ISSN : 2320 4850

BI MONTHLY

AJPRD

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

Volume - 02 Issue - 02 MAR-APR 2014

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

PREPARATION AND CHARACTERIZATION OF SPHERICAL CRYSTALS OF SIMVASTATIN TO ENHANCE THE SOLUBILITY AND MICROMETRIC PROPERTIES

***Janrao KK. Gadhave MV. Banerjee SK. Gaikwad DD.**

Department of Quality Assurance VJSM's, Vishal Institute of Pharmaceutical Education and Research, Ale, Pune

Received: April 2014 ***Revised and Accepted: May 2014***

ABSTRACT

Simvastatin is an Antihyperlipidemic commonly used in the treatment of hypercholesterolemia and dyslipidemia. Due to low solubility in water and poor micrometric properties of Simvastatin leads to low dissolution rate. The aim of present investigation was to improve solubility, dissolution rate and enhancement of micromeritic properties of the poorly solvable drug. The parameters optimized were type, extent, and method of addition of bridging agent. The spherical agglomerate/crystals of Simvastatin were prepared by solvent change method in the presence of hydrophilic polymer in different concentration. The solvent system used was Ethanol, water and chloroform as good solvent, antisolvent and bridging liquid respectively. Spherical agglomerates were subjected for determination of percent drug content and particle size analysis. The agglomerates were also characterized by Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), X-ray Powder Diffraction (XRD) and Scanning Electron Microscopy (SEM) analysis. The FTIR and DSC study showed no interaction between drug and polymer. XRD studies showed a slight decrease in crystallinity in agglomerates. Spherical agglomerates showed improvement in solubility, dissolution rate and micromeritic properties in comparison to that of the pure drug. The SEM also showed that the agglomerate possess a good spherical shape.

Keywords: *Simvastatin, spherical agglomeration technique, solubility, dissolution, micromeritic properties.*

INTRODUCTION

As the number of novel poorly aqueous soluble drugs is increasing [1], it is essential to discover ways of enhancing their solubility and bioavailability is becoming an important part of invention and development. Aqueous solubility and dissolution are two of the essential aspects enhancing drug absorption from the gastrointestinal tract (GIT). Less aqueous-soluble drugs are associated with deliberate drug absorption leading ultimately to low and variable bioavailability [2, 3].

**Corresponding Author:*
Janrao Kunal K.
Department of Quality Assurance, VJSM's, Vishal Institute of Pharmaceutical Education and Research, Ale
E-mail ID: kunaljanrao9099@gmail.com
Contact No.: +91 9503329099

Practically 40% of the innovative chemical entities presently being discovered are less water-soluble drugs [4, 5].The BCS class II drugs comprise less water-soluble entities with high permeability. Efforts to improve drug solubility of these therapeutic agents associate well with enhancement in their bioavailability [2].

Most formulation methodologies for such drugs are concentrating towards at enhancing their dissolution rate and/or solubility by attaining particle size reduction, solid dispersion, complexation with cyclodextrins, etc. Many scientific approaches relating to the improvement of dissolution characteristic of drugs with poor water solubility have been described such as micronization, formation of solvates, adsorbents, complexes, microspheres,

and solid dispersions [6]. Spherical agglomeration is a modern tactic for development of directly compressible drugs where the drug crystals were transformed to spherical form to increase flowability, compressibility, packability and to improve dissolution rate characteristics of poorly aqueous soluble drug. Spherical crystallization is a particle design approach. In this approach crystallization and agglomeration can be carried out instantaneously in one step [7].It was a very current approach in enhancing the dissolution behaviour of several drugs that consuming low aqueous solubility and a slow dissolution profile by using hydrophilic polymer throughout crystallization process.

Spherical Crystallization process converts the fine crystal obtained throughout crystallization into spherical agglomerate. The approach had been used to enhance the powder micromeritic properties such as flowability, compressibility and dissolution of drug. Then polymers were introduced in this system to alter their release. [8] Therefore the key attention of this study was to scrutinize the influence of the various factors were optimized in this such as type, amount and mode of addition of bridging liquid, temperature, agitation speed and reaction rate to get additional practical yield of spherical agglomerates. Universal methods for spherical crystallization exist spherical agglomeration, emulsion solvent diffusion, ammonia diffusion and neutralization methods. [9, 10]

Simvastatin (SIM), a crystalline compound, is practically insoluble in water and hence unwell absorbed from the GI tract [11, 12]. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase [13, 14], which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is commonly used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, enhancement in its solubility and dissolution rate may lead to improvement in bioavailability [15].In the present study, solubility and dissolution enhanced by spherical crystallization by using hydrophilic carriers in four different drug–carrier ratios were prepared by a solvent change method, evaluated for different parameters.

MATERIALS AND METHODS

Materials

SIM was obtained as a gift sample from Themis Laboratories, Mumbai, India. PVP K 90 was obtained as generous gift samples from S. D. Fine chemicals, Mumbai., India. All other reagents used were of AR grade and procured locally.

Preparation of Spherical Agglomerates of Simvastatin

The spherical agglomeration was carried out using solvent change method. The clear solution of Simvastatin (2.0 g) in Ethanol (20 ml) was added quickly to a 100 ml solution hydrophilic polymer (PVP-K90) in water at different concentration (2.5-10.0 w/v). The mixture was stirred continuously at 500 rpm by using a mechanical stirrer. After 15 Min. fine crystals begun to precipitate then dichloromethane (bridging liquid) was added drop wise to obtain spherical agglomerates. The agglomerates were collected by filtration using Whatman filter paper and dried for 24 h at room temperature and store in desiccators. [16, 17]

Table 1: Composition of Spherical Agglomerates of Simvastatin.

Ingredients	F1	F2	F3	F4
Simvastatin(gm)	2	2	2	2
Ethanol(ml)	20	20	20	20
PVP-K90 solution in water (%)	2.5	5	7.5	10
Chloroform(ml)	0.5	0.5	0.5	0.5

EVALUATION OF SPHERICALLY AGGLOMERATED CRYSTALS

Micromeritic Properties [18]

Flowability of Simvastatin and its spherical agglomerates were determined in expressions of the following parameters: Bulk density, Tapped density, Hausner's ratio, Carr's index and Angle of repose.

Bulk Density (ρ_b) [19]

It is defined as the mass of a powder divided by the bulk volume. This was determined by the following method. A sample of 25.0 cc of powder from each batch, which has been earlier lightly shaken in a bolted container to break any agglomerates formed, was introduced into a 100 ml graduated cylinder. The cylinder was then dropped at 2-s intervals onto a hard wood surface three times from a height of 1 inch. Thus, bulk density was acquired by dividing the weight of the sample in grams by the final volume in cc of the sample contained in the cylinder. Three replicate determinations were made and the mean calculated (Remi Motors, Bombay, India).

Tap Density (ρ_t) [19]

It is defined as the mass of a powder divided by the tap volume. A loosely packed volume of 25 cc of the powder from each batch was transferred in a measuring cylinder by means of a funnel, after shaking lightly in a closed container. After observing the initial volume, the cylinder was mechanically raised and allowed to fall under its own weight on a hard surface from a height of 2.5 cm at the rate of 120 taps per minute, until no further change in the volume was observed. The tap density was calculated by dividing the weight of the sample in grams by the final volume in c.c. of the sample contained in the cylinder. Three replicate determinations were made and mean calculated (Remi Motors, Bombay, India).

Carr's Index [20]

Carr derived this dimensionless quantity which verifies to be useful to the same degree as that of angle of repose values for predicting the flow behaviour and compressibility behaviour. Compressibility indirectly gives an excellent picture of uniformity in size and shape, cohesion and moisture content. The formula used was,

$$CI = \left[\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}\right] * 100$$

The computed values for the different batches of crystals were expressed in percent.

Hausner's Ratio [21]

Particles with high interparticulate friction or cohesiveness have Hausner's ratio greater than 1.6 and % compressibility values higher than 40, whereas powder with Hausner's ratio less than 1.2 and % compressibility between 5 and 17 can be classified as free flowing powders. Hausner's ratio was calculated using following formula.

$$\text{Hausners Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose (Φ)[22]

Angle of repose was determined for all the batches as an index of flow behaviour using basically, the method suggested by Pilpel. The height H and mean radius r measured from five different directions were used to calculate the angle of repose, using the formula,

$$\text{Angle of Repose}(\emptyset) = \tan^{-1}\left(\frac{H}{r}\right)$$

Five replicate determinations were made in similar conditions of relative humidity and mean angle of repose values were calculated.

COMPATIBILITY STUDIES:

Fourier transforms infra-red spectroscopy (FTIR):

Infra-red spectroscopy was performed on FTIR. The Pure drug PVP K -90&spherical agglomerates and Simvastatin withPVP K-90 mix with KBr in mortar and pestle. All above property analyzed in FTIR and the range from 400 to 4000nm was selected.

Differential scanning Calorimetry (DSC):

The DSC measurements were performed using METLer Toledo DSC 821e module controlled by STAR software (METLer Toledo GmbH, Switzerland). The sample size was 5-10mg, for each measurement was placed in sealed aluminium pans, before heating under nitrogen flow (20mL/min) at a scanning rate of 100C/min, over the temperature range of 50 to 2500C. An empty aluminium pan was used as reference.

Scanning electron microscopy (SEM):

Small samples were mounted directly on Scotsch double adhesive tape. Samples were coated with gold to a thickness of 100A0 using Hitachi Vacuum Evaporator, Model, and HUS 5GB. Coated samples were analyzed in a Hitachi Scanning Electron Microscope Model-S450 operated at 15kV and photograph

Powder X-ray diffraction studies:

The powder X-ray diffraction patterns were recorded using an X-ray Diffractometer (PW 1729, Philips, Netherland), with Cu as anode material and crystal graphite monochromator operated at a voltage of 90 kV and a current of 90mA. The samples were analyzed in the 2θ angle range of 5 to 800. The range and the chart speed were 2 x 103 CPS and 10mm/ 02θ, respectively.

Drug content:

Spherical agglomerates equivalent to 20 mg of SIM were weighed accurately and dissolved in 10 mL of ethanol. The stock solutions were diluted in distilled water and analyzed by UV-vis spectrophotometry (Shimadzu 1800, Japan) at 238 nm.

Saturation Solubility study [23]

Saturation solubility was determined by the shake-flask method [23]. Plain SIM and SSDs in excess quantity were placed in separate glass-stoppered flasks containing10 mL of distilled water. The samples were placed in an orbital shaker (CIS-24 Remi, India) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 238 nm.

Dissolution study of spherical agglomerates [24]

The in vitro dissolution studies for plain SIM and Spherical agglomerates were carried out in triplicate in USP Apparatus 2. Samples equivalent to 20 mg of SIM were added to 900 mL of 0.01 M phosphate buffer pH 7.0 with 0.5% sodium lauryl sulfate at 37 ± 0.5° C and stirred at 50 rpm [24]. Aliquots of 5 mL were withdrawn at specified time intervals and filtered through Whatman No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 238 nm. The Spherical agglomerates that showed maximum drug release and saturation solubility was characterized by PXRD, DSC, FTIR, and SEM and compared with pure drug.

RESULT AND DISCUSSION

Spherical agglomerates were prepared by solvent change method using three solvents (Ethanol, Chloroform, water). Ethanol a good solvent for Simvastatin, Chloroform was used as a bridging liquid and water was anti-solvent. Agglomeration was initiated by the

addition of as it acts as Chloroform bridging liquid. Moreover bridging liquid introduced into the dispersing medium after saturation point was immiscible and only coalescence of bridging liquid occurred, causing an increase in agglomerates. Generally hydrophilic materials are used to impart strength and sphericity to the agglomerates.

Micromeritic Properties:

The results of Carr's index, Hausner's ratio, angle of repose particle size distribution are presented in Table 2. These parameters were used to assess the packability, flow and compressibility properties of the agglomerates. The Carr's index, Hausner's ratio, Angle of repose value for pure drug of Simvastatin was 32.60%, 1.48, 38.45° respectively, indicating poor flow and packability properties. On the other hand, all prepared spherical agglomerates exhibited higher Carr's index, Hausner's ratio and Angle of repose as compared to pure drug. It also has good compressibility which designates good packability. The saturation solubility studies specify that the pure drug having the least solubility while as the formulations have the higher solubility.

Table 2: Micromeritic properties of Plain drug and spherical agglomerates.

Batch Code	Bulk Density	Tapped Density	Carr's Index	Hauser Ratio	Angle Of Repose
Plain Drug	0.31	0.46	32.60	1.48	38.45
F1	0.46	0.54	17.85	1.17	28.48
F2	0.44	0.52	15.38	1.18	27.52
F3	0.48	0.51	5.88	1.06	26.37
F4	0.47	0.52	9.61	1.10	25.58

Drug Content:

Drug content and percentage yield was carried out to recognise the any drug lose during formulation, the results were represented in Table 3. Yield for the formulations were within the range of (83.27- 87.15 %) and drug content was (92.8 - 96.7 %). These values revealed that the crystal yield is increases as increase in PVP K-90 concentration during crystallization

Table 3: Physicochemical Properties of Plain Drug and Spherical Agglomerates.

Batch Code	Practical Yield (%)	Drug Content (%)	Solubility mg/ml)
Plain Drug	-	-	0.30
F1	83.27	92.8	9.8
F2	86.12	95.5	24.9
F3	89.23	94.3	43.8
F4	87.15	96.7	75.5

In-vitro dissolution study:

The results of in vitro dissolution studies are shown in Table.4 and Figure.1. Pure drug solubility and dissolution rate of spherical agglomerates

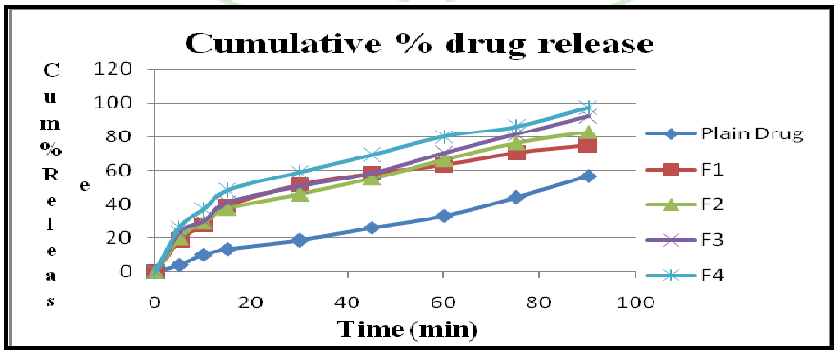

Figure 1: Dissolution profile of plain drug and spherical agglomerate.

Table 4: Drug Release Pattern for Plain Drug and Spherical Agglomerates.

Time (min)	Plain Drug	F1	F2	F3	F4
0	0	0	0	0	0
5	4.23	18.78	20.23	23.59	26.42
10	10.37	27.67	29.33	30.17	37.32
15	13.59	39.12	37.58	41.39	48.39
30	18.84	51.43	46.12	50.78	59.34
45	26.03	58.21	55.29	58.74	69.44
60	33.21	63.28	66.48	70.62	80.26
75	44.19	70.41	76.19	81.64	86.31
90	56.73	74.83	82.75	92.47	97.45

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectroscopy was used to study the probable interactions between SIM and PVP-K 90 in the Spherical agglomerates. There is no significant difference in the FTIR spectra of pure drug, and Spherical agglomerates (Figure 2). All key peaks of SIM observed at wave numbers 3553 cm-1 (free O–H stretching vibrations); 3011, 2959, and 2872 cm-1 (C–H stretching vibrations); and 1714 cm-1 (stretching vibration of ester and lactone carbonyl functional groups) were retained in Spherical agglomerates, which clearly designate that no interaction occurs between pure drug and PVP-K 90 in Spherical agglomerates

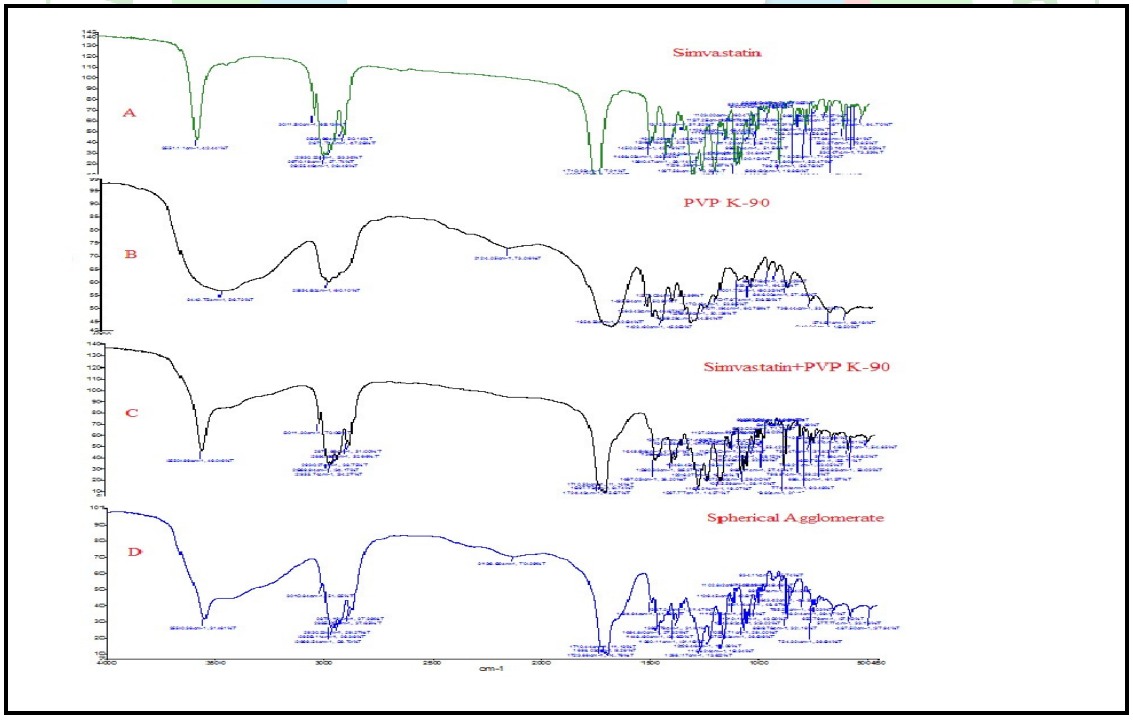

Figure 2: FT-IR Spectra of (A) Sim, (B),(C) Sim and PVP K-90 ,(D) Spherical Agglomerate.

Differential Scanning Calorimetry (DSC):

The DSC thermo gram of SIM reveals a sharp melting endotherm at 138 °C (Figure 3B). In Spherical agglomerates prepared with PVP-K-90, the melting endotherm of is marked in the temperature range of 48.24–99.70 °C and simvastatin in the temperature range of 137.53–142.56°C (Figure 3A),suggesting that there was no physical or chemical interaction in between and PVP-K-90, SIM Spherical agglomerates.

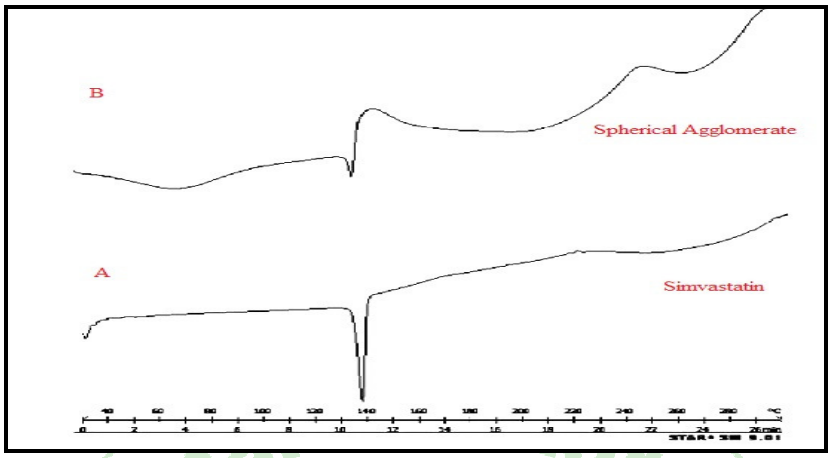

Figure 3: DSC thermograms of (A) simvastatin, (B) Spherical agglomerate.

Scanning Electron Microscopy (SEM):

SEM photomicrographs that expose the surface morphology of the samples are shown in (Figure 4).Characteristic needle-shaped crystals of simvastatin were perceived in the photomicrograph of pure drug SIM (Figure 4). SEM of the Spherical agglomerates (Figure 4) exposes irregular particles with several microscopic cracks and crevices, which provide additional surface for deposition of the drug particles. There is no evidence of drug crystals, which confirms the previous findings based on PXRD patterns.

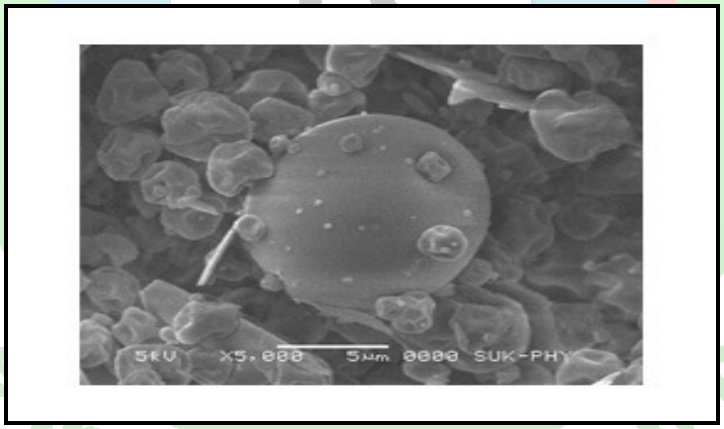

Fig.4: SEM of Simvastatin spherical agglomerates.

Powder X-Ray Diffractometry (PXRD)

The PXRD patterns of pure drug and solid dispersions are described in Figure 5. The diffraction patterns of the Simvastatin and Spherical agglomeratedesignate changes in the crystalline nature of the drug. The diffraction pattern of the pure drug simvastatin shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ (28.4°, 22.6°, 18.8°, 17.2°, 10.9°, and 9.3°) throughout the scanning range; on the other hand, PXRD of Spherical agglomerate shows a significant slightly change in the degree of crystallinity, as evident by the slightly disappearance of sharp distinctive peaks. It can be predicted that a larger proportion of simvastatin has been converted to the amorphous form. The relative reduction in the diffraction intensities in the Spherical agglomerate can be attributed to the change in orientation during the crystal growth phase. The shearing force applied by the stirrer produces intimate mixing of drug solution with carrier. Additionally, as the solution turn into supersaturated due to solvent evaporation;

the turbulence generated by the stirrer interferes with the nucleation and crystal-growth phases, leading to development of imperfect crystals or amorphization.

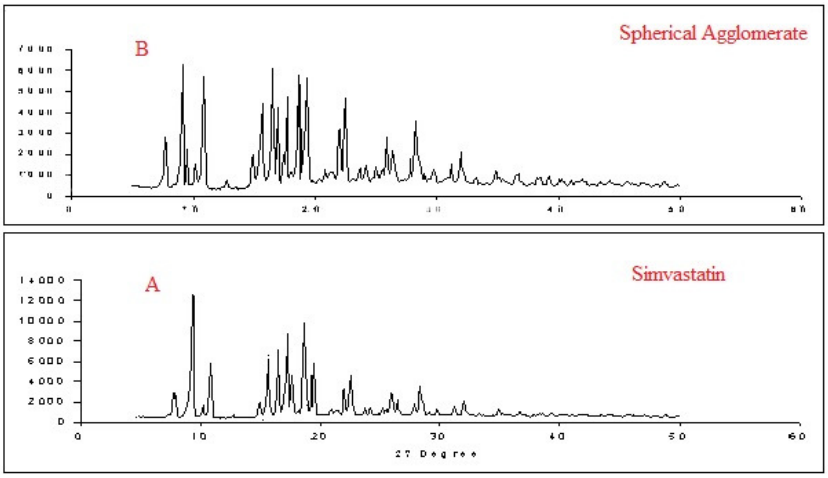

Figure 5: PXRD pattern of (A) simvastatin, (B) Spherical Agglomerate.

CONCLUSION

This technique can significantly increases the dissolution rate and flow properties of Simvastatinwithout changing crystal forms thus the spherical crystallization technology will provide the directly compressible spherical agglomerates with improved properties. The spherically agglomerates crystals of Simvastatin with PVP K-90 were productively prepared for improved dissolution rate properties of this drug by spherical crystallization technique. The micromeritic properties and also the dissolution profile of the drug were intensely affected by this technique.

REFERENCE

1. *Dubin, C. H. Formulation strategies for poorly soluble drugs. Drug Delivery Technology, 2006;6;6:34-38*
2. *Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 1995; 12:413–420.*
3. *Leuner, C., Dressman, J. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 2000; 50:47–60.*
4. *Lipinski, C.Poor aqueous solubility-an industry wide problem in drug delivery. Am. Pharm. Rev. 2002:5:82–85.*
5. *Hu, J., Johnston, K.P., Williams III., R.O. Rapid dissolving high potency danazol powders produced by spray freezing into liquid process. Int. J. Pharm. 2004; 271:145–154.*
6. *Kim D H, Park H J, Kang S H, Jun S W, Kim M S, Lee S. Preparation and characterization of lysozyme nanoparticles using solution enhanced dispersion by supercritical fluid (SEDS) process. Journal of Korean Pharmaceutical Sciences. 2005; 35:89–94.*
7. *Parida R et al., Overview of Spherical Crystallization in Pharmaceuticals, International Journal of Pharma and Bio Sciences. 2010;1:3*
8. *Yadav AV and Yadav VB, Preparation and evaluation of polymeric Carbamazepine spherical crystals by emulsion solvent diffusion technique, Asian Journal of Pharmaceutics. 2009; 3:1:18-25.*
9. *Patil SV and Sahoo SK, Pharmaceutical overview of spherical crystallization, Der Pharmacia Lettre. 2010; 2:1: 421-426.*
10. *Dixit M et al, Preparation and Characterization of Spherical agglomeratesof Ketoprofen by Neutralization Method, International Journal of Pharma and Bio Sciences. 2010; 1:4: 395-406.*
11. *Kang, B. K.; Lee, J. S.; Chon, S. K.; Jeong, S. Y.; Yuk, S. H.; Khang, G.; Lee, B. H.; Cho, S. H. Development of self-micro emulsifying drug delivery systems for oral bioavailability enhancement of simvastatin in beagle dogs. Int. J. Pharm. 2004; 274:1–2:65–73.*
12. *Ambike, A. A.; Mahadik, K. R.; Paradkar, A. Spray-Dried Amorphous Solid Dispersions of Simvastatin, a Low Tg Drug; In Vitro and In Vivo Evaluations. Pharm. Res. 2005; 22:6:990–998.*
13. *12. Cheng, H.; Sutton, S. C.; Pipikin, J. D. et al. Evaluation of sustained/controlled-release dosage forms of 3-hydroxy-3-methylglutaryl coenzyme A(HMG-CoA) reductase inhibitor in dogs and humans. Pharm. Res. 1993; 10:11:683–1687.*
14. *McClelland, C. A.; Stubbs, R. J.; Fix, J. A.; Pogany, S. A.; Zentner, G.M. Enhancement of 3-hydroxy-3- methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor efficacy through administration of a controlled-porosity osmotic pump dosage form. Pharm. Res. 1991; 8:7:873–876.*
15. *Dixit, R. P.; Nagarsenker, M. S. In vitro and in vivo advantage of celecoxib surface solid dispersion and dosage form development. Ind. J. Pharm. Sci. 2007; 69:3: 370–377.*

16. Jyothi Katta, Ake C. Rasmuson. Spherical crystallization of benzoic acid. International Journal of Pharmaceutics. 2008;348:61–69
17. Gupta V R. Formulation and evaluation of directly compressible agglomerates of Celecoxib, International Journal of Pharmaceutical Sciences and Nanotechnology,.2011;3:4:1193-1204,.
18. Newman, A. (1995) Micromeritics. In: Harry, B. eds. (1995) Physical Characterization of Pharmaceutical Solids. Drug and the Pharmaceutical Sciences, Volume 70. New York: Marcel Dekker Inc., p.253-280.
19. Martin A. Micromeritics: Physical Pharmacy: Physicochemical Principles in the Pharmaceutical Sciences. 4th ed. Baltimore, Maryland, USA: Lippincott Williams &Wilkins; 2002.
20. Carr RL. Evaluation flow properties and classifying flow properties of solids. Chem Eng. 1965; 72:163:72-69.
21. Wells J., Pharmaceutical Preformulation: the physicochemical properties of drug substances. In: Aulton ME editors. Ind Pharmaceutics – The Science of Dosage Form Design. 2nd ed. London: Churchill Livingstone; 2002.
22. Pilpel N., The flow properties of magnesia, J Pharm Pharmacol. 1964; 16:705.
23. Srinivas, M.; Parambil, A.; Krishnan, M.; Achuta, N. U. Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan-based solvent change approach. Int. J. Pharm. 2008; 350:1–2:279–290.
24. Marija, T. G.; John, M.; Hilfinger, G. L. Pharmacokinetics of the CYP 3A substrate simvastatin following administration of delayed versus immediate release oral dosage forms. Pharm. Res. 2007; 25:7:1591–1600.