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RESEARCH ARTICLE

Enhancing the Solubility of Poorly Water Soluble Statins by Different Techniques, Formulation and Evaluation

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ABSTRACT

The objective of the present study is to improve solubility, dissolution profile, absorption efficiency and bioavailability of poorly water soluble statins by using different techniques like co-solvents, solid dispersions, superdisintegrants and sublimation. Lovastatin is a member of statins, used as hypolipidemic agent (lowering cholesterol) in those with hypercholesterolemia and so preventing cardiovascular diseases. Lovastatin is a poorly soluble and highly permeable drug belongs to BCS class II. Rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal track. Tablets are most widely used solid dosage forms because of their advantages. Lovastatin tablets were prepared by direct compression technique. Solid dispersion of Lovastatin was prepared using PEG 6000 (1:1, 1:2, 1:3 ratios respectively), Crospovidone used as superdisintegrant (2%, 4% and 8%), Urea used as sublimating agent (2%, 4% and 8%). The tablets were subjected to thickness, weight variation test, drug content, hardness, friability, disintegration and *in vitro* release studies. In conclusion, the results suggest that the selected best formulation F_6 was shown improvement in dissolution rate (10% more than other methods) from superdisintegrant method and was preferred due to its low cost, easy method of preparation and industrial benefits.

KEYWORDS

Lovastatin, Direct compression, *in vitro* studies, co-solvents, solid dispersions, superdisintegrant

INTRODUCTION

Hypolipidemic drugs are the drugs which lower the levels of lipids and lipoproteins in blood. The hypolipidemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidemic individuals.[1]

According to Global Health Observatory data, a third of ischaemic heart disease is resultant to high cholesterol. Raised total cholesterol is a major cause of disease burden in both the developing and developed countries as a risk factor for Ischemic heart disease and stroke. In 2008, the global prevalence of raised total cholesterol among adults was 39%.

The prevalence of elevated total cholesterol was highest in the WHO Region of Europe 54% for both sexes, followed by the WHO Region of the Americas 48% for both sexes. The WHO African region and the WHO South East Asian region showed the lowest percentages 22.6% for African region and 29.0% for South East Asian region.

By studying the Hyperlipidemic risk factors, we selected this category and also selected Lovastatin as a drug, because of its poor solubility in aqueous medium. As solubility decreases, its absorption also decreases and

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reduces the therapeutic effect of the drug because of this reason here attempted to improve the solubility of the drug by using different solubilizing techniques.

By studying the different techniques like Particle size reduction, Super critical fluid (SCF) process, Inclusion complexes/ Complexation, Co-solvency, Micellar solubilisation, Hydrotropy, Nano crystallization, Solid dispersion, Sublimation and Superdisintegration to improve the solubility of the poorly water soluble drugs, here we selected the cosolvents, solid dispersion, superdisintegration and sublimating techniques to enhance the solubility of poorly water soluble drug Lovastatin.[2-8]

MATERIAL AND METHODS

Lovastatin obtained from the MSN laboratories, Hyderabad, India. Crospovidone obtained from the Rolex Chemical Industry, Mumbai, India. Polyethylene glycol 6000, Urea, Micro crystalline cellulose, Spray dried lactose, Starch, Magnesium and Talc obtained from the S.D Fine-Chem. LTD, Boisar.

Preparation of Solid Dispersion

The Melt solvent method of Lovastatin and carrier PEG was carried out using water bath. The weighed amount of carrier (Drug: Polymer; 1:1, 1:2, 1:3 ratios) was added to the china dish and kept it for melting using water bath the temperature should not exceed 60ºC.

After complete melting of polymer the drug previously dissolved in acetone was added and stirred continuously until it form a solid damp mass and cool it in the room temperature. Sieve the solid damp mass using #40 sieves to obtain a uniform particle size and store it in desiccators until further use.

Preparation of Lovastatin Tablets

The Lovastatin tablets were prepared by direct compression technique where in case of solid dispersion method drug equivalent to 20 mg was taken, in case of sublimation and superdisintegration method drug of 20 mg was taken and mixed thoroughly for 5 min with required quantity of micro crystalline cellulose, spray dried lactose, starch, crospovidone (2%, 4% and 8%) and urea (2%, 4% and 8%) which were previously passed through #60 sieve to get uniform size particles. At last 1% of magnesium stearate and talc were added, mixed again and compressed the tablet of each 100 mg table 1.

Angle of Repose

Angle of repose was determined by fixed funnel method. The powder mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the formulation powder. The powder was allowed to flow through the funnel freely onto surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the formula given below, limit is given in the table 4 and the result shown in the table 2.

$$\text{Angle of repose} = tan^{-1}\frac{h}{r}$$

Where, θ = angle of repose, h = height of the pile, r = radius of the pile base.

Bulk Density

Loose Bulk Density (LBD)

LBD was determined by placing powders into a graduated cylinder and measuring the volume and weight as it is and results are shown in the table 2.

$$\text{Loose bulk density} = \frac{\text{Mass}}{\text{Volume}}$$

Tapped Bulk Density (TBD)

TBD was determined by weighing the powder mixture and transferred to a graduated cylinder and tapped to a fixed number of taps. The TBD was determined by using the given formula and the results are shown in the table 2.

$$\text{Tapped bulk density} = \frac{\text{Weight of granules}}{\text{Tapped volume}}$$

Compressibility Index and Hausner Ratio

Compressibility index and Hausner ratio are simple, fast and popular methods to know the powder flow property.

Table 1: Formulation Table of Lovastatin Tablet

Ingredients	**Purpose**	**F_1 (mg)**	**F_2 (mg)**	**F_3 (mg)**	**F_4 (mg)**	**F_5 (mg)**	**F_6 (mg)**	**F_7 (mg)**	**F_8 (mg)**	**F_9 (mg)**
Lovastatin	Drug	20	20	20	20	20	20	20	20	20
PEG 6000	Solid dispersion carrier	20	40	60	–	–	–	–	–	–
Crospovidone	Super disintegrant	–	–	–	2	4	8	–	–	–
Urea	Sublimating agent	–	–	–	–	–	–	2	4	8
Starch	Binding agent	5	5	5	5	5	5	5	5	5
Sprayed dried Lactose	Diluent	2	2	2	19	17	13	19	17	13
Micro crystalline cellulose	Diluent and disintegrant	51	31	11	52	52	52	52	52	52
Magnesium Stearate	Lubricant	1	1	1	1	1	1	1	1	1
Talc	Glidant	1	1	1	1	1	1	1	1	1
Total weight		100	100	100	100	100	100	100	100	100

Table 2: Preformulation Results

Formulation	**Bulk density * (g/ml)**	**Tapped density ^ (g/ml)**	**Carr's index Δ (%)**	**Hausner's ratio Ψ**	**Angle of repose (º) $**
F_1	0.395±0.005	0.453±0.054	12.803±0.943	1.14±0.015	33.27±2.53
F_2	0.386±0.004	0.438±0.006	11.872±.865	1.13±0.011	32.59±3.05
F_3	0.392±0.035	0.448±0.057	12.5±0.928	1.14±0.012	33.14±2.59
F_4	0.456±0.004	0.511±0.004	10.763±0.457	1.12±0.009	31.25±2.56
F_5	0.466±0.055	0.523±0.049	10.898±0.154	1.122±0.010	32.58±2.98
F_6	0.472±0.053	0.530±0.008	10.943±0.286	1.122±0.011	31.98±3.01
F_7	0.411±0.009	0.508±0.056	19.094±0.685	1.23±0.016	37.29±3.52
F_8	0.396±0.005	0.494±0.032	19.83±0.842	1.24±0.014	36.59±1.98
F_9	0.385±0.051	0.496±0.004	22.37±0.198	1.288±0.008	38.14±2.48

All the data are presented in average ± SD, n=3

Table 3: Postformulation Results

Formu -lation	Thickness (mm)	Disintegration (min)	Weight* (mg)	Friability (%Loss)	Hardness (kg/cm^2)	% Drug content
F_1	2.05±0.02	21.20±0.52	103.4±3.69	0.369±0.026	2.2±0.22	96.35±2.31
F_2	2.01±0.03	17.40±0.81	101.4±4.51	0.398±0.054	2.3±0.15	98.22±3.01
F_3	2.01±0.02	15.45±0.62	101.9±3.12	0.192±0.081	2.07±0.25	101±2.26
F_4	2.03±0.00	1±0.5	101.45±2.05	0.39±0.072	3.14±0.22	99.58±1.3
F_5	2.01±0.00	2.40±0.34	100.35±2.22	0.192±0.05	2.8±0.35	103±2.32
F_6	2.03±0.02	2.08±0.65	102.1±3.11	0.193±0.068	3.6±0.11	101±2.01
F_7	2.02±0.03	0.40±0.36	96.5±1.25	0.198±0.035	0.98±0.39	102±1.01
F_8	2.02±0.01	0.45±0.3	95.1±2.15	0.38±0.046	0.95±0.51	99±2.37
F_9	2.01±0.00	0.42±0.32	94.3±2.10	0.609±0.067	0.94±0.24	98±3.21

All data are presented average ± SD, n=3, *n=20

Table 4: IP Specification

Parameter	Observed Value for the best formulation	Specification
Angle of repose (˚)	31.98±3.01	31-35 (Good flow property)
Carr's index (%)	10.943±0.286	11-15 (Good flow property)
Hausner's ratio	1.122±0.011	1.12-1.18 (Good flow property)
Friability (%)	0.193±0.068	Not more than 1% after 100 revolutions
Weight variation (mg)	102.1±3.11	± 7.5
Hardness (kg/cm²)	3.6±0.11	4.0-6.0
Disintegration (min)	2.08±0.65	2.0-5.0

Table 5: Post Compression Parameters of Most Satisfactory Formulation (F_6)

Parameters	Condition (40±2°C/75±5%RH)		
	1st month	3rd month	6th month
Physical appearance	White, Flat faced	White, Flat faced	White, Flat faced
Weight Variation (mg)	101.35±2.5	100.35±2.35	102.35±3.5
Hardness (Kg/cm^2)	3.4±0.12	3.2±0.10	3.3±0.11
Drug Content (%)	99.85	98.95	98.56
Disintegration time (min)	2.05±0.35	2.03±0.25	2.01±0.11

The compressibility index has been proposed as an indirect method of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because of all these can influence the observed compressibility index. The compressibility index and Hausner ratio are determined by measuring both the bulk volume and the tapped volume of powder. Based on LBD and TBD, the % compressibility of the powder mixture was determined by using the given formula, limit is given in the table 4 and the results are shown in the table 2.

$$\text{Compressibility index} = \frac{\text{TBD}-\text{LBD}}{\text{TBD}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Post Compression Study

Weight Variation

Weight variation was determined by selecting twenty tablets randomly, weighed individually and the average weight was determined for each formulation. The percentage deviation from the average weight was calculated, limit is given in the table 4 and the results are shown in the table 3.

Tablet Hardness

Hardness of the tablet was determined by using Monsanto hardness tester. The tablet to be tested was held between a fixed and a movable jaw and the reading of the indicator was adjusted to zero. The force was applied until the tablet breaks. The reading was noted from the scale which indicates the pressure required in kg/cm^2 to break the tablets. The test was carried out for each formulation. Limit is given in the table 4 and results were showed in the table 3.

Friability

Strength of the tablet is measured by friability. Roche Friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in a plastic chamber that revolves at 25 rpm at 4 min dropping the tablets from the distance of 6 inches with each revolution. After 100 revolutions the tablets were re weighed and the percentage loss in tablet weight was determined. Limit is given in the table 4 and results were showed in the table 3.

$$\% \text{ Friability} = \frac{(\text{Initial wt. of tablets} - \text{Final wt. of tablets})}{\text{Initial wt. of tablets}} \times 100$$

Thickness and Diameter

Thickness and diameter of the tablet are important for the uniformity of the tablet size. Thickness and diameter was measured for 10 randomly selected tablets using Screw gauge. Results were showed in the table 3.

Uniformity of Drug Content

The 5 tablets were weighed and average weight was calculated. All 5 tablets were crushed and powder weight equivalent to 20 mg of drug was taken and dissolve in 20 ml of acetone and made up to 100 ml with 0.1 N HCl and kept overnight for complete dissolution. The solution was filtered, 2 ml of filtrate solution was taken and dilute to 50 ml and measured the absorbance at 238 nm using UV spectrophotometer (Shimadzu-UV-1800). Results were showed in the table 3. The drug content was determined by using the formula:

$$\text{Drug content} = \frac{\text{Absorbance}}{\text{Slope}} \times \frac{\text{Dilution factor}}{1000}$$

Disintegration Study

Each tablet of each formulation was kept in glass tube and placed the disk on the tablet to avoid floating of the tablet in the disintegration apparatus (Electrolab ED-2L) and the apparatus was moved up and down through 5-6 cm distance in the 0.1 N HCl medium at 37±2˚C for 10 min at 28 to 32 rpm speed. The process was continued until the tablet disintegrates and the time was noted down. The results were shown in the table 3.

In vitro Release Study

The *In vitro* dissolution for Lovastatin was determined by using USP dissolution apparatus II Paddle type (Electrolab TDT-08L) at 50 rpm using 0.1 N HCl as dissolution medium at 37 ± 0.5ºC. 2 ml sample was withdrawn and filtered, 1 ml filtrate was diluted to 10 ml using 0.1 N HCl

dissolution medium for each 10 min interval for 2 h and absorbance was measured at 238 nm using UV spectrophotometer. The cumulative percentage drug release was plotted against time to determine the drug release profile and the results are shown in the Fig.1.

Accelerated Stability Studies for Best Batch

The study was carried out in order to determine the change in various drug properties on storage. The accelerated stability test of best batch carried out as per ICH guidelines i.e. at 40±2°C/ 75±5% relative humidity for 6 months. At 1st, 3rd and 6th month tablets were taken and analysed for any changes in hardness, friability, drug content, disintegration [Table 5] and *in-vitro* drug release [Fig.2]. *FT-IR* of the selected batch was done at the end of stability period to check the compatibility of the drug in the formulation and the results are shown in the Fig.3-7.

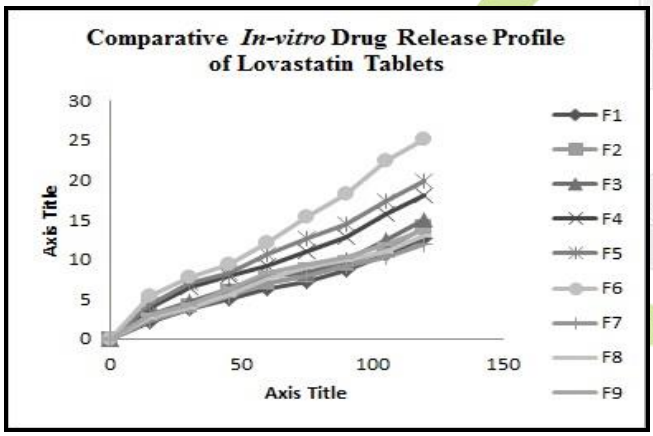

Figure 1: *In Vitro* Release Profile

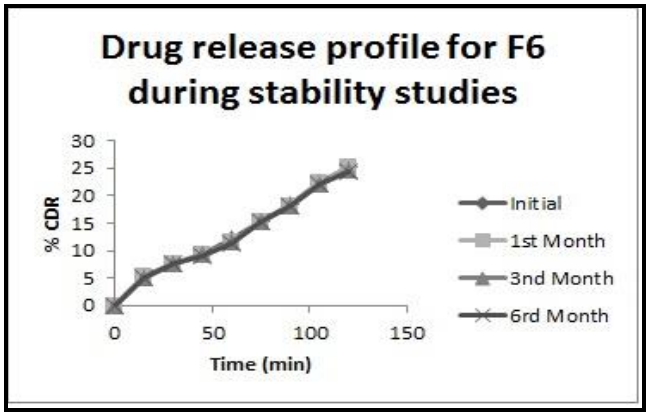

Figure 2: Drug Release Profile during Stability Studies

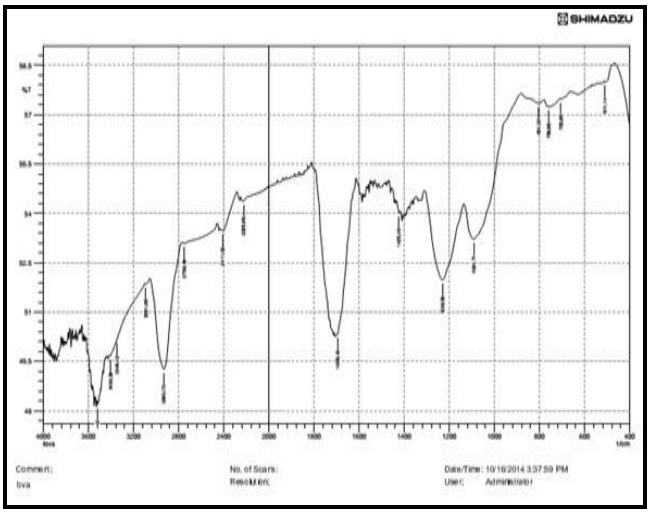

Figure 3: *FT-IR* Graph of Lovastatin Pure Drug

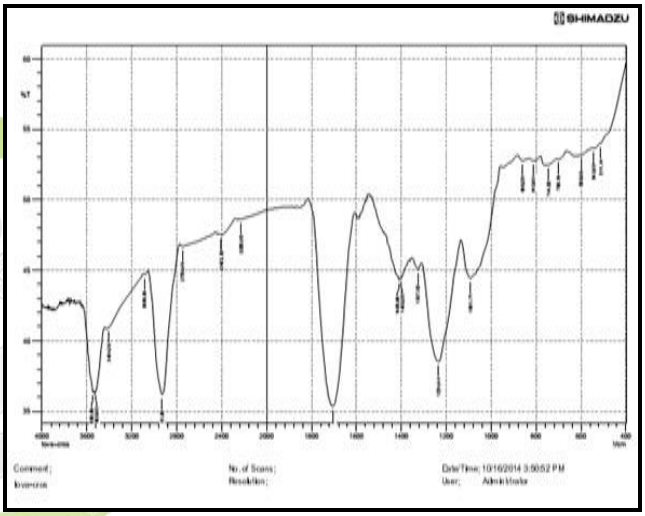

Figure 4: *FT-IR* Graph of Lovastatin and Crospovidone

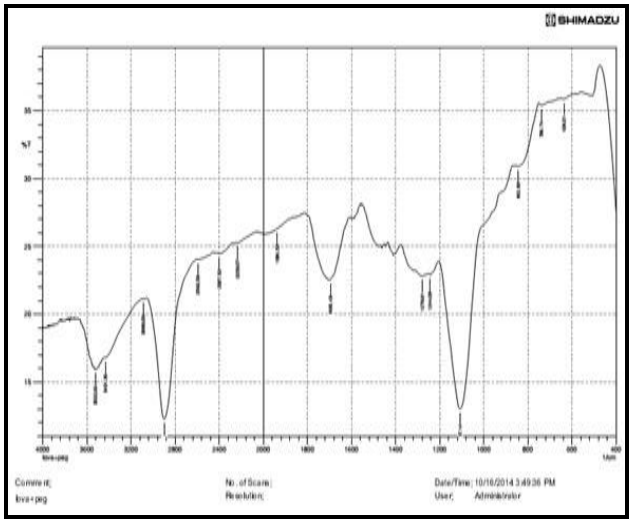

Figure 5: *FT-IR* Graph of Lovastatin and PEG 6000

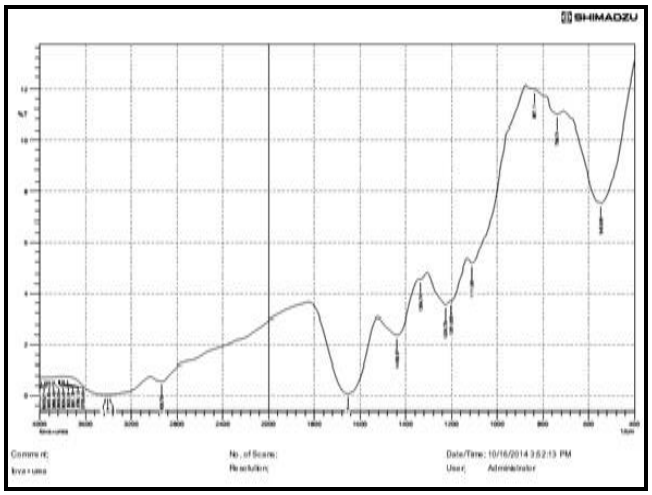

Figure 6: *FT-IR* Graph of Lovastatin and Urea

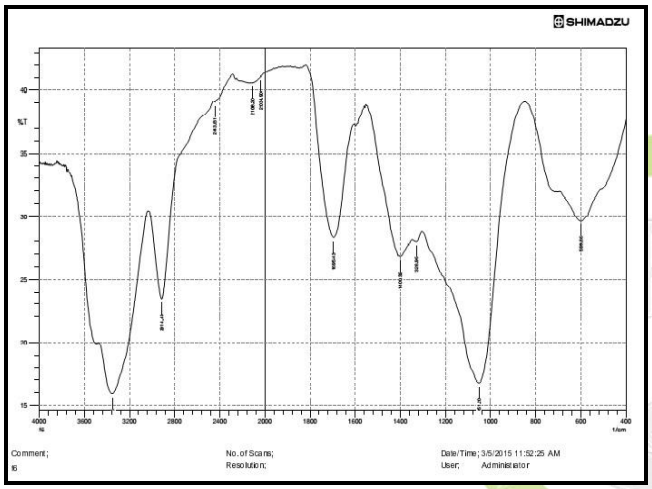

Figure 7: *FT-IR* Study of F_6 after 6 Months

RESULTS AND DISCUSSION

Solid dispersion of Lovastatin was successfully prepared using poly ethylene glycol 6000 polymer (1:1, 1:2 and 1:3) by melt solvent method. *FT-IR* studies revealed that there were no chemical interactions between Lovastatin and the polymers used in the study. Lovastatin tablets by incorporating solid dispersion (F_1, F_2 and F_3), using superdisintegrant (Crospovidone) in different percentage 2%, 4% and 8% (F_4, F_5 and F_6) and by using sublimating agent (Urea) in different percentage 2%, 4% and 8% (F_7, F_8 and F_9) were successfully prepared by direct compression technique. Formulations F_1-F_3 even though passes preformulation tests but failed in disintegration test as it showed more DT and there was no significant increase in the release of drug as increasing the polymer concentration as expected, therefore formulations F_1-F_3 fails. Formulations F_4-F_6 passes both preformulation and postformulation tests and there was significant increase in the release of drug as increasing the superdisintegrant Crospovidone concentration as expected, therefore formulations F_4-F_6 passes. F_6 shows the highest release of drug 25.045% CDR in 120 min therefore F_6 selected as the best formulation. Formulations F_7-F_9 also passes preformulation tests but failed in postformulation tests like hardness and disintegration tests. Very less hardness and disintegration time which indicates very less mechanical strength and there was no significant increase in the release of drug as increasing the sublimating agent Urea, as expected therefore formulations F_7-F_9 fails. The best formulation was subjected for stability test for 6 months at 40 ± 2°C and 75 ± 5% RH which showed no significant changes.

CONCLUSION

From the present research results, it is concluded that the F_6 selected as best formulation because it showed good results in all the evaluation tests. By including the superdisintegrating agent in the formulation of poorly water soluble drugs, can enhance the solubility of that poorly soluble drug.

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