Future Journal of Pharmaceutical Sciences

RESEARCH Open Access

Enhancement of in vivo hypoglycemic effect of gliclazide by developing self-microemulsifying pellet dosage form

Hetal Patel[1*], Niharika Pandey[1], Bhoomi Patel[1], Ketan Ranch[1], Kunjan Bodiwala[2] and Bhavin Vyas[1]

Abstract

Background: The present research was aimed to develop a self-microemulsifying drug delivery system (SMEDDS) pellet to increase the dissolution rate and in vivo hypoglycemic effect of gliclazide. Gliclazide belongs to BCS class 2 and it exhibits dissolution rate-limited absorption. Thus, dissolution enhancement of gliclazide from its dosage form is a prime requirement to achieve a better therapeutic effect. The solubility of gliclazide was estimated in oils, surfactants, and co-surfactants. A most effective self-emulsification region was identified using pseudoternary phase diagrams. The optimized liquid SMEDDS gliclazide formulation was converted to SMEDDS pellets using the extrusion-spheronization technique. The in vitro release and hypoglycemic effect of SMEDDS was compared with the marketed product.

Results: The optimized liquid gliclazide SMEDDS formulations contained mixtures of Tween 80 and PEG 400 and Capmul MCM C8. The gliclazide SMEDDS in liquid preparation quickly formed a fine oil-in-water microemulsion having a globule size of 31.50 nm. In vitro release of gliclazide from SMEDDS pellets was 100.9% within 20 min. SMEDDS pellets exhibited a significant reduction in plasma glucose levels in albino mice compared to the marketed product.

Conclusion: The results indicated that SMEDDS pellets could be effectively used to improve the oral delivery of gliclazide.

Keywords: SMEDDS, Hypoglycemic, Tween, Pellets, Extrusion, Dissolution

Background

Many active pharmaceutical ingredients (APIs) developed by the pharmaceutical industry belong to the "practically insoluble" category mentioned in Pharmacopeia. Formulation development of such drugs is a challenging task due to solubility issues [1]. As per the Biopharmaceutical classification system, class II drugs exhibit low solubility and high permeability. BCS class II drugs show dissolution rate-limited absorption and bioavailability [2].

Gliclazide belongs to BCS class 2 [3]. Azabicyclo-octyl group present in gliclazide provides superior properties of the basic sulfonylurea moiety. It acts on the sulfonylurea receptor present on the beta cell of the pancreas and stimulates insulin release. It specifically improves the abnormal first phase insulin release in type 2 diabetes and also affects the second phase. Lower occurrence of hypoglycemic episodes and weight gain were reported with usage of gliclazide compared with other sulfonylureas [4]. However, gastrointestinal (GI) absorption at a low rate and inter-individual variations in bioavailability were observed with gliclazide. The reasons for slow absorption are either low dissolution rate of gliclazide from the dosage form or poor permeability of gliclazide across the GI membrane. Thus, improvement

* Correspondence: hetalppatel1986@gmail.com; hetal.patel@utu.ac.in
[1]Maliba Pharmacy College, Uka Tarsadia University, Gopal Vidyanagar, Maliba campus, Surat, Gujarat 394350, India
Full list of author information is available at the end of the article

in the solubility of gliclazide and enhancement in the dissolution rate of gliclazide from its dosage form are prime requirements for better bioavailability and therapeutic efficacy of gliclazide [5, 6].

Various researchers tried to improve solubility, dissolution rate, and bioavailability of gliclazide using different approaches. Biswal et al. enhanced the solubility and dissolution rate of gliclazide by preparing its solid dispersions (SDs) with polyethylene glycol (PEG) 6000 [7]. Hiremath et al. prepared gliclazide inclusion complex with β-cyclodextrin by kneading method, and almost 20-fold increment in dissolution rate was reported [8]. Shavi et al. improved the dissolution rate and bioavailability of gliclazide by preparing solid dispersion and showed two-fold increments in peak plasma concentration compared to the pure drug in Wistar rats [9]. Ravouru et al. developed nanocrystals of gliclazide and proved better bioavailability of nanocrystals compared to the pure drug [10]. Mahajan developed a liquisolid compact of gliclazide and proved that the liquisolid system showed improved bioavailability with higher Cmax and faster Tmax than the gliclazide suspension, a reference drug product. All these techniques may pose one or more drawbacks like poor scale-up, instability, incompatibility, and biodegradability issues [11].

Developing a self-microemulsifying drug delivery system (SMEDDS) of the BCS class II drug is an effective way to improve solubility, dissolution rate, and absorption rate of those drugs. The SMEDDS composed of an isotropic mixture of oil, surfactant, and co-surfactant. Better absorption and bioavailability of lipophilic drugs like curcumin, oridonin, and silymarin in SMEDDS form are reported in the literature [12, 13].

SMEDDS provides many advantages like enhancement of bioavailability of poorly aqueous soluble drugs by dissolving those drugs into the GI tract, reducing inter-subject and intra-subject variability, and reducing food effect. Ease of manufacturing and scale-up and no influence of the lipid digestion process were other added advantages of SMEDDS [14]. However, SMEDDS is a liquid preparation which needs to feed into soft gelatine capsules and it involves many issues, like poor stability, high manufacturing costs, pharmaceutical incompatibility, drug leakage or precipitation, and capsule aging [15–17]. To solve these issues, solid SMEDDS has been explored as a substitute. An appropriate combination of adsorbent and diluent is needed for developing a solidified SMEDDS which can reduce the total mass and enhance drug dissolution [17]. Kumar et al. developed SMEDDS of mefenamic acid and solidify it by spray drying. The developed optimized S-SMEDDS proved multifold enhancement in in vitro dissolution rate and absorption profile of MFA, as compared with pure drug and the marketed product [18]. S-SMEDDS have been prepared by incorporating liquid SMEDDS (L-SMEDDS) into powders using different techniques, such as adsorption on solid carriers, wet granulation by high-shear mixer, extrusion/spheronization, conventional wet, and melt granulation [19].

Being a multiparticulate drug delivery system, pellets offer many therapeutic and technical benefits over unit dosage forms like capsules and tablets. Taken orally, pellets exhibit free dispersion in the gastrointestinal tract, and so maximize the drug absorption, minimize local irritation of the mucosa by certain irritant drugs because of the small quantity of drug in a single pellet, and reduce inter- and intra-patient variability [20]. Silva et al. prepared S-SMEDDS by hot-melt extrusion using hydroxypropyl methylcellulose acetate succinate as a matrix material. Extrudates prepared at the lowest drug concentration and highest temperature and recirculation time promoted a complete and rapid drug release in pH 6.8 giving rise to small and uniform microemulsion droplets [19].

Nipun et al. developed a self-emulsifying drug delivery system (SEDDS) of gliclazide [5]. The basic difference between SEDDS and SMEDDS is that SEDDS forms opaque emulsions and it achieves droplet size in the range of 100 and 300 nm, whereas SMEDDS produces transparent microemulsions and it achieves droplet size of less than 50 nm. The SEDDS includes 40–80% oil, whereas SMEDDS includes less than 20% oil [21–23].

The present research work aimed to formulate and evaluate gliclazide SMEDDS pellet forms for an improvement in solubility and dissolution of gliclazide.

Methods

Materials

Isopropyl myristate, oleic acid, ethyl oleate, Tween 20, Tween 80, propylene glycol, polyethylene glycol (PEG) 400, and PEG 600 were purchased from S.D. Fine Chemical Ltd., Mumbai, India. Capmul MCM C8 was received as a gift sample from Abitec Corporation Ltd., Mumbai, India. Miglyol and Captex were received as gift samples from Gattefosse, France. Gliclazide was received from IPCA Laboratories Ltd. Mumbai, India. Microcrystalline cellulose PH101 (MCC) was purchased from Balaji Drugs, Surat, India. The reagents used in this study were of analytical grade, and they were used as received.

Methods

Excipient selection

Careful selection of oil, surfactants, and co-surfactants is needed for the development of a self-emulsifying system so that these excipients can form a monophasic clear liquid with the drug when added to the aqueous phase and exhibit good solvent properties for lipophilic drugs [24].

Screening of oil The excess amount of gliclazide powder was added to 2 ml of oil (Capmul mcm C8, oleic acid, ethyl oleate, Captex, isopropyl myristate, Miglyol) and was kept on a magnetic stirrer for 48 h at room temperature. The resulting homogeneous mixture was centrifuged at 2000 rpm for 10 min. The sample of supernatant was adequately diluted with methanol and analyzed for drug solubility (mg/ml) in oil using UV visible spectroscopy. The absorbance of gliclazide in methanol was measured at 226.5 nm, and content was estimated using calibration equation Y = 0.0269X + 0.0492 (R^2 = 0.990). Each solubility assay was conducted in triplicate [25].

Screening of surfactant and co-surfactant The excess amount of drug was added to 2 ml of a surfactant (Tween 80, Tween 20) and co-surfactant (propylene glycol (PG), polyethylene glycol (PEG) 400, PEG 600) and kept on a magnetic stirrer for 48 h at room temperature. The resulting homogeneous mixture was centrifuged at 2000 rpm for 10 min. The sample of supernatant was adequately diluted with methanol and analyzed for drug solubility (mg/ml) in surfactant and co-surfactant. Each solubility assay was conducted in triplicate [26].

Optimization of oil and ratio of surfactant to co-surfactant (S:CoS) using a pseudoternary phase diagram

Construction of pseudoternary phase diagram by phase titration method Surfactant and co-surfactant (Smix) in each composition was mixed in two different weight ratios (2:1 and 4:1). These mixtures of oil and Smix were mixed to give the weight ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 so that the maximum ratio was covered to define the boundaries of phases precisely formed in the phase diagram. Water was added drop by drop and stirred using a magnetic stirrer until clear homogenous dispersion was achieved. The volume of water at which turbidity-to-transparency/transparency-to-turbidity transition occurred was noted down. A phase diagram was prepared using the prosim ternary diagram software, and those with the maximum isotropic region made us select corresponding Su:CoS as well as oil:Smix ratio [26].

Construction of pseudoternary phase diagram by phase inversion method Surfactant and co-surfactant (Smix) in each composition was mixed in two different weight ratios (2:1 and 4:1). These mixtures of water and Smix were mixed to give the weight ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 so that the maximum ratio was covered to define the boundaries of phases precisely formed in the phase diagram. Oil was added drop by drop and stirred using a magnetic stirrer until clear homogenous dispersion was achieved. The endpoint of the titration was the point where the dispersion becomes cloudy or turbid. The volume of oil at which turbidity-to-transparency/transparency-to-turbidity transition occurred was noted down. A phase diagram was prepared using the prosim ternary diagram software, and those with the maximum isotropic region made us select corresponding Su:CoS as well as oil:Smix ratio [26].

Preparation of gliclazide SMEDDS

Eight formulations of the microemulsion (M1 to M8) were selected from the constructed pseudoternary phase diagrams (Figs. 1 and 2). The batches were selected from the safest region of the phase diagram as there may be no chances of phase separation and instability of microemulsion formulation. Compositions of all batches (M1 to M8) are mentioned in Table 1. Smix ratio, i.e., surfactant to co-surfactant ratio, was maintained as 4:1 in batches M1 to M4, whereas in batch M5 to M8, this ratio was maintained as 2:1. In all the batches, 40 mg gliclazide was targeted in 0.5 ml formulation. The formulations were prepared by adding the fixed amount of drug in the mixture of surfactant, oil, and co-surfactant at room temperature (Table 1) into a stoppered glass vial and mixed. The drug was dissolved into the mixture of oil, surfactant, and co-surfactant at room temperature on a magnetic stirrer. The formulations were examined for signs of phase separation or drug precipitation after being sealed after 24 h and were stored at room temperature till further evaluation [14, 27].

Characterization of gliclazide SMEDDS

Dilution test One milliliter SMEDDS was diluted up to 10 and 100 times its volume with distilled water and checked visually for its transparency. A dilution test is performed to check the stability of the formulation [28].

Transmittance Transmittance (%) was observed against distilled water using a UV-visible spectrophotometer at 630 nm (UV-1800 double beam spectrophotometer, Shimadzu, Japan) by diluting SMEDDS with distilled water [28].

Dispersibility and emulsification test Standard USP dissolution apparatus–II (Paddle apparatus) can be utilized to check the self-emulsification capacity of oral SMEDDS. One milliliter formulation was added to 500 ml of water. Paddle speed and temperature selected in a paddle apparatus were 50 rpm and 37 ± 0.5 °C, respectively. The in vitro performance of the formulation was visually evaluated using the following grading system.

Grade A: Rapidly forming (within 1 min) microemulsion having a clear or bluish appearance.

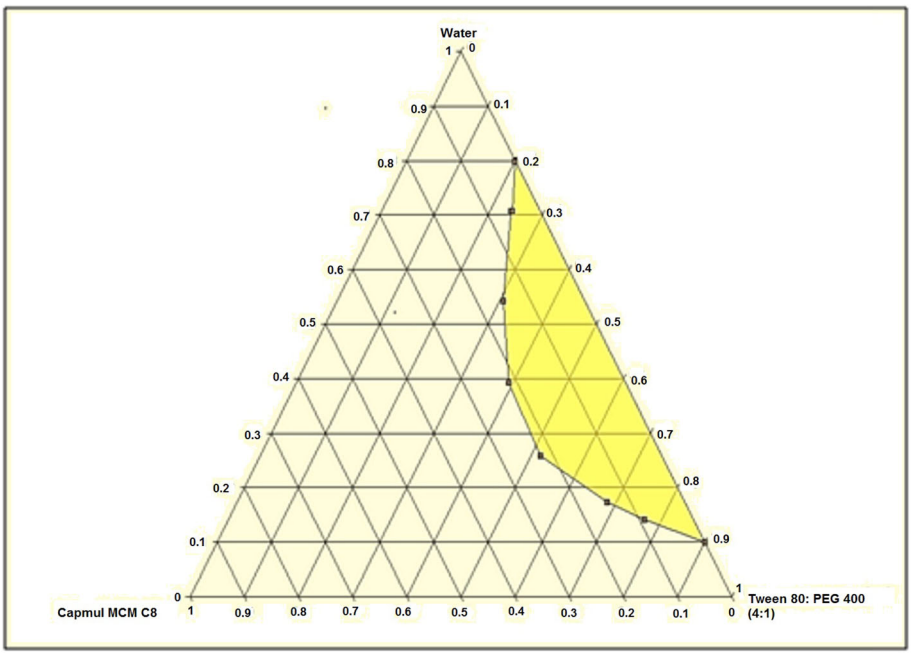

Fig. 1 Pseudoternary phase diagram showing microemulsion region containing S:CoS ratio of 4:1

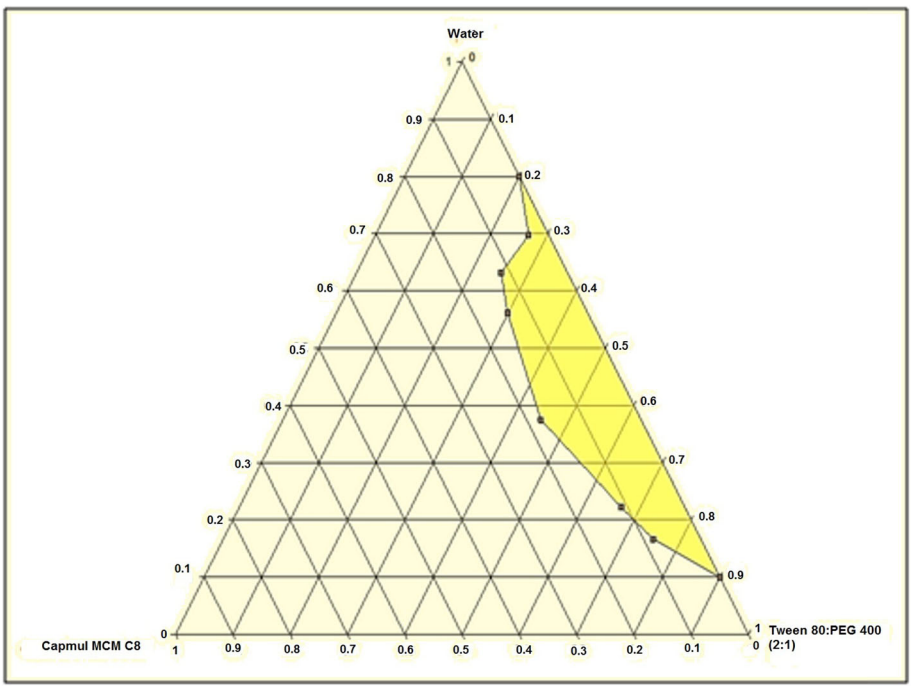

Fig. 2 Pseudoternary phase diagram showing microemulsion region containing S:CoS ratio of 2:1

Table 1 Composition of gliclazide SMEDDS batches (M1 to M8)

Batch	Oil (% v/v)	Surfactant (% v/v)	Co-surfactant (% v/v)
M1	12.50	70.00	17.50
M2	21.43	62.86	15.71
M3	16.67	66.67	16.67
M4	28.57	57.14	14.29
M5	10.42	60.42	29.17
M6	15.63	56.25	28.13
M7	11.27	59.15	29.58
M8	12.24	59.18	28.57

Grade B: Rapidly forming, slightly less clear emulsion having a bluish-white appearance.
Grade C: Fine milky emulsion that formed within 2 min
Grade D: Dull, greyish white emulsion having a slightly oily appearance that is slow to emulsify (longer than 2 min).
Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

The formulation which follows grade A and grade B passes the test as they can remain as microemulsion when dispersed in GIT [29, 30].

Globule size determination The stability and in vivo fate of microemulsion depends on its globule size [31]. The SMEDDS was added in distilled water, and the mean globule size and globule size distribution of SMEDDS were determined using Malvern Zetasizer (ZetaPALS). Dynamic light scattering principle was applied, and globule size was calculated from the translational diffusion coefficient using the Strokes-Einstein equation by the inbuilt software in Zetasizer [32].

Zeta potential determination Zeta potential measures the potential difference between the charged particle and the bulk of the liquid. It is one of the electrokinetic properties of the dispersion systems [33]. One milliliter of the formulation was diluted with milliQ water (10 ml) to measure zeta potential using Malvern Zetasizer (ZetaPALS) [34].

Polydispersity index Polydispersity or heterogeneity index determines the size range of globules in the system. The value should be less than or equal to 0.3. The polydispersity index (PDI) was reported using Malvern Zetasizer (ZetaPALS) [35].

Drug content The drug content of gliclazide SMEDDS was determined by HPTLC method. 0.5 ml formulation from batches containing 40 mg drug was dissolved in 50 ml methanol. The 1 ml solution was further diluted to 10 ml with methanol. A 6.25 ml aliquot of the solution was further diluted to 10 ml methanol. Fifteen microliters of the resulting solution was applied on TLC plate

Table 2 Chromatographic conditions used for the method

Sr. No.	Parameter	Chromatographic conditions
1.	Stationary phase	Aluminium plates pre-coated with silica gel 60 F254 (10 × 10 cm)
2.	Mobile phase	Toluene:ethyl acetate:0.1 glacial acetic acid (8:2:0.1 v/v/v)
3.	Chamber saturation time	30 min
4.	Temperature	Room temperature (25 + 2 °C)
5.	Migration distance	90 mm
Application parameters		
6.	Syringe	100 µl
7.	Application rate	100 nl/sec
8.	Band width	6 mm
9.	Distance from the plate edge	15 mm
10.	Distance from the bottom of the plate	15 mm
11.	Distance between the bands	10 mm
Scanning parameters		
12.	Wavelength of detection	226.5 nm
13.	Slit dimension	4.00 × 0.30 mm
14.	Scanning speed	20 mm/sec
15.	Lamp	D_2
16.	Measurement mode	Absorption

and development and scanning were done as per given chromatographic conditions (Table 2). The amount of gliclazide present in the sample solution was calculated by fitting area values of the corresponding peak into the calibration equation.

Determination of pH One milliliter of SMEDDS formulation was diluted up to 10 ml with distilled water, and pH of the microemulsions was measured using calibrated systemic digital pH meter at 25 °C. pH values of all formulations were taken in a triplicate [33].

Viscosity One milliliter of SMEDDS formulation was diluted 10 times and 100 times with distilled water and stirred on a magnetic stirrer. The viscosity was determined using Brookfield viscometer at 10 and 100 rpm for spindle no. 31 at 25 °C. The experiment was performed in a triplicate [36].

Formulation of gliclazide SMEDDS pellets

The extrusion-spheronization technique was used to prepare gliclazide SMEDDS pellets. The optimized gliclazide SMEDDS (M_3) was used for formulating a gliclazide SMEDDS pellet. Gliclazide (40 mg) was dissolved in an optimized mixture of oily liquid (0.5 ml) and mixed with microcrystalline cellulose (MCC) (500 mg). The resulting mass was passed through an extruder having a screen of 1.5-mm thickness and 1-mm apertures. The extrudates were added to the spheronizer (Cronimach, India) to obtain spherical pellets. The speed of the spheronizer was kept constant at 700 rpm. The schematic flow for the preparation of gliclazide SMEDDS pellets is given in Fig. 3. The drying of pellets was carried out at 50 °C till constant weight was achieved. The pellets were evaluated for pellet size analysis, flowability, compressibility, friability, drug content, and in vitro drug release [37, 38].

Characterization of gliclazide SMEDDS pellets

Pellet size analysis The sieving method was used to determine the mean pellet size and pellet size distribution. The sieves were set in a nest in which the coarsest sieve was kept at the top and finest at the bottom. Fifty grams of sample was kept on the coarsest sieve, and the nest was mechanically agitated for 10 min. The weight of retained pellets on each sieve was noted down. Calculation of mean pellet size was performed using Eq. 1.

$$\text{Mean Pellet Size} = \frac{\sum \text{XiFi}}{\sum \text{Fi}} \quad (1)$$

∑XiFi = Weight size
∑Fi = Weight retained in percentage

Scanning electron microscopy study Surface morphology and mean size of pellets were observed using scanning electron microscopy. The aspect ratio was calculated using the image analysis software Image J [39, 40].

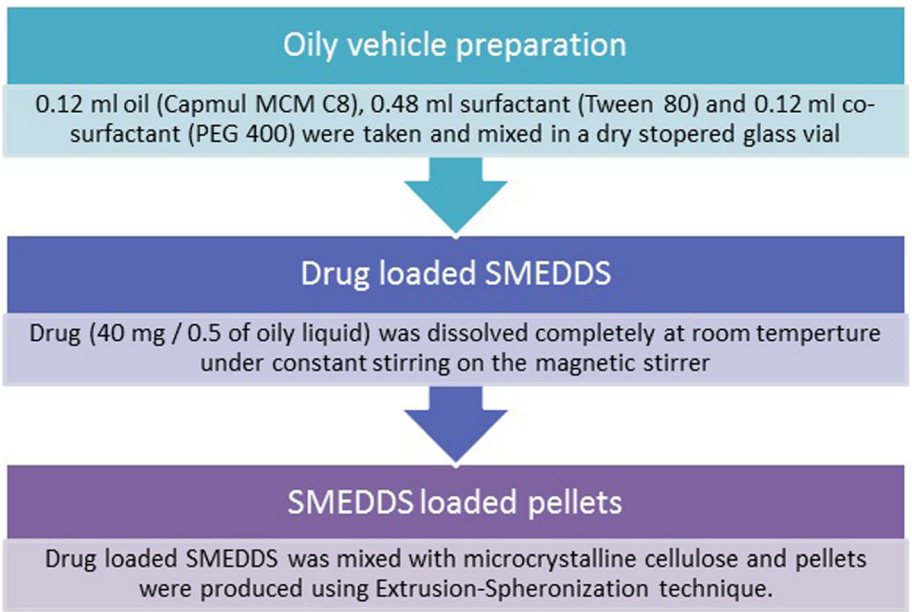

Fig. 3 Schematic flow for preparation of gliclazide SMEDDS pellets

Flowability and compressibility The flowability of the pellets was determined using Carr's compressibility index and Hausner's ratio. The compressibility of the pellets was checked using Carr's compressibility index. Twenty grams pellets were placed into a 100 ml measuring cylinder. The volume occupied by the pellets was noted down as V_0, without disturbing the cylinder. Then the cylinder was fitted in an instrument, and 500 taps were performed. After 500 taps, volume was noted down as Va. Again, after 750 taps, volume was noted down as Vb. The difference between Va and Vb was less than 2.0%, so tapped volume was noted down without further processing. Bulk density, tapped density, Carr's index, and Hausner's ratio were calculated using Eqs. 2, 3, 4, and 5, respectively [41].

$$\text{Bulk density} = \frac{\text{weight of sample (g)}}{\text{Bulk volume (ml)}} \quad (2)$$

$$\text{Tapped density} = \frac{\text{weight of sample (g)}}{\text{Tapped volume (ml)}} \quad (3)$$

$$\text{Carr}^{'}\text{s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (4)$$

$$\text{Hausner}^{'}\text{s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

Friability Ten grams pellets (F_s) with 200 glass beads of 4-mm diameter were kept in a Roche friabilator [42]. The sample was exposed to falling shocks for 10 min at 25 rpm. Afterward, the sample was passed through 250-μm mesh to remove fines. The fraction above 250 μm was denoted as F_a. The friability of pellets was calculated using Eq. 6.

$$\text{Friability (\%)} = \frac{(F_s - F_a)}{F_s} \times 100 \quad (6)$$

Assay HPTLC method was utilized to calculate drug content in gliclazide SMEDDS pellets. Pellet was weighed and crushed. The pellet powder equivalent to the 40 mg of drug was accurately weighed and dissolved in methanol in a 50-ml volumetric flask, and volume was made up by methanol. Drug content was further measured in the same manner as of drug content of liquid SMEDDS.

In vitro drug release study Gliclazide SMEDDS pellets were filled into the capsule, and the capsule was kept in 900 ml pH 7.4 phosphate buffer. The rotating speed of paddle and temperature of the medium were at 75 rpm and 37 ± 0.5 °C, respectively. Five milliliter sample was taken and substituted with fresh medium after 5, 10, 15, and 20 min. The sample was filtered and analyzed using HPTLC assay. The release profile from the marketed formulation of gliclazide (40 mg) and gliclazide SMEDDS pellets was compared [43].

Biological evaluation of gliclazide SMEDDS pellets All in vivo experiments in the present study were conducted as per the norms of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India and approved by the Institutional Animal Ethics Committee (protocol approval number: MPC/IAEC/09/2017). Healthy Swiss albino mice either sex weighing 20 to 25 g included in this study. Animals used in the study were procured from Jay Research Foundation, Vapi. Animals were randomly divided into three groups, six animals in each group and subjected to the oral glucose tolerance test (OGTT).

Group I, control (glucose 2 g/kg, p.o.); group II, marketed formulation (1 mg/kg, p.o.) + glucose 2 g/kg, p.o.; and group III, SMEDDS formulation (pellet equivalent to 1 mg/kg, p.o.) + glucose 2 g/kg, p.o.

Prior to the OGTT test, the mice have fasted for 16 h, and glucose solution (2 g/kg) was given orally to control group while in group II and group III were administered with SMEDDS and marketed formulation 30 min prior to glucose administration [5]. Pellets were suspended in 0.5% CMC solution. Blood samples were collected from mice from a tail cut (by removing the distal 2 mm of the tail) at 0, 30, 60, 90, and 120 min after the administration of glucose to measure glucose level (one-touch glucometer). There was no need to provide euthanasia or anaesthesia for blood collection from the tail. The animals were not killed after study, and after study, they were utilized for behavioural studies by post graduate students.

Statistical methods

All the data were presented as mean ± SD. Significance was evaluated at a P value of 0.05. Statistical analysis was performed using SPSS Ver. 19 (Trial version). A phase diagram was prepared using the prosim ternary diagram software.

Stability study

The optimized SMEDDS pellets were stored at 25 °C/60% RH and 40 °C/75%RH up to 6 months and analyzed for appearance, flowability, compressibility, mean pellets size, drug content, and in vitro drug release [44].

Results

Screening of oil

One of the major challenges of formulating SMEDDS is to avoid precipitation of the drug upon dilution in the in vivo gut lumen. Therefore, oils, surfactants, and co-

Table 3 Solubility of gliclazide in oil, surfactant, and co-surfactant

Sr. no.	Vehicle	Gliclazide solubility* (mg/ml)
1	Capmul MCM C_8 EV	**97.31 ± 6.12**
2	Oleic acid	25.53 ± 8.79
3	Miglyol	23.29 ± 6.46
4	Ethyl oleate	3.20 ± 0.19
5	Captex	2.04 ± 1.03
6	Isopropyl myristate	1.40 ± 0.97
7	Tween 80	**96.6 ± 9.01**
8	Tween 20	7.26 ± 1.79
9	Propylene glycol	6.7 ± 2.63
10	PEG 400	**15.8 ± 2.14**
11	PEG 600	11.12 ± 1.98

*Mean (n = 3) ± SD

surfactants used in the system should have high solubilization capability for the selected drug. The solubility of gliclazide in oils (Capmul MCM C8 EV, oleic acid, miglyol, Miglyol, ethyl oleate, captex, isopropyl myristate) is reported in Table 3.

Screening of surfactant and co-surfactant

Hydrophilic-lipophilic balance (HLB) value of surfactant and co-surfactant governs self-emulsification capacity. Usually, surfactants with HLB 12–15 show acceptable self-emulsification efficiency. HLB values of Tween 80 and Tween 20 were found to be 15 and 16.7, respectively. The solubility of a drug in surfactant and co-surfactant is mentioned in Table 3. The solubility of the drug in Tween 80 and Tween 20 was found to be 96.6 and 7.26 mg/ml, respectively. The solubility of gliclazide in propylene glycol, PEG 400, and PEG 600 was found to be 6.7, 15.8, and 11.12 mg/ml, respectively.

Optimization of oil and ratio of surfactant to co-surfactant (S:CoS) using a pseudoternary phase diagram

By combining the phase inversion and phase titration method, the boundary points were obtained in the phase diagram. The microemulsion regions have been developed for both S:CoS ratio, i.e., ratio of 4:1 and 2:1 and is shown in Figs. 1 and 2, respectively. Boundary point compositions of microemulsion formulations having S:CoS ratio 4:1 and 2:1 are reported in Table 4.

Table 4 Boundary point composition of microemulsion formulation having S:CoS ratio of 4:1 and 2:1

Series	% of components having S:CoS ratio of 4:1	% of components having S:CoS ratio of 2:1
1	Oil 5.4 Smix 23 Water 70	Oil 3.5 Smix 26.8 Water 69.7
2	Oil 9.8 Smix 26 Water 63	Oil 11.6 Smix 25.3 Water 63.2
3	Oil 15 Smix 30 Water 54	Oil 14 Smix 29.9 Water 56.1
4	Oil 21.6 Smix 39.2 Water 39.2	Oil 15.4 Smix 36.7 Water 47.7
5	Oil 22.4 Smix 51.7 Water 25.9	Oil 17.5 Smix 45 Water 37.5
6	Oil 18.2 Smix 59.9 Water 21.7	Oil 14 Smix 56.7 Water 29.5
7	Oil 14.3 Smix 68.4 Water 17.3	Oil 11.1 Smix 66.7 Water 22.2
8	Oil 11.8 Smix 72.2 Water 15.9	Oil 11.8 Smix 72.2 Water 15.9
9	Oil 9 Smix 76.8 Water 14.1	Oil 9.8 Smix 70.4 Water 19.7
10	Oil 5 Smix 81.5 Water 12.7	Oil 8.3 Smix 75 Water 16.7

Characterization of gliclazide SMEDDS

Dilution test

All the formulation of batches M1 to M8 remained clear after 10 times dilution. Formulation from batch M2, M4, to M6 was rejected as they became turbid after 100 times dilution. Formulation of batches M1, M3, M5, M7, and M8 remains clear upon 100 times dilution, which proved the system's compatibility with excess water [14].

Transmittance

Percentage transmittance of batches M1, M2, M3, M4, M5, M6, M7, and M8 at 630 nm was found to be 97.96 ± 1.01, 67.03 ± 0.77, 98.83 ± 0.68, 69.93 ± 0.80, 95.66 ± 0.04, 84.93 ± 0.15, 96.06 ± 1.14, and 95.82 ± 0.34, respectively. Percentage transmittance of formulations of batches M1, M3, M5, M7, and M8 was more than 95%. This result was in agreement with the dilution test, means batches M1, M3, M5, M7, and M8 can form the transparent microemulsion.

Dispersibility and emulsification test

Either phase separation or precipitation of a poorly soluble drug can occur upon infinite dilution of SMEDDS as SMEDDS are formed at a specific concentration of oil, surfactant, co-surfactant, and water. The formulations M1, M3, M5, M7, and M8 passed the criteria of grade A.

Globule size, polydispersity index, pH, and zeta potential

Due to high transmittance, batches M1 and M3 were subjected for further evaluation. The mean globule size of the formulation of batches M1 and M3 was found to be 90 and 31.50 nm, respectively. The PDI of the formulation of batches M1 and M3 was found to be 1.46 and 0.67, respectively. These findings thus indicated that the formulation of batch M3 confirmed a more uniform globule size distribution than batch M1 [21]. The formulations of batches M1 and M3 have zeta potential 11.38 and 0.90 mV, respectively. pH affects on the stability of dispersion as changes in the pH may change the zeta potential of the formulations. The pH of the formulations of batches M1 and M3 was 6.30 ± 0.07 and 6.38 ± 0.04, respectively.

Assay

The amount of gliclazide was calculated from the calibration curve by HPTLC method. The drug content in the formulation of batches M1 and M3 was found to be 79.15 ± 3.72% and 100.9 ± 2.69%, respectively. Formulation of batch M3 was considered as an optimized liquid SMEDDS.

Viscosity

The viscosity of formulations of batches M1 and M3 was found to be 5.31 cp and 5.91 cp after 10 times dilution. Thus, it confirmed that the external phase of the microemulsion is water which confirms the redispersion of SMEDDS into O/W microemulsion.

Characterization of gliclazide SMEDDS pellets

Pellet size analysis

The mean pellet size was found to be within 950–1000 μm which is an acceptable range as per reference [20].

Scanning electron microscopy study

As per the image of scanning electron microscopy study, the pellets were found to be spherical with a smooth surface. Aspect ratio (AR) and roundness of pellets were calculated from the SEM image (Fig. 4). They were found to be 1.012 and 0.946, respectively, which proved sphericity of the pellet [45].

Flowability and compressibility

Carr's compressibility index and Hausner's ratio of the SMEDDS pellets were found to be 3.04 and 1.03, respectively.

Friability

Friability (%) of the SMEDDS pellets was found to be 0.8% which is acceptable for pharmaceutical pellets.

Assay

The amount of gliclazide content in the SMEDDS pellets was found to be 102.2%.

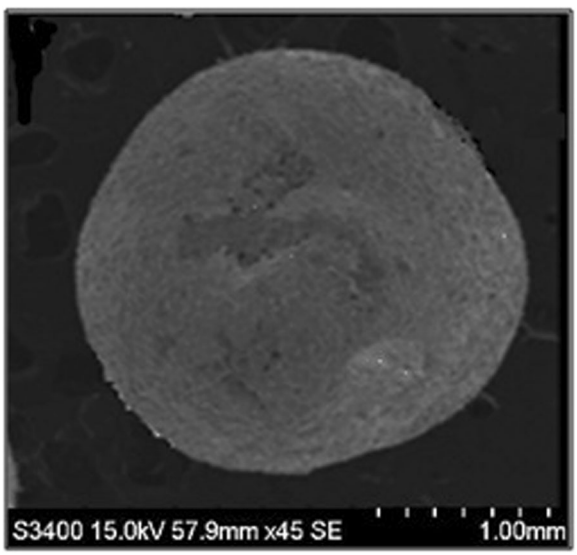

Fig. 4 Scanning electron microscopy (SEM) image of glicliazide SMEDDS pellet

In vitro drug release study

More than 70% of the drug was released within 10 min from the SMEDDS pellet formulation. The dissolution rate of the SMEDDS pellets was higher compared to the marketed formulation of gliclazide (Fig. 5).

Performance of SMEDDS on blood glucose level in albino mice

When SMEDDS and the marketed product were administered with glucose, the reduction in plasma glucose level was observed (Fig. 6). The results of ANOVA indicated that there was a significant difference in plasma glucose level among three groups (control, SMEDDS, and marketed) at 30, 60, 90, and 120 min. The results were also confirmed by the post hoc test using the SPSS software. It can be concluded that gliclazide SMEDDS is more effective than a marketed product.

Stability study

No significant differences were detected in appearance, Carr's compressibility index, Hausner's ratio, mean pellets size, drug content, and in vitro drug release of the optimized pellets at 25 °C/60% RH and 40 °C/75%RH up to 6 months (Table 5), indicating the stability of the optimized batch.

Discussion

Screening of oil, surfactant, and co-surfactant

Gliclazide exhibited the highest solubility in Capmul MCM C8 EV. The chemical name of Capmul MCM C8 is glyceryl monocaprylate. It is a glycerin mono and diester of caprylic acid (97%) and that of capric acid (~ 3%) [46]. Madan et al. reported that pioglitazone HCl exhibited good solubility in the Capmul MCM C8 and oleic acid [36]. As per their view, drug exhibits higher solubility in medium-chain triglycerides (MCT) rather than long-chain triglycerides (LCT) because MCT possesses higher ester content per gram than LCT.

Higher solubility of the drug observed in Tween 80 than Tween 20 is due to longer hydrocarbon chains of Tween 80 than Tween 20 [5]. The toxicity of nonionic surfactants is generally less than ionic surfactants as they are usually accepted for products given by the oral route [47]. Prajapati et al. also observed the highest emulsification efficiency of Tween 80 with oily phase Acrysol EL 135 [48].

PEG 400 showed more solubility of the drug than PEG 600 and propylene glycol. Guleria et al. also observed higher solubility of gliclazide in PEG 400 because of the complete dissolution of drug particles [49]. The performance of co-surfactants is affected by their structure and chain length as they work by penetrating interfacial surfactant monolayer [50].

Characterization of gliclazide SMEDDS

Formulations that remain clear upon 100 times dilutions were selected for further studies as larger dilutions simulate in vivo conditions in the stomach following the oral administration of SMEDDS (pre-concentrate) [51]. The selected batches M1, M3, M5, M7, and M8 formed transparent microemulsion. In the dispersibility and emulsification test, the emulsion was rapidly formed with a clear bluish appearance.

In the present study, we used distilled water as a dispersion medium because, as per the literature report, the insignificant difference was observed in the SMEDDS prepared using nonionic surfactants, dispersed in either water or simulated gastric or simulated intestinal fluid [29].

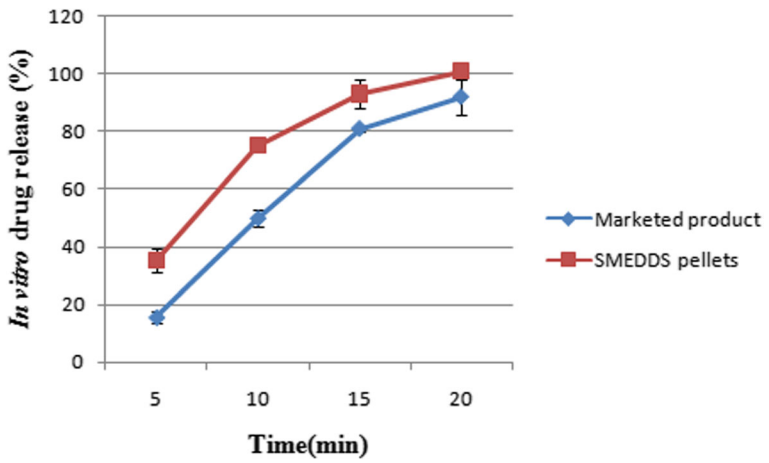

Fig. 5 Comparison of drug release of SMEDDS pellet with the marketed formulation

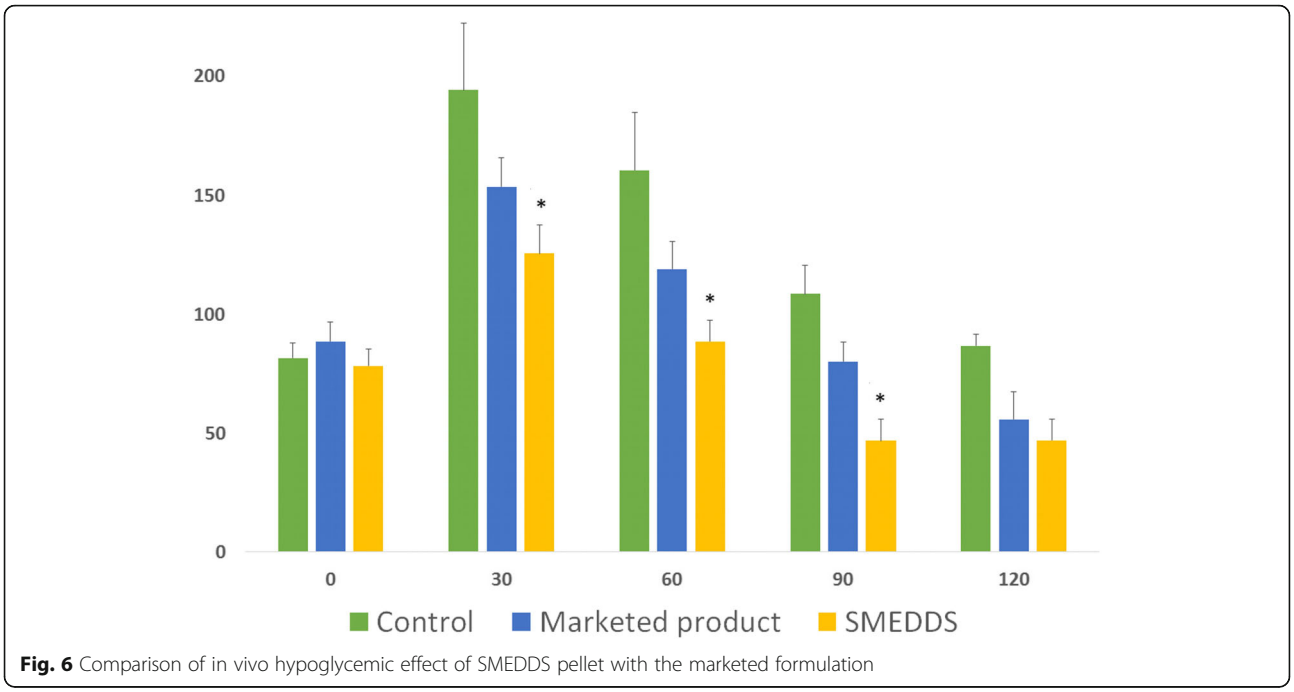

Fig. 6 Comparison of in vivo hypoglycemic effect of SMEDDS pellet with the marketed formulation

The globule size was in the acceptable range (< 100 nm) which may support the permeation of formulation through biological membranes. Nonionic surfactants can enhance penetration of the drug through the epithelial cells by improving the solubility and dissolution of the drug and also reducing the interfacial surface tension. The mean globule size of the formulation of batch M3 was less than 50 nm which can favor penetration of microemulsion at the site of absorption via the transcellular pathway.

Normally, high zeta potential (negative or positive) of dispersion indicates electrically stabilized dispersion as it prevents aggregation due to electric repulsion. In the case of low zeta potential, attraction predominant than repulsion and results in coagulates or flocculates. However, this assumption is not applicable to all colloidal dispersion, especially the dispersion which contains steric stabilizers. Surfactants used in this study were nonionic and they lowered zeta potential values. In addition, the M3 batch was found to be stable during the study period (3 months), which suggested that for such systems, stabilization might be promoted by a steric contribution from nonionic surfactants [52, 53]. pH for the formulation was near to neutral indicates suitability for oral administration.

Characterization of gliclazide SMEDDS pellets

Pellets were found to be spherical, and pellet size was found to be within an acceptable range. The values of Carr's compressibility index and Hausner's ratio suggested excellent flowability and compressibility of the pellets. Plasticity and good binding property of MCC are due to low bulk density, high surface area and high hygroscopicity of it. Fechner et al. compared the effect of

Table 5 Results of stability study of the optimized gliclazide SMEDDS pellets

Time	Carr's index (%)	Hausner's ratio	Mean pellet size* (μm)	Drug content*	Drug release at 15 min* (%)
0	3.04	1.031	969 ± 8.72	100.9 ± 2.69	93.00 ± 4.62
Product stored at accelerated condition of 40 °C/75% RH					
3 months	3.03	1.031	965.96 ± 9.14	99.9 ± 2.46	91.82 ± 3.96
6 months	3.03	1.030	972.84 ± 10.72	99.1. ± 3.06	92.16 ± 4.27
Product stored at room temperature					
3 months	3.03	1.031	968.19 ± 8.65	100.2 ± 3.16	93.1 ± 3.05
6 months	3.04	1.031	971.08 ± 6.19	99.9 ± 1.47	90.19 ± 4.27

*Mean (n = 3) ± SD

powder cellulose (PC), MCC 101, and MCC 301 on pellet quality and concluded that MCC 101 was the best substance, with easy handling and acceptable product properties [54]. The higher dissolution rate of SMEDDS pellets compared to the marketed formulation of gliclazide was due to micro-sized globule formation. Cui et al. improved the in vitro release rate and oral absorption of Pueraria lobata isoflavone by preparing self-microemulsifying tablets [55]. The major components of SMEDDS were ethyl oleate, Tween 80, and Transcutol P. They reported that more than threefold faster in vitro release rate of puerarin from SMEDDS was from Yufengningxin tablets. Laddha et al. improved solubility and dissolution rate of BCS (Biopharmaceutical Classification System) class II antiemetic agent, domperidone, by developing a self-microemulsifying drug delivery system (SMEDDS) [56]. A significant reduction in plasma glucose level in albino mice proved that gliclazide SMEDDS is more effective than the marketed product. The selected optimized batch was found to be stable as per ICH guidelines.

Conclusion

Solid SMEDDS (Self microemulsifying drug delivery system) can be a suitable therapeutic approach for effective anti-diabetic drug therapy. The low bioavailability of gliclazide is due to its poor water solubility and lower dissolution rate. Liquid gliclazide SMEDDS provided improved dissolution rate and in vivo hypoglycemic effect of the drug compared to the marketed formulation. SMEDDS pellets prepared from optimized liquid SMEDDS formulation by extrusion-spheronization method showed to retain all the properties of liquid SMEDDS and provided benefits of solid multiparticulate drug delivery system. Bioavailability enhancement and dose reduction study can be a future of the present research work. Using optimized formulation composition, S-SMEDDS of other BCS class II drugs can also be formulated and characterized.

Abbreviations

SMEDDS: Self-microemulsifying drug delivery system; SEDDS: Self-emulsifying drug delivery system; API: Active pharmaceutical ingredients; GI: Gastrointestinal; MCC: Microcrystalline cellulose; PEG: Polyethylene glycol (PEG); PG: Propylene glycol; PDI: Polydispersity index; HLB: Hydrophilic-lipophilic balance; MCT: Medium-chain triglycerides; LCT: Long-chain triglycerides; AR: Aspect ratio; BCS: Biopharmaceutical classification system; PC: Powdered cellulose; OGTT: Oral glucose tolerance test

Acknowledgements

The authors are thankful to Abitec Corporation Ltd. (Mumbai, India) and IPCA Laboratories Ltd. (Mumbai, India) for providing gift sample of Capmul MCM C8 and Gliclazide, respectively. The authors would like to thank Gattefosse, France, for providing Miglyol and Captex for the research work.

Authors' contributions

All authors have read and approved the manuscript. HP and NP contributed to conception, design of work, formulation, and evaluation of product, the acquisition analysis and interpretation of data, drafted a manuscript, and revised it. BV and BP contributed to in vivo study and interpretation of the data. KR contributed to the formulation development and evaluation of the product. KB contributed to the research guidance and analytical studies.

Funding

No funding was availed for the present investigation. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

All animal studies were approved by the Animal Center for Pharmaceutical Research, Maliba Pharmacy College, Tarsadi, India with protocol approval number MPC/IAEC/09/2017 and were conducted under the provisions of the CPCSEA guidelines

Consent for publication

Non applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Maliba Pharmacy College, Uka Tarsadia University, Gopal Vidyanagar, Maliba campus, Surat, Gujarat 394350, India. [2]L. M. College of Pharmacy, Ahmedabad, Gujarat 380009, India.

Received: 21 February 2020 Accepted: 12 May 2020
Published online: 25 May 2020

References

1. Savjani KT, Gajjar AK, Savjani JK (2012) Drug solubility: importance and enhancement techniques. ISRN Pharm 195727:1–10. https://doi.org/10.5402/2012/19572
2. Khadka P, Ro J, Kim K, Kim I, Kim JT, Kim H, Cho M, Yun G, Lee J (2014) Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci 9(6):304–316. https://doi.org/10.1016/j.ajps.2014.05.005
3. BCS classification of gliclazide (2009).http://www.tsrlinc.net/results.cfm. Accessed 26 Jan 2016.
4. Campbell DB, Lavielle R, Nathan C (1991) The mode of action and clinical pharmacology of gliclazide: a review. Diabetes Res Clin Pract 14(2):S21–S36. https://doi.org/10.1016/0168-8227(91)90005-x
5. Nipun TS, Islam SMA (2014) SEDDS of gliclazide: preparation and characterization by in-vitro, ex-vivo and in-vivo techniques. Saudi Pharm J 22(4):343–348. https://doi.org/10.1016/j.jsps.2013.06.001
6. More CG, Dabhade PS, Jain NP, Aher BO (2015) Solubility and dissolution enhancement of gliclazide by solid dispersion technique. Int J Pharm Chem Anal 2(2):51–58
7. Biswal S, Sahoo J, Murthy PN, Giradkar RP, Avari JG (2008) Enhancement of dissolution rate of gliclazide using solid dispersions with polyethylene glycol 6000. AAPS Pharm Sci Tech 9(2):563–570. https://doi.org/10.1208/s12249-008-9079-z
8. Hiremath SN, Raghavendra RK, Sunil F, Danki LS, Rampure MV, Swamy PV, Bhosale UV (2008) Dissolution enhancement of gliclazide by preparation of inclusion complexes with β-cyclodextrin. Asian J Pharm 2(1):73–76
9. Shavi GV, Kumar AR, Usha YN, Armugam K, Ranjan OP, Ginjupalli K, Pandey S, Udupa N (2010) Enhanced dissolution and bioavailability of gliclazide using solid dispersion techniques. Int J Drug Deliv 2:49–57. https://doi.org/10.5138/ijdd.2010.0975.0215.02011
10. Ravouru N, Venna RSA, Penjuri SCB, Damineni S, Kotakadi VS, Poreddy SR (2018) Fabrication and characterization of gliclazide nanocrystals. Adv Pharm Bull 8(3):419–427. https://doi.org/10.15171/apb.2018.049
11. Mahajan H (2013) Liquisolid compact of gliclazide for enhanced dissolution and oral bioavailability. 6:314–320
12. Zhang P, Liu Y, Feng N, Xu J (2008) Preparation and evaluation of self-microemulsifying drug delivery system of oridonin. Int J Pharm 355(1-2):269–276. https://doi.org/10.1016/j.ijpharm.2007.12.026

13. Khairnar DA, Darekar AB, Saudagar RB (2016) A review on self-micro emulsifying drug delivery system: evident to improve the oral bioavailability of hydrophobic drugs. Asian J Pharm Technol 6(2):131–134. https://doi.org/10.5958/2231-5713.2016.00018.0
14. Singh AK, Chaurasiya A, Singh M, Upadhyay SC, Mukherjee R, Khar RK (2008) Exemestane loaded self-microemulsifying drug delivery system (SMEDDS): development and optimization. AAPS Pharm Sci Tech 9(2):628–634. https://doi.org/10.1208/s12249-008-9080-6
15. Dokania S, Joshi AK (2015) Self-microemulsifying drug delivery system (SMEDDS)--challenges and road ahead. Drug Deliv 22(6):675–690. https://doi.org/10.3109/10717544.2014.896058
16. Cho W, Kim MS, Kim JS et al (2013) Optimized formulation of solid self-microemulsifying sirolimus delivery systems. Int J Nanomedicine 8:1673–1682. https://doi.org/10.2147/IJN.S43299
17. Yeom DW, Chae BR, Kim JH, Chae JS, Shin DJ, Kim CH, Kim SR, Choi JH, Song SH, Oh D, Sohn S, Choi YW (2017) Solid formulation of a supersaturable self-microemulsifying drug delivery system for valsartan with improved dissolution and bioavailability. Oncotarget 8(55):94297–94316. https://doi.org/10.18632/oncotarget.21691
18. Kumar M, Singh D, Bedi N (2019) Mefenamic acid-loaded solid SMEDDS: an innovative aspect for dose reduction and improved pharmacodynamic profile. Ther Deliv 10(1):21–36. https://doi.org/10.4155/tde-2018-0053
19. Silva LA, Almeida SL, Alonso EC, Rocha PB, Martins FT, Freitas LA, Taveira SF, Cunha-Filho MS, Marreto RN (2018) Preparation of a solid self-microemulsifying drug delivery system by hot-melt extrusion. Int J Pharm 541(1-2):1–10
20. Ghebre-Sellassie IKA (2007) Pelletization technique. In: Swarbrick J (ed) Encyclopedia of pharmaceutical technology. Informa health care, New York, pp 2651–2662
21. Wu L, Qiao Y, Wang L, Guo J, Wang G, He W, Yin L, Zhao J (2015) A self-microemulsifying drug delivery system (SMEDDS) for a novel medicative compound against depression: a preparation and bioavailability study in rats. AAPS PharmSciTech 16(5):1051–1058. https://doi.org/10.1208/s12249-014-0280-y
22. Jaiswal P, Aggarwal G, Harikumar SL, Singh K (2014) Development of self-microemulsifying drug delivery system and solid-self-microemulsifying drug delivery system of telmisartan. Int J Pharm Investig 4(4):195–206. https://doi.org/10.4103/2230-973X.143123
23. Pal VK (2011) Self-emulsifying drug delivery system. J Pharm Res & Opinion 1:80–84
24. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH (2004) Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 274(1-2):65–73. https://doi.org/10.1016/j.ijpharm.2003.12.028
25. Parakh DR, Patil MP, Sonawane SS, Kshirsagar SJ (2016) Application of factorial design approach in development and evaluation of self microemulsifying drug delivery system (SMEDDS) of mebendazole. J Pharm Invest 47(September):1–13. https://doi.org/10.1007/s40005-016-0279-3
26. Anton N, Vandamme TF (2011) Nano-emulsions and micro-emulsions: clarifications of the critical differences. Pharm Res 28(5):978–985. https://doi.org/10.1007/s11095-010-0309-1
27. Thakkar H, Nangesh J, Parmar M, Patel D (2011) Formulation and characterization of lipid-based drug delivery system of raloxifene-microemulsion and self-microemulsifying drug delivery system. J Pharm BioAlliedSci 3(3):442–448. https://doi.org/10.4103/0975-740dispersi6.84463
28. Rao BP, Baby B, Durgaprasad Y, Ramesh K, Rajarajan S, Keerthi B, Sreedhar C (2013) Formulation and evaluation of SMEDDS with Capmul MCM for enhanced dissolution rate of valsartan. RGUHS J Pharm Sci 3:33–40. https://doi.org/10.5530/rjps.2013.2.5
29. Hu X, Lin C, Chen D, Zhang J, Liu Z, Wu W, Song H (2012) Sirolimus solid self-microemulsifying pellets: formulation development, characterization and bioavailability evaluation. Int J Pharm 438(1-2):123–133. https://doi.org/10.1016/j.ijpharm.2012.07.055
30. Dixit AR, Rajput SJ, Patel SG Preparation and bioavailability assessment of SMEDDS containing valsartan. AAPS Pharm Sci Tech 11(1):314–321
31. Woo JS, Kim TS, Park JH, Chi SC (2007) Formulation and biopharmaceutical evaluation of Silymarin Using SMEDDS. Arch Pharm Res 30(1):82–89. https://doi.org/10.1007/bf02977782
32. Mirza MA, Ahmad S, Mallick MN, Manzoor N, Talegaonkar S, Iqbal Z (2013) Development of a novel synergistic thermosensitive gel for vaginal candidiasis: An in vitro, in vivo evaluation. Colloids Surf B: Biointerfaces 103:275–282. https://doi.org/10.1016/j.colsurfb.2012.10.038
33. De Campos VE, Ricci-Junior E, Mansur CE (2012) Nanoemulsions as delivery systems for lipophilic drugs. J Nanosci Nanotechnol 12(3):2881–2890. https://doi.org/10.1166/jnn.2012.5690
34. Jaiswal JJ, Solanki AJ, Yadav SK (2016) A review on solid-self microemulsifying drug delivery system: formulation strategies to improve the bioavailability of poorly soluble drugs. J Pharm SciBiosci Res 6(1):239–246
35. Li F, Song S, Guo Y, Zhao Q, Zhang X, Pan W, Yang X (2015) Preparation and pharmacokinetics evaluation of oral self-emulsifying system for poorly water-soluble drug Lornoxicam. Drug Deliv 22(4):487–498. https://doi.org/10.3109/10717544.2014.885615
36. Madan JR, Sudarshan B, Kadam VS, Kamal D (2014) Formulation and development of self-microemulsifying drug delivery system of pioglitazone hydrochloride. Asian J Pharm 8(1):27. https://doi.org/10.4103/0973-8398.134097
37. Setthacheewakul S, Mahattanadul S, Phadoongsombut N, Pichayakorn WR (2010) Development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats. Eur J Pharm Biopharm 76(3):475–485. https://doi.org/10.1016/j.ejpb.2010.07.011
38. Patel H, Patel K, Tiwari S, Pandey S, Shah S, Gohel M (2016) Quality by design (QbD) approach for development of co-processed excipient pellets (MOMLETS) by extrusion-spheronization technique. Recent Pat Drug Deliv formul 10(3):192–206. https://doi.org/10.2174/1872211310666160709193540
39. Sarkar S, Ang BH, Liew CV (2014) Influence of starting material particle size on pellet surface roughness. AAPS Pharm SciTech 15(1):131–139. https://doi.org/10.1208/s12249-013-0031-5
40. Takashimizu Y, Iiyoshi M (2014) New parameter of roundness R: circularity corrected by aspect ratio. Prog in Earth and Planet Sci 3:1–16. https://doi.org/10.1186/s40645-015-0078-x
41. United States Pharmacopoeial Convention. United State Pharmacopoeia 32-National Formulatory; 2009.
42. Patel H, Patel H, Gohel M, Tiwari S (2016) Dissolution rate improvement of telmisartan through modified MCC pellets using 32 full factorial design. Saudi Pharm J 24(5):579–587. https://doi.org/10.1016/j.jsps.2015.03.007
43. Tang B, Cheng G, Gu JC, Xu CH (2008) Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discov Today 13(13-14):606–612. https://doi.org/10.1016/j.drudis.2008.04.006
44. Bachhav YG, Patravale VB (2009) SMEDDS of glyburide: formulation, in vitro evaluation, and stability studies. AAPS PharmSciTech 10(2):482–487. https://doi.org/10.1208/s12249-009-9234-1
45. Gupta NV, Gowda DV, Balamuralidhara V, Khan SM (2011) Formulation and evaluation of olanzapine matrix pellets for controlled release. Daru 19(4):249–256
46. Borhade V, Nair H, Hegde D (2008) Design and evaluation of self-microemulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS PharmSciTech 9:13–21. https://doi.org/10.1208/s12249-007-9014-8
47. Porter CJH, Pouton CW, Cuine JF, Charman WN (2008) Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv Drug Deliv Rev 60(6):673–691
48. Prajapati ST, Joshi HA, Patel CN (2013) Preparation and characterization of self-microemulsifying drug delivery system of olmesartan medoxomil for bioavailability improvement. J Pharm 728425. https://doi.org/10.1155/2013/728425
49. Guleria R, Kaith NS, Singh R (2012) Peg based solid dispersions of gliclazide: a comparative study. Int J Pharm Pharm Sci 4(1):507–511
50. Gurram AK, Deshpande PB, Kar SS, Nayak UY, Udupa N, Reddy MS (2015) Role of components in the formation of self-microemulsifying drug delivery systems. Indian J Pharm Sci 77(3):249–257. https://doi.org/10.4103/0250-474x.159596
51. Akula S, Gurram AA, Devireddy SR (2014) Self-microemulsifying drug delivery systems: an attractive strategy for enhanced therapeutic profile. Int Sch Res Notices 2014:964051. https://doi.org/10.1155/2014/964051
52. Babchin AJ, Schramm LL (2012) Osmotic repulsion force due to adsorbed surfactants. Colloids Surf B: Biointerfaces 91:137–143. https://doi.org/10.1016/j.colsurfb.2011.10.050
53. Macroemulsions BP (1987) In: Schick MJ (ed) Nonionic surfactants: physical chemistry. Marcel Dekker, New York, pp 435–491
54. Fechner PM, Wartewig S, Futing M, Heilmann A, Neubert RH, Kleinebudde P (2003) Properties of microcrystalline cellulose and powder cellulose after

extrusion/spheronization as studied by fourier transform Raman spectroscopy and environmental scanning electron microscopy. AAPS Pharm Sci 5(4):E31–E39. https://doi.org/10.1208/ps050431
55. Cui S, Zhao C, Chen D, He Z (2005) Self-microemulsifying drug delivery systems (SMEDDS) for improving in vitro dissolution and oral absorption of Pueraria Lobata Isoflavone. Drug Dev Ind Pharm 31(4-5):349–356. https://doi.org/10.1081/ddc-54309
56. Laddha P, Suthar V, Butani S (2014) Development and optimization of self microemulsifying drug delivery of domperidone. Braz J Pharm Sci 50:91–100. https://doi.org/10.1590/S1984-82502011000100009

Publisher's Note