Introduction

The pervasiveness of diabetes among all age groups worldwide is expected to be 4.4% in 2030. Projections in mounting of total number of people globally is estimated to be from 171 million in 2000 to 366 million in 2030, urban population in developing countries is projected to double between 2010 and 2030 [1]. To clash with such a perilous disease several therapeutic molecules had been explored out of which one is RPG (2-ethoxy-4-[3-methyl-1-[2-(1-piperidyl) phenyl]-butyl] carbamoylmethyl] benzoic acid) which is an effective second generation oral hypoglycemic agent extensively utilized in the treatment of non insulin dependent diabetes mellitus, which acts by blocking ATP-dependent potassium channels in pancreatic beta cells, which in turn, stimulates insulin secretion. RPG acts in a dose-dependent manner and is characterized by a fast onset, yet short duration of action [2]. But still the battle does not end here since every potential candidate needs a sound formulation system for a successful onset of action and therapeutic effectiveness because of some associated issues like solubility, RPG has very low aqueous solubility (34μg/mL at 37 °C) and high lipophilicity (logP=3.97) hence if solubility issue of such a potential candidate can be taken away then definitely there would be fair chance of getting greater therapeutic effects [3].

In a pursuit of elimination of solubility issues several formulation strategies had been developed among which lipid based system had gained immense popularity over past years because of their ability to enhance the drug water-solubility and permeation, serving drug pass into the lymphatic vessels, and minimizing liver metabolism. Bypassing the dissolution process in the gastro-intestinal tract (GIT) by delivering the entire dose in solution thereby is considered to be one of the most
important qualifications of this system [4], overall lipid-based
drug delivery systems have been developed to overcome the
possible adverse influence of P-glycoprotein [5]. Among various
lipid based formulations self micro emulsifying based drug
delivery system (SMEDDS) had shown substantial improved
performance in resolving solubility issues. SMEDDS are
isotropic and thermodynamically stable solutions comprising
oil, surfactant, co surfactant and drug that instinctively form oil
in water microemulsion when mixed with water under gentle
agitation which is provided by digestive motility of stomach
and intestine in vivo [6]. Due to smaller droplet size SMEDDS
profers larger interfacial surface area resulting in enhanced
release and absorption properties [7,8]. In this study, SMEDDS
consisting RPG were formulated with the intention of enhancing
solubility and minimizing disparities in the bioavailability. The
optimized SMEDDS formulations characterized for various
physicochemical parameters (like droplets size and size
distribution, zeta potential, dilution studies, thermodynamic
stability studies morpholgy and thermal stabiliy studies).

Materials and Methods

Materials

RPG was a generous gift sample from Torrent
Pharmaceuticals Pvt. Ltd (Ahmedabad, India). Labrafac
(caprylic/capric triglyceride), Labrafil (PEG-5 Oleate), Labrasol
(Caprylocapryl macrogol-8 glyceride), Capryol 90 (Propylene
glycol monoacrylate), Transcutol (Diethylene glycol monoethyl
ether), (Maisine) glyceryl monolinoelate, plurol oleique CC 497
(Polyglyceryl-3 oleate) were provided by Gattefosse Pvt. Ltd
(Mumbai, India). Estol (Propylene glycol dicaprylate/caprate)
was supplied by Croda Pvt. Ltd (Mumbai, India). Capmul MCM
was provided by Abitec Corporation (USA). Chremophor RH40
was provided by BASF (Mumbai, India). Castor oil, olive oil, soya
bean oil, Tween 80, PEG 400, ethanol, glycerol, glycercine and
propylene glycol were purchased from (Sigma Aldrich Pvt. Ltd,
New Delhi, India). Isopropyl myristate (IPM) was obtained from
Loba chem. (Mumbai, India). All other chemicals and solvents
were of analytical grade. Double distilled water was prepared
freshly whenever required.

Methods

HPLC analysis of repaglinide: The concentration of RPG
was determined by HPLC method. The system consists of Agilent
1220 c infinity 2012 series with a manual injector, binary pump,
UV detector and chemstation software. The chromatographic
column was TC-C18 (250cm and 4.6mm i.d.) with 5μm particle
size. The mobile phase (filtered through a 0.45μm membrane
filter, degassed by ultrasonication for 15min) 70:30v/v was
methanol and ammonium phosphate buffer (pH 2.5). Injection
volume was 20µl and run time was 10min and flow rate 1.0ml/
min. The column was maintained at ambient temperature and
the eluent was detected at 242nm. The retention time of RPG
was 2.897min at ambient room temperature (Figure 1). The
calibration curve was plotted as concentration of the drug
versus the response at each level. The proposed method was
evaluated by its correlation coefficient and intercept value
calculated in the statistical study. They were represented by
the linear regression equation Y = -15.743+1031.19X, ‘r’ value=
0.9991. Slopes and intercepts were obtained by using regression
equation (y=mx+c) and least square treatment of the results
used to confirm linearity of the method developed. The method
was validated for accuracy, precision, specificity and solution
stability.

Figure 1: Suggestions of the Urban Women.

Solubility studies of RPG in various excipients: The
solubility of RPG in various lipids, surfactants and co surfactants
was verified. An excess amount of RPG was introduced to 2mL of
each excipient and the mixture in a capped cuvette was stirred
in a water-bath at 25 °C for 48h; a vortex mixer was used to
ease the solubilization if necessary. After standing for 24h and
reaching equilibrium at ambient temperature, each cuvette
was centrifuged at 3000rev min⁻¹ for 10min using a centrifuge.
Undisclosed RPG was removed by filtering with a membrane filter (0.45μm). The concentration of RPG was determined by the above-mentioned HPLC analysis.

**Construction of pseudo-ternary phase diagrams:**

Pseudo-ternary phase diagrams were constructed using the water titration method consisting lipid, surfactant and co-surfactant. Surfactant selected were Cremophor RH40, Tween 80, Labrasol, pleural oleique CC 497 and glycerine, pooled with cosurfactants as solubilizer namely (ethanol, propylene glycol, PEG 400 and glycerol). Lipids used were Labrafac, Labrafil, Estol, Maisine, Castor oil, olive oil, soyabean oil, isopropyl myristate (IPM, Capryol 90 and capmul MCM 18). A blend of surfactant with co-surfactant were made having different ratios of 1:2, 1:1, 2:1, 3:1 (i.e. Km, w/w) followed by blending of S_{m} (volumes of each surfactant and cosurfactant) with lipid in a ratio of 9:1 to 1:9 (w/w), then water was added in a drop-wise manner to each lipid- S_{m} mixture under moderate shaking at 37 °C. Observation and evaluation of appearance, dispersibility, droplet size/distribution and zeta potential were recorded. A clear distinction was notified between the microemulsion which was clear and slight blue and the crude emulsion which had a milky white appearance. The quantity of water, lipid, surfactant and cosurfactant added was noted down and calculated. The pseudo-ternary phase diagrams were constructed using sigma plot V.10 software according to the data. The microemulsion regions in the diagrams were plotted and the broader area showed the superior self-microemulsification efficiency.

**Preparation of RPG loaded liquid SMEDDS:**

After performing comparison of plotted phase diagrams, optimal combination of surfactant, co-surfactant and lipid were selected. SMEDDS formulations were further prepared by dissolving RPG into cosurfactant or S_{m} in a glass cuvette, heating at 37 °C in a water-bath or using a vortex mixer (Remi CM-101 PLUS, India) to facilitate the solubilization if necessary. Further this mixture was added to the calculated quantity of lipid into cuvette with continuous mixing until the homogenous mixtures had been formed. Ultimately, the mixture was kept at 25 °C. Formulations of SMEDDS of RPG were coded as (ME1, ME2, ME3, ME4, ME5 and ME6) and were subjected to further characterizations. Detailed compositions of SMEDDS formulations were presented in Table 1.

**Table 1: Formulation composition of RPG SMEDDS.**

| Composition          | ME1   | ME2   | ME3   | ME4   | ME5   | ME6   |
|----------------------|-------|-------|-------|-------|-------|-------|
| Repaglinide (mg)     | 4mg   | 4mg   | 4mg   | 4mg   | 4mg   | 4mg   |
| Labrafil (mg)        | 60.1mg| 64.1mg| 70.2mg| 97.5mg| 94.9mg| 93.1mg|
| Cremophor RH40 (mg)  | 99.6mg| 86.7mg| 92.1mg| 78.6mg| 70.7mg| 73.1mg|
| Propylene glycol (mg)| 86.4mg| 95.3mg| 83.7mg| 69.9mg| 80.4mg| 79.8mg|

**Preliminary in-vitro evaluation of self-microemulsification efficiency:**

Visual examination of SMEDDS concentration was performed after diluting with the medium, in which SMEDDS concentration of 0.2ml was taken in a volumetric flask and 20ml of 0.1 M HCL was added to it in a drop wise manner, temp kept was 37 °C. Dispersibility, appearance, flow ability and time of self emulsification was observed and recorded as per the five grading system presented in Table 2 [9-12]. Effect of pH on self-micro emulsification competence was evaluated by taking 0.1 M HCL as a diluting medium.

**Table 2: Classification of the SMEDDS Formulation in Accordance to Comparative Grades.**

| Composition          | ME1   | ME2   | ME3   | ME4   | ME5   | ME6   |
|----------------------|-------|-------|-------|-------|-------|-------|
| Repaglinide (mg)     | 4mg   | 4mg   | 4mg   | 4mg   | 4mg   | 4mg   |
| Labrafil (mg)        | 60.1mg| 64.1mg| 70.2mg| 97.5mg| 94.9mg| 93.1mg|
| Cremophor RH40 (mg)  | 99.6mg| 86.7mg| 92.1mg| 78.6mg| 70.7mg| 73.1mg|
| Propylene glycol (mg)| 86.4mg| 95.3mg| 83.7mg| 69.9mg| 80.4mg| 79.8mg|

**Characterization of SMEDDS**

Visual observation, phase separation of emulsion: Each formulation of SMEDDS containing RPG was diluted with 200mL of distilled water at 37 °C to check visual appearance, the diluted preparation was vortexes for 1min, and then the mixtures was stored for a period of 24hrs, and phase separation and precipitation observed visually [10]. Mixtures exhibiting a negligible phase separation were used for subsequent studies.

**Determination of self-emulsification time and optical clarity:** The efficiency of self-micro emulsification was estimated by using magnetic stirrer at 100rpm, water and 0.1 NHCl solutions as medium [10-12]. Temperature was maintained at...
The droplet size, studies were conducted after acquiring approval. Drug release experiments were performed with water (1:100). A drop of the diluted microemulsion was used as a visualizing aid. SMEDDS formulations were diluted with deionized water and 0.1 N HCl in a drop-wise manner at 25 °C under gentle shaking [13].

**Droplet size analysis and zeta potential:** The droplet size, size distribution and zeta potential were examined by dynamic light scattering with particle size apparatus (Malvern Zetasizer). Formulations were diluted with deionized water and 0.1 N HCl in a drop-wise manner at 25 °C under gentle shaking [13].

**Cloud point measurement:** This study provides information about stability of formulation system at body temperature. In this formulation was diluted with 50mL of water in beaker and placed on a water bath while gradually increasing the temperature until the diluted formulation turns cloudy [14].

**Thermodynamic stability studies of RPG SMEDDS:** The formulations were subjected to heating cooling cycle (4 °C and 45 °C) and freeze thaw cycle (-21 °C and +25 °C) with storage at each temperature of not less than 48h. For centrifugation stress, the formulations were centrifuged at 3500rpm for 15min and the extent of phase separation was monitored.

**Drug release studies:** Drug release experiments were conducted using a modified dialysis method [15]. At first, the dialysis tubing was soaked in the dialysis medium for 12h at room temperature which was treated at 40 °C before initiation of experiment. The diluted SMEDDS formulation (equivalent to 10mg) was placed in dialysis tubing and clamped on both sides. The secured dialysis tube was allowed to rotate freely in the dissolution vessel of USP type II dissolution apparatus (MODEL TDT-06T) (Electro lab, Mumbai, India) containing 900ml of simulated gastric fluid (SGF, pH 1.2 without enzyme) and simulated intestinal fluid (SIF, pH 6.8 without enzyme) as dialysis medium at 37±0.5 °C and stirred at 50rpm. RPG SMEDDS, conventional tablet (Eurepa, Torrent pharmaceuticals ltd, Repaglinide 2mg) were used for dissolution studies; results were compared with that of pure RPG. Samples were withdrawn at 5, 10, 20, 30, 45 and 60 min and filtered through 0.45µm membrane. An equal volume of fresh dissolution medium was concurrently replenished to maintain the volume constant. The amount of RPG dissolved in the dissolution medium was determined at 5, 10, 20, 30, 45 and 60 min and filtered through 0.45µm membrane.

Animals were checked for glucose level with glucometer (OneTouch® Horizon™ Blood Glucose Monitoring System, Johnson & Johnson) equipped with enzyme (glucose oxidase-peroxidase) loaded strips, for this 1.5µL of blood was taken out with microlitre syringe from tail vain and putted on the strip. Blood glucose levels were consistently monitored upto 3 weeks with a frequency of 0, 3, 7, 14 and 21 days. According to guidelines, animals detected with blood glucose levels more than 300mg/dL upto 3 weeks after the exposure were considered as diabetic, which was further evidenced by the glucometer readings which furnished values above 300mg/dL. Animals which had not shown glucose level above 300mg/dL were casted off. To evaluate the hypoglycemic activity of the prepared formulations, animals were given following treatment schedule. Group 1, as usual served as control with no such administration of RPG in any form, group 2 was administered with pure RPG 2mg/kg (distilled water) and group 3 was administered with conventional/PG 2mg/kg (distilled water dispersion), group 3 was administered with conventional/
marketed RPG formulation (2mg, Eurepa) and group 4 was treated with diluted RPG loaded SMEDD’s (equivalent to 2mg/kg) by oral administration. Further blood samples of all animals were collected by using the method mentioned above, timings were kept at first 0min (pre dosing) followed by gradual gaping upto 24hrs [18]. Glucose levels in collected blood samples were measured using glucometer. Statistical analysis All experimental data was furnished as mean±standard error of the mean (S.E.M), and statistical analysis was executed by using One way analysis of variance (ANOVA).

Results and Discussion

Solubility studies

RPG concentration in a variety of excipients at 25 °C was verified by HPLC. Chremophor RH40 and Propylene glycol provided higher solubility, which were used as surfactant and cosurfactant, and Labrafil was selected as the oil phase. The selection of high soluble components is very important for formulation of the optimal novel emulsion, with existence as a single phase. The solubility of RPG in various vehicles is presented in Table 3 and Figure 2 (mean±SD; n=3)

Table 3: Visible assessments of SMEDDS after dilution and phase separation, precipitation results of formed microemulsions.

| Grades | Dispersibility and Appearance | Time of Self-Microemulsification (min) |
|--------|-------------------------------|----------------------------------------|
| I      | Rapid forming microemulsion, which is clear or slightly bluish in appearance | <1 |
| II     | Rapid forming, slight less clear emulsion, which has a bluish white appearance | <2 |
| III    | Bright white emulsion (similar to milk in appearance) | <2 |
| IV     | Dull, grayish white emulsion with a slight oily appearance that is slow to emulsify | >3 |
| V      | Exhibit poor or minimal emulsification with large oils droplets present on the surface | >3 |

Preparation of pseudo-ternary phase diagrams

Area of microemulsion regions at 37 °C were detected by construction pseudo-ternary phase diagrams using water titration method. Formulations were added with purified water which was utilized as diluting medium. Investigation of appropriate ratio of one excipient to another in the SMEDDS formulation was done. Numerous formulations having different lipid and Km values (ratio of surfactant to co surfactant) were dispersed with water at 37 °C. Phase diagrams of the formulation consisting Labrafil, Cremophor RH40 and Propylene glycol, scaling with different Km values, are presented in Figure 3. Greyish part corresponds to o/w microemulsion existence region. Larger greyish part signifies better self-micro emulsification efficiency which was represented by the formulation having Labrafil as lipid in contrast to other formulations. Verification of most favorable ratio of the excipients in the formulation was also done with the help of phase diagrams. It was found out that when Km value was 1, the microemulsion region had the largest size.
Characterization of SMEDDS

Phase separation and visibility grade: The prepared SMEDDS formulations upon dilution with distilled water in ratio of 1:100 were investigated for phase separation and graded from A to E according to visibility grading system [19]. Formulation ME1, ME2 & ME3 showed no phase separation, precipitation and rapidly formed with a visibility grade A as shown in Table 4, hence were evaluated further.

Table 4: Visible assessments of SMEDDS after dilution and phase separation, precipitation results of formed microemulsions.

| S. No | Parameter          | ME1 | ME2 | ME3 | ME4 | ME5 | ME6 |
|-------|--------------------|-----|-----|-----|-----|-----|-----|
| 1     | Visibility grade   | A   | A   | A   | B   | B   | C   |
| 2     | Phase separation   | X   | X   | X   | +   | +   | +   |
| 3     | Precipitation      | XX  | XX  | XX  | ++  | ++  | ++  |

x: no phase separation; xx: no precipitation; +: phase separation; ++: precipitation.

Determination of emulsification time and optical clarity: In dilution to aqueous medium SMEDDS formulation must disperse rapidly under gentle agitation, evaluation of determined formulation was done in both the media of 0.1 N HCL and pH 6.8 phosphate buffer shown in Table 5 which furnished emulsification time below 60 seconds with fair propensity for emulsification. It was also noticed that with the increment in oil proportion, the emulsification time increased due to larger volume of oil and less surfactant concentration increase in the interfacial tension decreases the rate of emulsification. Optical clarity values demonstrate no much considerable alterations in absorbance values at 0 and 24hrs of dilution Table 5, which clearly indicate stability of formulation at end of 24hrs.
Table 5: Emulsification times of various SMEDDS formulations in 0.1 NHCI and Deionized water and optical clarity values at 0 and 24hrs.

| Formulation Code 0.1 N HCL | Emulsification time | Emulsification time | Optical Clarity |
|----------------------------|---------------------|---------------------|-----------------|
|                            |                     |                     | 0 Hrs           | 24 Hrs         |
| ME1                        | 16                  | Good               | 20              | Good           | 0.773 | 0.689 |
| ME2                        | 19                  | Good               | 21              | Good           | 0.242 | 0.373 |
| ME3                        | 17                  | Good               | 22              | Good           | 0.352 | 0.265 |

Droplet size and zeta potential: SMEDDS formulations subjected to determination of effect of dispersing media on zeta potential, for these formulations were dispersed with deionized water and 0.1N HCl, correspondingly. Minor difference in zeta potential was observed between the two dispersing media at the same dilution. Detailed assessments of optimized formulations are summarized in Table 6.

Table 6: Droplet size, polydispersity index and zeta potential optimized SMEDDS of RPG on dilution with deionized water and 0.1 NHCl.

| Parameter | Formulation |
|-----------|-------------|
| Assessment of SMEDDS Diluted with Deionized Water Grade | ME1 | ME2 | ME3 |
| Droplet size (after 0.15h)nm | 67±3.2 | 72±2.1 | 78±3.6 |
| Polydispersity index (after 0.15h) | 0.161 | 0.242 | 0.125 |
| Zeta potential (after 0.15h)mv | -10.2±0.7 | -7.8±0.8 | -9.6±1.8 |
| Droplet size (after 10h)nm | 71±3.6 | 67±2.7 | 84±3.8 |
| Polydispersity index (After 10h) | 0.11 | 0.08 | 0.115 |
| Zeta potential (after 10h)mv | -9.9±0.8 | -8.1±1.1 | -11.3±3.2 |

| Assessment of SMEDDS Diluted with 0.1 N HCl Grade | ME1 | ME2 | ME3 |
| Droplet size (after 0.15h)nm | 64±2.6 | 89±2.8 | 70±1.9 |
| Polydispersity index (after 0.15h) | 0.056 | 0.089 | 0.078 |
| Zeta potential (after 0.15h)mv | -9.6±1.2 | -7.9±0.9 | -9.9±1.3 |
| Droplet size (after 10h)nm | 69±1.5 | 86±0.8 | 78±1.6 |
| Polydispersity index (After 10h) | 0.15 | 0.181 | 0.112 |
| Zeta potential (after 10h)mv | -10.4±1.5 | -9.3±1.2 | -11.2±1.4 |

Cloud point measurement: Above cloud point temperature formulation clarity turns to cloudiness which is attributed to phase separation and drug precipitation of the emulsion. Cloud point should be above 37 °C since both the drug solubilization and stability of emulsion decreases with phase separation. The cloud point temperatures of different formulations determined were in the range of 64–78 °C. The reason for higher cloud point temperature may be attributed to solubility of drug in oil and surfactant system, optimized ratio of S/CoS and/or surfactants with higher HLB values; this infers good thermal stability of all the tested formulations.

Thermodynamic stability studies: Thermodynamic stability study assists in identification and avoidance of metastable SMEDDS formulations, in which formulation were subjected to different stress tests like centrifugation and freeze–thaw test. Further and frequent analysis was needed not to be executed during storage if prepared SMEDDS formulations could withstand this study. Content of surfactant (Chremophor RH40) in the formulation plays a crucial role in the thermodynamic stability of the formulations. All formulations were found to be stable in this study and were considered for further characterization.

Drug release studies: After oral administration when SMEDDS come across aqueous medium, drug may present in free molecular state or in emulsion form or in solubilized micellar solution. In order to release from emulsion drug should undergo interfacial transport across surfactant layer coated around droplet, which further enters into surrounding aqueous medium by diffusion and convective transport [20]. It indicates when those fine oil droplets are dispersed in the medium and it will not lead to drug diffusion into aqueous medium from oil droplet instantaneously. Under these circumstances, it is necessary to separate free drug molecules from those entrapped in the emulsion droplets or micelles to assess the real drug release pattern [21]. However to facilitate the real drug release pattern the dialysis bag method with a molecular weight cut-off of 12,000 was utilized in drug release studies. The formulations were diluted with SGF & SIF to circumvent the sticking of formulation with the membrane as reported [22]. The drug release pattern of SMEDDS shown in Figure 4 reveals that in contrast to other...
2 formulations along with marketed preparation and pure drug, the highest drug release was observed with ME1 formulation after 24h that could be due to proper compromise between proportions of oil and surfactant in the system. Though the formulation ME2 produced emulsions with better spontaneity and more clarity it showed 40% drug release this may be due to high Co surfactant proportion in the formulation. The formulation ME3 showed less drug release of around 50%, this may be due to higher proportion of oil resulting in larger droplet size, leading to lesser surface area exposed to the medium. The drug release pattern from ME1 formulation followed zero order. Based on the aforementioned results of spontaneity of emulsification, globule size analysis, stability and in-vitro drug release studies the formulation ME1 is considered to be the optimized formulation among the formulations studied.

**Figure 4:** In vitro release profiles of repaglinide from SMEDDS formulations (Mean±SD; n=3).

**Transmission electron microscopy:** The morphology of microemulsion was examined with a transmission electron microscope. The droplet on the microemulsion appears dark with the bright surroundings. TEM photographs (Figure 5a-c) further conformed that the globules are spherical in shape.

**Figure 5:** TEM photograph a ME1 formulation; b ME2 formulation; c ME3 formulation.

**Stability studies:** Samples of RPG SMEDDS were charged on accelerated and long term stability conditions. Chemical and visual observations of samples were shown in Table 7. No significant change in the drug content in the formulations was observed over the period of 3 months at accelerated and long-term stability conditions.
Table 7: Stability Assessment of SMEDDS Formulations.

| Formulations | Drug Content (%) | ME1 | ME2 | ME3 |
|--------------|------------------|-----|-----|-----|
| 40°C±2 °C/75%±5% RH-1 month Drug content (%) | 99.3 | 97.6 | 98.1 |
| Assessment of SMEDDS diluted with Deionized Water Visual Observation Grade | I | I | I/II |
| Droplet size (nm) | 64±2.1 | 90±1.9 | 75±2.9 |
| Polydispersity Index | 0.154 | 0.152 | 0.198 |
| Assessment of SMEDDS diluted with 0.1 NHCl Droplet size (nm) | 65±1.8 | 91±2.1 | 79±3.2 |
| 40°C±2 °C/75%±5% RH-3 month Drug content (%) | 99.6 | 98.3 | 99.1 |
| Assessment of SMEDDS Diluted With Deionized Water Visual Observation Grade | I | I | I/II |
| Droplet size (nm) | 66±2.3 | 95±2.1 | 62±1.2 |
| Polydispersity Index | 0.155 | 0.156 | 0.199 |
| Assessment of SMEDDS diluted with 0.1 NHCl Droplet size (nm) | 65±3.2 | 95±2.1 | 64±1.3 |
| Polydispersity Index | 0.143 | 0.157 | 0.188 |
| 25°C±2 °C/60%±5% RH-3 month Drug content (%) | 99.8 | 98.9 | 99.3 |
| Assessment of SMEDDS Diluted With Deionized Water Visual Observation Grade | I | I | I/II |
| Droplet size (nm) | 66±2.3 | 94±2.3 | 72±1.2 |
| Polydispersity Index | 0.151 | 0.134 | 0.178 |
| Assessment of SMEDDS diluted with 0.1 NHCl Droplet size (nm) | 62±1.3 | 95±3.2 | 77±1.3 |
| Polydispersity Index | 0.21 | 0.121 | 0.142 |

*In vivo Study:* Execution of determination of hypoglycemic activity was done by utilizing STZ-induced experimental diabetes in male Sprague dawley rats in a type 2 diabetes mellitus model. RPG acts by stimulating endogenous insulin secretion during meal by mimicking physiological insulin secretion pattern [23]. A comparative evaluation for hypoglycemic potential between pure RPG, conventional RPG tablets equivalent to 2mg and RPG loaded SMEDD’s was performed by blood glucose level measurement through glucometer strips in diabetic rats. Figure 6 shows blood glucose level readings monitored at different time intervals. Results suggested that at the end of 1hr blood glucose levels in untreated group was 96±1.2mg/dl whereas in Pure RPG drug, marketed formulation and SMEDD’s was 169.2±2.2mg/dl, 177.2±2.4mg/dl and 159.8±0.6 mg/dl respectively. At the end of 8th hour, Pure RPG drug (133.1±3.2mg/dl) and marketed formulation (130.1±0.4mg/dl) showed no decrement in blood glucose levels which indicates their completion of action, whereas RPG loaded SMEDD’s showed still reducing value (101.2±1.2mg/dl) which indicates not only its significant potential in hypoglycemic activity but also prolonged duration of action which may be imputed to elevated rate of absorption and increased plasma drug concentration in contrast to pure RPG drug and marketed formulation (Figure 6). From results, it is concluded that RPG loaded SMEDD’s had shown surpassing performance in contrast to pure RPG and marketed formulation, Hence administrating RPG in the form of SMEDD’s can significantly renders superior hypoglycemic performance and eventually bioavailability Figure 7.

![Figure 6: Blood glucose concentration-time profile of pure drug, RPG loaded SMEDD’s and marketed formulation in diabetes induced rats.](image-url)
Conclusion

An optimized RPG loaded SMEDDS formulation was successfully prepared consisting 24.04% v/v of Labrafil as lipid phase, 39.84% v/v of Chremophor RH40 as surfactant and 34.56% v/v of Propylene glycol as Co Surfactant. Above formulation was optimized on the basis of optimum globule size, zeta potential and Polydispersity index, emulsification and optical clarity, cloud point measurement etc. Results from stability studies at 25 °C±2 °C/60±5% RH & 40 °C±2 °C/75±5% RH indicated stability of RPG SMEDDS and there was no considerable changes in the observed physical parameters. Selected SMEDDS formulation ME1 showed highest % of in-vitro drug release in simulated gastric and intestinal fluid media in contrast to pure RPG drug and marketed RPG formulation. Results of in-vivo showed that developed SMEDDS formulation significant reduction in blood glucose levels in contrast to marketed formulation. Hence it is concluded that SMEDDS can be explored as a potential drug carrier for bioavailability enhancement of RPG and other lipophilic drug(s).

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