Research Article

Design and Characterization of Self Emulsifying Drug Delivery System of Repaglinide

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ABSTRACT

The aim of the present investigation was to develop and characterize Repaglinide based self emulsifying drug delivery system (SEDDS) to enhance the oral absorption of Repaglinide by improving its solubility and dissolution rate. SEDDS are the isotropic mixtures of oil, surfactant, co-surfactant and drug that form oil in water microemulsion when introduced into aqueous phase under gentle agitation. After self- dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. Repaglinide is an oral hypoglycemic agent administered orally has absolute bioavailability of only 56% due to the poor aqueous solubility (0.03 mg/ml). Solubility of Repaglinide was evaluated in various careers that included oils, surfactants, and co-surfactants. Pseudoternary phase diagrams were constructed to identify the self-micro emulsion region. Eight self micro emulsifying formulations were prepared using olive oil, Tween 80, PEG 400 in various proportions. Liquid SEDDS formulation was converted into free flowing powder by absorbing onto a solid carrier. In-vitro dissolution studies were carried out and compared with pure drug. The self emulsification properties, droplet size and zeta potential of the optimized formulation were studied upon dilution with water. The results indicated that the rate and extent of drug dissolution was significantly higher than pure drug. The results from this study demonstrate the potential use of SEDDS as a means of improving solubility, dissolution, and concomitantly the bioavailability.

Keywords: Bioavailability, Repaglinide, Self emulsifying drug delivery system (SEDDS).

INTRODUCTION

Oral route is the most oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of Patient compliance.[1] Approximately 40% of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system. A rate limiting step for the absorption of these drugs is often their solubilisation in the gastrointestinal tract. These drugs are classified as class II drug by Biopharmaceutical classification system (BCS), drugs with poor aqueous solubility and high permeability. Lipid-based drug delivery Systems have been demonstrated to be useful in enhancing the bioavailability of highly lipophilic compounds because they can keep the drug in the dissolved state until it is absorbed, thus overcoming the barrier of slow dissolution rates. In practice, lipid formulations range from pure oils to formulations containing some proportions of surfactants, co-surfactants or co-solvents. Recently a number of studies related to lipid formulations focused attention on micro emulsion formulations with particular emphasis on self-micro emulsifying or self emulsifying drug delivery systems to improve oral bioavailability of poorly water-soluble drugs.[2]

Self emulsifying drug delivery systems (SEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/surfactants. Upon mild agitation followed by dilution in aqueous media such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or micro emulsion.[3]

Repaglinide is Biopharmaceutical Classification System (BCS) Class II drug. Thus, it can be assumed that the low oral bioavailability of Repaglinide is due to its solubility and dissolution limitations. Repaglinide is an oral hypoglycaemic agent administered orally has absolute bioavailability of only 56% due to the poor aqueous solubility (0.03 mg/ml). Thus, formulating a lipid based system of Repaglinide can be viewed as an option for improving its oral bioavailability.

The main objectives of the study were to develop and evaluate an optimal SEDDS formulation containing Repaglinide and also formulate and evaluate Solid-SEDDS.

MATERIALS AND METHODS

Materials

Repaglinide was obtained as a gift sample from Pharmtech research laboratories, Hyderabad. Olive oil, Sunflower oil, Arachis oil and Soya bean oil was purchased from market. Labrafil M 2125 was obtained as a gift sample from BASF Corporation. Span 40, Span 80, Tween 20, Tween 80, Tween 80, PEG 400, Glycerine, propylene glycol were gift samples from SD-fine chemicals limited, Mumbai.

Methods

Solubility Studies

The most important criterion for the screening of components for microemulsion is the solubility of poorly soluble drug in oils, surfactants and co surfactants. The solubility of Repaglinide in various oils was determined by adding an excess amount of drug in 2 ml of selected oils (soya bean oil, arachis oil, sunflower oil, olive oil) and surfactants & co-surfactants (Tween-40, tween-80, span-40, span 80, labrafil, PEG-400, Propylene-glycol, glycerine, ethanol) in 5 ml capacity stopper vials, and mixed using a vortex mixer. The mixture vials were then kept at 25±1^0 C in an ultra-sonicator for 48 h to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 5000 rpm for 15 min. The supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of Repaglinide was determined in oils using UV Spectrophotometer at 243nm.[4]

Plot of pseudo ternary phase diagrams

On the basis of the solubility study of drug, oil, surfactants, co-surfactants and aqueous phase were used for construction of phase diagram. Oil, surfactant, and co-surfactant are grouped in four different combinations for phase studies For each phase diagram, oil, and specific surfactant ratio are mixed thoroughly in different weight ratio from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5.0:5.0, 6:4, 7:3, 8:2, 9:1) in different glass vials. Different combination of oils and Surfactants were made so those maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. Pseudo-ternary phase diagram was developed using aqueous titration method. Slow titration with aqueous phase is done to each weight ratio of oil and surfactant and visual observation is carried out for transparent and easily flow able o/w nano/micro emulsion. The physical state of the nano/micro emulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing surfactant. Ternary phase diagram were plotted with the help of CHEMIX School 3_60 software. [5]

Formulation of SEDDS

The formulations were prepared by initially dissolving the formulation amount of Repaglinide in co-surfactant at 60^{0}C in an isothermal water bath. Oil was then added and mixture was cooled to ambient temperature, then surfactant was added and the final mixture was sonicated until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 hours and examined for signs of turbidity (or) phase separation. The formulation which has been formulated had been solidified by using colloidal silicon dioxide (Aerosil) as a solid carrier. After complete drying the powder is punched as tablets using single tablet punching machine. Prior to punching, magnesium stearate and Crospovidone are added.

Evaluation of self-emulsifying drug delivery systems

For emulsion

Thermodynamic stability studies

The final preparations were divided into 3 sets, stored at 4^{0}C (refrigerator), room temperature and 40^{0}C (thermostatic oven) for not less than 48hrs. Those formulations, which are stable at these temperatures, were subjected to centrifugation test. Passed formulations were centrifuged at 3500 rpm for 30 min. Those formulations that did not show any phase separation were taken for freeze thaw stress test. Three freeze thaw cycles between -21^{0}C and +25^{0}C with storage at each temperature for not less than 48 hours was done for the formulations.[6]

Visual observation, phase separation of emulsion

Each formulation of SEDDS containing Repaglinide was taken in a small beaker and was diluted with 200 ml of distilled water at 37˚C,check visual appearance and the diluted preparation was vortexed for 1min, and then the mixtures was stored for a period of 24 hrs, and observe phase separation and precipitation visually. Mixtures exhibiting a negligible phase separation during the 2 hour period were used for subsequent studies.[7]

Determination of self emulsification time

The primary means of self micro emulsification assessment is visual evaluation. The efficiency of self micro emulsification could be estimated by using magnetic stirrer with 100 rpm, water and 0.1N HCl solution as medium. Temperature was maintained at 37±0.5˚C. Fill the beaker with 100ml of medium and pour the SEDDS formulation into the medium and the contents being mixed gently at 100rpm and determining the time required to form microemulsion upon dilution of SEDDS with water.[8]

Dispersibility test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP II dissolution apparatus. One millilitre of each formulation was added to 500 ml of water at 37 ± 0.5^{0}C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the Grading system.[9]

Droplet size & Zeta potential

The zeta potential of the diluted SEDDS formulation was measured using a zeta meter system. The SEDDS were diluted with a ratio o 1:2500 (v/v) with distilled water and mixed with magnetic stirrer. Zeta-potential of the resulting microemulsion was determined using the Zetasizer.[10]

Cloud point measurement

Dilute the formulation with 50 ml of water in beaker and placed on a water bath with gradually increasing the temperature until the diluted formulation turned to

cloudy. It gives the information about the stability of the microemulsion at body temperature.[11]

For tablets

Powder Characteristics (Preformulation studies)

All the solidified powders are evaluated for bulk density, tapped density, angle of repose, Hausner's ratio and Carr's consolidation index.

Post-compression parameters

All the tablets are evaluated for weight variation, hardness, friability, thickness and disintegration tests.[12]

Drug content uniformity

The drug content uniformity was determined by taking the powder equivalent to 10 mg, is dissolved in 100 ml of 0.1N HCl. The drug is allowed to dissolve in the solvent, the solution was filtered and 1 ml of filtrate was taken in 10 ml of volumetric flask and diluted up to the mark with 0.1N HCl. It was analyzed spectrophotometrically at 243 nm, the amount of Repaglinide was estimated by using standard calibration curve of the drug.[12]

In-vitro dissolution studies

The release of solidified SEDDS and tablet was studied by dissolution apparatus USP. II (paddle) in 0.1 N HCl as dissolution medium at 50 rpm of rotating speed and 37±0.5^{0}C in which one tablet is introduced. The concentration of Repaglinide was determined by UV-spectrophotometer at 243 nm by standard calibration plot. The release profiles of SEDDS were compared with the pure drug.[13]

RESULTS AND DISCUSSION

Solubility studies

Results from solubility studies are reported in figure 1. As seen from the figure, Tween 80 and PEG 400 showed the highest solubilisation capacity for Repaglinide, followed by Olive oil. Thus, for our study we selected Olive oil as oils and Tween 80, PEG 400 as surfactant and co-surfactant, respectively.

Plot of Pseudoternary Phase Diagrams

Pseudo ternary phase diagrams were constructed to determine regions of emulsification and to optimize surfactant to co surfactant ratio and the concentration of oil. The studied systems were composed of different oils, surfactants, co-surfactants and water. The pseudo ternary phase diagrams with different ratios of surfactant and co surfactant are shown in figure 2.

On the basis of ternary phase diagrams shown here in figure 2, it was observed that region of emulsification in case of Tween 80 and PEG 400 ratio 1:1 and in case of Tween 80 and PEG 400 ratio 2:1 is better compared to other components. It was therefore, decided to use Tween 80 and PEG 400 ratio 1:1 and 2:1 (iv & v diagrams) for further development of self emulsifying system of Repaglinide.

Thermodynamic stability studies (Freeze-thawing cycle)

Thermodynamic stability study (table 2) was performed to evaluate the precipitation of the drug in the excipients mixture. It was found that all the SEDDS formulations were physically stable and there was no precipitation of drug into lipid matrix and form a single homogeneous phase.

Visual observation, Phase separation of emulsion

All formulations F1-F8 showed no crystal growth or no precipitation and formed microemulsion upon dilution with aqueous media and remained physically stable for more than 24hrs, and the results were shown in table 3.

Dispersibility test

Assessments of efficiency of self emulsification were performed for all the formulations. The *In-vitro* performances of the formulation were visually assessed using the grading system and the results were shown in table 3.

Emulsification time

Emulsification times of the prepared formulations are shown in table 3, it was observed that emulsification time varied from 18 to 30 sec. It was less in case where co-surfactant concentration was low and maximum emulsification time was observed in case where all three components were at their higher levels. Emulsification time was minimum in F1 (18 sec) and maximum with formulation F5 (30 sec).

Drug content analysis

Table 3, indicates that the quantity of drug content of each formulation is more than 95.85% to the amount of drug loading. Therefore, it can be might be told that the entire drug is well uniformly distributed and there is no precipitation in the each formulation.

Droplet size analysis & Zeta potential

The best release result of *In-vitro* dissolution study F4 formulation was determined by photon correlation spectroscopy for zetasizer on droplet size analysis and the results are shown in figure 3.

Table 1: Formulation table of Repaglinide SEDDS

Tween 80 : PEG 400 (1:1)				
F	**Drug (mg)**	**% Olive oil**	**% Tween 80**	**% PEG 400**
F1	2	39.02	30.48	30.48
F2	2	61.79	19.10	19.10
F3	2	29.87	35.06	35.06
F4	2	29.41	35.29	35.29
F5	2	18.64	40.67	40.67
Tween 80 : PEG 400 (2:1)				
F6	2	50	33.33	16.66
F7	2	29.87	46.75	23.37
F8	2	50.61	33.33	16.04

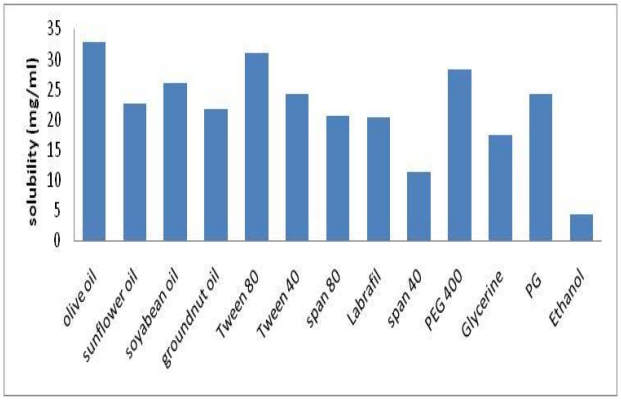


Figure 1: Solubility of Repaglinide in various oils and surfactants

Table 2: Thermodynamic stability study results

Formulation code	Centrifugation (3500 rpm)	Freeze thaw cycle (-20^{0}c and +25^{0}c)
F1	Passed	Passed
F2	Passed	Passed
F3	Passed	Passed
F4	Passed	Passed
F5	Passed	Passed
F6	Passed	Passed
F7	Passed	Passed
F8	Passed	Passed

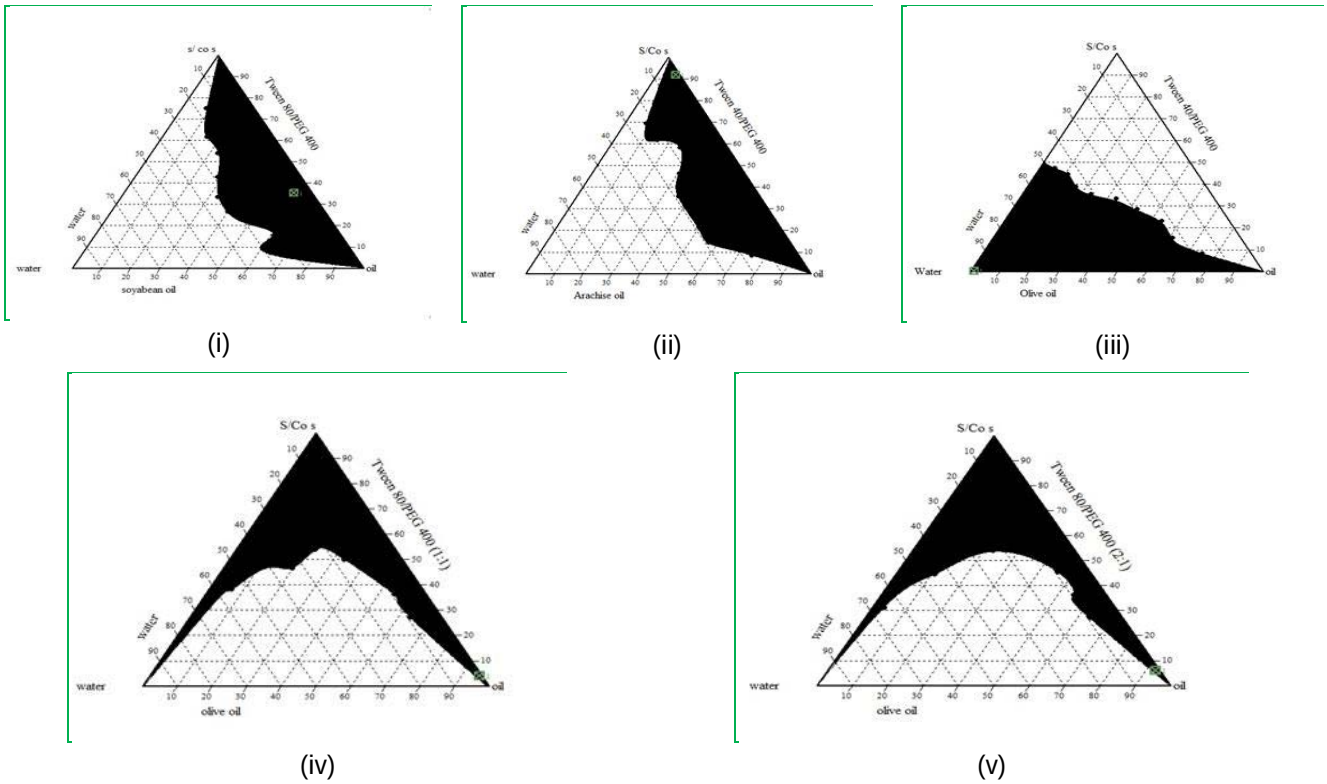


Figure 2: Pseudo ternary phase diagram of surfactant and co-surfactant in various ratios

Table 3: Results of various parameters

Formulation code	Visibility grade	Phase separation	Precipitation	Emulsification time (secs)	% of drug	Cloud point
F1	A	X	XX	18	96.94	71^0 C
F2	B	X	XX	22	95.85	74^{0}C
F3	A	X	XX	24	99.12	86^{0}C
F4	B	X	XX	28	99.33	78^{0}C
F5	B	X	XX	30	99.85	83^{0}C
F6	B	X	XX	20	100.29	88^0 C
F7	A	X	XX	25	99.42	80^0 C
F8	B	X	XX	23	96.8	77^0 C

X – No phase separation; XX- No precipitation

Grading system: Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance; **Grade B:** Rapidly forming, slightly less clear emulsion, having a bluish white appearance; **Grade C:** Fine milky emulsion that formed within 2 min; **Grade D:** Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min); **Grade E:** Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Table 4: Results of *in-vitro* dissolution studies

Time (min)	F1 % CDR	F2 % CDR	F3 % CDR	F4 % CDR	F5 % CDR	F6 % CDR	F7 % CDR	F8 % CDR	Pure drug % CDR
5	8.50	9.72	10.94	13.37	6.07	4.86	7.29	9.72	8.513
10	15.85	17.07	17.08	26.82	13.67	12.22	17.18	14.64	14.639
15	28.05	26.84	26.61	39.06	26.82	19.52	23.19	25.62	19.536
20	36.64	37.84	35.41	50.07	34.19	24.42	35.40	34.19	24.425
25	50.06	51.06	46.41	61.08	42.75	32.97	47.62	45.18	28.105
30	58.65	62.3	58.63	72.09	51.312	41.56	57.41	54.97	32.99
45	68.42	72.09	70.86	79.445	57.43	53.73	63.55	65.97	41.565
60	77.04	81.88	84.30	94.08	62.34	67.18	72.10	75.82	52.52

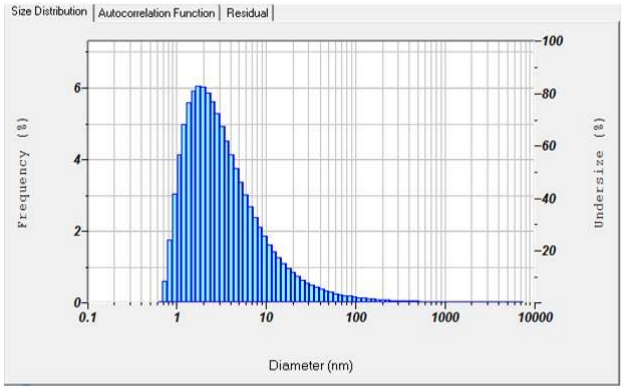
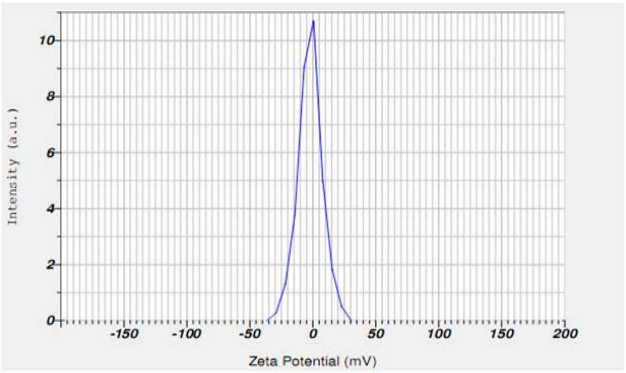
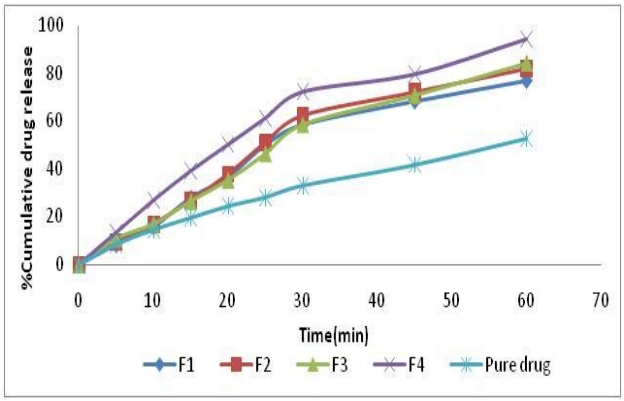


Figure 3: Particle size of optimised formulation (F4)



Peak No.	Zeta Potential	Electrophoretic Mobility
1	-2.1 mV	-0.000016 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Figure 4: Zeta potential of optimised formulation (F4)



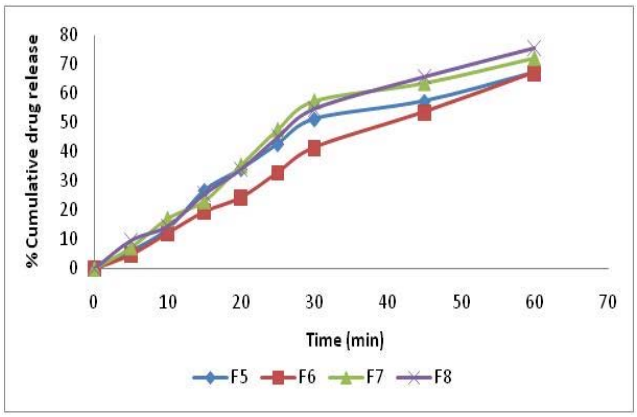


Figure 5: Comparison of *In-Vitro* drug release studies of all formulations (F1-F8)

Table 5: Kinetic values obtained from different plots of formulation F4

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korse-Meyer Peppas (R^2)
F4	0.915	0.967	0.950	0.931

The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have a large negative or positive zeta potential they will repel each other and there is dispersion stability. If the particles have low zeta potential values then there is no force to prevent the particles coming together and there is dispersion instability. A dividing line between stable and unstable aqueous dispersions is generally taken at either +30 or - 30 mV. Particles with zeta potentials more positive than +30 mV are normally considered stable. Particles with zeta potentials more negative than -30mV are normally considered stable. Zeta potential of the system negative (-) mV, which indicated the droplets of micro emulsion having negative charge, which is closer to range. The best release results of *in-vitro* dissolution study F4 formulation was determined by photon correlation spectroscopy for zeta potential meter on surface charge of the emulsion and the results are shown in figure 4.

In-vitro dissolution study

Drug release from the SEDDS formulation (F4) was found to be significantly higher as compared with that of pure drug. It could be suggested that the SEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of pure drug. Thus, this greater availability of dissolved Repaglinide from the SEDDS formulation could lead to higher absorption and higher oral bioavailability. The maximum drug release was found to be F4 formulation 94.08% and results were shown in table 4.

As observed from the table 5, all the formulation followed first order kinetics as correlation (R^2) values 0.967 and is higher than that of zero order release kinetics. The prepared tablets showed Fickian diffusion, as the values of release their correlation coefficient (R^2) value is 0.95 which are greater than the values of Korse-Meyer Peppas model.

CONCLUSION

Novel emulsion formulations i.e. SEDDS are a promising approach for the formulation of Repaglinide. The oral delivery of hydrophobic drugs can be made possible by SEDDS, which have been shown to substantially improve oral bioavailability with future development of this technology. These current results demonstrated that SEDDS containing 29.41 w/w olive oil (oil), 35.29% w/w, Tween80 (surfactant) and 35.29% w/w polyethylene glycol (co-surfactant) was successfully developed with an increased solubility, increased dissolution rate of a poorly water-soluble drug, Repaglinide. A result from stability studies confirms the stability of the developed formulation. Thus, the study confirms that the SEDDS for Repaglinide can be used as a possible alternative to traditional oral formulations of Repaglinide with improved solubility and drug release.

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