AAPS PharmSciTech, Vol. 9, No. 4, December 2008 (© 2008)
DOI: 10.1208/s12249-008-9171-4

Research Article

Solubility Enhancement of Lovastatin by Modified Locust Bean Gum Using Solid Dispersion Techniques

Manjil Patel,[1] Avinash Tekade,[1,2] Surendra Gattani,[1] and Sanjay Surana[1]

Received 4 June 2008; accepted 5 December 2008; published online 31 December 2008

Abstract. The aim of the present study was to improve the solubility of poorly water soluble drug lovastatin (LS) by solid dispersion (SD) techniques using modified locust bean gum (MLBG) as a carrier. The locust bean gum (LBG) was modified by heating and there observed irreversible decrease in viscosity, whereas swelling property remains unaffected. The advantage of modification of LBG was illustrated by difference in dissolution profiles of their SD. Effect of polymer concentration and methods of preparation on solubility enhancement were studied using solubility and dissolution studies, respectively. The result of solubility study showed increase in solubility of LS with increase in concentration of MLBG. It was found that the dissolution rate of LS from its SD was dependent on the method of preparation of solid dispersions. Dissolution study revealed that the modified solvent evaporation is most convenient and effective method for solubility enhancement of poorly water soluble drug LS, among various methods of preparation of SD. The prepared SDs were characterized by differential scanning calorimetry, scanning electron microscopy, and X-ray diffraction study. *In vivo* study was performed by measuring 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG Co-A) reductase inhibition activity. Significant reduction in HMG Co-A reductase activity was observed in case of solid dispersions of LS than plain LS. In conclusion, MLBG could be used as a potential carrier in enhancing the dissolution rate and bioavailability of LS.

KEY WORDS: dissolution enhancement; locust bean gum; lovastatin; modified locust bean gum; solid dispersions.

INTRODUCTION

Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their use in new applications. The dissolution rate of drugs from the formulations containing viscous carriers is generally low due to the formation of gel layer on the hydrated surfaces, which prevents the drug release during dissolution. This can be overcome during tablet formulation by adding disintegrants. Pulverization of the product is also another important draw back with the high viscosity carriers, which can be overcome by using decreasing order of polymer/drug ratio during formulation. However, it is reported that the swelling ability of the carrier improves dissolution rate of poorly water soluble drug. As the viscosity of the carrier reduces the dissolution rate, it is useful to modify the gum in such a way that its swelling ability remains same and viscosity reduced. This can be achieved by heating.

The rate at which poorly water soluble drug dissolves is often the slowest step and therefore exerts rate-limiting effect on drug bioavailability. In case of drugs with the dissolution rate limited absorption, reduction in particle size often increases the rate of dissolution and the amount of drug absorbed. The rate of absorption can be further increased using various techniques which include solid dispersions, solvent disposition, cosolvents, salt formation, pH control, cogrinding, etc. However, all these techniques have potential limitations. All poorly water soluble drugs are not suitable for improving their solubility by salt formation. Decreasing particle size increases solubility but there is poor wetting and flow. Solid dispersions can overcome these problems.

Many carriers used in solid dispersions also cause problems due to their hygroscopic nature. Hence, continuous search for new carriers and new techniques is going on which will be useful for large scale manufacturing. Many polymers have limitations in enhancing solubility of poorly water soluble drugs due to their high viscosity. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of polymers. Use of natural polymer is more beneficial because of their low cost, biocompatibility, and biodegradability (1).

Locust bean gum (LBG) is a natural polymer which is also called carob bean gum or carubin and is extracted from the seeds (kernels) of the carob tree *Ceratonia siliqua* family Leguminosae or Fabaceae. LBG is used as fat replacer (2). Also, it can be used as thickening and stabilizing agent. LBG is widely used because of its high swelling capacity, high water

[1] Department of Pharmaceutics, R.C.Patel Institute of Pharmaceutical Education & Research, Near Karvand Naka, Shirpur, 425 405 Dhule, Maharashtra, India.
[2] To whom correspondence should be addressed. (e-mail: avitekade@gmail.com)

retention capacity, easy digestible nature, binding ability, abound availability, and chemical compatibility. United States Food and Drug Administration approved limit from inactive ingredient database for LBG is 74.25 mg (Fig. 1).

Present work examines the influence of modified locust bean gum (MLBG) on solubility enhancement of poorly water soluble drug lovastatin (LS) in comparison to that of plain LBG. LS is a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG Co-A) reductase. Therefore, LS inhibits key rate-limiting step in the biosynthesis of cholesterol (Fig. 2).

In this study, the influence of concentration of gum and the method of preparation of solid dispersions on the dissolution rate was also studied. Apparent solubility, *in vitro* dissolution study, infrared spectroscopy, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) study were used to explain the phenomenon.

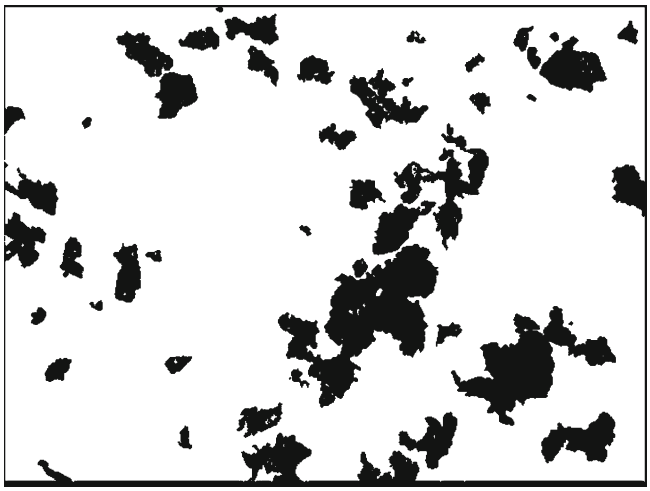

Fig. 1. Photo microscopic image of LBG

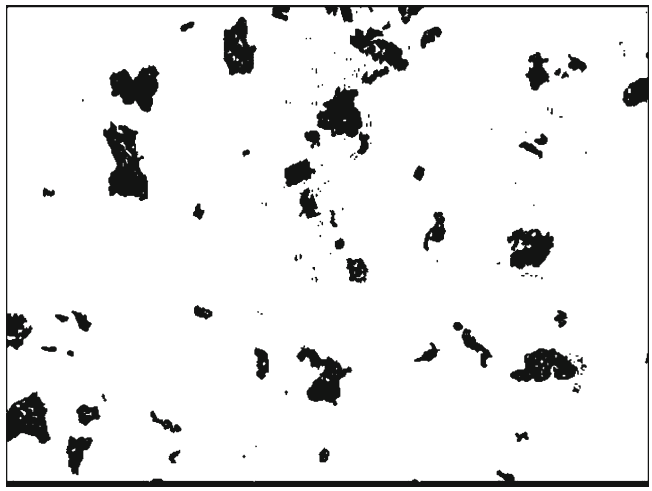

Fig. 2. Photo microscopic image of MLBG

MATERIALS AND METHODS

Materials

Lovastatin and locust bean gum were obtained as gift samples from Biocon, Banglore, India and Taiyo Lucid Pvt. Ltd., Mumbai, India, respectively. All other materials used were of analytical reagent grade.

Preparation of Modified Locust Bean Gum

The MLBG was prepared by the method reported by Murali Mohan Babu *et al*. (1). Powdered gum was placed in a porcelain bowl and subjected to heating in hot air oven for different time periods at different temperatures. The prepared MLBG was finally resieved (100 mesh) and stored in airtight container at 25°C.

CHARACTERIZATION OF LBG/MLBG

Swelling Index

LBG powder (1 gm) was accurately weighed and transferred to a 100-ml stoppered measuring cylinder. Initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100-ml mark with distilled water. The volume occupied by the gum sediment was shaken gently and set aside for 24 h at room temperature and ambient humidity (1). The volume occupied by the gum sediment was noted after 24 h. Swelling capacity of LBG/MLBG was expressed in terms of swelling index. Swelling index was expressed as a percentage and calculated according to the following equation:

$$SI = [(X_t - X_o)/X_o]] \times 100 \quad (1)$$

where X_o is the initial height of the powder in graduated cylinder and X_t denotes the height occupied by swollen gum after 24 h.

Viscosity Measurement

The viscosity of 1% (*w*/*v*) LBG/MLBG solution was measured according to the US Pharmacopeia (USP) specification, using Brookfield DV-E Viscometer (Middleboro, MA, USA).

Angle of Repose

The angle of repose was determined by the funnel method (3). The accurately weighed powder was taken in a funnel. The height of a funnel was adjusted in such a way that its tip just touches the apex of the heap of powder. The powder was allowed to flow through funnel freely on to the surface. The diameter of the powder heap was measured and angle of repose was calculated using the following equation:

$$tan\ (\theta) = H/R \quad (2)$$

H Height of powder heap
R Radius of powder heap

Moisture Sorption Capacity

Moisture sorption study was performed using programmable environmental test chamber (Remi Instruments, Mumbai, India). One gram of powdered LBG/MLBG was taken in a Petri dish of 9 cm in diameter and spread uniformly. Then, it was kept in programmable environmental test chamber at 37±1°C and 100% relative humidity for 2 days. The moisture sorption was calculated by recording weight difference of the sample before and after exposure to programmable environmental test chamber (3).

Photo Microscopic Study

Photo microscopic image of LBG and MLBG were taken at ×450 magnifications by photo microscope (DMWB2-223, Motic Instruments Inc., Richmond, British Columbia, Canada).

Hydration Capacity

The hydration capacity (HC) was measured according to the method described by Ohwavworhu and Adelakun (3). Weighed quantity of powdered LBG/MLBG (1.0 g) was taken in the 15-ml tare centrifuge tube. Then, 10 ml of distilled water was added to it and allowed to centrifuge for 10 min at 1,000 rpm. After the centrifugation process, the tare centrifuge tube was taken out and inverted to remove the supernatant. The decanted tube then weighed on digital balance (AUX 120, Shimadzu, Japan) and the hydration capacity was calculated using the following equation:

$$HC = Weight\ of\ hydrated\ sample / Weight\ of\ dry\ sample \quad (3)$$

Density

The loose bulk density (LBD) and tapped bulk density (TBD) of LBG/MLBG powder were determined. Powdered gum (2 gm) was poured into calibrated measuring cylinder (10 ml capacity) and noted initial volume. Then, the cylinder was allowed to fall under its own weight onto the hard surface from the height of 2.5 cm at 2-s intervals. The tapping was then continued until no further change in volume was noted. LBD and TBD were calculated using the following equation:

$$LBD = Weight\ of\ the\ powder / Volume\ of\ the\ packing \quad (4)$$

$$TBD = Weight\ of\ the\ powder / Tapped\ volume\ of\ the\ packing \quad (5)$$

Compressibility

Compressibility index (Carr's index) was determined by using the following equation (4):

$$Carr's\ index(\%) = [(TBD - LBD) \times 100] / TBD \quad (6)$$

METHODS OF PREPARATION OF SOLID DISPERSIONS

Solid dispersions were prepared by different methods to enhance the aqueous solubility of LS using MLBG except in case of modified solvent evaporation (SE) method where both LBG and MLBG were used for the preparation of SD.

Physical Mixture

The physical mixture (PM) of LS and MLBG was prepared by simple blending the LS and MLBG in 1:5 *w/w* ratio with a spatula and passed through a 100-mesh sieve.

Kneading Method for Solid Dispersions

Kneading method was used for solid dispersions formulation (1,5). In this method, weighed quantity of drug and polymer (MLBG) placed in a mortar and then the mixture was kneaded with 1.5 times the amount of either ethanol 70% *v/v* or water for 20 min. The kneaded mixtures were dried in oven at 40°C until it reached uniform weight and then pulverized and screened through 100-mesh sieve. The solid dispersion prepared by kneading method using water is KW and that of ethanol is KE.

Spray Drying Method for Solid Dispersions

Solid dispersions were prepared by spray drying (SP) technique (6,7) using spray dryer (Labultima, Mumbai, India). Drug and polymer (MLBG) were dissolved in methanol and then the solvent was evaporated by spray dryer. The operating parameters like inlet and outlet temperature were 70°C and 60°C, respectively. Aspirator speed was kept at 45 whereas feed pump speed was 5.

Solvent Wetting Method for Solid Dispersions

As described by Kim *et al.* (8), solvent wetting (SW) method was used for solid dispersions formulation. LS was dissolved in an appropriate amount of ethanol to its saturation solubility. The amount of ethanol used varied depending on the weight of drug and polymer. In this case, it was 1.5 times the total weight of drug and polymer. After complete dissolution of LS, solutions were dropped onto MLBG. Then, solvent was removed at room temperature.

Modified Solvent Evaporation Method

Drug was dissolved in ethanol at its saturation solubility with continued stirring up to 30 min. LBG/MLBG was suspended in sufficient amount of water (up to the wet mass of polymer). The drug solution was poured at once into polymer suspension. The entire solvent was evaporated under reduced pressure at 60°C to 70°C by Rota evaporator with solvent recovery. Rane *et al.* (9) has described this method for solid dispersions formulation. Solid dispersions prepared by modified solvent evaporation method using LBG and MLBG are SEL and SE, respectively.

CHARACTERIZATION OF SOLID DISPERSIONS

Solubility Study

The apparent solubility of LS, physical mixture, SD prepared by kneading method, SD prepared by spray drying method, and SD prepared by modified solvent evaporation method was determined in pH 7 phosphate buffer containing 2% sodium lauryl sulfate (SLS) at 37°C. For each preparation, an equivalent of 10 mg of drug was added to 20 ml of buffer in a glass vial with caps. The vials were kept on a glass shaker incubator maintained at 37±0.5°C for 24 h. After shaking, the vials were kept equilibrated in an incubator at 37±0.5°C for 12 h. Then, the solution was filtered through a 0.45-μm millipore filter and the filtrate was assayed spectrophotometrically at 238 nm.

In Vitro Dissolution Rate Study

Dissolution rates from different solid dispersions were determined in 900 ml of pH 7 phosphate buffer containing 2% SLS at 37±0.5°C with a stirrer rotation speed of 50 rpm using the USP dissolution test apparatus (TDT 08L—ELECTROLAB, Mumbai, India) employing a basket stirrer (method I). A 5-ml aliquot of dissolution medium was withdrawn at 5, 10, 15, 30, 45, 60, 90, 105, and 120 min with a pipette. The samples were suitably diluted and assayed spectrophotometrically at 238 nm. Each dissolution rate test was repeated three times. As a model independent approach, dissolution efficiency (DE) was employed to evaluate the dissolution rate of LS from different solid dispersions. DE is defined as the area under the dissolution curve up to the time t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. DE_{30} and DE_{120} were calculated from the dissolution data and used for comparison.

Infrared Spectroscopic Study

Fourier transformed infrared (FTIR) spectra of LS, MLBG, physical mixture, and solid dispersions of LS–MLBG were obtained on a FTIR (84005 Shimadzu, Japan) using the KBr disk method (2-mg sample in 200 mg KBr). The scanning range was 450 to 4,000 cm^{-1} and the resolution was 1 cm^{-1}.

Table I. Characterization of LBG and MLBG

Parameters	LBG	MLBG
Viscosity (cps)	1,670±60.82	526.66±46.18
Swelling index (%)	1,635±5.56	1623±1.52
Water retention capacity (ml)	48.94±1.12	47.29±0.93
Hydration capacity	2.8±0.24	2.77±0.2
Moisture sorption capacity (%)	6±0.52	10±0.78
Angle of repose	38.6598±1.13	37.2348±1.43
Carr's index (%)	20.06±1.01	18.74±0.67

$n=3$
LBG locust bean gum, *MLBG* modified locust bean gum

Table II. Solubility Study of LS (Mean ± Standard Deviation) from Physical Mixture and Solid Dispersions in Comparison with Pure LS

Product	Solubility (μg/ml)
LS	1.28±0.061
PM	3.078±0.112
KW	3.202±0.160
KE	3.399±0.179
SW	3.452±0.204
SP	3.613±0.200
SE	3.717±0.161

$n=3$
LS lovastatin, *PM* physical mixture of lovastatin & modified locust bean gum, *KW* SDs by kneading method using water, *KE* SDs by kneading method using ethanol, *SW* SDs by solvent wetting method *SP* SDs by spray drying method, *SE* SDs by solvent evaporation method

Scanning Electron Microscopy

The SEM photographs of LS and solid dispersions prepared by modified solvent evaporation method were obtained by scanning electron microscope (JSM 6390, JEOl, Peabody MA, USA) with 10-kV accelerating voltage.

Differential Scanning Calorimetry

DSC curves of LS, MLBG, physical mixtures (modified solvent evaporation method), and solid dispersions (modified solvent evaporation method) were obtained by a differential scanning calorimeter (DSC 60 Shimadzu, Japan) at a heating rate of 10°C/min from 30°C to 300°C in nitrogen atmosphere.

X-Ray Diffraction Studies

Powder XRD patterns of LS, MLBG, and solid dispersions (modified solvent evaporation) were recorded using diffractograms (PW 1140, Mettler Toledo, Columbus, OH, USA) and Cu-kα radiation. Diffractograms were run at a scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2θ.

In Vivo Evaluation of Solid Dispersions

An indirect method was used for assessing variation in 3-hydroxy-3-methylglutaryl-coenzyme A reductase (NADPH) activity in liver tissue, as described by Venugopala Rao and Ramkrishnan (10). 3-Hydroxy-3-methylglutaryl-Co A and mevalonate concentrations in the tissue homogenate were estimated in terms of absorbance and the ratio between the two was taken as an index of activity of the enzyme, which catalyzes the conversion of 3-hydroxy-3-methylglutaryl-Co A to mevalonate.

The HMG Co-A/mevalonate ratio was measured in liver tissue of male albino rats weighing150–200 g. The rats were divided into three different groups (control, standard, and formulation) of five rats each. All the animals were kept on a standard diet.

For 7 days, control group was given the standard diet only. The standard group was given 4 mg/kg dose of LS (11) with standard diet and the formulation group was given optimized solid dispersions equivalent to 4 mg/kg of LS.

Table III. Ratio Optimization of LS to MLBG

Drug/polymer ratio	% Solubility enhanced
1:1	47.7
1:2	54.7
1:3	66.2
1:4	69.0
1:5	75.2

After 7 days, the liver tissue was removed as quickly as possible and a 10% homogenate was prepared in saline arsenate solution. The homogenate was deproteinized using an equal volume of dilute perchloric acid and by centrifugation. This was then allowed to stand for 5 min and filtered. To 1 ml of this filtrate, 0.5 ml of freshly prepared hydroxylamine reagent (alkaline hydroxyl amine in case of HMG-Co A) was added. It was mixed and 1.5 ml of ferric chloride reagent was added after 5 min. The absorbance was read after 10 min at 540 nm *versus* a similarly treated saline arsenate blank. The ratio of HMG-Co A/mevalonate was calculated.

RESULTS

The results of characterization of LBG and MLBG are given in Table I. The results indicated that the viscosity of MLBG was markedly lower when retention capacity of MLBG was not reduced significantly comparing to that of LBG. Due to the swelling nature of the carrier, the extensive surface of the carrier is increased during dissolution, and the dissolution rate of drug is markedly enhanced. Water retention capacity of carrier is the amount of water retained in it which indicates the ability of carrier towards hydrophilic nature.

Solubility Study

The solubility data for LS, KW, KE, SP, SE, and SW are given in Table II. Solubility data show that the LBG and MLBG enhance the solubility of LS using different methods of solid dispersion formulations. It was proved that, as the concentration of gum increases, the solubility of LS increases.

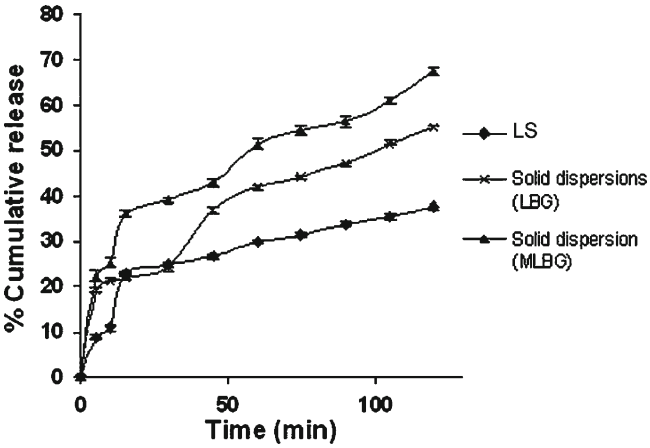

Fig. 3. Dissolution profiles of LS, solid dispersions LBG (SEL), and solid dispersions MLBG (SE) by modified solvent evaporation method

Table IV. Dissolution Efficiency Values (Mean ± Standard Deviation) of LS and Various Solid Dispersions

Product	DE_{30}	DE_{120}
LS	20.83±0.040	36.84±0.829
PM	25.72±0.235	38.06±0.869
KW	23.20±0.236	40.86±0.270
KE	27.19±0.352	49.36±0.406
SW	21.45±0.275	41.98±0.855
SP	24.44±0.448	55.04±0.516
SE	39.17±0.334	68.01±0.696
SEL	23.86±0.580	55.22±0.844

$n=3$
DE dissolution efficiency, *LS* lovastatin, *PM* physical mixture of lovastatin & modified locust bean gum, *KW* SDs by kneading method using water, *KE* SDs by kneading method using ethanol, *SW* SDs by solvent wetting method, *SP* SDs by spray drying method, *SE* SDs by solvent evaporation method using MLBG, *SEL* SDs by solvent evaporation method using LBG

The optimization of drug/polymer ratio was done by solubility measurement using PM of different drug/polymer ratios as shown in Table III. Drug/polymer in the ratio 1:5 significantly enhances the solubility of LS.

In Vitro Dissolution Rate Study

Figure 3 shows *in vitro* dissolution profile of LS, solid dispersions prepared by LBG (SEL), and MLBG (SE) using modified solvent evaporation method. The values of DE_{30} and DE_{120} are given in Table IV. The DE_{30} and DE_{120} values of LS are significantly lower than that of SEL. Thus, LBG/MLBG significantly enhanced the dissolution rate of LS. SE showed faster dissolution rate than that of SEL as shown in Fig. 3. However, the DE values of SEL are significantly higher than that of LS. The order of dissolution rate is pure LS < SEL < SE.

Figure 4 shows the dissolution profile of solid dispersions of LS with MLBG prepared by kneading (water/ethanol), spray drying, and modified solvent evaporation method. Their DE_{30} and DE_{120} are given in Table IV. By comparing that values order of dissolution rate was found to be LS < PM < KW < SW < KE < SP < SE.

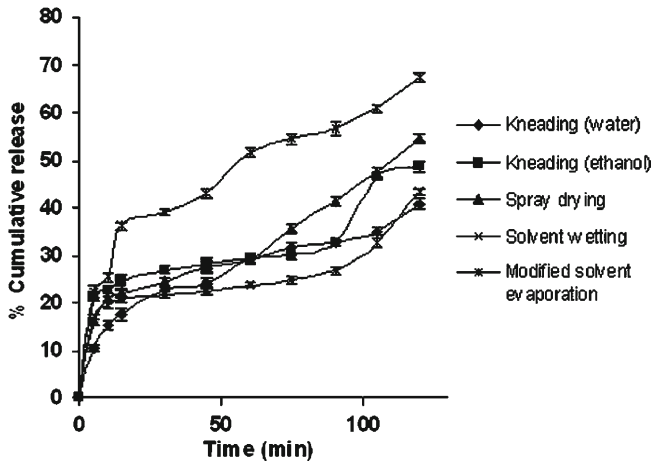

Fig. 4. Dissolution profiles of solid dispersions prepared by different methods

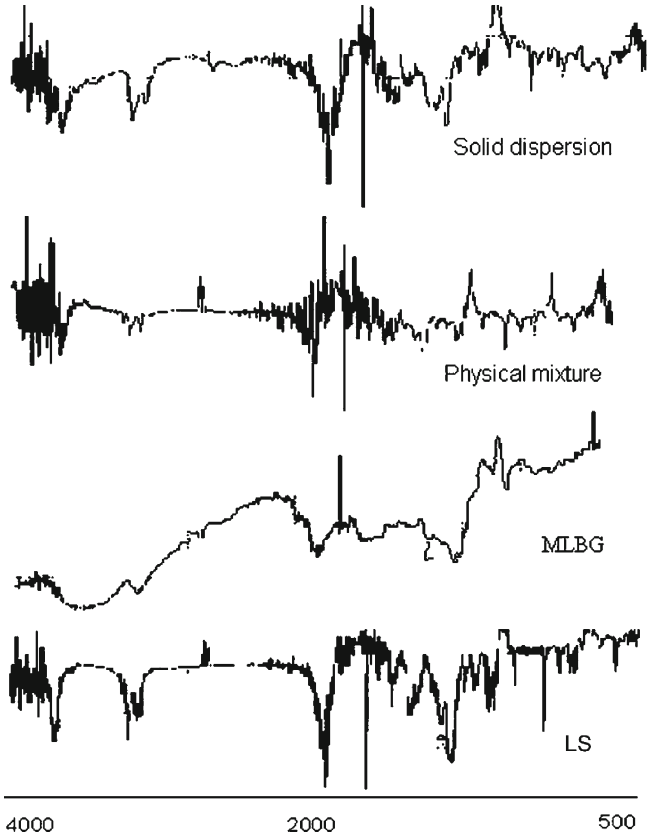

Fig. 5. FTIR spectra's of LS, MLBG, and solid dispersions (LS + MLBG)

It was proved that as the viscosity of the carrier increased, the dissolution rate was decreased (12). During the process of dissolution, as soon as the drug carrier particle comes in contact with dissolution fluid, seeping in of dissolution medium in to the drug-carrier particle takes place, which initiated the formation of gel layer of carrier around the particle. The diffusion of dissolved drug through the gelatinous layer is determining factor in the enhancement of dissolution rate. From the Stokes–Einstein equation, the diffusion coefficient is inversely proportional to viscosity. The viscosity of 1% *w/v* solution of MLBG at 28°C is lower than that of LBG. Thus, the dissolution rate of LS from the MLBG solid dispersion is higher than that of LBG. During the dissolution process, the drug-carrier particles are to be dispersed rapidly throughout the dissolution medium to promote the drug release. It was observed that the LBG which is more viscous than MLBG resulted in formation of lumps of drug-carrier particles during dissolution, whereas LS-MLBG particles dispersed rapidly.

Infrared Spectroscopic Study

Infrared spectra's of LS and its binary systems with MLBG are presented in Fig. 5. Pure LS spectra showed sharp characteristic peaks at 3,542, 2,929, 1,725, 1,711, and 1,359 cm^{-1}. All the above characteristic peaks appear in the spectra of all binary systems at the same wave number.

Scanning Electron Microscopy

The SEM photographs (Fig. 6) of LS show the longer crystals of LS particles and in solid dispersions (modified solvent evaporation method), there observed decrease in crystallinity.

Differential Scanning Calorimetry

The DSC thermograms of LS, MLBG, physical mixture (LS–MLBG), and solid dispersions (modified solvent evaporation method) are shown in Fig. 7. The thermograms of LS exhibited endothermic peak at 173.47 while MLBG exhibited a broad endothermic peak owing to its amorphous nature. The DSC thermograms of physical mixture as well as solid dispersions showed identical peaks corresponding to pure drug but sharpness of the peaks were decreased.

X-Ray Diffraction Studies

XRD spectra of pure LS, MLBG, and optimized batch of solid dispersions are presented in Fig. 8. The X-ray diffractogram of LS has sharp peaks at diffraction angles (2θ) 9.299°, 9.39°, 15.585°, 16.639°, and 18.853° showing a typical crystalline pattern. However, all major characteristic crystalline

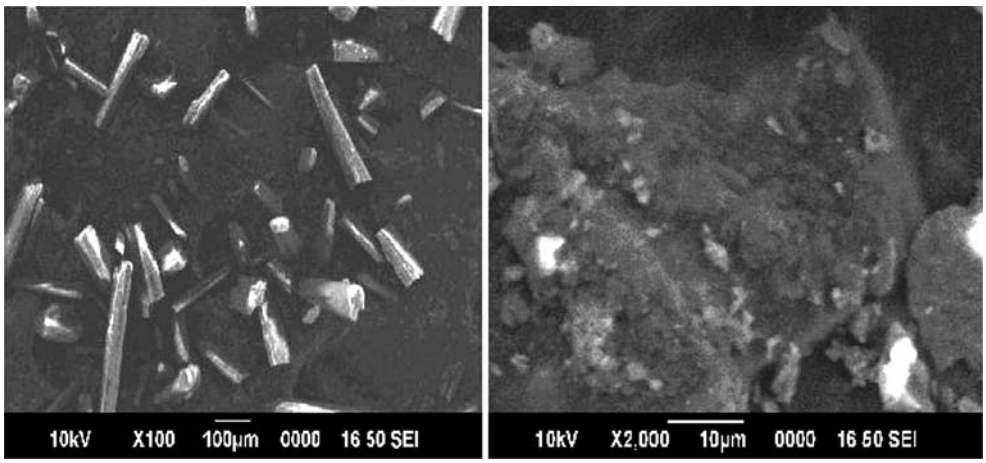

Fig. 6. SEM photographs of LS and its solid dispersions

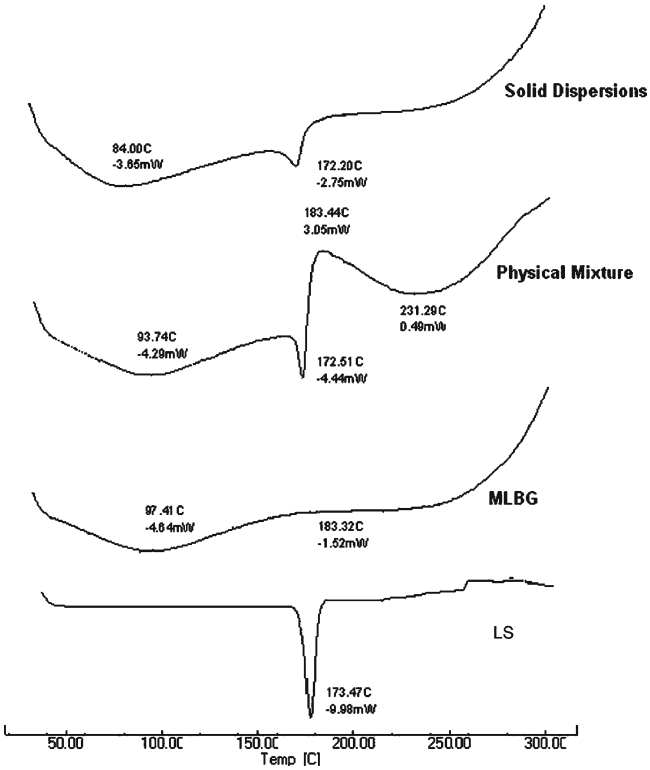

Fig. 7. DSC thermograms of LS, MLBG, physical mixture, and solid dispersions

peaks appear in the diffractogram of solid dispersions system but of low intensity.

The dissolution characteristics of LS, PM, and solid dispersions prepared by different methods are given in

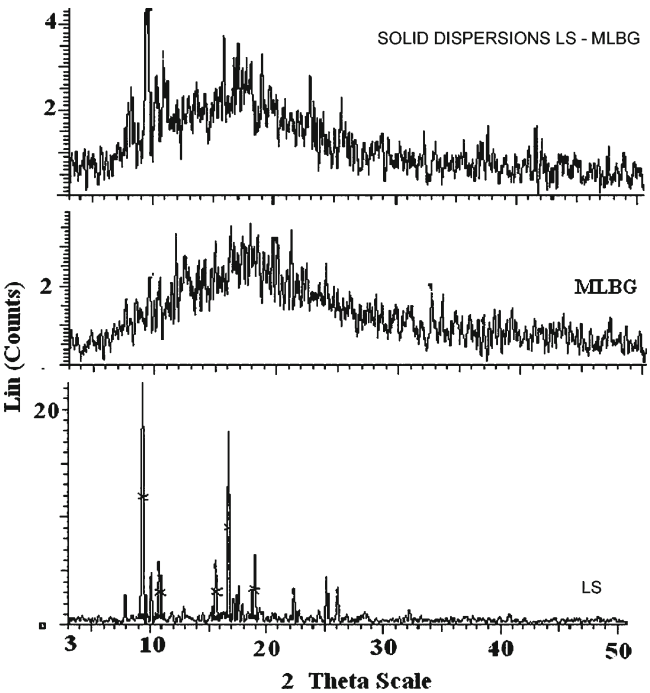

Fig. 8. X-ray diffraction studies of LS, MLBG, and solid dispersions LS–MLBG

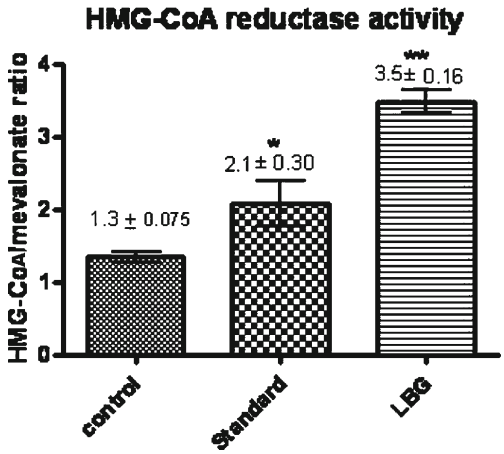

Fig. 9. *In vivo* evaluation of solid dispersions

Fig. 6 and the corresponding values of DE_{30} and DE_{120} are given in Table III. In all cases, solid dispersions exhibited faster dissolution rates than that of pure drug and the order of solid dispersions based on their DE values is LS < PM < KW < SW < KE < SP < SE (DE_{120}).

In Vivo Evaluation of Solid Dispersions

Result of *in vivo* study is given in Fig. 9. HMG Co A reductase inhibition activity was measured in terms of absorbance in all three groups. One-way analysis of variance was applied for comparison. All results are shown in mean ± standard error. HMG Co A to mevalonate ratio for solid dispersions was found to be 3.5±0.16 which was more than that of LS (2.1±1.30). *P* value for solid dispersion was less than 0.05.

DISCUSSION

The result of swelling capacity and viscosity studies revealed that the modified forms possessed swelling properties similar to that of LBG but viscosity was decreased as a function of temperature and exposure time. However, it was observed that LBG samples were charred when heated at 140°C. In the preparation of MLBG, no further change in viscosity of LBG was observed by heating it at 120°C for 2 h. Hence, these conditions of heating at 120°C for 2 h were selected to prepare MLBG. The prepared MLBG was finally resieved (100 mesh) and stored in an airtight container at 25°C.

The dissolution rate of LS from solid dispersions of LBG prepared by modified solvent evaporation method was low when compared with solid dispersions of MLBG because of high viscosity of LBG. Hence, various SD were prepared using MLBG than LBG to enhance the solubility of LS.

Improvement in dissolution rate of LS by PM compared with pure drug might be the solubilization effect and wetting ability of the MLBG on LS. On the basis of the results obtained, the method of preparation of solid dispersions also influences the rate of dissolution of LS. In the kneading method, synergistic effect of trituration and solubilization of used solvent reduces crystallinity leading to improvement in dissolution rate. The results shows that the dissolution rate of

LS from KW is less than that of KE which may be due to cosolvent effect of 70% *v*/*v* ethanol on LS.

Solvent wetting method enhances the dissolution rate of LS due to the wetting effect of the solvent. KE enhances the dissolution rate higher than that of SW because it has additional trituration effect on the drug. Spray drying enhances the dissolution rate of LS due to improved wettability of drug particles and significant reduction in particle size during spray drying process. The reason for higher dissolution rate of SE compared with other solid dispersions may be due to availability of increased surface area of particles in the suspension. Infrared spectra of LS and that of solid dispersions showed same characteristic peaks indicating no modification or interaction between the drug and the carrier. SEM photographs showed decrease in crystallinity of LS. These observations further confirmed by the results of DSC and XRD studies. The DSC thermograms of physical mixture as well as solid dispersions showed identical peaks corresponding to pure drug indicated well-defined chemical interaction between LS and MLBG. Further, the decrease in sharpness of LS endothermic peak in both the solid mixtures may be due to low amount of the drug in the dispersions and decrease in crystallinity of LS. IR and DSC studies support same hypothesis, which is confirmed by X-ray diffractometry. XRD spectra of LS showed sharp peak at different diffraction angles (2θ). All major characteristic crystalline peaks appear in the diffractogram of solid dispersions system but of low intensity. This proves decrease in crystallinity of LS as some of the drug gets converted to amorphous form in solid dispersions. *In vivo* studies were carried out using an indirect method for assessing variation in 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (NADPH) activity in liver tissue. HMG-Co A and mevalonate concentrations in the tissue homogenate were estimated in terms of absorbance and the ratio between the two is taken as an index of activity of the enzyme, which catalyzes the conversion of HMG Co A to mevalonate. HMG Co A/mevalonate ratio for solid dispersions was higher than that of LS. HMG Co A/mevalonate is inversely proportional to activity of HMG Co A reductase enzyme. Hence, the activity of the enzyme was significantly decreased by using solid dispersions in comparison with that of plain drug LS which indicates better performance of SD than LS.

CONCLUSION

In conclusion, our studies showed that MLBG could be used as a potential carrier in the dissolution rate enhancement of LS. The dissolution rate of LS from solid dispersions of LBG prepared by modified solvent evaporation method was low when compared with solid dispersions of MLBG because of high viscosity of LBG. Hence, various SD were prepared using MLBG than LBG. Increase in apparent solubility of LS from solid dispersions also increases the dissolution rate of LS. Increased wettability, dispersibility, and solubilization effect of LBG and MLBG enhances the solubility of LS. The results demonstrated that the optimum LS/MLBG ratio is 1:5. Among all the methods used in the preparation of solid dispersions, modified solvent evaporation method gave higher dissolution rate and required less amount of organic solvent. Result of *in vivo* study indicates better performance of SD than LS as there observed significant reduction in activity of HMG Co A reductase enzyme.

ACKNOWLEDGMENT

Authors are thankful to Biocon, Banglore, India and Taiyo Lucid Pvt. Ltd., Mumbai, India for providing gift sample of lovastatin and locust bean gum, respectively.

REFERENCES

1. G. V. Murali Mohan Babu, Ch. D. S. Prasad, and K. V. Raman Murthy. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine. *Int. J. Pharm.* **234**:1–17 (2002).
2. S. Roller, and S. A. Jones. *Handbook of fat replacers*, CRS, Boca Raton, FL, 1996.
3. F. Ohwavworhu, and T. Adelakun. Phosphoric acid-mediated depolymerization and decrystallization of α-cellulose obtained from Corn Cob: Preparation of low crystallinity cellulose and some physicochemical properties. *Trop. J. Pharm. Res.* **4**:509–516 (2004).
4. K. Reddy, S. Mutalik, and S. Reddy. Once daily sustained release matrix tablets of nicorandil: Formulation and *in vitro* evaluation. *AAPS PharmSciTech*. **4**:E61–E66 (2003).
5. A. Modi, and P. Tayade. Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS PharmSciTech*. **7**: E1–E6 (2006).
6. A. Paradkar, A. A. Ambike, and B. K. Jadhav. Characterization of curcumin—PVP solid dispersion obtained by spray drying. *Int. J. Pharm.* **271**:281–286 (2004).
7. B. Chauhan, S. Shimpi, and A. Paradkar. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying techniques. *Eur. J. Pharm. Sci.* **26**:219–230 (2004).
8. E. J. Kim, M. K. Chun, J. S. Jang, I. H. Lee, K. R. Lee, and H. K. Choi. Preparation of a solid dispersion of felodipine using a solvent wetting method. *Eur. J. Pharm. Biopharm.* **64**:200–205 (2006).
9. Y. Rane, R. Mashru, M. Sankalia, and J. Sankalia. Effect of hydrophilic swellable polymers on dissolution enhancement of carbamazepine solid dispersions studied using response surface methodology. *AAPS PharmSciTech*. **8**:E1–E11 (2007).
10. A. Venugopala Rao, and S. Ramkrishnan. Indirect assessment of hydroxymethyl glutaryl CoA reductase (NADPH) activity in liver tissue. *Clin. Chem.* **21**:1523–1525 (1975).
11. Y. Chao, J. S. Chen, V. M. Hunt, G. W. Kuron, J. D. Karkas, R. Liou, and A. W. Alberts. Lowering of plasma cholesterol levels in animals by lovastatin and simvastatin. *Eur. J. Clin. Pharmacol.* **40**(Suppl 1):S 11–S 14 (1991).
12. A. Portero, C. Rermunan-Lopez, and J. L. Vila-Jato. Effect of chitosan and glutamate enhancing the dissolution properties of poorly water soluble drug nifedipine. *Int. J. Pharm.* **175**:75–84 (1998).