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Original Article

Spherical Crystallization of Rosuvastatin Calcium for Enhanced Solubility, Dissolution, and Direct Compression Properties

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ABSTRACT

Objectives: Rosuvastatin calcium is crystalline, BCS Class II drug having low solubility and bioavailability approximately 20%. Crystalline nature of drug result in poor dissolution, flowability, and compressibility, which limit its direct compression. The aim of study is to develop and evaluate spherical agglomerates of rosuvastatin to enhance solubility, dissolution, and manufacturability. **Materials and Methods:** Spherical agglomerates of Rosuvastatin were prepared by using the solvent change approach. Acetone, a good solvent; dichloromethane, the bridging liquid; and water, poor solvent, were used along with HPMC E5 as a stabilizer to synthesize the ternary system. The central composite design was employed to optimize the formulation where HPMC content and stirrer speed were selected as independent variables and % drug released and Carr's index as responses (dependent variables). Spherical agglomerates of rosuvastatin were further characterized using microscopy, FTIR, DSC, and XRPD studies and evaluated for flow and compressibility properties along with compression studies. **Results:** The spherical agglomerates of rosuvastatin possessed a uniform spherical morphology and lower crystallinity. Hydrogen bonding was detected by FTIR and DSC studies of the drug and HPMC E5 without any incompatibilities. XRPD analysis proved crystallinity of rosuvastatin is reduced by 44.44%. Compared to rosuvastatin, agglomerated forms presented better physical properties such as higher flowability, increased bulk density, and good compressibility, being thus appropriate for direct compression. The dissolution of the tablets based on agglomerates was found to be significantly improved compared to conventional rosuvastatin tablets. **Conclusion:** The present study has shown successful improvement in dissolution characteristics and tableting ability because of alteration in particle size and amorphization of spherical rosuvastatin agglomerates. Spherical crystallization with HPMC E5 may therefore be considered an interesting approach to increase the solubility, processability, and potential bioavailability of rosuvastatin calcium.

Keywords: Rosuvastatin calcium, Spherical agglomeration, Central composite design, HPMC E5, Solubility enhancement, Flowability, Compressibility, Dissolution.

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INTRODUCTION

Hypercholesterolemia is a major risk factor for coronary heart disease and related cardiovascular events, primarily resulting from the accumulation of cholesterol rich plaques that impair blood flow to vital organs.[1] Statins, a class of hypolipidemic agents, are widely prescribed for the management of this condition due to their ability to inhibit 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis.[2,3] Among available statins, rosuvastatin exhibits superior potency and prolonged pharmacological action owing to its high binding affinity for HMG-CoA reductase and favorable pharmacokinetic profile.[4,5] Despite these therapeutic advantages, the clinical and manufacturing performance of rosuvastatin is compromised by its unfavorable physicochemical and micromeritic properties.

Rosuvastatin calcium falls under the category of Biopharmaceutics Classification System (BCS) Class II drugs because of their poor aqueous solubility but high permeability. The crystal nature of this drug makes it dissolve slowly in gastric juices, making dissolution the rate-limiting step for absorption; hence, oral bioavailability is low (about 20%).[6,7] Apart from having poor dissolution behavior, rosuvastatin has poor flow and compaction characteristics, which significantly restrict its suitability for direct compression. This situation has created a need to formulate this drug using formulation methods that would increase both solubility and manufacturability of the drug. Several studies have been done on improving the dissolution characteristics of such drugs through

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different means like micronization, making amorphous solid dispersions, formation of salts, cocrystallization, and liquisolid formulations.[8-14] Though the above methods can increase the solubility of the drug, they may end up producing a powder that lacks good flowability and compaction characteristics. Such characteristics are crucial when scaling up for manufacture into dosage forms like tablets since the direct compression method is the most economic way of tablet manufacturing because of simplicity and energy conservation.[15-17] Consequently, there is a compelling need for particle engineering strategies that address both biopharmaceutical and manufacturability constraints in a single platform.

In the current competitive pharmaceutical environment, the industry is increasingly focused on the development of cost-effective formulations without compromising product quality. To achieve this objective, pharmaceutical scientists require excipients and active pharmaceutical ingredients with high functionality and favorable processing properties. Various approaches have been employed to enhance excipient functionality, including modification of the physical properties of individual excipients and the development of co-processed excipients through the combination of two or more excipients using suitable processing techniques. While excipient engineering has significantly contributed to improved processability and functionality of pharmaceutical formulations, modification of the active pharmaceutical ingredient itself has gained increasing importance in recent years. Many APIs exhibit poor flowability, compressibility, and compactibility, which pose challenges during large-scale manufacturing. Particle engineering techniques such as spherical crystallization have emerged as promising approaches to modify the physical properties of APIs by producing spherical, dense, and free-flowing crystals. Furthermore, the co-processing of APIs with suitable excipients during spherical crystallization is another way to combine the improvement of API functionality and excipient performance, thereby improving overall process efficiency and enabling cost-effective formulation development.

Spherical crystallization is considered a promising approach to particle formation that is based on the combination of the processes of crystallization and agglomeration. Spherical crystallization was initially invented by Kawashima in 1974. It produces compact and spherical agglomerates which have better flowability, compressibility, and dissolution characteristics.[18-20] Thus, the process of spherical crystallization provides an additional opportunity to optimize the characteristics of BCS Class II drugs from both process and biopharmaceutical points of view. The process of spherical crystallization allows changing the shape, size, surface, and mechanical properties of crystals, therefore significantly increasing their properties. One of the advantages of spherical crystallization is that resulting agglomerates can be directly compressed into tablets, eliminating the need for the granulation stage.

While many benefits of spherical crystallization have been proven, the use of this method to rosuvastatin has received little attention, especially in optimizing not only the solubility but also the flowability and compressibility of the drug simultaneously. This study aimed to explore the possibility of using spherical crystal agglomeration as an approach that could solve two problems at once concerning the rosuvastatin. The purpose of this work is to develop optimized spherical crystal agglomerates with improved dissolution properties and better micromeritic properties appropriate for direct compression. Central composite design was applied in order to examine the effect of polymer concentration and agitation speed on drug release rate and Carr's index. The optimized agglomerates were formulated into tablets using direct compression and evaluated in comparison with a marketed formulation to assess improvements in pharmaceutical performance.

MATERIALS AND METHODS

Materials

Rosuvastatin was purchased from Dhamtech Pharma, Navi Mumbai. HPMC E 5, PEG 4000, acetone and dichloromethane was received as gift sample from Research Lab Pvt, Mumbai.

All other chemicals and reagents used were of analytical quality.

Preparation of spherical agglomerates of rosuvastatin

Selection of solvent

Solvents of different polarity including methanol, acetone, propylene glycol and water were selected of various categorized solvents including good solvent (in which drug is get dissolved) and poor solvent (drug is insoluble). Solvent selection was based on saturation solubility.[21]

According to the solubility study of rosuvastatin, it exhibits high solubility (105.24 mg/mL) in acetone and poor solubility (0.29 mg/mL) in water. Consequently, acetone is selected as a good solvent for rosuvastatin, while water is considered as poor solvent.

Selection of bridging liquid

It is important that bridging liquid be miscible with selected good solvent. Acetone (good solvent) was found to be miscible with Dichloromethane in proportions from 1:1 to 1:5 while it was immiscible with Chloroform in different proportions. Dichloromethane was therefore selected as a bridging liquid.

Selection of polymer

Several preliminary trials were conducted to screen excipients among various polymers, including PEG 4000 and HPMC. Hydrophilic polymers at concentrations of 0.5%, 1%, 1.5%, and 2% w/v were solubilized in water. All other processing parameters were maintain constant such as stirring speed (400 rpm) and

the ratio of good solvent to bad solvent (0.08 v/v). PEG 4000 yielded a sticky product, whereas HPMC E5 produced spherical agglomerates, leading to the selection of HPMC E5 for further studies.[21-23]

Preparation of Co agglomerate

Solvent change method was used for preparation of spherical agglomerates of rosuvastatin. 200 mg rosuvastatin dissolved in 3 mL acetone. The solution of rosuvastatin, was added at a rate of 1 mL/min to water containing polymer stirred at a specified rpm using magnetic stirrer. Then add 0.4 mL dichloromethane as bridging liquid. The stirring was continued for a period of 30 min after complete addition of bridging liquid. The crystals of rosuvastatin filtered by using Whatman filter paper and then dried at room temperature.

Experimental design

A central composite design was used to optimize the formulation of spherical agglomerate. Two-factor, two-level CCD was applied to evaluate the influence of experimental variables on their performance.[24,25] Table 1 presents the experimental runs summary. The levels of the independent variables were set between -1 and +1. % Drug release of spherical agglomerate and Carr's index were the dependent variables. A total of 13 experimental runs were conducted, including five center points (1.5% HPMC E5 and 300 RPM stirring speed).[26] The data from these runs were analyzed using Design-Expert software.

Characterization of Agglomerate

Flow property and Compressibility

Flow property of rosuvastatin and its spherical agglomerates was assessed by determining the bulk density, tapped density, angle of repose, Carr's index and Hausner ratio.[27,28]

Particle shape

Particle shape of rosuvastatin and spherical agglomerates was observed under optical microscope.

Percentage Yield

It is determined as the percentage difference between the actual amount of powder that was achieved and the maximum theoretical mass that might have been obtained.[29]

$$\%\ Yield\ = \frac{Actual\ mass\ of\ powder\ obtained}{Theoretical\ mass\ of\ powder} X\ 100$$

Saturation solubility

The amount of rosuvastatin agglomerate in excess was dissolved in distilled water (5 mL), and the saturated solutions were allowed to stand for 24 hr. at room temperature on a shaker bath with continuous stirring at a speed of 120 rpm. The mixture was filtered and diluted with distilled water, where after the measurements were done. The amount of rosuvastatin in each solvent was measured by UV-Visible spectrophotometer at λ=240 nm. The results were compared to those from a rosuvastatin standard solution of known concentration.[30]

Fourier transform infrared spectroscopy

In order to verify the chemical structure of the drug and check for its compatibility with the selected excipients, Fourier Transform Infrared Spectroscopy (FTIR) was used. FTIR spectra were obtained for pure rosuvastatin and physical mixture by using a Bruker Alpha FTIR spectrometer. The measurements were conducted in transmission mode from 4100 to 550 cm^{-1} with a spectral resolution of 2 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermal analysis for the study of drug's thermal properties is conducted through differential scanning calorimetry. The thermal analysis of rosuvastatin and SA-RSV was conducted by using DSC 60 Plus, Shimadzu, Japan. Accurate amount of the samples were loaded in aluminium crimped pans with pin-hole opening and then heated at 10 K/min rate between temperatures 30-350°C.

Powder X- ray diffraction analysis

To determine form of crystallinity of drug crystals PXRD was done. The crystallinity of the rosuvastatin and SA-RSV was evaluated using a Bruker X-ray diffractometer (D2 PHASER 2 ND GENERATION). Around 500 mg of powdered samples were evenly placed on the sample holder and subjected to analysis within a 2Θ range of 0° to 60°.

Heckel Analysis

Compacts of API and SA-RSV were prepared using a hand-operated KBr pellet press. There were compression loads of 1 Ton/cm^2 to 15 Tons/cm^2. It was placed in a desiccator for 24 hr before being checked for additional needs.[31-33] Relative densities (D), which are determined by dividing apparent density by true density, were measured in order to conduct the Heckel analysis. After compacts were recovered from the die, the apparent density was determined using the dimensions of compacts at various compressions. The vernier caliper was used to measure the compacts diameter and thickness.

$$\ln\left(\frac{1}{(1-D)}\right) = kP + A$$

Where, "K" represents the slope of the linear part while "P" is the applied pressure. "A" is determined by the original compact volume. The yield pressure Py is equal to the reciprocal of K. The yield pressure Py is inversely proportional to the capacity of a material to plastically deform.

Preparation and evaluation of tablets

Tablets of formulation were prepared according to composition given in Table 2. The compressions of tablets were performed

Table 1: Experimental runs as per Design-Expert software and obtained response of each run.

		Factor	Factor	Response	Response
Std	Run	A: Conc. of HPMC E5	B: Stirring speed	% Drug release	Carr's Index
		%	RPM	%	%
1	12	1	200	62.66	16.53
2	1	2	200	92.54	9.15
3	3	1	400	93.83	12.34
4	11	2	400	72.09	15
5	7	0.792893	300	63.53	16.25
6	10	2.20711	300	69.20	22.98
7	4	1.5	158.579	66.46	17.42
8	2	1.5	441.421	77.71	18.24
9	6	1.5	300	72.40	21.53
10	9	1.5	300	72.40	25
11	8	1.5	300	75	23
12	5	1.5	300	72.40	25
13	13	1.5	300	72.40	24

using rotary tablet compression machine with 8 mm flat round punches. The target weight for each tablet was set at 250 mg, ensuring consistency in tablet size and dosage.[34]

Hardness test

Tablet hardness is evaluated to check durability of tablets. Tablet hardness was measured by using Pfizer hardness tester.

Weight variation

The 20 tablets were randomly selected and then their weights individually measured using an electronic balance. The average weight was then determined along with the deviation of each tablet from the average weight.

Friability

The friability test for 10 tablets was done with the help of Roche friabilator. The Roche friabilator machine tests the effect of rubbing along with impact force on tablets in a plastic drum rotating at 25 rpm and falling from a height of either six inches in every rotation. Dedusting was done using a piece of muslin cloth. The friability (F) is given by formula,

$$F = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

Disintegration time

Disintegration time was determined by putting 6 tablets into each tube in disintegration test instrument. The disintegration test was done with distilled water in disintegration medium at 37±2°C.

Dissolution study

For the dissolution study of rosuvastatin tablets, the procedure was carried out in accordance with the Indian Pharmacopoeia (IP 2018) monograph. Dissolution testing was performed using a IP Type I (USP Type II) paddle apparatus. The dissolution apparatus (Model No. 8000) was manufactured by Labindia. Dissolution condition was maintained as 6.8 pH Phosphate buffer, 50 rpm paddle rotation speed at 37°C ± 0.5°C. At predetermined intervals of 5 min, samples (10 mL) were withdrawn from the central portion of the dissolution vessel using a standard 10 mL syringe, up to a total duration of 30 min.[35]

RESULT AND DISCUSSION

Spherical crystallization of rosuvastatin was successfully developed using the solvent change method. Optimization of rosuvastatin spherical agglomerates was carried out by screening critical formulation and process variables influencing dissolution behavior and flow properties. The methodology used for optimization was central composite sesign (CCD), while Design Expert® software (v 13.0.0) was used for the experimental design and data analysis.

Statistical analysis

% Drug release

The percentage drug release data from all experimental runs were analyzed using a two-factor Interaction (2FI) model. Analysis of variance (ANOVA) revealed that the model was statistically significant for percent drug release (p = 0.0015, α = 0.05). The lack-of-fit test was also significant (p = 0.0014) indicating that

there is variability in the response that is not explained and that the model does not explain all causes of variability. However, as indicated by the adjusted R^2 (Table 3) measure (which determines how well the data fits a regression model), the 2FI model provided a good fit for the data (R^2 = 0.7266). Therefore, even though the lack-of-fit test is statistically significant, the 2FI model is the best one and will be used to characterize the overall trend in percent drug release.

Fit Statistics

Since the negative value is obtained for R^2 prediction, the mean could be a better predictor of the response compared to the current one. Adequate Precision gives a measure of the signal-to-noise ratio. A signal-to-noise ratio larger than 4 is preferable. Since the ratio obtained is 10.2019, there exists an adequate signal, and therefore the model is navigable.

Drug release was primarily influenced by the concentration of HPMC and the stirring speed (Figure 1). At low levels of both factors, a relatively low drug release (~60%) was observed, which can be attributed to the formation of large and irregular agglomerates that hinder dissolution. Increasing the stirring speed while maintaining a low polymer concentration enhanced drug release to approximately 80%, likely due to the formation of smaller and more uniform agglomerates. At higher polymer-to-drug ratios, increased solution viscosity limits mass transfer and crystallization, leading to the formation of sticky agglomerates and inhibition of crystallization.[21,26] Additionally, a reduction in polymer content increases drug loading within the agglomerates, which may further contribute to an increase in percent drug release.[27]

The polynomial equation is as follows:

% Drug release = 74.05+2.02A+3.33B-12.90AB

% Drug release = 74.05 + 2.02polymer conc. + 3.33stirring speed - 12.90polymer conc. X stirring speed

Table 2: Composition of SA-RSV tablet formulation.

Ingredients	Amount
SA-RSV (mg)	17.50
Lactose(mg)	80.35
MCC (mg)	135.9
SSG (mg)	11.25
Talc (mg)	2.5
Magnesium stearate (mg)	2.5

Flowability of powder by using Carr's Index

The Carr's index values of all formulations ranged from 9% to 25%. The experimental data were fitted to a quadratic model, and ANOVA confirmed that the model was statistically significant (p = 0.0479, α = 0.05). The lack of fit test failed to be significant (p = 0.0971); thus, the model fit can be considered sufficient. So, a quadratic equation was deemed appropriate in this case; its coefficient of determination (R^2) is equal to 0.7429.

Carr's index showed higher values due to worse flowability at moderate amounts of polymers and stirring rate. At the same time, lower Carr's index was achieved when polymer content was low, but the stirring rate was high (Figure 2). Lack of sufficient agitation caused poor flowability because of forming irregular agglomerates.[36] whereas increased stirring promoted the formation of spherical granules with denser packing and enhanced flowability.[37] Moreover, the presence of polymers or surfactants increases solution viscosity and reduces interfacial tension, facilitating improved droplet sphericity.[23,38]Adsorption of polymer onto crystal surfaces retards crystal growth, producing smoother agglomerates with superior flow properties.[38]

The polynomial equation is as follows:

Carr's Index = 25.71+0.5997A+0.3525B+2.51AB-4.41A^2-5.30B^2

Carr's Index = 25.71+0.5997 Polymer conc. +0.3525 stirring speed+ 2.51 Polymer conc. stirring speed- 4.41 Polymer conc.^{2} stirring speed ^{2}

Optimization

Software Design-Expert 7.0.0 provides 25 different solution. One solution that included HPMC percentage as 1%, and stirring speed as 400 RPM, and its desirability factor was 1, was chosen as an optimum solution for preparation of spherical agglomerates (Table 4). The selected solution of spherical agglomerate exhibited % drug release and Carr's index as 88.26% and 18.41%, respectively.

Optical microscopy

Optical microscopy (Figure 3) revealed that pure rosuvastatin exhibits an irregular crystal morphology, whereas the optimized rosuvastatin agglomerate (SA-ROS) show a well-defined spherical structure, confirming the successful formation of spherical crystals.

Table 3: Fit statistics for % drug release.

Std. Dev.	5.74	R^2	0.7266
Mean	74.05	Adjusted R^2	0.6355
C.V. %	7.75	Predicted R^2	-0.0820
		Adeq Precision	10.2019

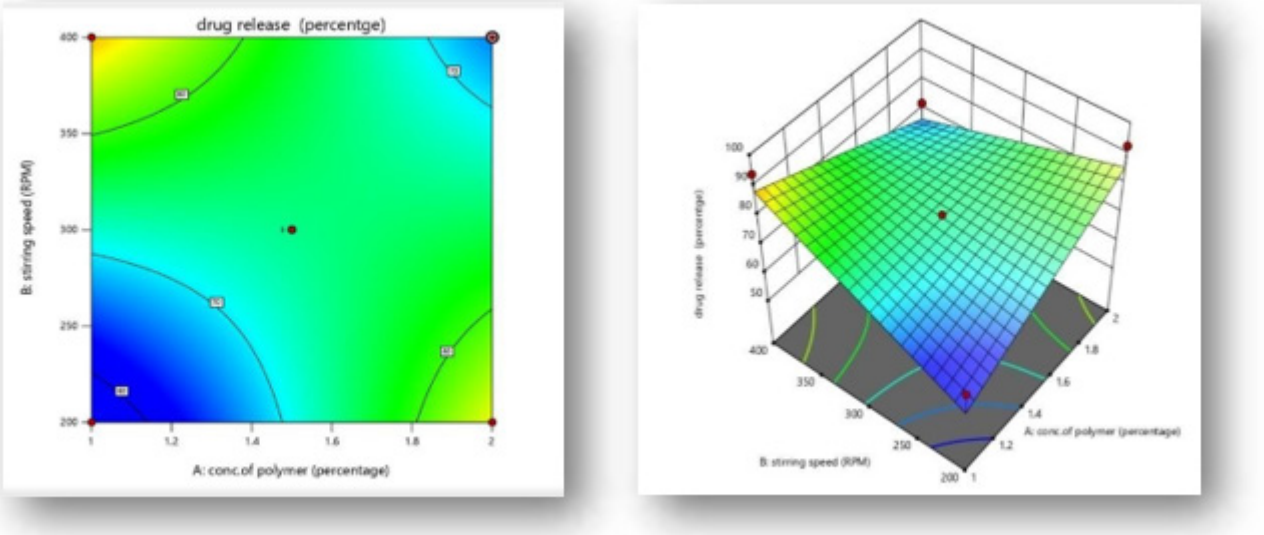

Figure 1: Contour and response surface plot of % drug release.

Table 4: Comparison of batch generated by software and its predicted response.

Response	Concentration of HPMC E5	Stirring Speed	% Drug release	Carr's index
Predicted	1%	400 rpm	88.26	13.23
Experimental			93.83	12.34

Note: Selected solution of spherical agglomerate (Optimized spherical agglomerate) was further evaluated and compared with pure rosuvastatin.

Flow property

The flow properties of pure rosuvastatin and the SA-ROS were evaluated and are summarized in Table 5. The results indicate that the optimized rosuvastatin agglomerate exhibited markedly improved flowability and compressibility compared with the pure drug. Statistical analysis using one-way ANOVA showed *p*-values less than 0.05, confirming that the differences observed in bulk density, tapped density, Carr's Index, and Hausner ratio between pure rosuvastatin and SA-ROS were statistically significant.

The percentage yield indicates minimal drug loss and an optimal crystallization process.

Fourier transform infrared spectroscopy

The FTIR spectra of rosuvastatin, its physical mixture with HPMC E5 and SA-ROS are presented in Figure 4. Rosuvastatin exhibited characteristic absorption bands at 3393–3328 cm^{-1} corresponding to O–H stretching, 1665 cm^{-1} to C=O stretching, 1324 cm^{-1} to aromatic C=C stretching, 1236 cm^{-1} to C–N stretching, and 1268–1010 cm^{-1} to S=O stretching vibrations. These characteristic peaks confirm the purity of rosuvastatin, as they correspond to its expected functional groups. The same characteristic peaks were retained in the physical mixture, indicating the absence of significant drug–polymer interactions and suggesting good physical compatibility between rosuvastatin and HPMC E5, with no evidence of chemical modification 22.

Also, no major changes were noticed in distinctive peaks of FTIR spectrum of the SA-ROS, which confirms that the chemical structure and purity of rosuvastatin was not altered throughout the agglomeration process. No solvent peaks are seen, thus indicating efficient elimination of residual solvents, and the broad band of hydroxyl corresponds to the strong hydrogen-bonding interaction between rosuvastatin and polymer.

Differential Scanning Calorimetry

Pure rosuvastatin has a distinct endothermic peak at 153.59°C, which corresponds to its melting point (Figure 5). The wide and narrow characteristics of the peak suggest highly crystalline structure with very little amorphous content supporting the semicrystalline nature and excellent purity of the drug. A little shift of the endothermic peak to around 121°C was observed for SA-ROS, indicating a lower crystallinity due to physical interactions between rosuvastatin and HPMC E5 or its entrapment inside the HPMC E5 matrix.[39]

X ray diffraction

XRD pattern (Figure 6) of pure rosuvastatin showed sharp and intense peaks in 2θ range of around 18-22° with maximum intensity of about 900 counts indicating rosuvastatin is primarily crystalline. The broad baseline under the peaks indicates a small amorphous component in agreement with the semicrystalline nature reported in the literature.[2] Whereas the SA-ROS show diffraction peaks in the same 2θ range but with much lower intensity (~ 500 counts) showing decrease in crystallinity. The PXRD profiles of the agglomerated crystals are superimposable with those of the pure drug demonstrating the preservation of the crystalline phase but with partial amorphization.[21,22] The percentage reduction in crystallinity of rosuvastatin agglomerate was 44.44% which was calculated from count of crystallinity peak of drug and solid dispersion. This reduction in crystallinity may

Table 5: **Preliminary characterization of rosuvastatin and optimized rosuvastatin agglomerate.**

Sr. No.	Parameters	Pure drug (Rosuvastatin)	Optimized rosuvastatin agglomerate (SA-ROS)
1	Bulk Density (g/cm3)	0.424±0.16	0.623±0.19
2	Tapped Density (g/ cm3)	0.561±0.17	0.71±0.21
3	Hausner Ratio	1.32±0.02	1.13±0.03
4	Powder Flow (sec)	0.50±0.01	0.68±0.00
5	Carr's Index (%)	24.42±0.22	12.34 ±0.25
6	Yield (%)	----	86

* *n*=03

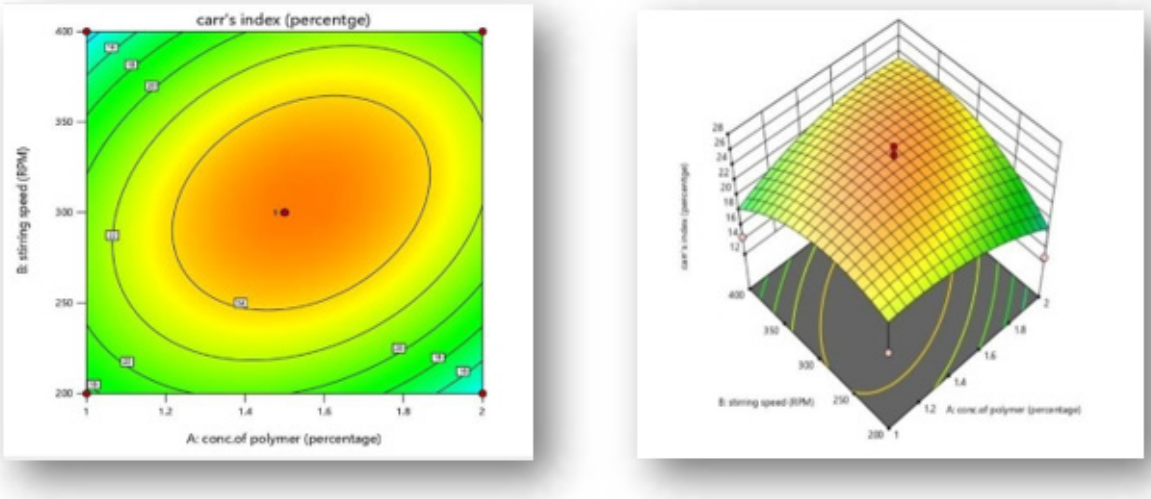

Figure 2: Contour and response surface plot of Carr's Index.

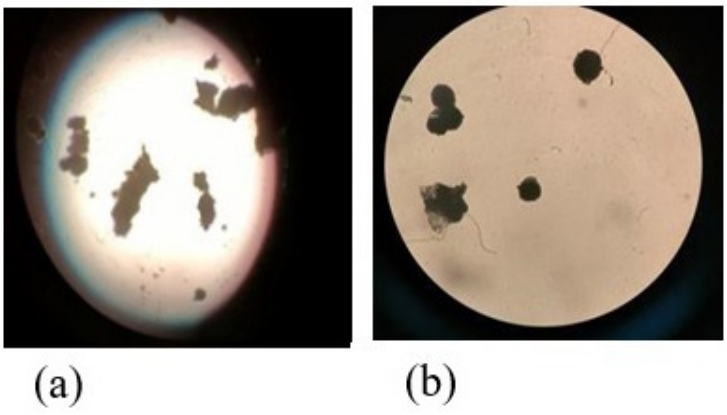

Figure 3: Optical microscope image showing shape of: (a) Rosuvastatin, (b optimized rosuvastatin agglomerate.

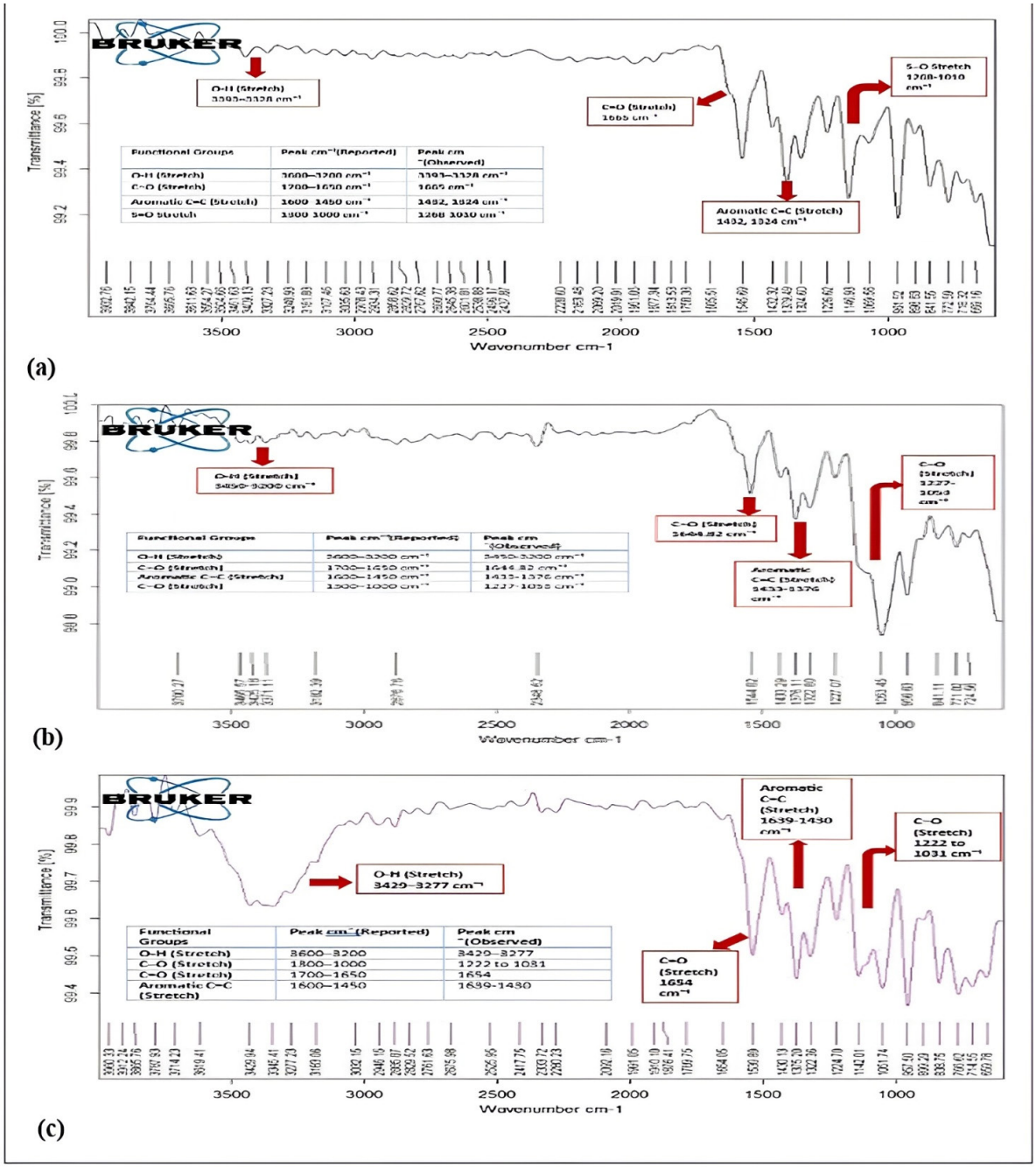

Figure 4: FTIR spectra of: (a) Rosuvastatin, (b) Physical mixture of rosuvastatin and HPMC, (c) Rosuvastatin spherical agglomerates.

contribute to improved solubility and dissolution rate, potentially enhancing the drug's bioavailability.

Heckel analysis

The pure rosuvastatin and SA-ROS were compressed and their densification behavior was evaluated by Heckel analysis given in Figure 7. The intercept (A) which represent the initial particle rearrangement and fragmentation at low compression pressures was somewhat greater for the SA-ROS (0.368) than for the pure drug (0.36). This indicates a higher degree of fragmentation and a more effective rearrangement of particles inside the agglomerates leading to a better packing in the initial stages of compression.

The slope (K) of the Heckel plot, which is indicate the plastic deformation behavior of the material, revealed similar values for rosuvastatin (0.27) and the SA-ROS (0.268).[31,40,41] The comparable K value means that the plastic deformation properties of rosuvastatin were not considerably affected by the spherical agglomeration. In line with this discovery, the yield pressure (Py), which is inversely related to plastic deformability and computed as the reciprocal of K, was almost same for the pure drug (3.70) and SA-ROS (3.72), thereby demonstrating similar resistance to plastic deformation.

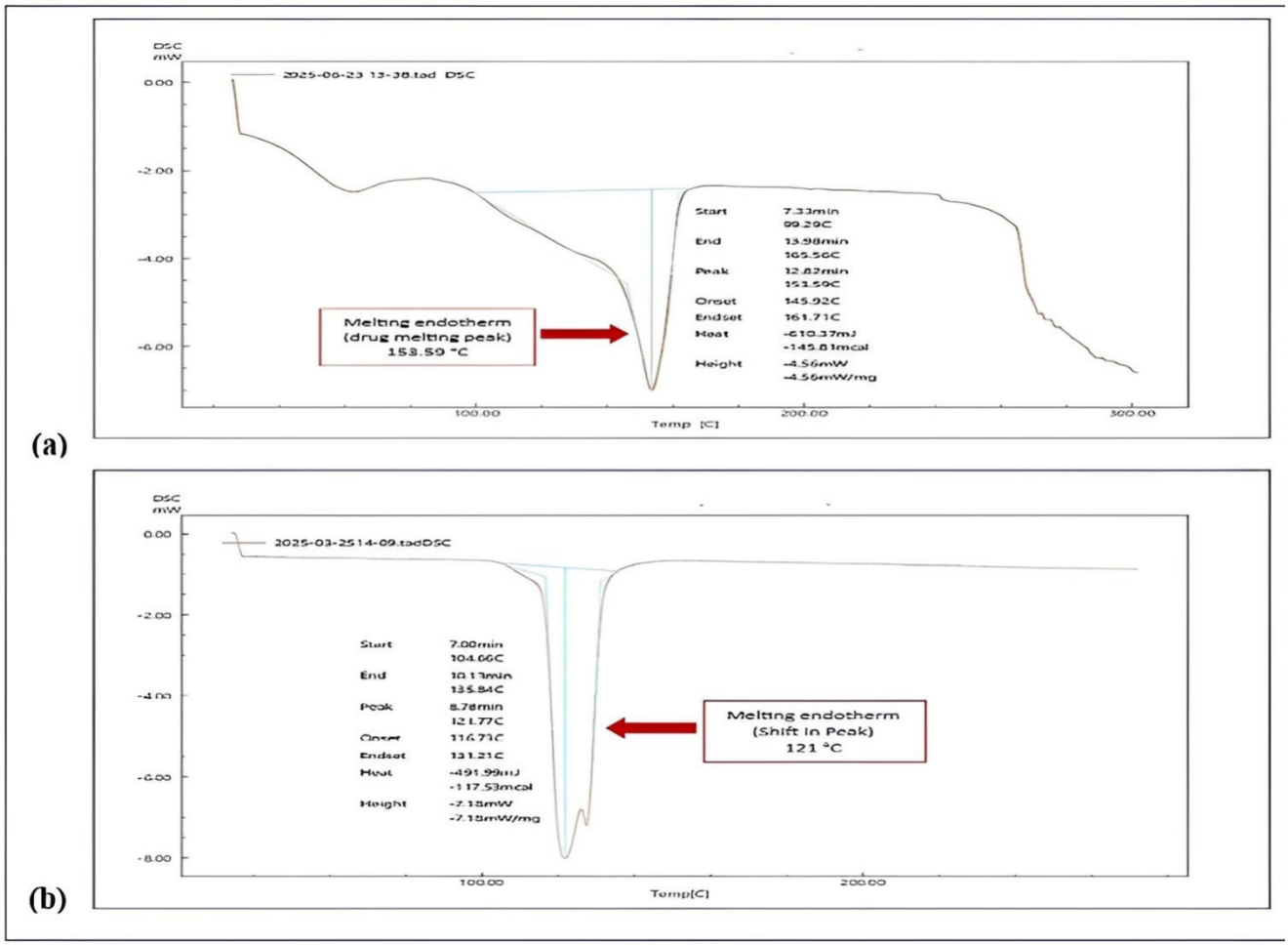

Figure 5: DSC thermogram: (a) Rosuvastatin, (b) Spherical agglomerates of rosuvastatin.

Table 6: Post compression evaluation of tablets.

Parameter	Result
Average weight	250±6.708
Hardness (kg/cm^2)	3.74±0.190
Friability	0.54±0.41
Disintegration time (min)	3.28±0.029
Drug content	94±0.816

The Heckel parameters, in general, show that the intrinsic plastic deformation properties of rosuvastatin were not changed after spherical agglomeration. The agglomerates have a slightly higher A value, indicating a better initial densification due to improved fragmentation and particle rearrangement. Thus, the SA-ROS have a somewhat superior compressibility during tableting, due to the higher packing efficiency rather than to an increased plasticity.

Saturation solubility

Solubility of rosuvastatin and SA-ROS was determined in distilled water and found to be 0.29 mg/mL and 13.05 mg/mL respectively. Hydroxypropyl methylcellulose (HPMC) is a hydrophilic polymer whose properties, including viscosity and gel-forming behavior, vary with grade and molecular characteristics. Upon incorporation of rosuvastatin during spherical crystallization, the drug molecules become uniformly dispersed within the hydrophilic HPMC matrix. When exposed to aqueous media, HPMC rapidly hydrates and swells to form a viscous, gel-like network around the drug particles. This hydrated gel matrix helps to prevent particle aggregation, enhances wetting, and maintains rosuvastatin in a finely divided state, thereby increasing the effective surface area available for dissolution and improving its apparent solubility. The gel barrier also inhibits drug crystallization and stabilizes the dispersed drug within the matrix, further facilitating enhanced dissolution behavior.[42]

Evaluation of tablets

Evaluation of tablet prepared by using SA-ROS is given in Table 6. A low standard deviation in weight variation signifies uniform tablet weight, which is essential for accurate dosing. The tablets demonstrated sufficient hardness (5 kg/cm^2), indicating their ability to withstand mechanical stress during handling and packaging. Friability values below 1% fall within acceptable limits,

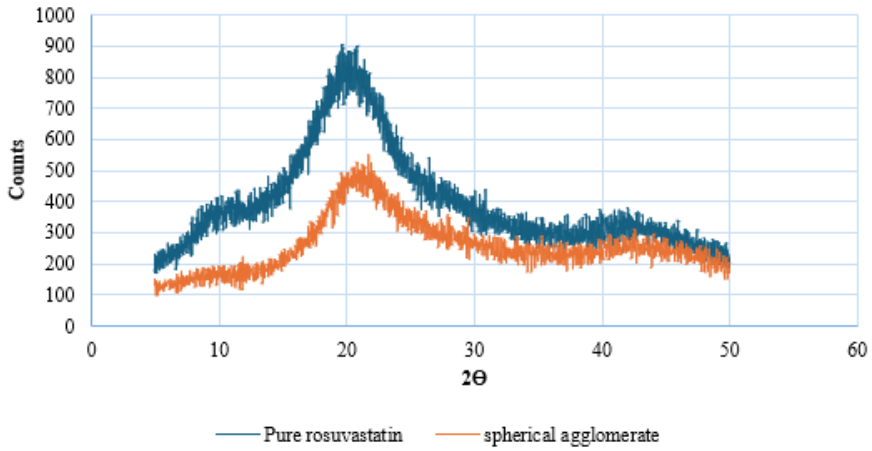

Figure 6: X-ray diffraction pattern of rosuvastatin and its spherical agglomerates.

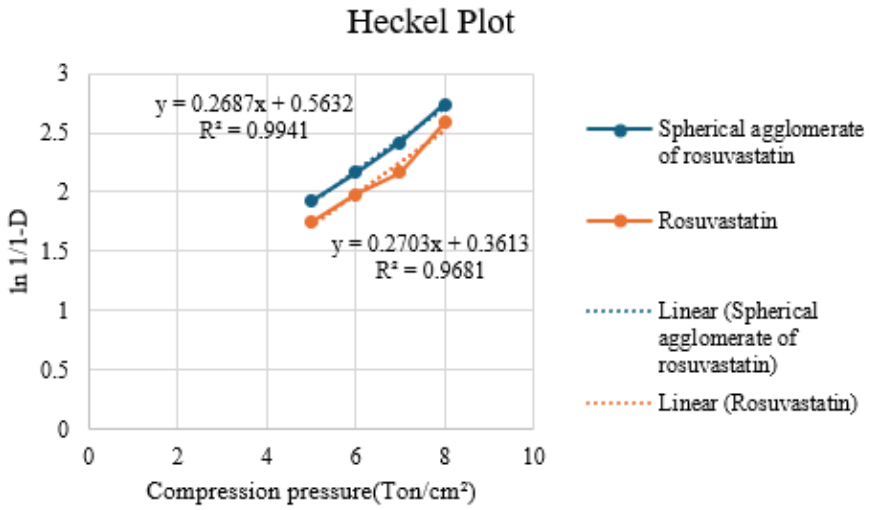

Figure 7: Heckel plot of rosuvastatin and spherical agglomerate of rosuvastatin.

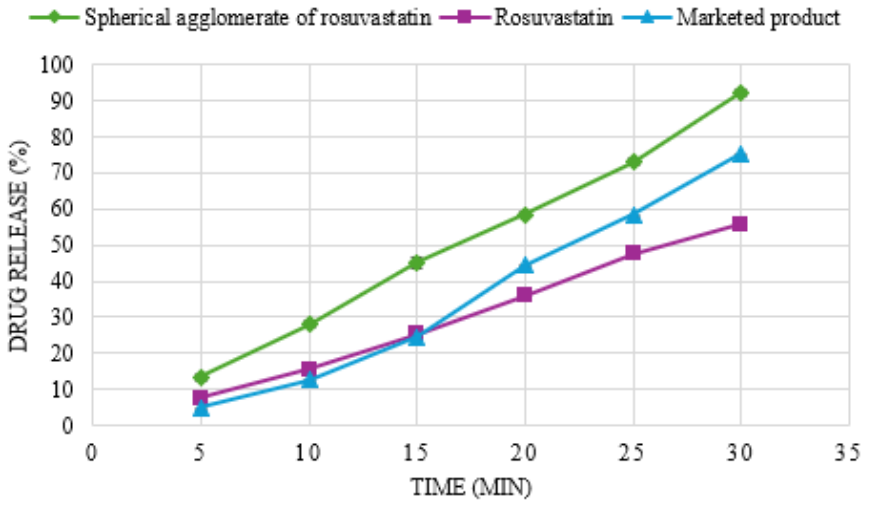

Figure 8: Dissolution profile of rosuvastatin tablet, rosuvastatin spherical agglomerates tablet and marketed product of rosuvastatin.

confirming the tablets' durability and resistance to breakage or powdering during transport. A short disintegration time is favorable, as it enables a quicker onset of action. Additionally, drug content close to 100% ensures consistent therapeutic effectiveness.

In vitro Dissolution Studies

SA-ROS dissolution profile showed 93.83% of drug release at 30 min while pure drug showed only 55.47% drug release (Figure 8). Thus, there was more than two-fold increase in the dissolution of rosuvastatin. The improvement can be attributed to the increased wettability and decreased crystallinity of the spherical agglomerates.[21,22] A *P*-value (0.0003) of less than 0.05 confirms a statistically significant difference in the percentage of drug release among the spherical agglomerates, pure rosuvastatin, and the marketed formulation.

Differences were observed in the dissolution profiles of the SA-ROS and rosuvastatin after analyzing the similarity factor (f2) of the two substances, which gave a result of 32.17%. Since this fall below the standard similarity criterion of 50%, this confirms that there were differences between their dissolution profiles. Similar results were obtained when the SA-ROS were compared with the marketed formulation with an f2 value of 40.41.

Therefore, the SA-ROS formulation is expected to exhibit improved bioavailability upon administration, due to enhanced dissolution during its intestinal residence. The order of dissolution of rosuvastatin within 30 min was SA-ROS formulation > marketed preparation > plain drug.

CONCLUSION

Spherical crystal agglomeration is a straightforward technique that uses minimal excipients and equipment to simultaneously improve the solubility and compressibility of a drug. The process was optimized using a two-level central composite design, and optimized batch was identified as the most effective formulation using Design of Experiments (DOE). FTIR, DSC, and XRD analyses confirmed that rosuvastatin's structure was preserved, with partial amorphization and increased wettability from hydrophilic polymers contributing to enhanced solubility and dissolution. Improvement in dissolution profile of drug is beneficial for enhancement of absorption and bioavailability of drug where dissolution is rate limiting step for absorption. The compressibility of the spherical agglomerates was significantly increased and therefore may be directly compacted in to tablets with higher mechanical strength and better compressibility. These results suggest that the agglomeration by solvent change greatly enhances the pharmaceutical efficacy of rosuvastatin, by improving the compressibility and solubility. Moreover, the obtained spherical agglomerates show good flowability and compressibility, which could minimize the variability during large-scale tablet manufacture.

ABBREVIATIONS

BCS: Biopharmaceutics Classification System; **CCD**: Central Composite Design; **DCM:** Dichloromethane; **DOE:** Design of Experiments; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared Spectroscopy; **HMG-CoA:** 3-hydroxy-3-methylglutaryl-coenzyme A; **HPMC:** Hydroxypropyl methylcellulose; **PEG:** Polyethylene Glycol; **PXRD:** Powder X-ray Diffraction; **RPM:** Revolutions Per Minute; **SA-RSV:** Spherical Agglomerates of Rosuvastatin; **SSG:** Sodium Starch Glycolate; **UV:** Ultraviolet.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DECLARATION

The authors disclose that they have no financial support or sponsorship for this work. Furthermore, the authors declare that there are no conflicts of interest, financial, personal, or institutional, that may have impacted the results or the interpretation of this study.

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