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Research article

Enhancement of Flow Properties, Solubility, and Dissolution of the Darunavir Ethanolate by Spherical Crystallization

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ABSTRACT

Crystal engineering is a field focused on designing and developing molecular solid particles with desired properties and functionalities. The crystal habit and polymorphic form of a substance play a crucial role in determining its physicochemical, mechanical, and biological behavior. Modifying the crystal habit alone can lead to the formation of distinct morphological forms, which directly influence particle orientation. Such alterations significantly affect critical parameters, including flowability, packing density, compressibility, syringability, and dissolution behavior of pharmaceutical powders. Particle size enlargement is typically accomplished through established conventional techniques, which are widely adopted in pharmaceutical manufacturing. The main objective of this study was to formulate sphere-shaped crystal agglomerates of Darunavir ethanolate (DRVE) having enhanced flowability, compression ability, solubility property and dissolution. DVRE spherical crystals were developed by using a 2^2 full factorial design approach. Plasdone 630 as polymer and methylene dichloride (MDC) as bridging solvent were considered as independent variables, and their effect was studied on drug content and solubility, considered as a dependent variable. The optimised spherical crystals were used in tablet formulations. The drug content of the spherical agglomerates ranged between 89.80 (SAD6) to 95% (SAD2). The solubility of the spherical agglomerates ranged between 0.20 (SA6) to 1.80 mg/mL (SAD2) with an 11.25-fold enhancement in solubility. FTIR study indicated the excellent compatibility of the drug with the polymer used in the formulation. XRD study suggested the amorphization of pure DVRE during the agglomeration process. The optimised SA2 spherical agglomerates were used to manufacture immediate release tablets by DC method (F1). Presence of spherical agglomerates has significantly improved the flow properties as well as compressibility of the blend in comparison to pure DVRE. The drug release of the F1 batch was found to be faster in comparison to F2 and F3 formulations. Nearly 100% release was observed within 15 minutes of F1. The study concludes that the use of spherical agglomerates leads to enhanced flow properties, compressibility, solubility, and dissolution behavior.

INTRODUCTION

Successful development of pharmaceutical tablet dosage forms through the direct compression (DC) process, there are various challenges that need to be overcome, which depend on the quantity as well as physical and chemical characteristics of the drug.[1] With a drug with a higher dosage (NLT 100 mg), formulating the dosage form becomes a significant task. In contrast, dug with lower dosage, the content uniformity (CU) challenge, which can be overcome by employing a different strategy of direct compression tablets that utilizes.[2] However, a comprehensive strategy to tackle the formulation problems associated with the higher dose drugs aforementioned technique is currently lacking. Moreover, 80 to 90% of new chemical entities in the pharmaceutical pipeline suffer from limited bioavailability due to poor solubility and dissolution.[3] In such cases, reducing the particle size of the active pharmaceutical ingredient (API) can significantly enhance its solubility and dissolution rates.[4] However, it is important to consider that smaller API

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particles tend to exhibit poorer flowability. Consequently, if the tablet formulation utilizes the same API loading, it can adversely affect the blend's flowability.[5] In such a scenario, increasing the size of particles plays a vital role in tablet manufacturing as it imparts various functional benefits. This includes enhancing factors such as flowability, solubility, dissolution, micrometric properties, compression, and compressibility.

Crystal engineering is the field dedicated to formulating molecular solid particles, aiming to achieve specific characteristics and functionalities.[6] The crystal habit and polymorphic shape substance significantly influence its physicochemical, mechanical, and biological behaviour.[7] By merely altering the crystal habit, different isomorphic forms can be obtained, which directly impact the orientation of particles. These modifications have profound implications on various aspects such as flowability, packing, compaction, syringability, suspension stability, and dissolution properties of powdered drugs.[8]

Particle size enlargement is commonly achieved through conventional processes that have gained wide acceptance. However, in recent times, modern methods developed for bigger particle sizes have emerged as viable alternatives. These techniques include extrusion-spheronization, melt solidification, melt granulation, melt extrusion, and spherical crystallization.[9]

Among all the reported method, spherical crystallisation has gained considerable interest of scientists to modify the physicochemical properties of API. Spherical crystallization process directly converts fine crystalline articles to tightly compressed sphere-shaped agglomerates during the crystallization stage. These spherical agglomerates possess excellent processability and are "ready-to-use," thereby reducing the validation effort required in the manufacturing process.[10] Spherical crystallization has demonstrated significant effectiveness in enhancing powder flow properties.[11-14] The utilization of spherical agglomerates has allowed for formulating DC tablet formulations with as high as 99% API content.[15] Moreover, the solubility and dissolution rate enhancement can also be achieved using spherical crystallization technique. The technique of spherical agglomeration has shown promising results towards altered solubility as well as dissolution properties. Notable examples include aceclofenac, gliclazide, mebendazole, mefenamic acid, celecoxib, and ibuprofen, where the use of spherical agglomeration has been reported to enhance their solubility and dissolution properties.[16]

Our research group has also successfully developed spherical agglomerates of atazanavir with enhanced flow properties, compressibility, solubility, and dissolution.[17] Hu *et al* developed spherical agglomerates of ceftriaxone sodium via membrane-assisted spherical crystallization and improved the various physicochemical properties of the drugs.[18] A thorough review of existing literature has revealed limited research on the utilization of spherical crystallization techniques for improving flowability, compressibility, solubility, and dissolution of high-dose molecules. In this particular study, Darunavir Ethanolate (DRVE), an antiviral drug, was selected as the model drug to formulate spherical crystals. Its crystalline nature characterizes DRVE and belongs to the BCS II, exhibiting very low solubility of 0.15 mg/mL.[19,20] Furthermore, the high dose (400 and 600 mg) of DRVE presents significant challenges due to its lower flow characteristic, low compressibility, lesser bulk density, making direct compression a difficult process. Therefore, the main aim of this study was to formulate sphere-shaped crystalline particles of DVRE showing enhanced flow properties, formulation properties compared to the original form. Thus, formulated spheres of crystalline agglomerates were then directly compressed and subjected to a comprehensive evaluation of dissolution and various other parameters.

The pharmaceutical advantage of this study lies in its potential to address critical formulation challenges associated with high-dose, poorly soluble drugs such as DRVE. By employing spherical crystallization, the study offers a viable strategy to significantly enhance the flowability, compressibility, and dissolution properties of DRVE, thereby facilitating its direct compression into solid dosage forms. This approach not only streamlines the manufacturing process by eliminating the need for granulation but also improves the bioavailability of the drug. In the current pharmaceutical landscape, where formulation efficiency and enhanced drug performance are of paramount importance, this technique presents a promising solution for developing robust, scalable, and patient-friendly oral formulations of poorly soluble, high-dose therapeutic agents.

MATERIALS AND METHODS

Materials

Darunavir ethanolate (DVRE) was received as a gift sample from J. Dunkan Healthcare Pvt. Ltd, Plasdone 630 polymer was obtained as a free sample from ashland, acetone and methylene dichloride (MDC) was taken from RUSA lab SRTMU Nanded, microcrystalline cellulose (GR 101 and GR 102), crospovidone (Kollidon CLF), hydroxypropyl cellulose (15 Cps), colloidal silicon dioxide and magnesium stearate was obtained from Alkem Laboratories Ltd.

Methods

Statistical Design of experiments (DOE)

A 2^2 full factorial design approach was employed in the development of spherical agglomerates. The 2^2 factorial design was chosen for its efficiency in evaluating the impact of two critical independent variables on the formulation with minimal experimental runs. This design allows us to systematically assess the main effects and interaction effects between these variables while maintaining resource efficiency. Given the scope of our study, the 2^2 factorial design provided a balance between experimental feasibility and statistical power. The independent variables considered for this study were the concentration of Plasdone 630 (A, mg), and MDC (B, mL). These variables were varied at two levels -1 and +1. The dependent variables of interest were the drug content (Y1) and solubility (Y2). The specific variables and their corresponding levels are provided in Table 1. Design-Expert® Software did the analysis of experimental data by statistical method.

Development of DVRE spherical Crystals using Bridging Solvent

An accurately weighed amount of DVRE was dissolved in 100 mL of acetone up to its saturation solubility (good solvent). Plasdone 630 polymer was dissolved in purified water and MDC was used as a bridging solvent. Super-saturated solutions of DRVE were separately stirred well. This super saturated mixture was then added to 100 mL of purified water (anti-solvent/bad solvent) and stirred at 500 rpm and then MDC was added to this mixture with the help of a syringe slowly and continued stirring till crystallization occurred.[21] The formulation batches are shown in Table 2.

Physicochemical parameters

Bulk Density

Accurately weighed spherical agglomerates were gradually poured into a 50 mL measuring cylinder, ensuring the bed remained uniform and undisturbed.[22,23] The volume was measured in milliliters, and the bulk density (BD) was calculated using the formula below.

$$\text{BD} = \frac{\text{mass of sample in g}}{\text{volume occupied by sample in ml}}$$

Tapped density (TD)

Spherical agglomerates were accurately weighed and poured into a measuring cylinder placed in a bulk density tester. The initial volume occupied by the sample was noted. The cylinder was then tapped (50, 100, or 250 times) until no change in volume was observed, and this final volume was recorded as the tapped volume.[22, 23] The tapped density (TD) was determined using the following formula.

$$\text{TD} = \frac{\text{Mass of sample in gm}}{\text{tapped volume occupied by sample in ml}}$$

Table 1: Variables and levels

Variable	*(-1) Low level*	*(+1) High level*
Independent		
A= Plasdone 630	20 (mg)	50 (mg)
B= MDC	2.5 (mL)	5 (mL)
Dependent		
Y1= Drug content		
Y2 = Solubility		

Compressibility Index (CI)

The following formula was used to calculate CI.[23]

$$\text{CI} = \frac{\text{TD} - \text{BD}}{\text{TD}} \text{X } 100$$

Hausner's Ratio (HR)

The presented formula can be used to calculate HR.[23]

$$\text{HR} = \frac{\text{TD}}{\text{BD}}$$

Drug content

The spherical agglomerates were triturated in a mortar and pestle. The triturated mixture weighing equal to 50 mg of DVR was taken to dissolved in 6.8 phosphate buffer under continuous stirring for 30 minutes and then strained using Whatman filter paper #41. The further dilutions were made using ethanol and the drug content was determined at 270 nm.[24]

Saturation solubility

Spherical agglomerates from each batch, pure DVR were dissolved separately in double-distilled water to make a saturated solution. All solutions were packed in screw capped glass bottles and kept in orbital shaker for 3 days at 37°C followed by centrifugation at 5000 rpm for 30 minutes. The resultant solutions were filtered through Whatman filter paper no.41 and appropriate dilutions were made using double-distilled water. The solubility of

Table 2: Formulation batches of spherical crystals

Batch	*Factor*	
	A (Plasdone 630)	*B (MDC)*
SAD1	-1 (20 mg)	-1 (2.5 mL)
SAD2	+1(50 mg)	-1(2.5 mL)
SAD3	-1(20 mg)	-1(2.5 mL)
SAD4	-1(20 mg)	+1(5 mL)
SAD5	+1(50 mg)	+1(5 mL)
SAD6	-1(20 mg)	+1(5 mL)
SAD7	+1(50 mg)	+1(5 mL)
SAD8	+1(50 mg)	-1(2.5 mL)

each sample was determined after being analysed at 270 nm using a UV spectrophotometer.[19]

FTIR analysis

By using the FTIR technique, the infrared spectra of DVR and optimized spherical agglomerates were obtained. The method employed potassium bromide pellet preparation. For each sample, the material was mixed with KBr in a ratio of 1:99 to triturate, and then compressed into pellets, which were then subjected to scanning at 4000 to 400 cm^{-1} to obtain the spectra.

Differential Scanning Calorimetry (DSC) Studies

Pure DVR and optimized spherical agglomerates were subjected to DSC analysis. About 3 mg of DVR and triturated spherical agglomerates were kept in separate pans. These pans must be hermetically sealed using a crimper. The sample pan, along with a reference pan, was then loaded into the DSC analyser. The temperature was increased to 400°C at a heating rate of 10°C per min. To create an inert atmosphere, N_2 gas was push with a speed of 100 mL per min.

X-Ray Diffraction (XRD) analysis

The XRD of pure DVR as well as optimized spherical agglomerates was obtained using an X-ray diffractometer equipped with a copper target. The instrument requires a voltage of around 30 kV and; 30 mA current for operation. The instrument operated at a speed of 2°C/min with a scale angle of 0 to 90° (2θ).

Residual solvent determination

The residual solvent (Acetone and Methylene Dichloride) from spherical agglomerates was determined by using the GC method. Spherical agglomerates of 200 mg were weighed accurately and transferred into a headspace vial and 2 mL diluent N-methyl-2-pyrrolidone (NMP) was added and sealed properly. The test sample, composite standard solution, was injected in to GC system (Shimadzu, GC2010 plus with Headspace sampler HS-20) equipped with DB-624 (60 m × 0.53 mm, 3.0 μm) capillary column and flame ionisation detector. Nitrogen was used as the carrier gas during analysis. The solvent flow rate inside the column was set as 4.59 mL/min. The column oven temperature was maintained between 40 to 2300C while detector temperature was set at 2400C. The GC cycle time was found to be 38 minutes. The residual solvent was determined using following formula.

$$Solvnet\left(ppm\right)=\frac{Ru}{Rs}X\frac{Ws\ X\ PF}{50}X\frac{5}{100}X\frac{2}{Wt}X1000000$$

Ru: Avg area of individual solvent peak obtained from test chromatogram

Rs: Avg area of respective solvent peak obtained from composite std solution

Ws: Wt of respective solvent in mg

Wt: Wt of test sample in mg

PF: Purity factor

Calculation of purity factor = Purity of respective solvent/100

Formulation and development of DVRE immediate release tablets

DVRE tablets containing spherical agglomerates using DC method, DVRE tablets containing pure API using the wet granulation method and DVRE tablets containing pure API using the DC method. These three approaches were used to manufacture the tablets. The details of all manufacturing methods are presented below.

Formulation of DVRE tablets containing spherical agglomerates

DVRE tablets containing spherical agglomerates were manufactured using direct compression (DC) method. DVRE agglomerates, microcrystalline cellulose (GR 102), colloidal Silicon dioxide and crospovidone must be sifted together using #30 and mixed approximately for 20 min in a polybag. Magnesium stearate also passed through sieve #60 and combined well in a polybag with above blend for approximately 5 minutes. The tablets were compressed using 18.0 × 8.0 mm capsule shape punches. The formulation parameter was shown in Table 3. The lubricated blend and compressed tablets were evaluated further.

Formulation of DVRE tablets using wet granulation method:

DVRE, microcrystalline cellulose (GR 101), and crospovidone were co-sifted through #30 and mixed approximately for 10 minutes in a polybag. HPMC was dissolved in purified water with stirring till get clear

Table 3: Formula composition of DVRE tablets with spherical agglomerates using DC method.

Darunavir Ethanoate Tablets (With Spherical Granules) (Formulation F1)			
Sr. No.	*Ingredients*	*mg/tab*	*%*
Dry Mix			
1	Darunavir Ethanoate Agglomerates	682.99	75.89
2	Microcrystalline Cellulose (GR 102)	187.01	20.78
3	Crospovidone (Kollidon CLF)	20.00	2.22
4	Colloidal Silicon Dioxide	5.00	0.56
Lubrication			
5	Magnesium stearate	5	0.56
Total		900.00	100.0

solution was obtained. Granulation was performed by hand in a bowl with the addition of HPMC binder solution to the dry mix. Thus prepared granules were subjected to dry in a tray drier at 50°C, then passed through #20 for uniform size granules. The remaining material was sifted through #30 to combine with dried granules by using the tumbling method. Magnesium stearate was sifted through #60 and mixed well in a polybag with the above pre-lubricated blend for approximately 5 minutes. The tablets were compressed using 21.0 X 10.0 mm capsule shape punches. The composition is presented in Table 4. The lubricated blend and compressed tablets were evaluated further.

Formulation of DVRE tablets using DC method

DVRE, micro-crystalline cellulose (GR 102), colloidal silicon dioxide and crospovidone passed through #30 and mixed approximately for 20 min in polybag. Magnesium stearate was passed through sieve no.60 and combined well in a polybag with the above blend for approximately 5 min. The tablets were compressed using 21.0 × 10.0 mm capsule shape punches. The formula composition is presented in Table 5. The lubricated blend and compressed tablets were evaluated further.

Characterisation of lubricated blend of F1, F2 and F3 batches

The lubricated blend of batches F1, F2 and F3 were evaluated for micromeritics properties. Bulk (BD) and tapped density (TD), Compressibility Index (CI), Hausner's Ratio (HR) were determined as per procedure mentioned previous section.

Evaluation of compressed tablets

Tablet thickness

Twenty tablets from each batch were randomly selected, and their thickness was measured using a vernier caliper. The thickness was determined along with the standard deviation.

Weight variation

In accordance with USP guidelines, twenty tablets were randomly selected from each batch. The tablets were weighed collectively using a digital balance, and the average weight was calculated.[25] To assess weight variation, the individual weights of the tablets were compared to the calculated average weight.

Hardness

The hardness of the tablet was measured using a Monsanto hardness tester.

Friability

In this test, ten tablets were randomly selected from each batch. These tablets were subjected to 100 rotations in an automatic friabilator. After removing any dust, the weight of the tablets was recorded. The friability was determined by calculating the mean of three measurements.[16] Typically, tablets with a weight loss of less than 1% were deemed acceptable.

Content uniformity

For the test, ten tablets from each formulation were weighed and finely powdered. About 20 mg of DVR dissolved in ethanol. The resulting solution was filtered

Table 4: Formula composition of DVRE tablets using the wet granulation method

Darunavir Ethanoate Tablets (Wet Granulation) (Formulation F2)			
Sr. No.	*Ingredients*	*mg/tab*	*%*
Dry Mix			
1	Darunavir Ethanoate	650.47	54.66
2	Microcrystalline Cellulose (GR 101)	475.53	39.96
3	Crospovidone (Kollidon CLF)	10.00	0.84
Granulation			
4	Hydroxypropyl Cellulose (15 Cps)	10.00	0.84
5	Purified Water	qs	qs
Pre-Lubrication			
6	Colloidal Silicon Dioxide	8.00	0.67
7	Crospovidone (Kollidon CLF)	26.00	2.18
Lubrication			
8	Magnesium stearate	10.00	0.84
Total		1190.00	100.00

Table 5: Formula composition of DVRE tablets using DC granulation method

Darunavir Ethanoate Tablets (DC) (Formulation F3)			
Sr. No.	Ingredients	Mg/tab	%
Dry Mix			
1	Darunavir Ethanoate	650.47	55.12
2	Microcrystalline Cellulose (GR 102)	475.53	40.30
3	Crospovidone (Kollidon CLF)	36.00	3.05
4	Colloidal Silicon Dioxide	8.00	0.68
Lubrication			
5	Magnesium stearate	10	0.85
Total		1180.00	100.00

through filter paper, and the content of DVR was determined by measuring the absorbance at 270 nm using a UV-vis spectrophotometer. Dilution was carried out as necessary to ensure accurate measurements.

In-vitro disintegration time

Six tablets were used in the disintegration test apparatus. A disintegration medium consisting of 900 mL of distilled water at a 37 ± 0.5°C was used. After complete disintegration and no remnant in the apparatus, was measured in seconds.

In-vitro dissolution study

The studies were using in USP type II dissolution test apparatus with 900 mL dissolution media (Tween-20 (2%) with 0.05 M Sodium Phosphate Buffer) at pH 3.0 as release media at 37 ± 0.5°C. The turbulence in the vessel was adjusted to 75 rpm. The 5 mL aliquots were pipetted out at different time intervals and sink conditions were maintained. The solutions were analysed at 270 nm to determine the drug release.

RESULTS AND DISCUSSION

Development of DVRE spherical Crystals using Bridging Solvents

The spherical crystals were developed by using a combination of polymer (Plasdone 630), acetone as good solvent, water as a bad solvent and MDC as a bridging solvent. In solution-based crystal growth, a solvent plays a crucial role in providing an environment for the constituent particles to come together and form a crystal.[26] A good solvent for spherical crystal formation has high solubility, slow evaporation, low volatility, and appropriate viscosity. It ensures sufficient solute concentration and allows for controlled assembly of particles, promoting the formation of spherical crystals. In contrast, a bad solvent has low solubility, fast evaporation, high volatility, or inappropriate viscosity, hindering spherical crystal growth by limiting solute concentration, causing irregular growth or aggregation, and deviating from the desired morphology. A bridging solvent, in this context, refers to a solvent that facilitates the formation of spherical crystals by connecting or bridging the individual particles [27].
Polymers act as templating agents, interacting with solute particles and influencing their nucleation and growth, leading to spherical crystal formation [28]. Good solvents with high solubility create super-saturated solutions where solute particles aggregate and grow into spherical crystals as the solvent evaporates or cools. Conversely, bad solvents with low solubility hinder spherical crystal formation, resulting in irregular growth. Bridging solvents, possessing properties like high boiling point, low volatility, and suitable viscosity, facilitate the assembly of solute particles into well-defined spherical structures. Polymer characteristics, solvent solubility, and solvent properties all impact crystal growth and morphology.

Evaluation of spherical agglomerates

Flow characteristics

The BD of the pure DVRE was found to be 0.333 ± 0.011 gm/cm^3, TD was found to be 0.435 ± 0.012. The HR of 1.31 ± 0.013 was observed while CI was found to be 23.45 ± 0.017. Formation of spherical agglomerates drastically improved the micrometric properties of of pure DVRE. The BD and other parameters of all batches of the spherical agglomerates were found to be increased in comparison to pure DVRE. The BD was arranged in a range of 0.478 ± 0.014 to 0.52 ± 0.016 gm/cm^3. The tapped density ranged between 0.502 ± 0.020 to 0.604 ± 0.014 g/cm^3. The HR was found in the range of 1.04 ± 0.013 to 1.19 ± 0.011 and the CI was found between 3.98 ± 0.012 16.26 ± 0.023. Housner's Ratio of 1.00 to 1.11 and Carr's Index between 0-10 portraits excellent flowability of sample.[29] Overall, flowability in all batches were found to be good. The comparative flow properties of the spherical agglomerates are shown in Table 6.
Spherical agglomerates improved the micromeritic properties of granules by reducing segregation and achieving higher packing densities. They have uniform particle size distribution and density, minimizing the separation of fine and large particles during storage or transportation. The cohesive nature of agglomerates promotes uniformity in the granule mixture. Additionally, the closely packed spherical structures enable efficient space utilization, leading to increased bulk density and decreased void spaces within the granule bed. These improvements contribute to improved uniformity, consistency, and flowability of granules.[30]

Table 6: Flow properties of the spherical agglomerates and pure DVRE

SR.No	*Batch*	*BD*	*TD*	*CI*	*HR*
1	Pure DVRE	0.333 ± 0.011	0.435 ± 0.012	23.45 ± 0.017	1.31 ± 0.013
2	SAD1	0.478 ± 0.014	0.523 ± 0.014	8.60 ± 0.013	1.09 ± 0.011
3	SAD2	0.52 ± 0.016	0.603 ± 0.017	13.76 ± 0.012	1.16 ± 0.014
4	SAD3	0.48 ± 0.021	0.511 ± 0.019	6.07 ± 0.016	1.06 ± 0.013
5	SAD4	0.482 ± 0.017	0.502 ± 0.020	3.98 ± 0.012	1.04 ± 0.013
6	SAD5	0.516 ± 0.015	0.604 ± 0.014	14.57 ± 0.011	1.17 ± 0.014
7	SAD6	0.498 ± 0.014	0.521 ± 0.017	4.41 ± 0.022	1.05 ± 0.012
8	SAD7	0.484 ± 0.013	0.578 ± 0.012	16.26 ± 0.023	1.19 ± 0.011
9	SAD8	0.482 ± 0.011	0.543 ± 0.022	11.23 ± 0.014	1.13 ± 0.017

Effect of independent variables on drug content (Y1) and statistical analysis

DVRE spherical agglomerates were developed by a combination of Plasdone 360, acetone, MDC and water and optimised using A 2^2 full factorial design approach. The formulation batches suggested by design expert software were manufactured and evaluated for drug content, which was considered as an independent variable. The results of the drug content and of all the formulations are presented in Table 7 along with the coded levels of the dependent variables.

The drug content of the spherical agglomerates ranged between 89.80 (SAD6) to 95 % (SAD2). SA2 agglomerates showed the highest drug content than other formulations. The diagnostic case statistics of drug content with actual and predicted values is presented in Table 8.

Its observed that drug content is directly in relation with the level of Plasdone 630 and inversely related to MDC concentration. All batches manufactured with higher level (+1) of Plasdone 630 concentration and lower level of MDC (-1) showed higher drug content. The effect of independent variables on drug content is presented in Figure 1.

Table 7: Results of drug content with levels of independent variables

Batch	*Factor*		*Drug content (%)*	*Solubility (mg/mL)*
	A (Plasdone 630)	*B (MDC)*	*Y1*	*Y2*
SAD1	-1	-1	91.27	0.47
SAD2	+1	-1	95	1.80
SAD3	-1	-1	91.55	0.50
SAD4	-1	+1	89.89	0.22
SAD5	+1	+1	93.54	0.87
SAD6	-1	+1	89.80	0.20
SAD7	+1	+1	93.62	0.90
SAD8	+1	-1	94.8	1.75

Higher polymeric concentration can help to encapsulate or accommodate, or bind with the maximum amount of drug, which may lead to higher drug content. In spherical crystallization, the bridging liquid (MDC) facilitates the generation of spherical agglomerates of drug particles. The bridging liquid acts as a binder that holds drug particles together, forming spherical granules or crystals. Low concentration of the bridging liquid can help improve the drug content in the spherical crystallization technique, which is also observed in our experiments. When the concentration of the bridging liquid is lower, there is a higher probability of drug particles coming into direct contact with each other. This increased contact facilitates the formation of larger drug agglomerates, resulting in higher drug content within the granules or crystals. Moreover, due to a lower concentration of the bridging liquid, the overall volume of liquid introduced into the system is reduced. This reduces the dilution effect on the

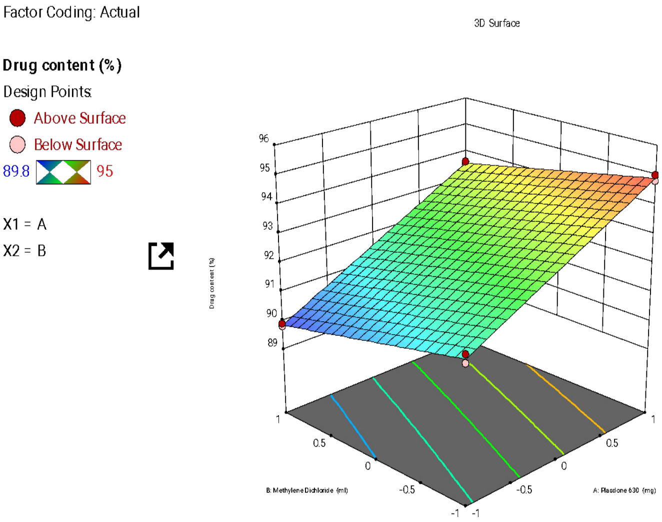

Figure 1: 3D surface responses of Plasdone 630 and MDC on drug content

Table 8: Diagnostic case statistics drug content

Run	*Actual Value*	*Predicted Value*	*Residual*	*Leverage*	*Internally Studentized Residuals*	*Externally Studentized Residuals*	*Cook's Distance*	*Influence on Fitted Value DFFITS*
1	91.27	91.35	-0.0788	0.375	-0.717	-0.677	0.103	-0.525
2	95.00	94.96	0.0387	0.375	0.353	0.320	0.025	0.248
3	91.55	91.35	0.2012	0.375	1.833	2.861	0.672	2.216$^{(1)}$
4	89.89	89.91	-0.0163	0.375	-0.148	-0.133	0.004	-0.103
5	93.54	93.52	0.0212	0.375	0.194	0.174	0.007	0.135
6	89.80	89.91	-0.1063	0.375	-0.968	-0.960	0.187	-0.744
7	93.62	93.52	0.1012	0.375	0.922	0.905	0.170	0.701
8	94.80	94.96	-0.1613	0.375	-1.468	-1.742	0.431	-1.349

Table 9: ANOVA for selected factorial model of drug content

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Model	30.29	3	10.10	607.81	< 0.0001	significant
A-Plasdone 630	26.10	1	26.10	1571.12	< 0.0001	
B-MDC	4.16	1	4.16	250.51	< 0.0001	
AB	0.0300	1	0.0300	1.81	0.2501	
Pure Error	0.0664	4	0.0166			
Cor Total	30.36	7				
Fit statistics						
Std. Dev.	0.1289		R^2	0.9978		
Mean	92.43		Adjusted R^2	0.9962		
C.V. %	0.1394		Predicted R^2	0.9912		
	Adeq Precision		55.4650			

Table 10: Solubility study results with levels of independent variables

Batch	Factor		Solubility (mg/mL)
	A (Plasdone 630)	B (MDC)	Y2
SAD1	-1	-1	0.47
SAD2	+1	-1	1.80
SAD3	-1	-1	0.50
SAD4	-1	+1	0.22
SAD5	+1	+1	0.87
SAD6	-1	+1	0.20
SAD7	+1	+1	0.90
SAD8	+1	-1	1.75

drug particles, allowing a higher concentration of drug within the agglomerates. During spherical crystallization, there is a possibility of drug dissolution in the bridging liquid, leading to a loss of drug content. Lower concentration of the bridging liquid reduces the quantity available for drug dissolution, thereby minimizing drug loss and improving the drug content in the final product.[31,32]

The final polynomial equation for drug content (Y1) in coded factors can be presented below

$$(Y1) = +92.43 + 1.81A - 0.7213B + 0.0613AB$$

In the given equation, Y1 denotes the drug content, while A and B represent the concentrations of Plasdone 630 and MDC, respectively. *P-values* below 0.0500 signify that the model terms are significant. Here, both A and B are significant model terms (refer to Table 9). The Model F-value of 607.81 indicates that the model is highly significant (Table 9), with only a 0.01% probability that such a large F-value could occur due to random noise.

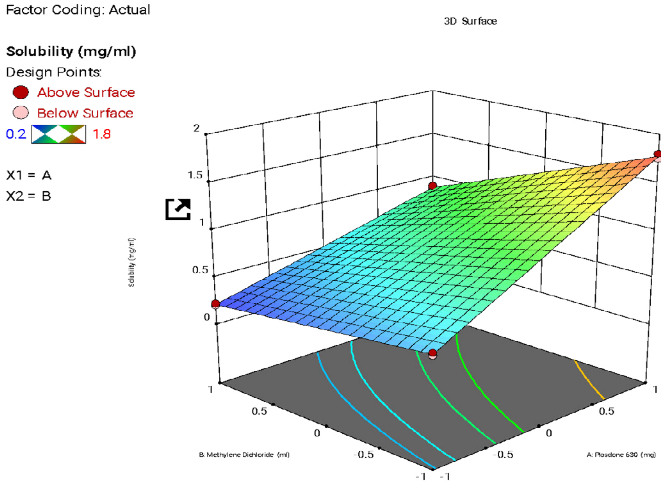

Figure 2: 3D surface responses of Plasdone 630 and MDC on solubility

The predicted R^2 of 0.9912 closely matches the adjusted R^2 of 0.9962, as their difference is less than 0.2 (Table 9). Adequate precision, which measures the signal-to-noise ratio, is considered desirable if it exceeds 4. In our model, a ratio of 55.465 demonstrates a robust signal.

Effect of independent variables on solubility (Y2) and statistical analysis

The outcome of the solubility of all the batches are presented in Table 10 along with coded levels of the dependent variables.

The solubility of the spherical agglomerates ranged between 0.20 (SAD6) to 1.80 mg/mL (SAD2). Pure DVRE has very low solubility of 0.16 mg/mL. A drastic enhancement in solubility was observed when DVRE was processed as spherical agglomerates. Among all these batches SAD2 batch showed highest solubility of 1.80 mg/mL i.e., 11.25-fold enhancement in solubility was observed.

Table 11: Diagnostic case statistics drug content

Run	*Actual Value*	*Predicted Value*	*Residual*	*Leverage*	*Internally Studentized Residuals*	*Externally Studentized Residuals*	*Cook's Distance*	*Influence on Fitted Value DFFITS*
1	0.4700	0.4850	-0.0150	0.500	-0.875	-0.843	0.191	-0.843
2	1.80	1.77	0.0250	0.500	1.459	1.846	0.532	1.846
3	0.5000	0.4850	0.0150	0.500	0.875	0.843	0.191	0.843
4	0.2200	0.2100	0.0100	0.500	0.583	0.528	0.085	0.528
5	0.8700	0.8850	-0.0150	0.500	-0.875	-0.843	0.191	-0.843
6	0.2000	0.2100	-0.0100	0.500	-0.583	-0.528	0.085	-0.528
7	0.9000	0.8850	0.0150	0.500	0.875	0.843	0.191	0.843
8	1.75	1.77	-0.0250	0.500	-1.459	-1.846	0.532	-1.846

Table 12: ANOVA for selected factorial model of drug solubility

Source	*Sum of Squares*	*df*	*Mean Square*	*F-value*	*p-value*	
Model	30.29	3	10.10	607.81	< 0.0001	significant
A-Plasdone 630	1.93	1	1.93	3286.15	< 0.0001	
B-MDC	0.6786	1	0.6786	1155.09	< 0.0001	
AB	0.1891	1	0.1891	321.89	< 0.0001	
Pure Error	0.0023	4	0.0006			
Cor Total	2.80	7				
Fit statistics						
Std. Dev.	0.0242		R^2	0.9992		
Mean	0.8387		Adjusted R^2	0.9985		
C.V. %	2.89		Predicted R^2	0.9966		
	Adeq Precision		91.3115			

The diagnostic case statistics of solubility with actual and predicted value is presented in Table 11.

Similar to drug content, it was discovered that solubility was negatively correlated with MDC concentration and directly correlated with Plasdone 630 concentration. The solubility of spherical agglomerates produced with higher levels (+1) of Plasdone 630 and lower levels (-1) of MDC was higher. The effect of independent variables on drug content is presented in Figure 2.

Higher polymeric content in spherical crystallization improves drug solubility by enhancing wetting, forming interactions, increasing surface area through solid dispersion formation, stabilizing the amorphous form, and reducing particle size. Polymeric materials reduce interfacial tension, promote dissolution, and prevent aggregation. They disperse drug molecules within the polymer matrix, enhance drug-polymer interactions, and inhibit recrystallization. Additionally, polymers aid in particle size reduction, preventing crystal growth and promoting smaller, more uniform drug particles.[30] Overall, higher polymeric content enhances solubility in spherical crystallization through multiple mechanisms.

Low concentration of the bridging solvent in spherical crystallization improves drug solubility through mechanisms such as supersaturation and precipitation, resulting in the formation of drug crystals.[31] It also leads to particle size reduction, increasing the surface area for dissolution. Controlled crystal growth at lower concentrations allows for the formation of more soluble crystal forms. Additionally, lower solvent concentration influences crystal morphology, favouring desirable spherical shapes that enhance flow properties and dissolution. Overall, lower bridging solvent concentration promotes supersaturation, particle size reduction, controlled crystal growth, and morphology control, all contributing to improved drug solubility in spherical crystallization.

The final polynomial equation for drug content (Y1) in coded factors can be presented below

$$Y2 = +0.8387+0.4913A-0.2913B-0.1538AB$$

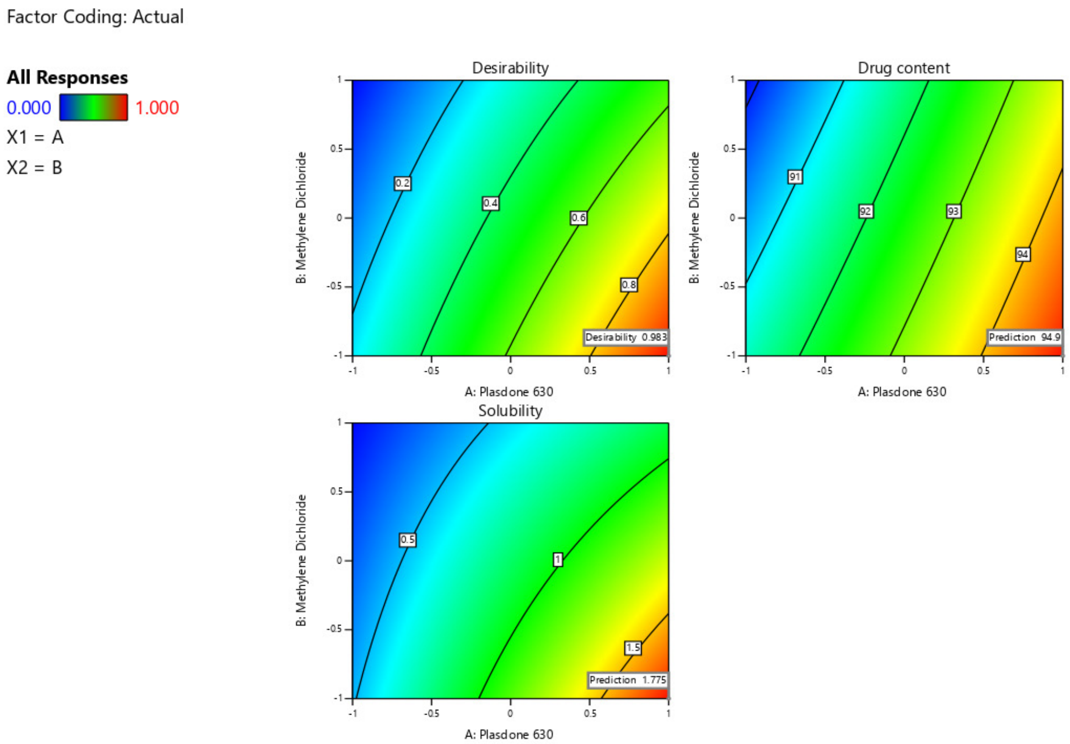

Figure 3: Desirability plots of Drug content and solubility

In the given equation, Y2 represents drug solubility, while A and B denote the concentrations of Plasdone 630 and MDC, respectively. The *p-values* below 0.0500 indicate that the model terms are significant. Here, both A and B are significant model terms (Table 12). The Model F-value of 1587.71 suggests that the model is highly significant (Table 12), with only a 0.01% probability that such a large F-value could occur due to noise. The predicted R^2 of 0.9966 is in reasonable agreement with the adjusted R^2 of 0.9985, as the difference is less than 0.2 (Table 12). Adequate precision, which measures the signal-to-noise ratio, should be greater than 4. In our model, a ratio of 91.311 indicates a robust signal.

Desirability plots of Drug content and solubility are presented in Figure 3.

FTIR analysis

The FTIR spectrum of DVRE exhibit differentiated peaks that represents to the different functional groups on drug molecule. The spectrum typically consisted of several large peaks within value of 3100-1500 cm^{-1} (Figure 4A). The most prominent peak due to carbonyl (C=O) stretching vibrations at 1750-1735 cm^{-1}. The stretching vibrations of aliphatic C-H bonds were appeared as a series of peaks at 3000-2800 cm^{-1}. The stretching vibrations of aromatic C-H bonds typically appeared as a set of peaks in the range of 3100-3000 cm^{-1}. These peaks confirmed the aromatic rings in the molecule. DVRE contains amide functional groups. The amide C=O stretching vibration typically appeared being strong peak in the range of 1670-1650 cm^{-1}. The amide N-H bending vibration observed as a peak around 1550-1520 cm^{-1}. Similar characteristic peaks were also observed at same wavenumber with reduced intensity in DVRE loaded spherical agglomerates (Figure 4B). This observation clearly indicated the excellent compatibility of the drug with polymer used in formulation.

XRD analysis

DVRE showed characteristic diffraction peaks between approximately 5° to 40° 2θ angles in its powder XRD pattern (Figure 5A). The sharp and distinct peaks in the diffractogram confirmed the crystalline habit of DVRE. The diffraction of DVRE-loaded spherical agglomerates exhibits broad peaks or diffuse scattering, which indicates that the material lacks long-range order and has a disordered or amorphous structure. The XRD spectra of DVRE-loaded spherical agglomerates exhibited smaller and less intense peaks compared to pure DVRE (Figure 5B), which may suggest that the drug underwent amorphization during the agglomeration process.

Crystallinity Index (CrI) Calculation

The Segal method was used to estimate the CrI, which is widely used for semi-quantitative assessment of crystallinity in pharmaceutical solids:

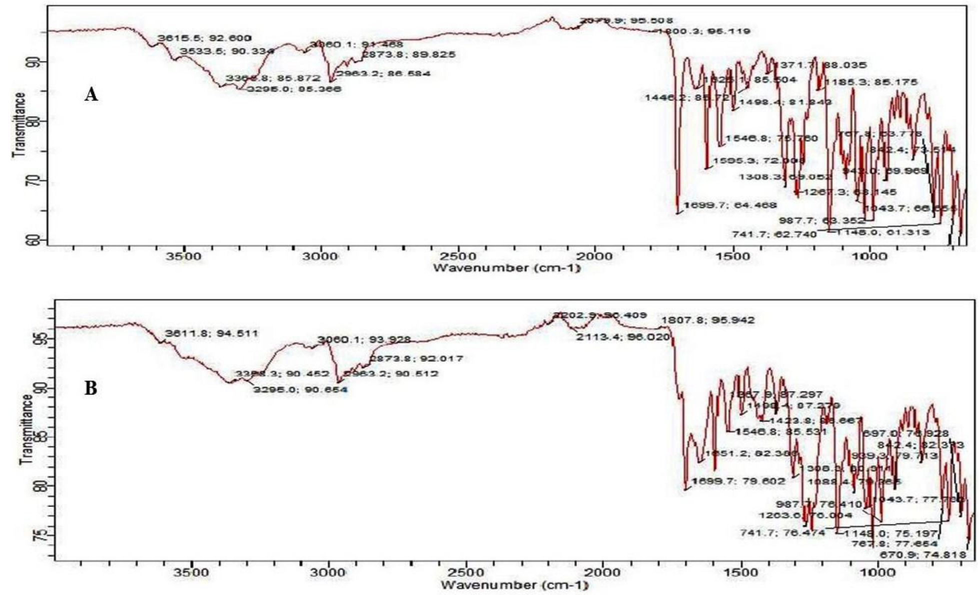

Figure 4: FTIR spectra of A: pure DVRE and B: DVRE loaded spherical agglomerates

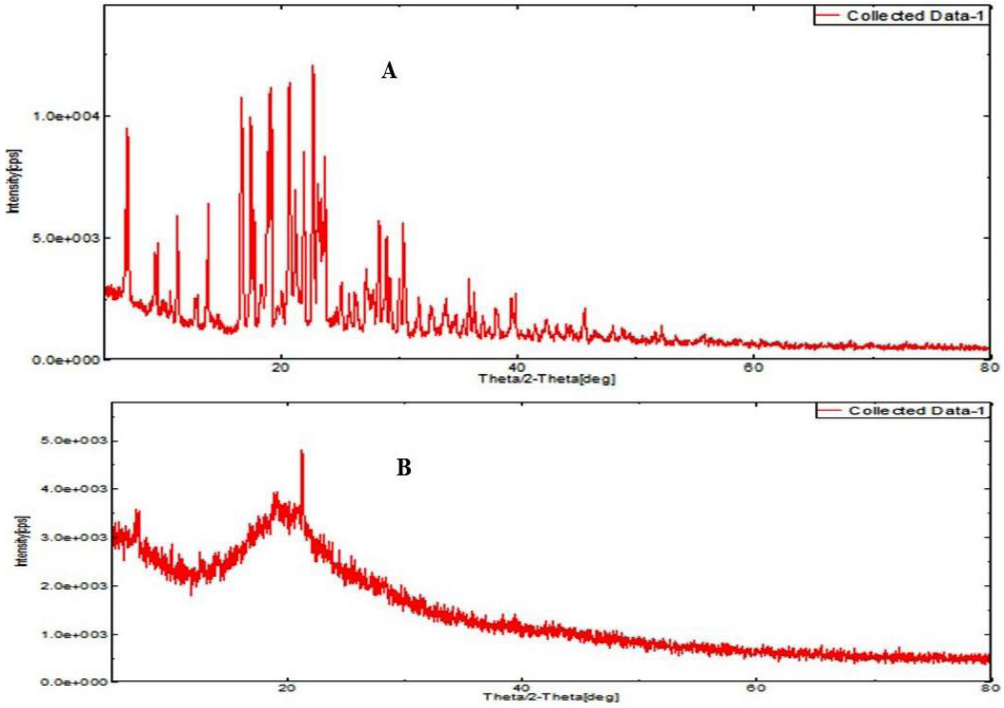

Figure 5: X-ray diffractogram of A: Pure DVRE; B: DVRE loaded spherical agglomerates

Crystallinity Index (CrI) = $(I_{crystalline} - I_{amorphous}) / I_{crystalline}$ X 100

Where,

$I_{crystalline}$ = maximum intensity of the crystalline peak (from Pure Darunavir Ethanolate – pattern A)

$I_{amorphous}$ = minimum intensity at the amorphous background (from Spherical Agglomerates – pattern B)

From Figure 5

$I_{crystalline}$ = 11,000 cps (strongest peak near 2θ = ~20°)

$I_{amorphous}$ = 3,200 cps (broad hump near 2θ = ~20° in pattern B)

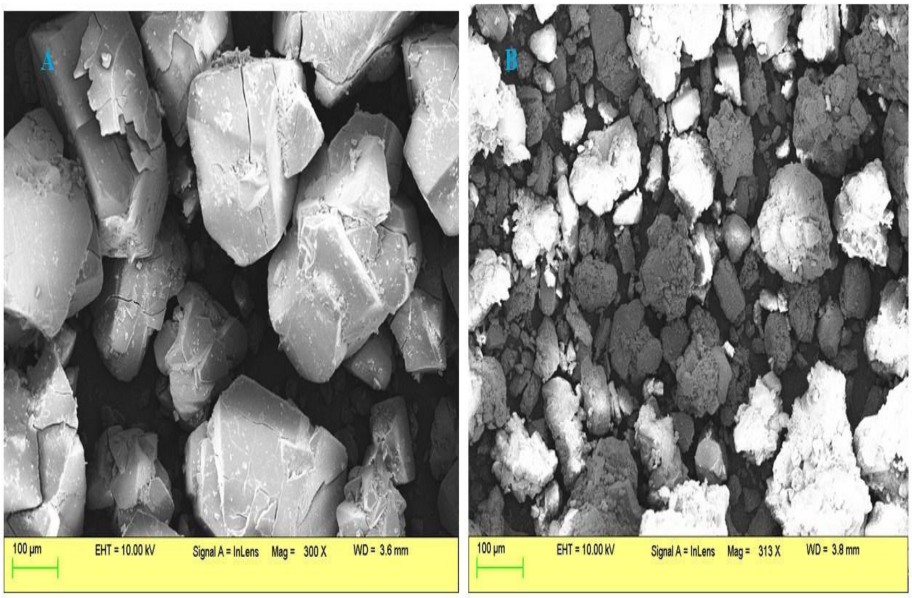

Figure 6: Scanning electron microscopy (SEM) of A: Pure DVRE; B: DVRE loaded spherical agglomerates

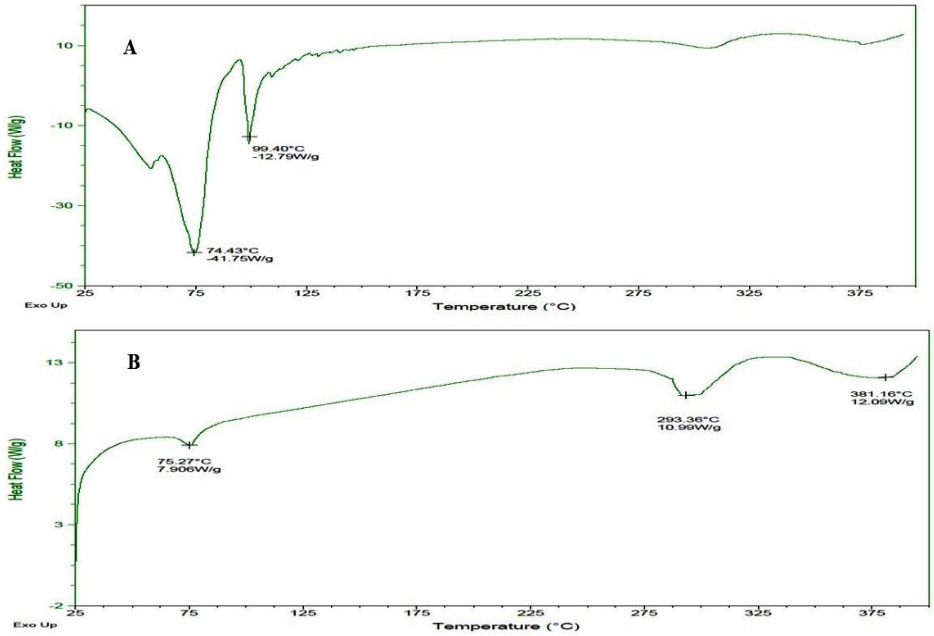

Figure 7: DSC thermograph of A: Pure DVRE, B: DVRE loaded spherical agglomerates

Crystallinity Index (CrI) = (11,000-3,200)/11,000 × 100 = 70.9%

The CrI of ~70.9% indicates significant reduction in crystallinity upon agglomeration, but not complete amorphization. This confirms that the spherical agglomerates exhibit a partially crystalline nature, as suggested. Thus, the broadening of peaks in the XRD pattern B is due to reduced crystallinity and crystal disorder, rather than total conversion to an amorphous form.

Scanning electron microscopy (SEM)

In SEM images, DVRE crystals were found to be irregular or slightly cubic-shaped particles with a smooth surface. The particles ranged from small to larger sizes as observed in Figure 6A. However, DVRE-loaded agglomerates were found to be spherical-shaped particles (Figure 6B). This spherical shape was typically formed when individual particles were adhered and agglomerated together during the manufacturing process.

DSC analysis

The DSC analysis revealed an acute endothermic peak of pure DVRE at 99.40°C corresponding to its melting point, ranging from 98 to 100^0C indicating its crystalline nature (Figure 7A). In contrast, DVRE-loaded spherical agglomerates showed complete absence of the sharp and distinctive peak of DVRE, indicating the amorphization of the drug within the polymeric matrix (Figure 7B). This disappearance of the endothermic peak could be attributed to the encapsulation of DVRE within the polymeric matrix.

Residual solvent determination

During the manufacturing of Darunavir-loaded spherical agglomerates acetone and Methylene Dichloride was used as solvent. Acetone and methylene dichloride were selected based on their solvent properties, which play a crucial role in the formation of spherical agglomerates. Acetone acts as a good solvent for DVRE, promoting drug dissolution, while methylene dichloride functions as a bridging liquid, facilitating controlled precipitation and agglomerate formation. This combination aids in achieving uniform spherical morphology with improved micromeritic properties. Additionally, the choice of solvents influences agglomerate porosity, which in turn impacts drug release characteristics.

Regarding safety considerations, both solvents were used within acceptable regulatory limits, ensuring minimal residual solvent content in the final formulation. Acetone is classified as a Class 3 solvent (low toxicity) by ICH guidelines, while methylene dichloride, a Class 2 solvent, was used in a controlled manner with proper drying procedures to minimize residue levels.

The residual amount of these solvents present in spherical agglomerates was determined to check whether the agglomerates meet the regulatory requirement of residual solvent criteria. The residual Acetone content in agglomerates was found to be 2.5 ppm, which falls within the acceptance criteria of 10.01 ppm. While for methylene dichloride maximum allowed residual concentration is 46.21 ppm and in spherical agglomerates, methylene dichloride concentration was found to be 10.50, which is also within the acceptance limit. These observations demonstrate that the Darunavir-loaded spherical agglomerates meet the residual solvent criteria for Acetone and Methylene Dichloride.

Table 13: Comparative micromeritics properties of the lubricated blend

Sr. No	*Formulation*	*BD*	*TD*	*CI*	*HR*
1	F1 (DC blend with Spherical agglomerates)	0.52	0.589	11.71	1.13
2	F2 (Wet Granulation blend with pure DVRE)	0.454	0.666	31.81	1.46
3	F3 (DC blend with pure DVRE)	0.373	0.595	37.31	1.59

Formulation and development of DVRE immediate release tablets

Characterisation of lubricated blend

The lubricated blend of batches F1, F2 and F3 was evaluated for micromeritics properties including BD, TD, CI and HR. The comparative outcome from all batches is presented in Table 13.

The lubricated blend manufactured in F1 batch showed higher BD and better flow properties in comparison to the blend manufactured in F2 and F3 batches. The compressibility index in case of F2 (31.81) and F3 (37.31) was found very poor (32-37 considered as very poor) while F1 blend (11.71) showed good compressibility (11-15 considered as fair). Similarly, HR was also found to be very poor (1.46 to 1.59) in case of F2 and F3 blends. F1 lubricated blend showed good HR (1.11 to 1.18).[29]

F2 and F3 exhibit poor flowability (CI > 30, HR > 1.45), affecting scalability and manufacturability. This can cause inconsistent die filling, weight and content uniformity issues, powder bridging, and segregation. High compressibility may lead to tablet hardness variations and dissolution inconsistencies, impacting large-scale production.

These observations clearly indicated that use of DVRE spherical agglomerates has significantly improved the flow properties as well as compressibility of the blend in comparison pure DVRE.

Spherical agglomerates of drugs enhance the flow properties and compressibility of granules by reducing interparticle friction, minimizing irregularities, optimizing packing efficiency, reducing interparticle forces, and increasing porosity.[33] The larger particle size allows for better flow by reducing interlocking, while the spherical shape reduces hindrances and resistance. Uniform packing of spherical agglomerates minimizes void spaces, improving flow and compressibility. Weaker interparticle forces due to binders or surface modifiers decrease cohesion, further enhancing flow. Controlled porosity promotes air circulation, reduces granule sticking, and facilitates compression. Overall, spherical agglomerates offer improved flow and compressibility, benefiting granule formulation and processing.

Evaluation of compressed tablets

The comparative evaluation parameters of the tablets are presented in Table 14

The tablets were compressed with capsule shape punches with dimensions mentioned in manufacturing procedure. All the batches comply with the weight variation test as per USP for uncoated tablets. According to USP, uncoated tablets weighing more than 325 mg has weight variation limit of 5%. In all batches the weight variation was found

Table 14: Compressed tablets evaluation parameters

Sr. No	*Batch*	*Weight (mg)*	*Thickness (mm)*	*Hardness (kg)*	*Friability (%)*	*DT (min)*	*% yield*
1	F1	900 ± 3%	5.9 ± 0.4	18 ± 4	0.20	1-2	98.0
2	F2	1190 ± 3%	6.3 ± 0.4	16 ± 4	0.60	5-6	95.1
3	F3	1180 ± 3%	6.2 ± 0.4	13 ± 4	0.80	5-6	97.5

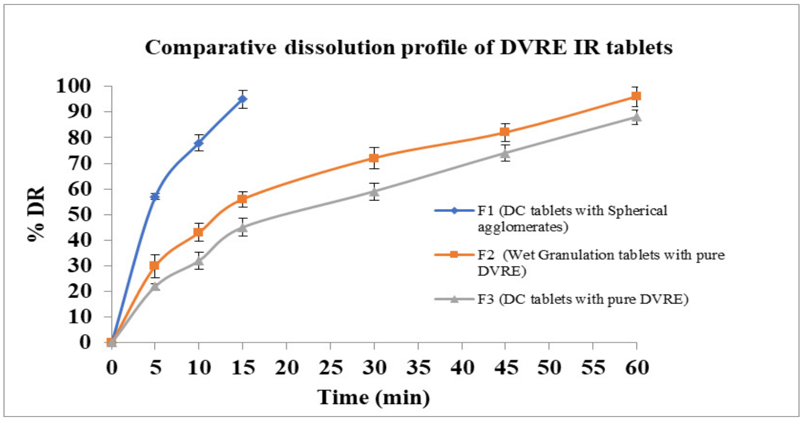

Figure 8: Comparative DVRE release from IR tablets

within acceptable limit.[34] The USP method was chosen as it provides a widely accepted and standardized approach for evaluating tablet uniformity, which is critical for dosage consistency and regulatory approval. We have now explicitly mentioned this in the revised manuscript for clarity and accuracy. Similarly, all three batches showed greater hardness as well as acceptable friability as per USP (NMT 1%). During the formulation stages, the hardness of tablets is an essential parameter to be considered. The compressibility of granules directly influences the tablet hardness. F1 batch with higher compressibility indexes demonstrated greater hardness, which ensured their ability to withstand physical abrasion. The increased hardness of tablets also played a crucial role in passing the friability test. F2 and F3 batches showed DT of 5-6 min at 3% concentration of crospovidone but F1 batch showed DT of 1 to 2 min even at 2% concentration of crospovidone. The presence of spherical agglomerates might have helped for rapid disintegration of the tablets in comparison to pure DVRE in other batches. Also, higher yield of 98 % was found in F1 formulation that may be due to uniform mixing of the spherical agglomerates with other excipients of the tablet.

In-vitro dissolution study

Spherical agglomeration significantly enhances the dissolution and release kinetics of drugs in tablet formulations through multiple physicochemical and microstructural mechanisms. Firstly, the spherical morphology increases the effective surface area, facilitating efficient solvent interaction and rapid dissolution. Additionally, improved wettability due to the uniform and porous structure of agglomerates enables faster penetration of the dissolution medium, reducing the lag time for drug release initiation. Moreover, controlled porosity within the agglomerates enhances permeability, allowing for efficient diffusion of the dissolution medium and promoting a faster disintegration process. The uniform distribution of drug particles within the agglomerates ensures consistent and predictable drug release kinetics, minimizing batch-to-batch variability. Furthermore, the optimized mechanical properties and lower interparticle cohesion contribute to better tablet disintegration, accelerating drug liberation from the dosage form. Collectively, these attributes result in an improved dissolution rate and bioavailability of the drug, making spherical agglomerates a promising strategy for formulating highly soluble and rapidly acting oral dosage forms.

The comparative release of all batches is presented in Figure 8. The profile of F1 batch was found to be faster in comparison to F2 and F3 formulations. Nearly 100% release was observed within 15 minutes from F1 formulation containing DVRE spherical agglomerates. Complete drug release was not observed even time period of 1 hour from F2 and F3 formulations.

The inferior dissolution and flow properties observed in F2 (wet granulation) and F3 (direct compression) formulations can be attributed to inadequate particle size control, suboptimal porosity, and poor wettability compared to the spherical agglomerates. These limitations highlight the advantages of spherical crystallization in enhancing micromeritic properties and dissolution behavior. However, we recognize that scaling up spherical crystallization presents challenges, including process reproducibility, solvent selection, and control over agglomerate size distribution. Despite these challenges, the method offers significant formulation benefits, and further optimization strategies, such as process parameter refinement and alternative solvent systems, could enhance scalability.

The pharmaceutical advantage of this study lies in its ability to overcome key formulation challenges associated with high-dose, poorly water-soluble drugs like Darunavir Ethanolate (DRVE). As a BCS Class II drug, DRVE suffers from limited aqueous solubility, which significantly restricts its dissolution rate and subsequent bioavailability. Furthermore, its crystalline nature and poor micromeritic properties, including low flowability, compressibility, and bulk density, complicate the direct compression process, often necessitating additional formulation steps such as granulation or the use of excipients to improve processability. In this study, spherical crystallization was employed as an advanced particle engineering approach to simultaneously modify the physicomechanical and biopharmaceutical characteristics of DRVE without altering its chemical structure. The formation of spherical agglomerates led to more uniform, compact particles with improved packing behavior, reduced inter-particulate friction, and enhanced surface area for better wettability. These modifications contributed to superior flow properties, enhanced compressibility, and significantly improved dissolution rates compared to the unmodified drug. This one-step, scalable technique not only offers a cost-effective and industrially feasible solution but also aligns with the growing demand for improving drug solubility and manufacturability through innovative crystal engineering strategies. In the current scenario, where rapid and efficient formulation development is critical, such an approach holds substantial promise for enhancing the performance and patient compliance of high-dose antiviral therapies like DRVE.

Spherical crystallization improves flow, solubility, and compressibility but faces limitations with high-dose APIs. Challenges include solvent selection, agglomeration efficiency, cohesiveness, and scalability. Precise control of process parameters is crucial to avoid irregular morphology and polymorphic transitions. Optimization, alternative excipients, or hybrid techniques can help overcome these issues for better formulation performance.

CONCLUSION

This study confirms the successful development of spherical crystals of the Darunavir Ethanolate using a blend of Palsdone 630, acetone, water and methylene dichloride. Furthermore, the present investigation demonstrates the successful improvement of flow properties, compressibility, solubility, and dissolution of the highest dose Darunavir Ethanolate molecule by employing the spherical crystallisation technique. The formation of spherical agglomerates resulted in a significant improvement in the micromeritic properties, including bulk density (BD), tapped density (TD), Hausner ratio (HR) and Carr's index (CI), indicating enhanced flow properties and compressibility compared to DVRE alone. These findings have important implications for the development of drug formulations with enhanced performance characteristics, potentially leading to improved therapeutic outcomes and patient compliance.

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