Original Research Article

Dissolution enhancement of glimepiride using modified gum karaya as a carrier

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Abstract

Objective: The aim of present investigation is to enhance *in vitro* dissolution of poorly soluble drug glimepiride by preparing solid dispersions using modified gum karaya. **Materials and Methods**: Solid dispersions of drug were prepared by solvent evaporation method using modified gum karaya as carrier. Four batches of solid dispersion (SD1, SD4, SD9, and SD14) and physical mixture (PM1, PM4, PM9, and PM14) were prepared and characterized by differential scanning colorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, powder X-Ray diffraction (X-RD), and scanning electron microscopy (SEM) studies. Equilibrium solubility studies were carried out in shaker incubator for 24 h and *in vitro* drug release was determined using USP Dissolution Apparatus-II. **Results**: Maximum solubility and *in vitro* dissolution were observed with Batch SD4. No significant enhancement of dissolution characteristics were observed in the corresponding physical mixture PM4. Low viscosity with comparable swelling characteristics as compared to GK of modified form of gum karaya may lead to improvement in dissolution behavior of solid dispersion batches. Also, the conversion of crystalline form of drug to amorphous form may be a responsible factor, which was further confirmed by DSC, FTIR studies, and X-RD studies. SEM photographs of batch SD4 revealed porous nature of particle surface. **Conclusion:** Modified forms of natural carriers prove beneficial in dissolution enhancement of poorly soluble drugs and exhibited a great potential in novel drug delivery systems.

Key words: Differential scanning colorimetry, glimepiride, modified gum karaya, physical mixture, scanning electron microscopy, solid dispersion, X-ray diffraction

INTRODUCTION

Oral route is the simplest and the most convenient way of administering various dosage forms. Solid oral dosages forms offer advantageous in terms of greater stability, smaller bulk, accurate dosage, and easy production. Therefore, most of the new chemical entities (NCE) are being developed as a solid dosage form that may lead to reproducible *in vivo* plasma profiles.[1,2] Also, most NCEs are poorly water-soluble; thereby exhibit low bioavailability as these are not completely released in the gastrointestinal tract.[3-5] Various techniques have been reported to improve the water solubility of drugs like micronization, salt formation, use of surfactants, solid dispersions (SD), and use of prodrug.[6,7] Among these SD is the most successful strategy to improve drug solubility. The solubility improvement occurs through decreased particle size, increased surface area, improved wettability, and increased amorphous state of water insoluble compound.[8] Sekiguchi and Obi, first introduced the concept of solid dispersions for improvement of bioavailability of poorly soluble drugs.[9] Chiou and Riegelman, 1971, defined the term solid dispersion as a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent evaporation, or melting-solvent method.[10] This technique has been widely used to improve the solubility, dissolution rate, and oral absorption of a number of poorly water-soluble drugs.[11,12] The use of natural polymers as drug carriers is increasing due to their low cost and high biodegradability.[13] Gum karaya (GK) is natural gum exudates of *Sterculia urens* (Family-*Sterculiaceae*). Its uniqueness lies in its high swelling and water retention capacity, high viscosity, inherent antimicrobial activity, and easy availability.[14,15] But high viscosity of natural gum is associated with processing and handling problems during preparation of solid mixtures, resulting into use of modified form of the gum, MGK for solubility enhancement of poorly water soluble drugs. The low viscosity along with comparable swelling index of modified form of natural carriers has been reported as tablet

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disintegrant.[16] Glimepiride (a BCS class II drug) is a second generation sulfonylurea oral anti-diabetic drug having high permeability and low solubility. Low water-soluble drugs often exhibit low dissolution profile and are thus often associated with oral bioavailability problems.[17,18]

Therefore, the objective of the present study was to improve the *in vitro* dissolution profile of glimepiride by preparing solid dispersions using modified gum karaya.

MATERIALS AND METHODS

Glimepiride was generously gifted by Ranbaxy Ltd, Gurgaon, India. Gum Karaya was procured by local supplier. Other chemicals used were of suitable analytical grade.

Preparation of modified gum karaya

The crude gum was pulverized using mortar pestle and sieved through mesh #80. The pulverized gum was heated at 120°C for 2h. The resultant solid mass was further pulverized and passed through mesh #80. The resultant modified gum karaya (MGK) was observed to be slightly brown powder. It was stored in a desiccator till further studies.

Characterization of GK and MGK

Characterization of MGK was done in terms of its swelling ratio and viscosity. The viscosity of GK and MGK was determined (n=3) using Brookfield viscometer and swelling studies were done using 1 gm gum in 1 ml water and kept for 24 h. The swelling index was calculated by taking the difference of final volume and initial volume divided by initial volume and multiplied by 100. The results obtained are summarized in Table 1.

Preparation of solid dispersion

Solid Dispersion of drug using MGK was prepared by solvent evaporation technique using rotary evaporator according to scheme shown in Figure 1. Solid dispersions (SD_1, SD_4, SD_9, and SD_{14}, respectively) were prepared using different ratios of drug: polymer (1:1, 1:4, 1:9, and 1:14) and evaluated.

Preparation of physical mixture

The four batches of physical mixtures of drug and modified gum karaya (PM_1, PM_4, PM_9, and PM_{14}) were prepared by simply mixing using spatula on ointment slab using different ratios of drug: polymer (1:1, 1:4, 1:9, and 1:14, respectively).

Evaluation of solid dispersion

Differential scanning calorimetry

The differential scanning calorimetry (DSC) thermogram of drug, carrier, solid dispersion and physical mixture were obtained using Differential Scanning Calorimetry (model Q10V9.0 Build 275, TA Instruments). Samples were heated under nitrogen atmosphere on an aluminum pan at the rate of 10°C per min over a temperature range of 30-300°C.

Table 1: Characterization of gum karaya and modified gum karaya

Products	Viscosity	Swelling index (%)
GK	2.367±0.058	70.667±1.155
MGK	1.246±0.0058	59.34±0.578

Fourier transform infrared spectroscopy

A small amount of powdered solid/formulation (1-2 mg) was added to pure potassium bromide powder (approx 100 mg) and ground up as fine as possible. This was then placed in a small die and put under pressure mechanically; the pressure was maintained for several minutes before removing the die and the KBr pellet thus formed was then placed in a sample holder and scanned in the scanning range of 400-4000 cm^{-1}.

Equilibrium solubility studies

Solubility studies were done in phosphate buffer (pH 6.8) using shaker incubator. The samples were kept overnight for 24 h and were then analyzed using UV visible spectrophotometer (SPECTROD 200-Analytik Jena, 07745 Jena).

In vitro release studies

In vitro release of glimepiride from the solid dispersion was studied in USP phosphate buffer solution (500 ml, pH. 6.8) maintained at 37±0.5°C using USP II dissolution test apparatus (model TDP-06P, Electrolab, Mumbai) at the paddle rotation speed of 75 rpm. Dissolution studies were performed on pure drug, solid dispersions, and the physical mixtures. Aliquots (5 ml) were periodically withdrawn and were analyzed spectrophotometrically at 226 nm.

Scanning electron microscopy

The sample of pure drug, MGK, selected batch SD_4, and the PM4 physical mixture were mounted onto the stubs using double sided adhesive tape and then coated with Gold Palladium alloy (150-200A°) using fine coat sputter (JSM 6600, Jeol, Japan). Samples were subsequently analyzed under scanning electron microscope (SEM) for external morphology.

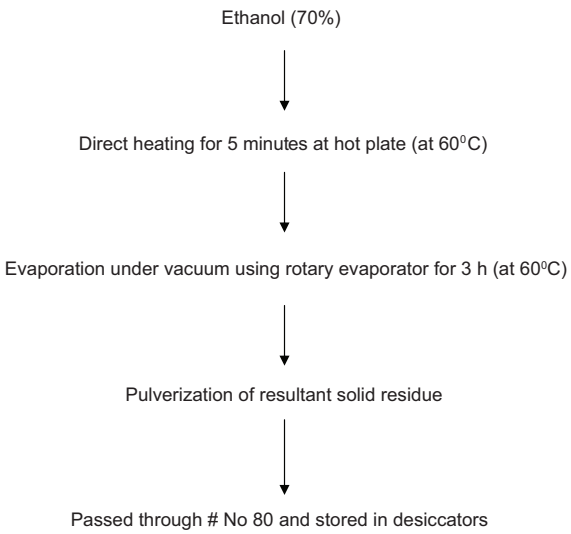

Figure 1: Scheme for preparation of solid dispersion

X-ray diffraction

The powder X-ray diffraction (X-RD) pattern was traced employing X-ray diffractometer (Table Top XRD Miniflex-2, Rigaku Corporation) for the samples using CuK (α radiation, a voltage of 30 kV, a current of 15 mA). The samples were analyzed over 2θ range of 10-80° with scanned step size of 0.0170° (2θ) and scanned step time 20 sec.

RESULTS AND DISCUSSION

Characterization of GK and MGK

The results of characterization of GK and MGK [Table 1] indicated that the viscosity of MGK was lower (nearly half) than GK. However, the swelling index of MGK was 59.34±0.578, whereas for GK it was observed to be much higher (70.667±1.155), and it had not reduced significantly rather than that of GK. Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, thereby enhancing the dissolution of the drug.

Differential scanning calorimetry

The differential scanning calorimetry (DSC) thermograms of glimepiride, GK, MGK, solid dispersion batches, and physical mixture are given in Figure 2. The thermograms of pure drug exhibited endothermic peaks at 210.30°C with enthalpy of fusion 194.2J/g corresponding to its melting point, indicating its crystalline nature; on the other hand, thermograms of GK and MGK exhibited a broad endothermic peak showing their amorphous nature. DSC thermograms of SD batches (SD_1, SD_4, SD_9, and SD_{14}) and physical mixture PM_4 showed identical peaks corresponding to pure drug indicated the absence of well-defined chemical interaction between drug and MGK. However, the decrease in the sharpness of pure drug's endothermic peak in SD batches and PM_4 was observed, which may be due to conversion of crystalline form of drug to amorphous form that was further confirmed by XRD analysis.

Fourier transforms infrared spectroscopy

An IR spectrum of sample was recorded as to ascertain the presence of different functional groups. Fourier transforms infrared (FTIR) of pure glimepiride [Figure 3] showed characteristic sharp peaks at 3369 cm^{-1} and 3288 cm^{-1} due to N-H stretching, 1707 cm^{-1} and 1674 cm^{-1} due to carbonyl group, 1345 cm^{-1} showing C-N stretching vibration, 1153 cm^{-1} showing S=O stretching vibration.

The infrared spectrum of different batches (SD_1, SD_4, SD_9, and SD_{14}) of solid dispersion and physical mixture PM_4 exhibited significant decrease in the intensity of characteristic peaks of glimepiride. The IR spectrum of MGK, SD_4, and PM_4 is shown in Figure 3.

Equilibrium solubility studies

Figure 4 shows the equilibrium solubility data of various batches of physical mixture and solid dispersion batches. Solid dispersion batch SD_4 exhibit maximum solubility out of all SD batches, whereas no significant enhancement of solubility was observed in case of all physical mixture batches. No further improvement in solubility was observed with increasing carrier concentration as indicated by the solubility values of Batch SD_9 and SD_{14}. This observation thus revealed that further increase in carrier (MGK) concentration after 1:4 ratios does not significantly enhance solubility characteristics.

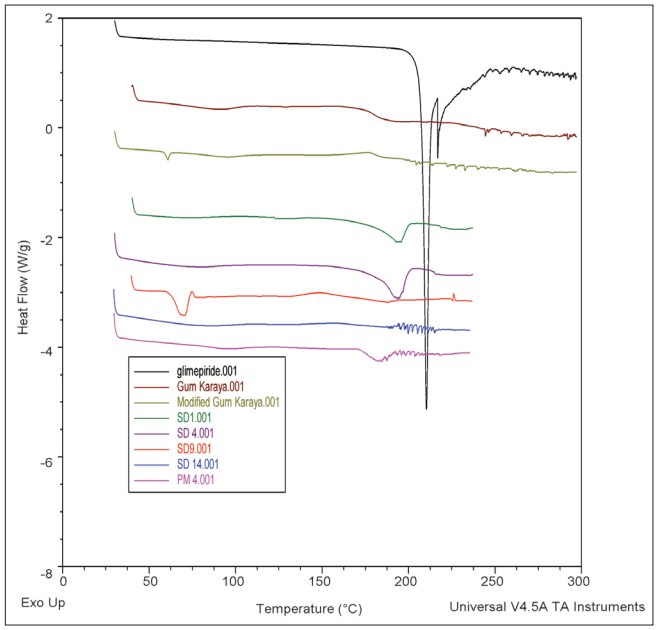

Figure 2: Differential scanning calorimetric thermograms of: glimepiride, GK, MGK, SD_1, SD_4, SD_9, SD_{14}, and PM_4

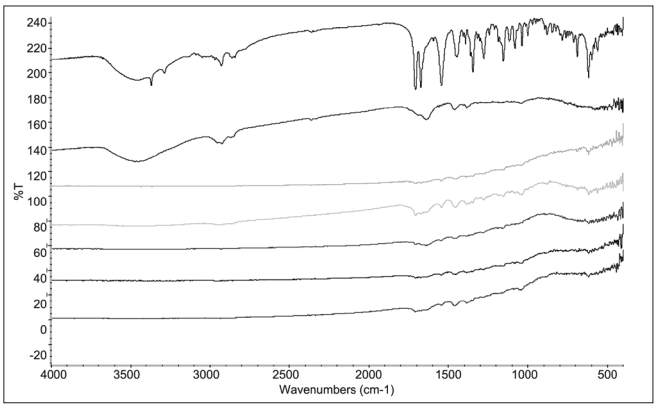

Figure 3: FTIR of: Glimepiride, MGK, PM_4, SD_1, SD_4, SD_9, and SD_{14}

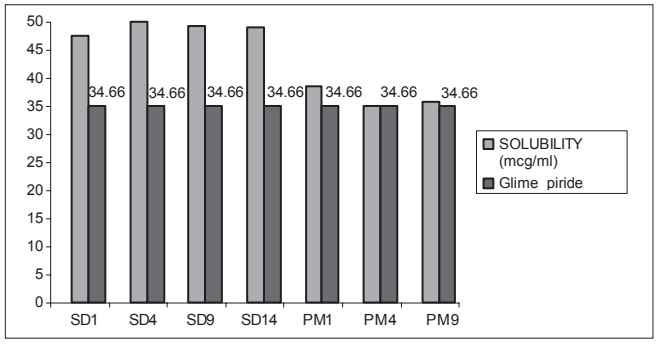

Figure 4: Equilibrium solubility of pure drug, solid dispersions batches (SD_1-SD_{14}) and physical mixture batches (PM_1-PM_{14})

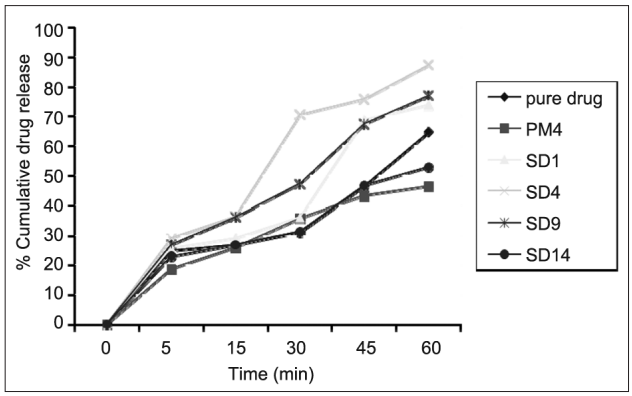

Figure 5: *In vitro* dissolution profile of pure drug, PM_4, SD_1, SD_4, SD_9, and SD_{14}

In vitro dissolution

The dissolution profiles of pure drug, solid dispersion batches (SD_1, SD_4, SD_9, and SD_{14}), and physical mixture (PM_4) are shown in Figure 5. The *in vitro* dissolution rates of solid dispersions were observed to be higher than that of pure drug and various authors have earlier reported similar influence of the drug polymer ratio on drug dissolution.[16,19] The improvement in glimepiride dissolution rate was found to be optimum at a ratio of 1:4. The results obtained give an indication of potential immediate release characteristics of the solid dispersion. However, no significant enhancement in dissolution was observed with the higher drug polymer ratio (Batch SD_9 and SD_{14}). This indicates that higher amount of carrier may affect diffusion of drug thereby decreasing dissolution. Solid dispersion batch SD_4 was selected

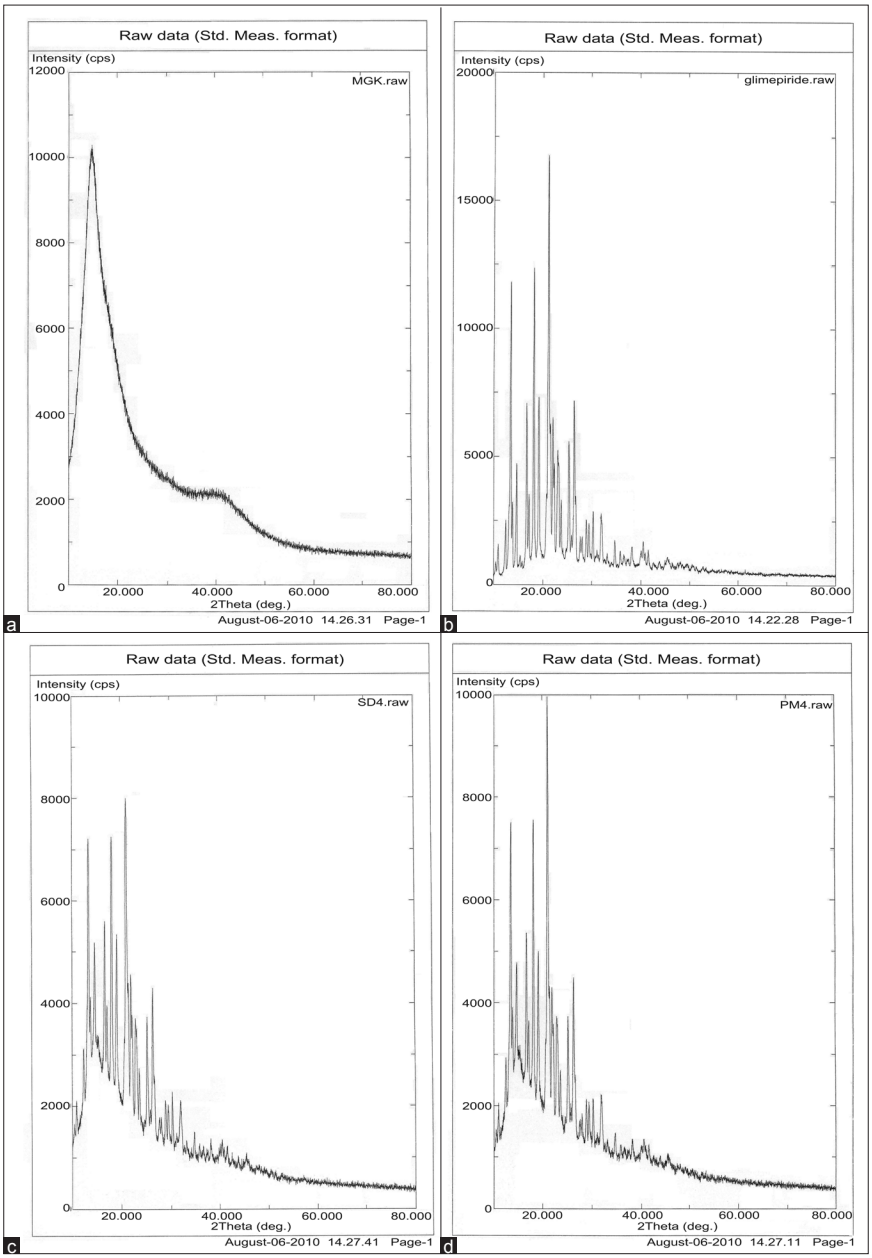

Figure 6: Powder X-ray diffraction spectra of: (a) MGK, (b) Glimepiride, (c) SD_4, (d) PM_4

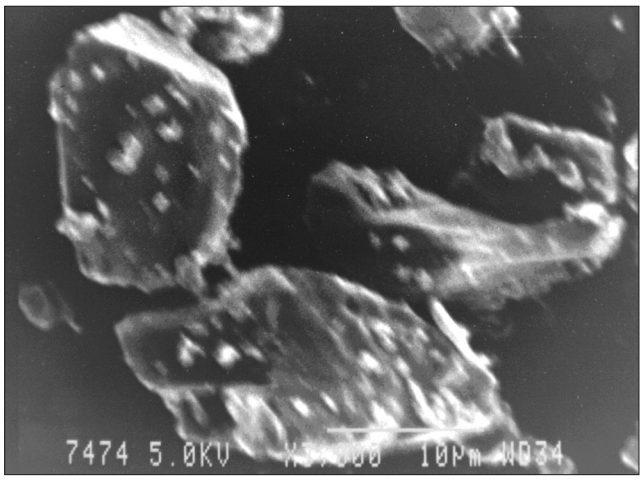

Figure 7: Scanning electron micrograph of pure drug (glimepiride) at ×1000

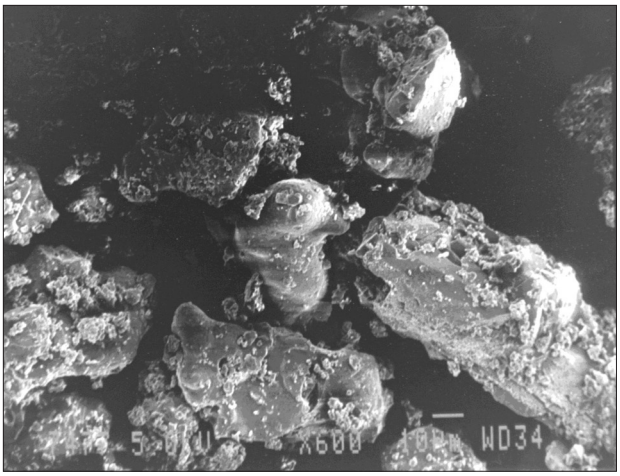

Figure 8: Scanning electron micrograph of solid dispersion (SD_4) at ×600

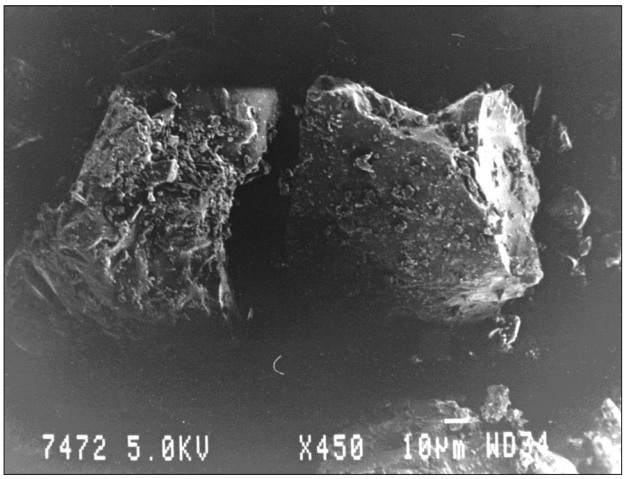

Figure 9: Scanning electron micrograph of physical mixture (PM_4) at ×450

for further SEM and X-RD studies owing to the existence of drug at molecular level as evidenced by shift in endothermic peak of drug (corresponding to its melting point, i.e., 210.30°C) during DSC studies, absence of characteristic peak of drug in IR spectrum and maximum cumulative drug release during *in vitro* dissolution studies.

X-RD studies

A change from crystalline nature to amorphous form of drug was further confirmed by comparing some representative peak heights in the diffraction of the solid dispersion with those of the pure drug glimepiride. Glimepiride showed sharp peak of the diffraction angle of 2θ at 13.52, 18.23, and 21.18° with peak intensities of 1216.66, 1293, and 1667.11, respectively, suggesting the crystalline nature of drug. The XRD patterns of SD_4 batch and PM_4 showed all the peaks of pure drug but the intensity of these peaks was markedly reduced [Figure 6a-6d] thus confirming the conversion to amorphous form of drug.

Scanning electron microscopy

Figures 7-9 illustrate the surface morphologies of glimepiride, solid dispersion batch SD_4, and physical mixture PM_4, respectively. Glimepiride appeared as smooth-surfaced rectangular crystalline structure. The topological changes observed in drug particles of the solid dispersion batch SD_4 and the drug surface seems to be more porous in nature. Solid dispersion appeared as uniform and homogeneously mixed mass with wrinkled surface. Moreover large crystalline forms of drug particles were transformed to small sized crystalline forms dispersed on the surface of gum particles.

CONCLUSION

The use of natural carriers in pharmaceutical dosage forms is of increasing interest due to low production cost and lesser toxic effects. The high viscosity and toughness of GK poses processing problems during trituration. The high viscosity generated by GK in the microenvironment of drug–carrier particle during dissolution reduces the diffusion rate of the drug, thereby decreasing the dissolution efficiency. MGK proved to be a potential carrier in the dissolution rate enhancement of glimepiride and overcomes the processing problems of higher viscosity of gum karaya. Though there is not much difference in the crystalline nature of glimepiride in MGK solid dispersions (as evident by DSC and XRD patterns), the dissolution rate of glimepiride from solid dispersions of MGK (except SD_{14}), was higher when compared to pure drug. The low viscosity and swelling ability of the carrier, decreased crystallinity and size of the drug crystals in the solid dispersion, increased solubility and improved drug wettability are supposed to improve the drug dissolution rate by solid dispersion technique compared with that of the pure drug.

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