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Research Article

ENHANCEMENT OF SOLUBILITY OF SIMVASTATIN BY USING LIQUISOLID COMPACT TECHNIQUE

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ABSTRACT

The present investigation was aimed to improve the dissolution rate of the poorly soluble drug simvastatin, by formulating it as a liquisolid compact. Different liquisolid compacts were prepared using mathematical formulae to calculate the required quantities of powder and liquid ingredients to produce acceptably flow able and compressible admixture. Aerosil-200, Syliod-244FP and Syliod-244FP and MCC, Lactose were employed coating and carrier material, non-volatile ((PEG 200) liquid vehicle, respectively. The various ratios of drug to liquid and carrier to coating were used to prepare liquisolid compacts. The formulated liquisolid tablets were evaluated for all pre compression and post compression parameters. The *in vitro* release characteristics of the liquisolid compacts as formulated by direct compression. The tableting properties of the liquisolid compacts were within the acceptable all standard limits and drug release rates were distinctly higher as compared to directly compressed tablets. The FTIR spectra showed no interaction between drug-excipient and disappearance of the characteristic absorption band of simvastatin in liquisolid formulations could be attributed to the formation of hydrogen bonding between the drug and liquid vehicle, which resulted in dissolution enhancement. Thus, the liquisolid technique was found to be a promising approach for improving the dissolution rate and solubility rate of a poorly soluble drug like simvastatin.

KEYWORDS: Simvastatin, Liquisolid compacts, PEG-200, carrier material, coating material.

INTRODUCTION

The most commonly employed route of drug delivery is by oral ingestion. The oral route is preferred route of drug administration due to its convenience, better patient compliance and low production costs. After oral administration, the dissolution of a drug in the gastric fluids is a prerequisite for the absorption of drug into the systemic circulation. The rate of absorption of poorly water soluble drug formulated as an orally administered solid dosage form is controlled by its dissolution rate in the fluid present at the absorption site i.e. the dissolution rate is often the rate limiting step in drug absorption[1,2]. According to biopharmaceutical classification system BCS, Class II drugs are defined as those with high permeability and low soluble. For these substances, dissolution is therefore the rate-determining step for drug absorption [3].

Thus one of the major challenges in drug development today is poor solubility, as estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and lipophilicity[4,5]. Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, which include, (a) solubilization in surfactants (b) pH adjustment (c) co-solvents (d) micro emulsion (e) self emulsification (f) polymeric modification (g).

Hypertriglyceridemia is typically treated with a various class of medications called statins, fibrates, niacin (nicotinic acid) and bile acid sequestrants. Medications most commonly used to treat high LDL cholesterol levels are statins, such as atorvastatin or simvastatin. These drugs work by reducing the production of cholesterol within the body. But statins are poorly soluble in water and result in low bioavilability. Hence in this study, simvastatin was formulated into liquisolid tablets, which is expected to enhance dissolution of this poorly soluble drug in the stomach and hence improve its oral bioavailability.

MATERIALS AND METHODS

Simvastatin was gifted by Divis labs pvt.ltd, Syloid-244FP from Grace GmbH8.Hollerhecke, Aerosil-200, Potassium hydrogen phosphate, NaOH , HCl , PEG-200, Magnesium stearate, Sodium starch glycolate and Talc from Lobachemie (Mumbai) , Propylene glycol from Cavasol w7 HP Pharma, MCC from IPR (Mumbai), Methanol from(Sd fine chemicals ltd).

Preparation of Standard Stock solution

10 mg of Sivastatin was accurately weighed and dissolved in 10 ml volumetric flask containing methanol. The volume was made up to 10 ml with the methanol to get concentration of (1 µg/ml).

Calibration curve in pH 7.4 phosphate buffer

The present analytical method obeyed beer's law in the concentration range of 2-10 µg/mL and it is suitable for the estimation of the Simvastatin solution. The value of R^2 (regression coefficient) for the linear regression equation were found to be range of 0.993-0.999. The results were reported in Table.

Solubility studies

Solubility profiles studies were performed with PH 2 0.01 N HCl, pH 5.8 phosphate buffer, pH 6.8 phosphate buffer and 7.4 phosphate buffer in order to determine the aqueous medium that offer good solubility condition for Simvastatin . The solubility of Simvastatin was also determined in pH 7.4 phosphate buffer &it shows more solubility compared to other solvents.

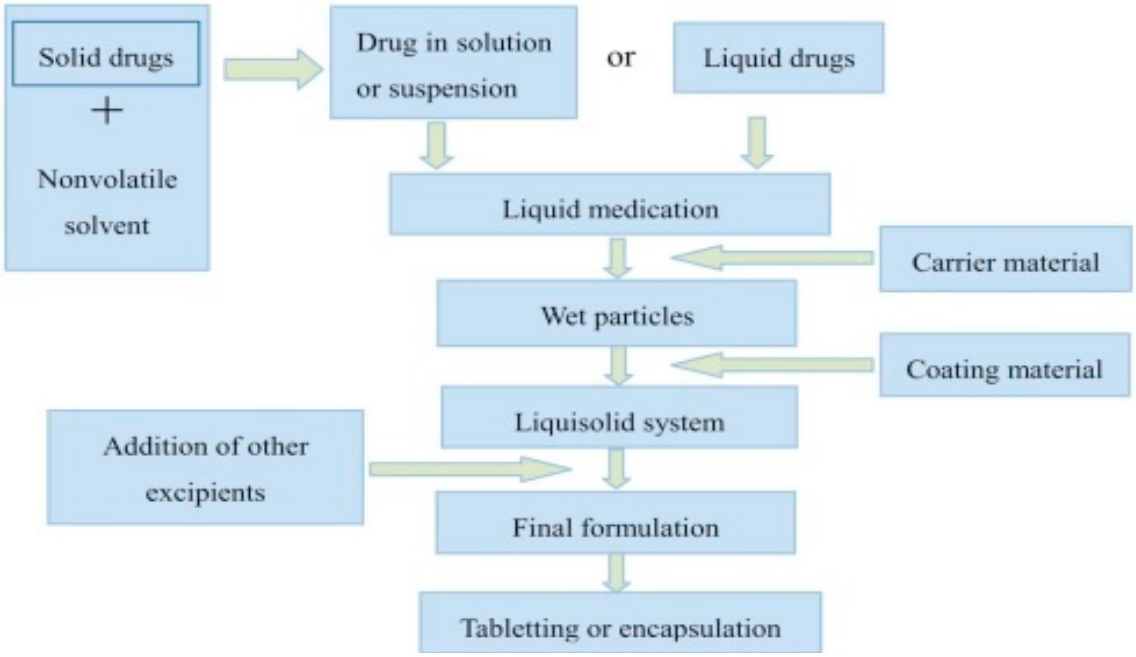

Fig 1. Steps involved in the preparation of liquid solid system

Formulation of Simvastatin Tablets by Liquisolid technique

Accurately weighed 80mg of Simvastatin was placed in motor and polyethylene glycol -200 (PEG-200) was added to it as non volatile solvent and mixed well to form dispersion. To the dispersion small amount of binary mixture containing carrier and coating material was added and mixed well. Finally, 5%(w/w) of sodium starch glycolate as disintegrant, 2% magnesium stearate and 1% of talc were added and mixed for 5 minutes. Final mixture was compressed on 12 mm punch and die, using the manual hydraulic press at constant pressure. Depending upon the type of carrier and coating materials in formulation, different liquid loading factors were employed in liquisolid preparations. The batch design is reported in Table.

EVALUATION OF FLOW PROPERTIES

Bulk density and Tapped density

An accurately weighed quantity of powder blend (M) was taken and carefully poured into the graduated measuring cylinder and the volume (V_0) of the powder was measured. Then graduated measuring cylinder was tapped 50 times and volume (V_t) were measured which was tapped volume of the powder blend. The bulk density and tapped density were calculated by using the formula's

Compressibility Index (CI) and Hausner's ratio (H)

Both the CI and Hausner's ratio were determined by using bulk density and the tapped density of the powder. The compressibility index has been proposed as an indirect measure of the size, shape, surface area, moisture content and cohesiveness of the materials.

Angle of repose

The angle of repose has been used to characterize the flow properties of solids and it is related to inter particulate friction or resistance to movement between particles. And the maximum angle possible between surface of pile of powder or granules and horizontal plane. The angle of repose was determined by funnel method suggested by Newman.

Table 1: Reference ranges to assess flow properties of powders

S.No	Flow character	Compressibility index	Hausner's ratio	Angle of repose
1.	Excellent	≤10	1.00-1.11	25-30
2.	Good	11-15	1.12-1.18	31-35
3.	Fair	16-20	1.19-1.25	36-40
4.	Passable	21-25	1.26-1.34	41-45
5.	Poor	26-31	1.35-1.45	46-55
6.	poorer	32-37	1.46-1.59	56-65
7.	poorest	>38	>1.6	>66

***IN-VITRO* EVALUATION TESTS**

Estimation of drug content

An accurately weighed quantity of Solid Dispersions equivalent to 10mg of Simvastatin, was taken into a 10 mL volumetric flask and dissolved in methanol and filtered through a Whatman No.1 filter paper (0.45µ). The filtrates were diluted suitably with pH 7.4 phosphate buffer. The content of Simvastatin was determined spectrophotometrically at 238 nm against suitable blank using UV-visible Spectrophotometer (UV-3000, LABINDIA).

Weight variation test

10 individual tablets of each formulation were weighed and their weights were recorded. The limits of deviation allowed as per IP were listed in Table.

Table 2: Specifications for uniformity of weight of tablets

Average weight	Percent deviation allowed
Less than 130mg	10
More than 130mg but less than 324mg	7.5
324mg or more	5

Hardness

The Hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average value with standard deviation of 10 tablets for each formulation.

Friability

For each formulation 10 tabs were weighed, placed in Friabilator (M/S Cambell Electronics, India) and were subjected to 100 rotations in 4 min. The tablets were reweighed and Friability was calculated along with mean and the standard deviation. The results are given in,

$$Friability = \frac{W_1 - W_2}{W_1} \times 100$$

Where " W_1" is the initial weight and "W_2" is the final weight of the tablets.

***In-vitro* disintegration test**

One tablet in to each tube was introduced and disc was added. The assembly was suspended in a beaker containing 1000mL of water and the apparatus was operated for 30 minutes. The time taken for complete disintegration of each tablet was noted. The tablets pass the test if all of them have disintegrated within the time (30 min).

***In-vitro* dissolution test**

The tablet was placed inside the dissolution vessel. The dissolution study of dispersion was conducted using dissolution testing apparatus II (paddle method) in 900 mL of 7.4 pH phosphate buffer solution at 37±0.5°C and at speed of 75 rpm. 5ml samples were withdrawn at time intervals of 5,10,15,20,30,45&60min intervals.The volume of dissolution fluid adjusted to 900mL by replacing 5ml of dissolution medium after each sampling. Each sample was analyzed at 238 nm using double beam UV-Visible Spectrophotometer against blank.

RESULTS AND DISCUSSION:

Calibration curve

The calibration curve of the Simvastatin was obtained in the range of 2-10 µg/mL at the wavelength of 238nm. The value of R^2 (regression coefficient) for the linear regression equation were found to be range of 0.993-0.999.

pH-Solubility studies

In the present work the drug is added to buffers like pH 1.2 HCL Buffer, pH 5.8 phosphate Buffer, pH 6.8 Phosphate buffer, pH 7.4 Phosphate Buffer as follows. The results of solubility studies revealed that Simvastatin is more soluble in pH 7.4 Phosphate Buffer. The order of solubility is 7.4 pH <1.2 pH<6.8 pH<5.8 pH.

Pre-compression parameters

The flow properties of liquisolid powders were analysed before compression to compact,it is vital for the performance of the tablet. By using bulk and tap density, hausners ratio, angle of repose and Carr's index. The bulk and tapped densities of various formulations were found to be in the range of 0.386 ± 0.01 to 0.518±0.002 (g/cc) and 0.417 ± 0.009 to 0.690 ± 0.18 (g/cc). The Hausner's ratio and Carr's index and angle of repose is 1.11±0.5 to 1.51±0.2 and 25.94 ± 0.07 to 34.16 ± 0.554 and 32.61 ±2.9 to 46.16±0.56 shows good flowability for direct compressible tablet. The Hausners ratio of batch F8 shows more than normal. The Carr's index of batch F3 and F6 shows more values. The results were reported in Table.

Post-Compression Evaluation of Liquisolid Compacts

The diameter and thickness of the tablets were varied with all batches because of the all bathes having variable in their weight. The uniformity of contents of tablets is between94.58 to 98.61% which is acceptable for further study. The FM (fraction of molecularly dispersed drug in liquid medication of the prepared formulation) of tablet is the range of 0.462-0.774. And FM value does not exceeds >1. The Hardness, thickness and friability of tablet was found to be between 3.7 to 4.1 kg/cm2, 2.06 to 3.81 & 0.07% to 0.77% respectively.

***In-Vitro* Release Study**

The In vitro dissolution studies were carried out by using USP Type II (Paddle type) (LABINDIA) dissolution test apparatus. Initially dissolution studies of pure Simvastatin were carried out in pH 7.4 phosphate buffer. The cumulative percent release of pure Simvastatin at 60 min was found to be 30.07% indicating the slower dissolution rate of drug. The dissolution enhancement of such poorly soluble drug was carried out by formulating liquisolid compacts. The effect of various dissolution enhancing agents on the drug release was studied by using Simvastatin dissolution enhancing agent like PEG200, Aerosil-200, Syloid-244FP as coating materials and MCC, Lactose as carrier materials with different ratio's. Dissolution profiles of Liquisolid compacts F1,F2,F3 formulations using MCC and Syliod-244FP shows 87.08% , 86.73% and 91.10% (by increasing the ratio of carrier material) in 60min. Formulations F4, F5 and F6 prepared using with same MCC as carrier and Aerosil-200 as coating material showed 84.11% , 85.33% and 94.43% release respectively at the end of 60 min. Formulations with Aerosil-200 as coating material showed lower release rates in F4 & F5 compared to F6 formulation. This may be due to lesser porosity of Aerosil-200 compared to Syloid-244FP. Formulations F7, F8 and F9 prepared using Lactose as carrier and Aerosil-200 as coating material showed 86.38% , 87.61 and 97.40% release respectively.

Formulations F10, F11 and F12 prepared using Lactose as carrier and Syloid-244FP as coating material showed 88.65% , 89.35% and 98.62% release respectively at the end of 60 min. Formulations with Aerosil-200 showed lower dissolution rates in these formulations compared to formulations prepared with Syloid-244FP. Higher dissolution rates with Syloid-244FP can be attributed to porous nature of Syloid compared to Aerosil-200 resulting in improved flow properties and efficient release of Simvastatin. From the results obtained it was found that formulations prepared by liquid-solid technique showed an increased dissolution rate of Simvastatin compared to pure Simvasatin. Among the two carriers and coating materials used, Syliod-244FP showed better dissolution enhancement properties and all the formulations, F12 containing Simvastatin:Syloid-244FP and showed superior drug release. The results were given in Table.

Table 3: Formulation table of Simvastatin Liquisolid compacts

S.No	Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	Drug + Non Volatile oil	22	22	22	22	22	22	22	22	22	22	22	22
2.	MCC	150	225	300	150	225	300	-	-	-	-	-	-
3.	Lactose	-	-	-	-	-	-	150	225	300	150	225	300
4.	Aerosil – 200	-	-	-	15	15	15	15	15	15	-	-	-
5.	Syloid244FP	15	15	15	-	-	-	-	-	-	15	15	15
6.	R value	10	15	20	10	15	20	10	15	20	10	15	20
7.	LF value	1.4	0.9	0.7	1.4	0.9	0.7	1.4	0.9	0.7	1.4	0.9	0.7
8.	SSG	10	10	10	10	10	10	10	10	10	10	10	10
9.	Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2
10.	Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total weight		211.4	270.9	370.7	211.4	270.9	370.7	211.4	270.9	370.7	211.4	270.9	370.7

Table 4: Solubility studies of Simvastatin

Aqueous Fluids	Amount of SIM solublized (mg/mL)
pH 1.2 0.1N HCL	0.419
pH 5.8 phosphate buffer	0.314
pH 6.8 phosphate buffer	0.338
pH 7.4 phosphate buffer	0.562

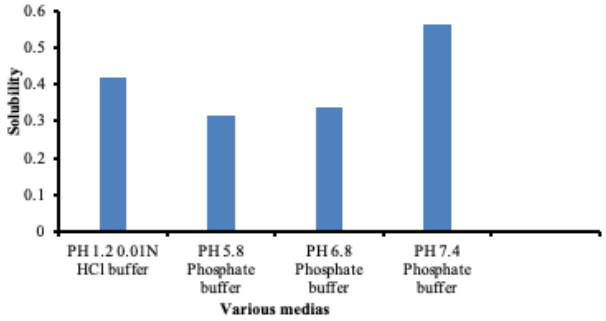

Fig: 2 Solubility studies of Simvastatin

Table 5 Interpretation of FT-IR spectral data

Functional group	Frequency range	Simvastastin	Aerosil	Syloid-244FP	F 12
N=H stretch	3500-3000	3550	3428	3442	3327
O−H stretch	3000-2500	3011	2928	2928	2977
C−H stretch	2900-2700	2871	-	2856	2900
C≡C stretch	2500-2000	-	-	-	2066
C=C stretch	2000-1500	1571	1626	1631	1658

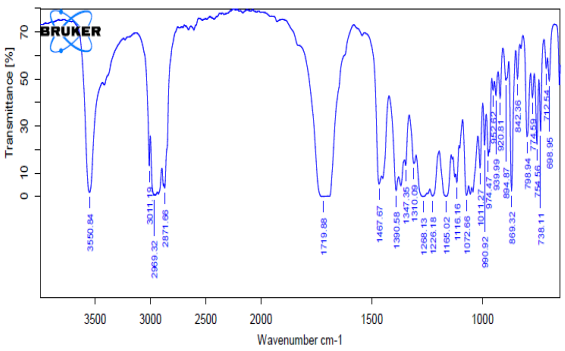

Fig 3 FTIR spectra of liquisolid technique of Pure Drug

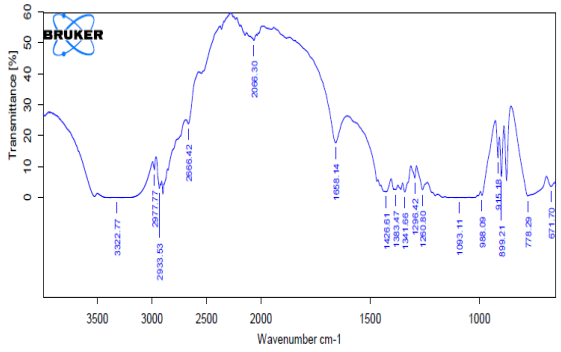

Fig 4 FTIR spectra of liquisolid technique of Formulation F12

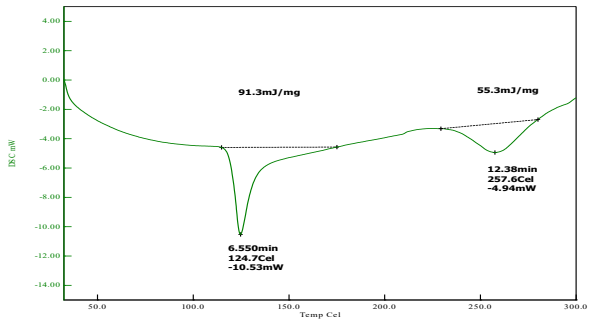

Fig 6 DSC Chromatogram of Pure Drug

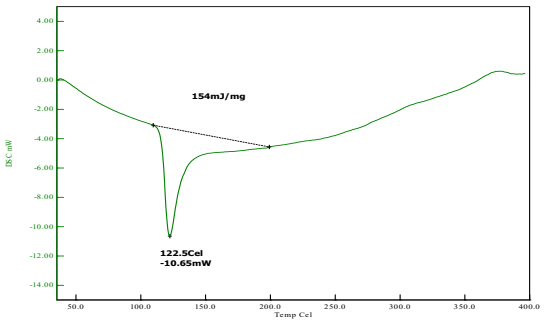

Fig 7 DSC Chromatogram of FormulationF12

Table 6: Flow properties of Liquisolid compressible powder

Batch	Bulk Density (gm/ml)	Tap Density (gm/ml)	Angle of Repose	Hausner's ratio	Carr's Index
F1	0.421 ± 0.04	0.502 ± 0.04	46.04 ± 3.65	1.36 ± 3.8	28.14 ± 1.46
F2	0.410 ± 0.009	0.472 ± 0.01	42.6 ± 2.8	1.33 ± 1.4	29.14 ± 1.03
F3	0.442 ± 0.01	0.503 ± 0.17	32.61 ± 2.9	1.11 ± 0.5	30.02 ± 1.88
F4	0.390 ± 0.042	0.456 ± 0.02	46.16 ± 0.56	1.41 ± 0.8	26.10 ± 2.30
F5	0.437 ± 0.007	0.497 0.009	45.00 ± 2.6	1.36 ± 0.6	28.66 ± 1.15
F6	0.379 ± 0.007	0.417 ±0.009	42.87 ± 4.2	1.31 ± 0.1	34.94 ±0.554
F7	0.386 ± 0.01	0.465 ± 0.01	44.1 ± 0.63	1.44 ± 0.5	31.77 ±1.74
F8	0.516 ± 0.02	0.620 ± 0.03	42.70 ±2.5	1.50 ± 0.3	27.85 ± 0.39
F9	0.406 ± 0.01	0.497 ± 0.01	41.98 ± 2.1	1.35 ± 0.9	27.49 ± 1.53
F10	0.443 ± 0.009	0.600 ± 0.16	36.16 ± 0.6	1.37 ± 0.4	30.98 ± 2.1
F11	0.487 ± 0.006	0.690 ± 0.18	45.00 ± 4.2	1.51 ± 0.2	29.41 ± 0.10
F12	0.518 ± 0.002	0.516 ± 0.14	42.76 ± 1.8	1.26 ± 0.6	25.16 ± 0.07

Table 7: Post-compression evaluation of liquisolid compacts

Batch	Thickness (mm)	Hardness (kg/cm²)	Diameter	Weight Variation(mg)	Friability	DT (sec)	FM
F1	3.02±0.01	3.7±0.08	12.14±0.1	210.45±0.81	0.09±0.04	154±0.69	0.771
F2	3.53±0.01	3.6±0.01	12.17±0.2	216.20±0.44	0.12±0.10	186±0.01	0.771
F3	3.45±0.01	4.1±0.09	11.89±0.1	221.16±0.2	0.07±0.07	175±0.16	0.578
F4	2.06±0.01	3.8±0.04	12.18±0.2	210.11±.95	0.09±0.01	210±0.89	0.771
F5	3.42±0.01	4.1±0.14	12.6±0.1	215.0±0.61	0.16±0.02	253±1.37	0.578
F6	3.63±0.00	4.1±0.12	12.14±.1	222.01±0.41	0.18±0.13	143±.81	0.578
F7	3.18±0.11	3.8±0.01	12.52±0.2	211.25±0.19	0.43±0.04	307±0.72	0.462
F8	2.84±0.01	3.7±0.00	12.17±0.1	216.84±0.42	0.12±0.06	226±0.16	0.771
F9	3.69±0.01	4.1±0.24	11.76±0.2	220.07±0.21	0.77±0.09	182±0.75	0.462
F10	2.18±0.01	4.1±0.07	12.61±0.1	210.62±0.9	0.32±0.00	254±1.03	0.462
F11	2.75±0.00	3.9±0.04	12.82±0.1	215.03±0.1	0.19±0.19	381±0.05	0.774
F12	3.81±0.01	4.1±0.14	12.41±0.1	221.86±0.7	0.64±0.08	274±0.02	0.578

Table 8: Formulae Percentage (%) Cumulative Drug release

TIME (min)	PURE	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	17.6	18.8	19.7	19.0	18.3	26.9	20.9	34.6	17.8	30.4	21.1	25	33.05
10	19.5	20.8	24.1	39.3	21.5	34.6	40.3	47.8	32.1	32.1	34.4	32.5	41.96
15	21.1	35.1	41.0	52.6	33.0	37.7	55.9	51.7	50.8	35.1	39.8	48.2	63.2
20	22.7	56.1	53.6	76.0	49.8	52.8	82.3	61.5	54.3	51.5	51.9	56.8	73.6
30	27.1	66.2	73.7	87.0	57.0	62.4	85.6	68.3	68.5	56.1	64.5	69.5	86.5
45	28.5	71.6	83.0	87.6	70.8	69.7	89.1	79.0	76.5	87.0	72.7	75.5	96.1
60	30.0	87.0	86.7	91.1	84.1	85.3	94.4	86.3	87.6	97.4	88.6	89.3	98.4

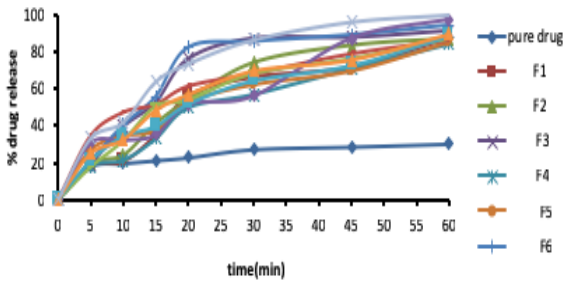

Figure 5: Comparative Dissolution Profiles LQST

CONCLUSION

In the current investigation, attempts are made to prepare and optimize liquid-solid compacts of Simvastatin with different ratios of carrier and coating materials the intention of enhanced dissolution rate with acceptable flow properties as well as better oral bioavailability. MCC, Lactose and Aerosil-200, Syloid-244FP were used as carrier material and coating material respectively. The dissolution rates of formulations i.e, F1,F2,F3.F4,F5,F6,F7,F8,F9,F10,F11 and F12 were higher than that of pure drug. The mechanisms responsible for this improvement could be a solubilization effect of the carrier. Among the two carriers and coating used, Syliod-244FP showed better dissolution enhancement properties and among all the formulations, F12 containing Simvastatin:Syloid-244FP and showed better *in-vitro* dissolution enhancement properties.

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