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Original Article

COMPARATIVE STUDY OF REVERSE WET GRANULATION WITH CONVENTIONAL WET GRANULATION IN SOLUBILITY ENHANCEMENT OF SIMVASTATIN

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ABSTRACT

Objectives: Simvastatin is a cholesterol- lowering agent widely used in hypercholesterolemia. It belongs to BCS class II drugs having low solubility and high permeability. Simvastatin is practically insoluble in water and poorly absorbed from the gastrointestinal tract. Therefore, it is necessary to introduce an effective method to enhance the solubility and dissolution rate of the drug. The main purpose of this work was to compare the reverse wet granulation with conventional wet granulation in enhancing the solubility of Simvastatin.

Methods: The Granules were prepared by both conventional wet granulation in which Simvastatin was added along with other dry excipients and reverse wet granulation in which Simvastatin was added in granulating solvent using water as granulating solvent and Povidone, Lactose, Sodium starch glycolate, Magnesium stearate and Aerosil as an Excipients. The granules were evaluated for flow properties, solubility study, X- ray diffraction and FTIR study.

Results: The flow properties of reverse wet granulation were found to be improved as compared to conventional wet granulation. The tablets were formulated from either type of granules which were subjected to a Hardness, Disintegration, Weight variation, Content of active ingredient, Friability, Wetting time and Dissolution test. The Simvastatin tablets of reverse wet granulation resulted in about 1.4 fold increase in dissolution rate when compared to conventional wet granulation tablets. The significant difference between flow properties and dissolution profile in between reverse wet granulation and conventional wet granulation was validated by statistical evaluation.

Conclusion: Reverse wet granulation can be successfully used over the conventional wet granulation for solubility enhancement of Simvastatin. The method is easy to adopt.

Keywords: Reverse wet granulation, Conventional wet granulation, Flow properties, Dissolution, Solubility, Wetting time.

INTRODUCTION

Granulation refers to the act or process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. It is the size enlargement process in which fine or coarse particles are converted into physically stronger and large agglomerates having good flow properties, better compressibility, and uniformity [1]. Granulation method can be divided into two major types, namely wet granulation which utilizes liquid to bind primary powder particles together and dry granulation which utilizes compression force [2].

Among the two methods wet granulation is most widely used method as it can be applied to all drugs with high dose and a very low dose and for highly soluble as well as poorly soluble drugs [3, 4]. Wet granulation has both advantages and disadvantages. The standard granulation process commonly used in pharmaceutical industry produces granules by adding a solution of a solid mixture of drug and other dry excipients. When the drug substance has a poor aqueous solubility, this process is found to be unsuitable because granules formed include large agglomerates and time duration of the process has a sharp end point. And though tablets formed from these granules shows acceptable dissolution characteristics they erode unevenly during dissolution testing.

These observed characteristics are believed to be related to non-uniform distribution of the binders in the granules due to inadequate and uneven contact in between the drug and hydrophilic polymer. These characteristics affect dissolution behavior and therefore it is necessary to overcome disadvantages of conventional wet granulation in the processing of poorly water soluble drugs. To overcome these disadvantages and dissolution issue the process "reverse wet granulation" was developed by Boyong LI et al [5]. In the process an API is intimately mixed with a solution or suspension of hydrophilic polymer to form drug-polymer slurry. The granules can then be formed by incorporating a mixture of other dry excipients into the drug- polymer slurry. The granules formed from this process comprise a core containing an API has a poor aqueous solubility, which is intimately associated with one or more hydrophilic polymers. Granules formed from this process after milling has good flow characteristics.

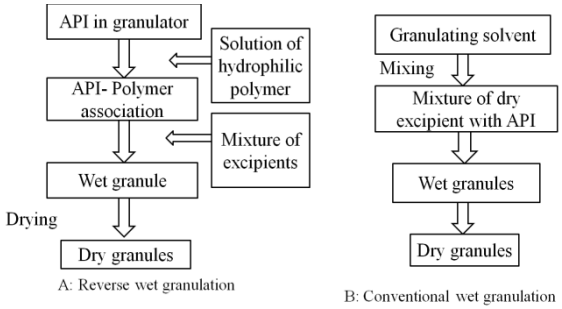

Fig. 1: Basic difference between reverse wet granulation and conventional wet granulation. A) Formation of granules of reverse wet granulation. B) Formation of granules of conventional wet granulation.

Tablets formed from these granules erode more uniformly during dissolution testing and pharmaceutical composition formed from these granules have more uniform wetting and dissolution as compared to conventional wet granulation. Fig. 1 represents the basic difference between the method of preparation of reverse wet granulation and conventional wet granulation. The objective of the present investigation was to study the effect of method of preparation of granules (reverse wet granulation and conventional wet granulation) on its solubility, dissolution, and flow properties.

The comparative study of conventional wet granulation with reverse wet granulation was carried out. The excipients employed in the preparation of the granules were polyvinyl pyrrolidone, lactose, sodium starch glycolate, crosspovidone, magnesium stearate, and sodium lauryl sulfate.

Simvastatin was selected as a model drug as it belongs to the BCS class II drug having low solubility. It is an HMG- CoA reductase inhibitor used in the treatment of hyperlipidemia [6, 7].

MATERIALS AND METHODS

Materials

Simvastatin was obtained as a gift sample from Watson Pharma, Ambernath, India. Polymer povidone K-30, lactose, magnesium stearate, sodium starch glycolate, and crosspovidone were obtained as a gift sample from the Getz pharma, Ambernath, India and Methanol from Modern scientific, Nashik.

Methods

FTIR analysis

Infrared spectroscopy (Shimadzu 8400s, Japan) was performed for pure drug. The sample was mixed with KBr and vacuum packed to obtain pellets, of which were then analyzed. The spectrum was scanned between 400 to 4000 cm^{-1}. Results are shown in [fig. 2].

DSC analysis

Thermal analysis was performed using DSC (Shimadzu Thermal Analyzer DSC 60, Japan) equipped with computerized data station. The sample of pure drug was weighed and heated at a scanning rate of 10°C/min between 40 and 200°C and 40 ml/min of nitrogen flow with an empty aluminum crucible as reference pan. Results are shown in [fig. 3**]**.

Formulation of granules by conventional wet granulation method

The granules were formulated by using formula shown in [Table 1**]**. Active ingredient simvastatin, diluents lactose except lubricant magnesium stearate and glidant colloidal silicon dioxide were mixed properly on a laboratory scale for 15 minutes. Then water with PVP as the binder solution was slowly added to above material and mixed well to get a uniform wet mass that was passed through mesh number 22. These granules were then dried in an oven (Thermolab, Japan) at 45°C to 60°C for 1 hour. The dried granules were then passed through mesh number 44. The dried granules were lubricated with magnesium stearate and aerosil by trigonal mixing in polythene bag. Sodium starch glycolate, and crosspovidone were added extra granularly. The above granules were compressed into tablets by tablet punching machine (shiv pharma, engineers, Ahmadabad. EBC- 1974, India) using 7 mm punch.

Table 1: Formula for reverse wet granules and conventional wet granules

Formulation Code	Drug (mg)	PVP (mg)	SSG (mg)	Crospovidone (mg)	Lactose (mg)	Magnesium stearate (mg)	Aerosil (mg)	Total (mg)
W_1/ R_1	20	5	5	-	140	1.25	0.5	170
W_2/ R_2	20	5	7	-	138	1.25	0.5	170
W_3/R_3	20	5	10	-	135	1.25	0.5	170
W_4/R_4	20	5	-	5	140	1.25	0.5	170
W_5/R_5	20	5	-	7	138	1.25	0.5	170
W_6/R_6	20	5	-	10	135	1.25	0.5	170
W_7/R_7	20	10	5	-	135	1.25	0.5	170
W_8/R_8	20	10	7	-	133	1.25	0.5	170
W_9/R_9	20	10	10	-	130	1.25	0.5	170
W_{10}/R_{10}	20	10	-	5	135	1.25	0.5	170
W_{11}/R_{11}	20	10	-	7	133	1.25	0.5	170
W_{12}/R_{12}	20	10	-	10	130	1.25	0.5	170

Formulation development by reverse wet granulation

The reverse wet granules were formulated by using a same formula mention in the above [Table 1], by changing the granulation method. PVP was dissolved in water to form polymer slurry. Simvastatin was added into the above polymer solution to form a drug - polymer solution. Lactose was then added into above drug-polymer solution to form dump mass. The resulted dump mass was then passed through mesh no. 22.

The resulted granules were dried in an oven at 45°C to 60°C. The dried granules were passed through mesh no. 44 to get uniform size distribution. Sodium starch glycolate was added extra granularly. The dried granules were lubricated with a magnesium stearate and aerosil by trigonal mixing in a polythene bag. Above granules were then compressed into tablets by using 7 mm punch.

Evaluation of granules of conventional wet granulation and reverse wet granulation

Flow properties of granules [8].

Bulk and tapped density

To determine bulk density and tapped bulk density 5 gm simvastatin granules of both formulations were introduced into a 10 ml measuring cylinder. Initial volume was measured as bulk volume; the cylinder was tapped for tapped volume. The tapping was continued until no further change in volume was noted. Bulk density and tapped density were calculated using the following formulas.

$$\text{Bulk density} = \frac{\text{Mass of Granules}}{\text{Volume of Granules before tapping}} \quad (1)$$

$$\text{Tapped density} = \frac{\text{Mass of Granules}}{\text{Volume of Granules after tapping}} \quad (2)$$

Compressibility index

Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials. The following formula was used to calculate compressibility index.

$$\%\ Compressibility\ Index = \left[1 - \frac{V}{V_0}\right] \times 100\ (3)$$

Where V and V_o are the volumes of the sample after and before the standard tapping respectively.

Angle of repose (θ)

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. Angle of repose of simvastatin granules was determined by the fixed funnel method. The granules were poured from a funnel on vibration free base. The granules were poured with the help of spatula until a hip of particular height was formed. The angle of repose was determined by measuring the height and diameter of the cone of granules and calculated from the following equation.

$\tan \theta = h/r$ (4)

Where, h = height of the heap of powder, r = radius of the base of the powder cone

Hausners ratio

It measures the compressibility of the powder. Powder with poor flow there is a greater difference between bulk and tapped density, this difference is measured by Hausners ratio, it was calculated by using the following formula:

Hausners ratio = tapped density / bulk density (5)

Solubility of granules compared with pure drug

The Granules equivalent to 20mg of drug of both conventional and reverse wet granulation were weighed and dissolved in 25 ml of distilled water in a conical flask. The above solutions were placed in shaking incubator (Remi, DGS- 2, India) for 24 hours at 37°C. Then these solutions were filtered through whatman filter paper and solutions were analyzed by UV (Shimadzu 2401pc, Japan) at 238 nm.

Evaluation of tablets of conventional wet and reverse wet granulation

Tablet thickness and diameter are important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers (Basto). The resistance of tablets to shipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by the Monsanto hardness tester (cadmach India). Friability is the measure of tablet strength. Roche type friabilator (Remi electronics, India) was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 RPM dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined. If the percent loss is more than 1%, then it fails the friability test.

$$\% \text{ loss} = \frac{\text{Initial wt. Of tablets} - \text{Final wt. Of tablets}}{\text{Initial wt. Of tablets}} \times 100 \quad (6)$$

Uniformity of weight was determined as per I. P by using 20 tablets which were selected randomly. Weight variation was calculated and compared with I. P. Standards**.** Uniformity of content was determined as per me. P. Twenty tablets were weighed and grounded into a fine powder. Powder equivalent to the weight of one tablet API was dissolved in methanol by ultra-sonication (Selec dtc 5033, Japan). Then the resultant solution was filtered through Whatman filter paper. Then suitable dilutions were made and Drug content was calculated by using a UV spectrophotometer at wavelength 238 nm.

Wetting time

Tablet wetting time is an important parameter which gives information about disintegration properties of tablet. Piece of tissue paper was folded twice and placed in a petri plate containing 10 mL of water with an Amaranth dying as a coloring agent. The tablet was placed on tissue paper in a Petri plate and time taken for complete wetting of the tablet was noted. Three tablets from wet and reverse granulation formulations were selected and the average time was calculated and consider as a wetting time.

Disintegration test

Disintegration time is one of the important criteria in selecting best formulation. The test was performed by using a USP apparatus (Dt-Kumar Mfg. ltd. Mumbai, India). One tablet was placed in each of the six tubes of the basket and the assembly was placed in 1000 mL beaker containing water maintain at 37± 2°C and operated the apparatus for 15 minutes. The time required for complete disintegration was noted.

In-*vitro* dissolution studies

The release rate of simvastatin tablets of each formulation was determined using USP dissolution testing apparatus II Paddle type (Elecrtolab, EDT- 08Lx, India). The dissolution test was performed using 900 ml of acidic buffer pH 1.2 at 37 ± 0.5°C and 75 rpm. A 5 ml sample solution was withdrawn from the dissolution apparatus for 5 min, 10 min, 15 min, 30 min, 45 min, and 60 min. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analyzed at 238 nm by UV Spectrophotometer. Cumulative percentage drug releases were calculated.

Comparative evaluation of reverse wet granulation with conventional wet granulation and marketed tablet

Tablets of conventional wet granulation and reverse wet granulation were subjected to comparative evaluation of the dissolution test and wetting time.

Statistical evaluation

ANOVA test was applied to dissolution data of conventional wet granulation, reverse wet granulation and marketed formulation. t-Test was applied to flow properties of reverse wet granulation and conventional wet granulation. Both tests were calculated by using Primer of biostat.

Comparison of dissolution profile [9]

Dissolution profile comparison is perform under identical conditions for the product before and after the change(s) is recommended. A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Moore 1996).

Using the mean dissolution values for both curves at each time interval, difference factor (f_1) and similarity factor (f_2) was calculated. Dissolution profile is considered to be similar if f_1 values are close to 0 (0 to 15) and f_2 values are close to 100 (50 to 100).

XRD analysis

XRD analysis of granules of reverse and wet formulations was done by using X- ray diffractometer (Rigaku Miniflex) in order to determine the crystalline nature of the formulation**.**

FTIR spectra of final granules

Granules of final formulation were analyzed by using FTIR.

RESULTS AND DISCUSSION

FTIR spectra of simvastatin

The FTIR absorption spectrum of drug is shown in [fig. 2**]**. FTIR spectrum of simvastatin showed all the peaks corresponding to the functional groups present in the structure of Simvastatin. 3549 for O-H stretch, 1706 for C=O stretch, 2955 for C-H stretch, and 1465 for C-H bending.

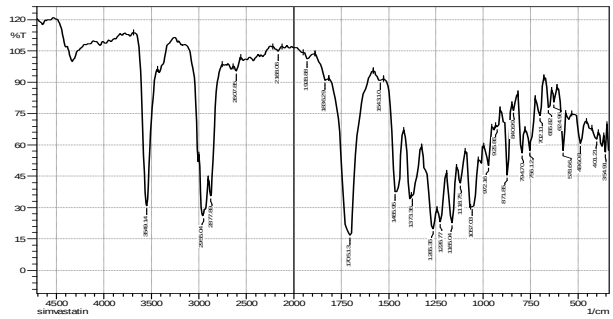

Fig. 2: IR spectrum of pure Simvastatin

Differential scanning calorimetry studies

The DSC thermogram of pure simvastatin exhibited a single sharp endothermic peak at 139°C corresponding to its melting transition temperature as shown in [fig. 3**]**.

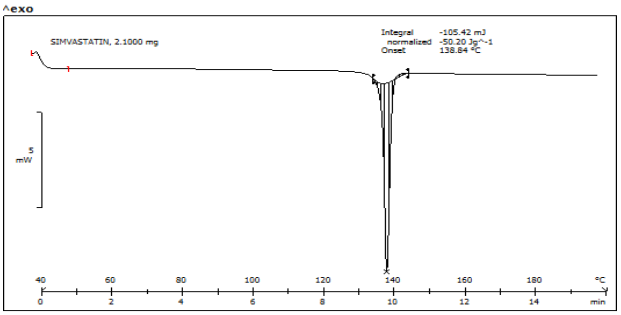

Fig. 3: DSC thermogram of simvastatin

Selection of drug concentration

Drug concentration was selected on the basis of marketed tablet strength.

Selection of polymer

In the present study polyvinyl pyrrolidone (20mg) was selected as a binder as per the literature survey and its ability to enhance the solubility of poorly water soluble drugs.

Selection of polymer concentration

The solubility of simvastatin in water was found to be 4.8µg/ml. Solubility studies of Simvastatin confirmed the solubility-enhancement capabilities of Povidone K-30. The aqueous solubility of simvastatin increases with increase in concentration of Povidone as shown in [Table 2]. Maximum solubility was observed with 10mg Povidone. But in case of 15mg povidone solubility was observed to be decreased, this could be due to maximum concentration of Povidone which might have lowered the solubility. T1 and T2 concentration was selected for further granulation.

Flow properties of conventional wet granulation

The granules prepared by conventional wet granulation showed variability in flow properties between different formulations as shown in table 3. Optimized formula was selected on the basis of flow properties of granules. Formulation W_1 to W_6 showed poor flow properties as compared to that of W_7 to W_{12}. Formulation W_7 to W_{12} showed enhanced flow properties, this could be due to a sufficient quantity of binder might have modified the surface roughness of granules thus affecting flow properties. Formulation W_9 showed maximum flowability and it was evidenced by low values of Carr's index, Hausner's ratio, and angle of repose and it was selected for further study.

Flow properties of reverse wet granules

The granules prepared by reverse wet granulation have showed variability in the flow properties of the granules of different formulas as shown in Table 4. Formulations R1 to R6 have poor flow behavior as compared to R_7 to R_{12}. This could be due to sufficient concentration of binder might have modified flow properties of R_7 to R_{12} formulations. Optimized formulation was selected on the basis of Flow properties of the granules. Formulation R_9 showed enhanced flow properties when compared with other formulation this could be due to polymer which may have enhanced the surface roughness of granules. From the evaluation of flow properties of conventional wet granules and reverse wet granules showed that reverse wet granules has enhanced flow properties when compared with conventional wet granules this result could be attributed due to the method of formulation.

Table 2: Selection of polymer concentration

Formulation code	Drug (mg)	PVP (mg)	Solubility (µg/ml)
	20	-	4.859
T_1	20	5	26.64
T_2	20	10	30.01
T_3	20	15	23.62

Table 3: Flow properties of Conventional wet granules

Formulation code	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index	Hausner's ratio	Angle of repose
W_1	0.7735±0.010	0.8418±0.012	8.1±0.58	1.08±0.010	23.59±1.03
W_2	0.7352±0.013	0.8559±0.013	14.10±0.68	1.16±0.012	23.66±1.02
W_3	0.7408±0.012	0.9055±0.013	18.1±0.57	1.22±0.010	23.44±1.05
W_4	0.7626±0.013	0.8523±0.012	10.5±0.54	1.11±0.014	23.31±1.04
W_5	0.7754±0.010	0.8552±0.010	9.33±0.65	1.10±0.013	23.42±1.05
W_6	0.7554±0.012	0.8543±0.013	11.57±0.54	1.13±0.012	23.63±1.02
W_7	0.7745±0.010	0.8278±0.012	5.42±0.67	1.07±0.013	21.98±1.06
W_8	0.7897±0.012	0.8747±0.013	9.71±0.66	1.10±0.012	21.64±1.05
W_9	0.7735±0.014	0.8178±0.012	5.41±0.81	1.05±0.014	21.34±1.04
W_{10}	0.7053±0.011	0.8075±0.010	6.80±0.51	1.14±0.011	23.68±1.02
W_{11}	0.7553±0.013	0.8078±0.013	6.49±0.86	1.06±0.013	22.98±1.05
W_{12}	0.7703±0.014	0.8108±0.012	5.99±0.76	1.05±0.013	22.48±1.06

Table 4: Precompression evaluation of reverse wet granules

Formulation code	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hausner's ratio	Angle of repose
R_1	0.7965±0.010	0.8549±0.010	7.6 ±0.58	1.07±0.010	22.16±1.04
R_2	0.7769 ±0.011	0.8417±0.011	7.8 ±0.68	1.08±0.012	22.49±1.08
R_3	0.7432±0.032	0.8425±0.032	11.7±0.47	1.13±0.010	22.31±1.05
R_4	0.7612±0.014	0.8314±0.014	8.4 ±0.34	1.09±0.014	23.41±1.09
R_5	0.7553±0.010	0.8436±0.010	10.46±0.65	1.11±0.013	24.25±1.05
R_6	0.7514±0.013	0.8424±0.013	10.80±0.54	1.12±0.012	22.61±1.05
R_7	0.7815±0.012	0.88419±0.012	7.1±0.67	1.07±0.013	23.96±1.07
R_8	0.7925±0.011	0.88445±0.011	6.1±0.66	1.06±0.012	22.63±1.05
R_9	0.7734±0.014	0.7950±0.012	2.70±0.81	1.01±0.014	19.23±1.04
R_{10}	0.7645±0.011	0.8406±0.010	9.05±0.41	1.09±0.011	24.86±1.06
R_{11}	0.78313±0.023	0.8409±0.023	6.8±0.86	1.07±0.013	22.91±1.08
R_{12}	0.7642±0.016	0.8808±0.012	13.87±0.76	1.15±0.013	21.63±1.05

Solubility of granules

The solubility of plane drug simvastatin is shown in [Table 5].

The Solubility study showed that reverse wet granules has enhanced more solubility as compared to conventional wet granules as shown in [Table 6]. This could be due to uniform wetting of drug in reverse

wet granulation in which drug is intimately associated with polymer as compared to conventional wet granulation where poor intimate contact between drug and polymer results in inadequate wetting and thereby less solubility. The solubility could also be enhanced as the drug is uniformly distributed in a polymer matrix, leaving drug in micronized form of the medium, which ultimately results in a decrease in particle size to increase in its surface area and thereby increase in solubility. Formulation W_9 and R_9 showed maximum solubility as compared to others and these were selected for further evaluation.

Table 5: Solubility of pure drug Simvastatin

Simvastatin (mg)	(mg/ml)
20mg	0.052

Table 6: Solubility of conventional wet and reverse wet granulation

Formulation code Conventional wet granulation	Solubility (mg/ml)	Formulation code reverse wet granulation	Solubility (mg/ml)
W_1	2.35±0.23	R_1	3.26±0.21
W_2	3.25±0.25	R_2	4.25±0.32
W_3	3.52±0.13	R_3	3.62±0.58
W_4	3.12±0.35	R_4	4.13±0.41
W_5	3.58±0.14	R_5	4.16±0.27
W_6	4.12±0.10	R_6	5.65±0.45
W_7	6.56±0.25	R_7	7.23±0.56
W_8	6.89±0.27	R_8	7.56±024
W_9	**6.96±0.34**	**R_9**	**8.75±0.42**
W_{10}	6.58±0.14	R_{10}	6.75±0.54
W_{11}	6.22±0.16	R_{11}	7.60±0.55
W_{12}	6.53±0.30	R_{12}	7.66±0.55

Table 7: Tablet size and thickness

Conventional wet granulation			Reverse wet granulation		
Formulation code	Thickness (mm)	Diameter (mm)	Formulation code	Thickness (mm)	Diameter (mm)
W_1	3.4±0.005	2.8±0.005	R_1	3.4±0.005	2.8±0.005
W_2	3.4±0.005	2.8±0.005	R_2	3.4±0.005	2.8±0.005
W_3	3.4±0.005	2.8±0.005	R_3	3.4±0.005	2.8±0.005
W_4	3.4±0.005	2.8±0.005	R_4	3.4±0.005	2.8±0.005
W_5	3.4±0.005	2.8±0.005	R_5	3.4±0.005	2.8±0.005
W_6	3.4±0.005	2.8±0.005	R_6	3.4±0.005	2.8±0.005
W_7	3.4±0.005	2.8±0.005	R_7	3.4±0.005	2.8±0.005
W_8	3.4±0.005	2.8±0.005	R_8	3.4±0.005	2.8±0.005
W_9	**3.4±0.005**	**2.8±0.005**	**R_9**	**3.4±0.005**	**2.8±0.005**
W_{10}	3.4±0.005	2.8±0.005	R_{10}	3.4±0.005	2.8±0.005
W_{11}	3.4±0.005	2.8±0.005	R_{11}	3.4±0.005	2.8±0.005
W_{12}	3.4±0.005	2.8±0.005	R_{12}	3.4±0.005	2.8±0.005

Table 8: Tablet evaluations

Conventional wet granulation				Reverse wet granulation			
Code No.	Hardness (Kg/cm^2)	% friability	Wetting time (Second)	Code No.	Hardness (Kg/cm^2)	% friability	Wetting time (Second)
W_1	3±0.577	0.23±0.02	86.23±0.2	R_1	4±0.455	0.23±0.03	72.23±0.2
W_2	3±0.544	0.25±0.02	79.65±0.3	R_2	3±0.465	0.12±0.03	73.42±0.5
W_3	4±0.56	0.17±0.02	75.23±0.3	R_3	4±0.435	0.18±0.02	71.13±0.6
W_4	3±0.46	0.12±0.03	88.26±0.1	R_4	4±0.355	0.24±0.02	74.25±0.2
W_5	3±0.46	0.25±0.03	84.23±0.3	R_5	5±0.475	0.17±0.02	70.21±0.2
W_6	3±0.58	0.23±0.02	76.35±0.4	R_6	3±0.475	0.32±0.03	70.14±0.3
W_7	4±0.58	0.17±0.02	66.23±0.2	R_7	6±0.524	0.20±0.03	62.23±0.2
W_8	6±0.54	0.15±0.03	64.45±0.2	R_8	7±0.567	0.21±0.03	61.20±0.5
W_9	6±0.53	0.23±0.03	63.46±0.1	R_9	6±0.534	0.12±0.02	59.65±0.3
W_{10}	6±0.52	0.25±0.02	73.86±0.4	R_{10}	8±0.423	0.14±0.02	70.62±0.1
W_{11}	6±0.59	0.12±0.03	72.76±0.3	R_{11}	6±0.412	0.16±0.03	69.11±0.3
W_{12}	6±0.54	0.14±0.02	74.23±0.2	R_{12}	7±0.419	0.23±0.02	71.36±0.5

Tablet size and thickness

Tablet size and thickness was measured by Vernier caliber are shown in [Table 7]. Every measurement was performed in triplicate.

Tablet hardness, friability, and wetting time

The tablets of both formulations were evaluated for hardness, % friability and wetting time as shown in [Table 8]. Tablets of W_1 to W_6 and R_1 to R_6 were unable to maintain the required hardness, this

could be due to less concentration of binder PVP which was only 2.9% of the tablet weight. Tablets of W_7 to W_{12} and R_7 to R_{12} able to maintain sufficient hardness this could be due to high concentration of binder which was 5.8% of total tablet weight. The percentage weight loss of tablets was less than 1%, which passes the friability test as per IP.

The W_7 to W_{12} and R_7 to R_{12} showed less wetting time this could be due increased concentration of disintegrants. The W_9 and R_9 formulation showed rapid wetting than other this could be due to the presence of SSG might have improved more porosity as compared to crospovidone. The results showed that tablet produced by reverse wet granulation wet rapidly as compared to tablet produced by conventional wet granulation. This may be resulted from a uniform distribution of binder in granules or uniform particle shape of granules making more space available for capillary action. Formulation W_9 and R_9 showed less wetting time as compared to other formulation. These formulations were selected for further study.

Uniformity of weight and uniformity of contents

Tablets of reverse wet granulation and conventional wet granulation passes the test of the uniformity of weight and uniformity of content as per IP. Results are shown in [Table 9].

Table 9: Uniformity of weight and uniformity of contents

Conventional wet granulation			Reverse wet granulation		
Code No.	**Uniformity of weight (mg)**	**Uniformity of content (%)**	**Code No.**	**Uniformity of weight (mg)**	**Uniformity of content (%)**
W_1	171±0.02	101.85±0.2	R_1	172±0.03	101.23±0.2
W_2	170±0.02	102.65±0.3	R_2	171±0.03	103.42±0.5
W_3	173±0.02	100.23±0.3	R_3	170±0.02	100.13±0.6
W_4	170±0.03	102.26±0.1	R_4	172±0.02	102.25±0.2
W_5	171±0.03	103.23±0.3	R_5	173±0.02	101.21±0.2
W_6	170±0.02	102.35±0.4	R_6	170±0.03	100.14±0.3
W_7	170±0.02	104.23±0.2	R_7	170±0.03	102.23±0.2
W_8	170±0.03	103.45±0.2	R_8	171±0.03	101.20±0.5
W_9	170±0.03	101.46±0.1	R_9	170±0.02	102.65±0.3
W_{10}	169±0.02	102.86±0.4	R_{10}	171±0.02	103.62±0.1
W_{11}	170±0.03	101.76±0.3	R_{11}	169±0.03	102.11±0.3
W_{12}	170±0.02	100.23±0.2	R_{12}	171±0.02	102.36±0.5

Table 10: Disintegration Time

Conventional wet granulation		Reverse wet granulation	
Formulation code	**Disintegration time (Minutes)**	**Formulation code**	**Disintegration time (Minutes)**
W_1	5.15±0.32	R_1	5.11±0.02
W_2	5.26±0.34	R_2	5.22±0.03
W_3	5.06±0.35	R_3	4.76±0.02
W_4	5.61±0.32	R_4	4.48±0.03
W_5	5.67±0.31	R_5	4.30±0.32
W_6	4.45±0.36	R_6	4.19±0.02
W_7	4.36±0.30	R_7	3.75±0.03
W_8	4.26±0.31	R_8	3.69±0.02
W_9	**3.61±0.32**	**R_9**	**3.15±0.03**
W_{10}	4.88±0.32	R_{10}	4.72±0.02
W_{11}	4.76±0.31	R_{11}	4.78±0.02
W_{12}	4.65±0.32	R_{12}	4.15±0.03

Disintegration test

All batches of reverse wet granulation and conventional wet granulation were evaluated in disintegration test. The results are shown in [Table 10]. The disintegration time decreases with increase in concentration of superdisintegrants. Disintegration time was found to be decreased with SSG as compared to Crosspovidone. Batch R_9 and W_9 showed the less disintegration time as compared to other batches and therefore these formulations were selected for further study.

Dissolution study

Dissolution study of conventional wet granulation

The Simvastatin tablets of conventional wet granulation were subjected to *in-vitro* dissolution study. The *in-vitro* dissolution profile of tablets in acidic buffer is shown in the [fig. 4]. Conventional wet granulation tablets of formulas W_1 to W_6 showed lower dissolution rate 13.46±0.30, 14.18±0.25, and 14.72±0.12, 16.18±0.23, 20.32±0.02 and 25.52±0.14% respectively. This could be due to less concentration of polymer which couldn't have increased its solubility as compared to W_7 to W_{12}. The W_7 to W_{12} batches showed enhanced dissolution 34.68±0.21, 34.71±0.13, 35.85±0.22, 32.76±0.24, and 32.46±0.12 and 31.33±0.32% respectively. This could be due to sufficient concentration of polymer. From dissolution study W_7 to W_9 formulation containing SSG as a super disintegrants showed improved dissolution, than other formulations. And W_9 formulation showed more dissolution than other formulations. This formulation was selected for further evaluations.

Dissolution study of reverse wet granulation

The Simvastatin tablets of reverse wet granulation were subjected to *in-vitro* dissolution study. The results are shown in [fig. 5]. The cumulative percent drug release from formulation R_1 to R_6 was found to be 24.51±0.12, 25.76±0.16, 28.85±0.24, 29.22±0.11, 32.65±0.32 and 39.20±0.21%, respectively, while from R_7 to R_{12} was found to be 47.88±0.02, 48±0.24, 52.92±0.21, 45.23±0.11, 46.52±0.16 and 44.60±0.15% respectively. From the dissolution study it was observed that all tablets formulated by using reverse wet granulation with same excipients as conventional wet granulation, but differ in the method of preparation showed enhanced dissolution as compared to tablets prepared by conventional wet granulation method. This could be due to uniform wetting of drug in reverse wet granulation as compared to

conventional wet granulation, where inadequate wetting take place due to inadequate contact in between drug and hydrophilic polymer. Tablet with R_9 formulation showed more dissolution than W_9 formulation having the same composition which vary by method of preparation. R_9 formulation was selected for further study.

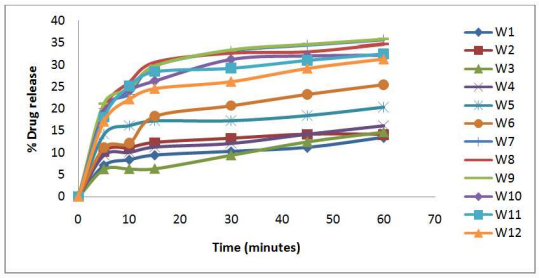

Fig. 4: Dissolution graph of conventional wet granulation

Wetting time

Tablet wetting time is an important parameter which gives disintegration properties of tablet. The results showed that tablet produced by reverse wet granulation wet rapidly as compared to tablet produced by conventional wet granulation as shown in [Table 11]. This could be resulted from a uniform distribution of binder in granules or uniform particle shape of granules making more space available for capillary action

Dissolution studies

The dissolution release profiles of simvastatin tablets produced by conventional wet granulation and reverse wet granulation are depicted in the [Table 12] and [fig. 6]. The result showed that the Tablets produced by reverse wet granulation has higher dissolution rate as compared to tablets produced by conventional wet granulation and marketed simvastatin generic tablet Simcard 20mg when tested for 60 minutes. This could be due to uniform wetting of an API in the binder solution which has increased wetting ability of the drug and due to method of preparation. Dissolution of reverse wet granulation showed 1.4 fold increase in dissolution as compared to conventional wet granulation.

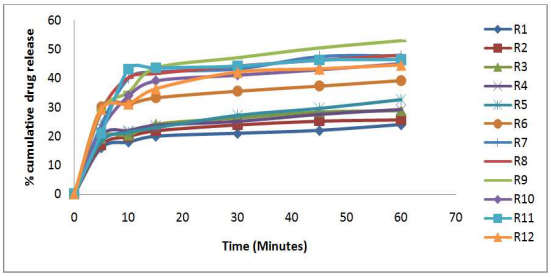

Fig. 5: Dissolution graph of reverse wet granulation

Comparative evaluation of reverse wet granulation with conventional wet granulation and marketed tablet

Table 11: Wetting time of tablets

Formulation	Wetting time in water (second)
Reverse wet granulation	58.75±2.83
Conventional wet granulation	65.48±1.85
Marketed formulation	61.30±1.20

Table 12: Dissolution study

	Cumulative % drug release		
Time (minutes)	Wet granulation	Reverse granulation	Marketed formulation
5	21	29.59	23
10	23.23	35.25	28.24
15	29.85	43.74	30.58
30	34.39	47.56	34.41
45	34.59	50.49	34.75
60	36	52.92	37.38

Table 13: Carr's index

Group	N	Mean	SD	SEM	95% CI for difference	t value	DF	P
1	3	5.373	0.1124	0.06491	2.495 to 3.185	35.408	2	*0.001
2	3	2.533	0.1527	0.08819				
Difference		2.84	0.1389	0.08021				

Table 14: Hausners ratio

Group	N	Mean	SD	SEM	95% CI for difference	t value	DF	P
1	3	1.247	0.09504	0.005487	0.01549 to 0.4822	4.335	2	**0.05
2	3	1.013	0.005778	0.003336				
Difference		0.2333	0.1002	0.1002				

Table 15: Angle of repose

Group	N	Mean	SD	SEM	95% CI for difference	t value	DF	P
1	3	21.55	0.7401	0.3022	1.159 to 3.717	4.9	5	**0.01
2	3	19.11	0.9661	0.3944				
Difference		2.438	1.219	0.4976				

Table 16: Similarity and dissolution factor

Formulation	Similarity factor (F_2)	Difference factor (F_1)
Wet and reverse	43	45
Marketed and reverse	46	37
Wet and marketed	79	6

Table 17: ANOVA table

Source of variation	Sum of square	DF	Variance Est. (MS)	F	P
Between group	657	2	328.5		
Within group	747.5	15	49.83	6.59	0.009
Total	1405	17			

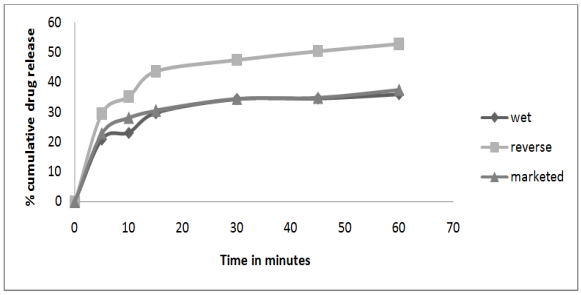

Fig. 6: Dissolution graph

Statistical Evaluations

t- Test

t- Test was applied to evaluate the statistical significant difference between the flow properties of reverse and wet granules**.** The results are depicted as follows.

Carr's index

From observed t-statistic calculated t = 35.408> tabulated t = 31.61. The P value is less than *0.05, it indicates that there is a statistically significant difference between the reverse and wet granules Carr's index. The result is shown in [Table 13].

Hausners ratio

From observed t – statistics calculated t = 4.335 > tabulated t = 4.303 and a P value is *0. 05, it indicates that there is statistically significant difference between reverse and wet granules Hausners ratio. The result is shown in [Table 14].

Angle of repose

From observed t- statistics calculated t = 4.9 > tabulated t = 4.03 and a P value is less than *0. 05, it indicates that there exists a statistically significant difference between reverse and wet granules angle of repose. The result is shown in [Table 15].

Comparison of dissolution profile

A dissolution profile comparison was performed under identical conditions showed that there exists no similarity among tablets prepared by reverse wet granulation and conventional wet granulation as F_2 is 43 and F_1 is 45 and marketed tablet formulation and reverse wet granulation as F_2 is 46 and F_1 is 37. This showed that the tablets prepared by reverse wet granulation have a different dissolution profile which has enhanced its dissolution rate. Tablets prepared by conventional wet granulation have some of the same dissolution profiles with marketed formulation. The result is shown in [Table 16].

Analysis of variance

ANOVA test was calculated by using a software Primer of biostat. It was found that F- value was found to be 6.39 at DF (2, 15) by referring F- distribution table, which is less than the calculated f-value 6.59. Calculated P- value was found to be **0.001 which is less than *0.05. The result showed that there exists a significant difference between dissolution profiles of three formulations. Multiple comparisons Dunnett test was applied, which showed that the dissolution profile of reverse wet granulation was different from dissolution of both conventional wet granulation and marketed formulation. The result is shown in [Table 17].

X- ray diffraction study

From X- ray diffraction studies, the characteristic peaks of the simvastatin in the 2θ range of 10° to 40° indicated that the pure simvastatin was in crystalline nature as shown in [fig. 6]. The sample of conventional wet and reverse granulation showed similar peak position (2θ) in X- ray diffraction as shown in fig. 7 and 8. However, relative intensities of XRD peaks were modified. The relative intensities of conventional wet granulation and reverse wet granulation were reduced to nearly half than that of pure drugs. The X- ray diffraction pattern of granulates of both formulations showed reduction in peak height and peak intensities. The reverse wet granules showed more reduction in peak height and peaks were more diffused as compared to conventional wet granulation which exhibit that reverse wet granulation method reduced the crystallinity of the drug more than conventional wet granulation. This could be due to more uniform wetting of a drug by polymer in reverse wet granulation when compared to conventional wet granulation where inadequate distribution of the drug and polymer leads to inadequate wetting. This proves decreased in crystallinity of Simvastatin as some of drug converted into amorphous form during conventional wet and reverse wet granulation has resulted in improved compression characteristics of poorly compressible drug Simvastatin which resulted in improved tabbleting properties. As the crystallinity of drug decreased its surface area exposed to dissolution media also increases and thereby its solubility and dissolution increased.

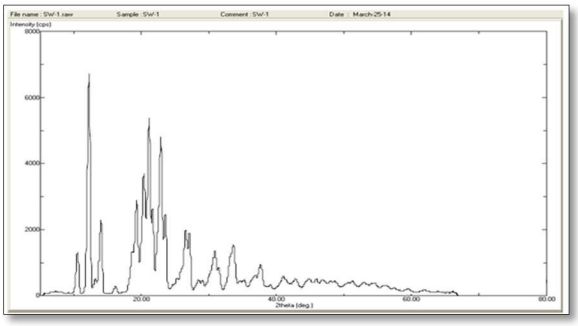

Fig. 7: XRD of pure simvastatin

Fourier Transform Infra-Red Spectroscopy of final granulation

Interaction between drug-polymer was studied by infrared spectroscopy by finding any change in frequency of functional group

in reverse and wet granulation with respective functional groups of simvastatin. The IR spectrum physical mixture of simvastatin and conventional wet and reverse wet granulation is shown in [fig. 9]. The spectral observations indicated that the principal IR absorption peaks observed in the spectra of simvastatin were close to those in the spectra of the simvastatin reverse wet and conventional wet granulation.

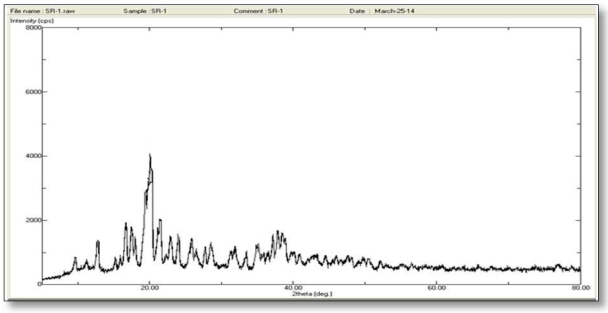

Fig. 8: XRD of reverse wet granules

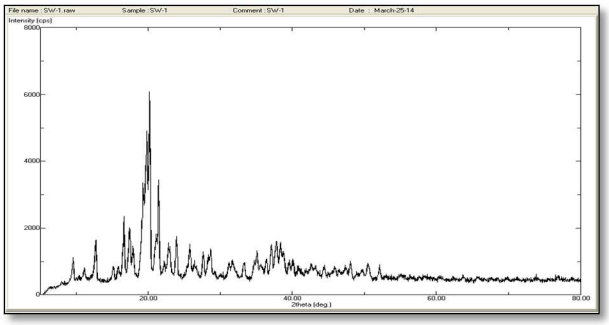

Fig. 9: XRD of conventional wet granules

IR spectra of the drug and granules showed characteristic bands at 3549, 2955, 1659, 1465, 1165 cm^{-1}. All the characteristic picks appear in the granules at nearby wave number indicating no modification or no strong interaction between the all excipients in granulation.

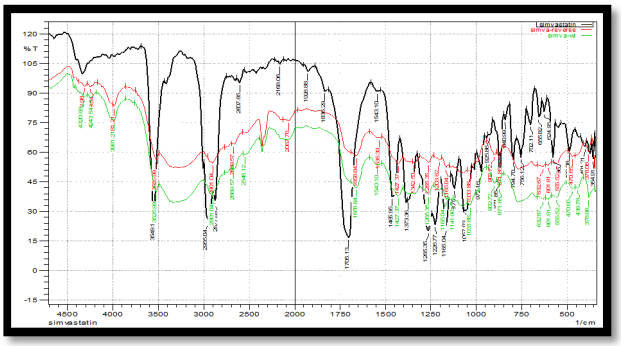

Fig. 10: FTIR of reverse wet granules and conventional wet granules of final formulation

CONCLUSION

PVP K-30 has a potential to be used for the enhancement of solubility and dissolution rate of simvastatin. The reverse wet granulation method with PVP K-30 enhances the solubility and dissolution of simvastatin by converting some of the drug into amorphous form by reducing particle size and increasing its usability. Form flow property evaluations it was observed that the flow properties of granules with the reverse wet granulation method has improved as compared to that of conventional wet granulation this effect could be attributed due to the method of preparation. Wetting time of tablets was found to be decreased in reverse wet granulation when compared with conventional wet granulation due to uniform wetting of drug with polymer. The XRD study indicates more reduction in peak intensity with reverse wet granules when compared to conventional wet granules due to more drug converted into an amorphous form in reverse wet granulation as compared to conventional wet granulation. Statistical evaluation showed that existence of significant difference between flow properties and dissolution profile of reverse wet granulation and conventional wet granulation. The results showed that reverse wet granulation effectively enhances solubility and thereby dissolution of simvastatin. Reverse wet granulation method is easy to adopt.

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CONFLICT OF INTERESTS

Declared None

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