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Research Article

Solubility Improvement and Dissolution Enhancement of Simvastatin using Fluidized Hot-melt Granulation Technique

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ABSTRACT

A fluidized hot melt granulation (FHMG) technique was used to enhance the solubility and dissolution of simvastatin. Employing meltable hydrophilic binders and then converting the melt dispersion into flowable and compressible dispersion granules to yield a rapidly dissolving tablet formulation. Granules prepared by using hydrophilic polymer polyethylene glycol 4000 or 6000, Gelucire 50/13 or 44/14, and Poloxamer 188 or 407, spray-dried lactose as a fluidized substrate. The binder used for spray granulation in this technique was a mixture of molten Gelucire 50/13 and simvastatin. Phase Solubility studies showed an increase in solubility ratio of 1:4 for Simvastatin: Gelucire 50/13. The prepared granules were characterized using FTIR, and DSC spectra exhibited drug excipients compatibility. XRD data exhibited a partial loss of crystallinity as indicated by significantly less intensity of simvastatin peak in a sample than pure simvastatin. Tablets with the faster dissolution of simvastatin (98.99% of the drug release with 30 minutes). This was achieved with lactose/MCC as filler. A significant enhancement *in-vitro* dissolution profile of the melted granules was observed compared to the pure drug and marketed product. Therefore, the results confirmed the high potential of the FHMG technique to produce granules with enhanced drug solubility and release rate.

Introduction

Drugs that belong to class II of the biopharmaceutical classification system (BCS) are characterized by high membrane permeability, slow dissolution rate (due to low aqueous solubility), and high peroral dose. Therefore, solubility or dissolution rate of a drug in this category is a key factor in determining the rate and extent of its absorption. Enhancement of the dissolution rate is vital to attain a suitable blood concentration for therapeutic effect, as their dissolution rates are typically the rate-limiting step for bioavailability. In this context, statin molecules, the well-known competitive and potent inhibitors of 3-hydroxy-3-methlyglutaryl-coenzyme A reductase, are classified as class II drugs.[1] Clinically, statins possess a potent cholesterol-lowering effect and reduce the risk of mortality and morbidity associated with coronary heart disease.[2-3]

This work aimed to study the fluidized bed granulation to improve the solubility and dissolution rate of simvastatin by hot melt method using a mixture of molten hydrophilic binders and simvastatin as a binder and spray-dried lactose as a substrate. The key FHMG factors that were investigated included the nozzle air flow rate, the binder/drug atomization rate, and the total weight of the binder/drug applied to the substrate.

Fluidized hot-melt granulation (FHMG) is still an under-developed process in the pharmaceutical industry. Granules prepared by FHMG technique use a fluidized-bed system only. In melt granulation, mixing with the drug may be performed by spraying the molten binder to the drug powder or by heating both components together.[4-5]

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A significant advantage of FHMG is that used hydrophilic materials/polymers may enhance the solubility and dissolution rate of poorly soluble drug yielding. The hot melt granulation technique is not more widespread in production; the FHMG technique is still at a very low level of development.

Materials and Methods

Materials

Simvastatin was procured from Intas Pharmaceuticals ltd, India. Lactose Monohydrate (Flowlac 100) from Meggle, Avicel PH102 (FMC), Polyplasdone XL10 (Ashland), and Magnesium Stearate was purchased from Ferro Synpro. Gelucire® 50/13 or 44/14 (Gattefosse Ltd, France), Polyethylene glycol 6000 or 4000 (Synth Ltd., Brazil), Poloxamer 407 or 188 (Synth Ltd, Brazil). All other materials used were of analytical grade.

Method

Phase Solubility Study in Different Binders

An excess amount of simvastatin was placed in a screw-cap glass vial to which 20 mL of distilled water containing concentrations (1:4) of Different Meltable binders (Gelucire 50/13 or 44/14, PEG 6000 or 4000, and Poloxamer 407 or 188) was added. The samples were shaken at 37°C for 72 hours on a mini rotary shaker 12R DX (Remi, India). After 72 hours, the samples were filtered through a 0.45 mm membrane filter (Auroco, Thailand). The filtrate was suitably diluted and analyzed at 238 nm by UV Spectrophotometer.

Screening of Drug to Binder Ratio

Fluid bed processing (FBP) (Glatt®-GPCP); Mixtures of meltable binders (Gelucire 50/13 or 44/14, PEG 6000 or 4000 and Poloxamer 407 or 188) in different ratios (1:1,1:2.1:3 and 1:4) along with simvastatin were prepared and kept in a jacketed vessel to obtain the desired temperature of near melting point with continuous heating and stirring. The molten binder and simvastatin were sprayed dropwise from the top over the lactose monohydrate (Flowlac 100) powder loaded in a fluidized bed chamber to prepare granules. The formed granules were then rapidly cooled down to room temperature by fluidization and collected for subsequent micrometrical characterizations.

Preparation of Tablets

Dried granules were sifted through 30# screen using a mechanical sifter and mixed with Avicel PH102 (40#), Polyplasdone XL100 (40#) in a double cone blender for 5 minutes at 10 ± 2 RPM and lubricated with magnesium stearate (60#). The lubricated granules were compressed using a tablet compression machine (RIMEK®) and evaluated for drug release & dissolution profile.

Selection of Appropriate Process Parameters of Fluid Bed Processing (FBP)

The effect of CPPs on product quality (e.g., average granule size) was analyzed and control manufacturing through timely measurements of critical quality and performance attributes of in-process materials, which were modeled out to ensure product quality, as revealed shown in Table 1.

Characterization

Micromeritical Properties

Dispersion granules showing maximum solubility were subjected to measurement of densities (bulk and tap densities), angle of repose, Carr's index, and Hausner's ratio, determined as per standard procedures.

Size Analysis and Drug Content Uniformity

The granule size distribution study carried out using a particle size analyzer (Model: Mastersizer 3000 and Make: Malvern) in the range of 65–1200 µm.

Ten milligrams of melt granules were added to 10 mL of distilled water, heated to 60–70°C, and allowed to cool at room temperature. The lipid was solidified, and the drug solution was filtered through Whatman filter paper no. 1. The samples were analyzed for drug content by UV spectrophotometer (Model: UV 1800 & Make: Shimadzu) at 238 nm after suitable dilution.

Differential Scanning Calorimetry (DSC) Analysis

The DSC measurements were performed on a DSC-60 (Shimadzu, Japan) with a thermal analyzer. All samples (about 1.25 mg of simvastatin or equivalent) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of 10°C/min from 25–250°C. An empty aluminum pan was used as a reference. DSC measurements were also performed for Gelucire 50/13, PM, and formulation to study the drug-polymer interaction.

X-ray diffraction study

X-ray diffraction (XRD) patterns were obtained at room temperature using a X'Pert PRO MPD (PANalytical, the Netherlands) with a Cu anode and a graphite monochromator operated at a voltage of 35 kV and a current of 20 mA. The samples were analyzed in the 2y angle range of 5–501, and the process parameters

Table 1: Selection of appropriate cpp limit parameters

No.	*FBP parameter*	*Limit*
1	Inlet temperature	50 ± 10°C
2	Outlet temperature	40 ± 10°C
3	Product temperature	30 ± 10°C
4	Spraying rate	3 gm/mL
5	Atomization air pressure	2.5 Bar

were set as scan-step size of 0.021 (2y) and scan-step time of 25 seconds.

Fourier Transform Infrared Spectroscopy Study

Simvastatin polymer interactions were assessed by FTIR spectroscopy. FTIR spectra of selected simvastatin and physical mixtures (PM) and formulation were recorded on IRAffinity-1 (Shimadzu, Japan) using KBr discs. The instrument was operated under dry air purge. Scans were collected at a scanning speed of 2 mm/s with a resolution of 4 cm^{-1} over the region 4000–400 cm^{-1}.

In-vitro Dissolution Study

In-vitro dissolution study of simvastatin was performed on USP type-II dissolution test apparatus in 900 mL of pH 7.0 phosphate buffer solution (PBS) with constant temperature 37 ± 0.2°C and speed 50 ± 2 rpm. Aliquots were withdrawn at 10, 20, and 30 minutes time intervals and analyzed by UV-visible spectrophotometric, and percentage release of drug was recorded.

Physical Parameters of Tablet

The prepared tablets were subjected to standard quality control tests. Weight variation was determined by weighing 20 tablets individually. The average weight was calculated, and the percentage variation of each tablet was determined. Hardness was determined by testing 6 tablets from each formulation using an Electrolab digital portable hardness tester EH-01 (Electrolab, India), and the average applied pressure (kg/cm^2) required to crush each tablet was determined. Friability was determined by firstly weighing 10 tablets then placing them in a friability tester EF-2W (Electrolab, India) which was rotated for 4 minutes at 25 rpm. After dusting, the total remaining weight of the tablets was recorded, and the percentage of friability was calculated. The disintegration time for the tablets was determined in 900 mL of distilled water using a programmable tablet disintegration tester ED-2L (Electrolab, India).

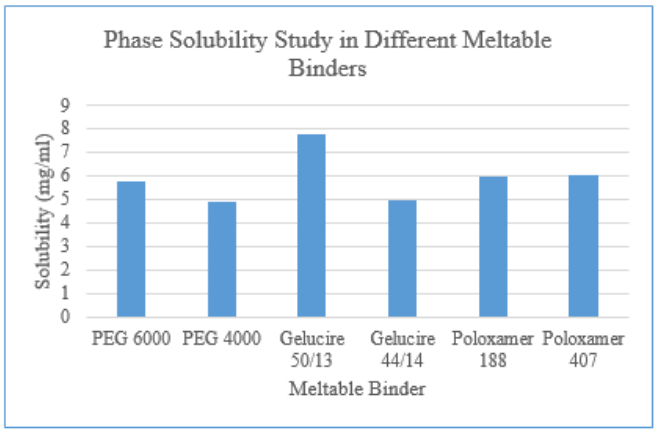

Fig. 1: Phase solubility study in different binders

Stability Study

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and enables recommended storage condition, re-test periods, and shelf life to be established. Stability studies were carried out for optimized formulations. A Formulation was stored at accelerated stability condition 40 ± 2ºC/75 ± 5% RH and 25 ± 2ºC/60 ± 5% RH for an interval of 1, 3, and 6 months. Samples were withdrawn and tested with regards to the parameters i.e., drug content and *in-vitro* drug release.

RESULTS AND DISCUSSION

Phase Solubility Study in Different Binders

The phase-solubility (Fig. 1) determined in distilled water was with respect to the increase in the weight fraction of the Gelucire 50/13 (1:4), indicating the solvent properties of Gelucire 50/13 for simvastatin giving solubility. The greater is the capacity of the polymer to solubilize the drug.

These results agree with the well-established formation of soluble complexes between water-soluble polymeric carriers and poorly water-soluble drugs. Increased solubility may be due to the improved wettability of the simvastatin particles in the aqueous solution of Gelucire 50/13.

Screening of Binder Concentration

Micromeritical Characterization

All tested formulations had a Carr's index ranging from 14.29 ± 0.31% to 28.53 ± 0.98% and the granules obtained from batch F12 showed good micrometrical properties, i.e., Carr's index 14.29 ± 0.31, Hausner's ratio 1.16 ± 0.06, bulk density 0.895 ± 0.301, tapped density 1.044 ± 0.027. Results of the characterization of the granules are shown in Table 2. The granulation using Poloxamer 407 as binder was not possible for two experimental conditions for the experimental design. This was due to the high viscosity of POL in the molten state.

Granules Size Analysis and Drug Content Uniformity Studies

The amount of fine powder (<70µm) and big lumps (size >1200µm) are less than 2 and 6%, respectively which confirmed that the parameters selected were correct. The majority of a fraction of the granules was between the size range of 150–400µm. More than 50% of the granules had a size in the range of 160–240µm. Results are shown in Table 3. The drug content in the prepared melt granules of batches F1 to F20 was determined and found to have 97.58 ± 1.98%w/v showed no or less wastage or deterioration of the drug melt granules formulation, results reported in Table 3.

Table 2: Screening of different binder ratio

Meltable binder	*Batch code*	*Drug:Binder ratio*	*Bulk density (gm/mL)*	*Tapped Density (gm/mL)*	*Hausner's ratio*	*Carr's index (%)*
PEG 6000	F1	1:1	0.455 ± 0.05	0.556 ± 0.05	1.22 ± 0.04	18.20 ± 1.68
	F2	1:2	0.514 ± 0.04	0.597 ± 0.032	1.16 ± 0.09	18.73 ± 0.58
	F3	1:3	0.432 ± 0.04	0.501 ± 0.037	1.15 ± 0.05	19.12 ± 0.64
	F4	1:4	0.517 ± 0.04	0.586 ± 0.038	1.13 ± 0.06	20.09 ± 0.29
PEG 4000	F5	1:1	0.526 ± 0.05	0.735 ± 0.015	1.39 ± 0.08	28.42 ± 0.58
	F6	1:2	0.501 ± 0.01	0.695 ± 0.021	1.38 ± 0.10	28.00 ± 0.89
	F7	1:3	0.538 ± 0.02	0.736 ± 0.034	1.37 ± 0.09	26.88 ± 0.84
	F8	1:4	0.535 ± 0.04	0.731 ± 0.050	1.36 ± 0.04	26.29 ± 0.18
Gelucire 50/13	F9	1:1	0.415 ± 0.048	0.501 ± 0.028	1.20 ± 0.03	17.19 ± 1.01
	F10	1:2	0.501 ± 0.042	0.556 ± 0.045	1.10 ± 0.01	16.52 ± 1.88
	F11	1:3	0.552 ± 0.021	0.652 ± 0.018	1.18 ± 0.05	15.38 ± 0.18
	F12	1:4	0.895 ± 0.301	1.044 ± 0.027	1.16 ± 0.06	14.29 ± 0.31
Gelucire 44/14	F13	1:1	0.524 ± 0.048	0.734 ± 0.025	1.40 ± 0.01	28.53 ± 0.98
	F14	1:2	0.499 ± 0.028	0.693 ± 0.031	1.38 ± 0.08	27.91 ± 1.20
	F15	1:3	0.536 ± 0.034	0.735 ± 0.024	1.37 ± 0.09	26.92 ± 0.18
	F16	1:4	0.534 ± 0.051	0.730 ± 0.040	1.36 ± 0.08	26.38 ± 1.18
Poloxamer 188	F17	1:1	0.669 ± 0.010	0.850 ± 0.028	1.27 ± 0.10	21.33 ± 1.08
	F18	1:2	0.568 ± 0.023	0.704 ± 0.036	1.23 ± 0.07	19.32 ± 0.15
	F19	1:3	0.432 ± 0.045	0.501 ± 0.037	1.15 ± 0.04	19.12 ± 0.64
	F20	1:4	0.517 ± 0.044	0.586 ± 0.038	1.13 ± 0.08	20.28 ± 0.84
Poloxamer 407	F21	1:1				
	F22	1:2	Due to High Viscosity of Molten mixture, didn't spray			
	F23	1:3				
	F24	1:4				

Table 3: Granules size analysis and % drug content

Meltable binder	*Batch code*	*Drug: Binder ratio*	*Granules size distribution D50 (µm)*	*% Drug content*
PEG 6000	F1	1:1	240	95.73 ± 0.98
	F2	1:2	236	96.13 ± 1.87
	F3	1:3	230	97.05 ± 0.42
	F4	1:4	228	96.37 ± 2.10
PEG 4000	F5	1:1	210	94.13 ± 2.15
	F6	1:2	208	97.55 ± 1.48
	F7	1:3	201	96.32 ± 2.36
	F8	1:4	188	96.70 ± 1.45
Gelucire 50/13	F9	1:1	177	95.90 ± 2.48
	F10	1:2	171	96.13 ± 1.64
	F11	1:3	169	97.01 ± 2.33
	F12	1:4	162	97.58 ± 1.98
Gelucire 44/14	F13	1:1	193	95.58 ± 0.41
	F14	1:2	189	96.90 ± 1.33
	F15	1:3	183	96.13 ± 1.98
	F16	1:4	175	95.62 ± 2.10
Poloxamer 188	F17	1:1	198	95.12 ± 1.57
	F18	1:2	206	97.42 ± 1.49
	F19	1:3	219	97.19 ± 1.63
	F20	1:4	225	96.18 ± 1.54

Differential Scanning Calorimetry (DSC) Studies

DSC curves shown in Fig. 2 Simvastatin shows a sharp melting peak 138°C. DSC curve of dispersion at higher proportions of GL 50/13 exhibited no drug endothermic peak. The absence of simvastatin melting endothermic in these samples due to the solubility of the drug in GL 50/13. It is clearly indicating the formation of solid dispersion and drug in the amorphous state.

X-Ray Diffraction (XRD) Studies

The intensity of the peak SIM in PM Dispersion sample shown in Fig. 3 was significantly less than of the pure drug due to partial loss of crystallinity. This suggested that the drug in PM Dispersion is amorphous as compared to the pure drug. Increased dissolution of the drug was observed an amorphous form dissolve at a faster rate than crystalline materials. The amorphous nature of simvastatin in the prepared dispersion granules ratified the solubility enhancement potential of excipients used for the preparation of dispersions granules.

Fourier Transform Infraradiation (FTIR) Studies

All Major Peaks of SIM and Gelucire 50/13 were observed in **Fig. 4** and were retained in Drug: GL 50/13 (1:4) Meltable Mixture, which indicated that no interaction occurred between pure drug and Gelucire 50/13.

In-vitro Dissolution Studies

The dissolution profile of all formulations is shown in Table 4 and Fig. 5. The figure indicated that the melt granules formulation 1:4 of Simvastatin: Gelucire 50/13 (Batch F12) gives a fast dissolution rate 98.99 ± 2.41% in 30 minutes compared to other Meltable binders. The melt granulation technique has improved the dissolution rate of simvastatin to a greater extent.

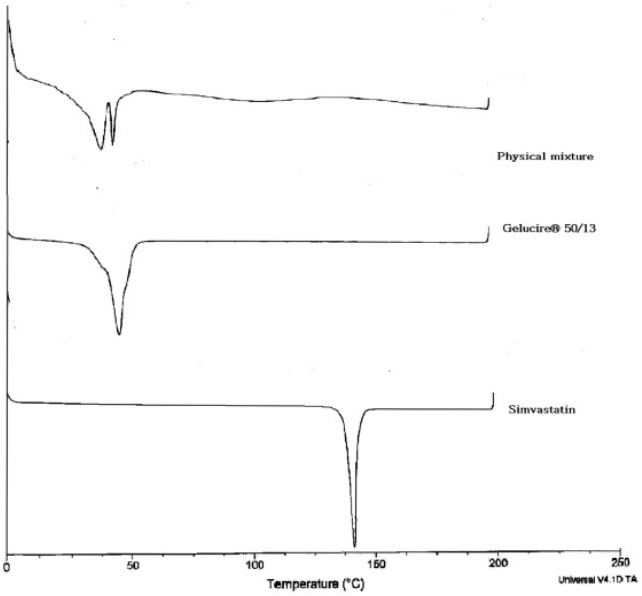

Fig. 2: DSC thermogram of A) Simvastatin B) Gelucire 50/13 C) Physical mixture blend

Physical Parameters of Tablet

Tablets obtained from granules prepared by the FHMG technique have shown faster disintegration time shown in Table 5. Faster disintegration corresponded to the lower hardness of tablet. DT of formulation batch F12 containing Drug: Gelucire 50/13 ratio of 1:4 have shown less than 4 minutes.

The hardness of the tablets was in the range of 8 kg/cm^2 to 15 kg/cm^2. This reveals that Avicel PH102 imparted the required compressibility. Gelucire 50/13 is a waxy material and tends to stick to the punches during compression. This problem was resolved by incorporating magnesium stearate.

Despite the corresponding lower hardness, these tablets were more resistant to mechanical stress, as demonstrated in the friability test. Friability values were

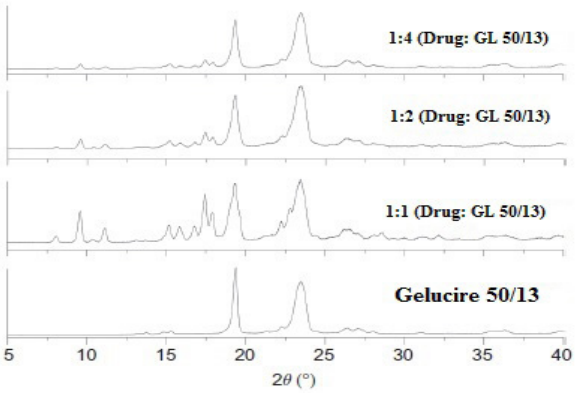

Fig. 3: X-ray diffraction spectra of gelucire 50/13 (A), 1:1 ratio dispersion (B), 1:2 ratio dispersion (C) and 1:4 ratio dispersion (D)

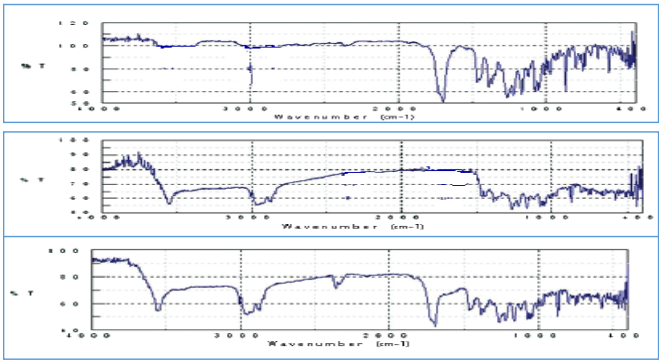

Fig. 4: FTIR of pure drug simvastatin (A), Gelucire 50/13 (B), Drug: GL 50/13 (1:4) Meltable Mixture (C)

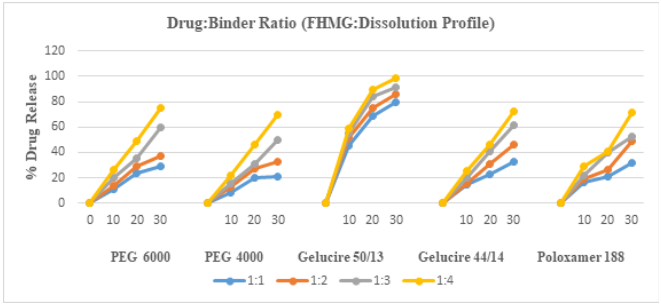

Fig. 5: Dissolution profile of drug: Binder ratio

Table 4: Drug release profile of formulations f1 to f20

Meltable binder	*Batch code*	*Drug: Binder ratio*	*Dissolution (%) in minutes*		
			10	*20*	*30*
PEG 6000	F1	1:1	11.52 ± 1.28	23.84 ± 1.05	29.42 ± 1.25
	F2	1:2	13.74 ± 1.87	29.35 ± 2.13	37.48 ± 1.04
	F3	1:3	20.13 ± 2.30	35.42 ± 2.10	59.98 ± 1.65
	F4	1:4	26.32 ± 2.15	48.98 ± 1.56	75.10 ± 2.01
PEG 4000	F5	1:1	8.12 ± 2.14	19.87 ± 1.04	21.31 ± 1.05
	F6	1:2	12.54 ± 1.55	27.48 ± 1.05	32.58 ± 2.31
	F7	1:3	15.96 ± 1.97	31.25 ± 1.52	49.91 ± 2.54
	F8	1:4	21.67 ± 1.94	45.89 ± 1.01	69.97 ±1.48
Gelucire 50/13	F9	1:1	45.23 ± 1.41	68.73 ± 1.14	79.52 ± 1.87
	F10	1:2	51.39 ± 1.25	75.1 ± 1.49	85.96 ± 2.30
	F11	1:3	55.63 ± 1.40	83.96 ± 1.47	91.42 ± 2.15
	F12	1:4	59.23 ± 1.65	89.52 ± 1.55	98.99 ±2.41
Gelucire 44/14	F13	1:1	15.1 ± 2.01	23.1 ± 1.78	32.98 ± 1.55
	F14	1:2	16.02 ± 2.31	31.26 ± 1.82	46.40 ± 1.94
	F15	1:3	20.15 ± 1.08	41.26 ± 1.15	61.60 ± 2.14
	F16	1:4	25.91 ± 1.84	45.98 ± 1.50	72.58 ± 1.88
Poloxamer 188	F17	1:1	16.21 ± 1.63	20.77 ± 1.23	32.15 ± 1.55
	F18	1:2	19.23 ± 1.86	26.45 ± 1.29	49.10 ± 2.68
	F19	1:3	21.5 ± 1.79	39.65 ± 1.19	52.16 ± 1.36
	F20	1:4	29.51 ± 1.41	41.23 ± 1.51	71.59 ± 1.48

Table 5: Physical parameters of tablet

Meltable binder	*Batch code*	*drug:Binder ratio*	*Hardness (kg/cm^2)*	*Weight (mg)*	*Friability (%)*	*Disintegration time (min)*
PEG 6000	F1	1:1	12 ±2.1	510 ± 0.9	0.191	6.2
	F2	1:2	10 ±1.3	512 ± 1.1	0.195	7.9
	F3	1:3	11 ±1.5	509 ± 0.4	0.201	6.2
	F4	1:4	9 ± 2.7	510 ± 0.6	0.199	5.6
PEG 4000	F5	1:1	15 ± 1.1	512 ± 0.6	0.208	10.8
	F6	1:2	13 ±1.5	514 ± 1.2	0.201	9.1
	F7	1:3	12 ± 1.8	511 ± 1.0	0.204	9.6
	F8	1:4	14 ± 0.9	512 ± 0.8	0.208	7.2
Gelucire 50/13	F9	1:1	10 ± 1.9	508 ± 0.1	0.125	5.0
	F10	1:2	9 ± 1.5	510 ± 0.6	0.128	4.5
	F11	1:3	8 ± 2.1	512 ± 0.8	0.127	4.2
	F12	1:4	8 ± 1.8	514 ± 1.2	0.123	3.9
Gelucire 44/14	F13	1:1	8 ± 2.9	511 ± 1.0	0.341	5.2
	F14	1:2	8 ± 1.9	513 ± 0.6	0.352	5.9
	F15	1:3	9 ± 1.4	510 ± 0.9	0.368	6.0
	F16	1:4	10 ± 1.6	511 ± 0.5	0.354	8.2
Poloxamer 188	F17	1:1	11 ± 2.5	513± 0.9	0.401	5.6
	F18	1:2	12 ± 2.1	516 ± 1.1	0.321	6.2
	F19	1:3	10 ± 1.8	512 ± 0.5	0.358	5.1
	F20	1:4	12 ± 1.6	513 ± 0.7	0.298	7.1

Table 6: Stability studies

	Optimized formulation: Batch F12						
Parameters	*40°C ± 2°C/75 ± 5% RH*				*25°C ± 2°C/60 ± 5% RH*		
Duration	*Initial*	*1M**	*3M*	*6M*	*1M*	*3M*	*6M*
% Drug Content	97.58 ±1.98	96.8 5± 1.08	97.09 ± 1.41	96.91 ± 2.15	97.28 ± 1.14	96.61 ± 1.38	97.10 ± 1.03
Dissolution	% Drug release						
10 min	59.23 ± 1.65#	51.06 ± 1.08	53.46 ± 1.56	58.21 ± 1.37	57.56 ± 1.87	54.08 ± 1.64	52.33 ± 1.71
20 min	89.52 ± 1.55	83.25 ± 1.50	84.76 ± 1.34	87.84 ± 1.49	87.41 ± 1.14	86.89 ± 1.03	84.56 ± 1.19
30 min	98.99 ± 2.41	97.99 ± 2.19	98.19 ± 1.48	98.23 ± 1.02	97.48 ± 2.08	98.48 ± 2.11	98.09 ± 2.38

*M= month, # = n for avg. three reading.

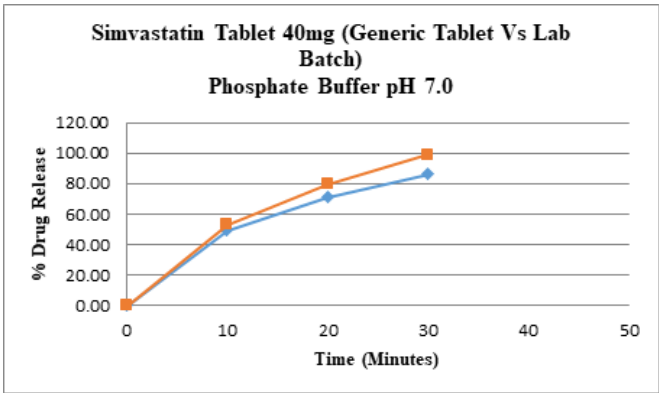

Fig. 6: Comparative in vitro drug dissolution study lab batch (orange line) and marketed sample (blue line)

in the range of 0.1 to 0.4%, which ensured no loss of materials from the surface or edge of tablets. This may be attributed to the waxy nature of Gelucire 50/13. All the formulations passed the weight variation test, which was an indication of good flowability.

Stability Studies

The optimized formulation Batch F12 was evaluated for stability studies as per ICH guidelines at 40°C ± 2°C/ 75 ± 5% RH and 25°C ± 2°C/60 ± 5% RH conditions and monitored for drug content and *in-vitro* drug release study at 1, 3 and 6 months. Table 6 indicated the results of the stability studies revealed no significant variation in drug content uniformity and *in-vitro* drug release profile up to 6 months.

Comparative *In-vitro* drug release profile study

The optimized formulation batch F12 prepared using FHMG technique using Gelucire 50/13 in the drug: binder ratio of 1:4 evaluated for *in-vitro* drug release profile study and compared with generic marketed formulation of a tablet containing 40mg simvastatin using 900 ml of pH 7.0 PBS for 30 min. The drug release rate of simvastatin from optimized formulation batch F12 was 98.99%w/v as compared with 86.23%w/v simvastatin release from marketed 40mg tablet at the end of 30 min shown in Fig. 6 indicated that the optimized formulation could be used to improve the therapeutic effect of simvastatin.

Discussion

The granulation of simvastatin by a fluidized hot melt technique using Gelucire 50/13 as a molten carrier and spray dried lactose as a substrate was demonstrated to be an effective alternative for pharmaceutical application. The process proved to be rapid and reliable, but special care was required to maintain the molten feed at a reproducible temperature. The granule size depended on nebulizing the primary air flow rate. It is easier to produce particles with a specified size. The granules exhibited acceptable flow properties that did not depend on the spray nozzle air flow rate, the molten liquid flow rate or the total weight of Gelucire 50/13 and simvastatin used. The mean size and flowability of the granules were adequate for further tableting. The DSC and FTIR analysis showed that there was no drug interaction during the process. The results of the XPD and SEM analyses showed the presence of simvastatin crystals on the granules. The dissolution profile of simvastatin was remarkably enhanced by granulation. The results confirmed the high potential of the FHMG technique to produce granules with enhanced drug solubility and release rates.

Conclusion

The fluidized hot melt granulation technique can be used to enhance the dissolution of the poorly water-soluble drug simvastatin. Gelucire 50/13 plays a significant role in the enhancement of drug solubility and dissolution. It imparts good flow and compressibility to dispersion granules, improves the dissolution rate by increasing the effective surface area. The ternary dispersion granules can be compressed into tablets without processing problems, which are often associated with the tableting of dispersion granules.

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