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Formulation and Evaluation of Gliclazide in Vegetable Oil-Based Self Emulsifying Delivery System

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ABSTRACT

Objectives*:* To formulate a poorly water-soluble, antidiabetic drug, gliclazide, in the vegetable oil-based self-emulsifying delivery system (SEDDS), as a trial to improve its dissolution and hence its bioavailability. **Material and methods***:* Solubility of gliclazide was investigated in different vegetable oils, surfactants and co-surfactants. The system was selected and the self-emulsification region was identified. Drug-loaded SEDDS was prepared and evaluated in terms of emulsification time, phase separation, droplet size and rate of drug dissolution. The formulation that showed good self-emulsifying properties, acceptable droplet size and high % drug release was further processed into solid- SEDDS by physical mixing with varying proportions of a mixture (2:1) of microcrystalline cellulose and lactose and characterized for crystalline, droplet size and in vitro drug dissolution properties. **Results and Conclusions***:* Formulation of gliclazide in liquid and solid SEDDS using olive oil resulted in significant (P < 0.05) improvement in its dissolution properties. Both differential scanning calorimetry and x-ray diffraction studies demonstrated the presence of gliclazide in the molecular state in all the prepared solid formulations. Solid SEDDS of gliclazide containing a lower proportion of adsorbent (G1) had comparable dissolution properties with its liquid form. Thus formulation of gliclazide in the solid self-emulsifying system may be a promising strategy to improve its dissolution properties.

INTRODUCTION

Type 2 diabetes mellitus is a serious health problem in Egypt associated with high mortality rates due to macrovascular and microvascular complications (Hegazi *et al*., 2015).

Gliclazide, a second-generation hypoglycemic sulfonylurea, is the drug of choice in prolonged therapy for the control of Type 2 diabetes mellitus (Harrower, 1994). It stimulates insulin secretion from pancreatic beta cells (Jung *et al*., 1999) and increases the sensitivity of the peripheral tissue to insulin (Shavi *et al*., 2010). Gliclazide shows low aqueous solubility and consequently slow and variable gastrointestinal absorption with low bioavailability after oral administration (Palmer and Brogden, 1993). The solubility and dissolution rate of gliclazide had been improved by different methods including inclusion complexes with beta-cyclodextrin (Sapkal *et al*., 2007), solid dispersion with different carriers (Biswal *et al*., 2008; 2009) and surface solid

dispersion (Mahajan *et al*., 2012). Continuing that research, the self-emulsifying delivery system was suggested to improve the solubility and dissolution rate of gliclazide.

Currently, lipid-based formulations have gained much interest as carriers for the oral delivery of poorly water-soluble drugs (Pouton, 2006). Self-emulsifying drug delivery system (SEDDS) is an example which is defined as a mixture of oil, surfactant, and co-surfactant that forms oil-in-water emulsion upon gentle agitation condition provided by gastrointestinal motion (Pouton, 2000). SEDDSs are capable of improving the oral bioavailability of many poorly water-soluble drugs (Tuleu *et al*., 2004). The large interfacial area generated by these small droplets promotes drug diffusion into intestinal fluids. In addition, the digestion of lipid-based formulations by bile salts, phospholipids, and cholesterol, induces a change in lipid composition and results in the formation of different colloidal phases including micelles, vesicles, and liquid crystalline phases in the intestinal lumen (Fatouros *et al*., 2007) and consequently improves the absorption of administered drugs (Iosio *et al*., 2008). It was reported that the presence of the drug in an oil droplet protects the drug from

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enzymatic or chemical degradation and activates lipoproteins promoting the lymphatic transport of lipophilic drugs (Craig, 1993). Moreover, emulsion droplets lead to a faster distribution of the drug in the gastrointestinal tract and hence minimizing the irritation due to the contact between the drug and the gut wall (Franceschinis *et al.*, 2011). However, liquid SEDDS has many disadvantages that include: low drug loading capacity, drug leakage, low stability, incompatibility problems with the capsule shell and possibility of irreversible drugs/excipients precipitation (Kallakunta *et al.*, 2012). Alternatively, solid- SEDDS has been already produced by loading liquid SEDDS on solid carriers using different technologies: extrusion/spheronisation (Iosio *et al.*, 2008), wet granulation in high shear mixer (Franceschinis *et al.*, 2005), spray drying (Yi *et al.*, 2008) and physical mixing (Dixit and Nagarsenker, 2008). Solid SEDDS offer many advantages which include: stability, facility of manufacturing, can easily be packed in hard gelatin capsules and disperse freely in the gastrointestinal tract. In general, solid SEDDS combine the advantages of lipid-based drug delivery systems with those of solid dosage forms (Kallakunta *et al.*, 2012).

Oils play a crucial role in the formulation of self-emulsifying formulations. Both long and medium chain triglyceride oils with different degrees of saturation are commonly used in the preparation of SEDDS (Khedekar and Mittal, 2013). Dietary vegetable oils with antioxidant activity such as olive oil and linseed oil are reported to be effective in cardiovascular diseases and associated metabolic disorders, including hyperglycemia and dyslipidemia (Berraaouan *et al.*, 2013; Samarji and Balbaa, 2014; Kaithwas and Majumdar, 2012).

Previous literature reported the formulation of liquid and solid self-emulsifying system of gliclazide using Capryol 90 as the oil phase (Wankhade *et al.*, 2012; Nipun and Ashraful Islam, 2014). The aim of this study is to incorporate gliclazide in vegetable oil-based solid-SEDDS in an attempt to improve its solubility and dissolution rate and hence its bioavailability. Liquid SEDDS was prepared using vegetable oil, Tween 80 as surfactant and propylene glycol as co-surfactant. Then the optimized formula was adsorbed on a mixture of microcrystalline cellulose and lactose by physical mixing and studied for its efficiency in improving drug dissolution properties.

MATERIAL AND METHODS

Gliclazide was obtained as a gift sample from Delta Pharma, Egypt. Tween 80, Tween 20 and Propylene glycol (PG) were purchased from Merck Specialities Pvt. Ltd., Mumbai. Polyethylene glycol 400 (PEG 400), Methanol, Soybean oil, Olive oil, Palm oil, Sunflower oil and Sesame oil were purchased from SD Fine Chemicals, Mumbai. Avicel PH 101 (Microcrystalline cellulose (MCC)) and Lactose were purchased from FMC

BioPolymer, USA.

Saturation solubility study

Vegetable oils are one class of lipid solvents that are safe as they are fully digested and absorbed after oral administration (Mohanvarma and Padavala, 2013). So, the solubility of gliclazide was determined in various vegetable oils, as well as, surfactants and co-surfactants. An excess amount of gliclazide (50 mg) was added to 5 ml of the selected vehicles in capped vials and the mixtures were sonicated (Ultrasonic model SS101H, Sonix IV, Huntington Beach, CA, USA) at 40-50°C to facilitate drug solubilization. Then the mixtures were transferred to a thermostatic shaker water bath (LSB-030S, Daihan Lab Tech Co., LTD, Indonesia) maintained at 25°C for 48 hr. After reaching equilibrium, vials were centrifuged (Nuve, NF 815, Ankara, Turkey) at 4000 rpm for 10 min and followed by filtration through a membrane filter (No 0.45 μm). The clear filtrate was diluted with methanol and measured spectrophotometrically at 226 nm (Apel Co., Ltd., Japan) (Palmer and Brogden, 1993). Triplicate measurements were taken and Mean ± SD was recorded.

Construction of ternary phase diagram & formulation optimization

Based on the results of solubility studies, oil, surfactant, and cosurfactant showing highest solubility of gliclazide were selected for construction of the phase diagram. Different blends were prepared using varying concentrations of oil (20, 30, 40 and 50%, w/w). Surfactant and cosurfactant (Smix) at each oil percentage were mixed by vortexing (JL6001-G/L, Mettler Toledo Co., Switzerland) in different weight ratios (1:1, 2:1, 3:1 and 4:1 w/w) (Table 1). About 0.2 ml of each blend was introduced into 100 ml of distilled water and the contents were mixed gently with a magnetic stirrer (magnetic stirrer, Thermolyne, Dubuque, IA, USA) at 100 rpm for 2 min at room temperature. The diluted products were inspected for clarity, phase separation and coalescence of droplets. Emulsions showing phase separation, cracking and coalescence of oil droplets were judged as unstable emulsions (Aboutaleb *et al.*, 2016). Phase diagram was constructed to identify the self-emulsifying region using CHEMIX software.

Preparation of gliclazide SEDDS

SEDDS formulations with gliclazide were prepared by adding the weighed amount of drug (Each 1 g formulation contained 40 mg of gliclazide) to surfactant followed by addition of co-surfactant and oil in a glass vials (Table 2). The resultant mixtures were stirred continuously by vortex mixing and heated at 40°C to obtain a homogeneous isotropic mixture. The SEDDS formulations were stored at ambient temperature until further use (Kallakunta *et al.*, 2012).

Table 1: Composition of different oil, surfactant and cosurfactant blends.

Ingredients (mg)	A1	A2	A3	A4	B1	B2	B3	B4	C1	C2	C3	C4	D1	D2	D3	D4
Olive oil	200	200	200	200	300	300	300	300	400	400	400	400	500	500	500	500
Tween80	400	533.3	600	640	350	466.7	525	560	300	400	450	480	250	233.3	375	400
PG	400	266.7	200	160	350	233.3	175	140	300	200	150	120	250	166.7	125	100

Table 2: Different formulations of gliclazide SEDDS.

Ingredients (mg)	A3	A4	B3	B4	C3	C4
Gliclazide	40	40	40	40	40	40
Olive oil	200	200	300	300	400	400
Tween80	600	640	525	560	450	480
PG	200	160	175	140	150	120

Characterization of SEDDS

Assessment of emulsification time

The emulsification time for different formulations was determined using Dissolution Tester apparatus II, rotating paddle (SP6-400, G.B. CALEVA Ltd., Dorset, England). One gram of each formulation was added to 500 ml of distilled water with gentle agitation at 70 rpm and at a temperature of 37°C. The time to form homogenous nanoemulsion was determined (Abdalla *et al.*, 2008).

Stability studies

(a) Phase separation & drug precipitation study

Since SEDDS are subjected to dilution in GIT after oral administration, so the ability of the prepared SEDDS to be diluted easily without any drug precipitation was determined. Different gliclazide SEDDS formulations were exposed to 100 and 500 folds dilution with distilled water. Examined formulations were stored at 25°C for 24 h and observed visually for phase separation and drug precipitation (Yin *et al.*, 2009).

(b) Refrigeration thaw cycle

A single refrigeration thaw cycle was performed by taking 2 ml sample of each formulation which subjected to refrigeration at 2°C for 24 h then thawing at 40°C. The samples were then observed for phase separation and drug precipitation.

(c) Centrifugation

A 5 ml sample of each formulation was centrifuged (REMI,11, Cama Industrial Estate, Walbhat Road, Goregaon East, Mumbai – 400063, India) at 4,000 rpm for 5 min. Thereafter, the samples were observed for phase separation and drug precipitation.

Determination of droplet size

The mean size of emulsion globules was determined by Zetasizer (Malvern Instruments, Malvern, UK) based on dynamic laser scattering. The dispersed formulations were measured after dilution (1:1000 v/v) with distilled water and mix for 1 minute with Cyclo mixer

In-vitro drug dissolution from liquid SEDDS

The in vitro dissolution test was performed in 900 ml distilled water maintained at 37 ± 0.5°C using USP Dissolution Tester apparatus II rotating at 70 rpm (SP6-400, G.B. CALEVA Ltd., Dorset, England). The SEDDS formulations (containing an amount equivalent to 40 mg gliclazide) were filled into hard gelatin capsules (size 00) and used for drug release studies compared with the plain drug. Samples (5 ml) were withdrawn and replaced with

fresh media after 5, 10, 15, 20, 30, 40, 50 and 60 min. Samples were filtered using a 0.45 μm filter and analyzed spectrophotometrically for gliclazide at 226 nm. Triple measurements were conducted for each formulation, and data presented as means ± SD. Percentage of cumulative drug dissolution at different time intervals was calculated and a graph plotted versus time. The dissolution data were analyzed in terms of initial dissolution rate over the first 10 min of dissolution (IDR = % dissolved/min) (Kallakunta *et al.*, 2013) and dissolution efficiency after 60 min (DE_{60}) which was calculated from the area under the dissolution curve at time 't' (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975).

Formulation of solid SEDDS

The liquid SEDDS that exhibited acceptable emulsification efficiency and high dissolution parameters was selected for preparation of solid SEDDS, in three different ratios (liquid SEDDS:carrier mixture ratio was 1:1, 1:2 and 1:3 w/w). The formulations G1-G3 were prepared with a carrier mixture of MCC: lactose, 2:1 w/w. The liquid SEDDS was triturated with a mixture of MCC and lactose using a mortar and a pestle. The wet mass was passed through sieve No.120 and was dried at ambient temperature (Bhagwat and D'Souza, 2012).

Characterization of solid SEDDS

Differential scanning calorimetry (DSC)

The DSC thermograms of gliclazide, MCC, lactose and different solid SEDDS formulations were recorded using differential scanning calorimeter (Perkin Elmer, USA). The samples were heated in an open aluminum pan from 35 to 200°C at a scanning rate of 10°C/min under the stream of nitrogen.

X-ray diffraction studies (XRD)

X-ray diffraction measurements of gliclazide, MCC, lactose and different solid SEDDS formulations were carried out with X-ray diffractometer (X'Pert PRO PA Nalytical, USA). XRD patterns were recorded at room temperature using monochromatic CuKa-radiation over a range of 2θ angles from 3° to 50° with an angular increment of 0.02° per second.

Determination of droplet size

Droplet size of the dispersed solid SEDDS was determined using the same procedure as mentioned before for liquid SEDDS.

In-vitro drug dissolution

An amount of powder equivalent to 40 mg gliclazide was filled into hard gelatin capsules (size 00) and the dissolution of gliclazide from different solid SEDDS formulations were done under the same conditions as mentioned before for liquid SEDDS.

RESULTS AND DISCUSSION

Saturation solubility study

Identifying the suitable oil, surfactant and co-surfactant having the maximal solubilizing potential for gliclazide is the

key factor for optimum drug loading and stability during storage (Miryala and Kurakula, 2013). The solubility of gliclazide in the screened vegetable oils, surfactants and co-surfactants is presented in Figure 1. Gliclazide exhibited high solubility in olive oil (1.09 mg/ml), tween 80 (2.01 mg/ml) and PG (1.94 mg/ml). Accordingly, olive oil, Tween 80 (surfactant) and PG (co-surfactant) were further used for the construction of ternary phase diagram.
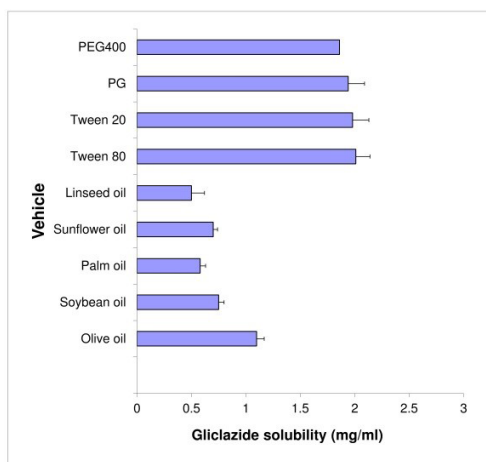

Fig. 1: Solubility of gliclazide in different vegetable oils, surfactants and co-surfactants (Mean ± SD).

Superior gliclazide solubility in olive oil than the other investigated oils may be ascribed to its higher ester value (190.86). It was reported that the solvent capacity of oils for drugs is mainly dependent on the concentration of ester groups (Zambiazi et al., 2007). It is known that the ester value is a measure of the percentage of glycerol present in oil (Azeem et al., 2009).

Tween 80, a hydrophilic nonionic surfactant of HLB = 15 and has a high solubilizing capacity (Kallakunta et al., 2012). It was reported that nonionic surfactants with high HLB values (12–15) facilitate the immediate formation of oil-in-water emulsions and rapid spreading of the formulation in aqueous media (Azeem et al., 2009). In addition, nonionic surfactants are most commonly used in oral formulations because of their lower irritation potential and toxicity, a wide range of compatibility, good physicochemical stability and being less affected by pH (Gershanik and Benita, 2000; Basalious et al., 2010). No remarkable difference of gliclazide solubility in either Tween 80 or Tween 20. However, Tween 80 was expected to produce better emulsification than Tween 20. Generally, surfactants are defined as molecules with polar heads and hydrophobic tails. Tween 20 is 20-mole ethoxylate of sorbitan monolaurate (12 C) while Tween 80 is 20-mole ethoxylate of sorbitan mono oleate (18 C). Thus, Tween 80 has a longer hydrophobic tail and expected to have bigger packing parameter and hence larger curvature of oil/water interfacial film with better emulsification (Mosca et al., 2013; Zeing et al., 2017).

For efficient emulsification, a single surfactant may not be able to produce the required reduction in O/W interfacial tension and fluid interfacial film, so the addition of co-surfactant is crucial. PG acts as a co-surfactant that is required to increase the flexibility of the interfacial film between oil and water and enable the dissolution of a large quantity of the drugs in the oil phase (Nepal et al., 2010). The flexibility of the surfactant film is

necessary to facilitate the existence of different structures including droplet-like shapes, aggregates and bicontinuous structures which enhance drug dissolution (Amemiya et al., 1999). In addition, PG increases the penetration of the oil phase into the surfactant hydrophobic tail thereby further decreases the interfacial tension (Zeing et al., 2017). Propylene glycol exhibited slightly higher solubilization capacity of gliclazide than polyethylene glycol that may be ascribed to a difference in surface tension of both alcohols i.e. 45.6 dyne/cm for PG compared to 48.4 dyne/cm for PEG (ACCU Dyne TestTM, www.accudynetest.com/visc_table.html; Talegaonkar et al., 2008).

Construction of ternary phase diagram & formulation optimization

Construction of ternary phase diagrams gives an idea about the nature of the diluted dispersions and consequently, assists in selecting optimum proportions of oil, surfactant, and co-surfactant. The ternary phase diagram of olive oil - Tween80 - PG in different ratios was constructed (Figure 2) and the results of visual observations of the diluted blends are represented in Table 3. It is clear that blends containing 20-40% w/w of oil produced clear and stable emulsions with increasing Smix ratios (formulations A3, A4, B3, B4, C3, C4) whereas the resultant emulsions of blends with lower Smix ratios (formulations A1, A2, B1, B2, C1, C2) resulted in translucent emulsions followed by phase separation.
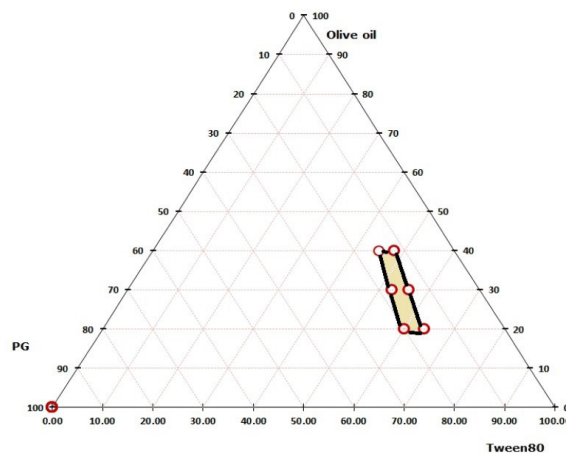

Fig. 2: Ternary phase diagram of SEDDS consisting of olive oil, Tween80 and PG.

Moreover, formulations containing higher oil content (50% w/w) produced milky emulsions with oil droplets on the surface when diluted with water.

According to the ternary phase diagram, formulations contained olive oil (20–40% w/w), Tween 80: PG ratio (3:1 & 4:1, w/w) were selected for the formulation of gliclazide loaded SEDDS.

The results revealed that high Smix ratios (3:1 & 4:1 w/w) with an oil concentration of no more than 40% w/w was important for the emulsification efficiency which was in agreement with the results reported by Czajkowska-Kośnik et al., 2015. This result may be explained on the basis of the presence of sufficient amounts of surfactant and co-surfactant to be adsorbed at oil/water interface thus reducing the free energy for emulsion formation and

also prevent coalescence of dispersed droplets resulting in stable nanoemulsions (Levy and Benita, 1990). Agubta et al., 2014, reported that efficient oil and water emulsification require the presence of a high concentration of surfactant to provide very low interfacial tension ($\leq 10^3$ mN/m). Gurram et al., 2015, reported that large molecular volume oils including long-chain triglycerides such as olive oil require higher surfactant concentration than short chain mono/diglycerides.

Table 3: Formulation optimization.

Formulations	Clarity	Stability
A1	translucent	Phase separation
A2	translucent	Phase separation
A3	clear	stable
A4	clear	stable
B1	translucent	Phase separation
B2	translucent	Phase separation
B3	clear	stable
B4	clear	stable
C1	translucent	Phase separation
C2	translucent	Phase separation
C3	clear	stable
C4	clear	stable
D1	milky	Phase separation
D2	milky	Phase separation
D3	milky	Phase separation
D4	milky	Phase separation

Presence of co-surfactant is essential for the emulsification process. The flexibility of the interfacial film which is imparted by the presence of co-surfactant allows the exchange of co-surfactant from the interfacial film to continuous phase and dispersed phase and exchange of surfactant between the interfacial film and water and hence good emulsion formation (Bagwe et al., 2001). However, only small amounts of co-surfactant (Smix of 3:1 & 4:1) is required for the stability of the formed emulsion as large amounts lead to an expansion of the interfacial film with a subsequent increase in droplet size (Saifee et al., 2013). In addition, higher amounts of co-surfactant results in precipitation of drug upon dilution due to the partitioning of co-surfactant into the aqueous phase (Lawrence and Rees, 2009).

Characterization of SEDDS

Assessment of self-emulsification

The results of self-emulsification are given in Table 4. Emulsification time varied from 31s to 81s. The emulsification time was directly proportional to the amount of oil phase and inversely proportional to Smix ratio. This result may be due to the presence of higher concentration of tween80 that has high ability to reduce the interfacial tension between O/W interface which in turn shows a positive impact on spontaneous emulsification process (Bhikshapathi et al., 2013). Agubata and coworkers, 2014, reported that ease of emulsification is dependent on the ease with which water penetrates the oil-water interface with the formation of liquid crystalline phase resulting in rapid emulsification.

Furthermore, increasing oil concentration results in increased viscosity of the formulation and hence prolonged emulsification time. Similar results were reported by Harshal et al., 2011.

Table 4: Emulsification time, droplet size and dissolution parameters of gliclazide loaded in olive oil based SEDDS compared with the plain drug (mean ± SD, n = 3).

Formulation	Emulsification time (Sec)	Droplet size (nm)	IDR (% per min)	DE (%)
Plain drug	NA	NA	1.5 ± 0.05	27.9 ± 0.78
A3	40 ± 1.7	230 ± 5.6	5.1 ± 0.59	59.9 ± 1.64
A4	31 ± 1.2	215 ± 2.3	5.8 ± 0.57	66.8 ± 5.1
B3	53 ± 2.3	263 ± 3.5	7 ± 0.57	76.4 ± 5.5
B4	45 ± 1.5	245 ± 2.8	8.0 ± 0.75	86.3 ± 3.5
C3	81 ± 3.1	411 ± 5.2	5.1 ± 0.39	68 ± 2.82
C4	77 ± 3.5	360 ± 3.4	5.4 ± 0.55	66.1 ± 1.24

IDR: initial dissolution rate after 10 min.
DE%: dissolution efficiency % after 60 min.

Stability studies

All SEDDS samples which were subjected to appropriate dilutions and storage for 24 h, single refrigeration/thawing cycle or centrifugation were found to be stable with no evidence of phase separation or drug precipitation suggesting that diluted gliclazide SEDDS can remain stable in gastrointestinal fluids.

Determination of droplet size

Since the rate and extent of drug release, as well as its gastrointestinal absorption, mainly depend upon emulsion droplet size, the droplet size of the prepared formulations was determined and the results are represented in Table 4. The formulations had droplets size in the range of 215–411 nm.

It was clear that droplet size decreased with the increase in Smix which was consistent with previous studies. (Ostertag et al., 2012; Mehrnia et al., 2016) At high Smix, there will be a great reduction in interfacial tension with surfactant diffusion into the aqueous phase facilitating the formation of fine droplets. On the other hand, at low Smix, the surfactant concentration at the oil-water interface will not be enough to completely cover the surface of drops; coalescence of droplets occurs and hence increased droplets size (Zeing et al., 2017).

The droplet size was negatively affected by the oil concentration. This result may be explained on the basis of collision theory. As the concentration of oil increased, a larger number of emulsion droplets will be formed and consequently will collide with each other resulting in the formation of larger droplets (Shahavia et al., 2015).

Contour plot

The two-dimensional contour plots were drawn to understand the variation of emulsification time and droplet size with oil concentration and Smix (Figure 3A & B). At low oil concentration and high Smix, rapid emulsification (<40 sec) and small droplet size (<250 nm) were obtained.

In-vitro drug dissolution from liquid SEDDS

Figure 4 and Table 4 demonstrate the dissolution profiles

and dissolution parameters of gliclazide from different SEDDS formulations, respectively. Table 5 summarizes the results of the ANOVA analysis. The dissolution parameters (IDR & DE%) of gliclazide from all SEDDS formulations were significantly ($P = 0.000$) higher than the plain drug. The maximal drug dissolution was obtained from the formulation B4 (containing oil of 30% w/w and surfactant/co-surfactant ratio of 4:1, w/w). The formulation B4 exhibited IDR of 8.0 ± 0.75 compared to only 1.5 ± 0.05 obtained by the plain drug, comprising a 5.3-folds increase in the initial dissolution rate within 10 min. Moreover, the dissolution

efficiency exhibited by the formulation B4 after 60 min was $86.3 \pm 3.5\%$ compared to only $27.9 \pm 0.78\%$ exhibited by the plain drug comprising a 3.1-folds increase in drug dissolution efficiency. This result may be ascribed to the presence of the drug in free molecular state or in emulsion form or in solubilized micellar solution when the formulation is subjected to aqueous medium compared to the crystalline form of the plain drug (Kallakunta *et al.*, 2012). Moreover, the optimum dissolution properties (IDR & DE%) achieved by the formulation B4 may be due to the proper balance between oil percentage and a surfactant system.

Table 5: Analysis of variance for the different SEDDS formulations compared with the plain drug.

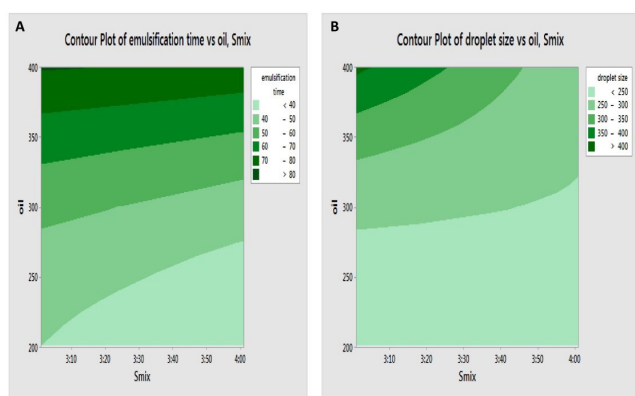| Value	Effect of the formulation of SEDDS (Plain drug against different SEDDS)		Effect of oil % at Smix 3:1 (A3, B3, C3)		Effect of oil % at Smix 4:1 (A4, B4, C4)		Effect of Smix at 20% oil (A3, A4)		Effect of Smix at 30% oil (B3, B4)		Effect of Smix at 40% oil (C3, C4)	
	IDR	DE%	IDR	DE%	IDR	DE%	IDR	DE%	IDR	DE%	IDR	DE%
P-value	0.000	0.000	0.007	0.004	0.005	0.000	0.227	0.089	0.14	0.039	0.453	0.346
R^2	94.79%	97.6%	80.55%	83.64%	83.2%	92.54%	33.71%	55.55%	45.82%	69.63%	14.72%	22.19%
R^2 adjusted	92.56%	96.58%	74.07%	78.19%	67.6%	90.05%	17.13%	44.44%	32.27%	62.04%	0.00%	2.74%
S-value	0.54	3.26	0.536	3.66	0.627	3.36	0.59	3.78	0.67	4.26	0.46	2.14

Fig. 3: Contour plots for the effect of oil concentration and Smix on (A) emulsification time; (B) droplet size.
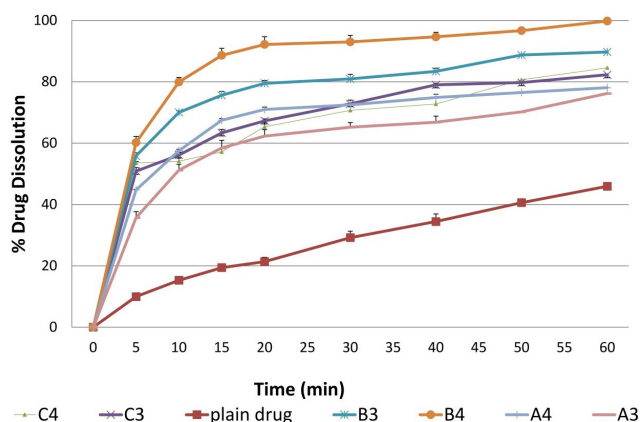

Fig. 4: In vitro dissolution profiles of gliclazide from liquid SEDDS formulations compared with the plain drug (mean ± SD, n = 3).

The results revealed that both IDR and DE% were negatively affected by oil concentration, droplet size and emulsification time (nonsignificant effect) and positively affected

by Smix (nonsignificant effect), Table 5 & Figure 5. These results were in agreement with Nigade *et al.*, 2012, who reported that surfactant concentration, oil/surfactant ratio, the polarity of the emulsion, droplet size and charge are critical parameters for oral drug absorption from SEEDS. Presence of excess surfactant in the formulation promotes the effective dispersion of the drug in the dissolution medium by the solubilization process, in addition to promoting drug spreading in fine oil droplets with larger surface area exposed to the dissolution medium (Suresh and Sharma, 2011). Moreover, the reduction in drug dissolution from formulations containing a higher percentage of oil (>30% w/w) may be due to the presence of insufficient proportion of surfactant and hence lesser reduction in interfacial tension between oil and aqueous phase followed by decreased drug partition into an aqueous medium (El-Laithy, 2008).

Values of correlation analysis are presented in Table 6 and Figure 6. Generally, the Pearson Correlation Coefficient (r) shows the nature and strength of correlation. The coefficient can vary between -1 and +1 while zero value describes no correlation. A positive sign of coefficient indicates a synergistic effect while a negative term indicates an antagonistic effect upon the response. It is clear that there was a nonsignificant correlation between dissolution parameters (IDR and DE%) and oil % and Smix. Alternatively, there was a strong positive significant correlation ($r > 0.9$, $P < 0.05$) between oil %, droplet size and emulsification time.

Formulation of solid SEDDS

Generally, liquid SEDDS suffers from many disadvantages such as leakage from capsules, handling and stability problems and difficulty in capsule filling. For our study, the selected SEDDS that showed good dissolution properties was (B4) which contained 30% w/w olive oil and hence it will be advantageous to convert the formulation into the solid form to increase the oxidative stability of olive oil and protect the formulation against rancidity.
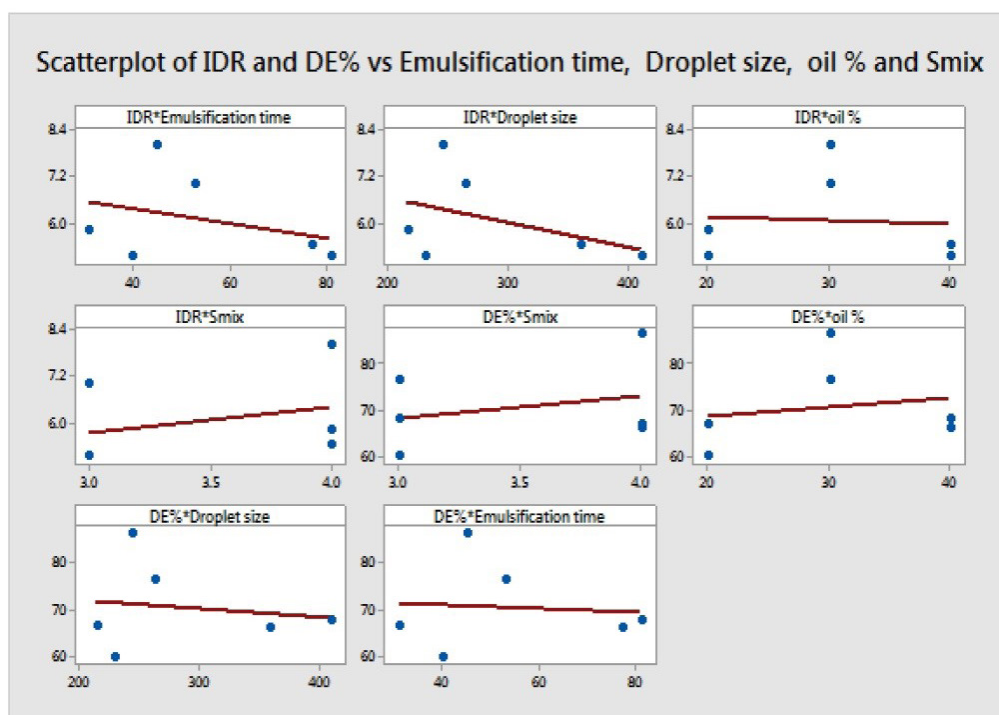
Fig. 5: Correlation between IDR and DE% versus oil percentage, emulsification time, droplet size and Smix.
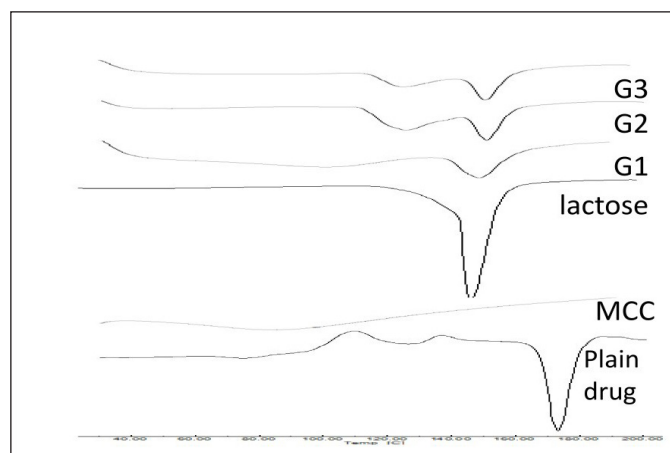

Fig. 6: Differential scanning calorimetric thermograms of plain gliclazide, MCC, lactose and different solid SEDDS.

The results showed that it was possible to convert the selected liquid SEDDS (B4) into solid forms with all liquid SEDDS:carrier mixture ratios used, while attempts to produce solid forms with higher proportions of liquid SEDDS (SEDDS:carrier mixture = 2:1) failed.

The selection of MCC was done on the basis of possessing high intraparticle porosity with good water swelling properties, as well as high adsorption capacity for lipid-based preparations (Parekh *et al*., 2017). Since MCC is a water-swellable polymer so it forms a network like structure in water which prevents nucleation, crystal growth and precipitation of drug upon dilution of SEDDS in GIT (Dokania and Joshi, 2015). In addition, MCC is a hydrogen bonding polymer which can form an intermolecular hydrogen bond with gliclazide resulting in retardation of drug

precipitation upon dilution in GIT (Chen *et al*., 2012).

Lactose is a water-soluble solid carrier with a small molecular weight which may provide good preservation of nanoemulsion droplet size after dilution (Li *et al*., 2013).

Table 6: Results of correlation analysis of IDR and DE% versus oil percentage, emulsification time, droplet size and Smix.

Factor		Emulsification time (min)	Droplet size (nm)	IDR (% per min)	Oil %
Droplet size (nm)	r	0.978			
	P	0.001			
IDR (% per min)	r	-0.334	-0.422		
	P	0.518	0.405		
Oil %	r	0.958	0.919	-0.076	
	P	0.003	0.01	0.887	
Smix	r	-0.189	-0.193	0.309	0.00
	P	0.72	0.714	0.552	1.00
DE%	r	-0.088	-0.153	0.953	0.177
	p	0.886	0.773	0.003	0.773

IDR: initial dissolution rate after 10 min.
DE%: dissolution efficiency % after 60 min.

Characterization of solid SEDDS

Differential scanning calorimetry (DSC)

The DSC thermograms of plain gliclazide, MCC, lactose and different solid SEDDS are illustrated in Figure 6. The thermogram of the plain drug showed a sharp melting endotherm at 173.3°C with $\Delta H = -150$ mJ indicated the presence of the drug in the crystalline state (Shavi *et al*., 2010). MCC showed

a broad peak at 85.24°C with ΔH = -22.96 mJ. Lactose showed a sharp endothermic peak at 153.4°C with ΔH = -327.11 mJ. No representative peaks for gliclazide were detected in all the prepared solid SEDDS with predominance of excipients peaks indicating the transformation of crystalline structure of gliclazide into molecularly dissolved state (Kallakunta *et al.*, 2012).
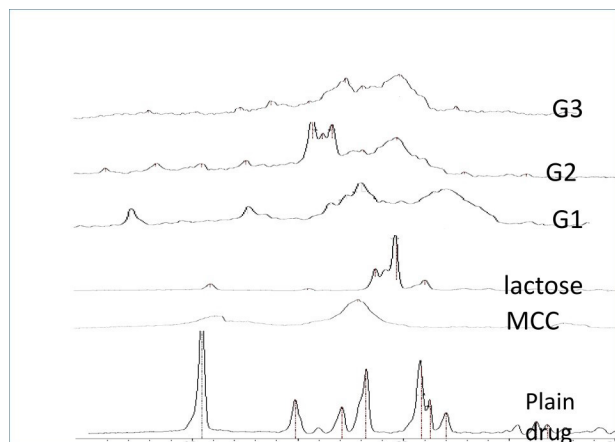

Fig. 7: X-ray powder diffraction spectra of plain gliclazide, MCC, lactose and different solid SEDDS.

X-ray diffraction studies (XRD)

The XRD patterns of plain gliclazide, MCC, lactose and different solid SEDDS are shown in Figure 7. The diffraction pattern of gliclazide showed high-intensity peaks at 2θ of 10.59, 14.98, 17.2, 17.85, 18.15, 22.07 and 25.42° confirmed the crystalline nature of pure gliclazide (Biswal *et al.*, 2009). Pure MCC showed three peaks at 2θ of 15, 16 and 23°. Lactose had distinct peaks at 2θ of 12.6, 19, 20 and 21°. The XRD patterns of all the prepared solid SEDDS showed the absence of drug peaks with a predominance of excipients peaks which may be due to the transformation of gliclazide into molecularly dissolved form in all the prepared solid SEDDS (Bhandari and Avachat, 2015).

Determination of droplet size

Droplet size of the different solid SEDDS (G1-G3) after dispersion compared with the corresponding liquid formulation (B4) was presented in Table 7 and Figure 8. The droplet size of the resultant nanoemulsions from different solid preparations was in the range of 265–560 nm. The PDI values of the solid SEDDS (G1) and liquid SEDDS (B4) were below 0.3 indicating good uniformity in the globule size distribution after dilution with water (Jaiswal *et al.*, 2014).
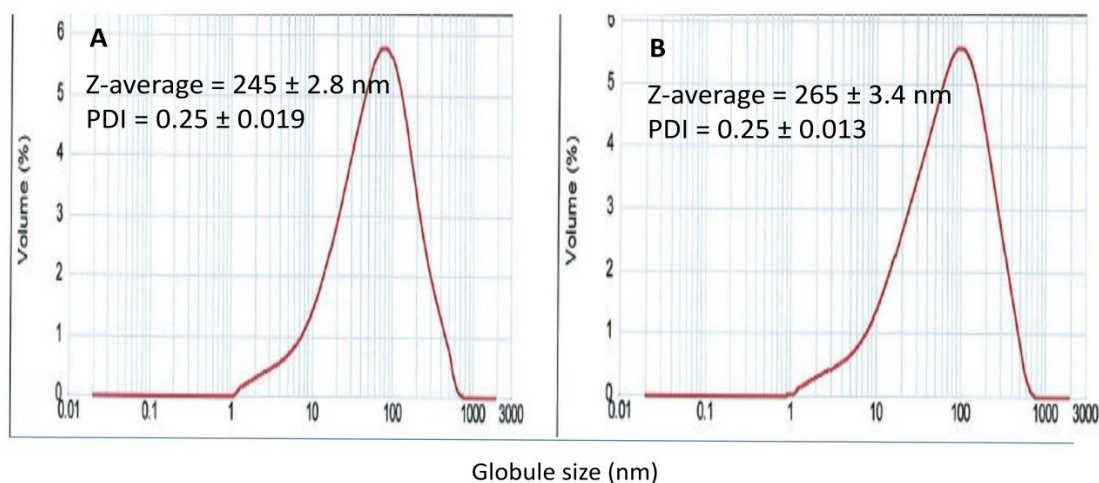

Fig. 8: Globule size distribution of (A) liquid SEDDS, B4, compared with (B) solid SEDDS, G1.

Comparing the droplet size of liquid SEDDS with those of the dispersed solid SEDDS, one can detect that they are significantly higher although still in the nano-size range which is required for absorption. In addition, the amount of adsorbent mixture had a positive significant effect on the droplet size. Jaiswal and coworkers reported that the presence of MCC as an adsorbent in the solid SEDDS leads to increase in globule size during dispersion of the formulations (Jaiswal *et al.*, 2014). MCC hydrates and swells in water forming fibrils on which hydrophilic surfactant molecules adhere to its surface. So, MCC interferes with the complete reconstitution of the emulsion from the solid SEDDS results in a reduction in surfactant concentration at O/W interfaces with a subsequent increase in droplet size (Nikolakakis *et al.*, 2015). This effect will increase with increasing proportions of MCC. It is worth noting that the presence of lactose did not oppose the negative effect of MCC on the droplet size.

Table 7: Droplet size and dissolution parameters of gliclazide loaded in solid olive oil based SEDDS compared with its liquid form and plain drug (mean ± SD, n = 3).

Formulation	Droplet size (nm)	IDR (% per min)	DE (%)
Plain drug	NA	1.5 ± 0.05	27.9 ± 0.78
B4	245 ± 2.8	8.0 ± 0.75	86.3 ± 3.5
G1	265 ± 3.4	7.8 ± 0.9	90.6 ± 0.00
G2	420 ± 2.3	5.8 ± 0.34	82.7 ± 0.5
G3	560 ± 5.1	5.1 ± 0.9	69.9 ± 1.2

IDR: initial dissolution rate after 10 min.
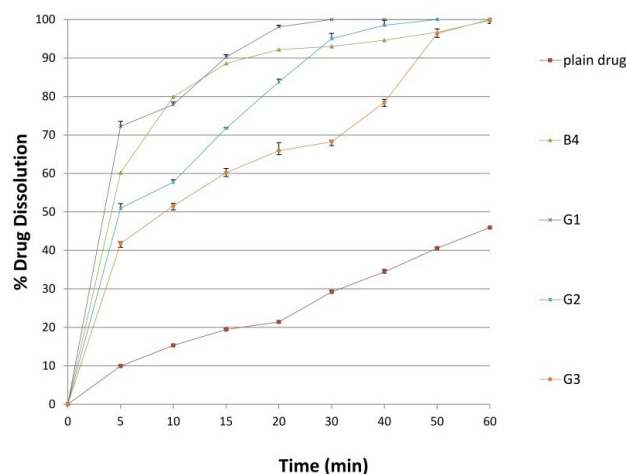
DE%: dissolution efficiency % after 60 min.

Fig. 9: In vitro dissolution profiles of gliclazide loaded in solid olive oil based SEDDS compared with its liquid form and plain drug (mean ± SD, n = 3).
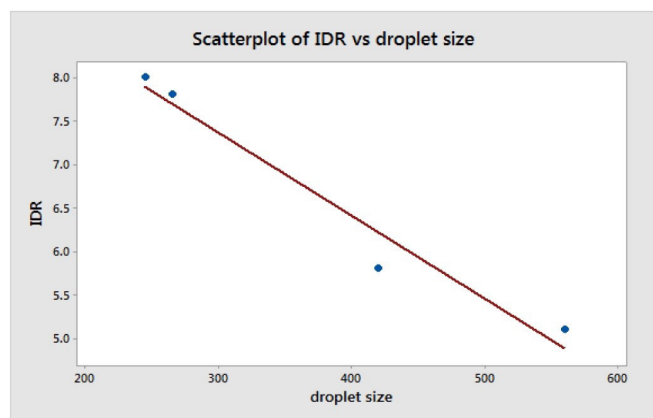

Fig. 10: Correlation analysis of IDR of gliclazide from liquid and solid SEDDS versus droplet size.

In-vitro drug dissolution

The calculated dissolution parameters (IDR & DE%) of the different solid SEDDS (G1-G3) compared with the corresponding liquid formulation (B4) and plain drug are presented in Table 7 and the release behavior is presented in Figure 9. It was clear that dissolution parameters of the different solid SEDDS were much superior (P = 0.00, R^2 = 94.67% and R^2 adjusted = 92.54%) when compared with the plain drug. About 4.2 and 2.9-folds increase in IDR and DE%, respectively of gliclazide from solid SEDDS formulations when compared with its plain form. Small droplet size of the formed nanoemulsion after the dispersion of the solid SEDDS results in a large surface area exposed for dissolution medium and hence rapid drug dissolution (Dixit and Nagarsenker, 2008; Cho *et al*., 2016).

Interestingly, for IDR and DE, there was no significant difference (P > 0.05) between liquid and solid SEDDS containing less adsorbent ratio (G1). However, gliclazide dissolution parameters from the other solid SEDDS were significantly (IDR: P = 0.003, R^2 = 80.25% and R^2 adjusted = 72.84%, DE%: P = 0.00, R^2 = 96.44% and R^2 adjusted = 95.1%) reduced than the liquid SEDDS. This result may be attributed to rapid emulsification and

small droplet size of the reconstituted dispersion. On the other hand, the reduced dissolution parameters of the preparations containing higher amounts of adsorbent (G2, G3) may be explained on the basis of increased droplet size of the solid-SEDDS after dispersion which is inversely proportional to the dissolution rate.

Correlation analysis revealed that there was a good correlation between the droplet size of the resultant nanoemulsions of the dispersed solid SEDDS and IDR values (Pearson correlation = -0.980, P = 0.020), Figure 10.

CONCLUSION

Olive oil based self-emulsifying delivery system containing 30% of oil and Tween 80: propylene glycol in 4:1 w/w can be successfully developed into solid form by mixing with a mixture of microcrystalline cellulose and lactose as an adsorbent in a weight ratio of 2:1 w/w. The solid self-emulsifying system of gliclazide (Formulation G1) showed improved dissolution properties which may be promising to overcome the problem of inter and intrasubject variability in bioavailability. In addition, the presence of olive oil in the formulation is expected to augment the antidiabetic effect of gliclazide which may confer an added value to the developed preparation. Future in vivo studies will be recommended.

CONFLICT OF INTEREST

The author discloses no possible conflicts of interest.

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