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Research Article

Enhancement of Solubility and Dissolution Rate of Simvastatin Tablets by Liquisolid Compact Approach

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Abstract

The aim of the current work was to improve the solubility and dissolution rate of poorly water-soluble drug, simvastatin (SM) by using the liquisolid compact technique (LS; SM-LS). Liquid load factors, and excipient ratios were used to calculate the required amounts of excipients necessary to prepare the SM-LS and compressed to tablets according to mathematical models. Avicel PH102, Aerosil 200 and Crosspovidone (CP) was used as carrier, coating material and disintegrant, respectively. Drug-excipient mixtures were evaluated compatibility by Attenuated total reflectance (ATR) and differential scanning calorimetry (DSC). Prepared SM-LS formulations were evaluated for various pre-compression and post-compressional parameters, in-vitro dissolution, and stability studies (40 ± 2°C / 75 ± 5% RH) for 3 months. Among the different formulations, LS10 formulation which contains 30% drug, 5% CP, Avicel pH 102: Aerosil 200 (1:10) showed 14-folds increase in dissolution rate when compared with pure SM powder. FTIR-ATR and DSC studies confirmed that there was no interaction between the drug and excipients. Further, the LS10 formulation had shown comparable dissolution profile with commercially available tablet formulation. The LS10 formulation showed no significant changes in the physicochemical properties over 3 months during stability studies. Therefore, the SM loaded LS formulation could be considered as an alternative approach to enhance the solubility and dissolution for commercial formulations.

Keywords: Liquisolids compacts, solubility, dissolution, carrier, coating material, stability.

INTRODUCTION

Simvastatin (SM) has been widely used in the treatment of hypercholesterolemia, dyslipidemia, and coronary heart disease. It has lower oral bioavailability[1] (5%), and it classified as class II drug based on Biopharmaceutics Classification System (BCS). SM has poor aqueous solubility and high membrane permeability, subsequently limited dissolution. Therefore, enhanced solubility and dissolution rate, which will ultimately, increases absorption and improvement in oral bioavailability of SM[1].

SM available in the market in various dosage forms, “FLOLIPID®” available as oral suspension by Salerno Pharms, “ZOCOR®” available as oral tablet dosage form. All these dosage forms have challenges for improving bioavailability of SM. Many researchers are attempted to increase an aqueous solubility of SM, such as conversion of crystalline molecule to its amorphous state[20], a particle size reduction via micritization[21], solubilization in surfactant systems[22], co-solvency[23], salt formation[24], and molecular encapsulation with cyclodextrin[25], solid dispersion[4] (SD) and lipid-based drug delivery systems.

Liquisolid compacts (LS) is one of the novel methods to increase the solubility, dissolution and oral bioavailability of poorly water-soluble drugs [5, 26]. The LS preparation mainly consists of solid drug substance is dissolved in non-volatile solvent to form a solution or a suspension[9, 10]. The liquid medicament is absorbed/adsorbed onto a suitable pours solid carrier material. The wet particles are formed and converted into dry particles by the addition of coating material. The liquisolid systems are made into compacts by the addition of other tablet excipients such as lubricants and disintegrants (immediate release) or matrix forming materials (sustained release) may be added to the liquisolid system to produce liquisolid compacts (LS)[7-10].

The Aim of the present study was to improve the solubility and dissolution rate of SM using LS technique. Initially, the SM-LS formulations were prepared and followed by compressed into tablets using suitable excipients. The prepared LS and compressed tables were evaluated for lead formulation based on physicochemical properties. The lead formulation was further evaluated for drug-excipient compatibility, stability and comparative in-vitro dissolution study against commercial formulation.

MATERIALS

SM was received as a gift sample from the Hetero Drugs Ltd., Hyderabad, India. Avicel pH 102, Aerosil 200 and Avicel PH 102 purchased from Himedia, Mumbai, India. Polyethylene glycol (PEG) 200, 400 and 600 were purchased from Millipore sigma, Mumbai, India. Propylene glycol (PG), Tween 20, Tween 80 and glycerol was received as a gifted sample from EMD Millipore, Mumbai, India.

METHODS

Saturation solubility studies

Solubility was performed in selected nonvolatile solvents that is PEG 200, 400, and 600, PG, Tween 20, Tween 80 and glycerol using shake flask method[9]. Excess quantity of SM was added to different selected non-volatile solvents and buffers, and the mixture was vortexed for 10 min in order to facilitate proper mixing of the drug with the vehicles. The mixture was then subjected to shaking on the incubator shaker for 24 h at 25°C. after 24 hours each solution filtered through 1.0 μm filter membrane, then filtered solution concentration was estimated by UV-visible spectrophotometer (Systronics UV-visible double beam 2202) at a wavelength of 239 nm.

Liquid load factor (L_f) for liquisolid blends

It is defined as the ratio of weight of liquid medication (w) to weight of carrier material (Q). It is determined by dissolving or dispersing the drug in non-volatile solvent and to this carrier-coating material admixture is added and blended. The amount of carrier-coating admixture is used to convert into free flow powder, and it is determined by using the following formula.[9-11]

$$L_f = \frac{W}{Q}$$

W= weight of liquid medication, Q= weight of carrier material

It is used to calculate the amount of carrier and coating material in each formulation.

The excipients ratio R of powders is defined as ratio of weight of carrier and coating material present in the formulation. R is suitably selected for successful formulation[13].

$$R = \frac{Q}{q}$$

Q = weight of carrier, q = coating material

Preparation of LS

The SM LS were formulated by mixing and blending process. Chosen non-volatile solvent[18] for the dissolving or dispersing the SM. Avicel PH 102 and Aerosil were used as carrier and coating materials. CP was used as a super disintegrants.

Calculated quantities of solid drug and propylene glycol (PG) were accuracy weighed and transfer into mortar and pestle and kneaded for 15 min to form a homogeneous mixture. Calculated quantities Avicel PH 102 and Aerosil were added to resulting liquid medicament and mixed well. Allow to wait for 30 min to absorb liquid drug in the internal layers of carrier and coating materials. Then pass this mixer through 40 mesh to make uniform sized particles. Then add super disintegrant to it and blend for 5 min. The final mixture blended with magnesium stearate for 5 min. The final blend was compressed into tablets by direct compression technique using embossed C25 concave punches in multi station tablet compression machine (Rimek).

Table 1: Formulation of Simvastatin (SM) liquisolid compacts (LS) compressed tablets

Formulation code	SM (mg)	PG (mg)	Drug concentration in PG (%w/w)	L_f (W/Q)	Avicel pH 102 (mg)	Aerosil (mg)	R (Q/q)	CCS	SSG	CP	Magnesium stearate	Tablet weight (mg)
		W			Q	q		(mg)	(mg)	(mg)	mg	
LS1	20	13.33	60	0.06	233.33	23.33	10	16.66	-	-	1.53	308
LS2	20	13.33		0.06	233.33	46.66	20	16.66	-	-	1.65	332
LS3	20	20	50	0.09	233.33	23.33	10	16.66	-	-	1.57	315
LS4	20	20		0.09	233.33	46.66	20	16.66	-	-	1.68	338
LS5	20	30	40	0.13	233.33	23.33	10	16.66	-	-	1.62	325
LS6	20	30		0.13	233.33	46.66	20	16.66	-	-	1.73	348
LS7	20	46.67	30	0.20	233.33	23.33	10	16.66	-	-	1.70	342
LS8	20	46.67		0.20	233.33	46.66	20	16.66	-	-	1.82	365
LS9	20	46.67		0.20	233.33	23.33	10	-	16.66	-	1.70	342
LS 10	20	46.67		0.20	233.33	23.33	10	-	-	16.66	1.70	342

L_f = liquid load factor; W = weight of liquid medication; Q = weight of carrier material; q = weight of the coating material; R = excipient ratio.

Pre-compression parameters

Bulk density (D_b)

The bulk density of the formulated SM liquisolid powder was evaluated using electrolab bulk density apparatus. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a graduated measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by.

$$D_b = \frac{M}{V_b}$$

Where, M - Mass of the powder, V_b – Bulk volume of the powder.

Tapped density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/ml and is given by

$$D_t = \frac{M}{V_t}$$

Where, M - Mass of the powder, V_t – Tapped volume of the powder.

Compressibility index (C.I)

Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flow ability of powder. Carr's index was calculated using following formula.

$$C.I = \frac{(D_t - D_b)100}{D_t}$$

Where, D_t – Tapped density of the powder, D_b – Bulk density of the powder

Hausner ratio

$$\text{Hausner ratio} = \frac{D_t}{D_b} = \frac{V_b}{V_t}$$

Where, D_t – Tapped density of the powder; D_b – Bulk density of the powder

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantity of powder was passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula[16].

$$\tan\theta = \frac{h}{r}$$

Where, h = height of the heap, r = radius of the heap

Post-compression parameters

Hardness

The tablet crushing load, which is the force required to break a tablet into halves by compression. Three tablets were taken from each batch and the hardness was determined using Monsanto hardness tester.

Thickness

The thickness of prepared SM liquisolid compacts (LS) tablets were measured using Vernier calipers.

Friability Test

Twenty tablets were weighed initially ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25rpm for 4mins or 100 revolutions. The tablets were dusted using a soft muslin cloth and reweighed (W_{final}). The friability (F%) was then calculated by the formula given below.

$$\% \text{ friability} = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

***In-vitro* disintegration Test**

On tablet was placed in each of the six tubes of the Disintegrating apparatus (Electro Lab, Hyderabad, India) at 37 ± 2 °C. The time taken for complete disintegration of the tablet was measured[15].

***In-vitro* dissolution studies**

In-vitro dissolution studies were conducted for both LS tablets were performed in Electrolab dissolution apparatus using paddle apparatus (USPII). Dissolution studies were carried out using 900 ml of phosphate buffer of pH 6.8 at 37 ± 0.5ºC at speed of 75 rpm. SM tablets were added to phosphate buffer. At regular intervals 5ml of sample was withdrawn and replaced with fresh phosphate buffer of pH 6.8 solutions. Solutions were immediately filtered and analyzed spectrophotometrically at 239.6nm. The dissolution profile was constructed by plotting percentage cumulative drug release versus time.

Dissolution profile comparison using similarity and dissimilarity factor.

A dissolution profile can characterize the product more precisely than a single point dissolution test. It helps to assure similarity in product performance and signals bioequivalence. The factor *f1* is proportional to the average indifference between two profiles, whereas factor *f2* inversely proportional to the average squared indifference between two profiles. The factor *f2* measures the closeness between two profiles; FDA has set a public standard of *f2* values range 50-100 to indicate similarity between two profiles[18].

$$f_1 = \{[\textstyle\sum_{i=1}^{p} |R - T|] / [\sum_{i=1}^{p} R]\}\, 100$$

$$f_2 = 50 \log\{[1 + \tfrac{1}{p}\textstyle\sum_{i=1}^{p}(R - T)^2]^{-1/2}\, 100\}$$

Where,

f1=Dissimilarity factor, *f2*=Similarity factor, p= time points, T= test sample

R= reference sample

***In-vitro* release kinetics**

Data obtained from *in-vitro* release studies were fitted to various kinetic models to find out the mechanism of drug release from the SM LS.

Zero-order equation

To know the dosage form follows zero order release, the graph was plotted as % cumulative drug release Vs time in mins.

$Q = Q_0 - k_0 t$

Where,

Q_0= fraction of drug released at time t, K= zero order rate constant, t= time

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. This is applicable to dosage forms like transdermal systems, coated forms, osmotic systems, as well as matrix tablets with low soluble drugs.

First order equation

$\ln Q = \ln Q_0 - kt$

Where,

Q_0= fraction of drug released at time t, K= first order rate constant, t= time

This model is applicable to study hydrolysis kinetics and to study the release profiles of pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices.

Stability studies[16]

The tablets were packaged (triplicate) in a clear glass bottle with a screw cap and subjected to stability testing at 40 ± 2 ºC and 75 % ± 5% RH for 3 months. The drug content, color, and dissolution (tablet formulation) were evaluated for 3 months period.

RESULTS AND DISCUSSION

SM[19] is a new class of anti-hyperlipidemic medications, and it has low water solubility and high permeability (BCS-II). For successful treatment of depression, it is essential to improve bioavailability which can be enhanced by increasing the solubility and dissolution rate. In the present investigation LS of SM were prepared and evaluated.

Saturation solubility studies of SM

Solubility studies of SM in selected non-volatile solvents are shown in figure 1. Based on the obtained results highest solubility observed (35.202±0.57 mg/mL) in propylene glycol (PG). Hence PG is selected as a model non-volatile solvent for the preparation of LS.

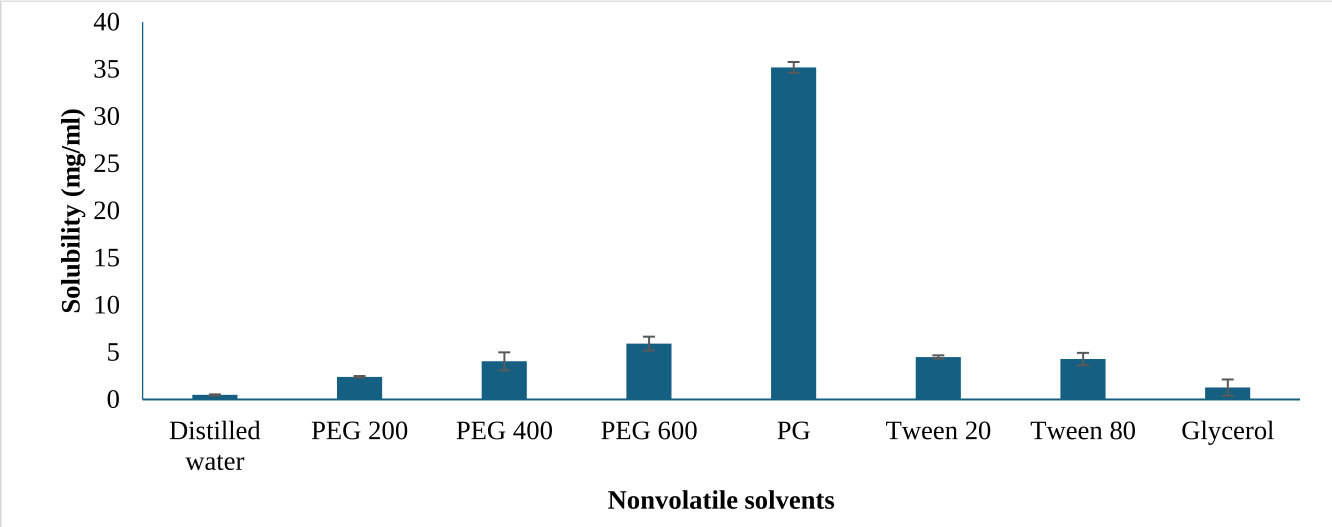

Figure 1: Solubility studies of Simvastatin (SM) in different nonvolatile solvents

Liquid Load Factors

The liquid form of a drug is converted into powder form by a mathematical approach. In the present study, microcrystalline cellulose (Avicel PH102) and aerosil 200 were taken as carrier and coating materials, respectively. The liquid load factor was calculated using the selected ratio of liquid medicament (ternary mixture), Selected carrier materials.

The Lf inversely proportional to the concentration of liquid medicament, Maximin Lf observed as 0.20 in LS7 and LS8 formulations with 30% drug solution concentration. All the formulations have acceptable flow properties, results shown in table 2. Further all formulated blend converted to tablet dosage form.

Evaluation Of Precompression Parameters For Power Blends

The LS of SM were prepared by direct compression technique. The prepared blends were evaluated for precompression parameters like angle of repose, compressibility index, hausner ratio, taped density and bulk density. The results were shown in table 2.

Table 2: Evaluation of liquisolid blend flow properties

Formulation no	Angle of repose (θ)* $\bar{X}$±SD	Bulk density* (gm/cm³) $\bar{X}$±SD	Tapped density* (gm/cm³) $\bar{X}$±SD	Hausner ratio* $\bar{X}$±SD	Carr's Index (%)*$\bar{X}$±SD
LS-1	32.27±1.31	0.355±0.018	0.415±0.004	1.169±0.012	14.457±0.012
LS-2	29.83±0.67	0.378±0.006	0.438±0.006	1.158±0.024	13.698±0.029
LS-3	37.32±0.49	0.394±0.010	0.482±0.001	1.223±0.013	18.257±0.067
LS-4	33.27±1.53	0.431±0.002	0.521±0.003	1.208±0.021	17.274±0.371
LS-5	31.92±1.27	0.409±0.006	0.525±0.008	1.283±0.026	22.095±0.18
LS-6	30.09±0.95	0.326±0.005	0.425±0.003	1.303±0.01	23.294±0.91
LS-7	33.76±1.02	0.368±0.009	0.463±0.010	1.258±0.038	20.518±0.338
LS-8	31.38±0.76	0.391±0.007	0.427±0.004	1.092±0.046	8.430±0.009
LS-9	32.78±1.27	0.423±0.003	0.510±0.006	1.205±0.056	17.058±0.018
LS-10	31.31±0.64	0.412±0.007	0.523±0.001	1.269±0.015	21.223±0.127
Note: *represent mean ± SD (n=3)					

The powder flow is influenced by so many interrelated factors which includes physical, mechanical, and environmental factors. Therefore, in our study, three flow measurement types were employed. The angle of repose (ɵ) is a measure of the internal friction and cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. The prepared liquisolid formulations of SM showed ɵ values in 29°-33°. All the formulations showed acceptable flowability according to the pharmacopeial limits. This was due to the less cohesion of powder particles.

Carr's consolidation index up to 21% is having acceptable flow properties. Hausner ratio was related to the inter particle friction, the powders with low interparticle friction, had ratios of approximately 1.25 indicating good flow. The SM LS blends have Carr's index in the range of 8-23%. The Hausner ratio of SM liquisolid blends was found to be 1.092-1.300. The prepared liquisolid blends showed good flowing properties.

Tablet Formulation

Prepared LS blend further processed to a direct compressible tablet dosage form for ease of administration. The final blend was compressed into tablets by direct compression technique using embossed C25 concave punches in multi station tablet compression machine (Rimek) and further evaluated for post compression parameters.

Evaluation of post-compression parameters

The SM-LS blends were converted to tablets by using direct compression technique. The prepared tablets were evaluated for post compression parameters like hardness, thickness, friability, weight variation, assay, disintegration, and *in-vitro* dissolution studies. The results were shown in table 3.

Table 3: Evaluation of Liquisolid compacts compressed tablets

Formulation code	Hardness* $\bar{X}$±SD (kg/cm²)	Thickness $\bar{X}$±SD (mm)	% Weight variation*** $\bar{X}$±SD	Assay %**$\bar{X}$±SD	% Friability*** $\bar{X}$±SD	Disintegration Time(sec)* $\bar{X}$±SD
LS-1	4.15±0.032	3.56±0.102	1.019±0.005	99.16±0.057	0.465±0.03	54±3
LS-2	4.08±0.021	3.61±0.077	1.040±0.007	101.23±0.04	0.494±0.02	57±2
LS-3	4.08±0.053	3.08±0.040	1.034±0.09	98.69±0.098	0.475±0.10	54±3
LS-4	4.11±0.032	3.60±0.114	1.028±0.39	98.24±0.049	0.504±0.05	58±2
LS-5	4.05±0.021	3.17±0.057	1.033±0.06	99.25±0.041	0.425±0.08	51±4
LS-6	4.12±0.024	3.14±0.049	1.03±0.018	98.39±0.057	0.461±0.06	53±1
LS-7	4.12±0.024	3.13±0.036	1.039±1.08	99.33±0.048	0.826±0.04	50±2
LS-8	4.12±0.048	3.11±0.053	1.084±0.087	99.48±0.008	0.814±0.02	52±1
LS-9	4.11±0.021	3.60±0.074	1.028±0.75	101.84±0.15	0.821±0.04	54±3
LS-10	4.15±0.032	3.53±0.4	1.019±0.058	99.04±0.16	0.724±0.05	43±2
* represent mean ±SD (n=6)			* * represent mean ±SD (n=10)		*** represent mean ±SD (n=20)	

Tablet requires a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of the SM LS formulations are uniform with 4.05-4.15 kg/cm² (n=3), which is required to maintain the mechanical strength. Percentage friability of Simvastatin (SM) liquisolid compacts (LS) formulations ranged from 0.425-0.826%. All the formulations showing acceptable friability loss.

The thickness of Simvastatin (SM) liquisolid compacts (LS) formulations ranged between 3.08-3.61mm. All the formulated tablets showed uniform thickness.

The %weight variation of various prepared Simvastatin (SM) liquisolid compacts (LS) formulations ranged from 1.019-1.084%. The weight variation of all the formulated tablets was within acceptable Pharmacopoeia limits.

The fundamental quality attribute for all pharmaceutical preparations is to maintain constant dose of drug between individual tablets. It was observed that all the formulations of Simvastatin (SM) liquisolids were ranged between 98.24-101.84%. It complies with the assay according to the USP.

The *in-vitro* disintegration time[17] of Simvastatin (SM) liquisolid compacts (LS) formulations was found to be 43-58sec. Faster disintegration rate is due to the presence of super disintegrants as well as microcrystalline cellulose (Avicel 102) and aerosil leading to an extremely fast water penetration into the tablets caused by wicking and subsequent widening of pores. From the results of investigation, it is evidenced that there is a relationship between liquid load factor (L_f) and disintegration time. The liquid load factor (L_f) inversely proportional to the disintegration time of tablets i.e., when the L_f is increased the disintegration time of the tablets will decrease.

Another finding was obtained from the results that there is relationship between coating material and disintegration time of the tablets having the same L_f. The coating material was directly proportional to the disintegration time of tablets i.e., when the coating material increased the disintegration time of the tablets will increase.

***In-Vitro* Dissolution Studies**

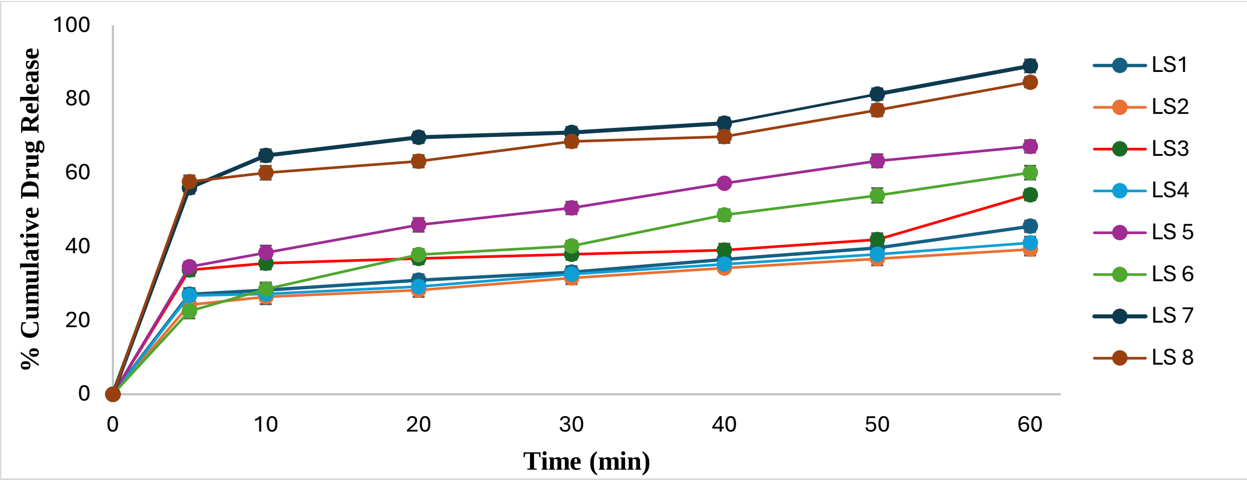

Figure 2: In-vitro release profiles of Simvastatin (SM) liquisolid formulation LS1, LS8 (mean ±SD)

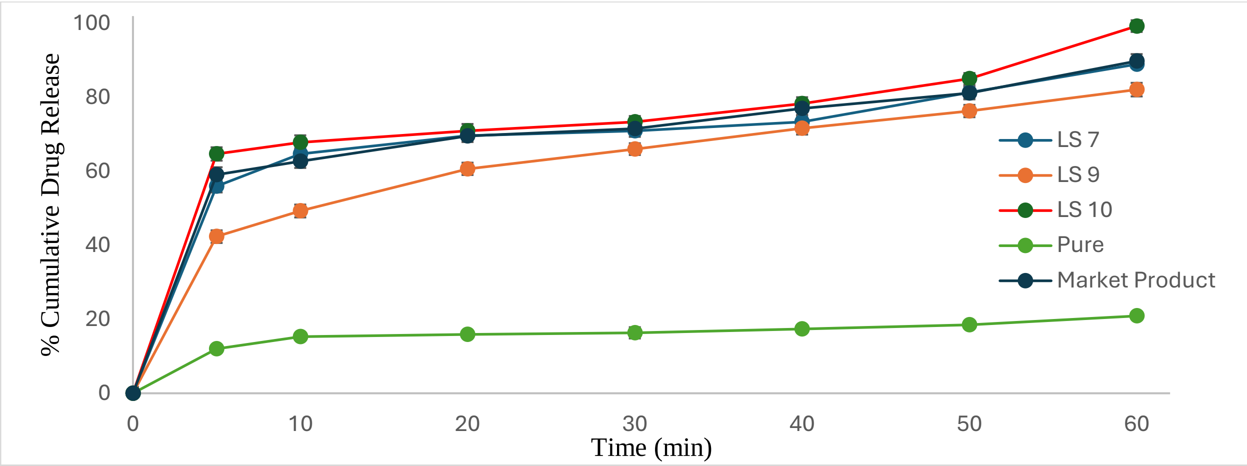

Figure 3: In-vitro release profiles of Simvastatin (SM) liquisolid formulation LS7, LS9, LS10, Pure and Marketed product (mean ± SD)

The *in-vitro* dissolution profiles of Simvastatin (SM) liquisolid tablets and marketed tablets were shown in table 6- 7 & fig.no.2-3. Pure Simvastatin (SM) showed poor dissolution profile i.e. only 20.91% of drug released at the end of 60min, whereas liquisolid formulations 99.29% of drug released at the end of 60min. This may be due to surface area available for dissolution is increased, in the liquisolid formulations the drug is in the liquid form or suspended form, and because of PG wettability increases further increase the dissolution rate. From the dissolution profiles it was found that LS10 formulation showed better drug release when compared to pure simvastatin and it releases drug of 66.03% in 10min and 73.41% in 30min and at the end of 60min it shows 99.29% of drug released.

From the results of investigation, the concentration of drug in liquid medication is an important aspect as it affects the drug release. As the concentration of drug solution decreases higher the release was observed. It may be due to at high concentrations drug tend to precipitate within the Aerosil pores and drug is previously dissolved or suspended in PG. The surface area available for dissolution is increased by addition of carrier and coating materials and due to the addition of PG wettability was increased hence the dissolution increases. At high excipient ratios drug release was found to be retarded as compared to other batches.

***In-vitro* release kinetics:**

From the kinetic data it was found that the correlation coefficient values of first order kinetics are more than the zero-order kinetics it indicates that the drug release from the Simvastatin (SM) liquisolid compacts (LS) are following first order kinetics[19]. The results were shown in Table 4.

Table 4: In-Vitro Release Kinetics

Formulation	LS1	LS2	LS3	LS4	LS5	LS6	LS7	LS8	LS9	LS10	PURE	MR
Zero Order R^2	0.684	0.662	0.545	0.529	0.583	0.608	0.589	0.577	0.738	0.565	0.616	0.949
First Order R^2	0.765	0.734	0.663	0.586	0.681	0.668	0.883	0.805	0.925	0.823	0.646	0.990
$DE_{30\%}$	27	24.1	26.0	34.14	35.2	24.58	61.87	57.5	52.29	65.41	16.35	45.96
T_{10min}	1.5	1.41	1.18	1.37	1.19	2.9	0.48	0.5	1.06	0.43	3.56	2.25
T_{30min}	4.24	25.50	16.30	22.30	4.01	11.03	2.20	2.37	3.15	2.07	-	14
T_{50min}	-	-	60	-	29	43.3	4.05	4.20	10.5	3.54	-	33.5
$K_1(h^{-1})$	0.0069 909	0.0046 06	0.0069 909	0.0046 06	0.0069 909	0.0046 06	0.0253 33	0.0207 27	0.0230 3	0.0322 42	0.0023 03	0.0184 24

From the calculations of dissolution efficiency at 30 mins it was found that the liquisolid formulation LS10 showed high efficiency i.e. 65.41% when compared to other liquisolid formulations it was further supported by high-rate constant value of LS10 formulation. From the results it was found that LS10 formulation showed 14 folds enhanced drug release when compared to the pure Simvastatin (SM).

Drug and Excipients Compatibility Studies

Differential Scanning Calorimetry (DSC) Studies[11]

DSC scan of about 5mg; using an automatic thermal analyzer system performed accurately weighed SM and tablet containing the same amount of drug. Sealed and performed aluminum pans were used in the excipients for all the samples. Temperature calibration was performed using indium as standard. An empty pan sealed in the same way as the sample was used as a reference. The entire samples were run at a scanning rate of 10˚C/min from 25-250˚C[12].

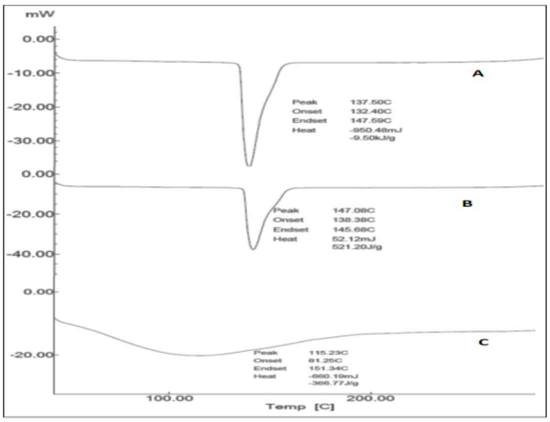

Figure 4: DSC thermogram of pure Simvastatin (A), LS10 formulation (B) and placebo (C) formulation

DSC thermogram of pure SM showed endothermic peak at 137.5 °C and formulation showed endothermic peak at 139.08°C. From the obtained results the drug and excipients were compatible.

ATR spectral studies

ATR spectra of pure SM were developed in the wave number of region 400-2000cm^{-1} using Bruker ATR spectroscopy. Samples were directly placed into the ATR and scanned over a scanning range of 400 - 2000cm^{-1}.

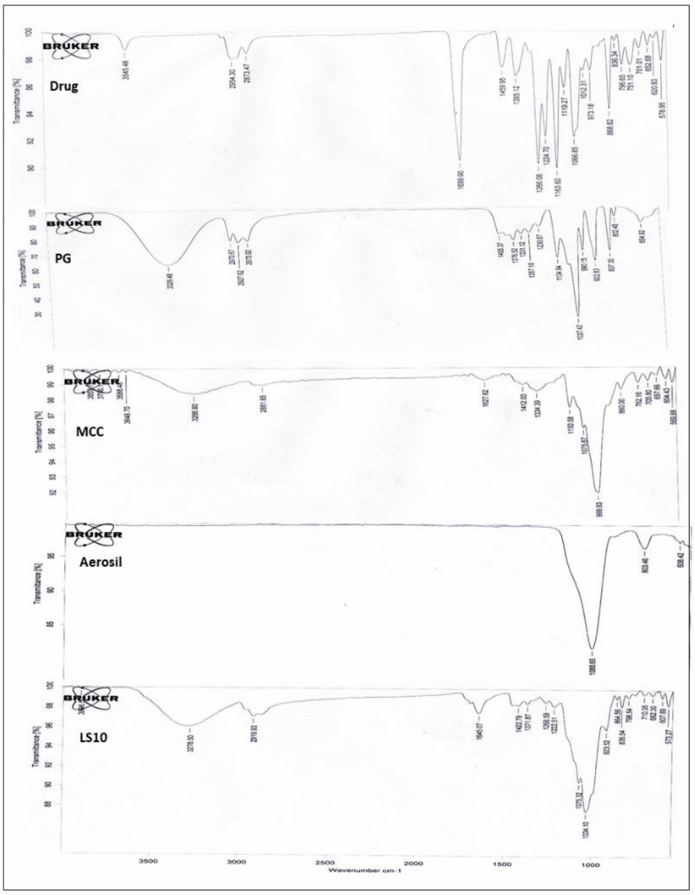

Figure 5: ATR spectrum of pure drug Simvastatin, PG, MCC, Aerosil and LS10 formulation

Table 5: Comparison of confirmatory groups in pure sample and physical mixtures

Characteristic bands (cm^{-1})	Pure sample	Liquisolid mixtures	Possible functionalities
3545	Present	Present	OH stretching
1450	Present	Present	C=C
1699	Present	Present	C=O
1224	Present	Present	C-O
1385	Present	Present	C-H bending
799	Present	Present	C-H out of plane
865	Present	Present	C-H out of plane

The ATR spectra of pure SM and PG, MCC, Aerosil and LS10 formulation are showed in figure 5. There is no change in the nature and position of the Characteristic band for drug and drug-polymers used in the formulation, hence concluded that there is no chemical interaction between the drug and polymer.

Stability studies

Optimized formulation packed in 40cc HDPE container and heat sealed the cap then loaded in accelerated stability chamber (40±2°C / 75±% RH) for 3 months as per ICH guidelines. After stability studies tablets were evaluated for Description, Assay and Dissolution profile. All the results were reported in Table 6. After the stability period, there was no discernible change in the Description, Assay and Dissolution profile of the liquisolid compacts.

Table 6: Stability data of optimized formulation (LS10) at the accelerated temperature of 40±2°C/ relative humidity of 75±5%

Test	Initial	40°C±2°C/RH 75±5% -3M
Appearance	White colour	No change in appearance
Drug content (%)	99.04±0.16	98.39±0.93
Drug release at 60 min (%)	99.29±1.58	97.47±1.72

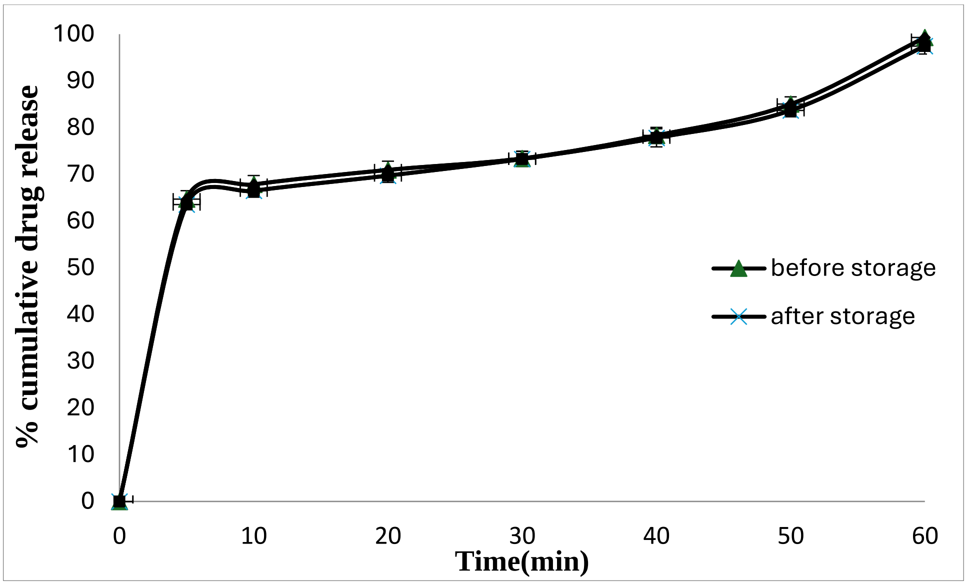

Figure 6: In-vitro drug release profiles of LS10 during stability studies

CONCLUSION

Simvastatin liquisolid compacts compressed tablets were successfully prepared and characterized to enhance the solubility and subsequent dissolution of SM. The lead formulation was stable for three months at testing conditions. Solid state analysis confirms no drug and excipient incompatibilities. The LC compressed tablet showed enhanced dissolution compared with control and similar to commercial tablet dosage form. Future *in vivo* studies will be needed to confirm the pharmacokinetic and pharmacodynamic behavior of the lead formulation. Taken together, LC compressed tablet dosage form could be considered as an alternative to enhance the therapeutic application of SM.

REFERENCES

1) Bakhaidar RB, Naveen NR, Basim P, Murshid SS, Kurakula M, Alamoudi AJ, Bukhary DM, Jali AM, Majrashi MA, Alshehri S, et al. Response Surface Methodology (RSM) Powered Formulation Development, Optimization and Evaluation of Thiolated Based Mucoadhesive Nanocrystals for Local Delivery of Simvastatin. Polymers 2022;14:5184. https://doi.org/10.3390/polym14235184 PMid:36501579 PMCid:PMC9737842

2) Spireas S, Bolton M, 1999. Liquisolid systems and methods of preparing same. US Patent 5968:550. https://ppubs.uspto.gov/dirsearch-public/print/downloadPdf/5968550 .

3) ZOCOR (Simvastatin) Tablets Package Insert. (2023). U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019766s104lbl.pdf .

4) Iyan S, Karyn E, Sandra M, Silmy K, Multicomponent crystals: Solubility enhancement of simvastatin using arginine and glycine coformers. Journal of Pharmacy & Pharmacognosy Research, 2024;12(6):1079-1089. https://jppres.com/jppres/pdf/vol12/jppres23.1898_12.6.1079.pdf . https://doi.org/10.56499/jppres23.1898_12.6.1079

5) Yalkowsky SH, 1981. Technique in solubilization of drugs. 1st ed. Madision Avenue (NY): Marcel Dekker.

6) Cherukuri S, Chappidi SR, Dindigala AK, Vadla A, Arepalli LA. "LIQUISOLID TECHNIQUE: A NOVEL APPROACH TO ENHANCE SOLUBILITY AND BIOAVAILABILITY OF BCS-II DRUGS". International Research Journal of Pharmacy 2012;3(7):108-115. https://www.irjponline.com/index.php/IRJP/article/view/1852/1581 .

7) Spireas S. Liquisolid systems and method of preparing same. US Patent 6423339; 2002 July 22. https://patentimages.storage.googleapis.com/93/df/2a/55f5bc82189b0b/US6423339.pdf .

8) Gliši'c, T.; Djuriš, J.; Vasiljevi'c, I.; Parojˇci'c, J.; Aleksi'c, I. Application of Machine-Learning Algorithms for Better Understanding the Properties of Liquisolid Systems Prepared with Three Mesoporous Silica Based Carriers. Pharmaceutics 2023;15:741. https://doi.org/10.3390/pharmaceutics15030741 PMid:36986602 PMCid:PMC10054079

9) Butreddy, A.; Dudhipala, N. Enhancement of Solubility and Dissolution Rate of Trandolapril Sustained Release Matrix Tablets by Liquisolid Compact Approach. Asian J. Pharm. 2015;9:1.

10) Mei Lu a, Haonan Xing a, Jingzheng Jiang a, Xiao Chen a, Tianzhi Yang b, Dongkai Wang a, Pingtian Ding a, "Liquisolid technique and its applications in pharmaceutics". Asian journal of pharmaceutical sciences. 2017;12:115-123. https://doi.org/10.1016/j.ajps.2016.09.007 PMid:32104320 PMCid:PMC7032177

11) Naureen F, Shah Y, Shah SI, Abbas M, Rehman IU, Muhammad SH, Goh KW, Khuda F, Khan A, et al. Formulation Development of Mirtazapine Liquisolid Compacts: Optimization Using Central Composite Design. Molecules 2022;27:4005. https://doi.org/10.3390/molecules27134005 PMid:35807252 PMCid:PMC9268088

12) Sowjanya G, Murthy TEGK, Evaluation of some methods for preparing Carvedilol-Hydroxy Propyl- B- Cyclodextrin inclusion complexes, 2011;1(2):676-83.

13) Ahmed TA, Alotaibi HA, Almehmady AM, Safo MK, El-Say KM, Influences of Glimepiride Self-Nanoemulsifying Drug Delivery System Loaded Liquisolid Tablets on the Hypoglycemic Activity and Pancreatic Histopathological Changes in Streptozotocin-Induced Hyperglycemic Rats. Nanomaterials 2022;12:3966. https://doi.org/10.3390/nano12223966 PMid:36432252 PMCid:PMC9695338

14) Shah P, Desai H, Vyas B, Lalan M, Kulkarni M. Quality-by-design-based development of Rivaroxaban-Loaded Liquisolid Compact tablets with Improved Biopharmaceutical attributes. AAPS PharmSciTech. 2023;24:176. https://doi.org/10.1208/s12249-023-02635-3 PMid:37639081

15) Sanjeshkumar R, Dhaval P, Priyank P, "FORMULATION AND IN-VITRO DISSOLUTION ENHANCEMENT OF BLONANSERIN USING LIQUISOLID COMPACTS" Journal of Emerging Technologies and Innovative Research (JETIR) March 2019, Volume 6, Issue 3.

16) International Council for Harmonisation (ICH). (2003). ICH guideline Q1A(R2): Stability testing of new drug substances and products.

17) Indian Pharmacopoeia Commission. (2020). Indian Pharmacopoeia (IP 2020). Ghaziabad, India.

18) Limpongsa E, Tabboon P, Pongjanyakul T, Jaipakdee N. Preparation and Evaluation of Directly Compressible Orally Disintegrating Tablets of Cannabidiol Formulated Using Liquisolid Technique. Pharmaceutics 2022;14:2407. https://doi.org/10.3390/pharmaceutics14112407 PMid:36365225 PMCid:PMC9695279

19) Chinthaginjala H, Ahad HA, Pradeepkumar B, Gandhi KS, Kalpana K, Pushpalatha G, et al. Formulation and in vitro evaluation of gastro retentive ofloxacin floating tablets using natural polymers. Res J Pharm Technol. 2021;14(2):851-6. https://doi.org/10.5958/0974-360X.2021.00151.7

20) Cecilia Martínez-Jiménez, Jorge Cruz-Angeles,Marcelo Videa and Luz María Martínez Co-Amorphous Simvastatin-Nifedipine with Enhanced Solubility for Possible Use in Combination Therapy of Hypertension and Hypercholesterolemia. Molecules 20182;3(9):2161; https://doi.org/10.3390/molecules23092161 PMid:30154310 PMCid:PMC6225140

21) Jiang T, Han N, Zhao B, Xie Y, Wang S, Enhanced Dissolution Rate and Oral Bioavailability of Simvastatin Nanocrystal Prepared by Sonoprecipitation. Drug Dev. Ind. Pharm. 20123;8:1230–1239. https://doi.org/10.3109/03639045.2011.645830 PMid:22229827

22) Cai T, Zhu L, Yu L. Crystallization of organic glasses: Effects of polymer additives on bulk and surface crystal growth in amorphous nifedipine. Pharm. Res. 2011;28:2458-2466. https://doi.org/10.1007/s11095-011-0472-z PMid:21638137

23) Priyanka P, Surendra G, Pankaj J, Lokesh K, and Sanjay S "Co-solvent Evaporation Method for Enhancement of Solubility and Dissolution Rate of Poorly Aqueous Soluble Drug Simvastatin: In vitro-In vivo Evaluation" AAPS PharmSciTech, 2008;9(4). https://doi.org/10.1208/s12249-008-9176-z PMid:19115110 PMCid:PMC2628261

24) Fahad MK, Mahmood A, Fakhra B "Enhancement of solubility and release profile of simvastatin by co-crystallization with citric acid" Tropical Journal of Pharmaceutical Research December 2019;18(12):2465-2472.

25) Parmar N, Bagda A, Patel M, Patel S. Formulation strategy for dissolution enhancement of simvastatin. Int J Pharm Sci Res. 2012;3(10):3817-22.

26) Meenakshi B, Geeta R, Kavita B, Sunita D "Formulation and optimization: Liquisolid of domperidone for solubility enhancement" Acta Pharm. Sci. 2024;62:(3). https://doi.org/10.23893/1307-2080.APS6234