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Solubility enhancement of fenofibrate by modified locust bean gum using solid dispersion techniques

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ABSTRACT

Introduction: Modern techniques, such as high-throughput screening or combinatorial chemistry, facilitate the speedy identification of new, highly potent chemical entities. Very often new compounds exhibit higher molecular weights and lower water solubility compared to drugs already on the market. Fenofibrate is poorly water-soluble (BCS class II) drug. **Aim and Objectives:** The aim of present study was to develop an alternative carrier to reduce the production cost and toxic effects and enhance the solubility of fenofibrate. **Results:** The solid dispersions were prepared using modified locust bean gum using kneading and solvent evaporation method that increased in apparent solubility and the dissolution rate of fenofibrate.

Key words: Fenofibrate, kneading, modified locust bean gum, solid dispersion, solvent evaporation

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 the gel layer on the hydrated surfaces, which prevents the drug release during dissolution. This can be overcome during tablet formulation by adding disintegrates. Pulverization of the product is a fenofibrate, another important drawback with the high viscosity carriers, which can be overcome using decreasing order of polymer:drug ratio during formulation. However, it is reported that the swelling ability of the carrier improves the dissolution rate of poorly water-soluble drug (Chiou and Riegelman 1969; 1971). 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 the same and viscosity reduced.[1,2] 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.[3-5] In case of drugs with the dissolution rate limited absorption, reduction in particle size (Patel *et al*., 2008) 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, and cogrinding. However, all these techniques have potential limitations.[6-8] All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. Decreasing particle size increases solubility, but there are poor wetting and flow. Solid dispersions can overcome these problems.[9,10]

Many carriers used in solid dispersions. Fenofibrate causes 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 the solubility of poorly water-soluble drugs due to their high viscosity. The use of polymers with low viscosity and high swelling capacity offers a better alternative for these types of polymers. The use of natural polymer is more beneficial because of their low cost, biocompatibility, and biodegradability.

Locust bean gum (LBG) is a natural polymer which 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 and it can be used as thickening and stabilizing agent. LBG is widely used because of its high swelling capacity, high water retention capacity, easy digestible nature, binding ability, abound availability, and chemical compatibility. The United States Food and Drug Administration approved limit from inactive ingredient database for LBG is 74.25 mg.[11]

The present work examines the influence of modified locust bean gum (MLBG) on solubility enhancement of poorly water-soluble drug. Fenofibrate acts through inhibhitor-mediated mechanism. It causes lipolysis and causes decreased production in very low-density lipoprotein level (Bart *et al*. 1998).

In this photo microscopic study, the surface characteristic of pure LBG is viewed by simple compound microscope to analyze surface morphology. Green-colored structures can be seen. The surface characteristics of MLBG are viewed with the help of simple compound microscope, and yellowish features are observed which gives clear indication of conversion of LBG to its modified form MLBG.[12]

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MATERIALS AND METHODS

Fenofibrate was obtained from USV pharmaceuticals, Baddi, Himachal Pradesh. LBG was obtained from Triveni Chemicals, Vapi, Gujarat, as a gift sample. All other reagents were found to be of analytical grade.

Preparation of MLBG

The MLBG was prepared by the method reported by Babu *et al.,* 2002. Powdered gum was placed in a porcelain bowl and subjected to heating in a hot air oven for different time periods at different temperatures, i.e., 140°C at 2 h. The prepared MLBG was finally resieved (100 mesh) and stored in an airtight container at 25°C.[13,14]

Characterization of LBG/MLBG

LBG powder (1 g) 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. 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:

$$SI = [(X_t - X_0)/X_0] \times 100$$

Where X_0 is the initial height of the powder in a graduated cylinder and X_t denotes the height occupied by swollen gum after 24 h.

Angle of Repose

The angle of repose was determined by the funnel method. 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.[15] The diameter of the powder heap was measured, and angle of repose was calculated using the following equation:

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

Photo Microscopic Study

Photo microscopic image of LBG and MLBG was taken at ×100 Magnification (LABINDIA, AMBALA).

Compressibility

Compressibility index (Carr's index) (Aulton. E. Michael 2007) was determined using the following equation:

$$\text{Carr's index}(\%) = \left[\frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}}\right] \times 100$$

Methods of Preparation of Solid Dispersions

Solid dispersions were prepared by different methods to enhance the aqueous solubility of FENOFIBRATE 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 (PM)

The PM of fenofibrate and MLBG was prepared by simple blending the FENOFIBRATE and MLBG in 1:1 and 1:5 w/w ratio with a spatula and passed through a 100-mesh sieve.

Kneading Method

In this method (Choudhary *et al*., 2009, Gaikwad *et al*. 2011), the drug and polymer MLBG was taken in different ratios (1:1, 1:2, 1:3, 1:4, and 1:5) in mortar and pestle and triturated properly with 70% v/v methanol until a paste-like consistency is obtained. The paste-like formation is well scrapped out and put in a tray drier at 45°C. It is collected and stored in airtight polybags placed in desiccators.[16,17]

Solvent evaporation Method

In this method (Sharma *et al*. 2009), the drug and polymer MLBG was taken in different ratios (1:1, 1:2, 1:3, 1:4, and 1:5) in a 100 ml beaker with 70% v/v methanol. The mixture was stirred on a magnetic stirrer and evaporated at 45°C. Paste-like formation is well scrapped out and dried in a tray drier. It was collected and stored in airtight polybags placed in desiccators.

Characterization of Solid Dispersions

Solubility study

The solubility of drug was analyzed in various different mediums, i.e., in phosphate buffer ph 6.8, phosphate buffer ph 7.4, distilled water, and 0.1 M sodium lauryl sulfate. Drug was taken in excess (10 mg) in glass vials containing the respective solutions (20 ml). Shaken for 24 h on a rotary shaker. Supernatant liquid was taken and filtered through Whatman filter paper (100 pores) and analyzed under UV at 290.5 nm, and solubility was calculated by respective calibration curve for each medium [Table 2].[18,19]

Phase Solubility Study

Phase solubility study of drug was carried with polymer MLBG. The excess amount of drug was taken in glass vials, and 20 ml of 0.1%, 0.2%, 0.3%, 0.4%, and 0.5% w/v solution of MLBG in phosphate buffer ph 7.4 was added and was shaken for 24 h on rotary shaker at 25 ± 2°C. These solutions were filtered through Whatman filter paper and analyzed under UV at 290.5 nm absorbance. Consecutively, solubility in different phases of polymer is determined [Table 3].[20,21]

In Vitro Dissolution Rate Study

Accurately weighed preparation equivalent to 40 mg of fenofibrate was added to 900 ml of dissolution media 0.1 M Sodium Lauryl Sulfate (FENOFIBRATE) contained in USP dissolution apparatus Type I maintained at 37 ± 0.5°C at 50 rpm. 10 ml aliquots were withdrawn at 5, 10, 15, 30, 45, and 60 and replaced by 10 of fresh dissolution media (37°C). The collected samples were analyzed after suitable dilution (if required) at 290.5 nm using UV spectrophotometer against the blank. The drug release studies were carried out in triplicate (Choudhary *et al*., 2009). The release profile data were analyzed cumulative percentage drug dissolved at different time intervals, and dissolution efficiency (DE) (Khan and Rhodes 1994, Ronak Patel *et al*. 2012) was calculated according to Khan *et al*.[22-25] [Table 4].

Infrared Spectroscopic Study

Fourier transformed infrared spectra of fenofibrate, MLBG, PM, and solid dispersions of fenofibrate–MLBG were obtained on a ATR (Bruker alpha, Germany) The scanning range was 600–4000 and the resolution was 1 cm^{-1}.

Scanning Electron Microscopy

The scanning electron microscope (SEM) photographs of

fenofibrate and solid dispersions prepared by modified SE method were obtained by SEM (DIYA LABS, NAVI MUMBAI).

Differential Scanning Calorimetry (DSC)

DSC curves of fenofibrate, MLBG, PMs, and solid dispersions (SE method) were obtained by a differential scanning calorimeter (DSC 60 Shimadzu, Japan) at a heating rate of 20°C/min from 50°C–300°C in nitrogen atmosphere.

X-Ray Diffraction (XRD) Studies

Powder XRD patterns of fenofibrate, MLBG, and solid dispersions (SE Method) were recorded using diffractograms (PW 1140, Mettler Toledo,) Cu-kα radiation. Diffractograms were run at a scanning speed of 2/mm and a chart speed of 2/2 cm per 2θ.

RESULTS

The results of the characterization of LBG and MLBG are given in Table 1. 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 the carrier is the amount of water retained in it which indicates the ability of carrier toward hydrophilic nature [Table 1]

Table 1: Preformulation parameters for MLBG and LBG

Characterization of API	LBG	MLBG
Bulk density	0.55 (g/cm³)	0.49 (g/cm³)
Tapped density	0.75 (g/cm³)	0.65 (g/cm³)
Carr's index	0.26	0.24
Hausner's ratio	1.37	1.32
Angle of repose	42.67°	40.98°
Viscosity	1650 cps	561 cps
Swelling index	4.5	3.0

MLBG: Modified locust bean gum, LBG: Locust bean gum

Table 2: Solubility study of drug (Fenofibrate) was performed in various solvents

Different media	Solubility (µg/ml)	Solubility (mg/ml)
Phosphate buffer pH 6.8	4.15	0.004
Phosphate buffer pH 7.4	22.28	0.022
Distilled water	12.68	0.012
0.1M SLS	20.26	0.020

Table 3: Phase solubility study of fenofibrate with MLBG

Concentration of MLBG (%)	Solubility(µg/ml)	Solubility(mg/ml)
0.1	4.33	0.043
0.2	9.98	0.009
0.3	18.33	0.018
0.4	26.96	0.026
0.5	36.88	0.036

MLBG: Modified locust bean gum

Table 4: DE of solid dispersions (Khan and Rhodes 1994)

Formulation code	DE at t_{10} (%)	DE at t_{30} (%)
SDK_1	31.90	36.00
SDK_2	30.24	42.40
SDK_3	39.66	41.73
SDK_4	24.67	43.46
SDK_5	31.12	44.43
SDE_1	31.44	42.40
SDE_2	15.44	40.20
SDE_3	32.18	46.43
SDE_4	12.43	19.19
SDE_5	26.37	22.50

DE: Dissolution efficiency

DISCUSSION

The above phase solubility of fenofibrate with MLBG shows positive deviation from the normal to A_p type.

From the above solubility study analysis, it was determined that, as the concentration of gum increases, the solubility of fenofibrate was enhanced in the increasing manner. The optimization of drug/polymer ratio was done by solubility measurement using different polymer ratios, and subsequently, methods were optimized which gives the best solubility, drug content, and subsequent parameters with enhanced dissolution profile. It was observed that 1:3 ratio significantly increases the solubility of fenofibrate prepared by SE method.

In Vitro Dissolution Rate Study

The *in vitro* dissolution profile shows a comparative study of PMs and various solid dispersions made by Kneading method and SE method. The DE is best shown by SDE-3 at DE_{10} and $DE_{30,}$ i.e. ,32.18% and 46.43%, consequently the % drug release shown by SDE-3 87.56%.

It was proved that, as the viscosity of the carrier increased, the dissolution rate was decreased. During the process of dissolution, as soon as the drug carrier particle comes in contact with dissolution fluid, seeping in of dissolution medium into the drug-carrier particle takes place, which initiated the formation of the 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 FENOFIBRATE 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 the formation of lumps of drug-carrier particles during dissolution, whereas fenofibrate–MLBG particles dispersed rapidly.

Infrared Spectroscopy Study

FTIR spectrum is shown in Figure 8.

Scanning Electron Microscopy

The above Figures 1-8 reveal the SEM pictures of pure drug (fenofibrate), MLBG, and solid dispersions, i.e., respectively, Figures 9-11 SEM figures completely show that fine surfaces of drug have become rough in solid dispersion made in Figure 11, showing drug entrapment.

Differential Scanning Calorimetry

The DSC thermograms of PM, MLBG, PM–MLBG, and solid dispersions (modified SE method) are shown in Figures 12-15. The thermograms of PM exhibited endothermic peak at 80.95, while MLBG exhibited a broad endothermic peak owing to its amorphous nature. The DSC thermograms of PM as well as solid dispersions showed identical peaks corresponding to pure drug, but sharpness of the peaks was decreased.

Figure 1: Photo microscopic image of locust bean gum

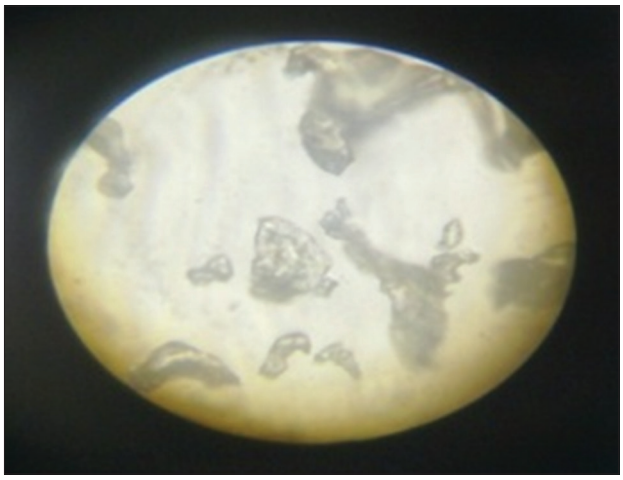

Figure 2: Photo microscopic image of modified locust bean gum

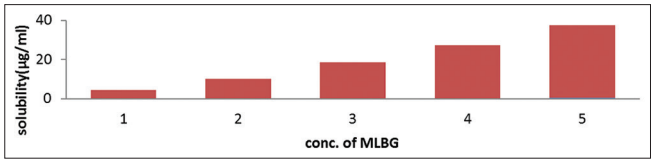

Figure 3: Phase solubility study with modified locust bean gum (Graphical Representation)

X-Ray Diffraction Studies

XRD spectra of pure PM, MLBG, and optimized batch of solid dispersions are presented in Figures 16-19. The X-ray diffractogram of PM has sharp peaks at diffraction angles (2θ) 23°, 21°, 22° showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of solid dispersions system but of low intensity.

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 the 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.

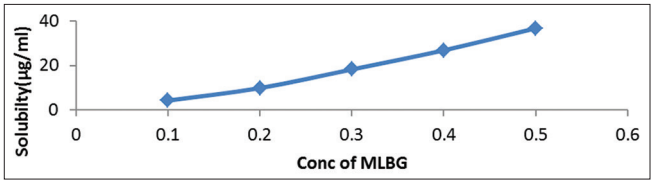

Figure 4: Phase solubility curve of fenofibrate with modified locust bean gum

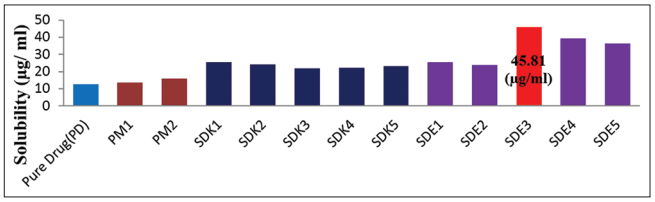

Figure 5: Solubility of physical mixtures and solid dispersions prepared by kneading and solvent evaporation method

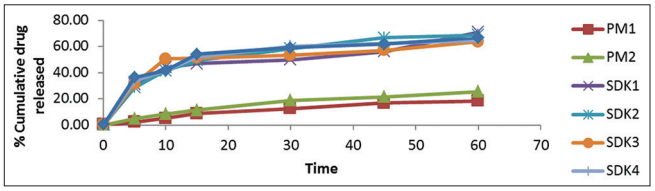

Figure 6: *In vitro* drug release of fenofibrate from solid dispersions prepared by Kneading method

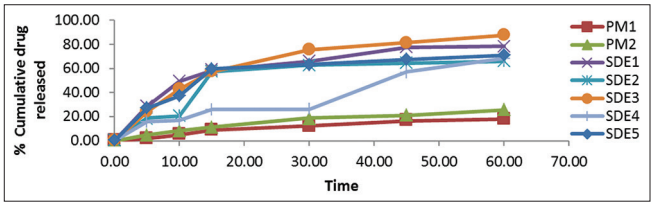

Figure 7: *In vitro* drug release of fenofibrate from solid dispersions prepared by SE method

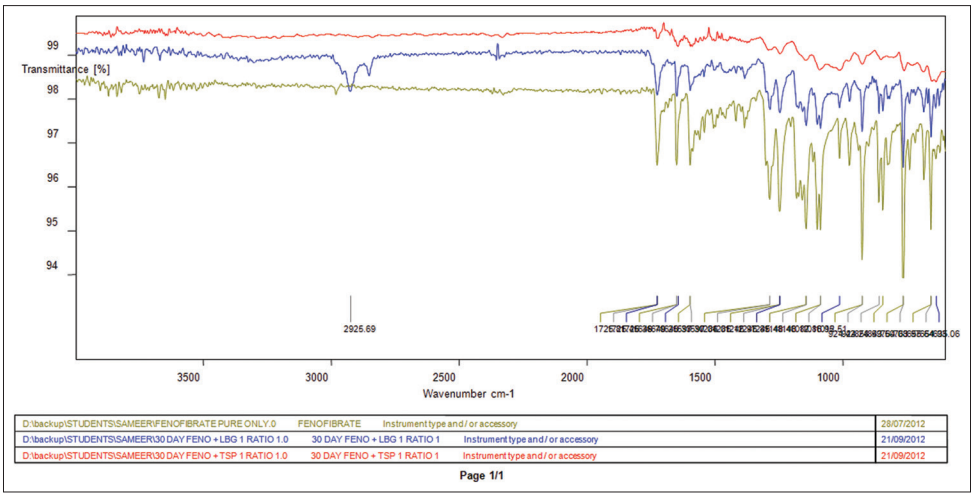

Figure 8: Infrared overlay of fenofibrate, modified locust bean gum, and solid dispersion

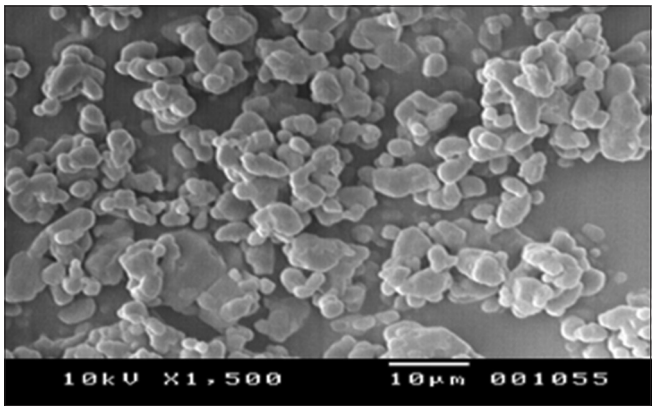

Figure 9: Pure drug

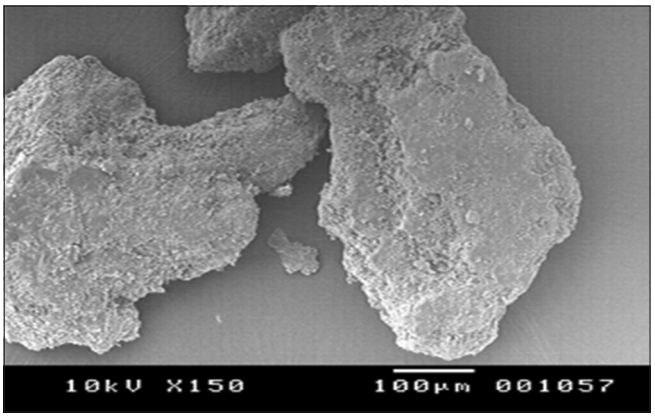

Figure 11: Solid dispersion

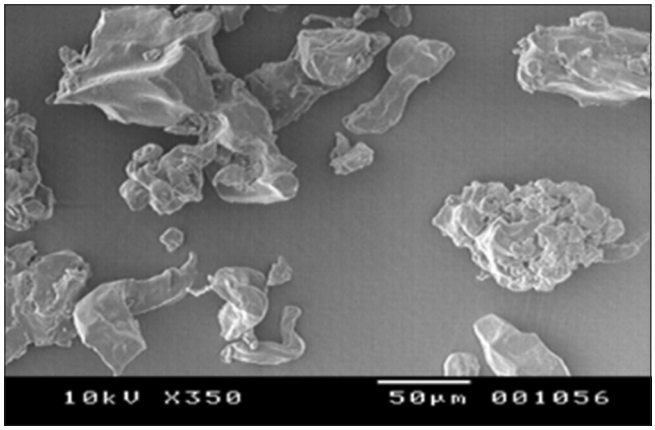

Figure 10: Modified locust bean gum (polymer)

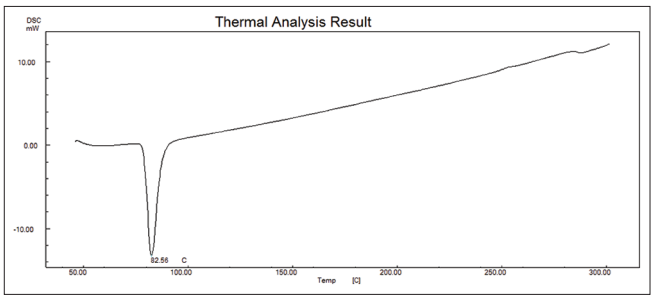

Figure 12: Pure drug

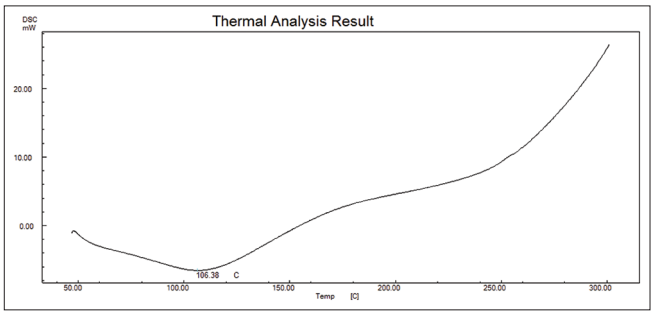

Figure 13: Modified locust bean gum

The dissolution rate of PM from solid dispersions of LBG prepared by modified SE method was low when compared with solid dispersions of MLBG because of high viscosity of LBG. Hence, various SDs were prepared using MLBG than LBG to enhance the solubility of fenofibrate. Improvement in dissolution rate of fenofibrate by PM compared with pure drug might be the solubilization effect and wetting ability of the MLBG on

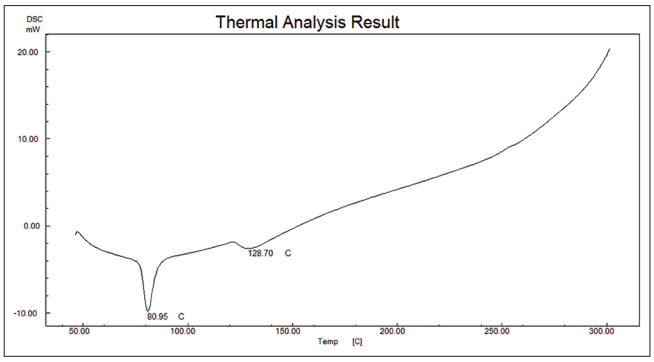

Figure 14: Physical mixture

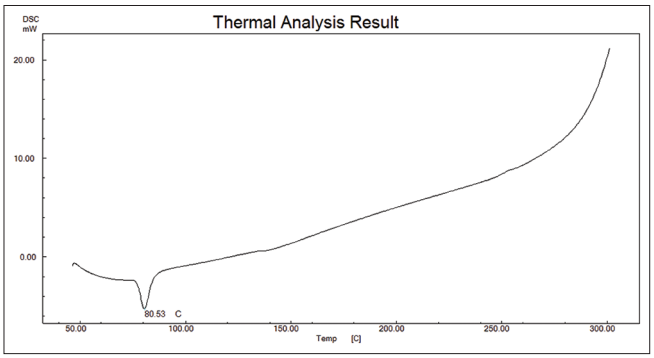

Figure 15: Solid dispersion

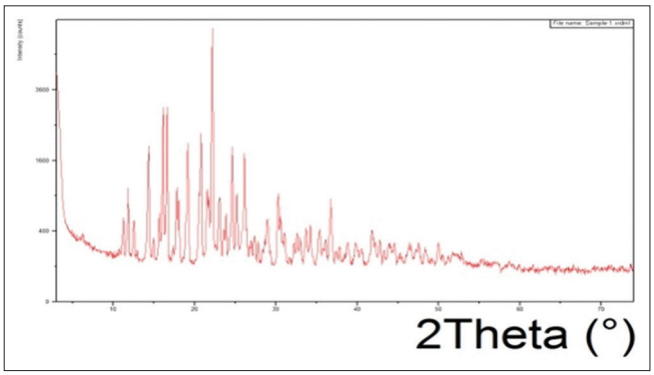

Figure 16: Pure drug

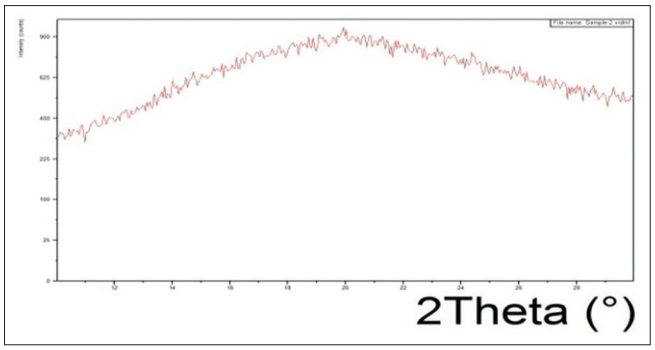

Figure 17: Modified locust bean gum

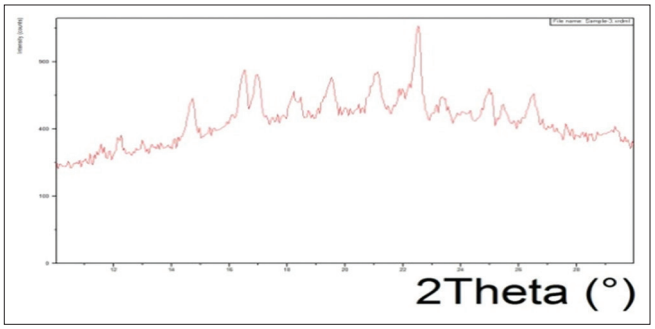

Figure 18: Physical mixture

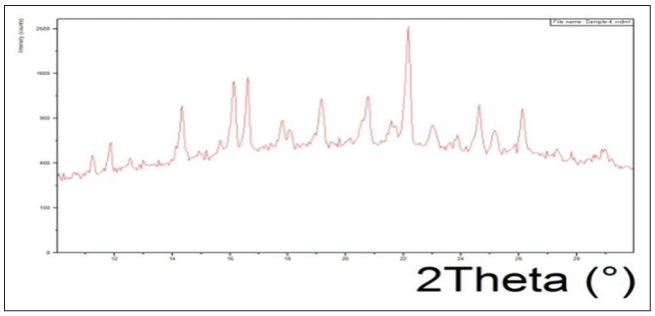

Figure 19: Solid dispersion

fenofibrate. On the basis of the results obtained, the method of preparation of solid dispersions of fenofibrate influences the rate of dissolution of fenofibrate.

The reason for higher dissolution rate of SE compared with other solid dispersions may be due to the availability of increased surface area of particles in the suspension. Infrared spectra of fenofibrate and that of solid dispersions showed the same characteristic peaks, indicating no modification or interaction between the drug and the carrier. SEM photographs showed a decrease in crystallinity of fenofibrate. These observations further confirmed by the results of DSC and XRD studies. The DSC thermograms of PM as well as solid dispersions showed identical peaks corresponding to pure drug indicated no well-defined chemical interaction between fenofibrate and MLBG. Further, the decrease in sharpness of fenofibrate endothermic peak in both the solid mixtures may be due to the low amount of the drug in the dispersions and decrease in crystallinity of fenofibrate. IR and DSC studies support the same hypothesis, which is confirmed by X-ray diffractometry. XRD spectra of fenofibrate 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 a decrease in crystallinity of fenofibrate as some of the drug gets converted to amorphous form in solid dispersions.

CONCLUSION

Our studies showed that MLBG could be used as a potential carrier in the dissolution rate enhancement of fenofibrate. The dissolution rate of fenofibrate from solid dispersions of MLBG prepared by SE method was high when compared with solid dispersions prepared by Kneading method because of proper drug entrapment in SE method, and dissolution is enhanced because of low viscosity of MLBG. Hence, various SDs were prepared using MLBG. Increase in apparent solubility of fenofibrate from solid dispersions increases the dissolution rate of fenofibrate. Increased

wettability, dispersibility, and solubilization effect of MLBG enhance the solubility of fenofibrate. The results demonstrated that the optimum fenofibrate:MLBG ratio is 1:3. Among all the methods used in the preparation of solid dispersions, modified SE method gave higher dissolution rate.

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