

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

Gamal M El Maghraby¹, Mohamed A Osman¹, Houyda E Abd-Elrahman^{1*}, Alaa E. Elsis²

¹Department of Pharmaceutical Technology, College of Pharmacy, University of Tanta, Tanta, Egypt.

²Department of Pharmacology and Toxicology, College of Pharmacy, University of Tanta, Tanta, Egypt.

ARTICLE INFO

Article history:

Received on: 16/06/2014

Revised on: 07/07/2014

Accepted on: 28/07/2014

Available online: 27/09/2014

Key words:

Repaglinide bioavailability;
nanoemulsion; diabetes;
blood glucose; repaglinide
metabolism

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).

* Corresponding Author

Email: houydaelshenawy@yahoo.com

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 ($\log P = 3.97$), repaglinide can take the benefit of formulation as SEDDs. 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 (Javadzdefh *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 Chemicals 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, μ Bondapak™, Waters, with an average particle size of 10 μ m.

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 μ 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 (L_f). Having Aerosil 200 as the coating material and Avicel PH 102 as the carrier at a ratio of 1:10, the L_f can be calculated as follow:

$L_f = \phi$ of the carrier + ϕ of the coat (1/R) (Saadia *et al.*, 2008).

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' (L_f) as shown in the following equation:

$L_f = W/Q$.

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 superdisintegrant and was included at a concentration of 5% of the tablet weight. The final mixture was compressed using single punch tableting 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 (Balasubramaian *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 1: Solubility of repaglinide in pure oils and self emulsifying drug delivery systems.

	Solubility (mg/mL)
Oleic acid	20.25 (2.75)
Isopropyl palmitate	0.94
Castor oil	6.5 (1.5)
Oleic acid:tween 20 5:95	14.3 (4.6)
Oleic acid:tween 20 10:90	15.87 (4.13)
Oleic acid:tween20:propylene glycol 5:47.5:47.5	17.98 (2.01)
Oleic acid:tween 20:propylene glycol 10:45:45	19.27 (1.72)

Values between brackets are S.D. (n = 3).

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 turbidimetric 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.

Table 2: Absorbance of oil surfactant system in absence and in presence of co-surfactant.

Oil surfactant system	Absorbance in absence of co-surfactant	Absorbance in presence of co-surfactant
5:95	0.013	0.003
10:90	0.027	0.238
15:85	0.692	0.631
20:80	0.840	1.084
25:75	1.340	1.450
30:70	1.394	1.310
35:65	1.337	1.217
40:60	1.851	1.102
50:50	1.646	1.127
60:40	1.002	1.387
70:30	0.384	0.817
80:20	1.7	0.596
90:10	1.385	0.483

Note: surfactant to: co-surfactant ratio is 1:1, absorbance less than 0.1 is considered microemulsion, absorbance more than 0.1 is considered coarse emulsion.

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.

Formula	Weight of formula in which drug dissolved	Dissolution Efficiency
F1 Oleic acid:tween20 5:95	0.5 gm	84.06 (5.4)
F2 Oleic acid:tween20 10:90	0.5gm	85.4 (2.2)
F3 Oleic acid:tween20:propylene glycol 5:47.5:47.5	0.5gm	87.6 (4.3)
F4 oleic acid:tween20:propylene glycol 10:45:45	0.5gm	85.729 (8.8)
F5 Oleic acid:tween20 5:95	0.25ml	85.8 (2.9)
F6 Oleic acid:tween20 10:90	0.25gm	84.5 (10.2)
F7 Oleic acid:tween20:propylene glycol 5:47.5:47.5	0.25gm	88.06 (2.8)
F8 oleic acid:tween20:propylene glycol 10:45:45	0.25gm	89.9 (3.4)
F9 Oleic acid:tween20:propylene glycol 5:47.5:47.5	0.125gm	82.06 (2.5)
F10 oleic acid:tween20:propylene glycol 10:45:45	0.125gm	87.8 (3.07)
F11 Oleic acid:tween20:propylene glycol 5:47.5:47.5 formulated as tablet	0.125gm	84.4 (2.3)
F12 oleic acid:tween20:propylene glycol 10:45:45 formulated as tablet	0.125gm	88.07 (1.1)
Pure drug	NA	30.7 (4.1)

Values between brackets are S.D. (n = 3).

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):

$$F_M = C_L / C_d$$

Where C_L 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:

$$D_R = [DA (C_s - C)] / h$$

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, C_s 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 (C_s) might be increased in the SEDDS due to the presence of oleic acid, Tween 20 and propylene glycol. The increase in C_s 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 lquisolid tablet

The lquisolid 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 lquisolid 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 (Φ -value)

Figure 4 shows the relation between the angles of slide and the corresponding Φ -values for Aerosil 200 and Avicel pH 102. This relationship was used to calculate the Φ -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 lquisolid tablet. The details of the components of prepared lquisolid tablets are presented in Table 4.

Table 4: The liquid load factor (LF) and composition of lquisolid tablets.

Formulation	LF	Liquid (g)	Avicel (g)	Aerosil (g)	Crosspovidone (g)
F11	0.228	0.125	0.548	0.054	0.036
F12	0.228	0.125	0.548	0.054	0.036

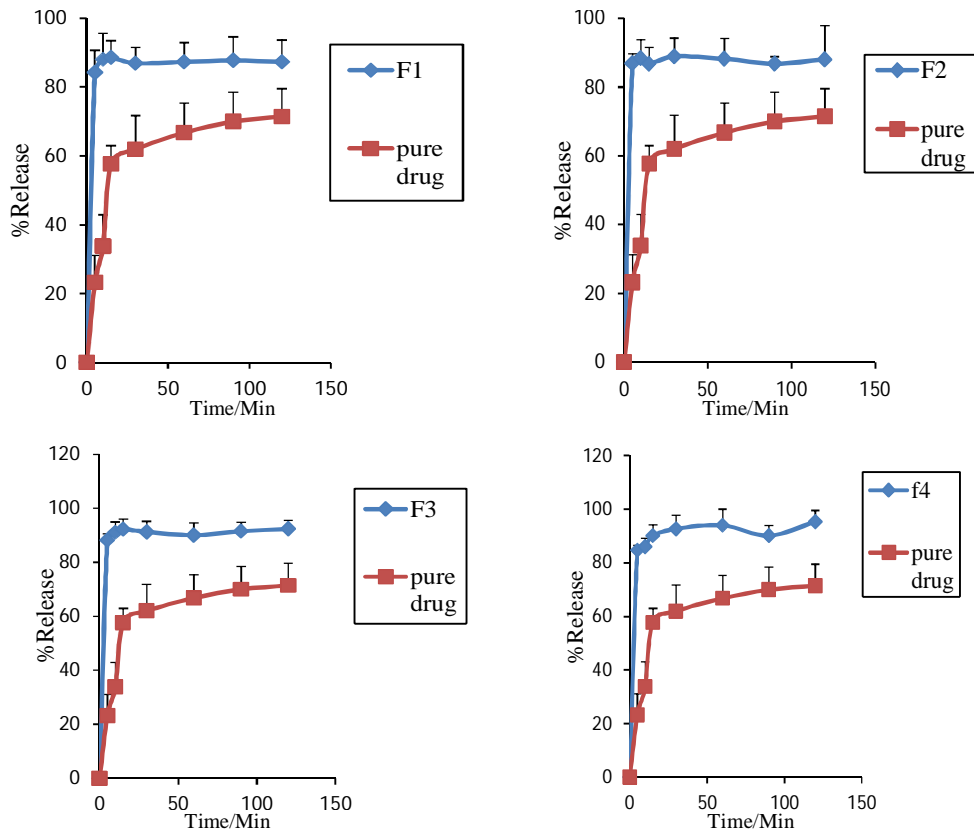


Fig. 1: The release profiles of repaglinide from pure unprocessed powder and after dispersion of 4 mg of the drug in 0.5 ml of various self emulsifying drug delivery systems. Formulation details are presented in Table 3.

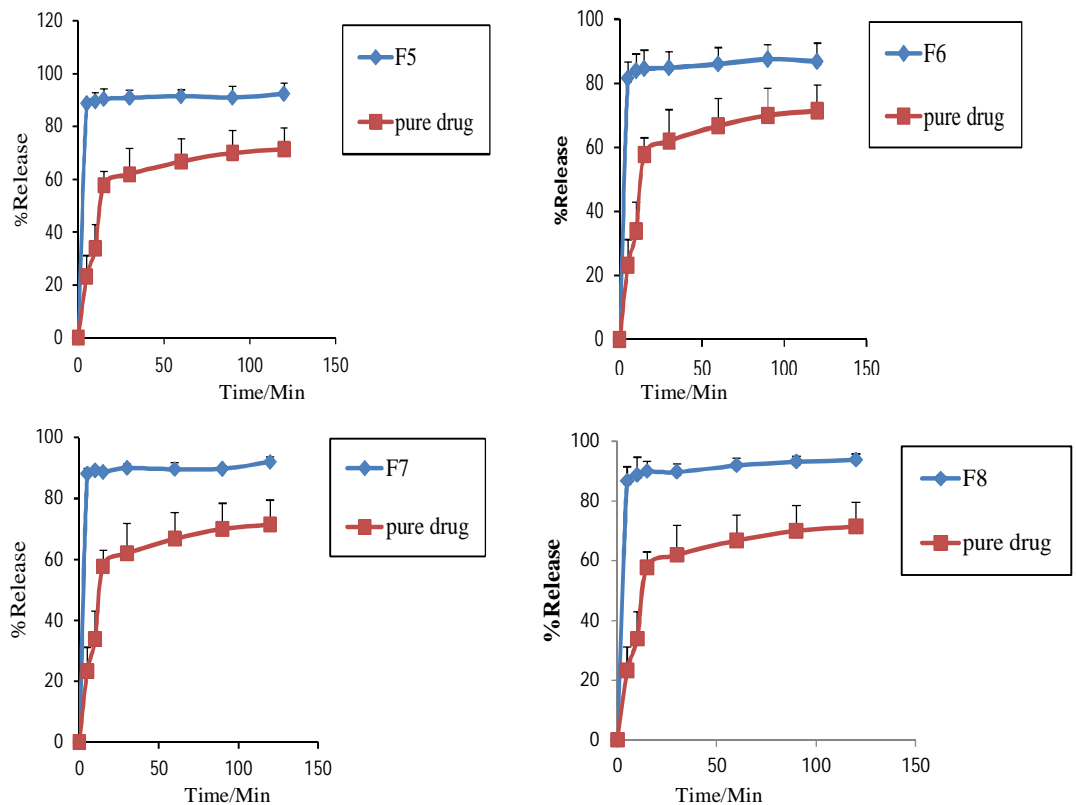


Fig. 2: The release profiles of repaglinide from pure unprocessed powder and after dispersion of 4 mg of the drug in 0.25 ml of various self emulsifying drug delivery systems. Formulation details are presented in Table 3.

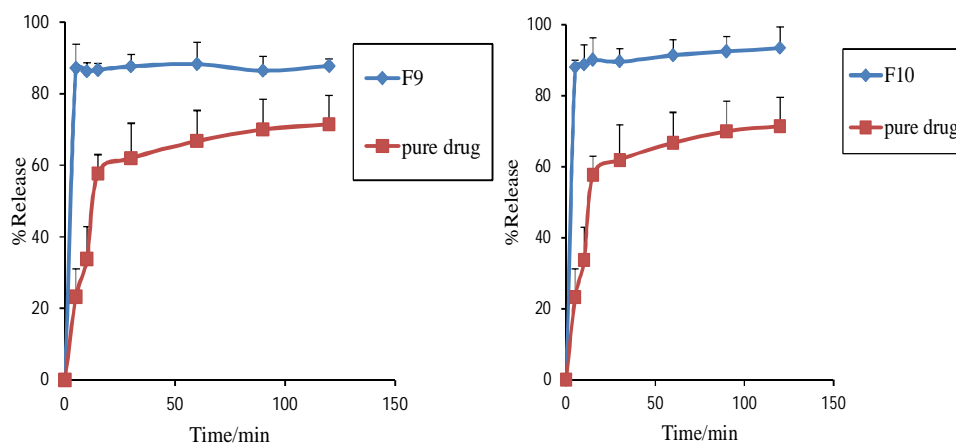


Fig. 3: The release profiles of repaglinide from pure unprocessed powder and after dispersion of 4 mg of the drug in 0.125 ml of various self emulsifying drug delivery systems. Formulation details are presented in Table 3.

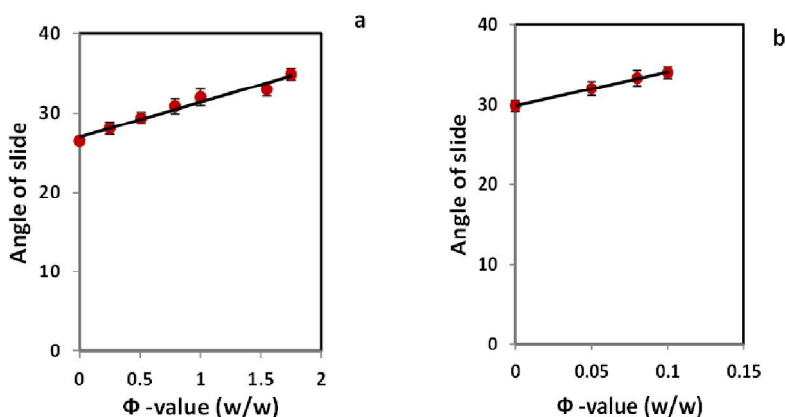


Fig. 4: Relationship between the angle of slide and ϕ -value for Aerosil 200 (a) and Avicel pH 102 (b)

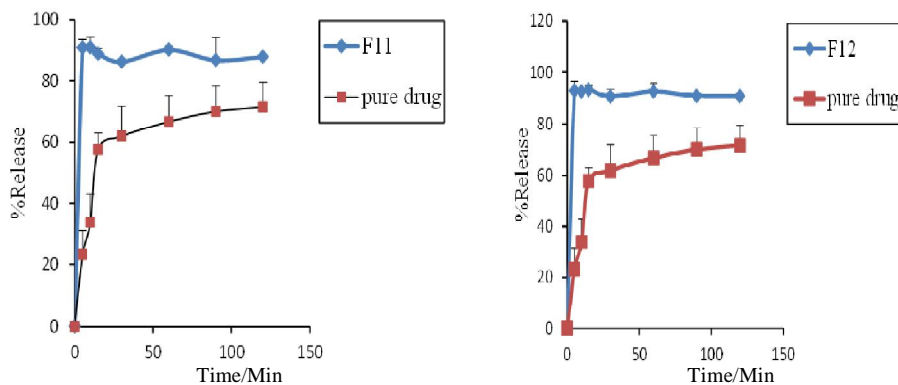


Fig. 5: The release profiles of repaglinide from pure unprocessed powder and liquisolid tablets. Formulation details are presented in Table 3.

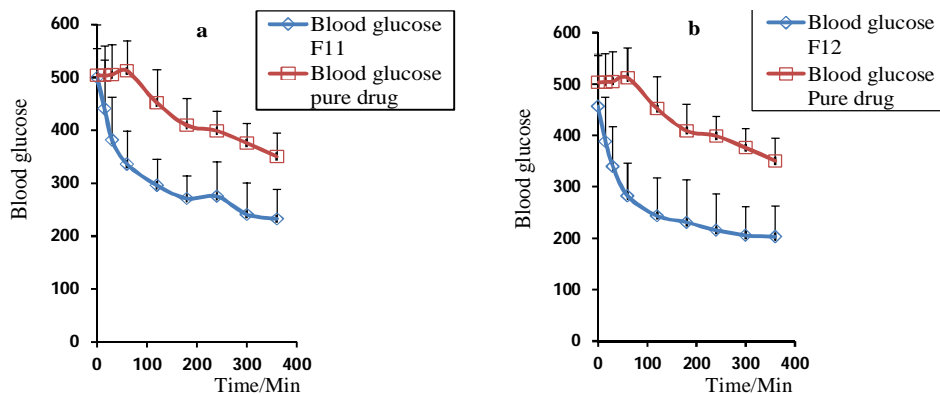


Fig. 6: Blood glucose versus time plots, obtained after oral administration of self emulsifying or unprocessed repaglinide formulations to albino rats. Formulation details are in Table 3.

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 $92 \pm 3.7\%$ for F11 and $93.4 \pm 3.1\%$ for F12. The disintegration time values were 40 seconds indicating the efficiency of croscopolvidone 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 and 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 carvedilol 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 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

Islam., 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.

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

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

Alany R.G, Tucker I.G, Davies N.M, Rades T. Characterizing colloidal structures of pseudoternary phase diagrams formed by oil/water/amphiphile systems. *Drug Dev. Ind. Pharm*, 2001; 27:31-38.

Araya H, Nagao S, Tomita M, Hayashi M. The novel formulation design of self emulsifying drug delivery system (SEDDS) Type O/W microemulsion: enhancing effects on oral bioavailability of poorly water soluble compound in rats and beagle dogs. *DrugMetab.Pharmacokinet*, 2005;20(4):214-256.

Balasubramaian R, Kasiappan R, Vengidusamy N, Muthusamy K, Sorimuthu S. Protective effect of macrocyclic binuclear oxovanadium complex on oxidative stress in pancreas of streptozotocin induced diabetic rat. *Chemico-Biological Interaction*, 2004; 149: 9-21.

Bhanja S.B, Ellaiah P, Nayak B.S, Mahapatra D.K, Sahu A, Padhy S.K, Panigrahi B.B. Enhancement of dissolution properties. Preparation and evaluation of immediate release tablets of poorly soluble drug repaglinide. *International Journal Of Pharmacy&Technology*, 2011; 3:2961-2991.

Bhikshapathi D, Madhukar P, Kumar, B.D, Kumar I G.A. Formulation and characterization of pioglitazone HCl self-emulsifying drug delivery system. *Scholars Research Library Der Pharmacia Lettre*, 2013; 5(2):292-305.

Culy C.R, Jarvis B. Repaglinide, a review of its therapeutic use in Type 2 diabetes mellitus. *Drugs*, 2001; 61(11):1625-1660.

Elkordy A.A, Tan X.N, Essa E.A. Spirolactone release from liquisolid formulations prepared with Capryol™ 90, Solutol HS-15 and Kollicoat SR 30 D as non-volatile liquid vehicles. *European Journal of Pharmaceutics and Biopharmaceutics*, 2012; 83; 203-223.

Fahmy R.H, Kassem M.A. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: In vitro and in vivo

evaluation. *European Journal of Pharmaceutics and Biopharmaceutics*, 2008; 69: 993-1003.

Gangineni R, Dontha P, Konda S.K. Formulation, Characterization and Evaluation of Self Emulsifying Drug Delivery System of Repaglinide. *JPR:BioMedRx: An International Journal*, 2013; 1(7): 665-672.

Gromada J, Dissing S, Kofod H, Frokjaer-Jensen J. Effects of the hypoglycemic drugs repaglinide and glibenclamide on ATP-sensitive potassium channels and cytosolic calcium levels in B TC3 cells and rat pancreatic beta cells. *Diabetologia*, 1995; 38:1025-32.

Hemalatha S, Wahi A.K, Singh P.N, Pnhansouria J. Hypoglycemic activity of Withania Coagulans Dunal in streptozotocin induced diabetic rat. *J of ethnopharmacology*, 2004; 93:261-264.

Hong S.S, Lee S.H, Lee Y.j, Chung S.J, Lee M.H, Shim C.K. Accelerated oral absorption of gliclazide in human subjects from a soft gelatin capsule containing a PEG 400 suspension of gliclazide. *J. Control Rel*, 1998; 51:185-192.

Javadzadeh Y, Siahi-Shadbad M.R, Barzegar-Jalali M, Nokhodchi A. Enhancement of dissolution rate of piroxicam using liquisolid compacts. *Il Farmaco*, 2005; 60:361-365.

Javadzadih Y, Stahi M.R, Asnaashari S, Nokhodchi A. Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties. *Acta Pharm*, 2007; 57:99-109.

Kang M.J, Jung S.Y, Song W.H, Park J.S, Choi S.U, Oh K.T, Choi H.K, Choi Y.W, Lee J, Lee B.J, Chi S.C. Immediate release of ibuprofen from Fujicalin®-based fast-dissolving self-emulsifying tablets. *Drug Dev Ind Pharm*, 2011; 37:1298-1305.

Khan F, Islam Md.S, Roni M.A, Reza U. J. Systematic Development of Self-Emulsifying Drug Delivery Systems of Atrovastatin with Improved Bioavailability Potential. *Sci Pharm*, 2012; 80:1027-1043.

Kumar V.K, Devi M.A, Bhikshapath D.V.R.N. Development of solid self emulsifying drug delivery system containing efavirenz: In vitro and In vivo evaluation. *International Journal of Pharma and Bio Sciences*, 2013; 4:869-882.

Maheswari P.D, Rambhau D, Narasu M.L. Micellar Solubilization in the Formulation Development of Poorly Soluble Naproxen. *Pharmaceut Reg Affairs*, 2013; 2:1-12.

Mahmoud E.A, Bendas, E.R, Mohamed M.I. Preparation and Evaluation of Self-nanoemulsifying Tablets of Carvedilol. *AAPS PharmSciTech*, 2009; 10:183-192.

Malaisse W. Repaglinide, a new oral antidiabetic agent: a review of recent preclinical studies. *Eur J Clin Invest*, 1999; 29: 21-29.

Mandic Z, Gabelica V. Ionization, lipophilicity and solubility properties of repaglinide. *J.Pharm.Biomed. Anal*, 2006; 41:866-871.

Micolescu C, Arama C, Monciu C. Preparation and characterization of inclusion complex of repaglinide with β -cyclodextrin, hydroxypropyl β -cyclodextrin and randomly methylated β -cyclodextrin. *Farmacia*, 2010; 58(5):620-628.

Nipun T.S, Ashrafal Islam S.M. SEDDS of gliclazide: Preparation and characterization by in-vitro, ex-vivo and in-vivo techniques. *Saudi Pharmaceutical Journal*, 2013; In Press.

Patil P, Patil V, Paradkar A. Formulation of a self-emulsifying system for oral delivery of simvastatin: in vitro and in vivo evaluation. *Acta Pharm*, 2007; 57:111-122.

Pouton C.W. Formulation of poorly water soluble drug for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *Eur J Pharm Sci*, 2006; 29:278-87.

Pouton, C.W. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. *Eur J Pharm Sci*, 2000; 11:S93-s98.

Purvis T, Mattucci M.E, Crisp M.T, Johnston K.P, Williams R..O. Rapidly dissolving repaglinide powders produced by the ultra-rapid freezing process. *AAPS PharmSciTech*, 2007; 8(3):E1-E9.

Raja jaya Rao Y, Divya sree K, Divya P. A Novel Technical Development and Evaluation of Self Emulsifying Drug Delivery System of Simvastatin. *International Journal of Research In Pharmacy and Chemistry*, 2014; 4(1):15-25.

Sarpal K, Pawar Y.B, Bansal A.K. Self-Emulsifying Drug Delivery System: A Strategy to Improve Oral Bioavailability. *Current Research and Pharmaceuticals Sciences*, 2010; 11:342-349.

Spireas S, Assadu S, Grover R. In Vitro Release Evaluation of Hydrocortisone Lquisolid Tablets. *Journal of Pharmaceutical Sciences American Pharmaceutical Association*, 1998; 7: 867-872.

Tayel S.A, Soliman II, Louis D. Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique. *Eur J Pharm Biopharm*, 2008; 69:342-7.

Wang F.E.I. Focus on Repaglinide: an oral hypoglycemic agent with a more rapid onset and shorter duration of action than the sulfonylureas. *Formulay*, 1998; 33: 25-30.

Yin L.F, Huang S.J, Zhu C.L, Zhang S.H, Zhang Q, Chen X.J., Liu Q.W. In vitro and in vivo studies on a novel solid dispersion of repaglinide using polyvinylpyrrolidone as the carrier. *Drug Dev Ind Pharm*, 2012; 38(11):1371-80.

How to cite this article:

Gamal M El Maghraby, Mohamed A Osman, houyda E Abd-Elrahman. Self emulsifying Lquisolid tablets for enhanced oral bioavailability of repaglinide: In vitro and in vivo evaluation. *J App Pharm Sci*, 2014; 4 (09): 012-021.