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Solid Dispersion of Simvastatin for Improved Solubility, Dissolution and Bioavailability Using Modified Locust Bean Gum

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ABSTRACT

The objective of this investigation was to improve solubility and dissolution rate of water insoluble drugs Simvastatin by Microwave Generated solid dispersion techniques. The solid dispersions prepared using natural polymer enhances solubility and dissolution rate of drug. Solid dispersions were characterized using DSC, SEM, XRD which indicates that crystallinity of Simvastatin has been reduced significantly. Solubility study result gave best ratio of drug and polymer. *In vitro* drug release from prepared immediate release tablet was compared with marketed formulation. *In vivo* study was performed in rats by measuring HMG Co-A reductase activity. A significant reduction in the HMG Co-A reductase activity was observed with Solid dispersions of Simvastatin as compared to plain drug. Therefore, the solid dispersions technique using natural polymer could be successful technique for enhancing the solubility of poorly water soluble Simvastatin.

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1. INTRODUCTION

Therapeutic success of a drug depends upon the bioavailability which is dependent upon the solubility and permeability of drug molecules. Solubility is one of the significant parameter to achieve desired concentration of drug in systemic circulation to achieve pharmacological response. Currently, only 8 % of new drug candidates have both high solubility and permeability. Poorly soluble drugs have number of limitations such as need of higher dosage and the consequential occurrence of side effects. The rate-limiting step in the absorption process for poorly water-soluble drugs is dissolution rate of such drugs in the gastrointestinal fluids rather than the rapidity of their diffusion across the gut wall. Thus, it is important to improve the oral bioavailability of poorly water soluble drugs by improving their dissolution rate and solubility. Solubility and dissolution rate of poorly soluble drugs can be enhanced using various techniques such as micronization, complexation, solubilization in surfactant system, drug derivatization etc. However, all this methods have limitations like poor flow properties, high energetic surfaces and particle agglomeration. Complexation with cyclodextrins shows low drug loading and limitations for drug selection. Among the methods to improve solubility and dissolution rate of poorly water soluble drugs, solid dispersion is one of the most popular techniques. Dispersion of poorly water-soluble drugs in an inert hydrophilic carrier or matrix at solid state provided by the kneading, melting and solvent evaporation methods leads to products referred to as solid dispersions (SD) (Chiou W. L. et al, 1971). Microwaves irradiation (MW) is a well-known method for heating and drying materials. (Mariarosa Moneghini. et al. 2008; Sofia Anastasios Papadimitriou et al. 2007). Microwaves, with their ability to penetrate any substance, allow the production of heat in any point of the sample at the same time. It has been reported that microwave energy can influence the crystalline status of the drug and the time of exposure plays an important role in achieving the amorphous state of the drug, thus improving its dissolution rate (Fawaz F.et al, 1996; Chen Y. et al, 2004). The application of microwaves represents a promising alternative to conventional preparative methods of solid dispersions of drugs as the microwave induced method involves much shorter preparation times.

Now a day there has been tremendous improvement in the usage of natural polymers as pharmaceutical excipients for oral use.

Simvastatin (SIM) was selected as model drug in this study. Simvastatin has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood (Moffat et al., 2004). This compound is practically insoluble in water and has high lipophilicity (log P = 4.937) (Martindale, 1989). Thus, the dissolution rate of simvastatin is expected to limit its absorption from the gastrointestinal tract.

Hence the present work is aimed to explore the applicability of polymer of natural origin such as Locust bean gum (LBG) in the enhancement of dissolution rate and thereby oral bioavailability of poorly water soluble drug. The influence of microwave induced solid dispersions prepared using Locust bean gum (MWLBG) as a hydrophilic carrier on solubility enhancement of poorly water soluble drug Simvastatin in comparison to that of plain drug was investigated.

2. MATERIALS AND METHODS

2.1 Materials

Simvastatin was obtained from Aritimis biotech Hyderabad, Locust bean gum was obtained from lucid colloids ltd, Mumbai. Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Sodium Starch Glycolate, Hydroxypropyl cellulose, Magnesium stearate, Talc, Colloidal silicon dioxide, Methanol, Hydrochloric acid (HCL), Sodium lauryl sulphate (SLS) Monobasic sodium phosphate, Sodium hydroxide used were of analytical grade.

2.2 Methodology

2.2.1 Characterization of polymers

Swelling Index (SI)

The swelling and water retention capacity of the Locust bean gum (LBG), and modified Locust bean gum (MWLBG) were estimated by a slightly modified method described by Gauthami and Bhat (1992). About 1.0 g of LBG, and MWLBG powder were accurately weighed and transferred to a 100 ml stoppered measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100 ml mark with distilled water. The cylinder was stoppered and was shaken gently and set aside for 24 h. The volume occupied by the gum sediment was noted after 24 h. Swelling capacity of LBG, and MWLBG was expressed in terms of swelling index as follows. Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$SI = \frac{[(X1 - X0)]}{X0} \times 100$$

Where, X0 is the initial height of the powder in graduated cylinder and Xt denotes the height occupied by swollen gum after 24 h.

Viscosity Measurement

The viscosity of a 1 % aqueous LBG, and MWLBG gums were measured according to USP specifications using a Brookfield DV-E viscometer (Belgamwar et al., 2009).

Modification of carriers

The natural gum LBG (Reymond et al., 2003) was modified by microwave heating method powdered carriers were taken in a porcelain bowl and kept in microwave oven at different watt, temperature and time.

2.2.2 Preparation of sample

2.2.2.1 Preparation of physical mixture

Physical mixture of drug (SIM) with carrier (LBG, MWLBG) were prepared respectively by simple blending of drug with polymer in 1:1 to 1:9 ratio (drug: gum) for 10 min. The physical mixture of drug with polymer were denoted as SIM (1-9), PLBG SIM (1-9),MWLBG SIM (1-9).

2.2.2.2 Preparation of microwave induced solid dispersions

Solid dispersions were prepared using the microwave induced fusion method. The optimized ratio was found to be 1:9 w/w. First SIM and polymer (MWLBG) were weighed in ratio 1:9 w/w followed by homogeneous slurry. A fixed amount of mixture (5g) was subjected to microwave for different time 10 and 20 min at a constant power of 560 W in a microwave instrument (Catalyst2R,Catalytic System). The temperature of the mixture at the end of treatment was noted with inbuilt temperature measurement probe. The samples were then grounded in glass motor and pass through sieve to get particle size from 80 to 250 um. The SD's of drug with polymer were denoted as, MWLBG SIM (1-9).

2.2.3 Ratio optimization (drug: polymer) by solubility

Sample of solid dispersion equivalent to 30 mg of SIM were placed in 10 mL solvent in Teflon coated screw capped vial and kept at equilibrium for period of 24 h on orbital shaking incubator (Remi Instrument Ltd.) at 37 ±0.5 ^{o}C and 50 rpm. The content of vial were filtered through 0.2 micron filter and analyzed using UV-Visible spectrophotometer (UV 1601, Shimadzu, Japan) at respective wavelength of the drug.

2.2.4 Solid mixture Characterization

2.2.4.1 Melting point

Melting point of drug, carrier, SD was measured by capillary method. The samples were filled into a glass capillary tube, which was sealed at one end. The temperature was noted when it is completely melted.

2.2.4.2 Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectra of pure drug, carrier (LBG), and SD of Simvastatin with modified carriers (MWLBG) prepared by microwave induced fusion method were obtained to study interaction if any between drug and gum in mixture using KBr disk method (1 mg of sample in 100 mg KBr).

2.2.4.3 Differential scanning calorimetry (DSC)

DSC thermograms of pure drug, pure carrier (LBG) and SD with modified carrier (MWLBG) prepared by microwave induced fusion method were obtained using DSC-60, Shimadzu, Japan, at a heating rate of 10° C/min from 0 to 300° C in nitrogen atmosphere.

2.2.4.4 X-Ray Diffraction study (XRD)

XRD study of pure drug, carrier (LBG) and SD with modified carriers (MWLBG) prepared by microwave induced fusion method were obtained using Philips diffractometer (PW 1140) and Cu-kα radiation. The diffractograms were run at a scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2Ø.

2.2.4.5 Scanning electron microscopy (SEM)

SEM photomicrograph of pure drug, carrier (LBG) and SD with modified carrier (MWLBG) prepared by microwave induced fusion method were obtained using scanning electron microscopy (JSM 5610 LV, JEOL, Datum Ltd, Japan).

2.2.5 Solubility study

The solubility study of SIM, PLBGSIM, and MWLBGSIM were determined in PH 6.8 buffer. The solubility of drug, SD's were determined by taking an excess amount of drug (30 mg), SD's (equivalent to 30 mg of drug) and added them in 10 ml of pH 6.8 phosphate buffer, in Teflon facing screw capped vials. The samples were kept at equilibrium for a period of 48 h on orbital shaking incubator at 37±0.5°C and 50 rpm. The supernatant collected from vial was filtered through 0.2 micron filter and analyzed by UV-Visible spectroscopy (UV 1601, Shimadzu, Japan) at a λ_{max} of SIM.

2.2.6 Drug content analysis

Drug content analysis was performed in order to study the amount of drug incorporated in SD's. Simvastatin was extracted from SD's by dissolving them in 25 mL methanol. Simvastatin content in the methanolic extract was analyzed spectrophotometrically at λ_{max} of SIM.

2.2.7 Preparation of immediate release tablets

The ratio of SD's which has shown best results in solubility and dissolution studies were selected for formulating the immediate release tablet. Tablets were prepared (F1 to F4 batch) using superdisintegrant for formulating tablet. The composition of tablet is given in Table 1. All the components of tablet were sieved through sieve # 40, mixed and compressed into tablet using 8.8 mm punch on rotary tablet minipress (Rimek, Ahmadabad, India).

Table 1. Composition of immediate release tablets of $MWLBG_{SIM}$

SN	Ingredient Name	Quantity mg/tablet			
		F1	F2	F3	F4
1.	Simvastatin solid dispersion ($MWLBG_{SIM}$)	50	50	50	50
2	Microcrystalline cellulose (Avicel PH 102)	X	80.5	180.5	175.5
3	Pregelatinised starch(Starch 1500)	X	10.0	10.0	10.0
4	Lactose monohydrate (Supertab 30 GR)	198.0	100.0	X	X
5	Hydroxypropyl cellulose (L HPC LH-11)	10.0	10.0	10.0	10.0
6	Croscarmellose Sodium (Ac-Di-sol)	5.0	5.0	5.0	10.0
7	Ascorbic acid	X	5.0	5.0	5.0
8	Citric acid	X	2.0	2.0	2.0
9	Butylated hydroxyanisole	X	0.5	0.5	0.5
10	Colloidal silicon dioxide (Aerosil 200)	2.0	2.0	2.0	2.0
11	Talc	2.0	2.0	2.0	2.0
12	Mg Stearate	2.0	2.0	2.0	2.0
13	Opadry white	6.0	6.0	6.0	6.0
Total weight		275	275	275	275

2.3 Evaluation of immediate release tablet

2.3.1 Pre compression evaluation

Pre-compression evaluation includes measurement of angle of repose and Hausner's ratio of optimized SD's and various formulation mixtures. All the tests were performed as per the procedure given in USP 30 (2007).

2.3.2 Post compression evaluation

Post compression evaluation includes measurement of weight variation, hardness, friability, drug content and disintegration time (DT) of prepared formulation. All the tests were performed as per the procedure given in USP 30 (2007).

2.3.3 Drug-excipients interaction study

Powder mixture of formulation components were subjected to FTIR and DSC studies to detect any interaction between various components of formulation.

2.2.4 Stability study

The accelerated stability study of tablets was checked for stability as per ICH guidelines at 40 º C/75 % RH up to 3 months. The tablet were filled in cap vials and packed in aluminum stripes and stored for 3 months in stability chamber (CHM 10S, REMI instruments Ltd. India). Sample was removed and analyzed for *in vitro* drug release in time interval of 0, 30, 60 and 90 days.

2.2.5 *In Vivo* Study

An indirect method was used to assess variations in 3-hydroxy-3 methyl glutaryl-coenzyme A reductase (NADPH) activity in liver tissue. The HMG CoA and mevalonate concentrations in the tissue homogenate were estimated in terms of the absorbance, and the ratio of the two concentrations was taken as an index of the activity of the enzyme, which catalyses the conversion of HMG CoA to mevalonate. The HMG CoA to mevalonate ratio was measured in liver tissues of male albino rats weighing 150–200 g. Rats were divided into five groups (normal, control, MWLBG SIM 200 mg/kg, MWLBG SIM 400 mg/kg, Simvastatin 200 mg/kg, Simvastatin 400mg/kg) each group consist of six animal. Animal in group I receives normal pallet diet, whereas group II, III, IV and V receives high fat diet (HFD) containing 2 % coconut oil, 1 % sodium cholate, 2 % pure cholesterol for 30 days. Simvastatin were administered from 0 day up to 30 days by orally as suspension to respective group. Blood sample were collected initially before the administration of diet i.e. on 0 day after 24 hrs of 30th day of blood sample were collected by retro orbital puncture. Serum were separated and used for biochemical estimation of lipid profile like total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), total protein, and total bilirubin by using Auto-span Diagnostic Kits Pvt. Ltd. India.

The study was approved and conducted as per the norms of the Institutional Animal Ethics Committee (Ref: HSK CP/IAEC, Clear/2010-11/1-12)

4. RESULTS AND DISCUSSION

As reported the LBG having surfactant activity and also increases wetting by reducing the contact angle, thus enhance the solubilization and dissolution of drug particles. (Rowe et al., 2003) and this additional microwave treatment is very green, effective and advanced way for formation of SD (P. Bergese et. al).

4.1 Physical characterization of polymer

Result of swelling and viscosity of polymers are shown in Table 2. From the result, it can be concluded that the viscosity of MWLBG is lower than LBG and swelling index of and MWLBG was not reduced significantly than LBG. Because of no significant changes in swelling nature of modified carriers extensive surface increased during the dissolution and dissolution rate of drug is enhanced (Westerberg et al., 1986) and due to significant reduction in viscosity they are less prone to the formation of sturdy matrix which will assist rapid liberation of the drug particles from SD.

Table 2: Characterization of polymer

Polymer	Viscosity (cp)	Swelling Index (%)
LBG	219 ± 5.79	2914 ± 23.1
MWLBG	83 ± 3.71	2648 ± 25.0

4.2 Solid mixture characterization:

4.2.1 Melting point: melting point of drug, carrier and modified carriers are given in table 3. From the melting point the conditions for modifications of carrier (LBG) were set up.

Table 3: Melting point of drug and carriers

Sr. No.	Samples	Melting range
1	SIM	133 -139 ^{0} C
2	LBG	245 – 265 ^{0} C
3	MWLBG	235 – 245 ^{0} C

4.2.2 Drug-carrier interaction study

4.2.2.1 FT-IR studies

FTIR spectroscopy was used to study the possible interactions between SIM, pure carrier (LBG), modified carriers (MWLBG) is shown in the following Figure 1. All major peaks of SIM observed at wave numbers 3545 cm^{-1} (free O–H stretching vibrations); 2970 cm^{-1} (Methyl C-H asymmetric stretch); 2872 cm^{-1} (Methylene C-H symmetric stretch); and 1695 cm^{-1} (Ester C=O stretch); 1265cm^{-1} (Lactone -C -O-C stretch). The principle peak values of drug remain unchanged in the microwave treated SD's. Thus it can be concluded that there is no chemical interaction between the drug and gum.

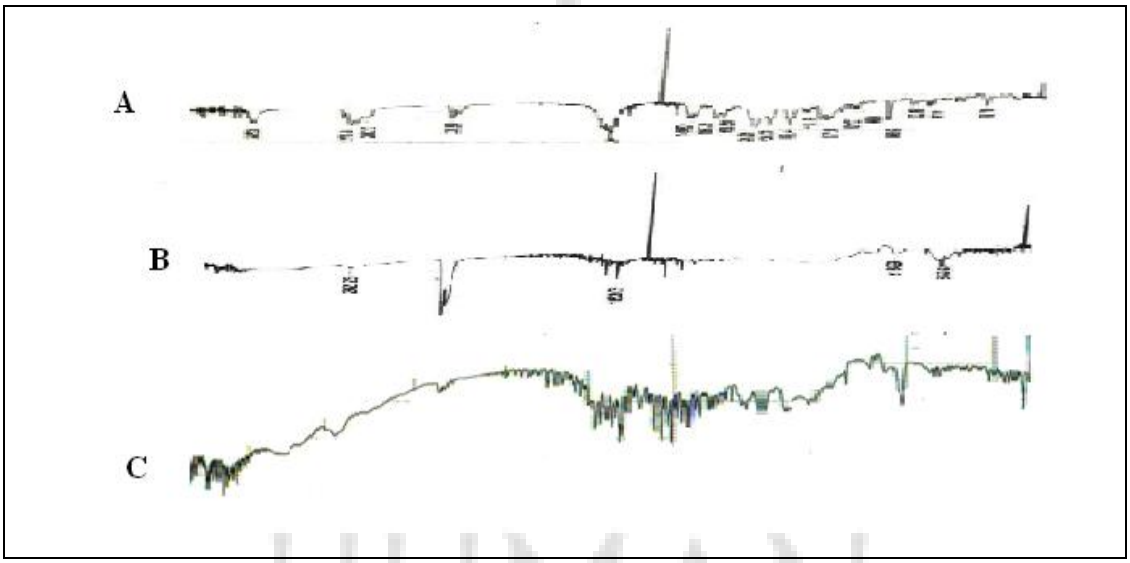

Figure 1: FT-IR Spectra of A) SIM, B) Microwave treated Locust Bean Gum (MWLBG) and C) Microwave Generated solid dispersion of SIM with LBG Physical ($MWLBG_{SIM}$)

4.2.2.2 DSC studies

DSC profile of drug, modified carrier (MWLBG) and SD of SIM, with modified carrier (MWLBG) is shown in the following figure 2. Crystalline nature of SIM can be easily recognized by the presence of sharp endothermic peak at around 165.33ºC. This endothermic peak is almost disappeared with broadened endotherm in DSC profile of indicating amorphous nature of SIM.

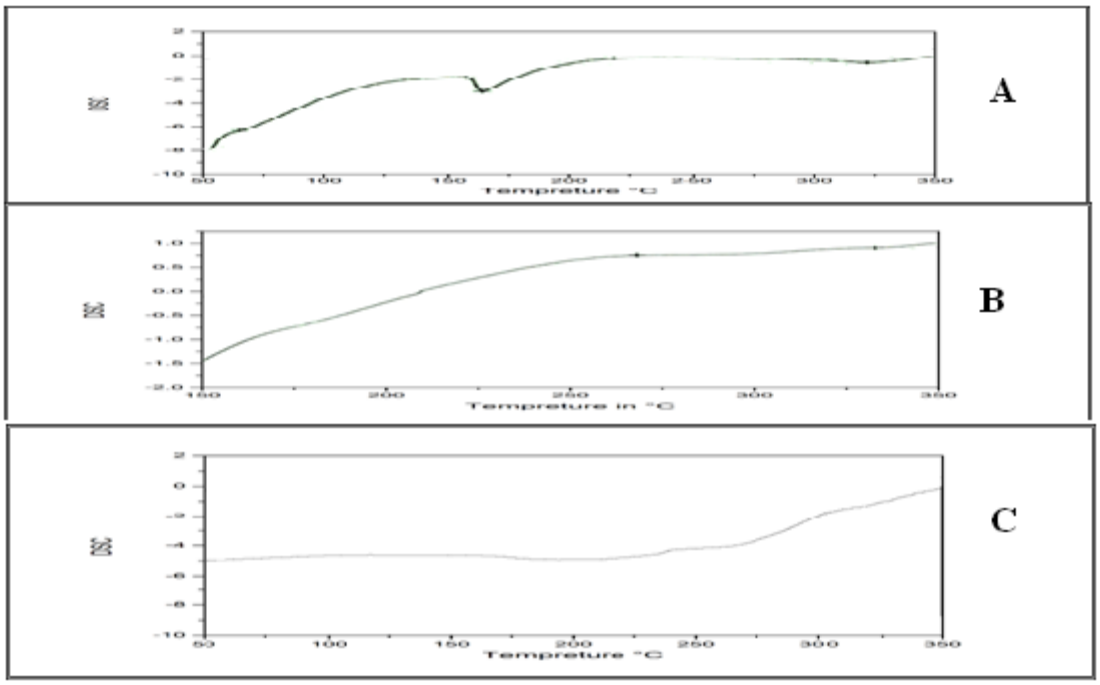

Figure 2: DSC thermograms of A) SIM, B) MWLBG and C) $MWLBG_{SIM}$

4.2.2.3 XRD studies

Powder X-ray Diffraction Studies of SIM, pure carrier (LBG), modified carrier (MWLBG) and SD of drug with modified carrier (MWLBG) are shown in figure 3. The pure SIM exhibited intense crystalline peak between 4^0 and 45^0. Characteristic diffraction peaks at 5.84 ^{0}, 8.97 ^{0}, 12.73 ^{0}, 16.26 ^{0}, 17.34 ^{0}, 18.60 ^{0}, 22.33 ^{0}, 25.66 ^{0}, 26.23 ^{0} were observed with intense peak it indicating the crystalline nature of SIM. On the other hand, in $MWLBG_{SIM}$ it is observed that peak intensity is reduced indicating conversion of Crystalline Drug to Amorphous form.

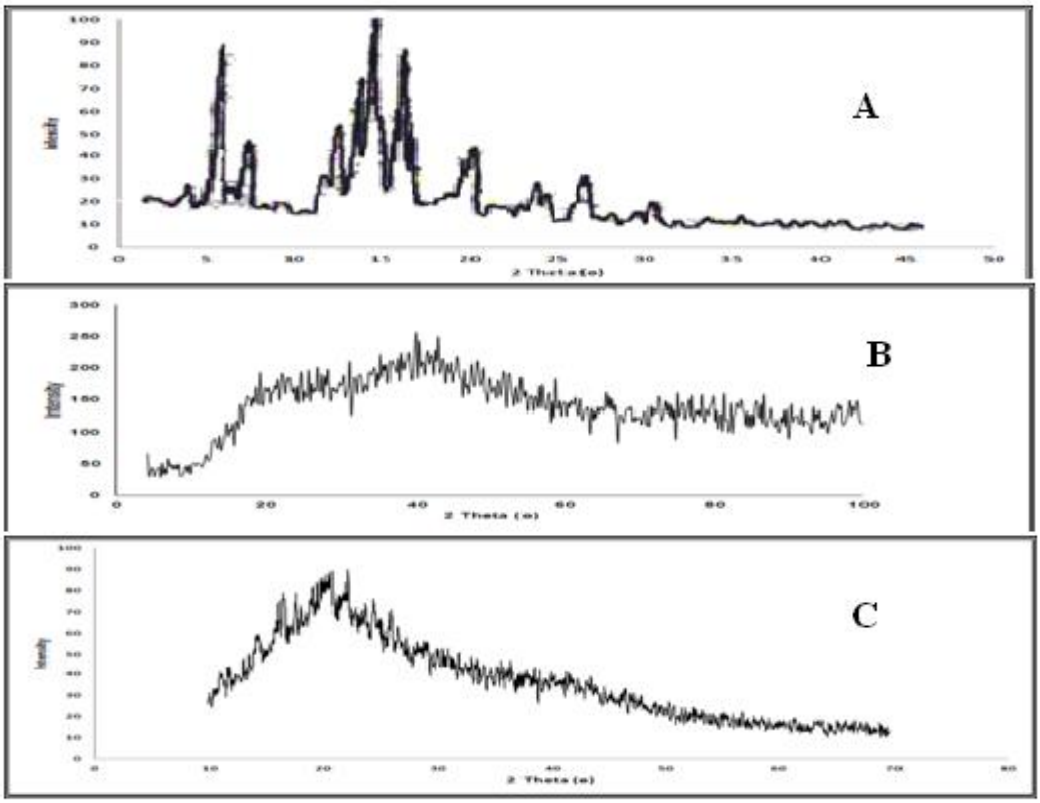

Figure 3: Powder X Ray Diffraction pattern of A) SIM, B) MWLBG and C) $MWLBG_{SIM}$

4.2.2.4 Scanning electron microscopy (SEM)

The SEM studies are generally done to study surface morphology of drug particles. The morphology of pure drug, modified carrier (MWLBG) and SD of drug with modified carrier are show in following figures. From the figure it can be concluded that SIM particles were plate shaped with smooth surface, while in case of MWLBG it was observed that they were of irregular shape and size. Figure clearly shows that crystal shape of SIM was completely changed in MWLBG showing embedded SIM crystals in the MWLBG matrix.

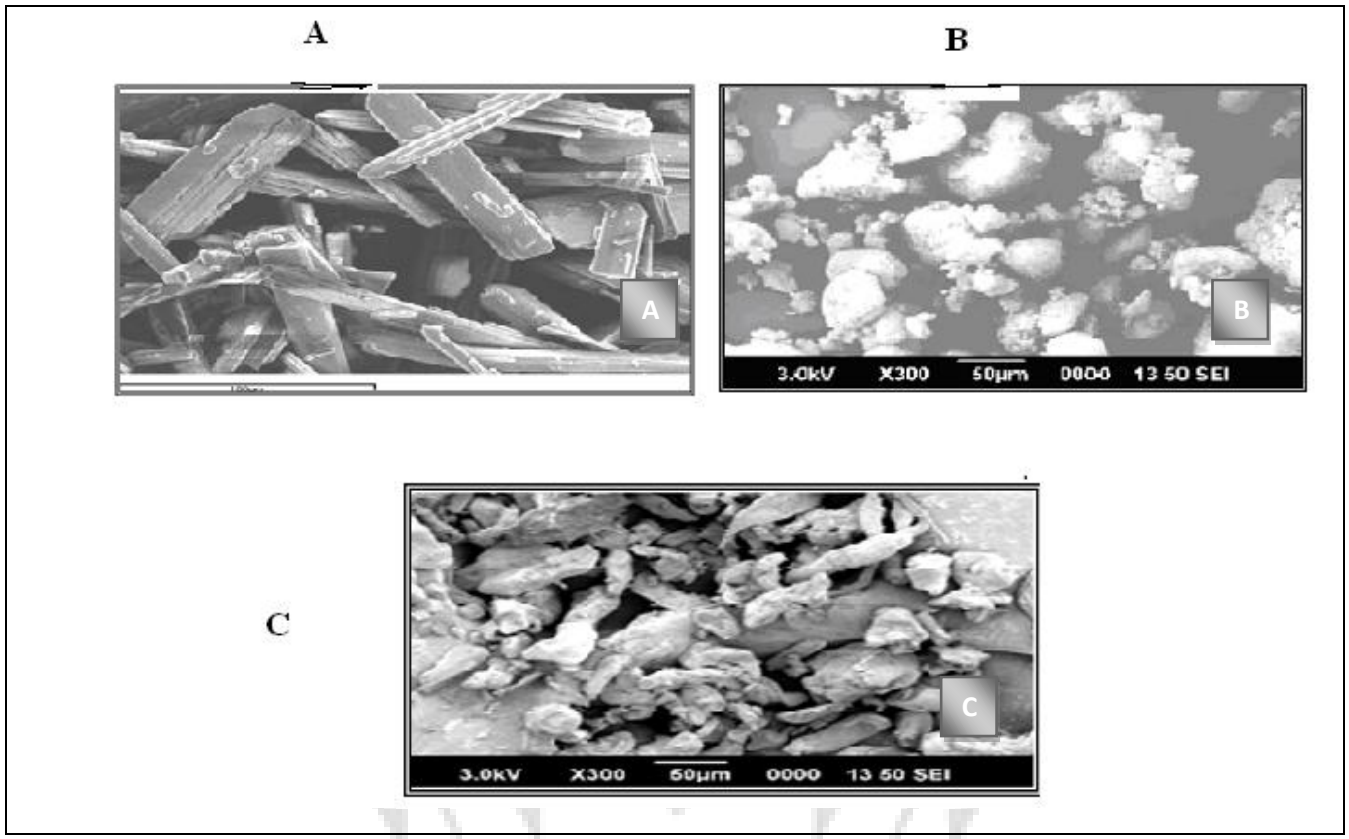

Figure 4: SEM photograph of A) SIM, B) MWLBG and C) $MWLBG_{SIM}$

4.2.3 Drug content analysis

Drug content analysis was performed in order to study the % amount of drug incorporated in SD's. After drug content analysis studies it was found that almost 96 to 101 % of drug was incorporated in the SD's which indicates uniform dispersion of drug.

4.2.4 Solubility Studies

Solubility studies gave the basis for selection of best ratio that is to be forwarded for formulation. Physical mixture of individual drug with individual polymer in various ratio as well as SD's of individual drug with individual modified polymer in various ratios was analyzed for solubility determination. The result of the same is shown in table. Solubility studies reveals modified carrier (MWLBG) is having very good solubility enhancing property as they have good surfactant property (Gatti et al.,2002/) and reduction of crystal size of the drug to amorphous form of SD's enhancing solubility. Solubility studies of physical mixtures and SD's clearly

indicated that as the ratio of drug to polymer increases solubility also increases .It was also found that after certain ratio i.e. 1:9 solubility remains constant hence 1:9 ratio was optimized.

Table 4: Solubility studies and ratio optimization of Simvastatin solid dispersion

Ratio	Concentration (mg/ml)	
	$PLBG_{SIM}$	**$MWLBG_{SIM}$**
1:1	0.10±0.010	0.85±0.035
1:2	0.11±0.010	0.93±0.045
1:3	0.13±0.010	1.02±0.070
1:4	0.13±0.010	1.17±0.040
1:5	0.15±0.007	1.67±0.064
1:6	0.17±0.015	1.63±0.085
1:7	0.22±0.009	2.17±0.020
1:8	0.23±0.005	2.16±0.030
1:9	0.28±0.005	2.45±0.015

4.2.5 Pre compression evaluation

Table 5: Pre compression parameters of lubricated blend of MWLBG-Simvastatin Formulation

CODE	Angle of Repose (θ)	Hausner's Ratio
$MWLBG_{SIM}$	33.98±2.90	1.44±0.01
F_1	28.66±1.20	1.95±0.03
F_2	23.49±1.94	1.15±0.30
F_3	24.15±1.56	1.58±0.01
F_4	21.15±1.56	1.11±0.01

4.2.6 Post compression evaluation

Prepared formulations were subjected to various compendia tests for post compression evaluation n such as hardness, friability, content uniformity of prepared tablets, disintegration time (DT).results of post compression evaluation are shown in table .All the parameters are within the limits given in the USP 30 (2007).

Table 6: Physical parameters of MWLBG-Simvastatin tablet

Batch $MWLBG_{SIM}$	Weight Variation %	Hardness (Kg/cm^2)	Friability (%)	Drug Content Uniformity (%)	Disintegration time (sec)
F1	3.26	4.23±0.13	0.82	101.25	63.18±1.82
F2	5.18	3.62±0.11	0.52	96.65	45.35±2.64
F3	2.65	3.47±0.20	0.38	102.33	53.14±3.61
F4	3.15	4.82±0.14	0.61	100.12	27.69±2.32

4.2.7 In vitro drug release studies of IR tablets

The optimized formulation ($MWLBG_{SIM}$ -trial-F4) based on disintegration studies were subjected to in vitro drug release study. Percentage drug release of optimized formulation was compared with % drug release of MKT sample (figure). Formulation $MWLBG_{SIM}$ trial-F4 showed 98.00±2.28 % drug release, which is higher than that of MKT (97.77±2.51 %). Similarity factor (f2) between optimized formulation F4 and marketed formulation was determined and was found to be 85. This showed that drug release from prepared formulation and marketed formulation showed quite similarity. optimized formulation was further subjected to in vivo evaluation.

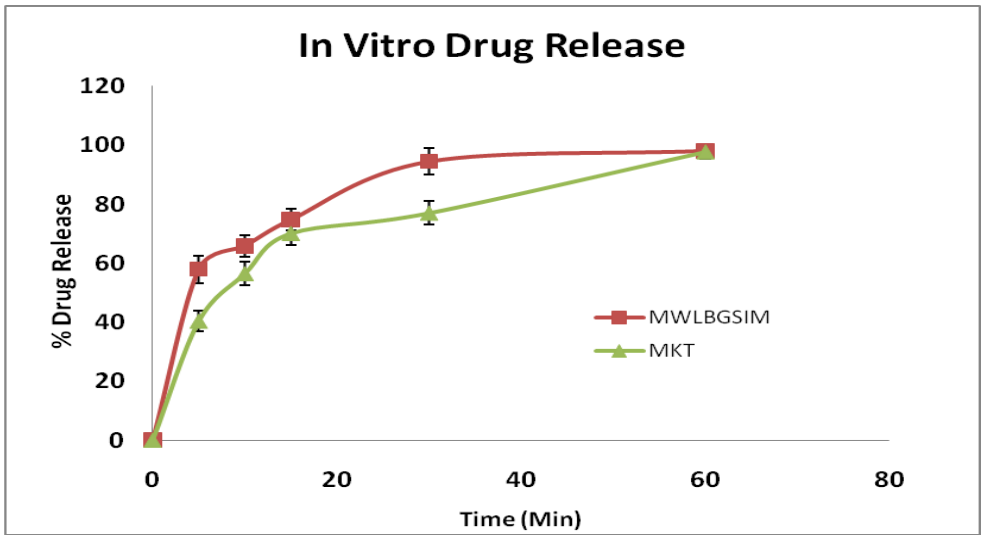

Figure 5: Dissolution profile of tablet samples $MWLBG_{SIM}$ –trial-F4 and MKT sample in pH 6.8 buffer

4.2.9 *In vivo* study and of Simvastatin solid dispersions in animal model

Hypolipidemic drug like Simvastatin (HMG-CoA reductase inhibitors) is known to reduce elevated total cholesterol and TG levels in blood, which promote the removal of cholesterol from peripheral cells and facilitate its delivery back to the liver (Jun et al., 2007). The SIM is the most marketed available drugs of hypolipidimic category. But this drug is having poor aqueous solubility. Hence, in present study solid dispersion of Simvastatin ($MWLBG_{SIM}$) with enhanced solubility was prepared and their anti-cholesterol and anti-lipidemic activity were confirmed and compared with pure drug (API) of SIM using indirect method for assessing variation in 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (NADPH) activity in liver tissue. HMG CoA reductase inhibition activity was measured in terms of absorbance in all the seven groups, the activity of enzyme which catalyzes the conversion of HMG CoA to mevalonate. One-way analysis of variance (ANOVA) followed by multiple comparisons Dunnet's test was used for comparison. All the results are shown as mean ± standard error. In the table, it shows fall in serum lipid levels in 30 days. Simvastatin showed a fall in serum cholesterol and protective HDL. The solid dispersion prepared by microwave induced fusion method as expected performed better than plain SIM.

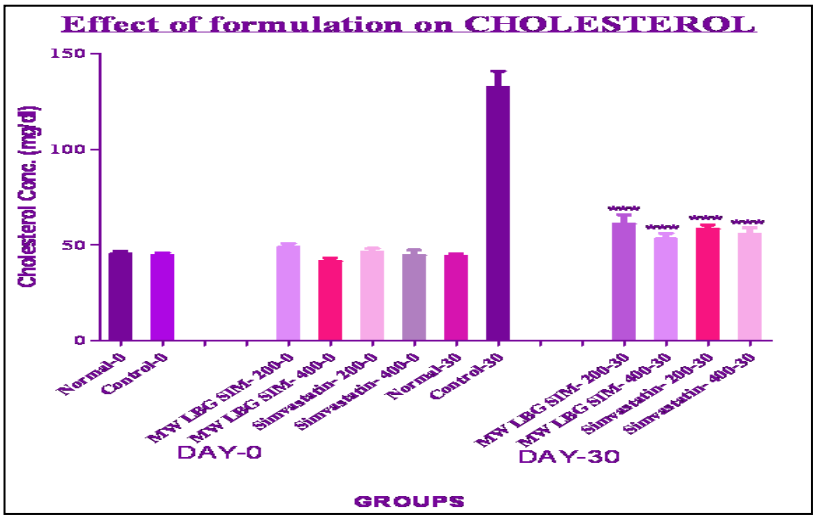

Figure 6: Anti-cholesterol effect of MWLBGSIM formulations on serum total cholesterol against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

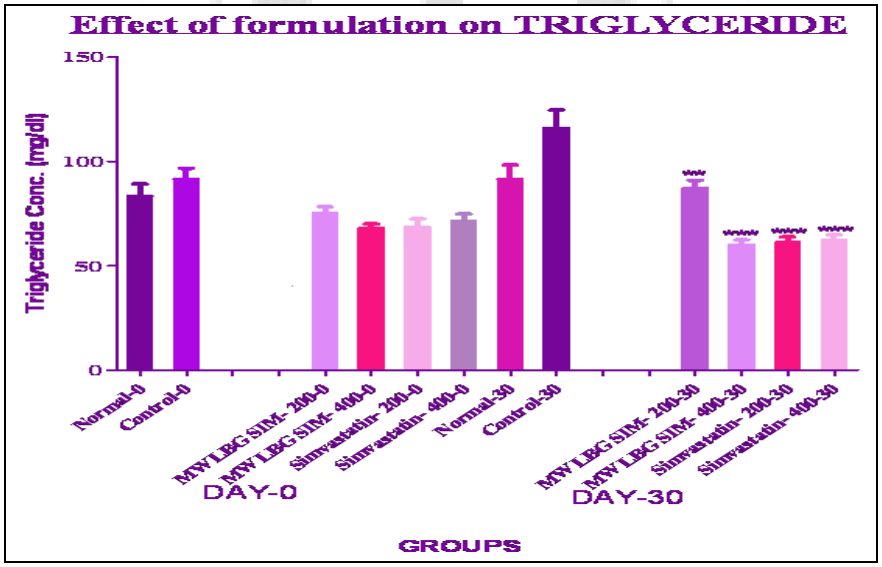

Figure 7: Anti-cholesterol effect of MWLBGSIM formulations on serum triglycerides against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

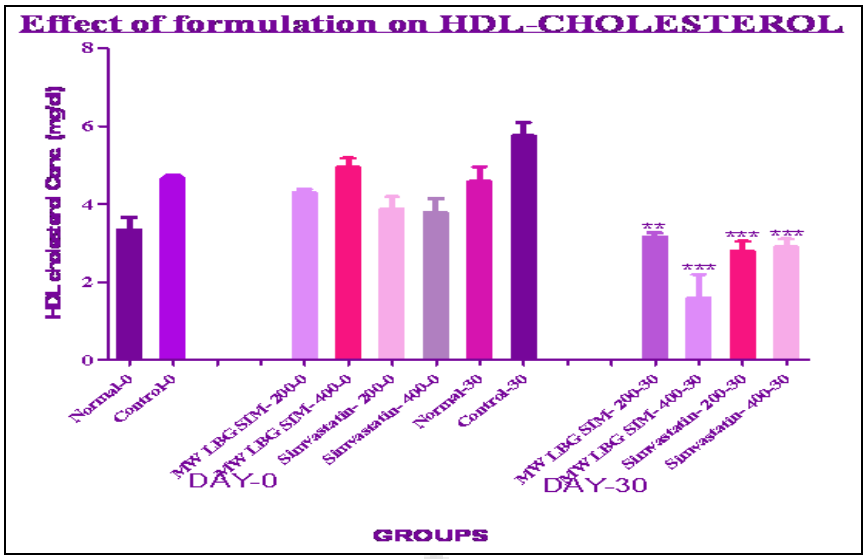

Figure 8: Anti-cholesterol effect of MWLBGSIM formulations on serum HDL cholesterol against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

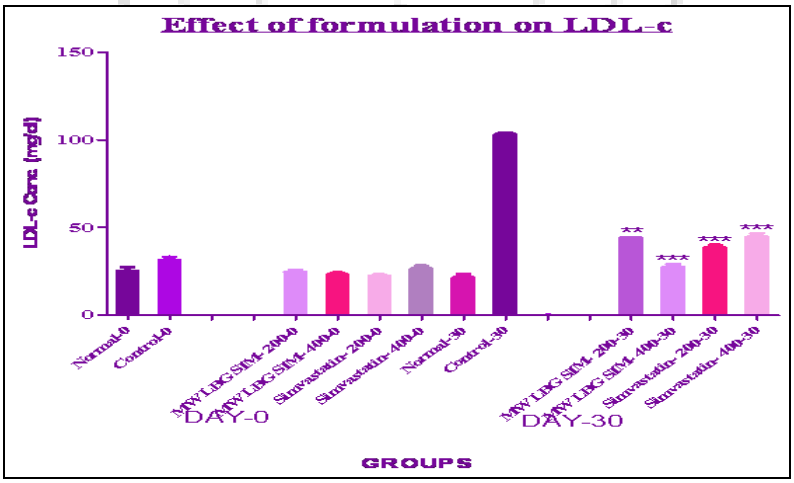

Figure 9. Anti-cholesterol effect of MWLBGSIM formulations on serum LDL Cholesterol against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

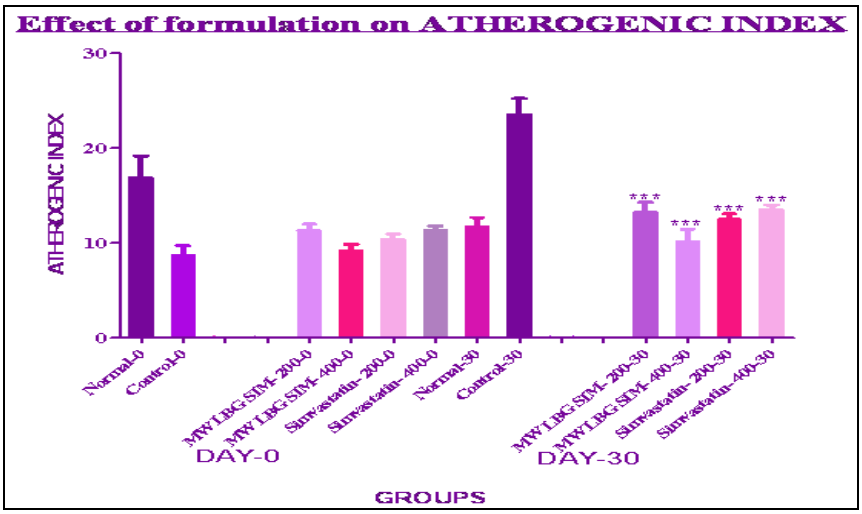

Figure 10. Anti-cholesterol effect of formulations MWLBG SIM against high cholesterol feed induced hyperlipedemia. Anti-cholesterol effect of MWLBGSIM formulations on serum LDL Cholesterol against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

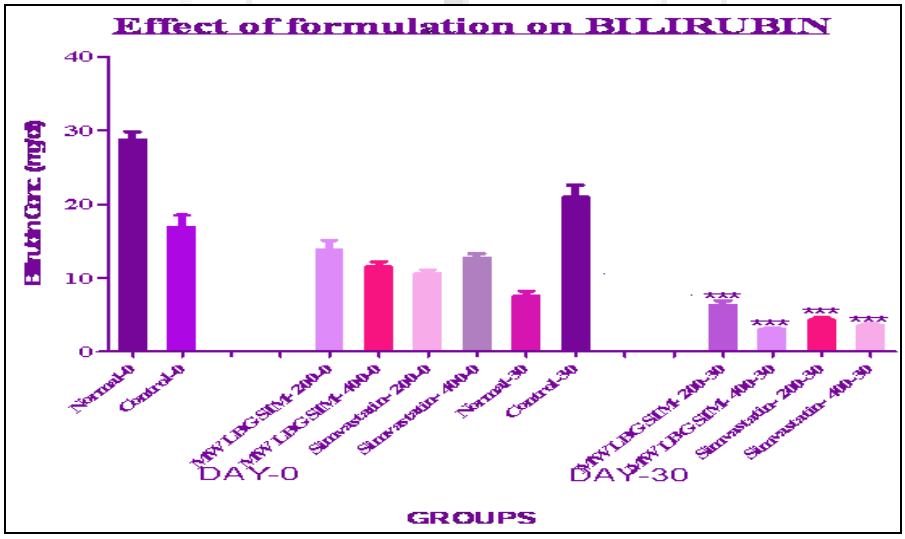

Figure 11. Anti-cholesterol effect of MWLBGSIM formulations on serum LDL Cholesterol against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

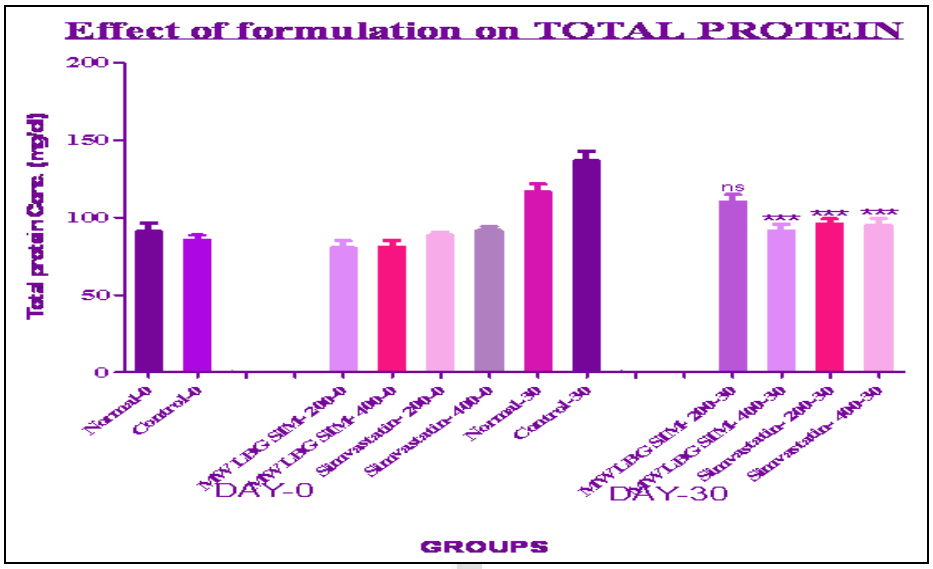

Figure 12. Anti-cholesterol effect of MWLBGSIM formulations on serum LDL Cholesterol against high cholesterol feed induced hyperlipedemia. All values are expressed as mean ± SEM, n=6, One way Analysis of Variance (ANOVA) followed by multiple comparisons Dunnet's test, ns = non-significant, *p<0.05, **p<0.01, ***p<0.001

5.0 CONCLUSION

The natural polymers having surfactant activity that enhances the solubility and dissolution rate of drug, but due to high viscosity many of these polymers also having limitation as carriers for dissolution enhancement (Portero et al., 1998), this problem is overcome by reducing the viscosity of polymers. This natural polymers having advantage over other synthetic polymer as this polymers are biocompatible, biodegradable and having low cost (Sawayanqagi et al., 1983; Imasi et al., 1991; Acaturk et al., 1992; Portero et al., 1998). On heating of the natural polymers (LBG) at particular time and temperature condition, it reduces the viscosity and changes the surface property which is useful to polymers for use as drug carrier for dissolution enhancement. Modified natural polymer locust bean gum and gaur gum have great potential for enhancement of solubility, dissolution rate and thereby bioavailability of poorly soluble Simvastatin. The SD's of Simvastatin with individual polymers enhances the solubility by converting it into amorphous form, reducing the particle size and increasing the wettability. The optimum ratio of drug to modified natural polymer was found to be 1:9 w/w for MWLBG which shows higher dissolution

as compared to marketed tablet. The selected SD's showed better anti-cholesterol and anti-lipidemic activity compared to plain drug.

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