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ORIGINAL ARTICLE

SEDDS of gliclazide: Preparation and characterization by *in-vitro*, *ex-vivo* and *in-vivo* techniques

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Abstract In the study, self emulsifying drug delivery system (SEDDS) of gliclazide, a poorly soluble drug, was developed and evaluated by *in-vitro*, *ex-vivo* and *in-vivo* techniques. Oil and surfactant were screened out according to their solubilizing capacity. Among the tested components Transcutol HP and Tween-80 showed good solubilizing capacity. These two components were used in different ratios to prepare gliclazide SEDDS. The SEDDS formulations were transparent and clear. Droplet size of the emulsion was determined by Laser Diffraction Technology of Malvern. Formulation F1 containing 1:1 (*m*/*m*) mixture of Transcutol HP/Tween-80 showed minimum mean droplet size (50.959 μm). *In-vitro* drug release from F1 was higher (99% within 20 min) than other formulations. The developed SEDDS was also evaluated for e*x-vivo* permeability profile by using chicken intestinal sac. Formulation F1 showed optimal drug diffusion. *In-vivo* performance of SEDDS was evaluated in albino mice using plasma glucose level as a pharmacodynamic marker parameter. The test formulation (F1) showed significant reduction in plasma glucose level, after oral administration. So SEDDS may be an alternative technique for the oral administration of gliclazide.

1. Introduction

Drugs are most often administered by the oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is difficult because of their low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality. To overcome these problems, various strategies are exploited including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions (Kumar et al., 2010; Aungst, 1993). Majority of these approaches have their limitations because of the need for specialized equipment, a complicated manufacturing process, longer processing time, and regulatory complexity. Lipid-based formulation approaches, particularly the self emulsifying drug delivery system (SEDDS), are well known for their potential as an alternative approach for the delivery of

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hydrophobic drugs (Pouton, 2000), which are associated with poor water solubility and low oral bioavailability (Kim et al., 2000).

SEDDSs are isotropic and thermodynamically stable solutions consisting of oil, surfactant, co-surfactant and drug mixtures that spontaneously form oil-in-water (o/w) emulsions when mixed with water under gentle stirring. The motility of stomach and intestine provides the agitation required for self-emulsification *in-vivo* (Shah et al., 1994). Selection of a suitable self-emulsifying formulation depends upon the assessment of the solubility of the drug in various components and the droplet size distribution of the resultant emulsion following self-emulsification (Kommuru et al., 2001).

Chemically gliclazide is [1-(3-azabicyclo(3,3,0)oct-3-yl)-3-p-tolylsulfonylurea], it is a second generation hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Prior reports reveal that the drug shows good tolerability, low incidence of hypoglycemia, and a low rate secondary failure (Harrower, 1994). In addition, it has a potential for slowing the progression of diabetic retinopathy. For the reasons stated gliclazide appears to be a drug of choice in long term sulfonylurea therapy for the control of NIDDM (Harrower, 1994). Gliclazide is a white crystalline powder, relatively insoluble in water. The pKa of gliclazide is 5.8. Gliclazide exhibits slow GI absorption rate and inter individual variations of its bioavailability (Palmer and Brogden, 1993). The slow absorption rate of the drug usually originates from either poor dissolution of drug from the formulation or poor permeability of the drug across the GI membrane.

The objective of the present work was to formulate a self-emulsifying drug delivery system (SEDDS) for gliclazide. Oil and surfactant were screened out according to their solubilizing capacity. Formulations were initially checked visually. Particle size of SEDDS formulation was determined by Laser Diffraction Technology of Malvern. Isotropic systems were then evaluated by *in-vitro* dissolution study.

SEDDS of gliclazide was further evaluated by *ex-vivo* permeability study as intestinal permeability represents one essential part in the prediction of oral bioavailability (Ginski and Polli, 1999). A number of methods for assessing the intestinal permeability of a given drug have been developed and reviewed (Ferrec et al., 1999). Isolated intestinal sacs of several animal species including rat, rabbit, pig, dog, and monkey can be used in permeability studies (Tukker, 2000). Irvine et al. (1999) reported that the chicken small intestine could be a useful model for intestinal absorption. Kale et al. (2007) performed absorption studies of slow drug release formulations by using the chicken intestine segment. Dias et al. (2010) also used the chicken intestine segment to investigate the effect of sodium lauryl sulfate as a permeation enhancer for muco-adhesive acyclovir tablets. In this study we also used the chicken intestine segment for permeability studies of gliclazide SEDDS based on the assumption that membrane permeability of drugs is not species-dependant, since the composition of plasma membrane of intestinal epithelial cells is similar across the species.

Pharmacodynamic marker parameters are often used to evaluate the performance of different classes of drugs. Patil et al. (2007) evaluated the *in-vivo* performance of simvastatin SEDDS in rats using pharmacodynamic marker parameters like plasma total cholesterol (CH), triglycerides (TG) and high-density lipoprotein (HDL-CH) for 21 days. In this study *in-vivo* performance of gliclazide SEDDS was evaluated in mice using plasma glucose level as pharmacodynamic marker parameters. Oral glucose loading animal model reported by Etuk (2010) was used for *in-vivo* performance in this study.

2. Materials and methods

2.1. Materials

Gliclazide was a kind gift from General Pharmaceuticals Ltd, Dhaka, Bangladesh. Transcutol HP, Labrafac lipophile WL 1349, Lauroglycol FCC, Maisine 35-1, Capryol PGMC, Labrafiil M1944Cs, Lauroglycol 90, Labrafac PG, Peceol, Plurololeique CC497, Labrafil M2125Cs, Labrasol, and Capryol 90 were kind gifts from Gatoforese, France. Tween 80, and Tween-20 were purchased from JHD Chemicals Ltd., India. Other reagents were of analytical-reagent grade and purchased from the local market. Water was deionised and double distilled. Marketed formulations of gliclazide tablet (denoted as A and B) were purchased from the local drug store in Dhaka city after checking their manufacturing license number, batch number, production and expiry date.

2.2. Solubility analysis of gliclazide in various excipients

According to Ashok and Pradeep (2007) the following slightly modified method was used to determine the solubility of gliclazide in various components (oil and surfactants). 1 gm of each of the vehicles was mixed with 100 mg gliclazide in different glass vials. After sealing, the system was mixed by using a vortex mixture (Digisystem Laboratory Instruments Inc. Taiwan.). Then the samples were sonicated (Power Sonic 505, Hwashin Technology, Korea) to facilitate the solubilization. Samples were then analyzed by HPLC to determine the solubility.

2.3. Formulation of SEDDS

To develop gliclazide SEDDS formulation, solubility of gliclazide in different oils, surfactants was determined. Among the excipients Transcutol HP (60 mg/gm) and Tween-80 (40 mg/gm) showed good solubilizing capacity. Various formulations were prepared with a constant amount of gliclazide (10 mg) and oil (Capryol 90 500 mg) with varying ratios of surfactant and co surfactant (Table 1). In brief, accurately weighed gliclazide, Capryol 90 (500 mg as oil phase) was mixed in a mixture of Transcutol HP (used as co-surfactant) and Tween-80 (used as surfactant) in stoppered glass vials. Then the components were mixed by gentle vortexing & sonicating until gliclazide was properly dissolved. The prepared formulations were stored at ambient conditions until further use.

Table 1 Formulation of SEDDS of gliclazide. (Different ratios of surfactants and co-surfactants containing 500 mg capryol 90).

Name	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Gliclazide	10	10	10	10	10
Transcutol-HP	500	350	250	750	650
Tween-80	500	650	750	250	350

2.4. Visual evaluation of gliclazide SEDDS

Gliclazide SEDDS formulations were visually examined for clarity, homogeneity and color. To observe the color of the formulations, normal visual examination was performed. Screw-cap vials containing SEDDS formulations were kept standing against light to examine the clarity. Presence or absence of precipitation was noticed to assess the homogeneity of the prepared formulations. The SEDDS formulations were then kept at optimum room temperature for 1 month. After 1 month, those properties of the SEDDS formulations were again examined to determine the stability of the formulation of gliclazide SEDDS.

2.5. Determination of droplet size of gliclazide SEDDS

Emulsion droplet size of SEDDS formula was determined by laser Diffraction Technology of MAIVERN (Mastersizer, 2000) equipped with 2000 hydro MU with a particle range of 0.02–2000 μm. 0.5 ml of SEDDS formulations were diluted with 50 ml buffer of pH 6.8. Then emulsion droplet size was determined. Droplet size distribution was characterized with the help of the droplet size distribution pattern.

2.6. In-vitro dissolution study of SEDDS formulation and comparison with market products

In-vitro dissolution study of gliclazide and gliclazide SEDDS was carried out in a USP Type II (paddle type) dissolution apparatus (Electrolab, India). 10 mg of pure gliclazide and SEDDS formulation equivalent to 10 mg of gliclazide were filled in a hard gelatin capsule shell (size #0) prior to dissolution study. Phosphate buffer pH 6.8 was used as dissolution medium that was maintained at 37 ± 0.5 °C and stirred at 100 rpm. Dissolution samples were withdrawn at predetermined time intervals. Each time 10 ml of the dissolution sample was withdrawn with a calibrated plastic disposable syringe and the media were replenished with fresh phosphate buffer of pH 6.8. Withdrawn samples were filtered with 0.2 μm syringe filter of Microswit (Hannover, Germany) and were analyzed for drug content by HPLC. Two brands of immediate release tablets were also included in this study for comparison.

2.7. Ex-vivo permeability study

Ex-vivo permeability study was carried out by using chicken intestinal sacs. Chicken was killed and the duodenal part of the small intestine was isolated and washed with distilled water to remove the mucous and lumen content and then put into an oxygen chamber. 3 cm long sacs were prepared by tying up the two end of the sac with cotton thread. SEDDS formulation equivalent to 10 mg gliclazide was taken inside the sac. Intestinal sac containing only excipients and another sac containing 10 mg pure drug suspended in 1 ml water were also included in this study for comparison. The sacs were then taken into different dissolution baskets containing 900 ml phosphate buffer of pH 6.8 maintained at 37 ± 0.5 °C and stirred at 100 rpm. Samples were withdrawn at predetermined time intervals. Each time 10 ml of the sample was withdrawn with a calibrated plastic disposable syringe and media were replenished with fresh medium. The samples were analyzed by the HPLC method. The permeability of gliclazide was checked for 5 h.

2.8. In-vivo performance study of SEDDS on glucose level of albino mice

Six healthy mice were included in this study. 1 gm of glucose was dissolved in 5 ml water. 100 μl of this solution was administered to each of the mice orally using a micro pipette and blood samples were collected from mice tails and the glucose level was checked using Bionime GM100 blood glucose meter after 0, 30, 60, 90, 120, 150, 180 min. After seven days the experiment was repeated by using glucose solution containing pure gliclazide. 1 gm of glucose and 10 mg gliclazide were mixed in 5 ml water. 100 μl of this mixture was administered to each of the mice orally. Then blood samples were collected from mice tails and checked for glucose level. The experiment was again repeated after seven days as wash out period by administering samples containing glucose and SEDDS formulation (F1) of gliclazide in the same dose as mentioned above.

3. Results and discussions

3.1. Solubility analysis of gliclazide in various excipients

Solubility of gliclazide in various components (oil and surfactant) was studied for the selection of oil & surfactants. Among the excipients Transcutol HP showed good solubilizing capacity (60 mg/gm of oil). Solubility of gliclazide in Labrafac lipophile WL 1349, Lauroglycol FCC, Maisine 35-1, Capryol PGMC, Labrafiil M1944Cs, Lauroglycol 90, Labrafac PG, Peceol, PlurololeiqueCC497, Labrafil M2125Cs was less than < 20 mg/gm and in Labrasol, Capryol 90 was < 30 mg/gm of oil. Among the surfactants, Tween-80 showed good solubilizing capacity (40 mg/gm). These two excipients (Transcutol HP and Tween-80) were used to prepare gliclazide SEDDS with capryl 90 as oil phase. Solubility of gliclazide in various media like buffer 1.2pH, 4.5pH, 6.8pH & distilled water, was also studied for the selection of dissolution medium. Among those media of pH 6.8 showed good solubilizing capacity and was thus used as a dissolution medium.

3.2. Development of HPLC method for the analysis gliclazide

A Shimadzu (Japan) HPLC system consisting of a CMB-20 Alite system controller, two LC-20AT pumps, SIL-20A autosampler and CTO-10ASVP column oven was used. Ultraviolet detection was achieved with a SPD-20A UV–VIS detector (Shimadzu, Japan). The drug analysis data were acquired and processed using LC solution (Version 1.2, Shimadzu, Japan) software running under Windows XP on a Pentium PC. Separation of the drug was achieved from C18 column (5 μ, 4.6 × 150 mm, Waters, USA) at 30 °C temperature with a mobile phase consisting of acetonitrile: phosphate buffer (pH 2.24) (ratio:70:30) at a flow rate of 1.5 ml/min. The method was validated for the parameters like system suitability, selectivity, linearity, accuracy, precision and robustness.

The system is found suitable in respect to retention time (%RSD 0.179) and mean theoretical plate count (%RSD 0.788). The absence of additional peaks of excipients

interfering with the target peak in the chromatogram indicates the selectivity and specificity of the method. The linearity of the method was determined at different concentration levels (1–25 μg/ml, r^2 = 0.998). For accuracy testing, six replicate runs of samples containing excipients and drug were performed. The % recovery value, which was 99.94 ± 0.67%, indicated the accuracy of the method. Precision was determined by repeatability (intra-day) and intermediate precision (inter-day) and assessed by %RSD (Table 2).

Finally robustness test was performed by changing the flow rate, column temperature and mobile phase composition and no marked changes in the chromatograms were observed, which demonstrated that the method was robust.

3.3. Physical properties of gliclazide SEDDS

SEDDS formulations were visually examined for clarity, homogeneity and color (Fig. 1). All the SEDDS formulations of gliclazide containing transcutol and tween-80 were transparent, homogenous and clear.

3.4. Emulsion droplet size analysis

Emulsion droplet size of SEDDS formulation was determined by the Laser Diffraction Technology of Malvern (Mastersizer, 2000). Particle size distribution was characterized with the help of droplet size distribution of 10% particles – d (0.1), droplet size distribution of 50% droplet – d (0.5), and droplet size distribution of the 90% particles – d (0.9). Droplet size range of the SEDDS formulation of system I–V was in the range of 9.10 μm to 246.444 μm.

Formulation F1 showed the smallest droplets which were 9.10 μm and formulation F4 showed the largest droplets which were 246.444 μm. For formulation F1 90% droplet was within 153.176 μm, 50% droplet was within 50.959 μm and 10% droplet was within 9.100 μm. In this formulation 50% transcutol HP and 50% tween-80 were used which produced a very clear emulsion when water was added with agitation.

Formulation F2 produces larger particle size (90% droplet was within 170.647 μm, 50% droplet was within 105.961 μm and 10% droplet was within 29.968 μm). In this formulation higher amount of tween-80 (65%) was used.

Behavior of formulation F3 was the same as of F2. In this formulation we also used higher concentration tween-80 (75%). Droplet size was larger than F1 and F2 (90% droplet was within 220.505 μm, 50% droplet was within 129.577 μm and 10% droplet was within 68.642 μm).

Formulations F4 and F5 were also produced in larger droplet sizes than F1 although higher amounts of transcutol HP were used in these formulations. So we can conclude that only formulation F1 containing 50% transcutol HP and 50% tween-80 produced SEDDS with lower droplet size.

Table 2 Accuracy and precision results of the HPLC validation method.

Validation parameters		Gliclazide
Accuracy	% Recovery	99.94 ± 0.67
	%RSD	0.67%
Precision	Repeatability	0.65%
(%RSD)	Ruggedness	0.69%

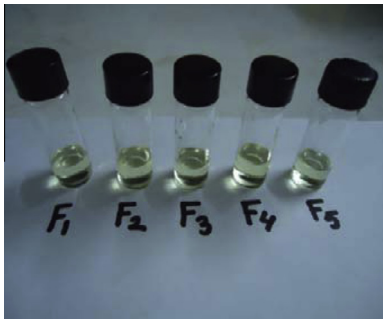

Figure 1 Formulations after preparation.

3.5. Release of active gliclazide in different media

In-vitro dissolution study of gliclazide was carried out in a USP Type II (paddle type) dissolution apparatus (Electrolab, India) using 10 mg gliclazide. Distilled water, buffer solutions of pH 1.2, pH 4.5 and pH 6.8 were used as dissolution media that were maintained at 37 ± 0.5 °C and stirred at 100 rpm. From the release study, it was found that the release rate of pure gliclazide was higher in buffer of pH 6.8 (75.141% within 40 min), due to the higher solubility of gliclazide in pH 6.8 (Bala et al., 2012). In other pH media (1.2 and 4.5), drug release was relatively lower (Fig. 2). This may be due to the pH dependent solubility of gliclazide. In distilled water gliclazide is slightly soluble and accordingly the release rate of gliclazide in distilled water was found to be lower (33.407% within 40 min).

3.6. In-vitro release profile of gliclazide from SEDDS formulations and marketed products

F1 formulation containing 1:1 (*m*/*m*) mixture of Transcutol HP/Tween-80 showed higher *in-vitro* drug release than other formulations (Fig. 3). Within 20 min 99% drug was released. This may be due to the small droplet size produced in the emulsion. Drug release from F2 formulation was lower than formulation F1. Within 30 min only 61% drug was released. This is due to the higher droplet size. So the drug release rate was found to depend on the droplet size of emulsion. Droplet

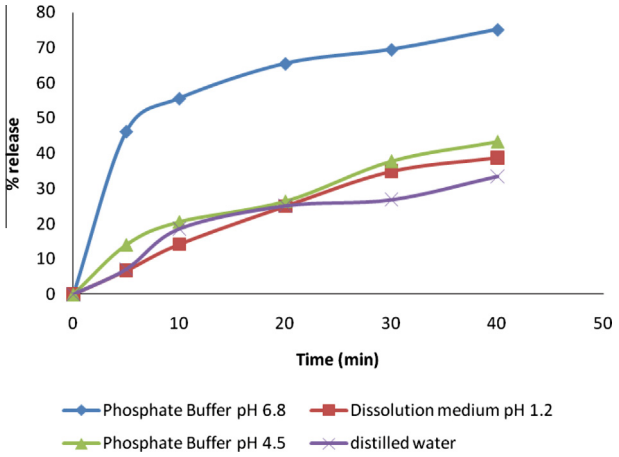

Figure 2 Dissolution profile of gliclazide in different media (n = 6).

size depended dissolution has also been reported earlier (Atef and Albert, 2008). Drug release from formulation F3 was lower than formulation F1 but higher than F2. Within 30 min 84% drug was released. Drug release from formulation F4 was lower than formulation F1 and F3 but higher than F2. Within 30 min 78% drug was released. Drug release from F5 formulation was lower than formulation F1 but higher than F2, F3 and F4. Within 30 min 97% drug was released.

Dissolution profiles of gliclazide immediate release tablets of two Brands (A and B) were also studied for comparison with SEDDS formulation. These two brands (A and B) released at 61% and 76% respectively within 30 min. This type of inter brand dissolution variation is common for water insoluble drugs (Oishi et al., 2011). Brand B may contain an alkalizing agent that may be responsible for better dissolution rate (Srivastav et al., 2011). On the other hand F1 formulation released 99% drug within 20 min and the pure gliclazide released 65.49% within 30 min. So from this study it was found that the drug release from SEDDS formulation of gliclazide was higher than that of market products and pure drug.

3.7. Permeability of gliclazide from SEDDS through chicken intestinal sac

In addition to conventional dissolution testing of SEDDS, *ex-vivo* permeability of gliclazide from SEDDS through chicken intestinal sac was studied. Drug diffusion studies using pretreated cellulose dialysis tubing have been well documented in the literature (Patil et al., 2007). Tukker (2000) described deferent methods for drug diffusion study by using the intestines of several animal species. Uses of chicken intestinal sac for permeability study are also reported earlier (Kale et al., 2007; Dias et al., 2010). In this study we used the chicken intestinal sac due to its higher thickness which makes it suitable for comparative permeability studies. Permeability profiles of different used samples did not show any significant differences during the initial 30 min. However, at the end of 5 h, formulation F1 showed about 97.6% diffusion against 99.26% from the drug solution in methanol. On the other hand pure gliclazide showed only 70% diffusion with in 5 h (Fig. 4).

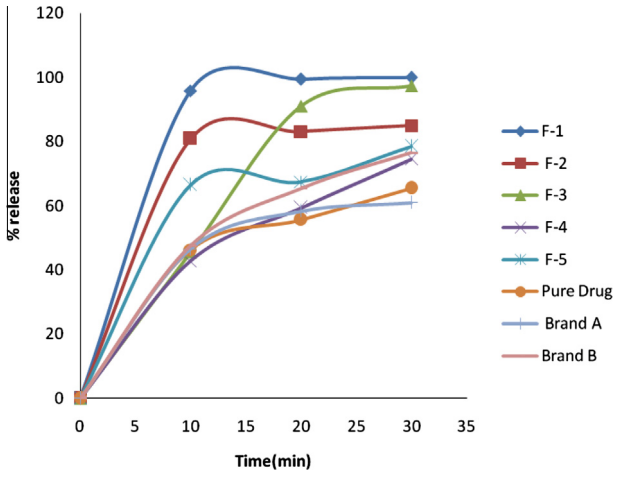

Figure 3 Dissolution profile of gliclazide from pure drug, SEDDS and marketed brands ($n = 6$).

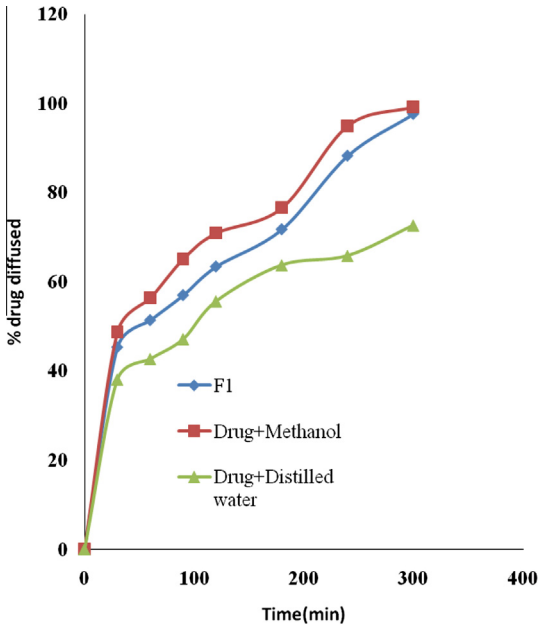

Figure 4 Permeability profile of gliclazide ($n = 3$).

3.8. Effect of pure gliclazide and SEDDS of gliclazide on the blood glucose level of mice

Pharmacodynamic marker parameters are often used to evaluate the *in-vivo* performance of different classes of drugs. Gliclazide is an anti-diabetic drug and it decreases the plasma glucose level. Hence plasma glucose level was used as a basis for the comparison of *in-vivo* performance of SEDDS of gliclazide. Oral glucose loading animal model reported by Etuk (2010) was used in this study. Plasma glucose level was found to increase sharply in the case of glucose administration. But Simultaneous administration of glucose and pure gliclazide decreased plasma glucose level slowly after the initial increase of the glucose level. Then the glucose level again increased. But when we administered the SEDDS (F1) along with glucose, the plasma glucose level decreased rapidly.

Statistical analysis of the plasma glucose level was performed to ascertain the effect of SEDDS formulation over pure drug using one-way analysis of variance (ANOVA, significance level $p < 0.05$) while the results were confirmed by Bonferroni's multiple comparison as a post hoc test. The analyses were undertaken for plasma glucose level at three time points (1–3 h). The results of ANOVA indicate that plasma glucose level due to administration of SEDDS and pure gliclazide was significantly different at the three time points at 0.05 level. From these observations, it can be concluded that SEDDS of gliclazide are more effective than pure gliclazide to lower plasma glucose level. This is due to the higher absorption of the drug from SEDDS formulation.

4. Conclusion

SEDDS formulations consist of oils, surfactants and cosurfactants, which are emulsified by aqueous medium under gentle digestive motility in the gastrointestinal tract. It is considered that the excipients in SEDDS could increase the dissolution and permeability of the drug significantly by decreasing the

droplet size. Gliclazide is a poorly aqueous soluble drug. The low bioavailability of gliclazide is due to its poor solubility. In this paper, we prepared gliclazide SEDDS formulations and assessed the dissolution *in-vitro*; permeability through chicken intestinal sac and *in-vivo* performance in mice. The concentration of gliclazide in various excipients was analyzed first. Then SEDDS was prepared and the droplet size of the emulsion was determined by Laser Diffraction Technology of Malvern. Optimal formulations containing 1:1 (*m*/*m*) mixture of Transcutol HP/Tween-80 showed a minimum droplet size, higher *in-vitro* drug release, optimal drug diffusion, and better control of plasma glucose level in mice. Our study indicates that the potential use of SEDDS for the oral delivery of gliclazide can be an alternative to improve its systemic availability.

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