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Original Article

ENHANCEMENT OF BIOAVAILABILITY OF GLIPIZIDE USING SOLID DISPERSIONS WITH GUM AEGLE MARMELOS

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ABSTRACT

Objective: The aim of the proposed study was formulation and *in vitro/vivo* evolution of solid dispersions of glipizide with gum *Aegle marmelos*.

Methods: The phase solubility of glipizide in 0.1N HCl was investigated in the presence of different concentrations of gum *Aegle marmelos*. The solid dispersions (SDs) of glipizide with gum *Aegle marmelos* were formulated using solvent evaporation method at ratios of 1:1, 1:2, and 1:5 (glipizide: gum *Aegle marmelos*). Dissolution studies were conducted. The physicochemical characterization of the formulations was performed by using Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD). Subsequently, bioavailability of pure glipizide, solid dispersion and marketed product was performed in rat.

Results: Glipizide solubility increased as the concentration of gum *Aegle marmelos* in 0.1N HCl was raised. The solubility study indicates spontaneous drug solubilization, which is supported by negative values of Gibb's free energy ($\Delta G\ ^{\circ}_{tr}$). Glipizide rate of dissolution was increased in SDs containing gum, and the rate increased as the concentration of gum in the SDs increases. After preparing SDs and physical mixtures with gum, the mean dissolution time (MDT) of glipizide decreases considerably. FTIR spectroscopy study revealed that stability and the absence of a well-defined glipizide-gum interaction. The amorphous condition of glipizide in SDs of glipizide with gum was revealed by DSC and XRD studies.

Conclusion: The DSC and XRD studies indicate conversion of drug from crystalline to microcrystalline or amorphous form after formulation of solid dispersion with Aegle gum. The solid dispersion of glipizide with Aegle gum (893.04±25.5) showed better therapeutic activity compared to pure glipizide (535.65±11.5) and marketed formulation (767.5±13.6).

Keywords: Glipizide, Solid dispersion, *Aegle marmelos*, Solubility, Dissolution

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INTRODUCTION

Bael, (*Aegle marmelos)* is oldest medicinally treasured tree species in the Globe as per Charak Samhita and also called as Golden Apple [1]. *Aegle marmelos* was one of the most important trees utilized by the ancient Indians in Ayurvedic therapy [2]. Ayurvedic medicine uses the plant's fruits, leaves, bark, roots, and seeds to cure number of ailments, including diarrhoea, dyspepsia, mal-absorption, neurological difficulties, edema, vomiting, and rheumatism [3, 4]. Bael fruit extracts and gum obtained from fruit exhibited anti-diabetic activities and also protective effects on pancreatic tissues [5-8]. Further, Aegle gum not only shows therapeutic effects but also it can be used as pharmaceutical excipients for formulation of various dosage forms as it consists of polysaccharide like D-galactose, L-rhamnose, L-arabinose and D-glucuronic in molar ratio of 9:3: 1:3 [9]. It is also reported by S. B. Shirsand *et al.*, 2016 that *Aegle marmelos gum* can be used as disintegrant in design of fast dissolving tablets [10]. Yogesh Joshi *et al.*, has also reported that *Aegle marmelos* gum can be used for sustained release matrix tablets [11].

The use of aegle gum as a tablet binder and mucoadhesive agent has been researched. Because of its high swelling index, high water retention capacity, digestibility, binding ability, and ease of availability, it is widely used in pharmaceutical research [12]. It has been also used as solubilizing agent for improvement of solubility of the poorly water-soluble drug [13, 14].

Researchers reported the use of natural gum for the improvement of solubility of poorly water-soluble drugs by using various techniques [15, 16]. Different synthetic polymers are used for improvement of solubility of poorly water-soluble drugs by use of solid dispersion technique while few reports are available for natural polymer for such purposes. Mallick S *et al.* reviewed the current trends in solid dispersion technique and its uses in pharmaceuticals [17].

Aegle gum shows water solubility, anti-diabetic and protective action on pancreatic tissue. Therefore, in this research work, glipizide, a poorly water-soluble BCS class II, anti-diabetic drug selected to improve its solubility and to synergize the anti-diabetic action of the said drug after forming solid dispersion with Aegle gum.

Moreover, more work has not been carried out using this natural gum. As this is an edible, biodegradable and biocompatible gum its scope to use is well utilized in the present solubility enhancement work. Work already carried out is reviewed and work covering *in vitro-in vivo* evaluation using rat model is carried out in extension.

Glipizide is also chemically known as 1-Cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido) ethyl] phenyl] sulfonyl] urea, belongs to the second generation of hypoglycemic sulfonylureas and is used to treat non-insulin-dependent diabetic mellitus (NIDDM). Glipizide appears to be the drug of choice in long-term sulfonylurea therapy for the control of NIDDM. It has better tolerability, a low incidence of hypoglycemia, and a low rate of secondary failure, as well as the potential to halt the progression of diabetic retinopathy.

MATERIALS AND METHODS

Materials

M/s Micro Laboratories Ltd, Bangalore, India provided a glipizide sample as a gift. Throughout the study, double distilled water was used, and all other compounds were of analytical quality. *Aegle marmelos* were collected from Mahuda, Berhampur, Ganjam, Orissa, India.

Preparation of SDs

Aegle gum was extracted from fruit pulp by extraction with acetone. The SDs of glipizide with Aegle gum comprising three distinct weight ratios (1:1, 1:2, 1:5) (Glipizide: Aegle gum) were formulated by solvent wetting method and termed as ASD1/1, ASD1/2, and ASD 1/5 respectively [17]. A solution of glipizide in chloroform was poured to Aegle gum in the solvent wetting procedure. Using a rotary evaporator, the solvent was evaporated under reduced

pressure at 40 °C, and the residue was then dried under vacuum for 3 h. In a Desiccator, the mixture was kept for overnight. The hardened product was pulverized in a mortar, sieved through a 40-mesh screen, and kept at room temperature until further usage in a screw-cap vial [18].

Physical mixtures (PMs) with the same weight ratio as SDs were made by completely mixing the requisite amounts of glipizide and Aegle gum in a mortar for 10 min. The resulting mixes were sieved through a 40-mesh sieve and given the designations APM 1/1, APM 1/2, and APM 1/5. The mixes were kept at room temperature in a screw-cap vial until they were used.

Solubility determinations of glipizide

According to Higuchi and Connors' approach, solubility determinations were done in triplicate [19]. In a nutshell, an excess of glipizide was placed in a screw-capped glass vial with 20 ml of aqueous solution containing varying concentrations of gum. Then the samples were shaken at 37±0.5 °C for 72 h in a water bath (Remi Pvt Ltd, Mumbai). Samples were filtered through a 0.45 µm membrane filter after 72 h. The filtrate was diluted appropriately and spectrophotometrically examined using a UV-VIS spectrophotometer at a wavelength of 227 nm (Shimadzu 1800, Japan). The solubility of glipizide in the presence of various amounts of Aegle gum was determined using a similar approach.

Dissolution studies

The dissolution study of glipizide in powder, SDs, and PMs was conducted by using the USP dissolution test apparatus-2 (LABINDIA Disso 2000) in 900 ml 0.1N HCl at 37±0.5 °C [20-22].

Fourier-transform infrared spectroscopy

An FT-IR spectrometer-430, Jasco Japan, was used to obtain Fourier-transform infrared (FT-IR) spectra. The samples (Glipizide, SDs, or PMs) were pulverized and thoroughly mixed with potassium bromide, an infrared transparent matrix, at a ratio of 1:5 (Sample: KBr). The KBr discs were made by compressing particles in a hydraulic press at a pressure of 5 tons for 5 min. From 4600 to 300 cm^{-1}, forty scans were acquired at a resolution of 4 cm^{-1}.

Differential scanning calorimetry

A DSC-6100 differential scanning calorimeter with a thermal analyzer (Seiko Instruments, Japan) was used for the DSC study. All correctly weighed samples (about 1.675 mg of glipizide or its equivalent) were placed in covered aluminum pans and heated in a scanning oven under nitrogen flow (20 ml/min) rate of 10 ˚C min^{-1} from 25 ˚C to 250 ˚C. As a standard, an empty aluminum pan was used.

X-ray diffraction

At ambient temperature, the X-ray powder diffraction patterns were acquired using a PW1710 X-ray diffractometer (Philips, Holland) with Cu as anode material and graphite monochromatic, operated at 35 kV, current 20 mA. The samples were evaluated in a two-angle range of 5–70 degrees, with the following process parameters: scan step size of 0.02 (2), scan step length of 0.5 seconds.

Assessment of therapeutic efficacy

These tests were carried out on a free drug, the ASD1/2, which was chosen based on data from dissolution studies and the marketed pharmacological product. (Glynase, B. No. 13014685, USV Private Ltd, India). This study used a single dose and a parallel group approach. Male Wistar rats (diabetic) weighing 180–240 g were fed on a regular diet for 10–14 d before the trial, fasted for 24 h, and then intraperitoneally injected with 50 mg/kg streptozotocin to induce diabetes [23, 24]. Three groups of three rats were formed from these rats. The fast take glucometer (SmartScan®) was used to measure fasting blood glucose levels [25]. In both laboratory and clinical settings, the fast take glucometer provides quick, accurate, and repeatable results [26]. The blood glucose level (BGL) was evaluated at various time intervals up to 24 h following intragastric tube administration of a single dose of 25 mg/kg of the drug or its equivalent amount of solid dispersion or marketed product. The animal's blood was taken from its orbital sinus [27, 28]. Because each animal served as its own control and, the hypoglycemic response was measured as a percentage decrease in blood glucose level and calculated as follows:

$$\% \text{ Decrease in BLG} = \frac{\text{BLG at t} = 0 - \text{BLG at t}}{\text{BLG at t} = 0} \text{X100} \quad \ldots\ldots (1)$$

The maximum percentage decrease in blood glucose level (E_{max}), time for maximum response (t_{max}), and area under percentage decrease in BGL versus time curve (AUC_{0-24h}), which was obtained by using the trapezoidal rule [29].

RESULTS AND DISCUSSION

Solubility studies

Solubility of glipizide is significantly affected by the presence of Aegle gum in 0.1N HCl (table 1). The phase solubility diagram is linear in a concentration range of 2-4% of gum and the stability constant of the said diagram is 0.221 ml^{-1} mg (A_L-type) [19]. Table 1, indicates that the solubility of the drug is increased by 1.3 times at 4% concentration of polymer. Table 1 shows the Gibbs free energy ($\Delta G_{tr}°$) values related with drugs water solubility in the presence of Aegle gum. By increasing the concentration of Aegle gum, the ΔG_{tr} ° values decreased, indicating that the reaction was more favorable as the concentration of Aegle gum increased.

Table 1: Effect of Aegle gum concentration and Gibbs free energy on solubility glipizide

Concentration of aegle gum (% w/v)	Concentration of glipizide (mg/ml) at 37 °C	ΔG_{tr} °(J/Mol)
0	0.81±0.02	0
2.0	0.83±0.01	-67.48
2.5	0.88±0.04	-218.29
3.0	0.93±0.03	-364.82
3.5	0.96±0.02	-442.65
4.0	1.00±0.03	-547.86

All values are presented as mean±SD, n=3

Dissolution studies

Table 2 shows the findings of the dissolution studies for individual samples (Glipizide, PMs, and SDs) over a one-hour period, with reported values being the mean of three measurements (CV<10 %). Table 2, shows the Q_{10}, Q_{20}, and Q_{30} values (percentage of drug dissolved in 10, 20, and 30 min). In comparison to pure glipizide and APMs, ASDs of glipizide with Aegle gum significantly increased dissolution rates within 30 min (table 2). After the formation of the physical mixture and solid dispersion, the values of % $DE_{10\ min}$ for pure drug were enhanced from 9.16 % to 22.91% in APMs and to 27.78 % in ASDs. The value of % $DE_{30\ min}$ for the pure drug was increased to 44.57 % in APMs and up to 51.74 % in ASDs. It is also revealed that the mean dissolution time after the formation of solid dispersion of glipizide was decreased from 12.5 min to 7.45 min.

From table 3, *in vitro* release data of the APMs is best fitted to Korsemeyer-Peppas except APM 1:2, which is best fitted to Higuchi-

Matrix where as other two ASDs is best fitted to Higuchi-Matrix except ASD1/1 (Korsemeyer-Peppas model) [30, 31].

The increased dissolution rate of drugs from Aegle gum SDs has been attributed to a variety of factors. The increase in dissolution kinetics is attributable to changes in surface qualities, such as a decrease in the contact angle value, which improves the powder's wettability. The creation of an Aegle gum layer over the drug particles, which affects the hydrophobicity of their surfaces, could improve the wettability of the powder [32].

Table 2: *In vitro* dissolution profile of glipizide, physical mixture of Glipizide and solid dispersion of Glipizide with Aegle gum in 0.1N HCl (pH 1.2)

Formulation	Dissolution parameters					
	$Q_{10\ min}$	$Q_{20\ min}$	$Q_{30\ min}$	$\%DE_{10\ min}$	$\%DE_{30\ min}$	MDT (min)
Drug	18.47±0.9	32.68±2.3	40.81±2.8	9.15±0.8	23.67±1.9	12.6±0.7
APM 1/1	20.4±1.2	31.9±1.4	41.3±3.2	10.18±1.2	24.31±1.2	12.36±0.6
APM 1/2	28.0±1.7	37.1±2.2	50.7±1.7	13.98±1.5	30.15±1.8	12.16±1.1
APM 1/5	45.8±2.4	56.9±1.9	62.0±2.4	22.91±1.8	44.57±2.3	8.43±1.4
ASD 1/1	21.0±1.3	32.7±1.6	44.0±1.3	10.52±2.5	25.23±1.8	12.18±0.8
ASD 1/2	30.6±2.1	42.0±2.5	51.7±1.6	15.30±2.1	32.80±1.9	10.95±1.1
ASD 1/5	55.6±1.4	65.2±1.8	68.8±1.8	27.78±2.6	51.74±3.1	7.45±0.9

All values are presented as mean±SD, n=3

Table 3: Statistical parameters of various formulations of glipizide with Aegle gum after fitting drug release data to various release kinetics models

	Zero-order model		First-order model		H-M model		P-K model		H-C model	
Formulations	R	K_1	R	K_2	R	k_3	R	$K_{4,n}$	R	K_5
Drug	0.9813	1.4736	0.9939	-0.0184	0.9893	7.1358	0.9952	3.4734	0.9905	-0.0057
APM 1/1	0.9605	1.1654	0.9918	-0.0169	0.9901	7.7231	0.9978	4.806, 0.627	0.9874	-0.0049
APM 1/2	0.9351	1.3739	0.9927	-0.0220	0.9966	9.1613	0.9949	7.680, 0.547	0.9830	-0.0062
APM 1/5	0.7563	1.6225	0.9441	-0.0296	0.9746	11.0477	0.9805	22.21, 0.308	0.9038	-0.0079
ASD 1/1	0.9590	1.2084	0.9902	-0.0180	0.9894	8.0098	0.9965	4.948, 0.629	0.9866	-0.0052
ASD 1/2	0.9354	1.4670	0.9845	-0.0252	0.9942	9.7769	0.9921	8.806, 0.526	0.9833	-0.0069
ASD 1/5	0.7268	1.8632	0.9622	-0.0424	0.9668	12.7129	0.9660	28.02, 0.283	0.9260	-0.0103

H-M indicates, Highuchi Matrix; P-K, Peppas-Korsmeyer; H-C, Hixon-Crowell; R indicates correlation coefficient; K_1-K_5, Constants of release kinetics; APM, Physical mixture with Aegle gum; ASD, Solid dispersion of Glipizide with Aegle gum prepared by the solvent wetting method.

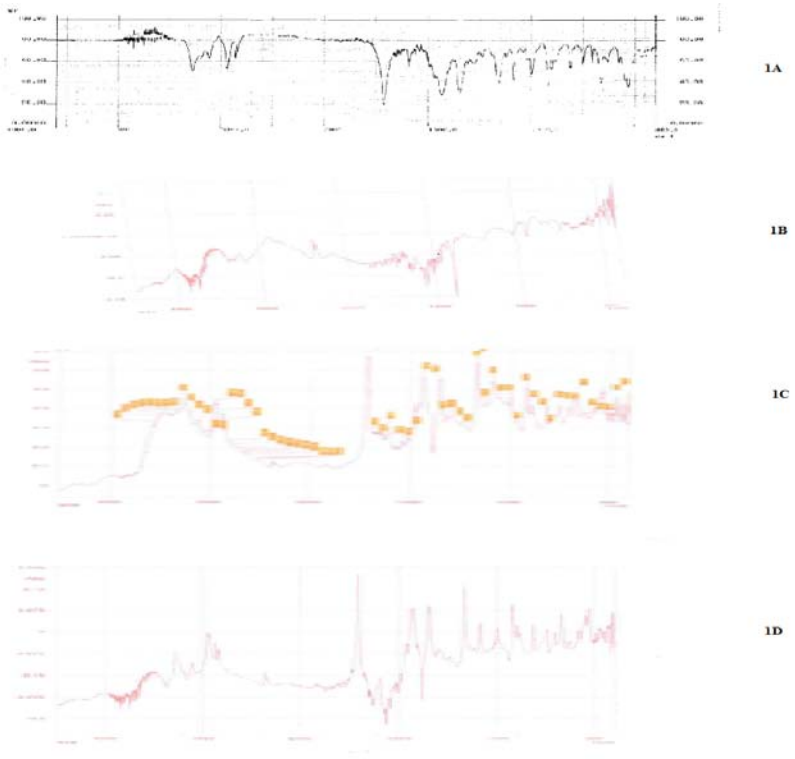

Fig. 1: FTIR spectrograms of pure lipizide (A), pure Aegle gum (B), Glipizide-Aegle gum PM at 1:2 ratio, (C), Glipizide-Aegle gum SD at 1:2 (D)

FTIR-spectroscopy

The APM and ASD IR spectra were compared to the glipizide reference spectrum. (fig. 1C, 1D, 1A). The carbonyl band was moved towards higher frequencies in the spectra of ASDs and APMs. In ASDs, the NH group, which is positioned at 3265 cm^{-1} in glipizide's IR spectra, migrated to 3640 cm^{-1}. The S=0 band's asymmetrically vibration peak was shifted lower frequencies in ASDs. The C-H stretching at 2915 cm^{-1}, the C-O stretching at 1119 cm^{-1}, and the-OH stretching at 3356 cm^{-1} are all important vibrations observed in the spectra of Aegle gum. Shift of peaks of glipizide in ASDs, could be as a result of physical interaction between the glipizide and Aegle gum, although it could be expected to have hydrogen bonding between the hydrogen atom of the NH group of glipizide and one of the ion pairs of oxygen atom in the Aegle gum.

X-ray diffractions (XRD)

Diffraction spectrum of the drug revealed that the substance was crystalline, as seen by several peaks. Glipizide diffraction peaks were seen at 2θ of 10.59, 14.98, 17.2, 17.85, 18.15, 22.07, 25.42, 26.25, 26.75, and 29.5 (fingerprint region), confirming crystalline nature of glipizide (fig. 2A). Pure Aegle gum revealed no peaks in fig. 2B, indicating that it is amorphous. In both APMs and ASDs, there were some alterations in the position peaks of the drug. The significant peaks of pure glipizide, which were seen at 2θ of 10.59, 14.98, 17.1, 18.15, and 22.07, were clearly seen at the same place in the APMs and in ASDs, but with lower intensities. The crystalline nature of the drug was retained; however, the relative drop in diffraction intensity of glipizide in ASD at these angles indicated that the quality of the crystals was reduced to microcrystal form [33]. The drug peak patterns in the APMs and ASDs were identical and superimposable, ruling out the possibility of well-defined chemical interaction and the production of novel compounds between these two components again. The findings suggest that glipizide is prevalent in ASDs in partly or microcrystalline form.

Differential scanning calorimetry

The DSC curve of pure glipizide showed a single endotherm, which corresponded to the melting point of drug. At 170.8 °C, melting began, and the associated heat of fusion (ΔH_F) was 171.8 J/g (fig. 3A), whereas pure Aegle gum exhibited no melting endotherm (fig. 3B). Thermogram of ASD (fig. 3D) revealed the presence of a glipizide melting peak at 164.69°C, with a heat of fusion (ΔH_F) of 32.8 J/g, indicating a change in glipizide crystalline nature. APM exhibits an endothermic peak at 167.61°C with a heat of fusion (ΔH_F) of 39.09 J/g (fig. 3C). In both APM and ASD, the DSC investigation identified no significant chemical interactions between the drug and the polymer.

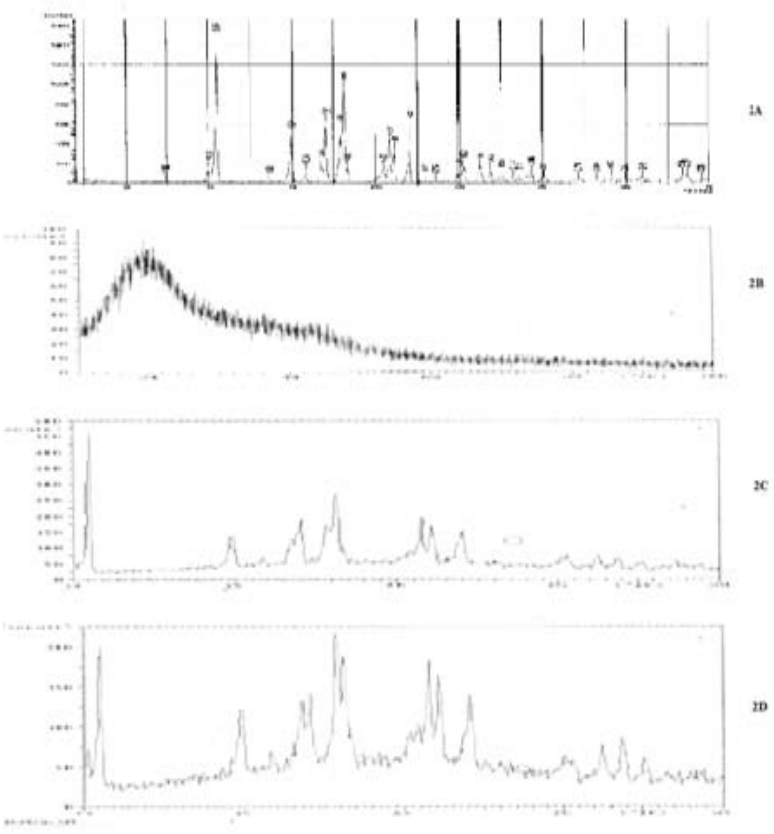

Fig. 2: X-Ray diffractograms of pure glipizide (A), pure Aegle gum (B), Glipizide-Aegle gum PM at 1:2 ratio (C), Glipizide-Aegle gum SD at 1:2 ratio (D)

Assessment of therapeutic efficacy

The mean percentage decrease in BGL of diabetic rats after administration of the pure drug, ASD1/2 and Glynase was obtained and the data are presented in table 4. It is clear that the ASD1/2 and Glynase both show somewhat identical mean maximum percentage decrease in BGL. The difference in mean maximum percentage decrease in BGL between ASD 1/2 and Glynase is significant (p>0.05), however, as compared to the free drug is highly significant (p<0.001). Table 4 shows that the time for maximum percentage drop in BGL (t_{max}), of the ASD1/2 has the lowest value and is the same as the Glynase, followed by the free drug. This suggests that the ASD1/2 has a faster onset of action than the free drug. The difference between the value of t_{max} of the ASD1/2 and that of the free drug is significant. The difference between the t_{max} value of the Glynase and that of the free drug is highly significant (p<0.01).

Table 4 demonstrates that the E_{max} values for ASD1/2 and Glynase are not the same and are greater than the free drug. According to statistical analysis, there is a significant difference between the E_{max}

value of the ASD1/2 and that of Glynase. The E_{max} of Glynase or the ASD1/2, on the other hand, is significantly different from that of the free drug. It indicates that the ASD1/2 and Glynase both have a significantly longer duration of effect than the free drug.

It is also found that $AUC_{0-24\ h}$ value for ASD1/2 is highest, followed by Glynase and then the free drug (table 4). The difference between the $AUC_{0-24\ h}$ value for the ASD1/2 and that of the free drug is very highly significant, while the difference between the AUC-value for the ASD1/2 and that of Glynase is significant. This would indicate that the ASD1/2 formula and Glynase exhibit better therapeutic efficacy compared to that of the free drug. The ASD1/2 exhibits better therapeutic activity as compared to Glynase as because the Aegle gum exhibits anti-diabetic activity.

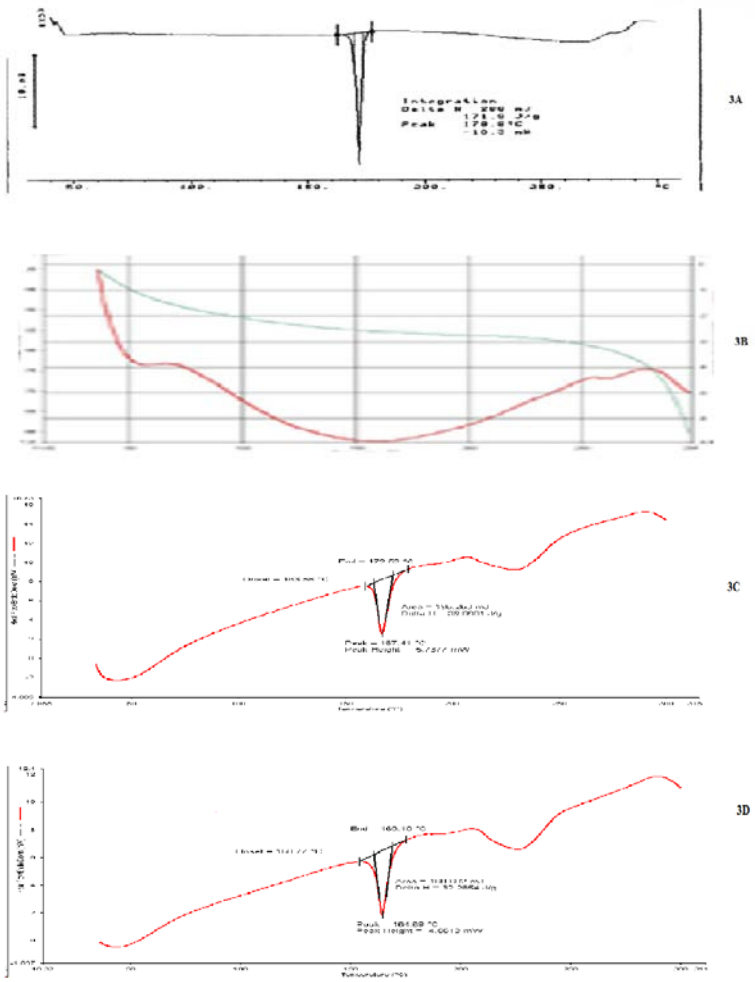

Fig. 3: DSC thermograms of pure glipizide (A), pure Aegle gum (B), Glipizide-Aegle gum PM at 1:2 ratio (C), Aegle gum SD at 1:2 ratio (D)

Table 4: The pharmacodynamic parameters of free drug, ASD1/2 and marketed formulation

Formulations	t_{max} (h)	E_{max} (%)	AUC_{0-24h}
Free drug	8	42.5±4.23	535.65±11.5
ASD1/2	4	57.14±5.23	893.04±25.50
Glynase	8	50.2±4.56	767.5±13.60

All values are presented as mean±SD, n=3

CONCLUSION

The use of solid dispersion of glipizide with Aegle gum could enhance the solubility, dissolution rate and bioavailability. The improvement of solubility of the drug after the formation of solid dispersion might be attributed to the reduction of particle aggregation of the drug, absence of crystallinity, increased wettability and dispersibility and alteration of the surface properties of the drug particles. DSC and XRD studies indicates conversion of drug from crystalline to microcrystalline form after formulation of solid dispersion with Aegle gum. Further FTIR spectroscopy ruled out well-defined interaction between Aegle gum and glipizide. The solid dispersion of glipizide with aegle gum (893.04±25.5) showed better therapeutic activity compared to pure glipizide (535.65±11.5) and marketed formulation (767.5±13.6). At last from this work, it was revealed that solid dispersion of glipizide with Aegle gum improve the solubility, dissolution rate and *in vivo* performance.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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