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Solid super saturated self-nanoemulsifying drug delivery system (sat-SNEDDS) as a promising alternative to conventional SNEDDS for improvement rosuvastatin calcium oral bioavailability

Hadel A. Abo Enin and Hend Mohamed Abdel-Bar
Pharmaceutics Department, National Organization of Drug Control and Research (NODCAR), Giza, Egypt

ABSTRACT

Objective: This study aims to illustrate the applicability of solid supersaturated self-nanoemulsifying drug delivery system (sat-SNEDDS) for the improvement of rosuvastatin calcium (RC) oral bioavailability.

Methods: Different sat-SNEDDS were prepared by incorporating different ratios of RC into SNEDDS using tween80/PEG400 (77.2%) as surfactant/cosurfactant mixture and garlic /olive oil (22.8%) as oil phase. The prepared systems were characterized viz; size, zeta potential, TEM and stability. Various hydrophilic and hydrophobic carriers were employed to solidify the optimized RC sat-SNEDDS. The influence of the carrier was investigated by SEM, XRPD, DSC, flow properties, in vitro precipitation, drug release and oral bioavailability study.

Results: The adsorption of the stable positively charged nanocarrier RC sat-SNEDDS onto solid carriers provided free flowing amorphous powder. The carrier could amend the morphological architecture and in vitro release of the RC solid sat-SNEDDS. Hydrophobic carriers as microcrystalline cellulose 102 (MCC) showed superior physical characters and higher dissolution rate over hydrophilic carriers as maltodextrin with respective T_{100%} 30 min and 45 min. The rapid spontaneous emulsification, the positively nanosized MCC-sat-SNEDDS improved oral bioavailability of RC by 2.1-fold over commercial tablets.

Conclusion: Solid MCC-sat-SNEDDS combined dual benefits of sat-SNEDDS and solid dosage form was successfully optimized to improve RC oral bioavailability.

1. Introduction

The oral administration is the most common and preferred route for the systemic drug delivery [1]. It possesses several benefits as ease of administration, pain avoidance, accuracy, and patient compliance [2]. The major factor in tailoring oral pharmaceutical delivery systems is the drug aqueous solubility. It influences the drug dissolution rate, its absorption and therefore, its bioavailability.

Self-nanoemulsifying drug delivery system (SNEDDS) is a thermodynamically stable isotropic mixture of oil, surfactant, co-surfactant that converted spontaneously to oil-in-water nanoemulsion with a droplet size less than 200 nm upon dilution under mild agitation [3]. SNEDDS has been employed mainly to enhance the solubility of poorly soluble drugs. It provides a higher interfacial area for drug absorption via micellization and sequentially improves oral bioavailability [4]. In addition, SNEDDS could protect drugs from chemical and enzymatic degradation. Furthermore, it could inhibit P-glycoprotein-mediated drug efflux, enhance lymphatic transport via peyer’s patches, and averts hepatic first pass metabolism [3,5].

Unfortunately, the majority of lipid-based systems as SNEDDS are digested after oral administration, which results in diminishing its solubilization capacity [6]. Moreover, the limited drug solubility in the SNEDDS preconcentrate may lead to administering several dosage form units to the patient, which may affect negatively the patient compliance. Supersaturated SNEDDS (sat-SNEDDS) provides a compelling means to combat the inevitable decrease in free concentration/thermodynamic activity that accompanies solubilization within colloidal species. It also stabilizes the drug in its supersaturated state by inhibiting its precipitation through shifting the position of equilibrium solubility and maintaining a metastable state of the drug in the gastrointestinal tract (GIT) for a sufficient length of time to allow its absorption [7–9]. Nevertheless, conventionally sat-SNEDDS are liquid dosage forms. The later shows some drawbacks as low stability due to susceptibility to temperature and humidity, high production cost, low transportability, leakage, and incompatibility with soft gelatin capsules [10,11].

Solid SNEDDS could be prepared by various methods as adsorption on inert carriers, spray drying, melt extrusion, and spheroidization. Among these techniques, the physical mixing of drug solution or suspension with a solid carrier is considered the easiest and simplest technique [10,12]. After the adsorption of the SNEDDS on the carrier, the obtained powder could enhance drug wettability, surface area to enhance the drug release and bioavailability [13]. Moreover, solid-SNEDDS plays an important role in vanquishing SNEDDS drawbacks. It is highly sought-after due to its ability to robust, scale up and decrease production costs compared to soft capsules as well as keeping all the liquid SNEDDS benefits [14,15].
Rosuvastatin calcium (RC) is a poorly water soluble antihyperlipidemic drug with low oral bioavailability (20%) due to its crystalline nature and extensive hepatic metabolism by oxidation, lactonization, and glucuronidation [16,17]. Hence, enhancing the solubility and bypassing the hepatic metabolism of RC are a desirable approach for improving its therapeutic performance.

Natural oil as olive oil and garlic oil are rich in unsaturated fatty acid and omega 3. They have a significant reduction effect on total cholesterol. They have a beneficial effect in the prevention of hypercholesterolemia, decrease in the tissue cholesterol, and minimization of the atherominal changes in the aorta [18,19].

Therefore, the aim of this study was to prepare RC solid sat-SNEDDS as a prospective drug delivery system to improve RC oral bioavailability. To achieve this ultimate goal different RC sat-SNEDDS was optimized and adsorbed onto different hydrophilic and hydrophobic carriers. The influence of carrier type on in vitro characters of solid sat-SNEDDS was investigated. Furthermore, the in vivo study was conducted to elucidate if solid sat-SNEDDS could improve oral bioavailability of RC over the commercially available tablet.

2. Materials and methods

2.1. Materials

RC was kindly provided by Merck, Spain. Gelatin capsules (size 3) were grant samples from Arabia gelatinea, Egypt. Tween 80 (T80) and polyethylene glycol 400 (PEG 400) were acquired from Merck, India. Microcrystalline cellulose (MCC) 101 and 102, garlic oil, olive oil (highly refined), mannitol, lactose, malodextrin (mal), PEG 4000, PEG 6000, colloidal silica, dextrose were obtained from Sigma, USA. Acetonitrile and methanol (HPLC grade) were purchased from Riedel-de Haen Gmbh, Germany. All other chemicals were of analytical grade and used as received.

2.2. Determination of RC saturated solubility in SNEDDS

Plain SNEDDS was prepared as described in our previous work [20] using garlic oil and olive oil in 1:1 ratio as an oily phase (22.8%, w/w), T80 (58.4%, w/w) as a surfactant and PEG 400 (18.8%) as a cosurfactant in 3:1 ratio at 37°C. RC saturated solubility in water and in SNEDDS was determined at 25°C and 37°C [21]. Briefly, an excess amount of RC was shaken in 5 g of water and SNEDDS, respectively, at each temperature using thermostatic shaker (D3006 Brug Wedal, Germany) for 48 h. Mixtures were centrifuged at 1000 rpm for 10 min then filtered through a syringe filter (Durapore® 0.45 µm, Millipore, USA) [22]. The supernatant was diluted with methanol and the RC concentration was quantified by a previously described HPLC method [22].

2.3. Preparation of RC sat-SNEDDS

The RC sat-SNEDDS was prepared in two consecutive steps as described by Thomas et al. 2012 with some modifications [23]. First, an amount of RC equivalent to its saturated solubility was added to SNEDDS with vigorous shaking at room temperature to produce a clear, isotropic solution. Finally, different amounts of RC exceeded its equilibrium solubility were added to the pre-concentrates system at room temperature. The obtained suspensions were sonicated for 3 min followed by a heating sonication cycle for 60 min at 60°C until obtaining clear solutions. The systems were allowed to cool down at room temperature overnight to produce RC sat-SNEDDS.

2.4. Characterization of RC sat-SNEDDS

2.4.1. The droplet size, polydispersity index (PDI), and zeta potential measurement

The prepared SNEDDS and sat-SNEDDS were diluted 100-fold with distilled water under gentle mixing. The average droplet size, PDI, and zeta potential of the diluted formulae were measured. The measurements were performed at 25°C using a scattered angle of 90° using zetasizer (Malvern Instruments, UK) [24].

2.4.2. Transmission electron microscopy (TEM)

The morphology of the prepared RC sat-SNEDDS was visualized by TEM (JEOL JEM-HR-2100, Japan). The droplets were negatively stained with 1% (w/v) phosphotungstic acid and air-dried before imaging.

2.4.3. Turbidity measurement

One gram of each system was diluted with 25 mL water at 37°C with gentle mixing and turbidity was measured using turbidity-meter (MARTINI 415 instruments, Romania) [25].

2.4.4. Thermodynamic stability studies

Stability studies on the prepared RC sat-SNEDDS formulae were assessed by visual observation for phase separation or precipitation and droplet size measurement after the following conditions [16]. The prepared formulae were subjected to three freeze-thaw cycles, each for 48 h at 25°C followed by another 48 h at −20°C. Moreover, the prepared formulae were centrifuged at 50,000 rpm for 30 min.

2.5. Preparation of solid RC sat-SNEDDS

The optimized RC sat-SNEDDS was converted into free flowing powder by adsorption of sat-SNEDDS onto different solid carriers. Each formula was added in increment ratio and blended with each carrier until the free powder was obtained. The prepared powder was sieved to get the uniform size and stored in a desiccator for further evaluation.

2.6. Characterization of solid RC sat-SNEDDS

2.6.1. Morphological analysis, X-ray powder diffraction (XRPD), and differential scanning calorimetry (DSC)

The morphological architectures of different solid RC sat-SNEDDS formulae were investigated using scanning electron microscope (SEM; FEI, The Netherlands), operating at 10 kV. The sample was fixed on SEM stub using double-sided adhesive tape and then coated with a thin layer of gold.

Pure drug and different solid RC sat-SNEDDS formulae were assessed by XRPD with Cu line as a radiation source. A 40-mA
The angle of repose was determined by measuring the diameter of the cone of powder and calculating the angle of repose, $\alpha$, from the following equation:

$$\tan \alpha = \frac{\text{height of the cone}}{\text{base of the cone}}.$$  \hspace{1cm} (1)

where $C$ is the initial theoretical solubility of the drug and $C_s$ is the saturation solubility of the drug. Solution is considered to be unsaturated when $\sigma < 0$, saturated at $\sigma = 0$ or supersaturated if $\sigma > 0$.

### 2.6.4. In vitro release study

In vitro release study of solid RC sat-SNEDDS formulae, RC sat-SNEDDS (sat-SNEDDS15%), and pure drug (all equivalent to 20 mg RC and filled in hard gelatin capsules, size 3) as well as the commercial product were conducted in simulated gastric fluid (SGF) and SIF (containing 100 U/mL pancreatein) using Dissolution Tester (Pharma Test, Germany) \[28-30\]. Each formula was placed in 100 mL of SGF and SIF, each for 120 min, at 37 ± 0.5°C. The paddle rotation speed was adjusted at 50 ±0.1 rpm. At the predetermined time intervals, aliquots of 1 mL were withdrawn from the release medium and replaced with the same volume. The drug content was estimated using the previously validated HPLC method \[20\].

### 2.6.5. In vivo pharmacokinetic study

The pharmacokinetic and bioavailability studies were done on rats provided by the veterinary service NODCAR (National Organization of Drug Control and Research, Egypt). All animals were handled in agreement with the ethical principles in animal experimentation adopted by the Ethics Committees Accreditation of laboratory Animal Experimentation Care (AAALAC) with protocol no. 25/2002. A simple crossover design on three phases with suitable washout period was applied. Male albino rats, weighing 200 g ±10%, were randomly divided into four groups each containing twelve rats. The animals were kept fasting overnight with free access to water through the experiment. Group I, II, III, and IV received RC commercial tablet suspension in water, pure RC suspension, RC sat-SNEDDS, and solid sat-SNEDDS, respectively. In all groups, RC was administered in a dose of 10 mg/kg/day via intragastric gavages \[31\].

The blood samples (0.25 mL) were collected from the retro-orbital plexus at the predetermined time points (0, 1, 2, 4, 8, 12, and 24 h) into heparinized microcentrifuge tubes. The collected blood samples were immediately centrifuged at 4000 rpm for 10 min at 4°C. The supernatant was separated and stored at −20°C until further analysis.

Plasma drug concentration was quantified by a modified validated method reported previously \[32\]. The samples were assayed using HPLC (Agilent 1100, Germany) equipped with G 1311A quaternary pump and UV detector (VWD-G1314A). A reverse phase C8 column (Thermo, BDS, 250 × 4.6 mm, 5 μm) at 25°C was used and the wavelength was set at 240 nm. The mobile phase consisted of acetonitrile:methanol:water (60:30:10, v/v) with a flow rate of 1 mL/min was used for RC separation. The coefficient of determination ($R^2$) was 0.9991 at a linearity ranged from 0.05 to 10 µg/mL with inter and intra-day precision (expressed as CV%) less than 2%.

The pharmacokinetic parameters including $C_{\text{max}}$ (µg/mL), $T_{\text{max}}$ (h), $AUC_{0-24}$ (µg h/mL), $AUC_{0-\infty}$ (µg h/mL), and relative bioavailability were analyzed by using non-compartmental analysis model. The half-life of elimination $T_{1/2}$ (h), elimination rate constant $K_{el}$ (h$^{-1}$), clearance CI (mL/h), and volume of distribution $V_d$ (mL) were also calculated \[33,34\].
3.1. Saturated solubility of RC in the prepared SNEDDS

RC saturated solubility in SNEDDS at 25°C and 37°C was performed to predict solubilization capacity during preparation and physiological conditions, respectively. RC saturated solubility increased significantly (p < 0.05) from 39 ±2.5 and 49.71 ±3.12 µg/g in water to 35.5 ± 2.01 and 49.87 ±3.54 mg/g after incorporation in SNEDDS at 25°C and at 37°C, respectively.

3.2. Preparation and characterization of RC loaded sat-SNEDDS

Supersaturated SNEDDS are thermodynamically stable SNEDDS that could stabilize high payload of RC in the metastable state in the GIT without precipitation [8,23]. The prepared system can be loaded by RC up to 15% and 20% (w/w) and referred as formula sat-SNEDDS15% and sat-SNEDDS20% respectively.

Table 1 shows that droplet size of all the prepared formulae was less than 200 nm and could be arranged in an ascending order as RC SNEDDS, sat-SNEDDS15%, and sat-SNEDDS20%. Therefore, the particle size is directly proportional to the incorporated amount of RC [35]. Furthermore, the small value of PDI (<0.25) indicates the formation of monodispersed systems [36].

The zeta potential of SNEDDS and sat-SNEDDS formula (sat-SNEDDS15%, sat-SNEDDS20%) was found to be +23.43 ± 2.58, +66.15 ±1.75, and +76.24 ±2.76 mV respectively (Table 1). A significant increase (p < 0.05) in zeta potential is associated with the increase in RC amount. This might be attributed to the calcium moieties of RC [11]. The high positive zeta potential value improves the repulsion force between the system particles and prevents its coalescence to maintain system stability [37]. Moreover, positively charged particles could interact with the negatively charged mucus membrane of the GIT. Therefore, it facilitates RC intestinal absorption by increasing its concentration at the absorption side and subsequently enhancing RC bioavailability [27,38]. Furthermore, it could be noticed that turbidity is directly correlated to RC concentration and formula particle size (Table 1).

TEM observation of RC sat-SNEDDS15% revealed scattered, non-aggregated spherical globules with diameter range in good agreement with the results determined by DLS (Figure 1(a)).

3.3. Stability test

Visual inspection for both sat-SNEDDS15% and sat-SNEDDS20% formulae proves the absence of any change in their appearance as precipitation, phase separation or color alteration. In addition, sat-SNEDDS15% showed a non-significant difference (p > 0.05) in droplet size and zeta potential before and after the stability test. On the contrary, sat-SNEDDS20% shows phase separation and drug precipitation after freeze thaw cycle. Thus, sat-SNEDDS15% was selected for the preparation of solid RC sat-SNEDDS.

3.4. Preparation of solid sat-SNEDDS

Various solid super sat-SNEDDS were prepared using hydrophilic (lactose, mannitol, maltodextrin, PEG 4000, PEG 6000, and dextrose) or hydrophobic carriers (MCC 101 and MCC102). The optimized formulations, which converted into free-flowing powder with high SNEDDS/polymer ratio (1:1, w/w) were selected. Thus, maltodextrin as a hydrophilic carrier (mal-sat-SNEDDS) and MCC 102 (MCC-sat-SNEDDS) as a hydrophobic carrier they were used for further investigations.

3.5. Characterization of solid sat-SNEDDS

The surface architecture of the pure RC, mal-sat-SNEDDS, and MCC-sat-SNEDDS inspected by SEM is illustrated in Figure 1. Pure RC appeared as a typical crystalline form with a smooth-surfaced rectangular crystals shape [Figure 1(b)]. MCC-sat-SNEDDS has a rough surface with a fiber-like shape [Figure 1(c)]. The absence of drug crystalline form indicates complete adsorption of SNEDDS on MCC 102 surface [39]. Unlikely, solid mal-sat-SNEDDS formula appeared as spherical particles with irregular and crushed shape [Figure 1(d)]. These results suggested that the sat-SNEDDS was absorbed in the hydrophilic carrier, maltodextrin, and formed a microsized microcapsule [40]. Thus, the crystalline state of RC was characterized by XRPD and DSC.

Pure RC demonstrated typical diffraction sharp peaks at approximately 13°, 19°, and 21° of 2θ [Figure 2(a)]. The disappearance of those sharp peaks in the case of MCC-sat-SNEDDS and mal-sat-SNEDDS suggested the incorporation of RC in the prepared solid sat-SNEDDS. Moreover, these results indicated the transformation of RC from the crystalline to an amorphous form of RC and [Figure 2(b,c)].

Table 1. Characterization of the prepared rosuvastatin calcium (RC)-loaded self-nanoemulsifying drug delivery system (SNEDDS) and super saturated SNEDDS (sat-SNEDDS).

<table>
<thead>
<tr>
<th>Formula code</th>
<th>RC amount (mg/g)</th>
<th>Particle size (nm) ± SD</th>
<th>PDI ± SD</th>
<th>Zeta potential (mV) ± SD</th>
<th>Turbidity (NTU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC SNEDDS</td>
<td>20</td>
<td>68.00 ± 4.11</td>
<td>0.200 ± 0.020</td>
<td>+23.43 ± 2.58</td>
<td>1.23</td>
</tr>
<tr>
<td>sat-SNEDDS15%</td>
<td>150</td>
<td>158.68 ± 3.02</td>
<td>0.191 ± 0.112</td>
<td>+66.15 ± 1.75</td>
<td>4.65</td>
</tr>
<tr>
<td>sat-SNEDDS20%</td>
<td>200</td>
<td>175.70 ± 4.01</td>
<td>0.175 ± 0.224</td>
<td>+76.24 ± 2.76</td>
<td>11.465</td>
</tr>
</tbody>
</table>

PDI: polydispersity index.
The physical state of RC in the solid sat-SNEDDS has a great influence on the in vitro and in vivo characteristics. The DSC thermograms of the pure RC, RC mal-sat-SNEDDS, and RC MCC-sat-SNEDDS were illustrated in Figure 2(d). Pure RC had an endothermic peak at 105°C with an enthalpy heat which indicated the crystalline form of it [Figure 2(d-1)]. However, No obvious peak for RC was detected in mal-sat-SNEDDS and MCC-sat-SNEDDS [Figure 2(d-2) and 3, respectively], which indicated the adsorption of RC onto the solid carriers and the transformation of RC into the amorphous or molecularly dissolved state.

The angle of repose is a measure of interparticulate friction or resistance to movement existing between particles of a powder. Both formulae show a good angle of repose value. The measured angle of repose of the prepared MCC-sat-SNEDDS was lower than that of mal-sat-SNEDDS with a respective value of 31.77 ±0.20 and 34.17 ±0.21. These results were inconsistent with the previous study, which proved the better flowability of hydrophobic carriers over hydrophilic type [10]. Generally, powders have good flow properties if the angle of repose is lower than 40° [10]. These results suggested the effortlessness of capsule filling procedures of the obtained powder blends.

3.6. In vitro drug precipitation test

In order to assess the degree of super-saturation and susceptibility of the drug to precipitate during release study of sat-SNEDDS and solid sat-SNEDDS, in vitro precipitation study was done. Upon dilution of sat-SNEDDS formulations, the drug might exist in three different forms; free, solubilized in the...
emulsion globules and precipitated form [41]. Filtration of samples allows measuring the concentration of different forms of the drug except for the precipitated form. Pancreatin, which is secreted in the intestine, is the main cause of precipitation of SNEDDS in the GIT through lipolysis process [42,43]. Therefore, SIF was chosen to study in vitro precipitation tendency of the prepared formulae.

From the data presented in Figure 3, it is obvious that after 30 min of mixing sat-SNEDDS with the aqueous medium, the apparent RC concentration decreased by 35.21% from 1.50 to 0.972 ± 0.182 mg/mL. While the apparent RC concentration over the 6 h was found to be 0.248 ± 0.094 mg/mL which is approximately close to the saturation solubility ($C_s$) of RC in the release medium. From these results, the sat-SNEDDS degree of super-saturation ($\sigma$) was calculated and equal 5.05, confirming the presence of RC in supersaturation state [28].

Figure 3 inferred that solid sat-SNEDDS (either using hydrophilic or hydrophobic carrier) were significantly more efficient in preserving the supersaturated state than sat-SNEDDS. Solid carriers as mal and MCC could act as precipitation inhibitors by the interaction with drug molecules by hydrogen bonds [28,44]. Such interaction allows the solid carrier to adsorb onto the drug crystal surface and hinder the aggregation of more drug molecules into the crystal lattice [28,45]. Finally, no significant difference in the degree of supersaturation could be noticed between MCC-sat-SNEDDS and mal-sat-SNEDDS (1.105 and 1.74, respectively). The absence of precipitation signs in all RC formulae may be attributed to the presence of T80 and PEG that increase solubilization capacity and delay digestion effect [4]. In addition, olive oil, which is rich in monounsaturated fat, could form colloidal vesicles and swollen mixed micelles. The later could enhance the drug solubility and might delay the digestion process [44]. Moreover, supersaturation ratio up to 50% improves system stability and prevents its precipitation (sat-SNEDDS15%) [4].

Moreover, the commercial tablet and pure drug released about 49.54% and 32.14% of RC in SIF in the same time period. Statistical analysis revealed nonsignificant difference between RC release from different formulae in SGF and SIF [30].

SNEDDS significantly improves RC dissolution rate over pure drug and commercial tablet ($p < 0.05$) in both release media. This may be attributed to the spontaneous nanoemulsion formation with its solubilization efficiency and small particle size. Figure 4(a) and (b) also shows that approximately 50% of RC was released from MCC-sat-SNEDDS and mal-sat-SNEDDS in 5 min. These results inferred that the adsorption of RC on solid carriers provided a higher surface area and rehabilitated RC from crystalline form to an amorphous form which is reported to improve dissolution rate [46]. Moreover, MCC-sat-SNEDDS had superior dissolution rate than mal-sat-SNEDDS. RC entrapment in MCC-sat-SNEDDS provided a vessel-like shape morphological architecture with a higher surface area for water penetration than sac-like shape in case of mal-sat-SNEDDS as depicted in Figure 1(c,d) [47,48]. In addition, when MCC hydrated, particles tend to adsorb water due to its hygroscopic characters [49]. This process enhances liquid transport into particles, accelerates both diffusion and capillary action and improves the dissolution rate [50,51].

From the previous results, MCC-sat-SNEDDS showed superior physical characters and higher dissolution rate. Therefore, this formula was chosen for in vivo study.

### 3.7. In vitro drug release study

As illustrated in Figure 4(a) and (b), $T_{100\%}$ of RC release were 30, 45, and 90 min for MCC-sat-SNEDDS, mal-sat-SNEDDS, and RC sat-SNEDDS15%, respectively, in both SGF and SIF. On the contrary, only 41.30% and 28.60% of RC was released in 120 min from commercial tablet and pure drug respectively in SGF.

### 3.8. In vivo pharmacokinetic study

Figure 5 illustrates in vivo plasma RC concentration following oral administration of commercial tablet suspension in water, pure drug suspension, sat-SNEDDS15% and MCC-sat-SNEDDS. Pharmacokinetic parameters of RC is calculated and presented in Table 2. Solid RC loaded MCC-sat-SNEDDS showed significantly
and oral absorption. The in vivo results are correlated to those expected according to the solubility and the dissolution results. In addition, MCC is capable of micelle formation in the GIT. Finally, micelles could reduce the uptake of the drug by the mononuclear phagocyte system, allowing longer circulation of the drug in the body and reduced its elimination [54].

The elimination rate constant (Kelu) and clearance (Cl) of RC in both sat-SNEDDS and MCC-sat-SNEDDS are lower than RC commercial tablet and suspension. That may indicate alteration of the drug metabolism [55]. Significant increase in half-life (p < 0.05) could be observed in RC sat-SNEDDS and RC MCC-sat-SNEDDS compared to commercial tablets and pure drug suspension (Table 2), which might be attributed to the avoidance of first-pass hepatic metabolism by intestinal lymphatic transport, which circumvents the liver through increasing the permeability and inhibition of P-glycoprotein efflux mechanism by T80 [56,57].

4. Conclusion
It could be deduced that a novel solid sat-SNEDDS approach of dual benefits of saturated SNEDDS and solid dosage form was successfully optimized to improve RC oral bioavailability. The prepared systems were mainly affected by RC amount incorporated and type of carriers. Solid MCC-sat-SNEDDS is a nano-sized positively charged stable system able to release 100% of RC within 30 min with improved bioavailability over commercial oral tablet by 2.1-fold. Based on the aforementioned results, further clinical pharmacodynamics/pharmacokinetic and toxicological studies are required to investigate the clinical possibility of the prepared system.

5. Expert opinion
Recently, a great effort has been developed toward the development of pharmaceutical products improves patient compliance. This has resulted in a noticeable increase in the number of formulations with easy use and with high bioavailability. Cost-effectiveness also must be sought to provide patient acceptability without impairing the access to patients of new medicinal products. Till now oral delivery is the most popular dosage form. Using saturated self nanoemulsifying drug delivery system is enabling the delivery of dose strengths and release profiles as well as being acceptable for broader patient populations. It can be effective in delivery drugs for more efficiently targeting and treating.

Table 2. Plasma pharmacokinetic parameters after oral administration of RC suspension, commercial tablets, sat-SNEDDS (S1), and solid MCC-sat-SNEDDS formula in rats (mean ± SD, n = 12).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>RC sat-SNEDDS15%</th>
<th>RC MCC-sat-SNEDDS</th>
<th>RC suspension</th>
<th>Commercial tablet®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>17.19 ± 2.14</td>
<td>21.48 ± 3.54</td>
<td>6.97 ± 2.61</td>
<td>4.88 ± 1.87</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.0 ± 0.12</td>
<td>4.36 ± 4.41</td>
<td>2.0 ± 0.21</td>
<td>2.0 ± 0.32</td>
</tr>
<tr>
<td>AUC0–t (µg h/mL)</td>
<td>31.42 ± 1.23</td>
<td>95.74 ± 3.24</td>
<td>45.54 ± 2.54</td>
<td>35.34 ± 1.24</td>
</tr>
<tr>
<td>AUC0–∞ (µg h/mL)</td>
<td>81.74 ± 2.94</td>
<td>25.03 ± 4.92</td>
<td>45.54 ± 2.54</td>
<td>35.34 ± 1.24</td>
</tr>
<tr>
<td>Relative bioavailability (F)</td>
<td>1.79</td>
<td>2.102</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>3.35 ± 0.12</td>
<td>3.67 ± 0.32</td>
<td>2.96 ± 0.18</td>
<td>2.54 ± 0.15</td>
</tr>
<tr>
<td>Kelu (h–1)</td>
<td>0.208 ± 0.09</td>
<td>0.198 ± 0.055</td>
<td>0.234 ± 0.42</td>
<td>0.221 ± 0.20</td>
</tr>
<tr>
<td>Cl (mL/h)</td>
<td>0.049 ± 0.040</td>
<td>0.053 ± 0.024</td>
<td>0.060 ± 0.017</td>
<td>0.051 ± 0.020</td>
</tr>
<tr>
<td>Vd (mL)</td>
<td>0.118 ± 0.039</td>
<td>0.1234 ± 0.029</td>
<td>0.104 ± 0.017</td>
<td>0.114 ± 0.019</td>
</tr>
</tbody>
</table>
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Declaration of interest

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References

Papers of special note have been highlighted as of interest (*) to readers.


* This article gives important reference to describe how the supersaturation could avoid GIT precipitation.


* This article gives important reference to explain the influence of solid carrier on S-MEDDS.


* This article gives important reference to on sat-SNEDDS preparation method.

* This article gives important reference to describe how supersaturated SNEDDS could improve bioavailability of poorly soluble drugs.