Self emulsifying Liquisolid tablets for enhanced oral bioavailability of repaglinide: In vitro and in vivo evaluation

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ABSTRACT

The aim of this work was to enhance dissolution rate and oral bioavailability of repaglinide. This was achieved by development of liquisolid tablet with the liquid component being self emulsifying drug delivery system (SEDDS). Thus SEDDS was prepared using oleic acid as oil and Tween 20 or its mixture with propylene glycol surfactant/cosurfactant system. Formulations containing different oil concentrations were loaded with various amounts of drug and subjected to in vitro evaluation. Optimum formulations were prepared and evaluated as liquisolid tablets. This involved administration to diabetic rats and monitoring blood glucose level. Incorporation of repaglinide in the SEDDS enhanced the dissolution rate of the drug irrespective to the fraction of molecularly dispersed drug, compared to unprocessed drug. Formulation of the optimum system as liquisolid tablet did not change the dissolution pattern of the SEDDS indicating that the drug exists in solution or partially dissolved form. The in vivo study revealed enhancement of the rate and extent of drug absorption after incorporation into the SEDDS, this was evidenced by the rapid onset of action and higher area above the blood glucose versus time curve compared to the unprocessed drug. Overall, the developed system was able to increase the bioavailability of repaglinide.

INTRODUCTION

Rapid intestinal absorption of oral hypoglycemic drugs is required to avoid rapid increase in the concentration of blood glucose after meals (Hong et al., 1998). Repaglinide is one of the newly developed oral hypoglycaemic agents. It is chemically unrelated to sulphonylureas, metformin or acarbose. It produces its oral hypoglycemic effect by stimulating the release of insulin from pancreatic beta-cells by inhibition of potassium efflux resulting in closure of ATP regulated K+ channels. This results in depolarisation of the cell and subsequent opening of calcium channels, leading to influx of calcium into the cells, which causes release of insulin (Gromada et al., 1995). The peak plasma concentration of repaglinide is reached within one hour after oral administration, suggesting rapid absorption. However it possesses low oral bioavailability (56%) which was attributed to poor dissolution (BCS class II) and hepatic first pass metabolism (Wang, 1998; Malaisse et al., 1999; Culy et al., 2001).

Repaglinide has very low water solubility (34 μg/mL at 37°C) and high lipophilicity (logP = 3.97) (Mandic et al., 2006). Accordingly, enhancing repaglinide dissolution can be taken as a tool to improve the bioavailability of this drug. The benefit becomes even greater if the selected technique and/or additive can reduce the first pass effect while increasing the dissolution rate of the drug. Various formulation strategies have been developed to overcome poor dissolution solubility of repaglinide. These include as micellar solubilization (Maheswari et al., 2013), complexation with cyclodextrin (Micolescu et al., 2010), nano structured particles (Purvis et al., 2007) and solid dispersion (Yin et al., 2012). Lipid based systems can provide another alternative. These systems can improve the bioavailability of poorly soluble drug candidates (Pouton, 2006). Lipid based formulations offer a variety of options like solution, suspension, solid dispersion and self emulsifying drug delivery system (SEDDs) (Pouton, 2000).

Self emulsifying formulations compromise isotropic mixture of natural or synthetic oil with lipophilic or hydrophilic surfactant and co-solvents. These systems spontaneously emulsify when exposed to gastrointestinal fluid to form oil in water emulsion or microemulsion (Sarpal et al., 2010).
SEDDS enhance absorption of drugs by increasing the secretion of bile salts (BS) and endogenous biliary lipids. This can increase the solubilization capacity of the gastrointestinal tract and enhance dissolution of the drug at absorptive site. In addition, these systems can promote lymphatic intestinal transport so enhance the bioavailability by reduction of first pass metabolism (Sarpal et al., 2010). Being highly lipophilic (logP = 3.97), repaglinide can take the benefit of formulation as SEEDs. The benefit becomes even greater if such system was incorporated into solid dosage form to increase patient compliance. Liquisolid tablets can help in this direction. The liquisolid tablet formation involves the conversion of liquid lipophilic drugs or drug suspensions or drug solutions in suitable non-volatile solvent systems, into “dry” nonadherent, free-flowing and readily compressible powder by blending the liquid with selected carriers and coating materials (Javadzadeh et al., 2007). Accordingly, the objective of this work was to develop and evaluate self emulsifying tablet of repaglinide with the goal of enhancing its dissolution and bioavailability.

MATERIALS AND METHODS

Materials

Repaglinide was purchased from Zhengrui Pharma and Chemical co, china. Streptozotocin was purchased from Sigma-Aldrich, St. Louis, MO, USA. Acetonitrile (HPLC grade) was obtained from BDH, England. Oleic acid, Tween 20, propylene glycol, potassium dihydrogen phosphate (pharmaceutical grade), sodium hydroxide and hydrochloric acid (analytical grade) were obtained from El Nasr Pharmaceutical Chemical Co., Cairo, Egypt. Avicel pH 102, Aerosil 200 and crosspovidone were kindly provided by Sigma Pharmaceutical Industries, Quesna, Egypt.

Animals

Male albino Wister rats aged 7–8 weeks (150-200 g) were used. Animals were kept in animal house at an ambient temperature of 25 ± 1 °C and 45–55% relative humidity with a 12 h each of dark and light cycle. Animals were fed pellet diet and water ad libitum. The experimental protocol has been approved by the College of pharmacy ethical committee.

Solubility studies

This study was conducted with goal of selecting the best oil for preparation of SEDDS. Excess amounts of drug were added to the oil (oleic acid and isopropyl palmitate and castor oil). This was incubated under continuous magnetic stirring at ambient temperature for 72 hours. The excess drug was removed by centrifugation and the supernatant was suitably diluted with ethanol before determination of the drug content by spectrophotometry at 243nm. The solubility of repaglinide was calculated accordingly.

Construction of phase diagram

Oleic acid was selected as the oil phase as it solubilized the largest amount of the drug. Tween 20 was used as the surfactant as it was able to solubilize the greatest amount of water on titration compared to Tween 80, Tween 60 or Tween 40. This was monitored by preparing mixture of the oil and surfactant at 1:1 weight ratio before titration with water (Alany et al., 2001). The phase diagram was constructed both in presence and absence of propylene glycol which was similarly selected as cosurfactant. On using cosurfactant the surfactant/cosurfactant mixture was prepared at a weight ratio of 1:1. Mixtures of oil with surfactant or surfactant-cosurfactant system was prepared at ratios of 0.5:9.5, 1:9, 1:5:8.5, 2:8, 2.5:7.5, 3.7, 3.5:7.5, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1; oil to surfactant system respectively. These mixtures were vortex mixed before mixing 50 mg with 20 ml 0.1N HCl. The resulting emulsion system was left mixed and left to equilibrate before analysis for transmittance at 600 nm on UV/Visible spectrophotometer.

High pressure liquid chromatography

Drug analysis employed high pressure liquid chromatography (Waters™ 600 controller, USA) equipped with a variable wavelength UV detector (Waters™ 486, USA) and an automatic sampling system (Waters™ 717 Plus Autosampler, USA). Separation was achieved on a reversed phase column 150 mm x 4.6mm (i.d.) C18, μBondapak™, Waters, with an average particle size of 10μm.

The mobile phase was a mixture of 20 mM potassium dihydrogen phosphate (adjusted to pH 4 with phosphoric acid) and acetonitrile (40:60). This was pumped at a rate of 1.3 ml/min with the effluent being detected at 243 nm. The whole system was under computer control with chromatograms being monitored using Millennium software.

The developed method was validated for linearity, selectivity, precision, lower limit of detection (LOD) and lower limit of quantification (LOQ) are 0.033 and 0.102 g/ml, respectively.

Preparation of liquisolid tablet

Determination of the angle of slide of Aerosil 200 and Avicel PH 102

Constant weight of each powder (10 g) was placed at one end of a glass plate. This end was gradually elevated to create an angle with the horizontal plane. The process continued to reach an angle at which the powder was about to slide. This angle was measured and was recorded as the angle of slide. The recorded angle of slide was taken as a measure for the flow properties of the powders. An angle of slide corresponding to 33° was considered as the maximum angle indicating acceptable flow for liquisolid tablet manufacture (Saadia et al., 2008).

Determination of flowable liquid retention potential for Aerosil 200 and Avicel PH 102 (ϕ-value)

Increasing amounts of the liquid SEDDs were mixed well with 10 g of either Aerosil 200 or Avicel PH 102 powder. The angle of slide was determined for each of these mixtures. The ϕ-value of each mixture was calculated using the following equation:
ϕ-value = weight of liquid/weight of solid
The ϕ-values were plotted graphically against the corresponding angles of slide. The ϕ-values corresponding to an angle of slide of 33° was taken as the flowable liquid retention potential of Aerosil 200 (Saadia et al, 2008).

Preparation and mixing of the powders
The amounts of excipients depended on their ϕ-values, as well as liquid load factors (Ll). Having Aerosil 200 as the coating material and Avicel PH 102 as the carrier at a ratio of 1:10, the Ll can be calculated as follow:

\[ L_l = \phi \text{ of the carrier} + \phi \text{ of the coat} (1/R) \]

R is the fraction of the weights of carrier (Q) and coating (q) materials present in the formulation.

The amounts of excipients used to prepare the tablets are related to the amount of liquid medication (W) through the ‘Liquid Load Factor’ (Ll) as shown in the following equation:

\[ L_l = \frac{W}{Q} \]

The selected weight of medicated SEDDS was mixed with the carrier followed by the coating material to produce free flowing powder. This order of mixing was proved to produce the most optimal release rate. Cross povidone was used as superdisintigrant and was included at a concentration of 5% of the tablet weight. The final mixture was compressed using single punch tabletting machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India).

Determination of dissolution rate
The USP paddle method was used for dissolution studies. The dissolution medium was 500 ml of simulated gastric fluid without pepsin (0.1N HCl, pH 1.2). This was maintained at 37 ± 0.1 °C with the rate of stirring being 75 rpm. The drug (4 mg) was added in the form of untreated powder, dispersion in SEDDS or liquisolid tablets. Samples (5ml) were taken at appropriate time intervals (5, 10, 15, 30, 60, 90, 120 min). These were immediately filtered through a 0.45 µm Millipore filter. The dissolution medium was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed by the HPLC method after neutralization with 0.1N sodium hydroxide solution. The study was conducted in triplicates.

Evaluation of liquisolid tablets
Uniformity of weight
The USP weight variation test was conducted by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The allowed percentage deviation is 10%. The tablets meet the USP test if no more than two tablets are outside the limit and no tablet differs by more than twice the limit according to USP.

Tablet friability
The friability of the tablets was measured in the Erweka friabilator (Germany). A pre-weighed tablet sample (30 tablets) was placed in the friabilator and subjected to 100 revolutions. The tablets were carefully deducted and weighed again. The friability was calculated as the percentage loss which should not exceed 1% according to USP.

Drug content
To ensure uniform potency, a content uniformity test was applied by random selection of 30 tablets. At least 10 tablets of them were individually subjected to drug content determination. Each tablet was powdered and dispersed in ethanol with aid of sonication to dissolve the drug. This was filtered before determining the drug content was then determined by HPLC after suitable dilution. The tablets were considered acceptable if the content of each of at least 9 tablets was in the range of 85–115% of the labeled amount of repaglinide. The tenth tablet should not contain < 75% or >125% of the labeled content. If these conditions were not met, the remaining 20 tablets must be analyzed individually and all of them should be within the limit according to USP.

Disintegration test
The test was carried out on six tablets using tablet disintegration tester (Copley Scientific Clowick Quays, United Kingdom) using 0.1 N HCl pH 1.2 as a disintegration media and the time taken for complete disintegration of the tablet was recorded

Induction of experimental diabetes
The animals were fasted overnight and diabetes was induced by a single intraperitoneal injection of a freshly prepared solution of streptozotocin (50 mg/kg body weight) in 0.1 M citrate buffer (pH 4.5) (Hemalatha et al., 2004). The animals were allowed to drink 5% glucose solution to overcome the drug induced hypoglycemia (Balasubramania et al., 2004). On the third day of streptozotocin injection, the rats were fasted for 6 h and blood was withdrawn from the tail vein under light ether anesthesia. The blood glucose level was measured using Bionime GM 100 using Bionime GS 100 glucose oxidase test strip. Rats that had fasting blood glucose levels >250 mg/dl were considered diabetic and were used to monitor the efficacy of repaglinide formulation.

Determination of the hypoglycemic effect of repaglinide
On experiment day rats were given free access to the pellet diet for 15 minutes at the end of which the food was restricted with a free water access being allowed for 2 hours to provide stable blood glucose. The formulations were dispersed in water to produce 2 mg/ml dispersions before orally administering 0.5 ml of the test dispersion to each rat. Blood sample were withdrawn from the tail vein before administration and at different time intervals after administration (15, 30, 60, 120, 180, 240, 300 and 360 minutes). The blood glucose was measured by Bionime GM 100 using Bionime GS 100 test strip. The blood glucose level was plotted as a function of time and the area above the curve was
determined and used for monitoring the efficacy of different formulations. In addition, the amount of reduction in blood glucose level was calculated and plotted as function of time to determine the time corresponding to maximum reduction in blood glucose level (Tmax).

**Statistical analysis**

Statistical analysis employed ANOVA to test for significance.

**RESULT AND DISCUSSION**

**Solubility studies**

Self emulsifying system (SEDDS) was selected as the liquid component of the liquisolid tablet. This selection is based on the previous reports indication that such system is very promising in enhancing the dissolution rate of highly lipophilic drugs like repaglinide (Araya et al., 2005). To select the components of such system, the solubility of the drug was determined in a series of oil. Table 1 presents the solubility of repaglinide in different oils and different SEDDS. With respect to the solubility of the drug in pure oils, oleic acid was shown to solubilize the largest amount of the drug followed by castor oil and isopropyl palmitate. The recorded solubility values for the drug in oleic acid and castor oil are close to the published data (Gangineni et al., 2013). Oleic acid was thus selected as the oily phase of the system. To select the best surfactant, oleic acid was mixed with equal amounts of either Tween 80, Tween 60, Tween 40 or Tween 20. The mixtures were then titrated with water to determine the capacity of the system to solubilize water without separation. Based on this investigation Tween 20 was selected as the surfactant. Propylene glycol was similarly selected as cosurfactant after comparison with ethanol.

<table>
<thead>
<tr>
<th>Solubility (mg/mL)</th>
<th>Oleic acid</th>
<th>20.25 (2.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isopropyl palmitate</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Castor oil</td>
<td>6.5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Oleic acid:tween 20 5:95</td>
<td>14.3 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Oleic acid:tween 20:propylene glycol 5:47.5:47.5</td>
<td>17.98 (2.01)</td>
<td></td>
</tr>
<tr>
<td>Oleic acid:tween 20:propylene glycol 10:45:45</td>
<td>19.27 (1.72)</td>
<td></td>
</tr>
</tbody>
</table>

**Construction of phase diagram**

Self emulsifying systems form fine oil-water emulsions or microemulsions with only gentle agitation, upon their introduction into aqueous media. Surfactant and co surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the emulsion or microemulsion formulation (ME). However, for this process to take place the ratio of oil to the surfactant cosurfactant system should be optimum. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion (Gangineni et al., 2013). Accordingly, the oil was mixed with Tween 20 in absence and presence of propylene glycol. The mixtures were mixed with aqueous phase and the resulting system was characterized visually and spectrophotometry. Table 2 presents the recorded absorbance values after introduction of each mixture to the aqueous phase. All the tested mixtures were able to form SEDDS visually but the turbidemtric studies revealed variation in the absorbance. More turbid system was taken as indication of larger globule size. This was taken into consideration in selection of the SEDDS for preparation of liquisolid tablets with the systems producing less turbid emulsion being considered. Thus the selected formulations comprised oleic acid with Tween 20 at a ratio of 5:95 or 10:90 and oleic acid with Tween 20 and propylene glycol at ratios of 5:47.5:47.5 or 10:45:45. Repaglinide (4 mg) was dispersed in 0.5 gm, 0.25 gm or 0.125 gm of each formulation and the release of drug from each formulation was monitored.

**Drug release from SEDDS**

Figures 3-5 show the release profile of repaglinide from unprocessed powder and from various SEDDS systems in which the drug was dispersed at different concentrations. The calculated dissolution efficiency values are presented in Table 3. The release of repaglinide from the pure unprocessed powder was slow. Only 23% of the labeled amount was dissolved in the first 5 minutes followed by slow release over the time course of the study with a maximum of 71% of the being released after 2 hours. The overall dissolution efficiency of pure drug was only 30.7% (Figure 1 and Table 3). This release pattern is similar to the previously recorded release profile for the same drug (Bhanja et al., 2011). The recorded slow release pattern is considered responsible for the variable and low bioavailability of repaglinide after oral administration (Wang, 1998; Malaisse et al., 1999; Culy et al., 2001; Hardman et al., 2001). Incorporation of the drug in various SEDDS formulations resulted in significant increase in the dissolution rate. This is indicated from the amount of the drug released in the first 5 minutes which ranged 82% in case F2 and
89% in case of F5. The overall dissolution efficiency ranged from 82% to 89.9%. This rapid release pattern is advantageous for poorly soluble drug especially those that are subject to first pass metabolism. This enhanced dissolution pattern can be explained on the bases that the SEDDS is dispersed in the dissolution medium forming microemulsion or coarse emulsion with small droplet size and thus large surface area into which the drug can be dissolved. The high solubility of the drug in the selected components of SEDDS provides another explanation. This differentiates the system from the unprocessed drug which is in crystalline state that dissolves slowly in the dissolution medium. Similar SEDDS based on oleic acid were shown to be efficient in enhancing the dissolution rate of poorly water soluble drugs such as atorvastatin, pioglitazone and simvastatin (Khan et al., 2012; Bhikshapathi et al., 2013; Raja jaya Rao et al., 2014).

Table 3: The composition and dissolution efficiency of each formula.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Weight of formula in which drug dissolved (g)</th>
<th>Dissolution Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Oleic acid:tween20 5:95 0.5 gm</td>
<td>84.06 (5.4)</td>
</tr>
<tr>
<td>F2</td>
<td>Oleic acid:tween20 10:90 0.5gm</td>
<td>85.4 (2.2)</td>
</tr>
<tr>
<td>F3</td>
<td>Oleic acid:tween20:propylene glycol 5:47:5 0.5gm</td>
<td>87.6 (4.3)</td>
</tr>
<tr>
<td>F4</td>
<td>oleic acid:tween20:propylene glycol 10:45:45 0.5gm</td>
<td>85.729 (8.8)</td>
</tr>
<tr>
<td>F5</td>
<td>Oleic acid:tween20 5:95 0.25ml</td>
<td>85.8 (2.9)</td>
</tr>
<tr>
<td>F6</td>
<td>Oleic acid:tween20 10:90 0.25gm</td>
<td>84.5 (10.2)</td>
</tr>
<tr>
<td>F7</td>
<td>Oleic acid:tween20:propylene glycol 5:47:5 0.25gm</td>
<td>88.06 (2.8)</td>
</tr>
<tr>
<td>F8</td>
<td>oleic acid:tween20:propylene glycol 10:45:45 0.25gm</td>
<td>89.9 (3.4)</td>
</tr>
<tr>
<td>F9</td>
<td>Oleic acid:tween20:propylene glycol 5:47:5 0.125gm</td>
<td>82.06 (2.5)</td>
</tr>
<tr>
<td>F10</td>
<td>oleic acid:tween20:propylene glycol 10:45:45 0.125gm</td>
<td>87.8 (3.07)</td>
</tr>
<tr>
<td>F11</td>
<td>Oleic acid:tween20:propylene glycol 5:47:47.5 formulated as tablet 0.125gm</td>
<td>84.4 (2.3)</td>
</tr>
<tr>
<td>F12</td>
<td>oleic acid:tween20:propylene glycol 10:45:45 formulated as tablet 0.125gm</td>
<td>88.07 (1.1)</td>
</tr>
</tbody>
</table>

The dissolution study was conducted using various formulations with the drug being included at different concentration which resulted in presence of the drug either as solution (molecularly dispersed) or as solution with excess drug crystals. To verify this, the fraction of molecularly dispersed drug was calculated for each formulation. This was performed using the following equation (Elkordy et al., 2013):

\[ F_{M} = \frac{C_{i}}{C_{d}} \]

Where \( C_{i} \) is the saturation solubility of repaglinide in the formula, and \( C_{d} \) is the drug concentration used in the formula.

The results of calculations indicated complete solubility of the drug in case of F1, F2, F3, F4, F7 and F8 which have \( F_{M} \) value equal to unity. Other formulations showed variable \( F_{M} \) values which were 0.89, 0.98, 0.56 and 0.6 for F5, F6, F9 and F10, respectively. It is interesting to note that the enhanced dissolution rate was recorded after incorporation of the drug into SEDDS irrespective to the fraction of the molecularly dispersed drug. This can be explained on the bases of the “diffusion layer model” (Spireas et al., 1997) which derived from Noyes-Whitney equation which is described as follow:

\[ D_{R} = \frac{[DA (Cs - C)]}{h} \]

where, \( D_{R} \) is the dissolution rate, \( h \) is the thickness of the stagnant diffusion layer formed by the dissolving liquid around the drug particles, \( D \) is the diffusion coefficient of the drug molecules transported through it, \( A \) is the surface of drug available for dissolution, \( Cs \) is the saturation solubility of the drug in the diffusion layer, and \( C \) is the drug concentration in the bulk of the dissolving medium (Spireas et al., 1997). Having conducted all the dissolution studies at a constant rotational paddle speed (75 rpm) and identical dissolution medium, it can be assumed that the thickness (\( h \)) of the stagnant diffusion layer and the diffusion coefficient (\( D \)) of the drug molecules remain almost identical. Accordingly, the observed higher dissolution rates of repaglinide from SEDDS are due to the significantly increased surface of the molecularly dispersed repaglinide (Javadzadeh et al., 2004). In addition, the saturation solubility of the drug in the microenvironment (\( Cs \)) might be increased in the SEDDS due to the presence of oleic acid, Tween 20 and propylene glycol. The increase in \( Cs \) will create higher concentration gradient and more driving force for drug dissolution. The later explains the efficacy of the SEDDS irrespective to the fraction of the molecularly dispersed drug (Javadzadeh et al., 2004). Formulation of liquisolid tablet

The liquisolid hypothesis suggests that incorporation of drug solution into a carrier material which has a porous surface and closely matted fibers in its interior both absorption and adsorption take place. This means that the liquid will be absorbed initially by internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles takes place. The coating material is also included with its high adsorptive properties and massive surface area to produce the free flowing ability for the liquid solid system (Fahmy and Kassem, 2008). Avicel was thus selected as the carrier with Aerosil being used as the coating system.

**Determination of Flowable Liquid Retention Potential (\( \Phi \)-value)**

Figure 4 shows the relation between the angles of slide and the corresponding \( \Phi \)-values for Aerosil 200 and Avicel pH 102. This relationship was used to calculate the \( \Phi \)-value at 33° which was calculated as 1.5 and 0.073 for Aerosil 200 and Avicel pH 102. These values were used to calculate the LF which was used to calculate the amount of solid to be used in formulation of liquisolid tablet. The details of the components of prepared liquisolid tablets are presented in Table 4.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>LF (°)</th>
<th>Liquid (g)</th>
<th>Avicel (g)</th>
<th>Aerosol (g)</th>
<th>Crosspovidone (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F11</td>
<td>0.228</td>
<td>0.125</td>
<td>0.548</td>
<td>0.054</td>
<td>0.036</td>
</tr>
<tr>
<td>F12</td>
<td>0.228</td>
<td>0.125</td>
<td>0.548</td>
<td>0.054</td>
<td>0.036</td>
</tr>
</tbody>
</table>
**Fig. 1:** The release profiles of repaglinide from pure unprocessed powder and after dispersion of 4 mg of the drug in 0.5 ml of various self-emulsifying drug delivery systems. Formulation details are presented in Table 3.

**Fig. 2:** The release profiles of repaglinide from pure unprocessed powder and after dispersion of 4 mg of the drug in 0.25 ml of various self-emulsifying drug delivery systems. Formulation details are presented in Table 3.
Fig. 3: The release profiles of repaglinide from pure unprocessed powder and after dispersion of 4 mg of the drug in 0.125 ml of various self emulsifying drug delivery systems. Formulation details are presented in Table 3.

Fig. 4: Relationship between the angle of slide and \(\Phi\)-value for Aerosil 200 (a) and Avicel pH 102 (b).

Fig. 5: The release profiles of repaglinide from pure unprocessed powder and liquisolid tablets. Formulation details are presented in Table 3.

Fig. 6: Blood glucose versus time plots, obtained after oral administration of self emulsifying or unprocessed repaglinide formulations to albino rats. Formulation details are in Table 3.
Evaluation of liquisolid tablets

The prepared tablets were found to be of uniform weight with the recorded deviation from the average weight being in the range of 0.52-2.4%. This reflects proper mixing and good flowability of the formulation. The recorded friability values were 0.69% for F11, 0.64 for F12. This is acceptable based on the acceptance criteria of the USP. The drug content was in the range 92 ± 3.7% for F11 and 93.4 ± 3.1% for F12. The disintegration time values were 40 seconds indicating the efficiency of crosspovidone as superdisintegrant.

Drug release from liquisolid tablet

Figure 5 shows the release profile of repaglinide from the prepared self emulsifying liquisolid tablets and the unprocessed drug powder. The prepared tablets employed self emulsifying liquid containing Tween 20 with propylene glycol as surfactant cosurfactant mixture with oleic acid being included at a concentration of either 5 (F11) or 10% w/w (F12). The release data indicates rapid drug release pattern from the liquisolid tablet. The amounts of drug released in the first 5 minutes were 86 and 92.7% of the labeled amounts for F11 and F12, respectively. These values are significantly higher than that released from the unprocessed powder after the same period of time (23%). The dissolution efficiency values were 84.4 88.07% for F11 and F12 which are significantly higher than that recorded with the unprocessed powder (30.7%) (Table 3). The recorded release data of the drug from the liquisolid tablets were comparable to that recorded for the corresponding liquid self emulsifying formulation (F11 versus F9 and F12 versus F10, Table 3 and Figures 3 and 5). This release pattern indicates that absorption and adsorption of the drug onto the solid matrix with subsequent compression did not affect the release of the drug. It is important to note that the presence of superdisintegrant in the tablet formulation was adequate resulting in fast disintegration (40 seconds) which allowed rapid dissolution of the drug. Such short disintegration time eliminated the effect of compression. Similar data was recorded for carbidilol which resulted in similar release pattern from the liquid formulation and the corresponding liquisolid system (Mahmoud et al., 2009) and ibuprofen (Kang et al., 2011).

In vivo evaluation of the self emulsifying liquisolid formulation

Monitoring the pharmacodynamic marker par parameters can be taken as a tool to for evaluation of the in vivo performance of different classes of drugs. Being an oral hypoglycemic agent, repaglinide decreases the plasma glucose level. Accordingly, the plasma glucose level was monitored and was taken as a parameter for evaluation of the in vivo performance of repaglinide from SEDDS compared with the unprocessed drug. The drug was thus administered and the plasma glucose level was monitored as a function of time. This was plotted to produce the profile of plasma glucose concentration. The area above this curve was calculated and used for comparison. In addition, the amount of reduction in blood glucose level was calculated at different time intervals and was used as another parameter for comparison. The blood glucose versus time plots are shown in Figure 6 and the calculated parameters are presented in Table 5. Administration of the unprocessed drug resulted in a reduction in the blood glucose level with the onset of action starting 2 hours after administration of the drug. The area above the blood glucose versus time plots was calculated to be 26727 mg minute/dl (Figure 6 and Table 5). Administration of repaglinide in the form of SEDDS resulted in a significant reduction in the blood glucose level with the onset of action starting 15 minutes after administration of the drug. This was the same in cases of both F11 and F12. The area above the curve was calculated to be 72811 and 74831 mg minute/dl for F11 and F12, respectively (Figure 6 and Table 5). Statistical analysis of the data revealed significant enhancement of the pharmacodynamic effect of repaglinide after administration as SEDDS compared with the control (unprocessed drug). There was no significant difference between F11 and F12 with respect to the onset of action or the area above the curve (p > 0.05). Taking into consideration the fact that the absorption of repaglinide is limited to dissolution rate, the recorded onset of action of the pure drug (2 hours) can be attributed to the slow dissolution of the drug. It is interesting to note that the peak plasma concentration of the drug was achieved one hour after administration to human when administered before meal (Wang, 1998; Malaisse et al., 1999). The superiority of the SEDDS formulation over the pure drug with respect to the onset of action and area above the curve indicate that the formulated developed liquisolid system can increase both the rate and extent of drug absorption. The increase in the rate of drug absorption compared to the pure drug suggests rapid dissolution rate of the drug. This provides good correlation between the in vitro and in vivo data. This correlation is based on the fact that in vitro release studies showed rapid dissolution of drug from liquisolid systems with the unprocessed drug showing slower dissolution rate. This was reflected in the recorded onset of action. The increase in the extent of action can suggest increased bioavailability of the drug after administration in the form of SEDDS. Taking into consideration the fact that the low bioavailability (56%) of repaglinide is attributed to poor dissolution and hepatic first pass metabolism (Wang, 1998; Malaisse et al., 1999; Culy et al., 2001), the recorded enhancement can be explained on the bases of enhanced dissolution and reduced presystemic metabolism. The enhanced dissolution has been already documented from the in vitro data. With respect to the reduction of the presystemic metabolism, it can be achieved from rapid absorption of large number of drug molecules which was dissolved rapidly. This can provide a chance for more drug to escape from the metabolizing enzymes due to possible saturation of the enzyme system. Another possible reason for reduction of the presystemic metabolism can depend on the ability of the SEDDS to deliver the drug via the lymphatic pathway bypassing the liver metabolism (Sarpal et al., 2010). Previous studies recorded the success of liquisolid system and SEDDS for enhanced dissolution and bioavailability of lipophilic drugs like simvastatin, gliclazid and famotidine. The authors reported good in vitro in vivo correlation like the current study (Patil et al., 2007; Fahmy and Kassem., 2008; Nipun and
Isam., 2013). Overall the recorded data reveal successful development of liquisolid system for enhanced dissolution and oral bioavailability of repaglinide.

Table 5: The reduction in blood glucose level and the area above the blood glucose level versus time curve (AAC), obtained after oral administration of different repaglinide formulations to diabetic rats.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F11</th>
<th>F12</th>
<th>Pure drug</th>
<th>No change</th>
<th>60.25 (21.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>58.25 (17.7)</td>
<td>68.5 (17.6)</td>
<td>No change</td>
<td>42.75 (13.9)</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>69.5 (17.7)</td>
<td>48.62 (9.7)</td>
<td>No change</td>
<td>25.375 (16.7)</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>45.7 (7.5)</td>
<td>57 (12.5)</td>
<td>No change</td>
<td>15.25 (16.7)</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>39.75 (18.7)</td>
<td>38.75 (22.7)</td>
<td>60.25 (21.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>25.375 (16.7)</td>
<td>13 (4.3)</td>
<td>42.75 (13.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td>No change</td>
<td>15.25 (16.7)</td>
<td>10.25 (22.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>34.5 (10.8)</td>
<td>9.75 (18.2)</td>
<td>23.125 (12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>360</td>
<td>8.125 (28)</td>
<td>2.875 (11)</td>
<td>25.375 (16.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAC</td>
<td>72811 (7004)</td>
<td>74831 (7504)</td>
<td>26727 (5357)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values between brackets are S.E.M (n = 8).

CONCLUSION

Incorporation of repaglinide into self-emulsifying drug delivery system enhanced the dissolution rate of the drug compared to the unprocessed drug. The dissolution enhancement was recorded irrespective to the fraction of molecularly dispersed drug. Formulation of such system into liquisolid tablet did not efficiency of SEDDS with enhanced dissolution being preserved. SEDDS was able to enhance both the rate and extent of drug absorption with possible avoidance of the presystemic metabolism.

REFERENCES


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