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Research Article

EFFECT OF TEMPERATURE AND STIRRING RATE ON FLOW AND COMPACT-ABILITY PROPERTIES OF SIMVASTATIN SPHERICAL CRYSTALS

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ABSTRACT

Simvastatin is a water insoluble drug used as a hypocholestrolemic agent. Its pharmacological effects are limited by its poor water solubility. After successful production of simvastatin spherical crystals by emulsion solvent diffusion method and improvement its dissolution rate, the aim of present study was to determine the effect of processing temperature and stirring rate on micromeretic properties of prepared crystals. Particle size analysis, dissolution rate profiles, pack ability, hydrophobicity, and flow properties of spherical crystals were studied. The particle size of spherical aggregates was about 37 μm and the dissolution efficiency of simvastatin up to 60 min increased to about 2 fold in phosphate buffer solution containing 0.5% sodium dodecyl sulfate (pH 7) using the rotating paddle method. At high temperature the high stirring rate and at low temperature the low stirring rate resulted in free flow crystals. Untreated powder had better flow ability and compressibility than crystals, but spherical crystals showed enhanced solubility due to their higher hydrophilicity compared to the untreated powder. Spherical crystallization is an effective technique to improve the dissolution rate of simvastatin but its flow should be facilitated by some free flow excipients.

Keywords: Enhanced solubility. Spherical crystallization. Compact-ability. Flow. Angle of repose

INTRODUCTION

Simvastatin is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase and a cholesterol-lowering agent that is widely used to treat hypercholesterolemia[1]. It is a crystalline powder, practically water insoluble that is obtained as a fermentation product of *Aspergills terreus* and is poorly absorbed from the gastro-intestinal (GI) tract[2, 3]. Therefore, it is very important to enhance its dissolution rate substantially leading to its improved bioavailability[4].

Some of the reported methods for improvement of low bioavailability of simvastatin as a poor water soluble drug are use of self-micro-emulsifying oral drug delivery system, use of surfactants like sodium dodecyl sulfate and Brij 35 micelles[5], use of supercritical antisolvent (SAS) process[6] and production of inclusion complex with α-cyclodextrin and β-cyclodextrin[7]. After successful production of spherical crystals of simvastatin and increasing its dissolution rate by this technique[8], the aim of the present study is to find if this technique can enhance the other properties of simvastatin like flow-ability, compact-ability, and its physicochemical properties as good as its dissolution rate or not.

Wet-ability, release[9], dissolution rate[10], the micromeritic[11] and compression properties of many drugs[12] have been improved by the spherical crystallization technique. Three types of solvents are used in spherical agglomeration method: a good solvent in which the drug is very soluble, a poor solvent of the drug that is freely miscible with the good solvent. Interaction between these solvents is stronger than drug interaction with the good solvent, so immediate crystallization of drug causes its precipitation. The third solvent or 'bridging liquid' just wets the precipitated crystals and is not miscible with the poor solvent but, it is added to the system while stirring and can collect the crystals due to capillary negative pressure and interfacial tension between the interface of solid and liquid[13].

Spherical agglomerates can modify compact-ability and micromeretic properties of the drug significantly that is specially too important in the tabletting process of the drug. The production of simvastatin spherical crystals was reported by the authors before. It was shown that dissolution rate of this drug was enhanced significantly by this technique. The aim of the present study is to find if this technique can alter other properties of simvastatin like flow-ability, compact-ability, and its physicochemical properties or not. These are important characteristics in production of tablets from obtained agglomerates.

MATERIALS AND METHODS

Materials

Simvastatin (Ranbaxy, India), isopropyl acetate, ethyl alcohol, dichloromethane, methanol, sodium dodecyl sulfate and other reagents were all analytical grades and from (Merck Chemical Company, Germany).

Preparation of agglomerates

Spherical crystals of simvastatin were prepared as reported before[8]. Briefly, 4.75 g simvastatin was dissolved in 25 ml boiling dichloromethane (good solvent) to make quasi-saturated solution. This solution was then poured into 5°C water (poor solvent) while stirring at 1000 rpm. Then 44 ml of isopropyl acetate (wetting agent) was added thermally controlled at various temperatures (80, 30 and 5°C) under agitation with a propeller type agitator with four blades. In order to investigate the effect of stirring rate on simvastatin agglomerates the above solution was stirred at 333, 666 and 1000 rpm for 20 min. The agglomerates were separated from the solution through filtration under vacuum and then were placed in an oven at 50°C for 12 h.

Light microscopy studies

The shape of agglomerated crystals and untreated powder of simvastatin was studied by a light microscope (Nikon, HFX–DX, Japan) with ×40 magnifications.

In vitro dissolution test

The dissolution apparatus (Erweka, Germany) by rotating paddle method was employed for study the dissolution profiles of agglomerated crystals or untreated powder. The dissolution medium was 900 ml phosphate buffer solution (pH 7) containing 0.5% sodium dodecyl sulfate maintained at 37±0.1°C. Stirring rate of the dissolution medium was 50 rpm. At predetermined time intervals (0, 5, 10, 20, 30, 45, and 60 min) samples of the solution were withdrawn, filtered through a membrane filter (0.45μm) and analyzed spectrophotometerically (Perkin-Elmer, 550SE, US) at λ_{max} of 238 nm.

Particle size analysis

Particle size and size distribution of agglomerated crystals and standard crystalline powder was determined by a laser diffraction particle size analyzer (Mastersizer, X long bed Ver.2.15, Malvern, UK).

Measurement of powder flow

Flow ability of untreated simvastatin and agglomerates was assessed by determination of angle of repose and Carr's index (CI). Angle of repose was determined by fixed funnel method. The mean of 6 determinations was reported.

The powder was carefully filled into a mounted measuring cylinder with known tare. The powder bed was leveled with a spatula, and the maximum bulk volume was read. Tapped density was determined by tapping the samples into a 25 ml measuring cylinder. A single tap was employed, and the volume was read again. This procedure was repeated as 20 taps[14]. Hence, the minimum powder volume (to give the maximum bulk density) had been reached. The measuring cylinder was then weighed to determine the powder mass. The CI was calculated from the poured and tapped densities. The CI was calculated according to the following equation[15].

CI=[(Tapped density-Bulk density)/Tapped density] ×100 Eq. 1

Angle of repose

Static repose angle has been measured with a hopper with a discharging orifice 5 mm wide, and a height of 40 mm. Powder is poured on the plane through the hopper, on a paper sheet with concentric graduated circles coaxial with the hopper's orifice. The diameter of the base D_A is taken as the average of 4 diameters. The repose angle is given by a simple geometrical construction as:

$$\alpha_r = \tan^{-1}\left[\frac{2h}{(D_A - d)}\right]$$

Eq. 2

Where *d* is the diameter of the orifice and *h* the height of the cone of powder.

Compact-ability

The pack-ability was evaluated by the tapped density according to Kawakita[16] and Kuno's[17] equation as follows:

(n/C)=(1/ab)+(n/a)
Eq. 3

Where n is the tap number, C denotes the volume reduction which can be calculated according to the equation 3, 1/a defines the degree of volume reduction at the limit of tapping, termed compact-ability and 1/b is a constant related to cohesion, termed cohesiveness[16].

$C = (V_0-V_n)/V_0$ Eq. 4

Where V_0 and V_n are the powder bed volumes at initial and n^{th} tapped state, respectively.

The plot of n/C versus n is linear and the compact ability 1/a and cohesiveness 1/b are obtained from the slope (1/a) and the intercept (1/ab) of the plot of the modified Kawakita equation[16].

The data were also analyzed by Kuno[17] equation:

$Ln (\rho_f-\rho_n) = -k_n+ln (\rho_f-\rho_0)$ Eq. 5

Where ρ_f, ρ_n and ρ_0 are the apparent densities at equilibrium, n^{th} tapped and initial state, respectively, and k is the constant.

Powder bed hydrophilicity test

A wet-ability test was carried out to explain the differences observed in dissolution rates of different crystals. The agglomerated crystals or untreated powder of simvastatin (0.5 g) was placed on a sintered glass disk forming the bottom of a glass tube. The whole device was adjusted at 1 mm under the surface of the water. Some methylene blue crystals were put on the surface of the drug. The time taken for the capillary rising of water to the surface was noted. This time is visualized by the dissolution of the methylene blue crystals, which color of the powder surface intensively. The shorter rising time would correspond to the most hydrophilic substance, leading to good wet-ability[18].

RESULTS AND DISCUSSION

Preparation of agglomerates

To prepare the spherical crystals an emulsion solvent diffusion method was used. Dichloromethane was used as the good solvent, water as the non-solvent and isopropyl acetate as the bridging liquid. The addition of the bridging liquid promotes the transfer of the drug to the emulsified phase in which crystal agglomerates are condensed and grow spherically. The results of our prior study showed that the optimal ratio for spherical crystal formation is found in the proportion of dichloromethane 25%/ water 31%/ isopropyl acetate 44% named as point I. To investigate the effects of stirring rate, and the difference in temperature between the simvastatin solution and non-solvent during crystallization on the physico-mechanical properties of spherical agglomerates (*Table 1*), three different temperatures (80, 30 and 5º C) were studied along with different stirring rates (1000, 666 and 333 rpm) to find the best situation of production of spherical crystals.

Table 1: Different situations for production of spherical agglomerates of simvastatin with composition of point I (dichloromethane 25%, water 31%, isopropyl acetate 44%)

Sample	Temperature of non-solvent (water) (ºC)	Rotation speed (rpm)
I_1	80	1000
I_2	80	666
I_3	80	333
I_4	30	1000
I_5	30	666
I_6	30	333
I_7	5	1000
I_8	5	666
I_9	5	333

Light microscopy studies

The optical microscopy photographs are seen in *Figure 1*. As this figure indicates the crystals produced at similar temperatures but with slower stirring rate have greater size so that, in I_3 we see greater spheres compared to I_1 and I_2, while I_6 is greater than I_4 and I_5 and at last I_8 has greater agglomerates compared to I_7. Having a more precise look to these figures gives us a more realistic idea about the procedure of spherical agglomeration. When the dissolved drug in dichloromethane is added to the stirring water, its solubility reduces and begins to precipitate. During the time and by evaporation of dichloromethane a void space will be produced inside the aggregates which is obvious in the micrographs. After complete evaporation of this good solvent and by adding isopropyl acetate the crystals will be wet and attached together due to the interfacial pressure and capillary forces[14].

In vitro dissolution test

Table 2 shows the results of dissolution efficiency after 60 min (DE_{60}%) of dissolution test (*Figure 2*) and micromeretic properties of untreated powder and spherical agglomerates of simvastatin (I) prepared at 8 different conditions. As this table indicates crystals of I_7 has the greatest DE_{60}% among the other formulations compared to the pure or untreated powder which is desirable from enhanced dissolution properties point of view. The DE_{60}% of the agglomerates is increased more than 2 fold compared to the untreated drug. As *Figure 2* indicates the simvastatin is dissolved more than 80% from the agglomerates after 60 min while the untreated powder is just dissolved about 40% at comparable time. The slow drug release from crystals of I_1 is possibly due to the high crushing strength of

these agglomerates which causes lack of intra granular disintegration and lack of solvent penetration inside them. This low dissolution rate is seen in three batches that have been prepared at 80°C i.e., I_1, I_2 and I_3 crystals and their dissolution rate is significantly lower than other crystals that have been prepared at lower temperatures. In other words, it may be concluded that high temperature of preparation and the high stirring rates (1000 rpm) used in production of I_1 crystals has caused agglomerates with lower intra granular disintegration. Similar results were obtained from carbamazepin[11] and celecoxib[20] spherical crystals.

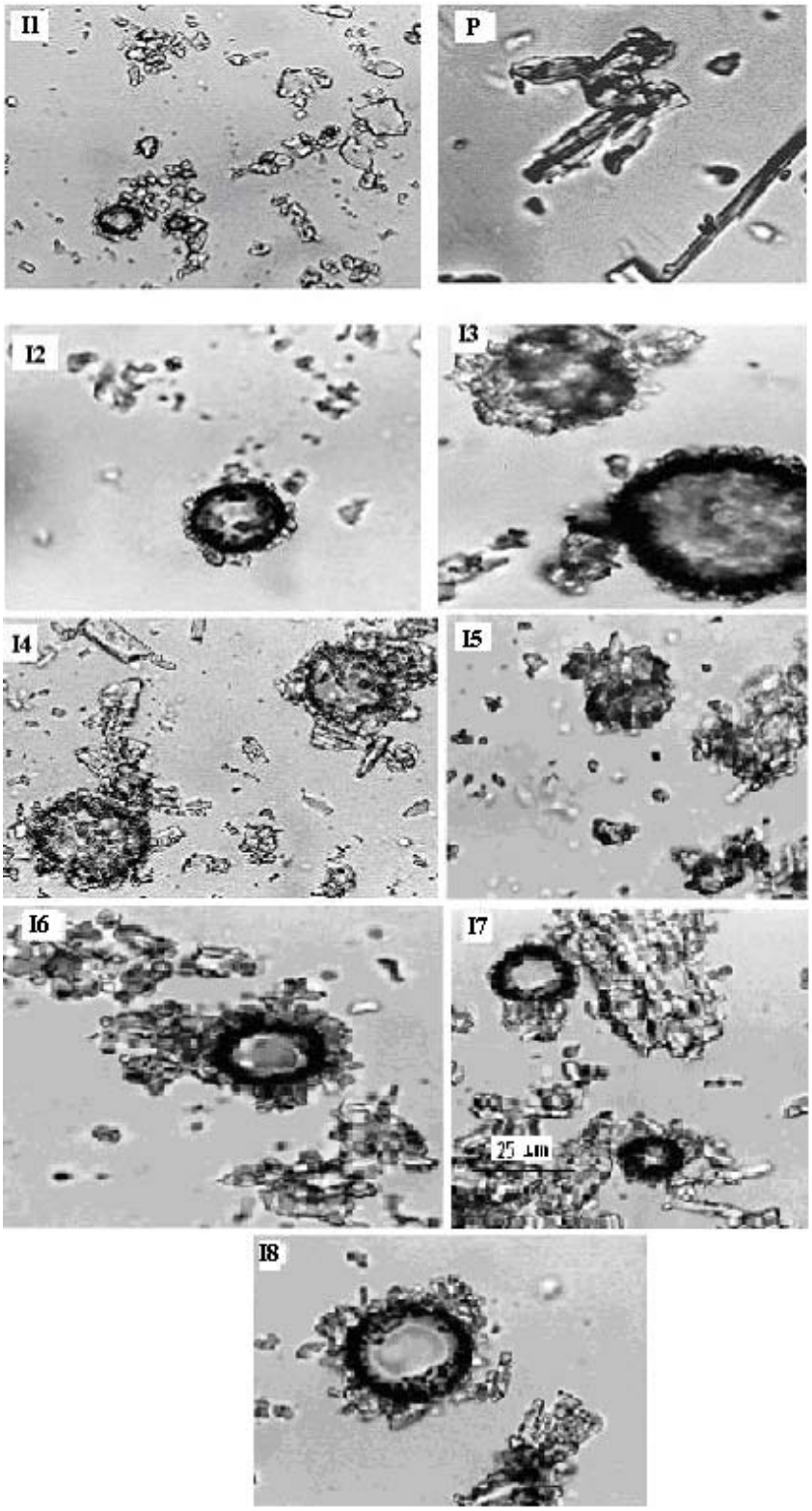

Fig. 1: Optical micrographs of pure powder (P) and spherical agglomerates of simvastatine (×40)

Table 2: Micromeretic properties and dissolution efficiency after 60 min of dissolution test (DE_{60}%) of untreated powder and spherical agglomerates of simvastatin (n=3)

Sample	Bulk density (g /cm³)	Tap density (g /cm³)	Angle of repose (º)	Compressibility index (%)	Hausner ratio	DE_{60} (%)
P	0.44±0.00	0.55±0.00	14.51±0.84	20.33±0.57	1.25±0.00	35.1±3.2
I_1	0.32±0.00	0.37±0.00	21.43±0.00	12.62±0.56	1.14±0.01	26.3±5.0
I_2	0.39±0.00	0.47±0.01	22.33±3.27	17.29±2.10	1.20±0.03	43.9±4.6
I_3	0.44±0.00	0.54±0.00	26.81±5.85	18.32±0.57	1.22±0.01	41.5±5.4
I_4	0.19±0.00	0.26±0.00	39.64±4.07	29.31±1.16	1.40±0.02	66.0±3.2
I_5	0.29±0.00	0.38±0.00	34.66±5.58	24.66±0.58	1.32±0.01	63.1±4.5
I_6	0.31±0.00	0.38±0.01	30.09±5.08	18.65±2.32	1.23±0.03	61.3±3.3
I_7	0.18±0.00	0.27±0.00	49.69±2.06	33.98±0.00	1.51±0.00	78.0±0.3
I_8	0.22±0.00	0.33±0.00	40.31±3.16	32.99±0.99	1.49±0.02	60.6±1.4

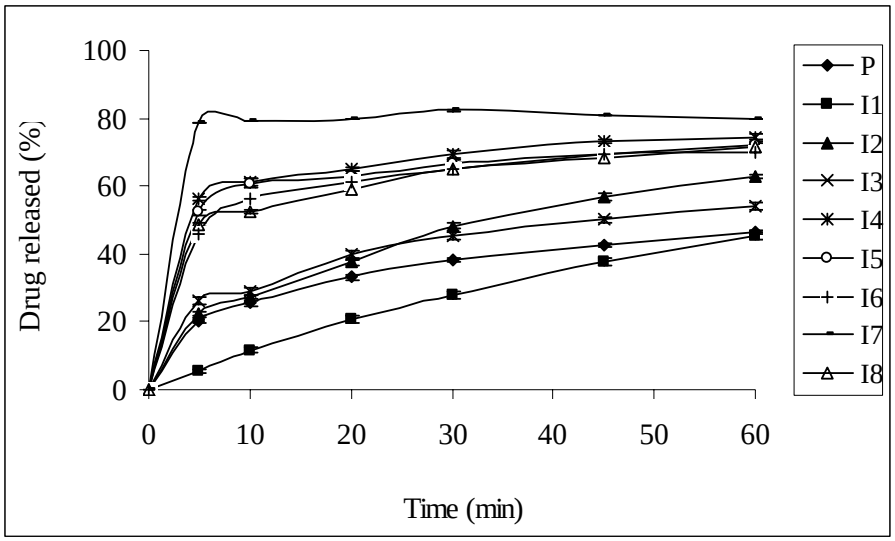

Fig. 2: Release profiles of simvastatin from its spherical agglomerates (I) prepared at 8 different conditions compared to its untreated powder (P)

Measurement of powder flow

Table 2 shows the higher temperatures of production the agglomerates lead to free flowing of the crystals. At 80ºC the greater stirring of the mixture results in lower angle of repose and compressibility index of the crystals but at 5 and 30ºC the lower the stirring rate, the better the flow of the crystals. In other words, at high temperature the high stirring rate and at low temperature the low stirring rate result in free flow crystals. The lower angle of repose and compressibility index, the better the flow ability of the powders. Accordingly, formulation I_7 has poor flow properties compared to the untreated powder regarding high angle of repose and compressibility index (*Table 2*). The pack ability of the crystals compared to the untreated simvastatin powder was studied by Kawakita[16] and Kuno's[17] equations. The results are shown in *Table 3*. According to Kuno's equation the lower *b* values show the higher cohesiveness and the greater compressibility of the powder. The high value of K_n also shows the greatest rate of compressibility[17] and low amounts of *a* shows the greater compaction of the powder as a result of tapping. From *Table 3* it is obvious that I_3 crystals have the best compact-ability for production of tablets by direct compression method but in spit of their good compression properties as they have less dissolution rates than I_7 crystals, they were not chosen as the optimized formulation.

The mean particle size of the spherical crystals of I_7 and the untreated powder were 37.33 and 19.58 µm respectively.

Powder bed hydrophilicity test

The hydrophobicity test revealed that the I_7 agglomerates were wetted at 30 min while this time was 58 hr for the untreated powder. This indicated the hydrophilic nature of the bed of the agglomerates which causes enhancement of water absorption by agglomerates more than the untreated powder. In other words, while the particle size of agglomerates has grown up about twice in comparison with the untreated powder, but as the hydrophobicity of the agglomerates has decreased and they can be wetted better in the dissolution media, the dissolution rate has increased about 2-fold which means the particles size is not the only impact factor in the dissolution rate of the agglomerates. To enhance the micromeretic properties of these crystals for producing their tablets by direct compression method it is also suggested to use the crystallo-co-agglomeration technique[21] using excipients like hydroxypropyl methyl cellulose to obtain a directly compressible material.

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