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Novel Super Saturated Self- Emulsifying System for Oral Delivery of Griseofulvin: Design, Preparation and ex-vivo Intestinal Permeability

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A B S T R A C T

The Objective of the study was to prepare and design a stable formulation for self-emulsifying drug delivery system in order to enhance the solubility and oral absorption of a poorly-soluble drug, called griseofulvin. The prepared self-emulsifying systems were evaluated regarding their refractory index, particle size, emulsifying strength, drug release, and rat intestine permeability. The results showed that a mixture of oleic acid (as a fatty acid) with Labrafil-Tween 20 (as a surfactant), Labrafac PG (as a co-surfactant), and Poloxamer and hydroxypropyl methylcellulose (as a polymer) led to prepare stable emulsions with a refractive index higher than acidic medium and water. The particle size of the formulations was obtained between 310 to 834 nm. The particle size of samples was influenced by S/C ratios, so that the mean particle size decreases with an increasing in the S/C ratios. The percentage of drug release after 24 hours for formulations was 22.38 to 46.95. The correlation between the percentages of drug released after 24 hours with S/Oil and S/C ratios was significant. In Ex-vivo intestinal permeability, there was a significant and direct correlation between Q4 and surfactant/oil ratio. The selected formulations showed drug permeability through the rat intestine 3- folds more, compared with the control.

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Introduction

In comparison with other drug administration methods, the oral route is the easiest, safest and most convenient method. Other advantages of oral delivery systems are, high patient compliance; cost - effectiveness; least sterility constraints and flexibility in the design of the dosage form [1, 2]. Because of the poor water solubility of approximately 40% of new chemical drugs, one of the major challenges in oral drug formulation is low and poor bioavailability [3]. Numerous technological approaches have been developed to enhance the bioavailability of drugs with low solubility, including solid dispersions, complexation with cyclodextrins, micronization, salt formation, solid lipid nanoparticles, microemulsions, self-emulsifying drug delivery systems(SEDDSs) and liposomes [2, 4-6].

Griseofulvin is an antifungal antibiotic administered orally in the treatment of dermatophyte and ringworm infections [7]. Griseofulvin with molecular weight 352.766 g/mol and logP 2.15, is insoluble in water (8.64 mg/lit) [8] and according to the Biopharmaceutics Classification System, it belongs to Class II drugs [9]. The oral bioavailability of griseofulvin is highly variable (25-70 %) and strongly influenced by interaction by food and gastrointestinal contents [10]. Hence, the absorption of griseofulvin would be rate-limited by the dissolution process [11]. Therefore, different approaches have been applied to improve the bioavailability by increasing the drug solubility and dissolution rate. Among these approaches, the potential of Super self-emulsifying drug delivery systems as drug delivery system to increase drug solubility has been widely reported.

SEDDSs are isotropic mixtures of oils, surfactants and/or co-surfactant and may be a promising strategy to improve the solubility and bioavailability of highly lipophilic compounds. SEDDS can form fine oil–in–water (o/w) emulsions when exposed to an aqueous phase such as gastrointestinal fluid under gentle agitation, which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption [12,13]. Super Saturated Self- Emulsifying Drug Delivery System (S-SEDDS) formulations have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs. S-SEDDS formulations differ from the conventional SEDDS formulations as they contain different amount of surfactant and a polymer as precipitation inhibitor agent (e.g., water-soluble cellulosic polymers), in order to generate and maintain a supersaturated state of the drug following mixing with water [14].

The purpose of the present study was to evaluate the effect of S-SEDDs on griseofulvin aqueous solubility and *ex- vivo* permeability through rat intestinal membrane.

Materials and Methods

Chemicals

Griseofulvin was purchased from the DarouPakhsh Pharmaceutical Company (Iran). Oleic acid and Span 20 were obtained from Merck (Germany) Inc.; also, hydroxypropyl methylcellulose (HPMC) and Poloxamer were obtained from Sigma-Aldrich Company. Labrafac PG (Propylene glycol dicaprylocapraye) and labrafil 1944CS were gifts from the GATTEFOSSE Company (France). Castor oil was a gift from Kim agar Toss Co. (Iran). Dialysis bag was purchased from Armaghane Kalaye Javan Co, Tehran, Iran.

Animals

A total 8 adult male Wister rats،four month of age، weighing 192±10.3 g were purchased from the laboratory Animals Care and Breeding Center of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. All rats were sacrificed using chloroform; then, animal intestines were removed and divided into three equal parts. All parts of intestine were washed in a cold Ringer's solution. The experiments were performed in accordance with the guidelines for the use of animals in Ahvaz Jundishapur University of Medical Sciences and approval for the animal studies was obtained from the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (ref no. 843)

Screening of oils for SEDDS

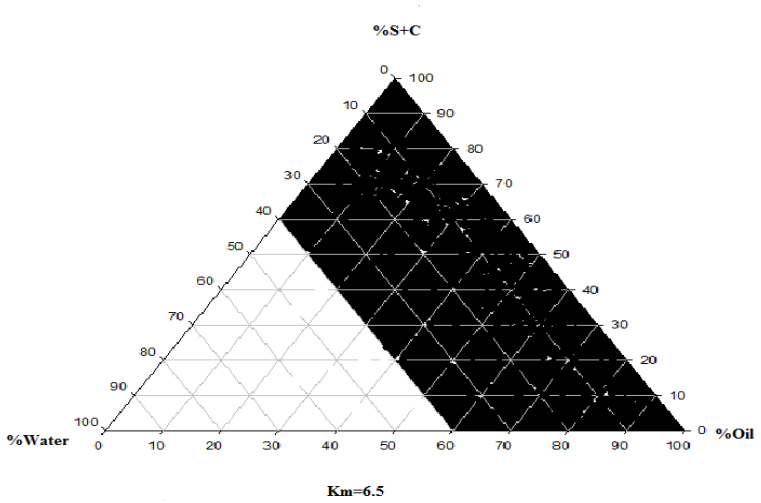
The solubility of griseofulvin in different oils (Castor oil, oleic acid and labrafac PG) was measured as follows: 5 mL of each selected oil (shown in Table 1) was added to excess amount of griseofolvin and stirred for 30 min at 37°C, and then for one day (24 h) at room temperature. Afterwards, the mixture was centrifuged at 3000 rpm for 15 minutes and the supernatant was cleared, and the amount of dissolved drug was determined using an ultraviolet/visible (UV) spectrophotometer at 294nm after extraction with methanol [15].

Table 1. The solubility of griseofulvin in various oils (mean ± SD, n=3)

Oil	Drug solubility (mg/ml)
Oleic acid	0.75 ± 0.06
Castor oil	0.53 ± 0.04
Labrafac PG	0.62 ± 0.06

Construction of ternary phase diagram

To investigate a concentration range of components for the existing boundary of SEDDS, pseudo-ternary phase diagrams were constructed at room temperature using the water titration method (Figure 1). Two ternary phase diagrams were prepared with the 6.5:1 (Km=6.5) and 13:1 (Km=13) weight ratios of Labrafil M 1944CS-Tween 20/Labrafac PG. Oil phase (oleic acid) and the surfactant – co surfactant mixture were then mixed at the weight ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1. These mixtures were diluted drop wise with double distilled water, under moderate agitation [15]. Full factorial design was used concerning with 3 variables at
2 levels for formulations. Major variables take part in determination of SEDDS properties include surfactant/cosurfactant ratio (S/C), surfactant/oil ratio (S/O) and type of polymer (P).



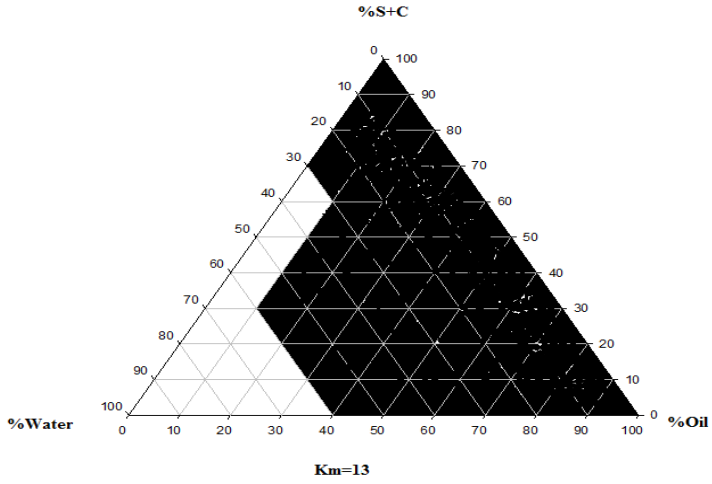


Fig. 1. The Pseudo-Ternary Phase Diagrams of the Oil-Surfactant/CoSurfactant Mixture–Water System at 6.5:1 and 13:1 Weight Ratio of Labrafil M 1944CS- Tween 20/Labrafac PG at Ambient Temperature. (Dark area represent emulsion region)

Preparation of Self emulsifying drug delivery system (SEDDS)

A series of self-emulsifying drug delivery systems (SEDDSs) were prepared by admixing the various ratios of surfactant (Labrafil M 1944CS and Tween20), co-surfactant (Labrafac PG), oil and polymer (Table 2). Then, 5mg griseofulvin was added to the mixture, shaked well and then kept this mixture at 40° C for 20minutes to solve the drug. Finally, two series of formula were obtained, which in both polymers were HPMC and Poloxamer, respectively [16].

Table 2. Different amount of compounds used in the SEDDS formulations of Griseofulvin.

Formulation No.	Factorial design condition	labrafil (g)	Labrafac (g)	S/C ratio	S/O ratio	Tween 20 P(g)	Polymer (g)
1	+ - +	2	0.2	13	0.26	0.6	HPMC (0.06)
2	+ - -	2	0.2	13	0.26	0.6	Poloxamer (0.06)
3	+ + +	5	0.43	13	0.56	0.6	HPMC (0.08)
4	- - +	2	0.4	6.5	0.26	0.6	HPMC (0.06)
5	- - -	2	0.4	6.5	0.26	0.6	Poloxamer (0.06)
6	+ + -	5	0.43	13	0.56	0.6	Poloxamer (0.08)
7	- + +	5	0.86	6.5	0.56	0.6	HPMC (0.08)
8	- + -	5	0.86	6.5	0.56	0.6	Poloxamer (0.08)

Abbreviations: S, Surfactant; CS, Co-Surfactant; S/C ratio, Surfactant/ Co-Surfactant; S/O ratio, Surfactant/ Oil, oil amount (10 g), drug amount (5mg).

Visual observation

For evaluation of self-emulsification properties of different formulations, 1 ml of each formulation was added to 50 ml of 0.1N hydrochloric acid under persistent stirring (60 rpm) at 37°C. Then, tendency to emulsify spontaneously and also the progress of emulsion droplets were observed. The formulations were categorized as non – clear and clear. On the other hand, refractive metric indexes of various formulations were determined and compared with the 0.1 N hydrochloric acid.

Griseofulvin assay

The quantitative determination of drug released and permeated through the rat intestine was performed using UV spectroscopy at wavelengths of 285 nm. The validity of the assay method, including, repeatability, accuracy, linearity, and limit of quantification (LOQ) were calculated.

Particle size analysis

After diluting formulations (0.1 mL) in 10 mL of 0.1 N hydrochloric acid solutions, the particle size of formulations was measured using particle size analyzer (Scatterscop 1 Qudix, South Korea).

In vitro drug release

In-vitro drug release studies were carried out using vertical glass Franz diffusion cells(with an approximated effective diffusion area of 3.4618 cm^2) with a cellulose membrane were utilized to determine the release rate of griseofulvin from various SEDDS formulations. The cellulose (molecular weight 12000 G) membrane was first hydrated in the double distilled water solution at 25°C for 24 hours. The membrane was then clamped between the donor and receptor chambers of the cells. Then, diffusion cell was filled with 22 mL of 0.1 N hydrochloric acid. The receptor medium was constantly stirred by externally driven magnetic bars at 100 rpm at 37 ± 0.5 °C throughout the study. The SEDDS formulation without drug was used as blank.
Griseofulvin SEDDS samples (1 ml and containing 0.05mg drug) were accurately weighed and placed on the membrane. At 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 -hour time intervals, 2 mL sample was removed from receptor for spectrophotometric analysis and replaced immediately with an equal volume of fresh 0.1 N hydrochloric acid (similar to gastric fluid). Samples were determined by a UV visible spectrophotometer at 285 nm. The results were plotted as cumulative released drug percent versus time [17].

Drug Permeability through the Rat Intestine

Male wistar rats were sacrificed and the small intestine was excised and placed in the ice-cold bubbled (carbogen, 95:5 O2/CO2) ringer buffer(containing 7.2g NaCl ,0.17g$CaCl_2$ and 0.37g KCl in 1 liter of distilled water and adjust the pH to 7.4).The jejunum 15-20 cm distal from the pyloric sphincter was removed and rinsed with ringer buffer. 1 ml of SEDDS containing 0.05mg/ml of griseofulvin was poured into the rat intestine and closed from both sides. Then tissue was kept in organ bath filled with 25 ml of phosphate buffer solution (PBS) pH 7.4 and it was continuously stirred during the experiments with continuous aeration for 4 hours at 37°C. At definite time intervals (0.5, 1, 2, 3and 4 h), 2ml sample was removed from media and then analyzed spectrophotometrically 292 nm for the drug content and replaced immediately with an equal volume of fresh phosphate buffer solution (PBS) pH 7.4. The same test was performed for the saturated aqueous suspension of griseofulvin as a control and thus the amount of drugs passed between SEDDS sample and suspension was compared. Apparent permeability coefficient (Papp), Percentage permeated and permeability enhancement ratio were calculated with the equation 1 and 2.

$$Papp = {}^{dQ}\!/_{dt} \times {}^{1}\!/_{A.C0} \qquad (1)$$

dQ/dt is steady state apparent rate on the acceptor side of the tissue. A is the area of the tissue (cm^2) and C_0 is the initial concentration of the drug in the donor phase .

$$permeability\ \text{enhancement ratio} = \frac{\text{Papp of the SEDDS formulation}}{\text{Papp of the simple solution as control}} \qquad (2)\ [7]$$

Statistical analysis

In this study, an ANOVA test was used for statistical analysis of different formulations of the permeated drug through the intestine in comparison with the blank formula (Control) and also to compare the effect of SEDDS and suspension on the amount of the passed drug. Level of significance chosen in all stages of this research was less than 0.05.

Results and Discussion

Validity of drug measurement method

The correlation coefficient for the concentration-absorbance was $r^2 = 0.999$, which means that 99.9 % of the absorbance values are estimated by the concentration. Regression analysis showed a significant relationship between concentration and light absorbance (P = 0.003). In this study, the lack-of-fit, which appears in the estimated absorbance changes, was not significant (P = 0.102. Accuracy of measurement indicated those concentrations that were close to the actual values. The results of this stage showed the desired repeatability of the measured method achieved within and between days. All the concentrations observed in this study were higher than the LOQ (0.000405 mg/mL).

Droplet size

The mean particle size of griseofulvin - Loaded SEDDS samples was in a range of 300 to 840 nm with poly-dispersibility less than 0.05.(Table 3) Multivariate regression was utilized for analyzing the correlation between independent variables and particle size of samples. The obtained results show that the correlation between mean particle size with surfactant to co-surfactant ratio (S/C) was significant (P =0.037). Herein, the correlation between the surfactant and co-surfactant with particle size was significant in such a way that the increased ratio makes a significant decrease in the mean particle size. Thus, the mean particle size indicates emulsion formation after adding SEDDS to water.

Table 3. Polydispersity index (PDI) and particle size of SEDDS formulations prepared with HPMC and Poloxamer (mean ± SD, n=3).

Formulation No.	Factorial design Condition	Droplet Particle Size (nm)	polydispersity index (PDI)
1	+ - +	720±65	0.31 ± 0.18
2	+ - -	534 ±42	0.48± 0.17
3	+ + +	597± 69	0.37± 0.10
4	- - +	310± 25	0.47± 0.27
5	- - -	834± 59	0.49± 0.21
6	+ + -	779± 82	0.44± 0.14
7	- + +	824± 55	0. 42± 0.18
8	- + -	530 ±37	0.48 ± 0.19

Solubility and Visual Observation Study

The strength of oil phase in drug solubility plays an essential role in the efficacy of SEDDS formulation. Solubility studies were performed to identify suitable oil that has the good solubilizing capacity for griseofulvin. Solubility in various oils is shown in Table 1. Among the used oils, the oleic acid and castor oil showed maximum and minimum solubility for griseofulvin, respectively. Oleic acid (HLB = 7) had more strength to solve griseofulvin than castor oil (HLB = 14). However, it seems that in the present study, by increasing oil-phase of HLB, the drug solubility did not increase. This finding was in agreement with the results presented by other people [18]. Therefore, oleic acid was used as oil phase in SEDDS griseofulvin formulations. On the other hand, surfactant used in preparing SEDDS formulations must have one important characteristic. It should be non-stimulating, the reason that non- ionic surfactant is used and has high HLB, is its ability to induce a rapid emulsion in the gastrointestinal tract. There are numerous potential mechanisms whereby SEDDS formulations may increase bioavailability, and especially in the case of Carvedilol solubility [19]. SEDDS formulation can produce oil in water emulsion after dilution in gastrointestinal fluids with mild agitation

provided by gastric mobility, which leads to a large interfacial area for drug partitioning between oil and water phases and an increase in solubility rate and the extent of absorption [20].

Because the effect of SEDDS formulations depends on their strength in the emulsion formation post entering the gastrointestinal tract, so after the addition of the various formulation to 0.1N hydrochloric acid the strength of emulsion formation was evaluated using both optical illusion method and refractive index (RI) as the criterion of being a transparent system (Table4). In the optical illusion method, after the increased 0.1 N hydrochloric acid, formula was observed; Poloxamer formulations were translucent and anaphase, and HPMC formulations were milky and anaphase. Therefore, in the poloxamer and HPMC formulations, the emulsion has been generated and percentages of used oil, surfactant and co-surfactant, HPMC and poloxamer did not affect the emulsion formation.

The closure of the formulations refractive index value of water and 0.1N hydrochloric acid is indicating the transparency property of the formulation being in the hydrochloric acid environment.

Table 4. The Emulsion Formation Strength Using Optical Illusion Method and Refractive Index (RI) SEDDS Formulations (mean ± SD, n=3)

Formulation No.	Factorial design Condition	Refractive index (RI)	optical illusion
1	+ - +	0.2±0.007	Milky and anaphase
2	+ - -	0.17±0.005	translucent and anaphase
3	+ + +	0.14±0.009	Milky and anaphase
4	- - +	0.01±0.001	milky and anaphase
5	- - -	0.01±0.005	translucent and anaphase
6	+ + -	0.07±0.002	translucent and anaphase
7	- + +	0.1±0.003	milky and anaphase
8	- + -	0.04±0.002	translucent and anaphase

After adding 0.1N hydrochloric acid, there was a significant difference between the factor RI for all formulations with water and 0.1N hydrochloric acid itself (Table 4). In other words, the phase behavior of SEDDS formulations and percentages of used oil, surfactant co-surfactant and water were established stable emulsion, but in the area outside the range stable emulsion has not been created (Figure 1). Furthermore, Labrafil (HLB = 4) and Labrafac PG (HLB=2) were used respectively as surfactant and co-surfactant. In the SEDDS prepared after adding the formulation to 0.1N hydrochloric acid, established stable emulsions and appearance of HPMC formulations No. 1, 3, 4 and 7 were milky and anaphase (Table 4). Poloxamer formulations (No.2, 5, 6 and8) were translucent, and anaphase.

Therefore, in the poloxamer and HPMC formulations, the emulsion has been generated and percentages of used oil, surfactant and co-surfactant and type of polymer did not affect the emulsion formation; because the effect of SEDDS formulations depends on their strength in the emulsion formation after entering the gastrointestinal tract, after the addition of the various formulations into 0.1 N hydrochloric acid in stomach media.

In Vitro Drug Release

The percentages of drug released after 2 and 24 hours (R2 and R24) in the SEEDS formulations were from 1.39 - 6.57 and 22.38 - 46.95, respectively (Table 5). As it can be observed, S/O ratio and polymer type had a significant effect on drug release after 2 hours. The results showed that an increase in S/O (p=0.013) ratio and using of Poloxamer as polymer (p=0.003), leads to an increase in R2. Poloxamer formulations have higher drug release percentage (R24) than HPMC formulations; also formulation No. 5 has maximum R24.

Release profile from SEDDS griseofulvin formulations shows a two-step process. First, a rapid release rate; secondly a slow release profile. The relationship between surfactant to Oil ratio (S/O) and surfactant to co-surfactant ratio (S/C) with R24 in the HPMC and poloxamer formulations was significant (p=0.003), in a way that the increase in S/O and S/C leads to an increase in R24. In this study, we illustrated that physicochemical properties and drug released depended upon the type of polymer، ratio of S/O and S/C in formulations.

Table 5. Percent Drug Released from SEDDS Formulations (mean ± SD, n=3).

Formulation No.	Factorial design condition	R_2	R_{24}
1	+ - +	2.34±0.37	23.34 ±1.37
2	+ - -	2.37±0.35	27.76 ±2.30
3	+ + +	5.24±0.69	43.94 ±2.57
4	- - +	1.39±0.15	22.38 ±2.80
5	- - -	2.18±0.2	25.47 ±1.48
6	+ + -	6.33±0.82	46.95 ±3.27
7	- + +	5.11±0.41	34.72 ±3.10
8	- + -	6.57±0.49	37.42 ±4.38

Griseofulvin permeability through the Rat intestine

The drug permeability through the rat intestine from different formulations is illustrated in table 6 and figure 2. The percentage of drug permeability after four hours (Q4) was between 8.11-18.87%. The maximum percentage of drug permeability after four hours (Q4) was obtained at 18.87% (formulation No. 8) in poloxamer formulations. The enhancement ratio in the formulation No. 8 was 3.05 times higher than those of saturated water solution of griseofulvin. The relationship between surfactant to oil ratio (S/O) with Q4 in the poloxamer and HPMC formulations was significant (P = 0.01) indicating that in relation to the increased S/O ratio, the Q4 has increased. No significant difference existed between S/C ratio and type of polymer with Q4 in the SEDDS formulations. Formulation No. 8 has the highest S/O ratio; therefore, it seems that the highest S/O ratio has an essential role in the rat intestine permeability. Figure 3 represents in vitro griseofulvin diffusion through the rat intestine from SEDDS formulations. Measurement of Papp and the enhancement ratio indicated that an increase in the permeability of griseofulvin from the SEDDS with the maximum amount of 3.25 that obtained by formulation No. 8. The drug percent permeability through the rat intestine from various SEDDS formulations and control in different times are shown in Table 6. The impact of different lipid based formulations of griseofulvin on in vitro solubilization and intestine ex-vivo permeability was investigated [21]Short chain triglyceride formulations caused enhanced permeation with doubled permeability coefficient. It seems that SEDDS that were applied in present study increased griseofulvin permeability coefficient more than lipophilic formulations.

Table 6. The griseofulvin Permeability through Rat Intestine from Different SEDDS Formulations and Control after 4 hrs. (mean ± SD, n=5)

Formulation No.	Factorial design condition	Q_4	P app (cm/h)	Permeability enhancement ratio
1	+ - +	11.77± 1.53	0.08±0.005	2.27
2	+ - -	12.38± 1.35	0.084±0.006	2.4
3	+ + +	14.65± 1.59	0.093±0.005	2.65
4	- - +	8.11 ± 0.75	0.063±0.003	1.8
5	- - -	9.29 ± 0.88	0.072±0.004	2.06
6	+ + -	17.88± 1.47	0.104±0.002	2.97
7	- + +	13.32±1.15	0.098±0.006	2.8
8	- + -	18.87± 1.37	0.114±0.004	3.25
SUSPENSION		6.19 ± 0.48	0.035±0.003	1

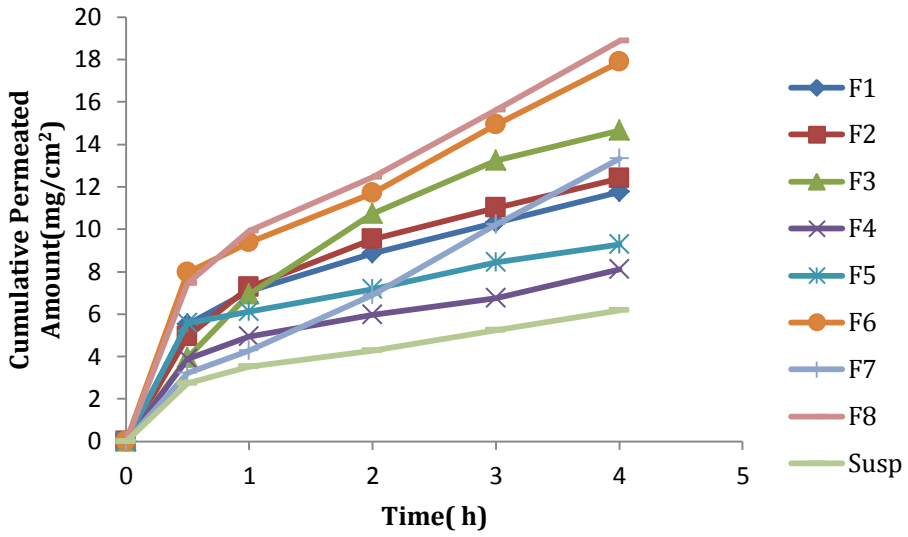


Fig. 2. In Vitro Griseofulvin Diffusion through the Rat Intestine from SEDDS Formulations

Conclusions

Our results indicated that all SEDDS formulations could improve griseofulvin aqueous solubility, drug release and drug permeability through rat intestine. The amount of surfactant in formulations was critical factor. The maximum percentage of drug permeability after four hours (Q4) was obtained at 18.87% in poloxamer formulations. The maximum permeability enhancement ratio in SEDDS formulations was obtained 3.25 times higher than those of saturated water solution of griseofulvin.

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Conflict of Interests

Authors certify that there is no actual or potential conflict of interest in relation to this article.

References

[1] Chaudhary B, Maheshwari K, Patel D. Self-Emulsifying Drug Delivery System: A Novel Approach for Enhancement of Bioavaibility. J. pharm. sci. bio-sci. res.2011:1:31-36.
[2] Krishnaiah YS, Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequiv Availab. 2010;2:28-36.
[3] Sunitha R, Sireesha DS, Aparna MVL. Novel Self-emulsifying Drug Delivery System-An approach to enhance bioavailability of poorly water soluble drugs. Int J Res Pharm Chem. 2011; 1:828-838.
[4] Bajaj H, Bisht S, Yadav M, Singh V, Singh M. Self-emulsifying drug delivery system: an approach to enhance bioavailability. Int J Pharma Res Dev., 2008;3:59-75.
[5] Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. Expert Opin Drug Deli. 2007;4:403-416.
[6] Liu L, Pang X, Zhang W, Wang S. Formulation design and in vitro evaluation of silymarin-loaded self-micro emulsifying drug delivery systems. Asian J Pharm Sci. 2007;2:150–60.
[7] Moghimipour E, Salimi A, Hassanvand S. Permeability Assessment OF Griseofulvin Microemulsion through Rat Skin. Int J pharm chem biol sci. 2013;3:1061-1065.
[8] Arida AI, Al-Tabakha MM, Hamoury HAJ. Improving the high variable bioavailability of griseofulvin by SEDDS. Chem Pharm Bull. 2007;55:1713-1719.
[9] Amidon GL, Lennernäs H, Shah VP and Crison JR. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res.1995;12:413-420.
[10] Dongowski G, Fritzsch B, Giessler J, Hartl A, Kulmann O, Nubert RHH. The influence of bile salts and mixed micelles on the pharmacokinetics of quinine in rabbits. Eur J Pharm Biopharm. 2005; 60:147-151.
[11] Fujioka Y, Metsugi Y, Ogawara K, Higaki K , Kimura T. Evaluation of in vivo dissolution behavior and GI transit of griseofulvin, a BCS class II drug. Int J Pharm. 2008;352:36-43.
[12] Neslihan G.R., Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58:173-182.
[13] Shah N, Carvajal MT, Patel CI, Infeld MH, Malick AW. Self-emulsifying drug delivery systems (SEDDS) with polyglycolyzed glycerides for improving in vitro dissolution and oral absorption of lipophilic drugs. Int J Pharm. 1994;106:15-23.
[14] Gao P , Morozowich W. Development of super saturatable self-emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. Expert Opin Drug Deli. 2006; 3:97-110.
[15] Salimi A, Sharif Makhmal Zadeh B, Moghimipour E. Preparation and characterization of cyanocobalamin (vit B12) microemulsion properties and structure for topical and transdermal application. Iran J Basic Med Sci. 2013;16:865–872.
[16] Moghimipour E, Salimi A, Karami M, Isazadeh S. Preparation and Characterization of Dexamethasone Microemulsion Based on Pseudo ternary Phase Diagram. Jundishapur J Nat Pharm Prod. 2013;8:105-12.
[17] Moghimipour E, Salimi A, Leis F. Preparation and evaluation of tretinoin microemulsion based on pseudo-ternary phase diagram. Adv Pharm Bull.2012;2:141-147.
[18] Tang J, Sun J, Gui He Z. Self- Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs. Curr Drug ther. 2007;2:85-93.
[19] Sachan R, Khatri K, Kasture S.B. Self-emulsifying drug delivery system a novel approach for enhancement of bioavailability. Int J Pharm Tech Res. 2010;2:1738-1745.
[20] Gursoy RN, Benita S. Self-emulsifying drug delivery systems (EDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58(3):173–182.
[21] Dahan A, Hoffman A. The effect of different lipid based formulations on the oral absorption of lipophilic drugs: the ability of in vitro lipolysis and consecutive ex vivo intestine permeability data to predict in vivo bioavailability in rats. Eur J Pharm Biopharm. 2007;67:96-105.

