 nm. In this study the control batch of agglomerates obtained was 90.62 % and optimized batch of agglomerates was 92.28 %. The results indicated good loading efficiency.

3.4.2. Crushing strength of CCA

The crushing strength of control batch and optimized batch were 34.41 ± 0.82 and 51.56 ± 1.039 gm. This could be attributed to the increased agglomeration of crystals with good bridging due to presence of suitable polymers [27]. Improved crushing strength of the particles revealed the improvement in mechanical and handling properties. This was due to increased cohesive interaction between particles caused better binding and close packing between crystals [24].

3.4.3. Flow and Packability parameters

Table: 9 Flow properties of agglomerates

Sr.No.	Batches	Angle of repose (ɵ) Mean ±SD*	Carr's index Mean ±SD*	Hausner's ratio Mean ±SD*
1	Pure drug	48.01±0.70	32.14±0.12	1.47±1.20
2	Control batch	41.57±0.51	29.5±0.87	1.41±0.43
3	Optimized batch	23.17±0.65	11.66±0.23	1.13±0.35

***** Each reading is mean ±S.D of three readings

Table 9 shows that flow properties of agglomerates obtained in the presence of excipients was excellent compared to pure DIA. Lower AoR correspond to free flowing powders, whereas higher angles indicate a cohesive or poor flowing material (Cain, 2002). Remarkable reduction in AoR of agglomerates compared to pure drug indicated improvement in flow and packing ability of agglomerates.

CI empirically estimates the powder flow from packing density and compressibility. The prepared agglomerates depicted lower value of CI (as compared to pure drug) which confirmed their enhanced flowability and compressibility. Particle/agglomerates shape and size are commonly recognized as important particulate properties for powder packing and flow.

Generally cohesive materials have a HR greater than 1.4. Results of HR depicted in Table 9 revealed that DIA had very poor flowability while low value of HR for optimized batch of agglomerates depicted significantly higher flowability. These observations were generally attributed to spherical shape and smooth surface of the agglomerates obtained from the process of agglomeration.

Table 10 Packability parameters study for pure drug and prepared CCA

Sample	Kawakita constant (K)				Kuno's constant
	a	Conclusion	1/b	Conclusion	
Pure drug	0.5534		7.13337		0.8895

Control batch	0.46918		1.46454		1.0693
Optimized batch	0.38039	Improved	0.36289	Improved	1.3047

Here, decreased values of ***a*** (compressibility or extent of densification due to tapping) and ***1/b*** (cohesiveness, or how fast/easily the final packing state was achieved) than pure drug in Kawakita equation was an indication of improvement in Packability of CCA compared to pure drug. Increased values of ***K*** (Kuno's constant) compared to pure drug, calculated using Kuno's equation, showed marked improvement in compressibility and Packability of CCA.

3.4.4. Hackel plot study of Crystallo-co-agglomerates

Accurately weighed quantity of prepared crystallo-co-agglomerates was compressed using 12-mm flat-faced punch at the constant compression at different pressures ranging from 2 to 10 tons by keeping 1 min. dwell time [28].

True density was considered as the density of compacts when the highest pressure applied on the powder (here, 10 tons).

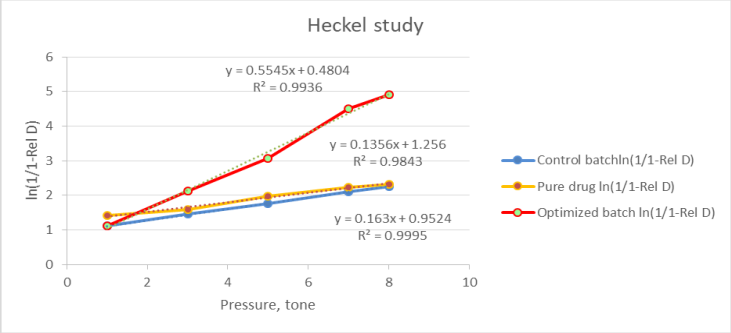


Figure: 5 Hackel plot of Diacerein and CCA optimized batch

Table: 11 Heckel plot parameters

Batch	Pressure yield (Py) Mean ±SD*	Constant (A) Mean ±SD*	Slope (K) Mean ±SD*	Yield strength (σ0) Mean ±SD*	R2
Pure drug	7.3746±0.112	1.256±0.928	0.1356±0.782	2.4582±0.628	0.9843
Control batch	6.1538±0.245	0.9524±0.428	0.1625±0.345	2.0512±0.702	0.9995
CCA batch	1.8021±0.328	0.4776±0.478	0.5549±0.520	0.6007±0.827	0.9937

***** Each reading is mean ±S.D of three readings

Crystallo-co-agglomerates showed remarkable improvement in the Packability compared to pure drug (Figure 5). The true density of CCA (2.14 mg/cm3) and pure drug (4.57 mg/cm3) indicated that, CCA were improved in its compaction properties compared to pure drug (Figure 8).

The constants of heckel plot of pure drug and CCA evaluated are displaced in Table 11. The slop of heckel plot 'K' is an indicative of plastic behaviour of the material (Kawashima Y. et al., 2003). Larger the value of 'K', greater is the plasticity in material. The linearity in the graph (Figure 8) was an indication of plastic deformation. Table 11 below shows parameters of heckel plot. 'A' value of CCA was less than pure drug. This finding suggested that, Low compression pressure was required to obtain closest packing. Yield strength (σ0) is an indication of tendency of the materials to deform either by plastic flow or fragmentation (Paroren P. et al., 1953). Low value of yield strength (σ0) an indication of low resistance to pressure, good densification and easy compaction (Patra N. et al., 2007) Thus, Heckel plot data suggested that, all the particles were fractured easily and new surface of particles produced might contributed to promote plastic deformation under applied compression pressure [10].

3.4.5. Tensile strength measurement of Crystallo-co-agglomerates

Tensile strength of Crystallo-co-agglomerates was increased with pressure, which indicated improved mechanical properties of CCA (Table 12). The maximum tensile strength was obtained at

compression pressure 10 tons. The high tensile strength of compacts was an indication of strong interparticulate bonding between the particles. [28]. Figure: 6 shows the tensile strength of the compact compressed at different compaction pressures. CCA possessed superior strength. In particular, CCA compressed into compacts showed considerable hardness without capping even at high compaction pressure.

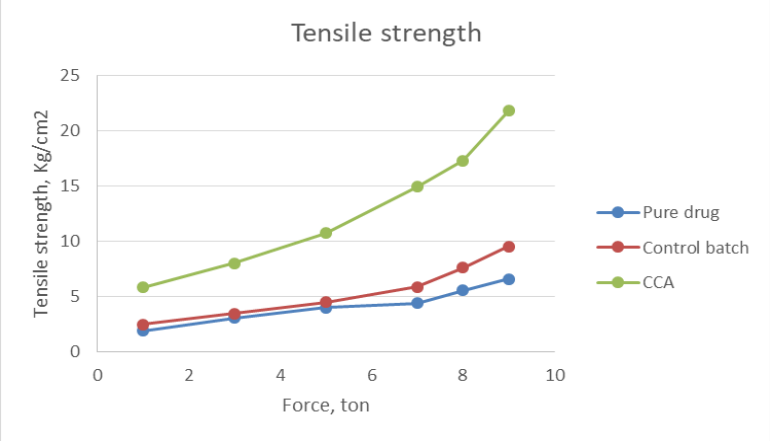


Figure: 6 Pressure – tensile strength relation between diacerein and its prepared samples

Table: 12 Tensile strength

Tones	Pure drug Tensile strength (kg/cm2) Mean ±SD*	Control batch Tensile strength (kg/cm2) Mean ±SD*	Optimized batch Tensile strength (kg/cm2) Mean ±SD*
1	1.890±0.46	2.414±0.02	5.813±0.2
3	3.048±0.98	3.450±0.02	7.993±0.4
5	3.980±0.23	4.467±0.34	10.729±0.7
7	4.371±0.48	5.827±0.02	14.906±0.1
8	5.554±0.34	7.570±0.07	17.274±0.2
9	6.555±0.12	9.487±0.08	21.762±0.9

* Each reading is mean ±S.D of three readings

3.4.6. Elastic recovery(ER) measurement of Crystallo-co-agglomerates

The result for the elastic recovery for optimized batches is given in the following Table 13 Elastic recoveries of samples were smaller than that of original drug crystals. These findings suggest that agglomerated crystals are easily fractured and the new surface of crystals produced might contribute to promote plastic deformation under compression. Table 13 showed very little elastic recovery which is negligible.

Table: 13 %Elastic recovery

Sr.no	Batch	%Elastic recovery±S.D.*
1	Pure drug	4.0324±0.4952
2	Control batch	2.1003±0.3885
3	CCA batch	0.7745±0.1751

*Results are Mean ± S.D. of five observations.

3.4.7. Moisture content measurement

In all the batches, moisture content was as per the compliance with U.S. Pharmacopeia National Formulary, 1994. All the batches were containing moisture content with in the limit.

3.4.8. Aqueous solubility study of CCA

The solubility of CCA was determined in different solvents such as distilled water, pH 1.2 buffer, and phosphate buffer pH 6.8. The Absorbance of the solutions was than measured at 258 nm by diluting with Phosphate buffer pH 1.2 using same media as blank. All the Determinations were performed in triplicate.

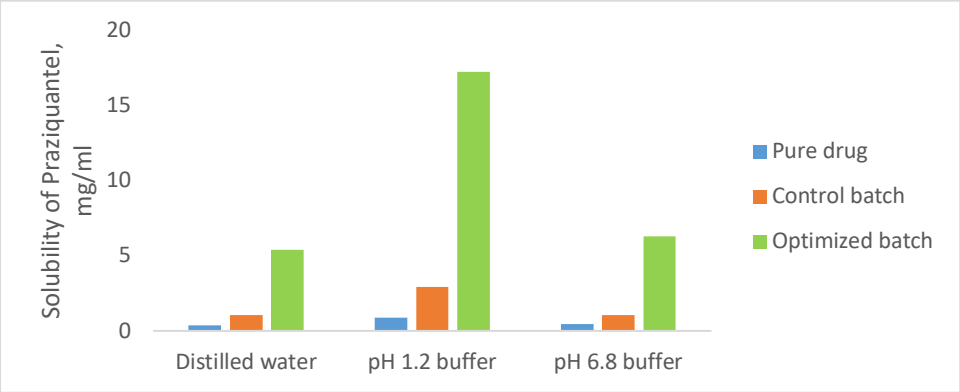


Figure: 7 Solubility of pure drug, control batch and CCA mixture in distilled water, buffer solution of pH 1.2, and 6.8

3.5. Characterization of Crystallo-co-agglomerates

3.5.1. Microscopic determination and surface topography

As shown in Figure 8, the shape of pure drug crystals was like needle, plates, and rods with more quantity of fines resulting in more electrostatic charges which ultimately lead to very poor flow[33]. Photomicrographs of optimized batches of CCA showed marked improvement in the surface morphology and sphericity compared to pure drug. Here, the polymers improved sphericity as well as surface smoothness. These improvements lead to improved flow due to reduced interparticulate friction [34].

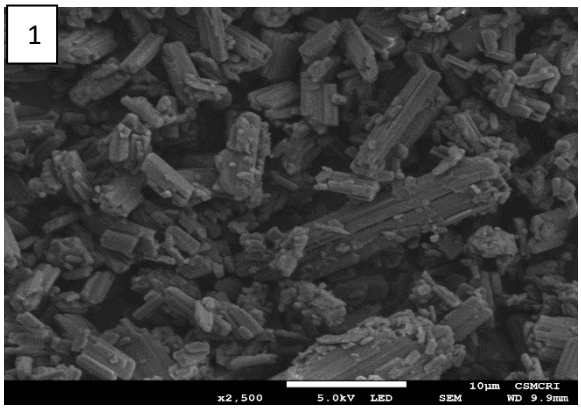


Figure 8 Surface photography of 1. Pure drug and 2. Optimized batch

3.5.2. Differential scanning calorimetery (DSC) of crystallo-co-agglomerates of Diacerein

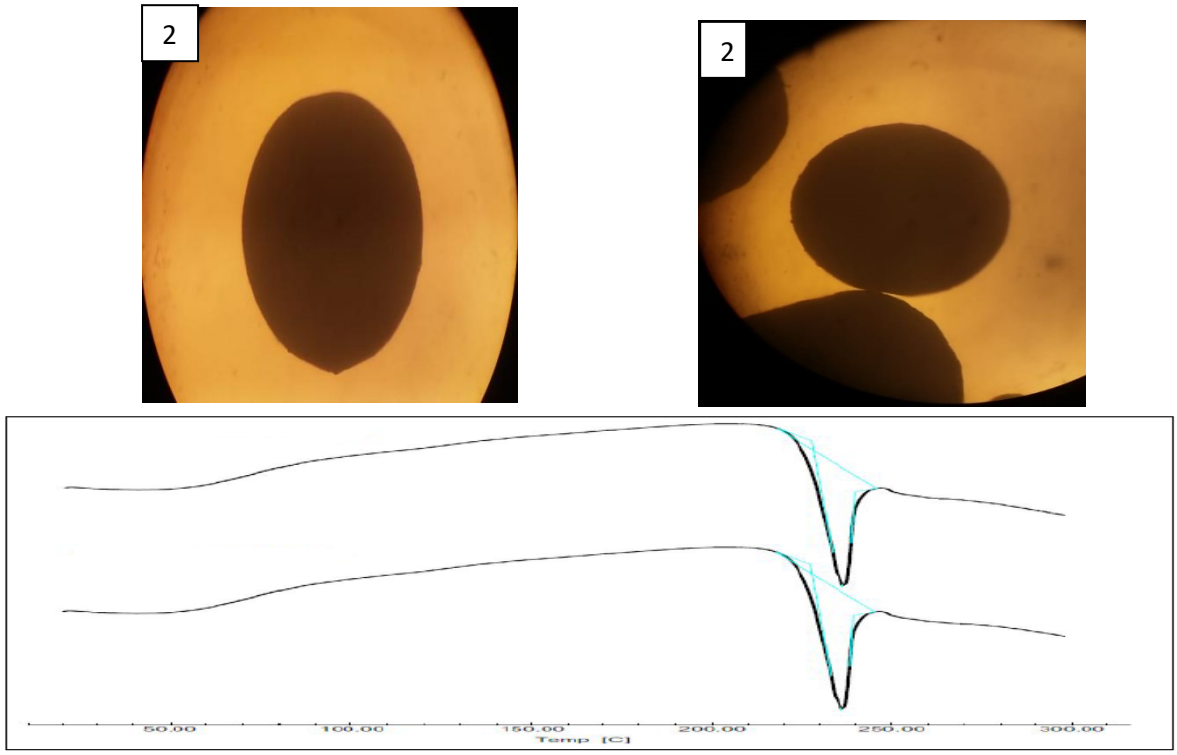


Figure: 9 DSC Thermogram of A. Pure drug and B. Optimized batch

As shown in Figure 9 Diacerein pure showed a single sharp endothermic melting peak with onset at 237.17 ºC (Figure 9) and optimized batch showed a single but less sharp then pure drug melting peak with onset at 236.58ºC (Figure 9).

DSC thermogram of Crystallo-co-agglomerates showed slight upward shift. The thermal behavior of CCA was distinct and unique from the pure drug; this suggests that formation of new phase.

3.5.3. Fourier Transform Infra-Red (FT-IR) Spectroscopy of Crystallo-co-agglomerates of Diacerein

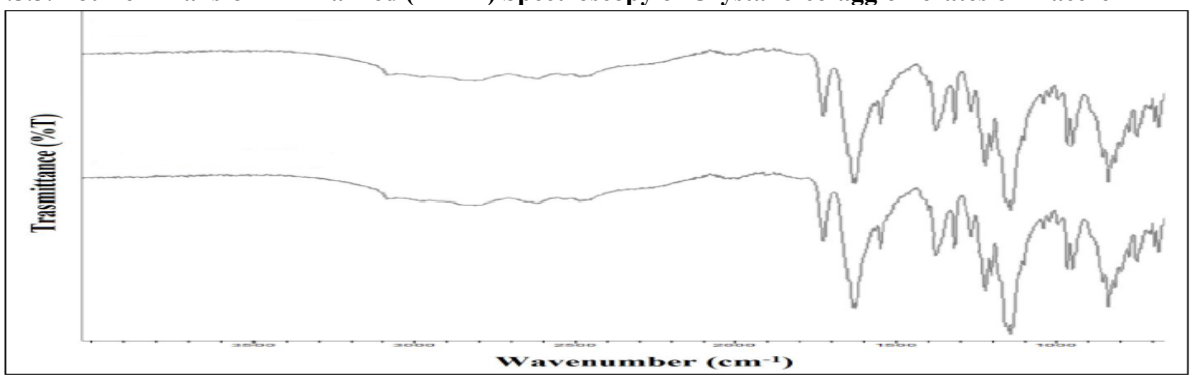


Figure: 10 FT-IT Spectra of A. Diacerein pure and B. Optimized batch of crystallo-co-agglomerates

As shown in Figure 10 FT-IR spectra of DIA displayed a broad −OH stretch at 3069 cm−1 and two C=O stretches at 1785 and 1679 cm−1 for the acetoxy groups. The spectrum of Optimized batch shows characteristic peak −OH stretch at 3069 cm−1 and two C=O stretches at 1785 and 1679 cm−1 for the acetoxy groups. The spectrum crystallo-co-agglomerates optimized batch shows all the characteristics peaks of drug as well as excipients. The findings indicated that, Diacerein and excipients did not show interaction by absence of any peak.

3.5.4. Powder X-Ray Differectometery (pXRD) of crystallo-co-agglomerates

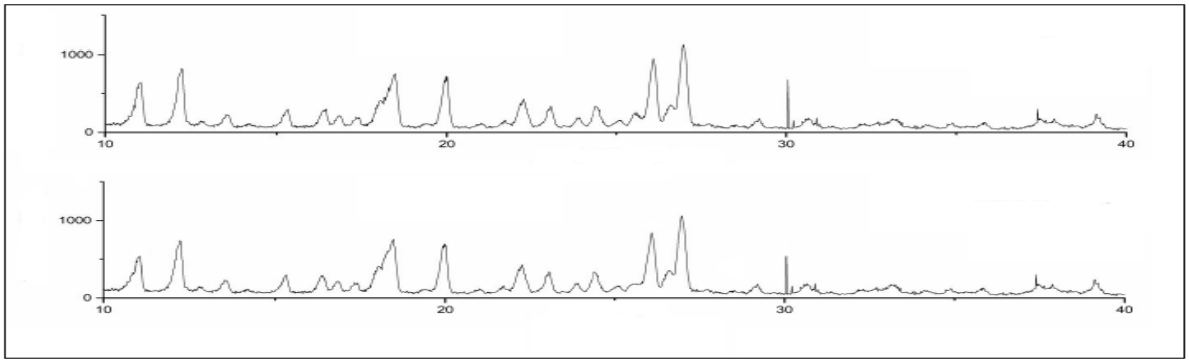


Figure: 11 p-XRD Spectra of A. Diacerein, and B. Optimized batch of Crystallo-co-agglomerates

As shown in Figure 11 DIA showed characteristic peaks at 2θ values of 11.0°, 22.2°, 26.1°, and 27.0°. A shift in peaks was observed in case of agglomerates generated in presence of various excipients. Moreover, as per the XRD spectra, overall peak intensities are also less in CCA spectra compared to pure drug. This was an indication of decrease in crystallinity.

3.5.5. Scanning electron microscopy (SEM) of Crystallo-co-agglomerates

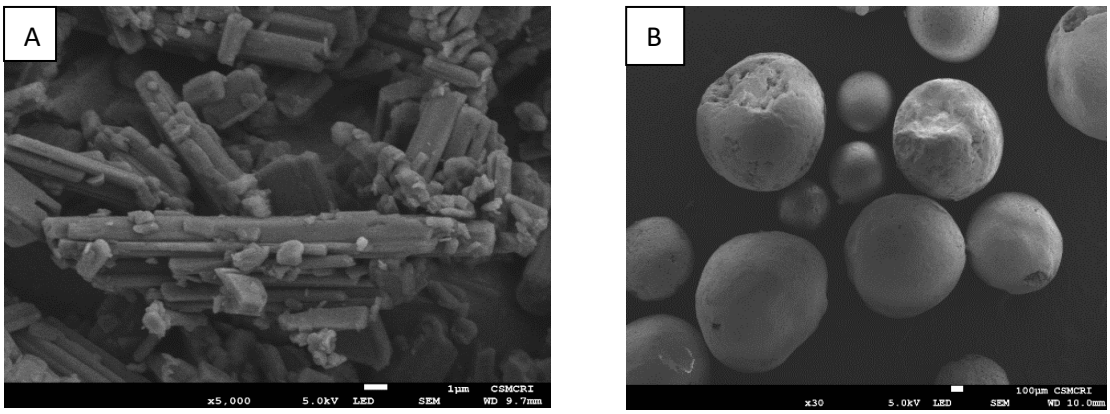


Figure 12 Scanning electron microscopy of (A) Pure Diacerein (B) Optimized batch of Crystallo-co-agglomerates

As shown in Figure 12 The Shape of pure drug crystals was like acicular shape and rods shape with more quantity of fines resulting in more electrostatic charges which ultimately lead to very poor flow and agglomerates were spherical in shape which provide good flow.

Figure 15 shows that image of CCA, from pure drug shows very loos aggression and rough surface with small and irregular shaped crystals, which also had very poor flow and compression properties. Due to good agglomeration of crystals and smooth surface, the CCA prepared with addition of additives had very good flow and compaction properties as compared to pure drug. Also, the agglomerates were very porous in nature, which increased an effective surface area.

3.6. PREPARATION OF DOSAGE FORM OF PRAZIQUANTEL AND ITS EVALUATION

Tablets containing 100 mg equivalent to Diacerein (tablet for pure drug and CCA) were prepared by direct compression using different formulation excipients as shown in Table 14. CCA were sieved to achieve similar particle size distribution (# 22) for each batch and other formulation excipients were added into it. All the ingredients for tablets prepared from CCA were weighed separately and mixed properly in “V” cone blender. The material for each tablet was weighed introduced manually into the die

and compressed in the tablet machine using round-shaped, 15mm flat, concave punch. Tablets prepared from CCA were containing very less amount of MCC (Table 14), which was a considerable improvement in the properties of drug for making directly compressible form. The formulations for tablets and its evaluations are also given in Table 14.

Table: 14 Formulation and evaluation of tablets of Diacerein

Formulation and evaluation	**Tablets prepared from**	
	Pure drug	Crystallo-co-agglomerates
Diacerein, (mg)	50	52 (Equivalent to 50 mg of DIA.)
HPMC E50 LV, (mg)	0.8	-
PVP K30, (mg)	8	-
Sodium starch glycolate, (mg)	80	80
Aerosil, (mg)	4	4
Magnesium Stearate, (mg)	8	8
Talc, (mg)	16	16
Microcrystalline cellulose, (mg)	83.2	90
Total weight of tablet, (mg)	**250**	**250**
Hardness, (Kg/cm2)	2.4 ±0.3	4.7 ± 0.27
Friability (%)	0.9753	0.4696
Disintegration Time (sec.)	43 ±0.5	91±0.8
Diameter, (mm)	12.03±0.21	12.02±0.43
Thickness, (mm)	3.35 ± 0.03	3.34 ± 0.05
Weight variation, (mg)	250.2±0.11	249..5±0.54

3.7. In vitro dissolution study

In vitro dissolution study for the prepared CCA, pure drug, and their prepared formulations was performed using USP type II apparatus. The dissolution medium was 900 ml buffer phosphate (pH 6.8) equilibrated to 37 ± 0.5 °C. Peddles/baskets were rotated at 50 RPM. The concentrations of Diacerein in the solutions were determined by UV spectrophotometer at 258 nm by diluting with phosphate buffer pH 6.8 using the same media as blank. Dissolution profile given in Figure 13 showed large improvement in the rate of drug release. This might be due to hydrophilic polymer inclusion in the formulation. The greater porosity of prepared CCA (as shown in SEM photos) was also responsible for providing greater effective surface area and exposure of a large surface to the dissolution media [30]. The solvent evaporation during formation of CCA and attrition with the stirrer might attributed toward greater porosity in the CCA. Tablets formulated from agglomerates of optimized batch and pure drug showed 76.654 ± 0.51% (20.12 ± 0.57% for pure drug) drug release within 30 min and 95.052 ± 0.74% (34.24 ± 0.72% for pure drug) within 60 min. All the determinations were performed in triplicate.

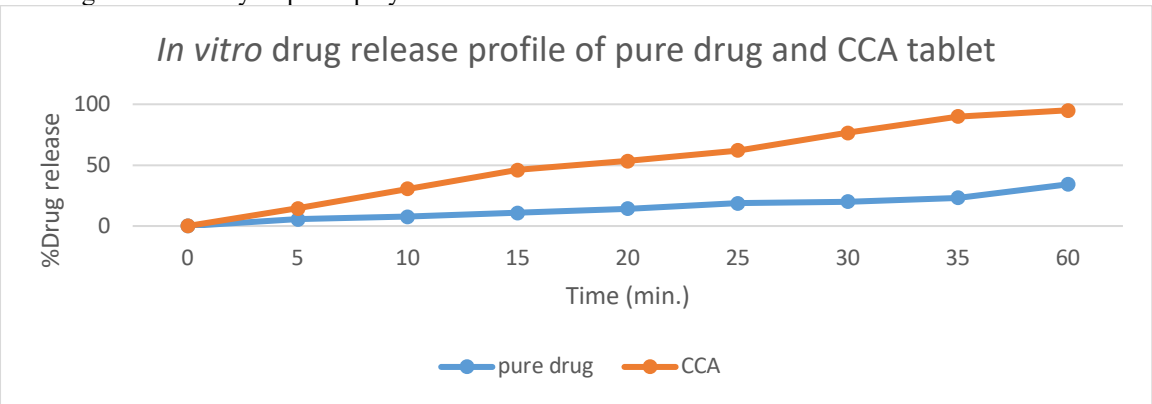


Figure: 13 *In-vitro* Dissolution for Tablet dosage form of pure drug and CCA

4. CONCLUSIONS

In the present work, CCA of Diacerein was formulated to improve its physicochemical and mechanical properties by integrating QbD. QTPP, CQA, CPP, and

CMA were identified which could affect the formation of CCA. Risk assessment was performed using Fishbone diagram. After applying Central composite design, it's further controlling using response surface methodology. Prepared CCA were improved in micromeritic and mechanical properties along with its dissolution and compressibility. Reduction in crystallinity was observed in pXRD study. Scanning electron microscopy showed porous nature of CCA with spherical shape which helped in imparting better flow property and improved dissolution. Overall, the study evident that use of QbD for formation of CCA in the presence of polymers/excipients as a particle engineering tool is the most helpful approach for improving the physicochemical and mechanical properties. It may be helpful to design any formulation as per the current FDA requirements. CCA has been proven as a potential approach for direct compression, instead of using a highly tiresome, lengthy, uneconomical, and complex wet granulation technology.

Disclosure statement

The authors declared no conflict of interest.

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