IJPSR (2021), Volume 12, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 June 2020; received in revised form, 12 October 2020; accepted, 03 May 2021; published 01 June 2021

PREPARATION AND *IN-VIVO* EVALUATION OF SIMVASTATIN CRYSTALLO-CO-AGGLOMERATES

Ganesh S. Shinde and Shrinivas Mohite *

Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon - 415404, Maharashtra, India.

Keywords:

Simvastatin, Crystallo-co-agglomeration, Factorial design, Dissolution, Flowability

Correspondence to Author:
Prof. Dr. Shrinivas Mohite

Vice Principal & Head, Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon - 415404, Maharashtra, India.

E-mail: ganesh72522@rediffmail.com

ABSTRACT: The purpose of this research was to obtain directly compressible agglomerates of simvastatin using a crystallo-co-agglomeration technique and determine its *in-vivo* performance in rats. Simvastatin Dicalcium phosphate co agglomerates were prepared from Dichloromethane: Isopropyl Myristate: Distilled water system containing polyvinyl pyrrolidone (PVP). Dichloromethane acted as a good solvent for simvastatin, the water acted as a bad solvent, and isopropyl myristate acted as a bridging liquid for agglomeration. 2^3 factorial design was used for optimization, wherein the factors were stirring speed, polymer concentration, and amount of bridging liquid. The responses evaluated were dissolution, b value, and Carr's index. The agglomerates were characterized by powder x-ray diffraction (PXRD), which showed that there is a decrease in crystallinity or partial amorphization of the drug in its agglomerated form. Micromeritic and compression properties of the agglomerates were affected by an incorporated polymer. Dissolution of agglomerates (91.73%) increased as compared to a pure drug (25.96%). The agglomeration increased the flow property of Simvastatin which was indicated by Carr's index of a drug (40.81) and an optimized batch of agglomerates (11.72). *In-vivo* pharmacokinetic studies on rats demonstrated increases in C_{max} and AUC of Simvastatin Dicalcium phosphate crystallo–co–agglomerates as compared to that of marketed formulation.

INTRODUCTION: Powder technology has many methods to design particles with desirable properties, such as enhancement in solubility, obtaining suitable polymorph, improvement in micromeritic and compression properties, and modification of bioavailability. Particle size enlargement has become an important tool in modifying the primary and secondary properties of pharmaceuticals [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(6).3272-80

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(6).3272-80

In recent times, particle engineering techniques are widely used in pharmaceutical industries to modify primary (particle shape, size, crystal habit, crystal form, density, porosity, dust generation, *etc*.) as well as secondary (flowability, compressibility, compatibility, consolidation, reduced adhesion of formulation to the processing equipment, reduction in air entrapment during processing, *etc*.) properties of pharmaceuticals.

Especially, improvement in the efficiency of the manufacturing process and a high degree of particle functionality can be achieved by these techniques. Though conventional technique like wet and dry granulation enjoys wide popularity at the industrial scale, other novel techniques like extrusion-

spheronization, fluidized bed granulation, spray drying, spray congealing, solution atomization and crystallization by sonication, melt solidification, melt sonocrystallisation, liquisolid technology, co-crystallization, spherical crystallization (SC), crystallo-co-agglomeration (CCA), *etc*. have been considered as a value addition to existing ones [2-5].

Spherical crystallization techniques are restricted to size enlargements of single high-dose drugs only. CCA is a modification of the spherical crystallization techniques in which a drug is crystallized and agglomerated with an excipient or with another drug. This technique is used for size enlargement of low dose, high dose, poorly compressible drugs, and combination of drugs with or without diluents [6-7].

Present work describes preparation and evaluation of crystallo-co-agglomerates of simvastatin having poor aqueous solubility, poor micromeritic properties, poor bioavailability (35–65%), and difficulty in the formulation. The *in-vivo* pharmacokinetic study in wistar rats was done to evaluate the *in-vivo* performance of formulated agglomerates.

MATERIALS AND METHODS:

Materials: Simvastatin was a kind gift from Aristo pharmaceuticals LTD, Daman. Polyvinyl pyrrolidone (PVP K30) was obtained from BASF, Solvents such as dichloromethane, isopropyl myristate were of analytical grade.

Methods:

Crystallo-co-agglomeration: Simvastatin agglomerates were prepared using a three solvent system comprising Dichloromethane: Isopropyl Myristate: Distilled water (good solvent, bridging liquid, and bad solvent, respectively). In a beaker, polymer PVP K-30 was dissolved insufficient amount of distilled water. To this polymeric solution, Dicalcium Phosphate (DCP) was added. Simvastatin was dissolved in 4 ml Dichloromethane. Bridging liquid Isopropyl Myristate was added drop-wise in the drug solution.

The latter dispersion was added immediately to the dispersion containing dissolved polymer and Dicalcium Phosphate under constant stirring conditions (300-500 rpm) at room temperature. The stirring was continued for 20 min to obtain agglomerates, which were then filtered and dried overnight.

A 2^3 factorial Design containing 8 experimental runs to evaluate three variables *viz*. polymer concentration, drug stirring speed, and amount of bridging liquid at 2 levels were employed to determine their effect on three responses, *i.e.,* b value of kawakita equation, dissolution, Carr index and their interaction there in [8]. The variables with levels and responses of the experimental design are shown in **Table 1**.

TABLE 1: VARIABLES AND THEIR LEVELS USED IN 2^3 FACTORIAL DESIGN

Independent variables	Symbol	Levels	
		-1	1
Stirring Speed (rpm)	A	300	500
Polymer Concentration (g)	B	0.50	1.0
Bridging liquid (ml)	C	1	3
Dependent variables	Units	Constraint	
Y_1 = Dissolution	%	Maximize	
Y_2= Carr's index	%	In Range	
Y_3= b Value		Maximize	

Evaluation of Simvastatin and Crystallo-Co-Agglomerates:

Micromeritic Properties: The flow properties of pure simvastatin and agglomerates were determined in terms of angle of repose, bulk density, tapped density, Carr's Index, and Hausnar's ratio [9, 10, 11].

Kawakita Plot: Kawakita equation was used to analyze the compression process of agglomerated crystals and assessed their compactibility.

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a}$$

Where, C Degree of volume reduction, P Pressure, a and b are constants

The agglomerates (10 g) were added to measuring cylinder the volume was noted. The cylinders were subjected to definite number of tapping's *i.e.* 2, 5, 10, 15…50 so on but in a continuous manner and the volume after each serial tapping was noted. The number of taps and corresponding volume was used to construct kawakita plot [12].

Determination of Drug Content: Drug content was determined by dissolving samples of Crystallo-co-agglomerates in methanol. The solution was filtered through Whatman filter paper no. 41 were suitably diluted to get a concentration of 10 µg/ml, and absorbance was measured at 238 nm using a double beam UV spectrophotometer (Jasco 550, Japan) [13].

***In-vitro* Dissolution Studies:** *In-vitro* dissolution was evaluated using a conventional dissolution test. Dissolution studies were carried out first on the pure drug Simvastatin and prepared agglomerates. Each test was carried out in a 900ml dissolution medium at 37 ºC and at a stirring speed of 100 rpm with Apparatus no. 1. The dissolution medium used was phosphate buffer pH 6.8. An accurately weighed quantity of each sample equivalent to 5 mg of Simvastatin was subjected to the test. Aliquots were taken at an appropriate time interval. The volume of the dissolution was kept constant throughout the run by replacing the removed sample with an equivalent volume of fresh dissolution medium. Sample was filtered, suitably diluted, and analyzed at 238 nm using UV Vis spectrophotometer [14].

Powder X-ray Diffractometry (PXRD): PXRD is an important tool to determine the formation and changes that occurs in the nature of crystals of Simvastatin with diluents. Also, it indicates the % crystallanity of crystallo-co-agglomerates. The X-RD data of Crystallo-co-agglomerates of optimized batch of PVP K-30, DCP, and pure drug were recorded. The conditions were: 40 kV voltages; 40 mA current; at room temperature. The samples were loaded onto the diffractometer and scanned over a range of 2θ values from 10 to 800 at a scan rate of 0.050 /min.

Particle Size Determination: The particle size analysis of the prepared Simvastatin CCA were performed using Malvern Zetasizer ZS 90 (Malvern Instruments, Worcestershire, UK), utilizing laser diffraction with beam length 2.40 mm, range lens of 300 RF mm, and at 14.4% obscuration. The sample was diluted with Glycerin: Water (7:3) prior to the analysis. The mean diameter and the polydispersity index of each batch were recorded.

Scanning Electron Microscopy (SEM): The surface morphological properties of Crystallo-co-agglomerates of optimized batch and the pure drug was investigated by scanning electron microscopy (SEM - Jeol Instruments, JSM-6360, and Japan). Samples were mounted on a double-faced adhesive tape, sputtered with gold. Scanning electron photographs were taken at an accelerating voltage of 20kV, and obtained micrographs were examined at ×100, magnification.

Saturation Solubility Studies: The saturation solubility of simvastatin was determined in distilled water and phosphate buffer pH 6.8 by flask shake method. An excess amount of drug was added in 25ml of the medium, the bottle was screwed capped with stopper, and flasks were kept for shaking about 24 h in orbital shaker. Finally, the absorbance of the sample was measured at 238 nm.

***In-vivo* Pharmacokinetictic Analysis of Prepared Spherical Agglomerates:** Standard stock solution of Simvastatin and Rosuvastatin were prepared by dissolving 10 mg of each drug in 10 ml of methanol in separate volumetric flasks to get the concentration of 1000 µg/mL. The stock solution of Simvastatin was further diluted with methanol to get working standard solution having concentration 2 µg/mL. Working stock solution for Rosuvastatin was prepared by diluting appropriately stock solution for Rosuvastatin with methanol to get the final concentration of 50 µg/mL.

The rats were fasted for 12 h with free access to water. Three groups (6 rats each) were included in the study. The control group was administered water; the second group simvastatin suspension in water, and the third group was administered crystallo-co-agglomerates orally using a feeding tube. Blood samples (0.5ml) were collected from the tail vein after capillary anaesthetization at time intervals of 1, 2, 4, 6 h. Plasma was immediately separated from blood samples by centrifugation for 10 min and then frozen at −20 °C until analysis, then these plasma samples were analyzed by HPLC. Calibration Curve for in Simvastatin Plasma (5 µg/ml of Rosuvastatin as Internal Standard) was prepared on Jasco HPLC system consisting of Jasco PU-2080 plus HPLC pump and MD 2010 PDA detector, and JASCOBorwin PDA 1.5 version software was used for analysis. Samples were injected using a Rheodyne injector with 20 µL loop. Mobile Phase used was Methanol: 0.1M sodium acetate (pH 3.5) in ratio of (80:20 v/v). Flow Rate was 1 ml/min, using Neosphere C_{18} (4.6 × 150 mm, 3.5 micron) column protected with guard column at Wavelength of 238 nm.

RESULTS AND DISCUSSION:

Calibration Curve of Simvastatin: The parameters found in the calibration curve are shown in **Table 2.** The calibration curve **Fig. 1** was

found to be linear in the concentration range 2-12 µg/ml having correlation coefficient value r^2 = 0.991 and y = 0.0728x + 0.0992 at 238 nm (λ_{max}).

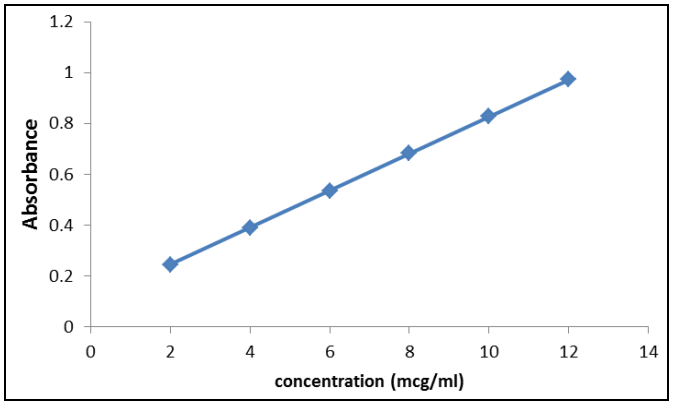

FIG. 1: CALIBRATION CURVE FOR SIMVASTATIN

TABLE 2: PARAMETERS FOUND IN CALIBRATION CURVE

S. no.	Parameters	Results
1	Detection Wavelength (λ_{max})	238 nm
2	Regression Equation	y = 0.0728x + 0.0992
3	Correlation Coefficient	0.991

Crystallo-Co-Agglomeration: Simvastatin is an antihyperlipidemic drug belonging to BCS Class II drug having poor compaction and flow properties. The agglomerates of simvastatin were prepared using a crystallo-co-agglomeration technique.

Simvastatin was crystallized from Dichloro-methane: Isopropyl Myristate: Distilled water system and agglomerated with hydrophilic polymer PVP K30. Simvastatin is freely soluble in acetone but practically insoluble in water. Also, it is soluble in DCM (bridging liquid), which is immiscible with water. Hence, these solvent systems were selected for the present study. In this process, crystallization of the drug was performed by the addition of the anti-solvent phase (water) to the drug solution. The addition of bridging liquid (DCM) promotes the formation of liquid bridges between the drug crystals to form crystallo-co-agglomerates. The agglomerated crystals are formed by coalescence of these dispersed crystals [15].

Evaluation of Simvastatin and Crystallo-Co-Agglomerates:

Micromeritic Properties: The angle of repose of pure Simvastatin was found to be 54.59 ± 0.84° hence it can be concluded that Simvastatin has poor flow property. Also, compressibility index of Simvastatin was found to be 32.97±0.73% and the Hauser's ratio 1.56±0.015 of which shows the drug has poor compressibility.

Formulation of Spherical Agglomerates: The agglomerates prepared using an optimum amount of PVP-K30 has shown adequate sphericity and mechanical strength to the agglomerates, whereas its excess addition imparts ellipticity and deformation to agglomerates, DCP (diluent) addition helps in improving flow property, bridging liquid resulting into reduction in the force of cohesion between particles leading to generation of small size spherical agglomerates.

Optimization:

Experimental Design: The experiments were designed to study the effect of three independent variables, namely speed of rotation, polymer concentration, and amount of bridging liquid at two levels on b Value (Kawakita Plot), % release of Simvastatin and Carr index. The traditional approach to developing a formulation is to change one variable at a time. By this method, it is difficult to develop an optimized formulation, as the method reveals nothing about the interactions among the variable. Among all the Response surface methods, 2^3 design reduces the number of experiments in a 3-factor experimental design and requires fewer runs. A 3-factor, 2 levels full factorial design would require a total of 8 unique runs [16]. Experimental runs and responses for optimization design are shown in **Table 3.**

TABLE 3: EXPERIMENTAL RUNS AND RESPONSES FOR OPTIMIZATION DESIGN

Std.	A: Polymer Concentration gm	B: Stirring Speed rpm	C: Amount of Bridging Liquid ml	Carr's Index %	Drug Release %	(b Value) Kawakita
1	0.5	300	1	9.61	88.26	0.1107
2	1	300	1	14	75.26	0.1491
3	0.5	500	1	9.8	87.98	0.1289
4	1	500	1	11.72	91.73	0.2136
5	0.5	300	3	17	82.1	0.1916
6	1	300	3	16.2	73.91	0.17
7	0.5	500	3	13	70.21	0.1925
8	1	500	3	10	77.37	0.2179

Influence of Independent Variables on the Drug Release: The drug release from agglomerates of Simvastatin was improved over bulk Simvastatin and the % dissolved ranged between 70.21 to 91.73% **Table 3**. The statistical models proposed has a correlation coefficient, R^2 for drug release to be 0.9994, which indicated a good fit of the model.

Drug release = +80.85-1.29*A+0.97*B-4.96*C+4.01* AB+1.03*AC-3.08*BC – equation (1)

Fig. 2 illustrates the interplay between various factors studied for their effect on dissolution. The dissolution equation shows an inverse relationship with all three variables. The combined effect of polymer and bridging liquid shows that decrease with an increase in dissolution. The combined effect of bridging liquid and polymer only show an increase in dissolution.

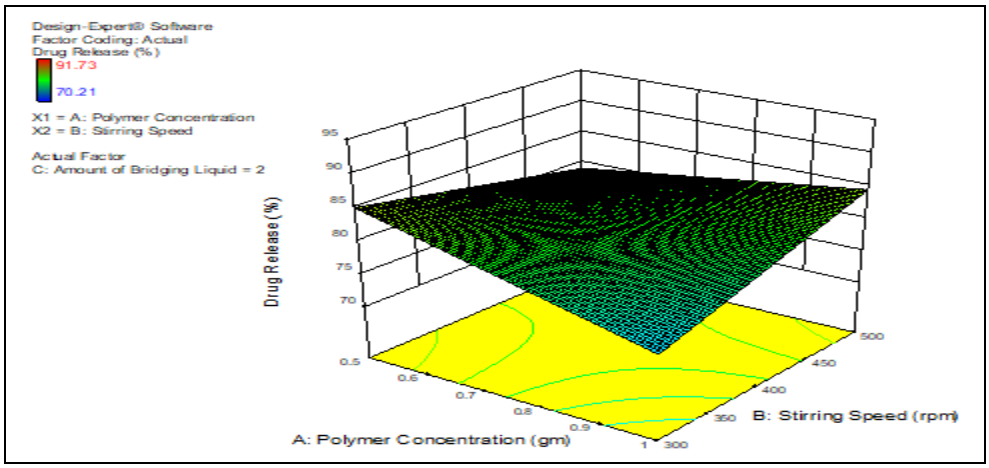

FIG. 2: THE 3-D RESPONSE SURFACE PLOTS SHOWING EFFECT OF VARIOUS PROCESS PARAMETERS ON DRUG RELEASE

Influence of Independent Variable on the Carr's Index: The value of correlation coefficient, R^2 for Carr's Index was found to be 0.9998, which indicated good fit of the model. The Carr's index from agglomerates of Simvastatin was improved over bulk Simvastatin; the ranged between 9.61 to 16.2%.

Carr's Index = +12.67+0.31*A-1.54*B +1.38*C-0.58*AB-1.26*AC-1.01*BC– equation (2)

Fig. 3 illustrates the effect of variable combinations on Carr's index; the Carr's index indicates the flow behavior and cohesiveness between particles. A value of 14-18% is desirable; the equation shows that speed and polymer contribute to an increase in Carr's index. This means at a low concentration of bridging liquid, and low speed is desired to obtain desired values for Carr's index. An increase in agitation speed causes an increase in the average diameter of agglomerates and their shape because increasingly irregular. This is due to the decreased thickness of the bridging liquid layer adsorbed on surface leading.

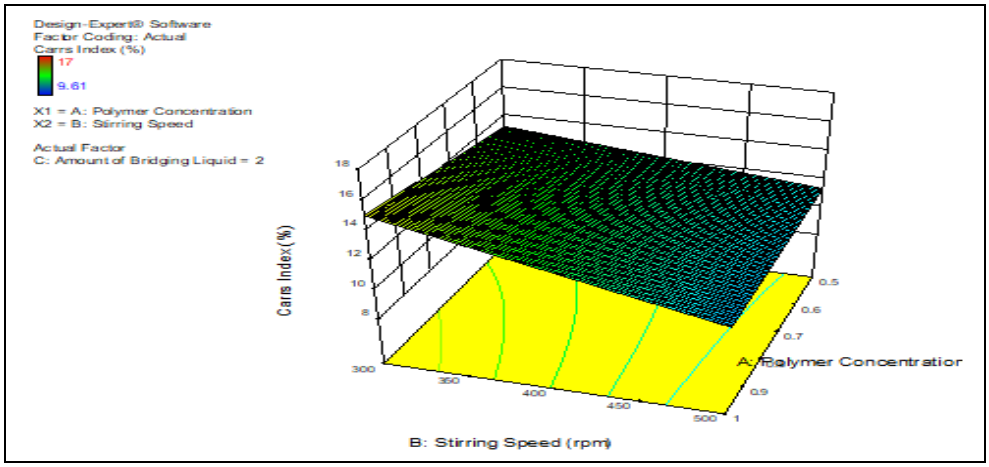

FIG. 3: THE 3-D RESPONSE SURFACE PLOTS SHOWING EFFECT OF VARIOUS PROCESS PARAMETERS ON CARR'S INDEX

Influence of Independent Variable on The b Value (Kawakita): Kawakita equation was used to analyze the compression process of agglomerated crystals and assessed their compatibility. The value of the correlation coefficient, R^2 for b Value (Kawakita) was found to be 1.0000, which indicated a good fit of the model. The values of b Value (Kawakita) ranged between 0.1107 to 0.2107.

b Value (Kawakita) = +0.17-0.016*A-0.016*B-0.021*C+ 0.012*AB-0.015*AC-4.237E-003*BC – equation (3)

The equation for b value indicates the positive contribution of variables, the mild effect of stirring speed, and the enhanced effect of polymer concentration. At low, stirring speed the porosity is higher, leading to low b values. The polymer causes wetting of the surface, leading to more adhesion between particles and strong agglomerate; hence a lower concentration is useful; however, it may be noted that the concentration should be sufficient to cause adhesion between particles **Fig. 4**.

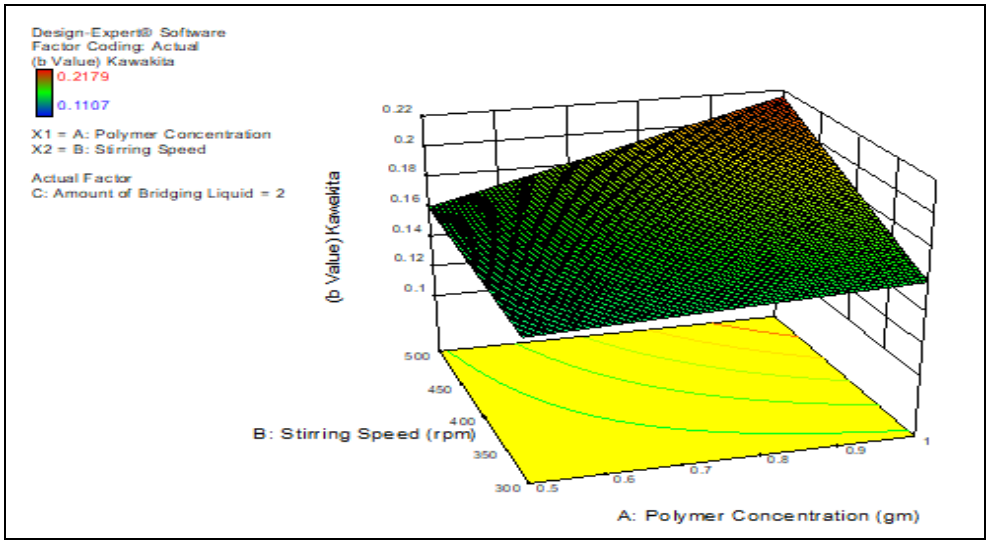

FIG. 4: INDICATES THE 3-D RESPONSE SURFACE PLOTS SHOWING EFFECT OF VARIOUS PROCESS PARAMETERS ON b VALUE (KAWAKITA)

Micromeritic Properties: All F1 to F8 batches compared with the Simvastatin drug powder properties **Table 4**. The bulk density varied between 0.47-0.49 mg/ml. angle of repose between 26.8 to 39.7 and Carr's index between 7.9-17.02. This shows the effect of various parameters on agglomerate property. In all F4 batch indicates a very good result.

TABLE 4: MICROMERITICS PROPERTIES (n=3)

Batch code	Bulk Density mg/ml	Tap Density mg/ml	Angle of repose (º)	Carr's Index	b Value (Kawakita)
F1	0.4807	0.5391	26.88	9.62	0.1207
F2	0.480	0.5681	33.18	14.03	0.1701
F3	0.4901	0.5434	28.9	7.9	0.1889
F4	0.4901	0.5694	32.79	11.73	0.2053
F5	0.4807	0.601	39.7	17.02	0.2516
F6	0.4761	0.5641	38.27	16.22	0.1380
F7	0.4901	0.564	32.14	13.84	0.2695
F8	0.4761	0.528	24.67	10.57	0.3079

TABLE 5: COMPARISON OF PREDICTED AND OBSERVED VALUES OF RESPONSE PARAMETERS

	Predicted Values	Observed Values	% error (P-O/Px100)
Carr Index	11.72	12.4	5.8 %
Kawakita b Value	0.1289	0.1312	1.78 %
% Dissolved	91.73	92.14	0.44%

There was very good agreement between predicted and observed values of optimized formula explaining prognostic ability of the design **Table 5.**

Drug Content: The drug content in spherical agglomerates is given in **Table 6**. The drug content of spherical agglomerates was in the range 70.21 -

91.73%, indicating negligible loss of drug during the crystallization process.

TABLE 6: DRUG CONTENT IN SPHERICAL AGGLOMERATES (n=3)

Formulation code	Drug content %
F1	88.26
F2	75.26
F3	87.98
F4	91.73
F5	82.1
F6	73.91
F7	70.21
F8	77.37

***In-vitro* Dissolution Study:** The result of *in-vitro* dissolution studies is shown in **Fig. 5** and **Table 7**. Pure drug exhibited less release, 25.96 at the end of 30 min, while the polymeric spherical agglomerates showed a significant increase in drug release as compared to pure drug. *The in-vitro* release profile of the formulations (F1-F8) was ranging from 70.21-91.73±0.10%.

Among the formulations prepared, F4 (prepared with 1.0 w/w of PVP-K30) showed the highest drug release, 91.73±0.10%. The increase in drug release of agglomerates could be attributed to the deposition of polymer on the drug surface and better wettability of the spherical agglomerates.

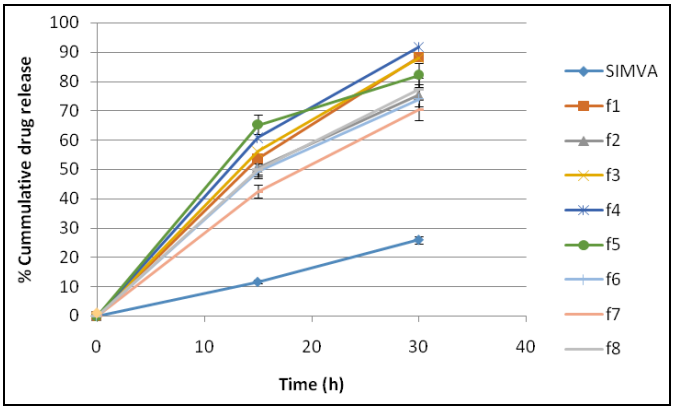

FIG. 5: *IN-VITRO* DISSOLUTION PROFILE PURE DRUG AND F1-F8 FORMULATION

TABLE 7: DISSOLUTION OF PURE DRUG AND F1-F8 FORMULATION (n=3)

	% Cumulative Drug Release (mean ± SD)								
Time	**SIMVA**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0	0
30	25.96	88.26	75.26	87.98	91.73	82.1	73.91	70.37	77.37

Powder X-Ray Diffraction (PXRD): The result of X-ray diffraction pattern of Simvastatin and spherical agglomerates (F4) are shown in **Fig. 6**. Pure drug exhibited intense and long peaks whereas spherical agglomerates showed a halo pattern with less intense peaks, which indicate a considerable decrease in crystallinity or partial amorphization of the drug in its agglomerated form.

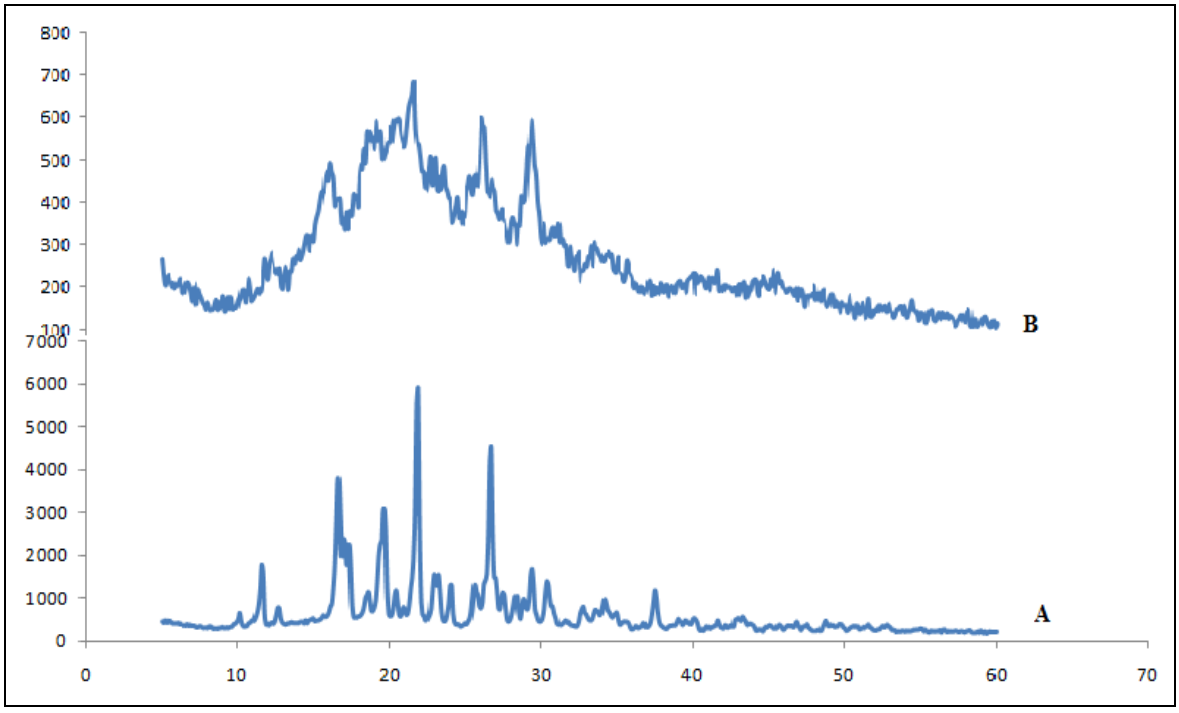

FIG. 6: PXRD STUDIES OF PURE DRUG (A) AND F4 BATCH (B)

Particle Size Determination: The Simvastatin drug and CCA sample was diluted with Glycerin: Water (7:3) prior to the analysis. The mean diameter and the polydispersity index of each batch were recorded.

TABLE 8: RESULTS OF PARTICLE SIZE ANALYSIS

Formulation	Z-Average (d.nm)	PDI
Simvastatin Drug	**667.7**	**0.300**
F1	670.9	0.574
F2	912.7	1.000
F3	796.3	0.128
F4	530.9	0.687
F5	342.8	0.395
F6	275.4	0.444
F7	472.8	0.272
F8	293.2	0.488

Scanning Electron Microscopy (SEM): The results of Scanning electron microscopy are shown in **Fig. 7**. The pure drug is characterized by the presence of crystalline particles. The presence of the polymers contributes to improved sphericity and roughness of the agglomerates. Improved sphericity may be attributed to coating developed on the crystals before binding into agglomerates, which results in sphericity. SEM obtained at higher magnifications revealed that the agglomerates were formed by very small crystals, which were closely compacted into spherical form. These photo-micrographs show that the prepared agglomerates were spherical in shape, which enabled them to flow very easily.

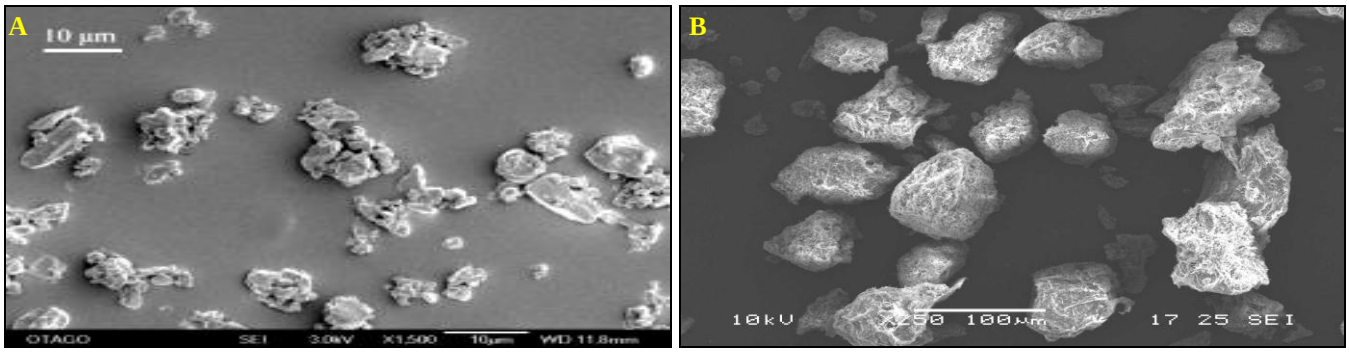

FIG. 7: SEM IMAGES OF A) SIMVASTATIN AND B) SIMVASTATIN CCA

Saturation Solubility Studies: The results of solubility studies indicate that pure Simvastatin possesses a very low solubility in water 3.0×10^{-2} mg/ml, whereas there was an increase in solubility of spherical agglomerates at 4.260×10^{-1} mg/ml.

***In-vivo* Pharmacokinetic Analysis of Simvastatin Crystallo-Co-Agglomerates:**

Calibration Curve for Simvastatin in Plasms: The calibration curve of simvastatin in plasma obeyed Beers law within a concentration range of 0.1-0.5 µg/ml. The equation of line was Y= 1.9871X + 0.0221 and R^2 was 0.9974.

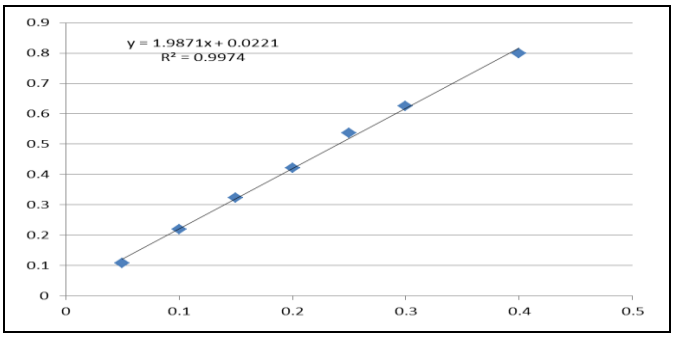

FIG. 8: CALIBRATION CURVE FOR SIMVASTATIN IN PLASMA

Pharmacokinetic Data of Crystallo-Co-Agglomerates: The *in-vivo* pharmacokinetic profiles of simvastatin marketed formulation and crystallo-co-agglomerates are presented in **Fig. 9**.

In comparison to marketed formulation, Simvastatin Crystallo- Co- Agglomerates shows significant increase in C_{max} from 0.275 µg/ml to 0.371 µg/ml and AUC from 4.1 to 6.718 µg.h/ml. The pharmacokinetic parameters are presented in **Table 9**.

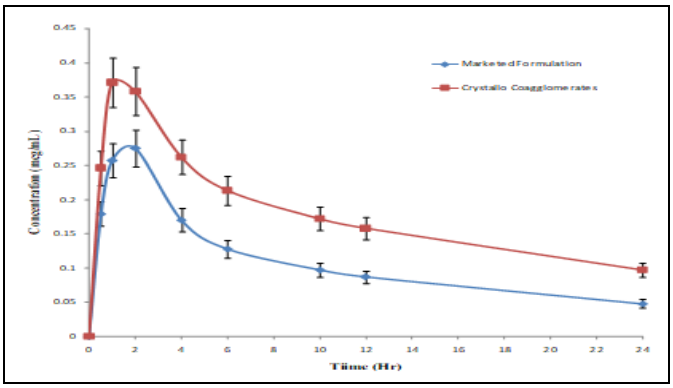

FIG. 9: PHARMACOKINETIC PROFILE FOR SIMVASTATIN MARKETED FORMULATION AND SIMVASTATIN

TABLE 9: SUMMARY OF PHARMACOKINETIC ANALYSIS

Pharmacokinetic Parameters	Marketed Formulation	Crystallo-Co-Agglomerates	% Increase
C_{max} (µg/ml)	0.275	0.371	134.91
AUC (0-24h) µg.h/ml	4.10	6.718	163.85
t_{max} (h)	2.0	1.0	

Thus, the increase in $C_{max,}$ and AUC along with decrease in t_{max} confirms the improvement in *in-vivo* bioavailability of simvastatin from crystallo-co-agglomerates.

CONCLUSION: The crystallo-co-agglomeration is a useful technique where the poorly soluble low-dose drug such as simvastatin is crystallized from saturated organic solution in the presence of a diluent. The agglomerates formed have good flow properties, compression behavior as well as improved dissolution and *in-vivo* bioavailability.

ACKNOWLEDGEMENT: Authors are thankful to Rajarambapu College of Pharmacy, Kasegaon 415404, Maharashtra, India, for providing the necessary facilities to carry out the experiment.

CONFLICTS OF INTEREST: The author(s) declare no conflict of interest.

REFERENCES:

1. Khadkaa P, Roa J and Kima HK: Pharmaceutical Particle Technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian Journal of Pharmaceutical Sciences. 2014; 9(6): 304-16.
2. Arora P, Kaur A, Haneef J and Chadha R: Solubility improvement of telmisartan by cocrystallization with citric acid. International Journal of Pharmaceutical Sciences and Research 2017; 8(9).
3. Singh MC and Loharkar RR: Spherical crystallization of sitagliptin phosphate monohydrate for formulation of directly compressible tablets. Int J Pharm Sci & Res 2020; 11(5): 2082-92.
4. Sirisha VR, Suresh K, Vijayasree K, Devanna N, Murthy PN: Recent Advances in Pelletization Techniques. A Review: International Journal of Pharmaceutical Sciences Review and Research 2014; 27(1): 217-23.
5. Chatterjee A, Gupta MM, and Srivastava B: Spherical crystallization: A technique use to reform solubility and flow property of active pharmaceutical ingredients. International Journal of Pharmaceutical Investigation 2017; 7(1): 4-9.
6. Paradkar AR, Maheshwari M, Ketkar AR and Chauhan B: Preparation and evaluation of ibuprofen beads by melt solidification technique: International Journal of Pharmaceutics 2003; 255(1-2): 33-42.
7. Deshkar SS, Borde GR, Kale RN, Waghmare BA and Thomas AB: Formulation of cilostazol spherical agglomerates by crystallo-co-agglomeration technique and optimization using design of experimentation. International Journal of Pharmaceutical Investigation 2017; 7(4): 164-73.
8. Cavazzuti M: Design of experiments in optimization methods. Theory to design, Springer-Verlag Berlin Heidelberg 2013; 18.
9. Leon L and Herbert L: The Theory and Practice of Industrial Pharmacy: Third Edition 2009.
10. Aulton ME: Aulton's Pharmaceutics: The Design and Manufacturing of Medicines. Third Edition. New York, USA; 2007.
11. Subrahmanyam CVS: Textbook of Physical Pharmaceutics. Vallabh Prakashan, Second Edition 2000.
12. Autamashih M, Isah AB, Allah TS and Ibrahim MA: Analyses of granules of the crude leaves extract of vernonia galamensis prepared using gelatin as binder. International Journal of Pharmaceutical Sciences and Research 2011; 2(10): 2566-71.
13. Kumar S, Mishra DN and Singh SK: Enhancement of dissolution and bioavailability of fenofibrate by solid dispersion with sodium citrate, HPMC and sugar derivatives. Der Pharmacia Lettre 2015; 7(3): 162-73.
14. https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getallData.cfm.
15. Hitesh D: Spherical agglomeration to improve dissolution and micromeritic properties of an anticancer drug, Bicalutamide. Drug Development and Industrial Pharmacy 2019; 45(6): 968-80.
16. Singh B, Kumar R and Ahuja N: Optimizing drug delivery systems using systematic "Design of experiments." Part I: fundamental aspects. Critical Reviews in Therapeutic Drug Carrier Systems 2005; 22(1): 27-105.

How to cite this article:
Shinde GS and Mohite S: Preparation and *in-vivo* evaluation of simvastatin crystallo co agglomerates. Int J Pharm Sci & Res 2021; 12(6): 3272-80. doi: 10.13040/IJPSR.0975-8232.12(6).3272-80.