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Research Article

Extended Release Felodipine Self-Nanoemulsifying System

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Abstract. The purpose of the present study was to formulate a self-nanoemulsifying system (SNES) containing model lipophilic drug, felodipine (FLD), to improve its solubility. The SNES was formulated using varying amounts of Miglyol® 840 (as an oil), Cremophor® EL (as a surfactant), and Capmul® MCM (as a co-surfactant). The SNES were characterized for turbidity, droplet size and *in vitro* FLD release. The SNES containing oil, surfactant, and co-surfactant in the weight ratio of 3.5:1.0:1.0, respectively, showed good emulsification, median droplet size of 421 nm, and rapid FLD release (>90% release in 15 min). Gelling was induced in the SNES by addition of Aerosil® 200 (A 200). Rheological studies clearly demonstrated the formation of gelled microstructure with enhanced elasticity for SNES with A 200. Since FLD warrants extended delivery for management of hypertension, the gelled SNES was further encased within the hydrophobic Gelucire® 43/01 (GEL) coat to extend the release of FLD. Caprol® PGE-860 (CAP) was added to this coat as a release enhancer. No interaction was seen between GEL and CAP in differential scanning calorimetry. The effect of two formulation variables in the encased SNES, viz., the gelling agent (A200) and the release enhancer (CAP), on the *in vitro* FLD release was evaluated using 3^2 factorial design experiments. CAP by virtue of channel formation in GEL coat favored the FLD release, while the A200 retarded the FLD release by inducing gelling. At later time points, an interaction between these two variables was found to govern extended release of FLD. The developed gelled SNES encased within the GEL coat can be used as an extended release composition for lipophilic drugs.

KEY WORDS: extended release; felodipine; gelucire 43/01; self-nanoemulsifying system.

INTRODUCTION

Self-emulsifying system is a mixture of oil and surfactants and/or co-solvent. They have the ability to emulsify spontaneously in aqueous media even under gentle agitation (1). Upon peroral administration, these systems readily form fine emulsion in the gastrointestinal tract by virtue of mild agitation provided by gastric mobility and, thus, present the contained drug in solublized form *in vivo*. Therefore, these self-emulsifying systems have the potential to improve the rate and extent of absorption of lipophilc (BCS Class II) drugs showing dissolution as a rate-limiting step for *in vivo* absorption (2–4). Renaissances in the use of self-emulsifying system over the past two decades are inviting increasing attention. Recent trends are focused on the development of modified self-emulsifying solid or semi-solid formulations as an alternative to the conventional liquid self-emulsifying system. These include spray-dried emulsion (5), enteric-coated solid-state pre-microemulsion concentrates (6), self-nanoemulsified tablets containing ubiquinone (7), supersaturable self-emulsifying system of paclitaxel (8), and self-emulsifiable pellets (9,10). Solid self-emulsifying system comprising goat fat and Tween 65 was formulated for the delivery of diclofenac (11). Booth *et al.* (12) prepared solid self-emulsifying system using extrusion spheronization technique, wherein lactose and microcrystalline cellulose were used as solidifying aids. Gelled self-emulsifying system containing ketoprofen was formulated as an intermediate for semi-solid or solid dosage forms (13).

However, very few reports are available in the literature that relate to extended drug release systems wherein the self-emulsifying system has been advantageously employed to increase the solubility of lipophilic drug. Barthelemy and Benameur (14) invented a self-emulsifying system loaded cellulose matrix composition, which in aqueous media formed microemulsion. This microemulsion released the drug in a sustained manner. Schwarz (15) developed solid self-emulsifying dosage form for sustained delivery of active principle by

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ABBREVIATIONS: A 200, Aerosil® 200; CAP, Caprol® PGE-860; CTAB, Cetyl trimethyl ammonium bromide; DSC, Differential scanning calorimeter; FLD, Felodipine; *G′*, Solid modulus; *G″*, Viscous modulus; GEL, Gelucire® 43/01; HLB, Hydrophilic lipophilic balance; Hz, Hertz; JCIC, Japanese Cosmetic Ingredients; LC, Liquid crystal; Log P, Partition coefficient; LVR, Linear viscoelastic region; mg/g, Milligram per gram; mg/ml, Milligram per milli-liter; N, Normal; *n**, Complex viscosity; Pa, Pascal; PEG, Polyethylene glycol; Ph.Eur, European Pharmacopoeia; R, Coefficient of correlation; R^2, Coefficient of determination; SNES, Self-nanoemulsifying system; SNES II A, Self-nanoemulsifying system II with 25 mg A200; SNES II B, Self-nanoemulsifying system II with 50 mg A200; USP/NF, United State Pharmacopoeia/National Formulary; μm, Micrometer; *w/v*, Weight by volume.

using large amounts of adsorbent and hydrophilic polymers. Serratoni *et al.* (16) prepared a self-emulsifying system containing water insoluble methyl and propyl paraben, which was loaded on pellets. These pellets were further coated with polymers for controlled release of parabens.

Gelucire® is a family of vehicles derived from the mixtures of mono-, di-, and triglycerides with polyethylene glycol esters of fatty acids. These are available with a variety of properties depending on their hydrophilic–lipophilic balance (HLB) range (HLB 1–18) and melting point range (33–70°C) (17–19). They have a wide variety of applications in fast- and sustained-release pharmaceutical formulations (20,21). Gelucire® 43/01 (GEL) is a hydrophobic lipid with an HLB value of 1 and melting point of 43°C. It is a blend of saturated triglycerides of different fatty acids, viz., C_8 (3%), C_{10} (2%), C_{12} (29%), C_{14} (2%), C_{16} (17%), and C_{18} (36%). Sutananta *et al.* (22) reported sustained release GEL matrices, where merely 1.7% theophylline was released within 20 h. Sustain release ability of the GEL has been attributed to its extreme hydrophobicity.

FLD (oral dose, 5–10 mg/day) is a crystalline drug (melting point 145°C) and is practically insoluble in water (water solubility, 19.7 mg/L; log *P*, 4). Few attempts revealed in the literature underline the need for dissolution rate enhancement of FLD. Major reported approaches are formation of glassy forms (23), micronization and subsequent complexation with beta cyclodextrin (24), solid dispersion (25), and nanodispersions (26). These techniques suffer from certain disadvantages like generation of high static charges, poor wettability and flow properties, agglomeration, polymorphic conversions, and periodic recrystallization. In addition, FLD warrants extended delivery for management of hypertension (27) and is marketed as extended release tablets (Plendil®; 2.5-, 5-, and 10-mg strengths). Conventional extended release formulation of FLD can offer the solubility-dependent release rather than formulation-dependent due to its poor aqueous solubility. In this study, FLD-loaded SNES was prepared using different oils and surfactants. Prepared SNES formulations were evaluated for emulsifying properties, droplet size measurement, rheological properties, and *in vitro* drug release. Effect of formulation variables on *in vitro* drug release was studied using 3^2 factorial design. Optimized SNES was further encased within hydrophobic GEL coat. The unique advantage of the developed system is that the drug is in dissolved state, and hence, formulation-dependent extended release can be achieved.

MATERIALS AND METHODS

Gelucire® 43/01(USP/NF, Ph. Eur.) (waxy solid, melting point=43°C, HLB=01) was a gift from Gattefosse, France. FLD (USP) was a gift by Wockhardt Ltd., India. Glyceryl mono- and dicaprate (Capmul® MCM) and oleic acid esters of decaglycerol (Caprol® PGE-860: CAP) were supplied by Abitec Corp., USA as gift samples. Propylene glycol dicaprylocaprate (Miglyol® 840; Ph. Eur., JCIC) was provided by Sasol Corp., Germany. Polyoxyl 35 castor oil (Cremophor® EL; USP/NF) and colloidal silicon dioxide (Aerosil® 200: A 200; USP/NF; Degussa Corp., Germany) were gift samples from BASF Corp., New Jersey and Get Rid Pharmaceuticals, Pune, India, respectively. All other reagents were of analytical grade.

Formulation of FLD SNES

FLD [50 mg, weighed using Mettler Toledo (AB204-S) balance, Switzerland with readability of 0.1 mg] was dissolved in Miglyol® 840 (700 mg) by heating on temperature-controlled water bath to 50°C in a glass vial. To this, varying amounts of Cremophor® EL and Capmul® MCM were added and mixed well (Table I). The resultant mixture was cooled to ambient temperature (30°C) and was observed after 10 h for drug precipitation, if any. Emulsifying properties of prepared SNES was examined upon dilution with water.

Evaluation of FLD SNES

Turbidimetry

SNES (0.2 ml) was added to purified water (150 ml) under continuous stirring (50 rpm) on magnetic plate (Ika®-Werke, Germany) at 30°C and equilibrium turbidity was measured using Systronic turbidimeter (Systronics®, Type 131, Ahmadabad, India).

Table I. Composition and Evaluation of FLD SNES

	SNES		
Composition/evaluation parameter	I	II	III
Composition (% *w*/*w*)			
FLD	3.7	4.35	3.7
Miglyol® 840	51.85	60.87	51.85
Cremophor® EL	29.63	17.39	14.81
Capmul® MCM	14.81	17.39	29.63
Evaluation parameter			
Visual quality of emulsion produced	Very Good	Very good	Moderate
Turbidity[a] (NTU)	104.21±14.18	86.43±18.54	196.3±32.24
Median droplet size[a] (nm)	394.42±21.24	421.43±18.54	664.86±7.83
Drug content[a] (mg/g)	35.87±2.13	43.21±1.89	36.12±2.97

FLD felodipine, *SNES* self-nanoemulsifying system
[a] Mean±SD, $n=3$

Droplet Size Measurement

Droplet size measurement was performed by using laser diffractometer (Mastersizer 2000 version 2.0, Malvern Instruments, Malvern, UK). The measurements were based on Mie theory. SNES were diluted with water (200 times) before measurement, and all measurements were performed in triplicates after 2-min stirring. The data was presented in terms of median diameter (D_{50}), which was calculated by Malvern Software version 5.22. For each measurement, obscuration was in the range of 10–20%, while weighted residual was less than 2%.

Drug Content

SNES (500 mg) was dissolved in 100 ml methanol to obtain stock solution. This solution, after stepwise dilution with methanol, was analyzed for FLD content by UV spectrophotometric analysis (Jasco® V-530, Japan) at 362 nm against similarly treated placebo SNES as blank.

In Vitro Drug Release

In vitro drug release studies (in triplicates) were carried out using USP 24 type II dissolution test apparatus (Electrolab® TDT-06P, Mumbai, India). FLD SNES (equivalent to 5 mg FLD) was added to 900 ml phosphate buffer (pH 6.5) with 0.5% *w*/*v* cetyl trimethyl ammonium bromide (CTAB), added to effect the sink condition (28). Dissolution media was thermostated at 37±0.5°C and stirred at 100 rpm. Aliquots were collected periodically and replaced with fresh and pre-warmed dissolution medium. The aliquots, after filtration through Whatman paper (pore size 0.45 μm), were analyzed using spectrophotometer at 362 nm (against similarly treated placebo SNES as blank) for FLD content. The data was analyzed using PCP Disso version 3.0 software (Pune, India).

Preparation of Blank GEL Carriers

Pre-weighed quantities of GEL (350 mg each) were melted on a temperature-controlled water bath to 50°C in a glass vial. To the molten mass, varying amounts of CAP was added and mixed well (Table II). Approximately 75% of such mixture was poured into pre-chilled specially fabricated stainless steel mould (internal die length, 15 mm; die diameter, 10 mm) and then allowed to solidify. Central cavity of 11-mm length and 6.5-mm diameter was created in this molten semisolid mass by virtue of stainless steel rod (length, 15 mm; diameter, 6.5 mm). Both speed of penetration (2 mm/min) and penetration depth (11 mm) of steel rod were controlled by advanced force gauge (Mecmesin, West Sussex, England). After 2 min, the rod was removed (2 mm/min), thus creating an open cavity. Dilute aqueous potassium permanganate solution (0.25 ml) was poured in the cavity, which was then sealed by spreading the remaining amount of molten GEL mixture onto it. This was allowed to further solidify at cold conditions (2–8°C) overnight. Before evaluation, GEL carrier was equilibrated to 30°C for 5 h.

Evaluation of Blank GEL Carriers

Blank carriers were evaluated for weight uniformity, leak test, cavity volume, and coat thickness (Table II). Leak test was performed by placing the blank carriers (filled with dilute aqueous potassium permanganate solution) in distilled water at 37°C and stirring for 15 min. The appearance of pink color in outer aqueous media was an indication of leakage from carrier. Mean cavity volume was measured by breaking ten blank carriers and emptying their contents in a measuring cylinder. Coat thickness of ten blank GEL carriers was measured using vernier caliper.

Differential scanning calorimetry (DSC) thermograms of untreated GEL (A), blank carrier containing 350 mg GEL with 25 mg CAP (B), blank carrier containing 350 mg GEL with 50 mg CAP (C), and blank GEL carriers after 2 and 5 h hydration (D and E, respectively) were obtained using a Mettler Toledo® DSC 821e instrument equipped with an intracooler (Mettler Toledo, Switzerland). The hydration medium was 900 ml of phosphate buffer (pH 6.5) with 0.5% *w*/*v* CTAB maintained at 37±0.5°C and stirred at 100 rpm. Indium standard was used to calibrate the DSC temperature and enthalpy scale. GEL carrier (between 5 to 10 mg) was hermetically sealed into a pierced aluminum crucible and heated at a constant rate of 10°C/min over a temperature range 0°C to 100°C. Inert atmosphere was maintained by purging nitrogen at a flow rate of 50 ml/min.

Table II. Composition and Evaluation of Blank GEL Carriers

	Blank GEL carrier		
Composition/evaluation parameter	A	B	C
Composition			
GEL (mg)	350	350	350
Caprol® PGE-860 (mg)	–	25	50
Colored solution (ml)	0.25	0.25	0.25
Evaluation parameter			
Weight[a] (mg)	605±5.32	621±5.32	646±5.32
Leak test	Negative	Negative	Negative
Cavity volume[a] (ml)	0.24±0.05	0.25±0.06	0.25±0.04
Coat thickness[a] (mm)	1.32±0.14	1.29±0.17	1.30±0.15

GEL Gelucire® 43/01
[a] Mean±SD, $n=10$

Preparation of Gelled SNES Containing FLD

To 500 mg of optimized SNES composition, either 50 mg [SNES II (A)] or 100 mg [SNES II (B)] of A 200 was separately added in sealed glass containers. These systems were mixed thoroughly and kept at 40°C for 3 h and then stored at 30°C.

Rheological Studies of FLD SNES

Rheological study of SNES containing FLD was carried out using a controlled stress rheometer (Viscotech®, Rheologica Instruments AB, Lund, Sweden). The aim of the study was to evaluate the effect of gelling agent on viscoelastic properties of FLD SNES. Data analysis was done using Stress RheoLogic Basic software, version 5.0. A cone and plate geometry was used with 25-mm diameter and cone of 1.0°. Fresh sample was used for each measurement, and measurements (in triplicate) were carried out at 25°C. The sample was subjected to a stress of 1 to 200 Pa at a fixed frequency of 1 Hz. Solid modulus (G'), viscous modulus (G''), complex viscosity (n^*), and loss tangent (tan δ) were recorded over a range of applied stress to determine the ability of SNES to resist the deformation under applied stress.

Preparation of Factorial Batches of GEL Carriers with FLD SNES

The effect of two formulation variables, viz., gelling agent (A 200) and release enhancer (CAP), on the *in vitro* drug release was evaluated using 3^2 factorial design and response surface methodology. The batches (using 3^2 factorial design) were prepared by similar method employed for blank carriers, except different FLD SNES compositions [II, II (A) and II (B)] were added to the GEL cavities formed in lieu of dilute aqueous potassium permanganate solution. In addition, the composition of carrier varied with respect to the amounts of CAP, as described in Table III.

In vitro Drug Release

In vitro FLD release from prepared GEL carrier was determined in 900 ml 0.1 N hydrochloric acid (pH 1.2) for first 2 h and thereafter in 900 ml phosphate buffer (pH 6.5) with 0.5% *w/v* CTAB. Both dissolution media were maintained at 37±0.5°C and stirred at speed of 100 rpm. The release profiles were statistically treated for non-linear regression analysis using PCP Disso version 3.0 software (Pune, India) to calculate time required for *X*% (i.e. 25%, 50%, and 75%) drug release and coefficients were recorded.

RESULTS AND DISCUSSION

Preliminary studies were focused on screening of different pharmaceutically acceptable oils for FLD solubilization. Various oils and blank SNES compositions thereof were studied for their ability to solubilize FLD (as determined visually by observing precipitation on overnight storage at 30°C. Miglyol® 840 was selected as an oil phase, as blank SNES compositions thereof showed better drug solubility (between 35 and 45 mg/g) in trial runs. Hence, Miglyol® 840 was used along with different ratio of hydrophilic surfactant (Cremophor® EL) and lipophilic cosurfactant (Capmul® MCM) (Table I). SNES I and SNES II with 2:1 and 1:1 *w/w* ratio of Cremophor EL to Capmul® MCM, respectively, yielded emulsions of very good visual quality. Median droplet size for SNES I was around 394 nm and that for SNES II was about 421 nm. SNES III produced moderate quality emulsion with median droplet size about 664 nm due to insufficient amount of hydrophilic surfactant, Cremophor® EL (HLB 12–14). The drug content of formulated SNES ranged between 35 and 44 mg/g, depending on the quantity of carrier aids. In spite of the change in the emulsion droplet size, SNES I, II, and III showed rapid *in vitro* drug release (>90% in first 15 min) with no significant difference ($p>0.05$) (data not shown). SNES II with highest drug content (about 43% mg/g) and smaller droplet size was selected for gelling and further evaluation.

Gelled SNES was obtained by addition A 200 in SNES II and subsequent mixing at 30°C. Gelling might have induced by formation of H-bonds between the silanol (Si–OH) groups present on the surface of A 200, in a non-polar milieu (here, the SNES) as reported by Raghwan *et al*. (29). Gelled SNES containing FLD showed significant increase ($p<0.01$) in median droplet size [541.73±23.55 nm for SNES II (A) and 581.66±27.33 nm for SNES II (B)] as compared to liquid SNES II (421.43±18.54 nm). With the addition of A 200, the drug content for SNES II (A) and SNES II (B) were observed to decrease to 40.86±1.89 and 38.32±2.97 mg/g, respectively (because of dilution). The drug release in

Table III. Batches Prepared Using 3^2 Factorial Design with Coded Levels and Actual Values of Variables

Batch no.	Variable X_1: Amount of A 200 (mg) per 250 mg of SNES II	Variable X_2: Amount of Caprol® PGE-860 (mg) per 350 mg of GEL
1	0 (−1)[a]	0 (−1)
2	0 (−1)	25 (0)
3	0 (−1)	50 (+1)
4	25 (0)	0 (−1)
5	25 (0)	25 (0)
6	25 (0)	50 (+1)
7	50 (+1)	0 (−1)
8	50 (+1)	25 (0)
9	50 (+1)	50 (+1)

GEL Gelucire® 43/01
[a] Values in parentheses indicate coded levels of variables

phosphate buffer (pH 6.5) with 0.5% *w/v* CTAB from gelled SNES [II (A) and II (B)] was slower (about 75% in 30 min and 1.5 h, respectively) than that of SNES II due to the presence of A 200. The increased median droplet size and comparatively slow drug release from both gelled SNES might be due to increased viscosity of liquid crystal (LC) phase. Similar results were observed in our previous study (13).

Rheological properties of material can be evaluated by dynamic (oscillatory) and static measurements. The dynamic measurement provides a more direct correlation with microstructure than static rheology since the materials can be examined in their at-rest state without causing any disruption of their underlying structures (30,31). The term "viscoelasticity" is used to describe behavior, which falls between the classical extremes of elastic response by the Hookean solids and the Newtonian liquids. Viscoelastic materials exhibit simultaneous existence of viscous and elastic properties. The knowledge of viscoelastic properties is pivotal for SNES because the microstructural environment or mobility are responsible for curvature formation, which further influence the observed droplet size and rate of drug diffusion. Thus, these properties can be indirectly probed using these viscoelastic measurements. An oscillation stress sweep test is a dynamic test where the solid modulus G' and viscous modulus G'' are measured as a function of stress at a constant frequency. G' is a measure of the energy stored in a cycle of oscillation while G'' represents the energy dissipated per cycle. In stress sweep measurement, linear viscoelastic region (LVR) is determined, where the ratio of stress and strain is a function of time alone. The results of oscillatory stress sweep of SNES with and without A 200 are shown in Table IV. From Table IV, it was evident that A 200 induced gelling in SNES II (B) as seen from nearly 170,000-fold increase in G' and 33,000-fold increase in complex viscosity as compared to SNES II. SNES II (B) presented higher G′ and longer LVR in stress sweep, confirming its elastic nature (32). It was further observed that induced elasticity increased with an increase in A 200 concentration. An elastic system will resist the deformation induced by applied stress and, thus, on emulsification will yield droplets with higher radius of curvature. Therefore, SNES II (B) with higher elasticity had presented large size droplets on emulsification as compared to SENS II. An augment in elasticity of SNES with addition of A 200 might be the result of enhanced particle–particle interaction, especially intermolecular hydrogen bonding (24). This phenomenon might be responsible for observed gelling. Loss tangent (tan δ) is the ratio of viscous modulus (G'') to solid modulus (G'). The higher the loss tangent, the lesser is the elasticity of the material (33). The tan δ for SNES II was much higher than SNES with A 200. Among SNES II (A) and SNES II (B), the tan δ of the later was lower. From observed tan δ values, it was further confirmed that, with an increase in A 200 concentration, the elasticity of the SNES was increased (Table IV). In drug release studies, SNES II (B) had exhibited slower drug release. The drug release from self-emulsifying system is reported to be governed by diffusion (13). The rate of diffusion is function of elasticity of the system. The higher the elasticity, the lower is the rate of diffusion. Results of rheological studies and drug release studies revealed similar phenomenon. Therefore, from rheological studies, it can be concluded that, with the addition of A 200, the elasticity as well as complex viscosity of the SNES was increased, which resulted in large droplet size and retardation of drug diffusion.

Blank GEL carriers containing potassium permagnate solution did not show any leaking, confirming the ability of adopted method to produce leak proof sealing. No significant variations in the weight, cavity volume, and coat thickness were observed for different batches of blank carriers ($p>0.05$; Table II), presumably due to the similar conditions maintained during their preparation.

DSC thermograms of pure GEL (Fig. 1A) and blank carriers with 25 and 50 mg of CAP (Fig. 1B, and 1C, respectively) did not show any difference in their melting behavior. This indicated an absence of any physical interaction between them. The normalized energy of the melting endotherm, however, decreased with increasing amount of highly viscous release enhancer. This may be due to decreasing weight fraction of melting component (GEL) in the blank carriers B and C (Table V). In addition, the blank GEL carriers hydrated in dissolution media for 2 h (Fig. 1D) and 5 h (Fig. 1E) have not shown any change in melting temperature of GEL, thus ruling out possibility of potential polymorphic transitions in GEL during *in vitro* release. However, the enthalpy of melting endotherm decreased significantly at these time points because of hydration of GEL domain. The presence of small endotherms above 80°C in thermogram E (Fig. 1) may be ascribed to gradual evaporation of water of hydration. Thus, from DSC studies, it was confirmed that there was neither any physical interaction observed between GEL and CAP nor there was any polymeric transformation even after 5 h hydration of GEL.

Erosion pattern of blank GEL carriers was studied in 900 ml of phosphate buffer pH 6.5 (similar to "*In vitro* Drug Release"). Erosion was observed after 2 h. The particle size analysis of dissolution media at initial stage and after 2 and 5 h of hydration was performed using laser diffractometer. The droplet size measurements were based on Mie theory. The size range of eroded particles was between 400 and 800 nm. Therefore, the dissolution media appeared turbid after 2 h. Similar study was carried out for GEL carriers with increasing amounts of release enhancer (CAP). The coarse

Table IV. Results of Oscillatory Stress Sweep for Different SNES

Batch	LVR[a]	G'^a (Pa)	n^a (Pa s)	tan δ^a
SNES II	10±1.52–130±6.11	0.0971±0.0035	0.018±0.0008	12.5±0.6237
SNES II (A)	10±2.31–140±5.50	0.0838±0.0022	0.167±0.0061	0.691±0.0294
SNES II (B)	15±3.29–200 ±7.01	170.8±6.9174	33.01±0.7427	0.687±0.0331

LVR linear viscoelastic region, *SNES* self-nanoemulsifying system
[a] Mean±SD, $n=3$

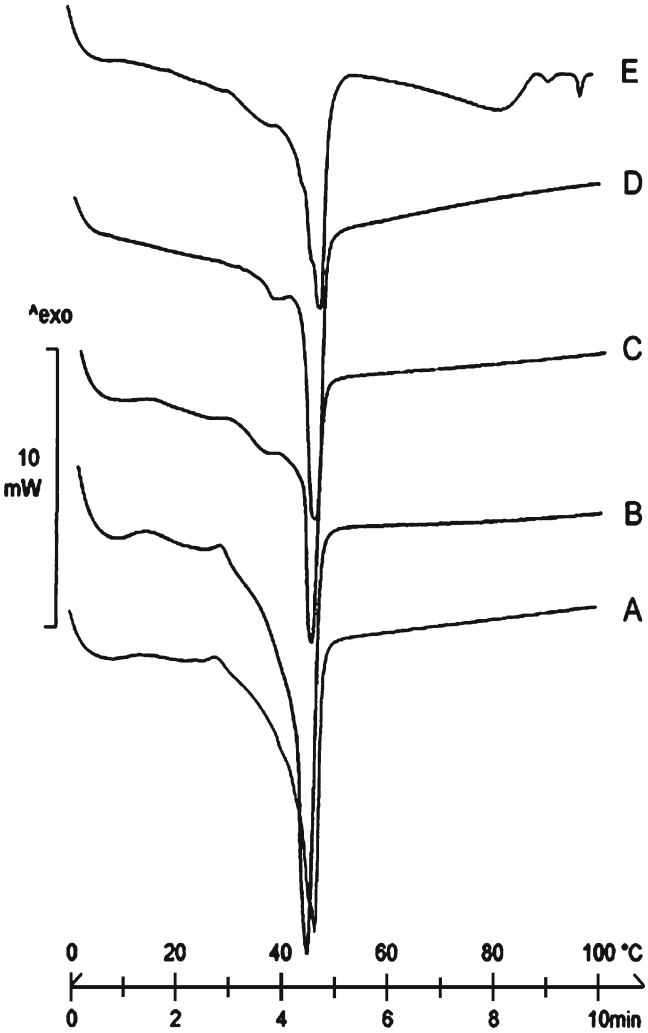

Fig. 1. DSC thermograms *A* neat GEL; *B* GEL/Caprol (350:25 *w/w*); *C* GEL/Caprol (350:50 *w/w*); *D* neat GEL after 2 h hydration in dissolution medium; *E* neat GEL after 5 h hydration in dissolution medium

particles (size range 3 to 5 μm) were observed in the dissolution media, indicating leaching of release enhancer and GEL fraction.

In order to study the effect of two important variables, viz., amount of gelling agent (A 200) in FLD SNES and amount of release enhancer (CAP) in GEL coat, 3^2 factorial design was adopted. Such experimental design enabled evaluation of the effect of these variables (and their interactions, if any) at three different levels on *in vitro* drug release profile from GEL-coated formulation (Table III). The *in vitro* drug release profiles of studied SNES batches are given in Table VI. The amount of drug released as a function of time was mathematically treated to fit into a simple, semi-empirical model developed by Korsmeyer *et al.* (34) relating exponentially the drug release to the elapsed time (t):

$$M_t/M_\infty = k\,t^n \tag{1}$$

where k is a constant incorporating structural and geometric characteristics of the dosage form, n is the release exponent, indicative of the drug release mechanism and M_t/M_∞ is fractional release of drug as a function of time. This model is more applicable for dosage forms wherein there are more than one type of release phenomenon that could be involved (35). The *in vitro* FLD release data from the factorial batches were treated for model fitting using PCP Disso version 3.0 software (Pune, India). For the best-fit models of all factorial batches, the n values ranged between 0.83 and 1.70, while the k values were between 0.7 and 9.6 (with R values between 0.9908 and 0.9996). Therefore, it can be concluded that there was no clear discrimination among these batches with respect to the drug release pattern.

Sutananta *et al.* (22) investigated the mechanism of drug release from different grades of GEL. The nature of GEL was found to strongly affect the underlying drug release mechanism. The drug release was primarily controlled by diffusion in case of hydrophobic variants of Gelucire (Gelucire 43/01 and 54/02), whereas erosion was the predominant mechanism in case of hydrophilic Gelucire (Gelucire 55/18 and 50/13). Abdalla and Mader (36) recently evaluated the release kinetics from the lipid self-emulsifying formulation comprising C_{18} mono and diglycerides and macrogol 15 hydroxy stearate. The release kinetics, assessed by electron spin resonance spectroscopy, revealed that the hydrophobic spin probe used in the study was localized mainly in the lipid environment indicating the release of lipophilic drugs through lipid barrier, primarily by diffusion process. In the present study as well, FLD was present in the lipid (oil) milieu that comprises surfactants, and such composition was further encased within the hydrophobic GEL. Deriving analogy from the reports by Sutananta *et al.* (22) and Abdalla and Mader (36), the drug release from studied system can be

Table V. DSC Integrated Data of Blank GEL Carriers

Sample	DSC integrated data			
	Normalized energy (J/g)	Onset temp (°C)	Peak temp (°C)	Endset temp (°C)
Untreated pure GEL (A)	−74.19	40.43	45.16	47.34
GEL/Caprol®: 350:25 *w/w* (B)	−76.90	40.07	43.21	45.76
GEL/Caprol®: 350:50 *w/w* (C)	−60.54	41.55	43.45	45.87
GEL after 2 h hydration[a] (D)	−43.90	42.94	44.98	47.63
GEL after 5 h hydration[a] (E)	−36.07	43.17	46.95	49.03

DSC differential scanning calorimetry, *GEL* Gelucire® 43/01
[a] Hydration of pure GEL was done in dissolution media

Table VI. *In vitro* Release Profiles of Factorial Batches

Time (h)	Drug released[a] (%)								
	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9
0	0	0	0	0	0	0	0	0	0
2	10.5±6.8	16.8±6.4	20.1±6.1	8.9±6.9	10.5±6.5	14.6±7.3	2.56±6.4	4.9±5.9	8.6±6.8
4	21.5±5.6	29.6±6.7	35.9±6.3	14.6±6.8	16.2±5.4	22.1±5.9	8.86±5.8	14.2±6.1	16.8±5.2
8	38.0±6.7	45.2±5.4	58.6±6.7	33.2±6.7	35.6±6.1	46.8±6.1	29.4±5.8	32.1±5.9	37.5±6.4
12	58.4±5.6	64.5±6.1	72.6±5.9	50.3±5.6	57.9±5.2	64.8±6.4	47.6±6.4	52.3±6.3	58.6±4.9
16	78.4±6.1	81.5±5.8	88.6±4.9	71.8±5.3	72.8±5.9	79.8±5.8	67.2±5.3	68.3±5.4	77.7±4.6
20	89.7±4.8	89.9±4.6	94.5±5.2	78.0±5.3	81.3±4.9	87.6±5.4	74.3±4.9	78.3±4.8	83.2±5.9

[a] Mean±SD, $n=3$

attributed to diffusion mechanism. However, this hypothesis needs further evaluations using advanced and sophisticated instruments.

The data of time required for X% drug release from factorial batches were calculated and further subjected to multiple regression analysis using PCP Disso version 3.0 software (Pune, India). The data were fitted into following equation.

$$Y = \beta 0 + \beta 1\ X1 + \beta 2\ X2 + \beta 11\ X1\ X1 + \beta 22\ X2\ X2 + \beta 12\ X1\ X2 \quad (2)$$

Responses obtained for time required for X% drug release from factorial batches after multiple regression analysis and removing the insignificant variables are depicted in Fig. 2. Time required for 25% and 50% drug release was found to be directly dependent on the amount of gelling agent and inversely proportional to the amount of release enhancer (Fig. 3a, b). However, at these time points, no interaction between these two variables was observed to affect the *in vitro* drug release kinetics, as shown in the following equations.

$$T_{25\%rel}(h) = 5.09 + 1.57X1 - 1.17X2 \quad (R^2 = 0.952; P = 0.004) \quad (3)$$

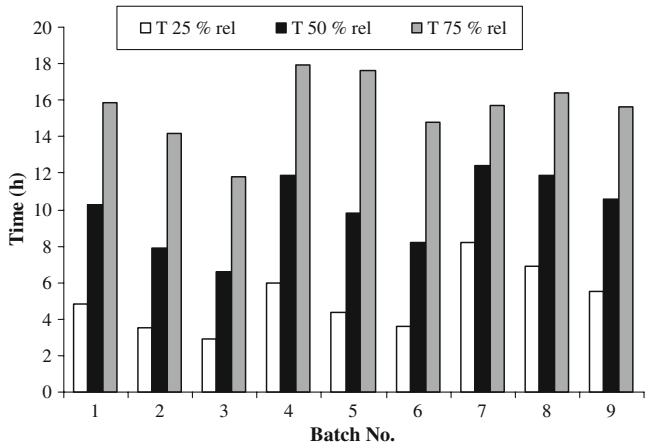

Fig. 2. Responses obtained for time required for X% drug release from factorial batches

$$T_{50\%rel}(h) = 9.96 + 1.68X1 - 1.53X2 \quad (R^2 = 0.952; P = 0.007) \quad (4)$$

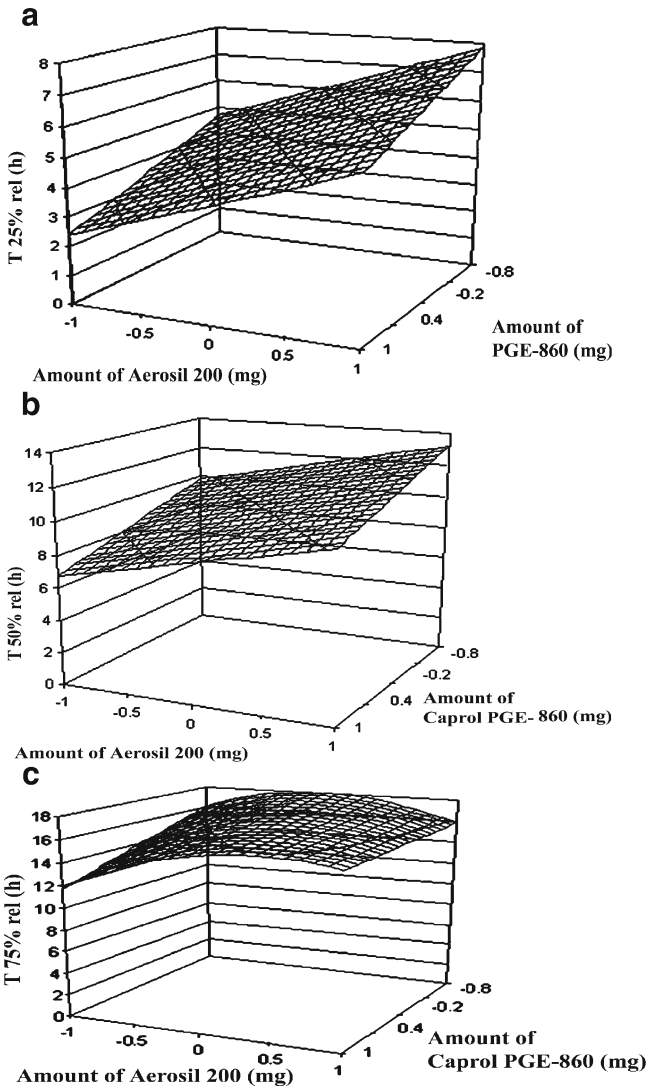

Fig. 3. **a** Effect of variables on time required for 25% drug release. **b** Effect of variables on time required for 50% drug release. **c** Effect of variables on time required for 75% drug release

The retardation of *in vitro* drug release by addition of gelling agent in SNES was in line with the earlier report (13). Moreover, such retardation effect was potentiated by encasing the gelled SNES in the hydrophobic GEL coat (22). On the contrary, leaching of CAP during the release resulted in the formation of aqueous channels, thus promoting drug diffusion through hydrophobic GEL barrier. This mechanism was further confirmed using stereomicroscopic observation of the coat surface during *in vitro* release. Fine and irregular cracks were developed on the blank GEL coat surface after 4 to 5 h. For GEL coats containing release enhancer, similar cracks were observed at earlier time points (after 2 to 3 h), which eventually got enlarged at the later time points (data not shown). Interestingly, as evident form Eq. 5 below, the magnitude of retardation effect of gelling on drug release at later times (e.g., $T_{75\%\ rel}$) was remarkably less (β_1=0.81) as compared to the enhancing effect of channeling agent (β_2= 1.22) owing to leaching of CAP and formation of water filled channels across the GEL wall. This favored the hydration of SNES and subsequent drug diffusion (Fig. 3c).

$$T_{75\%rel}(h) = 16.67 + 0.81\ X1 - 1.22\ X2 - 1.99\ X1X1 + 0.96\ X1X2 \quad (5)$$
$$\left(R^2 = 0.945; P = 0.018\right)$$

Also at this juncture, a potential interaction (β_{12}=0.96) between gelling agent and release enhancer was observed to affect drug release as one of the factors. Thus, the rate of drug release at earlier time points was governed by two independent variables, and the same, at later time points, was additionally governed by complex interaction between these two variables.

Thus, this study demonstrated the feasibility of new formulation comprising SNES encased in a hydrophobic coat for extended drug release.

CONCLUSIONS

The formulated SNES containing FLD improved the dissolution rate markedly and can be utilized for the fabrication of extended release system. Gelled SNES containing FLD encased in a hydrophobic GEL coat can serve as an alternative for conventional extended release formulations. Moreover, by varying the contents of release enhancer and gelling agent in such composition, the release profile of FLD can be manipulated as required. Thus, formulation-dependent extended release of lipophilic FLD was achieved with studied system.

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REFERENCES

1. Charman SA, Charman WN, Rogge MC, Wilson TD, Pouton CW. Self-emulsifying drug delivery systems: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. Pharm Res. 1992;9:87–93.
2. Pouton CW. Self-emulsifying drug delivery systems: assessment of the efficiency of emulsification. Int J Pharm. 1985;27:335–48.
3. Shah NH, Carvajal MT, Patel CI, Infeld NH, 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.
4. Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58:173–82.
5. Hansen T, Holm P, Schultz K. Process characteristics and compaction of spray-dried emulsions containing a drug in lipids. Int J Pharm. 2004;287:55–66.
6. Kim CK, Shin HJ, Yang SG, Kim JH, Oh YK. Once-a-day oral dosing regimen of cyclosporin A: combined therapy of cyclosporin a premicroemulsion concentrates and enteric-coated solid-state premicroemulsion concentrates. Pharm Res. 2001;18:454–59.
7. Nazzal S, Nutan M, Palamakula A, Shah R, Zaghloul AA, Khan MA. Optimization of self-nanoemulsified tablet dosage form of ubiquinone using response surface methodology: effect of formulation ingredients. Int J Pharm. 2002;240:103–14.
8. Gao P, Rush BD, Pfund WP, Huang T, Bauer JM, Morozowich W, *et al.* Development of supersaturable SEDDS formulation of paclitaxel with improved oral bioavailability. J Pharm Sci. 2003;92:2386–98.
9. Newton M, Petersson J, Podczeck F, Clarke A, Booth S. The influence of formulation variables on the properties of pellets containing a self-emulsifying mixture. J Pharm Sci. 2001;90:987–95.
10. Tuleu C, Newton M, Rose J, Euler D, Saklatvala R, Clarke A, *et al.* Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension. J Pharm Sci. 2004;93:1495–502.
11. Attama AA, Nzekwe IT, Nnamani PO, Adikwu MU, Onugu CO. The use of solid self-emulsifying systems in the delivery of diclofenac. Int J Pharm. 2003;262:23–8.
12. Booth SW, Clarke A, Newton JM. Spheronized self-emulsifying system for hydrophobic and water sensitive agents. United States Patent number 6,630,150, 2003.
13. Patil P, Joshi P, Paradkar A. Effect of formulation variables on preparation and evaluation of gelled self-emulsifying drug delivery system (SEDDS) of ketoprofen. AAPS PharmSciTech. 2004;5:E 42.
14. Barthelemy P, Benameur H. Composition with sustained release of active principle, capable of forming microemulsion. United States Patent number 6,309,665 (2001).
15. Schwarz J. Solid self-emulsifying dosage form for improved delivery of poorly soluble hydrophobic compounds and the process of preparation thereof. United States Patent Application Publication number 20030072798 (2003).
16. Serratoni M, Newton M, Booth S, Clarke A. Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system. Eur J Pharm Biopharm. 2007;65:94–8.
17. Sutananta W, Craig DQM, Newton JM. The effects of ageing and thermal behavior and mechanical properties of pharmaceutical glycerides. Int J Pharm. 1994;111:51–62.
18. Ainaoui A, Ouriemchi EM, Bidah D, El Amrani MK, Vergnaud JM. Process of drug release with oral dosage forms with lipidic gelucire matrix. J Polym Eng. 1997;17:245–57.
19. Ainaoui A, Vergnaud JM. Modeling the plasma drug level with oral controlled release forms with lipidic Gelucire. Int J Pharm. 1998;169:155–62.
20. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. *In vivo* evaluation of rapid release and sustained release gelucire capsule formulations. Int J Pharm. 1990;65:85–100.
21. Barker SA, Yap SP, Yeun KH, McCoy CP, Murphy JR, Craig DQM. An investigation into the structure and bioavailability of

alpha tocopherol dispersion in gelucire 44/14. J Control Release. 2003;91:477–88.
22. Sutananta W, Craig DQM, Newton JM. An evaluation of mechanisms of drug release from glycerides bases. J Pharm Pharmacol. 1995;47:182–7.
23. Trojak A, Kocevar K, Musevic I, Srcic S. Investigation of the felodipine glassy state by atomic force microscopy. Int J Pharm. 2001;218:145–51.
24. Sharma VK. Preparation of micron-size pharmaceutical particles by micro-fluidization. United States Patent number 6,555,139, 2003.
25. Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int J Pharm. 2005;301:199–208.
26. Karavas E, Georgarakis E, Bikiaris D. Felodipine nanodispersions as active core for predictable pulsatile chronotherapeutics using PVP/HPMC blends as coating layer. Int J Pharm. 2006;313:189–97.
27. Pannarale G, Puddu PE, Monti F, Collauto F, Serafini G, Schiariti M, *et al.* 24-hour antihypertensive efficacy of extended release felodipine. Am J Hypertens. 1995;8:73A.
28. Eklund M, Lofroth J, Sundgren M. New pharmaceutical formulation. Patent Cooperation Treaty Application Publication number WO/2001/005376 (2001).
29. Raghavan SR, Walls HJ, Khan SA. Rheology of silica dispersions in organic liquids: New evidence for salvation forces dictated by hydrogen bonding. Langmuir 2000;16:7920–30.
30. Barnes HA, Hutton JF, Walters K. An introduction to rheology. In: Rheology Series, Elsevier, Amsterdam, 1989.
31. Eccleston GM, Barry BW, Davis SS. Correlation of viscoelastic functions for pharmaceutical semisolids: comparison of creep and oscillatory tests for oil-in-water creams stabilized by mixed emulsifiers. J Pharm Sci. 1973;62:1954–61.
32. Kobayashi M, Ishikawa S, Samejima M. Application of nonlinear viscoelastic analysis by the oscillation method to some pharmaceutical ointments in the Japanese Pharmacopeia. Chem Pharm Bull. 1982;30:4468–78.
33. Davis SS. Viscoelastic properties of pharmaceutical semisolids III: nondestructive oscillatory testing. J Pharm Sci. 1971;60:1351–5.
34. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25–35.
35. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13:123–33.
36. Abdalla A, Mader K. Preparation and characterization of a self-emulsifying pellet formulation. Eur J Pharm Biopharm. 2007;66:220–6.