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NOVEL APPROACH FOR ENHANCED SOLUBILITY AND DISSOLUTION RATE OF SIMVASTATIN USING SPHERICAL CRYSTALLIZATION TECHNIQUE.

Yerukala Eswar, Badugu Swarupasri, Bingadoddi Prasad, Katti Shiva Krishna and Jhansi Priya Marabathuni*

Department of Pharmaceutics, Bellamkonda Institute of Technology & Science, Podili. A.P-523240.

Corresponding Author: Jhansi Priya Marabathuni

Department of Pharmaceutics, Bellamkonda Institute of Technology & Science, Podili. A.P-523240.

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ABSTRACT

Simvastatin is water insoluble drug commonly used in the treatment of hypercholesterolemia and dyslipidemia. The objective of the present investigation was to develop simvastatin spherical agglomerates to improve its solubility and dissolution characteristics by spherical crystllisation method. Methods: In preparation of simvastatin spherical agglomerates crystallization media used were methanol, water, and chloroform as bridging liquid and PVP K-30 as a polymer. The process variables such as amount and type of (bridging liquid and polymer), stirring speed, and stirring time were optimized. The spherical agglomerates were characterized by suitable analytical techniques and further subjected for determination of % drug content, particle shape analysis, solubility, and dissolution rate. The spherical agglomerates of the optimized batch were directly compressed into tablet; the dissolution profile of prepared tablet was compared with dissolution profile of marketed tablet. Result: The spherical agglomerates obtained with methanol (7 ml), water (50 ml), chloroform (1.5 ml), and PVP K-30 (0.5%) at 500 rpm and 15 minutes stirring time showed significant improvement in solubility and dissolution from a value of 0.029 mg/ml and 25.53% for pure simvastatin to 6.42 mg/ml and 91.31% of spherical agglomerate, respectively. The simvastatin tablet obtained with spherical agglomerates showed 89.65% cumulative drug release as compare to 80.28% of marketed tablet. Conclusion: A significant result obtained with the study indicates that spherical crystallization by spherical agglomeration technique can successfully be further explored and employed to improve solubility and dissolution characteristic of poorly soluble drugs.

KEYWORDS: simvastatin.

INTRODUCTION

Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the crystallization process into a spherical shape. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form and which has been successfully utilized for improvement of solubility and dissolution.[1] Poor physical and mechanical properties of drug particles have been masked by various wet granulation methods, such as high-shear and fluid bed wet granulation, which generally involve mixing, atomization and spraying of granulation liquid on powders, drying steps, sieving, and so on. Both agglomeration methods are an energy-consuming process. Other agglomeration techniques, such as dry granulation, hot melt granulation, melt extrusion, spray congealing, or melt solidification have been introduced in recent years, and have yielded some innovative solutions for improving the physical and mechanical properties of drug particles; however, they are still less economical than direct compression tableting. Spherical agglomeration is the most commonly used method and involves the use of polymer and/or bridging liquids to simultaneously crystallize and agglomerate. Spherical agglomeration technique improves flow property and compression characteristics of the drug which can be directly compressed into tablet. A number of drugs such as salicylic acid, naproxen, celecoxib, ibuprofen, mefenamic acid, and nabumetone are reported in literature that has been processed using spherical agglomeration technique.[2] In this study, simvastatin was chosen as the model drug for spherical agglomeration. Simvastatin, a biopharmaceutics classification system class II drug, is a lipid-lowering agent that is derived synthetically from the fermentation of Aspergillus terreus.[3,4] It is a potent competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase which is the rate-limiting enzyme in cholesterol biosynthesis.[5,6] Micronization process gives rise to increased free surface energy and thus poor flowability and compressibility of powders which makes them difficult to use in downstream processing in the pharmaceutical industry such as direct tablet-making or capsule-filling processes. Therefore, this study involved optimization of spherical agglomeration aimed at

improving the physico-technical properties, solubility, and dissolution characteristic of simvastatin.

MATERIALS AND METHODS

Materials Simvastatin was gifted from Watson India Ambernath, Mumbai and Cipla Pvt. Ltd. PVP K-30 and hydroxypropyl methylcellulose were obtained from Colorcon Asia, (Goa). The other reagents and solvents were of analytical grade purchased from Universal Labs, Mumbai. Methods Preparation of spherical agglomerates by using different bridging liquid The spherical crystal is obtained through spherical agglomeration technique. Nine batches were prepared depending on the change in concentration and type of bridging liquid (Table 1). Simvastatin was dissolved in methanol and poured in water followed by addition of bridging liquid (dichloromethane/ chloroform/methanol) dropwise with different stirring speed and stirring time. The obtained precipitated agglomerates of simvastatin were dried for 24 hrs at room temperature.

Preparation of spherical agglomerates using chloroform as bridging liquid with polymers The spherical crystal is obtained through spherical agglomeration technique. Six batches (B10 to B15) were prepared depending on the change in concentration and type of polymers (Table 2). Simvastatin was dissolved in methanol and poured in the mixture of water and polymer followed by addition of bridging liquid (chloroform) dropwise with different stirring speed and stirring time. The obtained precipitated agglomerates of simvastatin were dried for 24 hrs at room temperature to enlarge the size of the agglomerates.[7, 8] Further six batches (B16 toB21) were prepared to optimize stirring speed and time (Table 2). Preparation of tablet with optimized spherical agglomerates The tablets were prepared by using direct compression method. The powder ingredients, i.e., optimized spherical agglomerates and excipients, viz., microcrystalline cellulose, talc and magnesium stearate were weighed and mixed thoroughly to prepare homogeneous mixture. The homogeneous mass was compressed in tablet compression machine (Company: Karnavati; Model: Mini press II MT) using punch size 4 mm to obtain tablets of uniform size and shape (Table 3). The optimized spherical agglomerates of simvastatin directly compressed and compared for percent cumulative drug release with a marketed tablet. Evaluation of optimized spherical agglomerates Optical microscopy The external morphology of spherical agglomerates was studied by optical microscopy. The sample was taken on the glass slide and is observed under 10×, 45× and 100× magnifications.[9]

Tables for calculation

Percent drug content The optimized formulation was triturated in mortar and pestle. Powder equivalent to a dose of simvastatin was weighed and dispersed into 100 ml of methanol and sonicated using an ultrasonicator for 20 minutes. The resultant solution was filtered through Whatman filter paper No. 41, and a drug content was spectrophotometrically determined at 238 nm (model-ultraviolet (UV) 1700 Shimadzu, Japan). Solubility analysis The optimized formulation was mixed with 2 ml of water to make saturated solution of simvastatin. The solution was placed inside orbital shaker for 48 hrs followed by centrifugation in laboratory centrifuge at 300 rpm for 15 minutes. The resultant solution was then filtered through Whatman filter paper No. 41 and further diluted with distilled water. Solubility was spectrophotometrically determined at 238 nm (model-UV 1700 Shimadzu, Japan).[12,13] Dissolution studies Drug release studies of prepared agglomerates were performed by USP dissolution apparatus 2 (DT 60, Veego Instruments) with 900 ml of phosphate buffer pH-7.0 as dissolution medium at 37±0.1°C. The speed of the paddle was adjusted to 50 rpm. The prepared agglomerates were packed inside muslin cloth and tied to the paddle. An aliquot of 1 ml was collected at an interval of 10 minutes and diluted with Phosphate buffer pH-7.0 up to 10 ml then, analyzed for the content of simvastatin by UV-spectrophotometer at 238 nm. An equivalent volume (1 ml) of fresh dissolution medium was added to compensate for the loss due.[14,15] Differential scanning calorimeter (DSC) DSC spectra of pure drug and spherical agglomerates were carried out using DSC equipment. Powder X-ray powder diffraction Powder X-ray diffraction (PXRD) patterns were carried out by X-ray diffractometer for the samples. The samples were analyzed at 1 minutes/second over the 1-50 diffraction angle (2θ) range. Evaluation of formulated tablets prepared with optimized spherical agglomerates[16,17] Dissolution studies Drug release studies of formulated tablets were performed by USP dissolution apparatus 2 (DT 60, Veego Instruments) was used with 900 ml of phosphate buffer pH-7.0 as dissolution medium at 37±0.1°C. The speed of the paddle was adjusted to 50 rpm. Friability Friability testing of the tablets is carried out by roche friabilator. 20 tablets are placed inside of rotating drum which rotates at 25 rpm. The timer is set for 4 minutes to complete 100 rotations. The tablets are removed and % weight loss is calculated. Hardness Hardness testing of the tablets is carried out by Monsanto hardness.

Composition of Spherical crystal agglomerates of Simvastatin by using Ethyl acetate as bridging liquid

S.No	Ingredients	Formulation code														
		EF 1	EF 2	EF 3	EF 4	EF 5	EF 6	EF 7	EF 8	EF 9	EF 10	EF 11	EF 12	EF 13	EF 14	EF 15
1.	Simvastatin(mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
2.	Isopropyl alcohol(ml)	2	10	4	16	10	20	10	4	20	14	25	27	20	40	45
3.	Ethyl acetate(ml)	12	8	20	16	4	14	10	6	30	26	15	8	40	20	5
4.	Distilled water(ml)	86	82	76	68	86	66	80	90	50	60	60	65	40	40	50
5.	RPM	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400

Composition of Spherical crystal agglomerates of Simvastatin by using Chloroform as bridging liquid

S.No	Ingredients	Formulation code														
		CF 1	CF 2	CF 3	CF 4	CF 5	CF 6	CF 7	CF 8	CF 9	CF10	CF 11	CF 12	CF 13	CF 14	CF15
1.	Simvastatin(mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
2.	Isopropyl alcohol(ml)	2	10	4	16	10	20	10	4	20	14	25	27	20	40	45
3.	Chloroform(ml)	12	8	20	16	4	14	10	6	30	26	15	8	40	20	5
4.	Distilled water(ml)	86	82	76	68	86	66	80	90	50	60	60	65	40	40	50
5.	RPM	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400

Based on the evaluation test results best formulation was selected.

Table.No.9: Physical Properties of Simvastatin SCA formulations (chloroform as bridging liquid).

S. No	Formulation code	Physical properties of Simvastatin SCA							
		Angle of repose ^{0} ± SD	Loose Bulk density g/cm^3 ± SD	Tapped bulk density g/cm^3 ± SD	Hausner ratio ± SD	Compressibility index % ± SD	Solubility µg/ml ± SD	% Yield± SD	Particle size µm ± SD
1	Pure drug	40°2'±0.855	0.242±0.007	0.357±0.0	1.48± 0.41	32.22± 1.9	10.49±0.007	---	117.6±3.55
2	CF1	25°04'±0.571	0.395±0.014	0.395±0.04	1.19± 0.69	16.03± 4.67	22.15±0.002	81.42±1.01	425±4.8
3	CF2	---	---	---	---	---	---	---	---
4	CF3	27°10'±0.623	0.375±0.016	0.456±0.0	1.21± 0.52	17.39± 3.49	27.91±0.004	92.63±2.517	565.6±6.25
5	CF4	24°40'±0.522	0.349±0.014	0.406±0.019	1.16.007	13.97±0.55	25.24±0.002	89.74±3.25	495.2±4.3
6	CF5	---	---	---	---	---	---	---	---
7	CF6	22°06'±0.471	0.471±0.026	0.500±0.0	1.06± 0.06	6.06± 5.25	45.12±0.001	96.36±1.55	712.3±6.75
8	CF7	24°05'±0.506	0.431±0.04	0.485±0.026	1.13± 0.05	11.19± 3.63	20.05±0.002	75.31±2.021	533±5.2
9	CF8	---	---	---	---	---	---	---	---
10	CF9	26°30'±0.483	0.366±0.016	0.442±0.022	1.20± 0.06	17.03± 3.85	34.25±0.003	85.25±3.704	672.3±4.85
11	CF10	23°3'±0.509	0.429±0.022	0.467±0.026	1.09±0.1	8.33± 8.33	29.27±0.006	91.61±1.809	518±5.74
12	CF11	27°4'±0.674	0.283±0.009	0.366±0.016	1.29± 0.86	22.55± 5.07	31.25±0.004	77.92±2.919	619.4±5.65
13	CF12	29°1'±0.730	0.284±0.018	0.375±0.016	1.32± 0.03	24.46± 1.61	35.47±0.003	74.16±3.055	647.7±4.84
14	CF13	---	---	---	---	---	---	---	---
15	CF14	---	---	---	---	---	---	---	---
16	CF15	---	---	---	---	---	---	---	---

± SD - Standard deviation (n = 3)

Table.No.13: In vitro drug release data for CF6.

S. No	Time (min)	Absorbance	Concn. (µg /ml)	Concn. (mg /ml)	Amount released (mg)	Cum. Amnt. Released (mg)	%Cum. drugrelease	%Cum. drugremain.	log % Cum. drug remaind	Square root time	log time	log % Cum. drug release
1	0	0	0	0	0	0	0	100.0	2.00	0	-	-
2	10	0.072	3.4660	0.0035	3.12	3.12	15.60	84.40	1.93	3.16	1.00	1.1930
3	20	0.106	5.1225	0.0051	4.61	4.61	23.07	76.93	1.89	4.47	1.30	1.3630
4	30	0.180	8.7277	0.0087	7.85	7.86	39.32	60.68	1.78	5.48	1.48	1.5946
5	40	0.295	14.3305	0.0143	12.90	12.91	64.57	35.43	1.55	6.32	1.60	1.8101
6	50	0.378	18.3742	0.0184	16.54	16.57	82.84	17.16	1.23	7.07	1.70	1.9183
7	60	0.438	21.2973	0.0213	19.17	19.22	96.09	3.91	0.59	7.75	1.78	1.9827

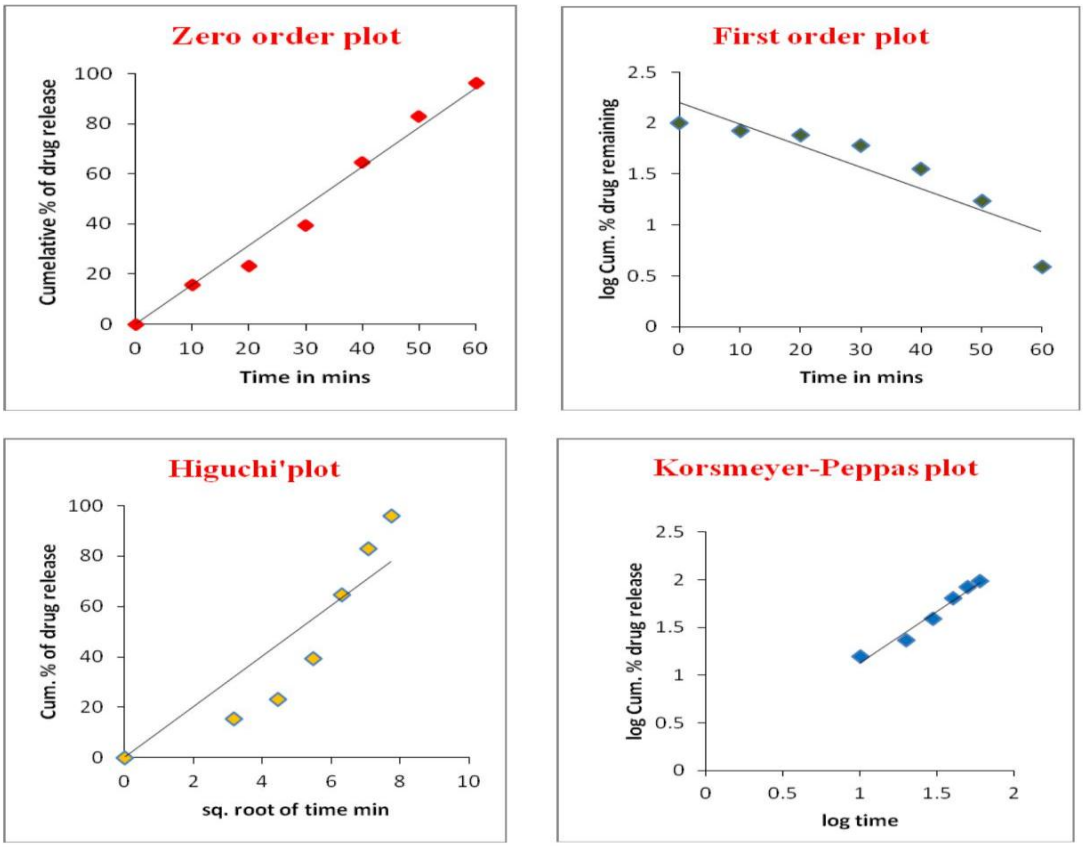

Fig.No.14: *In vitro* drug release kinetics data for formulation CF6.

The *In vitro* drug release data were used to explain the mechanism of drug release by fitting into various kinetic models. The *In vitro* drug release kinetic study was done with zero order, first order, higuchi's model and Korsemeyer peppas model. The results were shown in Table No.30.

Table. No. 30: Summary of *In vitro* drug release kinetics data of all formulations:

S. No	Formulation code	Zero order		I order		Higuchi's plot		Korsemeyer Peppas	
		slope	regression	slope	regression	slope	regression	n	regression
1	CF1	0.9634	0.9961	0.0139	-0.9817	0.1183	0.9295	0.9902	0.9943
2	CF3	1.2517	0.9980	0.0221	-0.9731	0.0923	0.9410	1.0488	0.9997
3	CF4	1.1157	0.9942	0.0180	-0.9659	0.1018	0.9281	1.0156	0.9989
4	CF6	1.6581	0.9920	0.0489	-0.9093	0.0682	0.9260	1.1077	0.9969
5	CF7	0.7457	0.9869	0.0095	-0.9782	0.1466	0.9001	0.9470	0.9421
6	CF9	1.0670	0.9950	0.0166	-0.9689	0.1064	0.9277	1.0075	0.9983
7	CF10	1.1636	0.9959	0.0195	-0.9650	0.0984	0.9340	1.0284	0.9994
8	CF11	0.8825	0.9928	0.0120	-0.9844	0.1274	0.9204	0.9720	0.9843
9	CF12	0.8408	0.9898	0.0112	-0.9819	0.1320	0.9113	0.9663	0.9689
10	CF16	1.0992	0.9807	0.0183	-0.9361	0.1001	0.9121	0.9953	0.9952
11	CF17	1.5337	0.9898	0.0339	-0.9351	0.0723	0.9104	1.1000	0.9946
12	CF18	0.9081	0.9837	0.0126	-0.9608	0.1191	0.8933	0.9667	0.9779
13	CF19	1.0091	0.9666	0.0149	-0.9309	0.1017	0.8628	0.9714	0.9734
14	CF20	0.7936	0.9832	0.0106	-0.9621	0.1369	0.8984	0.9274	0.9833
15	CF21	0.9106	0.9831	0.0129	-0.9582	0.1199	0.9028	0.9707	0.9879
16	CF22	1.5820	0.9800	0.0363	-0.9182	0.0677	0.9028	1.1063	0.9862

Where
Ko = zero order rate constant
R^2 = correlation coefficient
K1 = first order rate constant
KH = higuchi's rate constant
n = release exponent ased on the results obtained all the formulations following Zero order release with korseymeyer peppas model. Since the Zero order correlation coefficient values are greater when compared to First order.

7.7 CHARACTERIZATION OF SIMVASTATIN SCA

7.7.1 Optical Microscopy

The shape of the agglomerates was observed under an optical microscope (10x magnification) fixed to a camera.

Fig.No.27: Optical microscopic photographs of Simvastatin pure drug.

Fig.No.28: Optical microscopic photographs of Simvastatin SCA.

CONCLUSION

The objective of the present work was to improve the solubility and micromeritic properties of Simvastatin. The SCA's were produced by Spherical agglomeration method. The choice of Bridging liquid and solvent composition for spherical crystallization was estimated by constructing the ternary diagram. Various formulations were prepared by changing the stirring speed, stirring time, temperature of non solvent and diameter of stirring vessel. The prepared Simvastatin SCA were evaluated for the physical properties namely loose bulk density, tapped bulk density, hausner's ratio, angle of repose, carr's index, solubility, and % yield. The formulation CF6 showed loose bulk density value of 0.471 g/cm^3 and tapped bulk density value of 0.5 g/cm^3. The solubility of Simvastatin SCA was 45.12 µg/ml which was better than pure Simvastatin value of 10.49 µg/ml. The formulation evidently improved solubility, flowability. The *In vitro* drug release was found to be maximum of about 96.09% for CF6 formulation compared to other formulations. Formulation CF6 containing Isopropyl alcohol 20ml, distilled water 66ml and chloroform 14ml was selected as best formulation. The best formulation (CF6) was characterized by subjecting to DSC, PXRD and SEM studies.

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