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Effect of Formulation Variables on Preparation and Evaluation of Gelled Self-emulsifying Drug Delivery System (SEDDS) of Ketoprofen

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ABSTRACT

The purpose of this study was to formulate a gelled self-emulsifying drug delivery system (SEDDS) containing ketoprofen as an intermediate in the development of sustained release solid dosage form. Captex 200 (an oil), Tween 80 (a surfactant), and Capmul MCM (a cosurfactant) were used to formulate SEDDS. Silicon dioxide was used as a gelling agent, which may aid in solidification and retardation of drug release. Effect of concentrations of cosurfactant and gelling agent on emulsification process and in vitro drug diffusion was studied using 3^2 factorial design. Multiple regression analysis data and response surfaces obtained showed that liquid crystal phase viscosity increased significantly with increasing amount of silicon dioxide, which in turn caused an increase in average droplet size of resultant emulsion and slower drug diffusion. Drug release from the formulation increased with increasing amount of cosurfactant.

KEYWORDS: SEDDS, ketoprofen, gelled SEDDS, silicon dioxide, LC phases.

INTRODUCTION

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing cosolvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation.[1] Recently, SEDDS have been formulated using medium chain triglyceride oils and nonionic surfactants, the latter being less toxic. Upon peroral administration, these systems form fine emulsions (or microemulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.[2,3] Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the hostile environment in gut.[4,5]

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The process of self-emulsification proceeds through formation of liquid crystals (LC) and gel phases, the properties of which significantly affect the formation of droplets and interface available for partitioning of drug.[5-8] Many workers claim various rational applications of SEDDS for delivering and targeting lipophilic drugs (eg, WIN 54954,[1] N-4472,[9] idebenone,[10] coenzyme Q10,[11] vitamin E,[12] halofantrine,[13] and cyclosporin A[14]). However, very few reports are available of SEDDS of poorly soluble hydrophobic compounds like indomethacin[15] for reduction of gastric irritation. Ketoprofen, a moderately hydrophobic (log P 0.979) nonsteroidal anti-inflammatory drug (NSAID), is a drug of choice for sustained release formulation and has high potential for gastric irritation during chronic therapy. Also because of its low solubility, ketoprofen shows incomplete release from sustained release formulations. Vergote et al. (2001)[16] reported complete drug release from sustained release formulations containing ketoprofen in nanocrystalline form. Different formulation approaches that have been sought to achieve sustained release, increase the bioavailability, and decrease the gastric irritation of ketoprofen include preparation of matrix pellets of nanocrystalline ketoprofen,[16] sustained release ketoprofen microparticles[17] and formulations,[18] floating oral ketoprofen systems,[19] and transdermal systems of ketoprofen.[20] Preparation and stabilization of nanocrystalline or improved solubility forms of drug may pose processing, stability, and economic problems. Therefore the concept of using ketoprofen in SEDDS was considered for the present study, where the drug is present in solution form.

A recent trend to formulate semisolid self-nanoemulsifying drug delivery systems (SNEDDS)[21] and solid SEDDS[22,23] has been observed. Attempts have been reported for transformation of SEDDS in solid dosage forms by addition of large amounts of solidifying excipients (adsorbents and polymers). But to obtain solids with suitable processing properties, the ratio of SEDDS to solidifying excipients must be very high,[24] which seems to be practically nonfeasible for drugs having limited solubility in oil phase. In this regard, it was hypothesized that the amount of solidifying excipients required for transformation of SEDDS in solid dosage forms will be significantly reduced if SEDDS is gelled. Colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which may serve the dual purpose of reducing the amount of solidifying excipients required and aiding in slowing drug release.

Table 1. Formulations of Self-emulsifying Systems Using 3^2 Factorial Design, With Coded Levels and Actual Values of Variables*

Batch† (SES No.)	Variable X_1: Amount of Capmul (mL)	Variable X_2: Amount of Aerosil (mg)
1	0.15 (-1)‡	0 (-1)
2	0.15 (-1)	10 (0)
3	0.15 (-1)	20 (+1)
4	0.30 (0)	0 (-1)
5	0.30 (0)	10 (0)
6	0.30 (0)	20 (+1)
7	0.45 (+1)	0 (-1)
8	0.45 (+1)	10 (0)
9	0.45 (+1)	20 (+1)

*SES indicates Self-emulsifying system.

† All the batches were clear and isotropic, as observed visually.

‡ Values in parentheses indicate coded levels of variables.

Thus, the aim of the present investigation was to explore the potential applications of gelled SEDDS as an intermediate in the development of a sustained release solid dosage form of a moderately hydrophobic model drug, ketoprofen. Effect of formulation variables on the process of self-emulsification and drug release has been studied. The formulation of SEDDS in the present study consisted of an oil, Captex 200; a nonionic surfactant, Tween 80 (HLB 15); a lipophilic cosurfactant, Capmul MCM (HLB 5); and a gelling agent, colloidal silicon dioxide (Aerosil 200). To study the effect of concentration of cosurfactant and silicon dioxide on the different variables (eg, time required for complete emulsification, nepheloturbidimetric measurements, viscosity, particle size analysis, in vitro drug diffusion studies), 3^2 factorial design was adopted. The results obtained were subject to statistical analysis by surface response methodology.

Materials and Methods

Materials

Ketoprofen (B, No. K-02–003) was obtained as a gift sample from BEC Chemicals Pvt Ltd (Roha, India). Diesters of caprylic/capric acids (Captex 200 [Captex], Captex 355) and C_8/C_{10} mono-/diglycerides (Capmul MCM [Capmul]) were generous gifts from Abitec Corp (Cleveland, Ohio). Medium chain triglyceride oil (Miglyol 812) and medium chain diesters of propylene glycols (Miglyol 840) were a generous gifted from Sasol Corp (Werk Witten, Germany). Medium chain triglyceride (Labrafac CC, HLB 1) was a gift sample provided by Gattefosse (Gennevilliers, France). Polyoxyethelene 20 sorbitan monooleate (Tween 80) was purchased from Merck Ltd (Whitehouse Station, NJ). Sigma Dialysis Tubing (seamless cellulose tubing, MWCO 12 000) was purchased from Sigma Chemical Co (St Louis, MO). Aerosil-200 (Aerosil) (Degussa Corp, Dusseldorf, Germany) was a gift sample from Get Rid Pharmaceuticals (Pune, India). All other reagents were of analytical grade and were used as received.

Methods

Preliminary Studies

Preliminary screening of various oils was done to study their accommodation ability for ketoprofen and the gelation with Aerosil. Increasing proportions of ketoprofen and Aerosil were added separately to specific volume of oils taken in test tubes. All the mixtures were mixed thoroughly and warmed at 45°C for 30 minutes. Afterward, the mixtures were kept at ambient conditions for ~5 hours. Mixtures of oils and ketoprofen were observed for undissolved fractions of drug, while mixtures of oils and Aerosil were observed for gelation and subsequent increase in viscosity.

Preparation of Self-emulsifying Systems

A mixture of Captex and Tween 80 (4:3 parts, by volume) was prepared by simple mixing and ketoprofen (1 g/7 mL) was dissolved in it to get a clear solution. To study the effect of variables, different batches were prepared using 3^2 factorial design, each batch containing 100 mg ketoprofen and varying amounts of Capmul and Aerosil as 2 independent variables. Coded and actual values of variables for each batch and the experiment design are shown in Table 1. All the systems were visually observed for isotropicity.

Turbidimetric Evaluation

Nepheloturbidimetric evaluation was done to monitor the growth of emulsification. Self-emulsifying system (0.5 mL) was added to 0.1N hydrochloric acid (150 mL) under continuous stirring (50 rpm) on magnetic plate (Ika-Werke, Staufen, Germany) at ambient temperature, and the increase in turbidity was measured using a turbidimeter (type 131, Systronics, Ahmedabad, India). However, since the time required for complete emulsification was too short, it was not possible to monitor the rate of change of turbidity (rate of emulsification).

Viscosity Determination

Viscosities of the systems as such and after dilution with 5% vol/vol water were determined using Brookfield DV III programmable rheometer (spindle no CPE40, Brookfield Engineering Laboratories, Inc, Middleboro, MA) at ambient temperature. Under varying shear rate, viscosities were measured and the data obtained were further analyzed by regression treatments, using Unistat (Megalon, Novato, CA) software.

Table 2. Responses Obtained for the Studied Parameters From Experimental Batches*

	Parameters				
SES No.	Time Required for Emulsification (seconds)	Turbidity (NTU)	Viscosity of Undiluted SEDDS at 1.0 rpm (cP)	Viscosity of LC Phases at 1.0 rpm (cP)	Droplet Size ± SD (nm)
1	50	291	79.9	97.7	133.5 ± 1.8
2	55	282	73.3	92.9	137.3 ± 2.4
3	45	255	89.9	158.5	193.9 ± 7.0
4	30	78	73.9	82.8	98.3 ± 1.1
5	30	109	118.0	100.1	96.4 ± 1.3
6	30	108	101.4	209.0	273.6 ± 11.7
7	30	78	55.8	58.5	90.8 ± 7.3
8	30	63	57.5	72.5	142.8 ± 2.6
9	30	82	99.6	100.0	129.0 ± 8.1

*SES indicates Self-emulsifying system; NTU, Nepheloturbidimetric unit; SEDDS, self-emulsifying drug delivery system; and LC, liquid crystal.

Droplet Size Analysis

Properly diluted samples of self-emulsifying systems were used for droplet size analysis using a Zetasizer 3000 HAS (Malvern Instruments, Worcestershire, UK). Average droplet size and polydispersity index were determined and the data obtained were further treated with regression analysis, using Unistat software.

In Vitro Diffusion Study

In vitro diffusion studies were performed for all the formulations developed, using a dialysis technique. The dialyzing medium was phosphate buffer pH 6.8. One end of pretreated cellulose dialysis tubing (7 cm in length) was tied with thread, and then 1 mL of self-emulsifying formulation was placed in it along with 0.5 mL of dialyzing medium. The other end of the tubing was also secured with thread and was allowed to rotate freely in 200 mL of dialyzing medium and stirred continuously at 100 rpm with magnetic bead on magnetic plate at 37°C. Aliquots of 1 mL were removed at different time intervals and diluted further. Volume of aliquots was replaced with fresh dialyzing medium each time. These samples were analyzed quantitatively for ketoprofen dialyzed across the membrane at corresponding time by using UV-visible spectrophotometer (Jasco V-530 series, Hachioji, Japan) at 260 nm. Data obtained were analyzed using PCP Disso V 3.0 software (PCP, Pune, India).

Results and Discussion

Preliminary studies were performed for selection of oil, which was an important and critical requisite for formulation of SEDDS. Solvent capacity for less hydrophobic drugs can be improved by blending triglycerides with mono- and diglycerides.[5] For this purpose, different oils, namely, Captex 200, Captex 355, Miglyol 812, Miglyol 840, and Labrafac CC, were screened for their ability to accommodate unit dose of ketoprofen. It was observed that, with Captex 200 and Miglyol 840 (both chemically, propylene glycol dicaprylate/dicaprate, diglycerides) as the oil phase, it was possible to achieve more concentrated SEDDS because both of them could dissolve higher amounts of ketoprofen. Other triglycerides showed less affinity for ketoprofen because of their high nonpolar nature. Of these 2 oils, Captex 200 was used for further studies. Viscosity of Captex 200 (7-13 cP) increased significantly after addition of Aerosil. Aerosil (fumed silica) has polar silanol (Si-OH) groups on its surface, which render it hydrophilic. The behavior of Aerosil in polar and nonpolar systems has been extensively studied by Raghavan et al[25,26] who reported that the nonpolar liquids interact weakly with the silica surface, thus enabling adjacent silica particles to interact through H-bonds formed between the surface silanol groups. Such particle-particle bonds lead to the formation of 3-dimensional gel structures. Gelling of SEDDS in the presence of Aerosil may affect the progress of emulsification as well as the release of drug from the droplets.

On the basis of this preliminary study, different compositions of Captex 200 and Tween 80 were prepared and observed for isotropicity. The mixture containing Captex 200 and minimum amount of Tween 80 (4:3 parts, by volume) yielded a clear and visually isotropic system. This particular system, with ketoprofen (1 g/7 mL of mixture), was further used to study the effect of variables.

The performance of SEDDS was evaluated with respect to progress of emulsification and in vitro diffusion studies. Various parameters studied to monitor progress of emulsification include emulsification time, turbidimetry, viscosity measurements, and droplet size analysis. Responses obtained for all these parameters from the batches of factorial design experiments are summarized in Table 2. The data were subjected to multiple regression analysis using Unistat software. The data were fitted in Equation 1.

Table 3. Summary of Regression Results for the Measured Responses*

Parameters	Coefficients							
	β_0	β_1	β_2	β_{11}	β_{22}	β_{12}	r^2	*P*
Time required for emulsification (seconds)	36.67	-10.0	-	-	-	-	0.706	0.001
Turbidimetry (NTU)	149.56	-100.8	-	-	-	-	0.821	0.001
US-n†	7.37	-2.5	-	-	-3.85	-	0.651	0.043
LC-n‡	3.65	-1.95	-	-	-	-	0.493	0.035
Average droplet size (nm)	143.95	-	45.65	-	-	-	0.465	0.004
$T_{10\%}$ (minutes)	37.56	-5.18	6.78	-	-	-	0.846	0.000
$T_{20\%}$ (minutes)	80.48	-12.88	14.73	6.7	6.45	-	0.929	0.000
$T_{30\%}$ (minutes)	132.11	-21.88	23.15	13.05	11.0	-	0.938	0.000
$T_{40\%}$ (minutes)	187.82	-31.95	31.93	20.61	15.9	-	0.937	0.000
$T_{45\%}$ (minutes)	216.88	-37.25	36.19	24.83	18.7	-	0.934	0.000

*NTU indicates Nepheloturbidimetric unit; US indicates undiluted SEDDS; LC, liquid crystal, and T, time

† Slope of power law curve for undiluted systems.

‡ Slope of power law curve for LC phases.

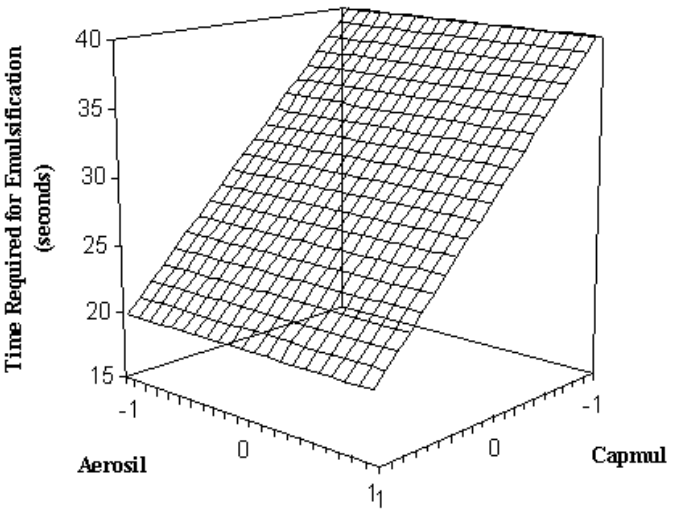

Figure 1. Response surface plot for effect of variables on time required for emulsification.

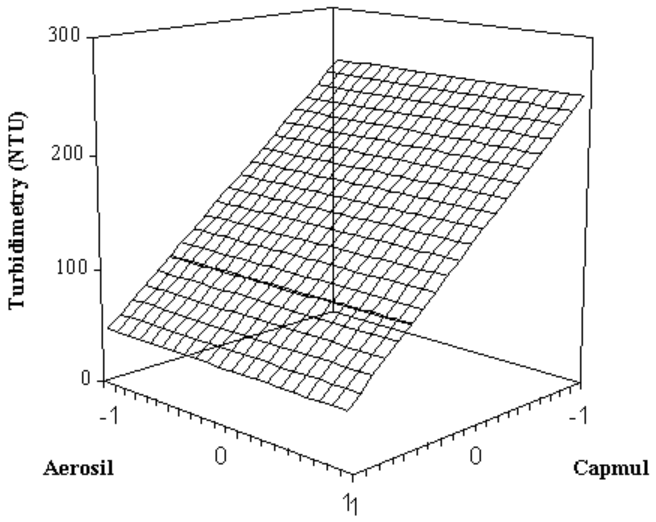

Figure 2. Response surface plot for effect of variables on turbidimetry.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1 X_1 + \beta_{22} X_2 X_2 + \beta_{12} X_1 X_2 \quad (1)$$

The results of multiple regression analysis for all the parameters studied are summarized in Table 3. Insignificant variables were removed, and adequacy of fitted model was checked by analysis of variance (ANOVA). The response surface plots were generated using PCP Disso V 3.0 software. Figure 1 and Figure 2 show response surface plots of time required for emulsification and turbidimetry, respectively.

Viscosities of all the systems as such and after dilution with 5% vol/vol water were determined. It was observed that with the addition of 5% vol/vol water to systems, LC phases were formed that had higher viscosities as compared with undiluted systems, at all shear rates. No significant correlation was observed between the viscosity of SEDDS and concentration of Aerosil. However, it was noted that SEDDS containing lower amounts of Aerosil (less that 2% wt/vol) exhibited almost similar viscosity, while SEDDS with high amounts of Aerosil showed comparatively high viscosity values. This observation indicated less H-bonding interactions between adjacent Aerosil particles, when its amount per unit volume was less, and certain minimum concentration (around 2% wt/vol) is required for H-bonding interactions to occur, resulting in shear thickening flocculated systems. Raghavan et al[26] reported that the magnitude of shear thickening effect progressively increases with increasing Aerosil concentration (above 2% wt/vol). Because of capacity-limited accommodation of Aerosil in SEDDS, it was not possible to incorporate higher amounts of Aerosil.

Also at constant rate of shear, viscosities of LC phases formed were found to be directly proportional to the concen-

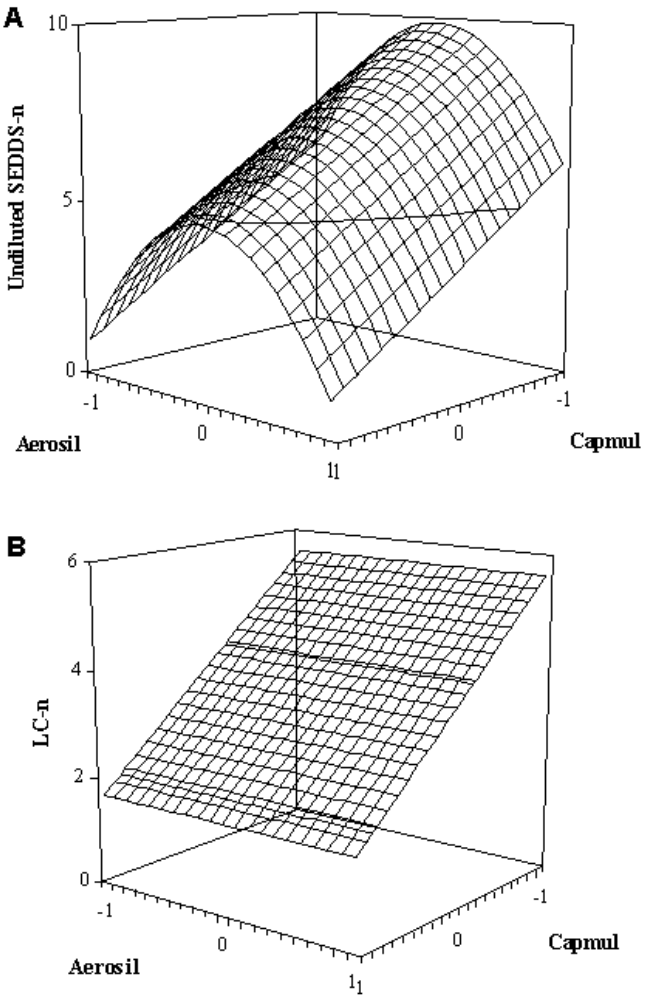

Figure 3. Effect of variables on coefficient of viscosity (n): (A) Undiluted SEDDS and (B) LC phases.

trations of Aerosil, indicating its ability to swell in SEDDS has significant effect on the formation of LC phases and their viscosities.

$$\text{Viscosity of LC Phase} = 108.0 + 38.083\ (\text{Amount of Aerosil})\ (P < .05) \quad (2)$$

Power law relates rate of shear with shear stress, and the relationship is given as

$$\text{Rate of Shear} = K\ \tau^n \quad (3)$$

where K is constant and τ is shear stress. Exponent "n" is the viscosity coefficient, which indicates the deviation from Newtonian behavior (n = 1). For shear thinning (pseudoplastic) systems, n > 1 and for shear thickening (dilatant) systems, n < 1.[27]

The viscosity data of both undiluted SEDDS and LC phases were found to obey power law, and the power law curves yielded slope (n) values less than 1 for all the systems, indicating their shear thickening nature. Also "n" values were

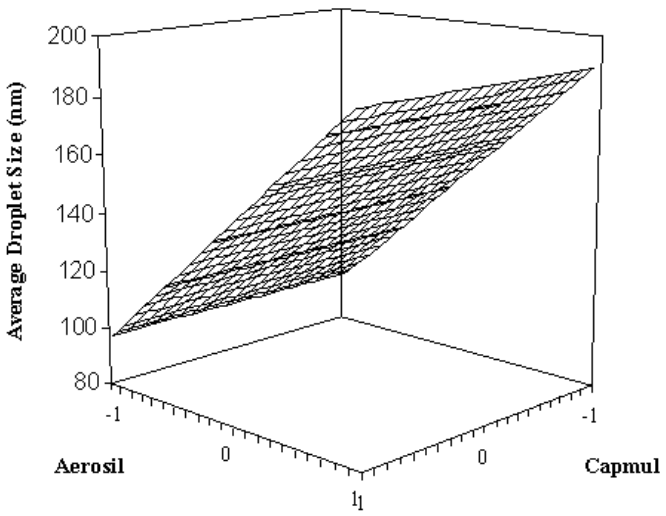

Figure 4. Response surface plot for effect of variables on average droplet size.

inversely proportional to Capmul concentration for both undiluted SEDDS and their LC phases, as shown by the response surfaces in Figure 3.

Since the formation of droplet is greatly influenced by viscosity of LC phases, the average droplet size was found to be directly proportional to the viscosity of LC phase, as follows:

$$\text{Average droplet size} = 20.047 + 1.147(\text{Viscosity of LC Phase})\ (P = .0003) \quad (4)$$

First, it is important to note that although no significant changes in the viscosities of SEDDS were observed at lower Aerosil concentrations, increase in average droplet size can also be attributed to a certain extent ($r^2 = 0.465$) with increasing Aerosil concentration in SEDDS (Figure 4). Second, incorporation of increasing amounts of Capmul was expected to result in formation of smaller droplets because, as a cosurfactant, it reduces the angle of curvature during droplet formation and minimizes H-bonding between adjacent Aerosil particles by rendering the system more polar. However, this effect of Capmul was probably overweighed by the significant increase in the viscosity of LC phases owing to the presence of Aerosil, and the resultant average droplet size obtained was found to be independent of Capmul concentration.

Many studies reported in the literature involve dissolution testing of SEDDS using United States Pharmacopeia apparatus.[3,9] Complete drug release in the initial few minutes has also been reported.[9] In this study, it was observed that the entire drug was released within 5 to 10 minutes from each SEDDS formulated (data not shown). Release of drug from SEDDS is highly dependent on LC formed at the interface, since it is likely to affect the angle of curvature of the droplet formed and the resistance offered for partitioning of drug into aqueous media. Effect of LC will be more prominent for

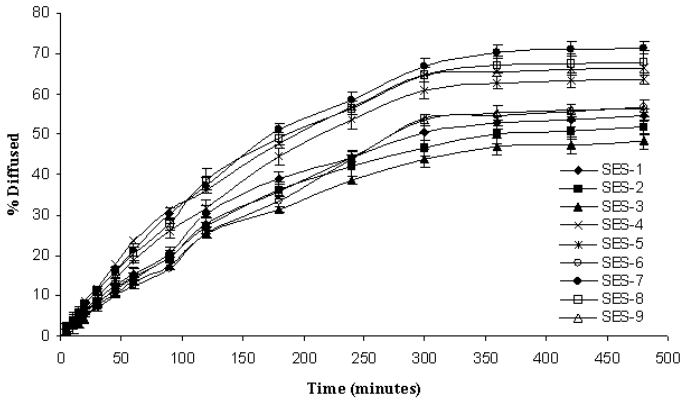

Figure 5. Comparative diffusion profiles of SEDDS from different batches. SES indicates Self-emulsifying system.

semisolid or solid SEDDS because LC phases are formed in situ, and the drug diffuses through LC phases into aqueous media. On this basis, it was decided to monitor drug release from the LC phase by dialysis technique. Dialysis has been previously used by Kim et al (2000),[15] where the system was emulsified, and transport across the dialysis membrane was studied, the technique which ensured the drug was released from the droplets. In further studies of solid SEDDS, this gelled system will be present in a sustained release tablet dosage form, where it will undergo controlled hydration rather than free emulsification. Therefore the dialysis study was performed with suitably hydrated SEDDS inside the dialysis bag. Comparison of diffusion profiles and response surfaces at different time intervals are shown in Figure 5 and Figure 6, respectively. It can be noted that the in vitro diffusion of drug from LC phases was directly proportional to Capmul concentration and was inversely proportional to Aerosil concentration. Incorporation of increasing amounts of Capmul rendered the system more polar and also interfered with H-bonding of adjacent Aerosil particles, thereby facilitating the diffusion of drug across LC phases to the surrounding aqueous media. Concurrent with the observations of viscosities of LC phases and Aerosil concentration, response surfaces reflected less inhibitory effect on drug diffusion when Aerosil concentration was lower in the systems. Prominent resistance to drug diffusion was caused by high viscosity of LC phases in the presence of a high amount of Aerosil. The resultant drug diffusion from the formulation was the net result of these 2 variables acting in opposite directions.

CONCLUSION

In SEDDS containing ketoprofen, incorporation of a gelling agent increased the LC-phase viscosity, which led to formation of coarser droplets and slower drug diffusion. Although Capmul had no effect on average droplet size, it increased drug diffusion from the formulation. Further studies are indicated for potential applications of gelled SEDDS for transformation in sustained release solid dosage forms.

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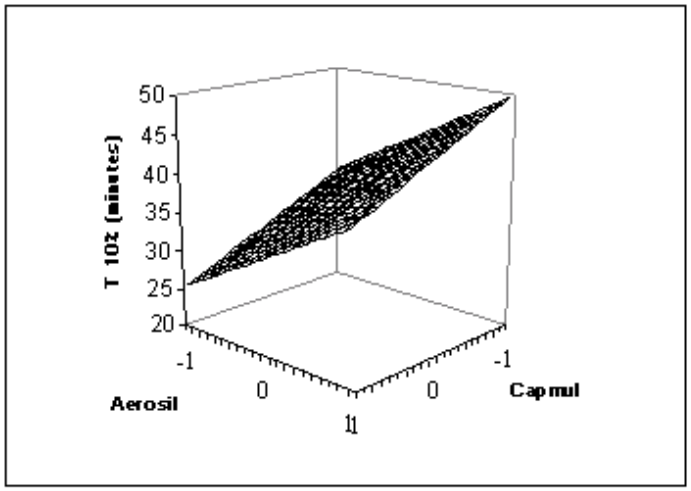
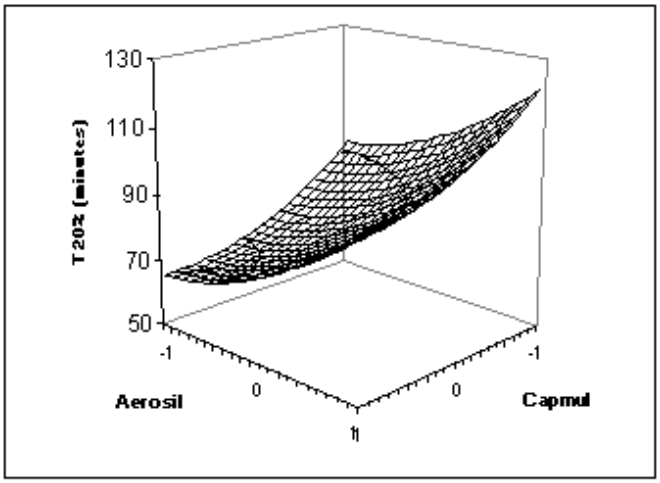
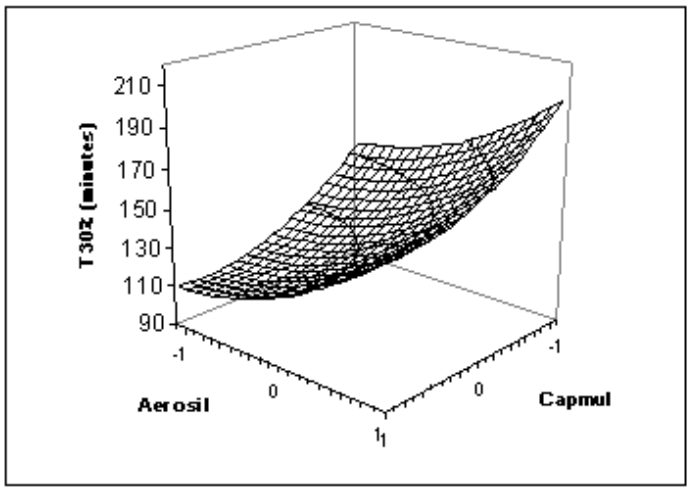


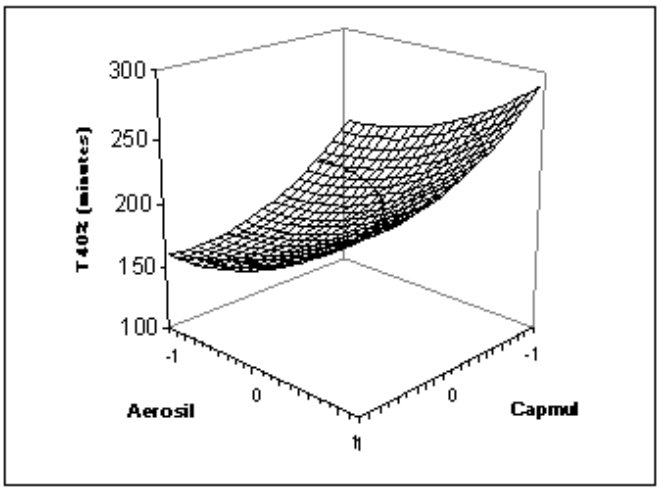
$T_{10\%}$



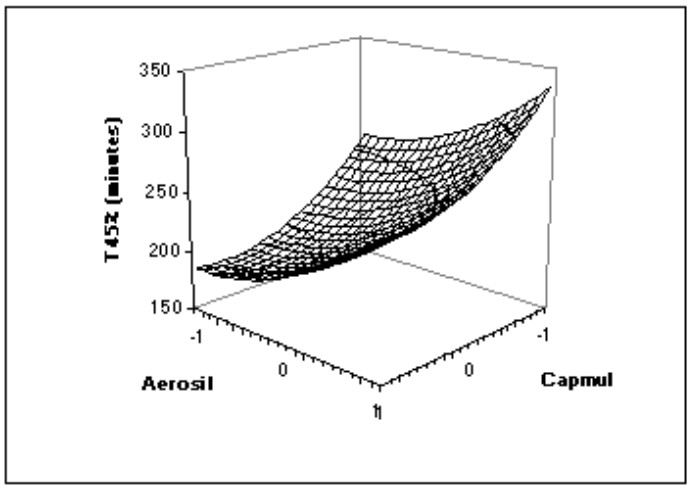
$T_{20\%}$



$T_{30\%}$



$T_{40\%}$



$T_{45\%}$

Figure 6. Effect of variables on drug diffusion profiles of SEDDS.

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