Research Article

Formulation development and evaluation of self-nanoemulsified liquisolid compacts of a poorly soluble biopharmaceutics classification system Class II drug

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ABSTRACT

Aim and Objective: The aim and objective of the present study was to formulate and develop self-nanoemulsified liquisolid compacts of an antihypertensive biopharmaceutics classification system (BCS) Class II drug of felodipine which has poor aqueous solubility and low oral bioavailability (19.7 mg/L; log P, 4). **Methodology:** Felodopine was identified by ultraviolet–visible spectroscopy at λmax of 364 nm. A series of self-nanoemulsifying formulations F1-F9 were prepared using isopropyl myristate as oily phase, labrasol as surfactant and capmul C8 as cosurfactant, respectively. The prepared liquid self-nanoemulsifying system was solidified using solid carrier colloidal silicon dioxide (Aerosil 200). Initially, the solubility was examined in different oils, surfactants, and cosurfactant, and ternary phase diagrams were constructed to optimize the ratio of excipients having a greater microemulsion region. **Results and Discussion:** The self-nanoemulsified liquisolid compacts were developed and evaluated for droplet size determination, particle size distribution, dilution studies, and in vitro drug release studies. The in vitro dissolution studies revealed that the release patterns of the formulation (F2) containing 60% surfactant, 10% oil, and 30% cosurfactant show the least emulsification time and maximum drug release of 95% within 1 h concluding that the prepared self-emulsified liquisolid compacts with promising in vitro characteristics were expected to solve the oral delivery problems encountered for highly potent lipophilic drugs. **Conclusion:** The present study concluded that the prepared self-emulsified liquisolid compacts of felodipine were promising carriers to solve the oral delivery problems encountered for highly potent lipophilic drugs.

KEY WORDS: Aerosil 200, Felodipine, Liquisolid compacts, Self-nanoemulsifying

INTRODUCTION

Self-nanoemulsifying drug delivery systems (SNEDDSs) are isotropic mixtures of oil, surfactant, and cosurfactant, and they form transparent nanoemulsions with a droplet size of <200 nm.[1-2] When compared with emulsions, which are sensitive and metastable dispersed forms, SNEDDS is physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles.[3-5] The design of an optimal SNEDDS requires preformulation solubility and phase diagram studies. In the case of prolonged self-emulsifying drug delivery systems, formulation is made by adding the polymer or gelling agent. The SNEDDS thus formulated with the optimized ratios of excipients was evaluated for droplet size, drug loading, zeta potential, polydispersity index, optical clarity, turbidity, cloud point, viscosity determination, self-emulsification time assessment, and *in vitro* drug release studies.

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Aim and Objective of the Study

The aim and objective of the present study were to design and evaluate self-nanoemulsified liquisolid compacts of poorly soluble BCS Class II antihypertensive drug of felodipine by improving its solubility and dissolution characteristics and thereby enhancing its relative bioavailability.

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MATERIALS AND METHODS

Materials

Felodipine and Neusilin were generously gifted by Shasun Pharmaceuticals, Pondicherry. Capmul MCM-C8 was gifted by Abitec, USA. Labrasol was obtained as a gift sample from Gattefosse, France. Isopropyl myristate, Aerosil 200, monobasic sodium phosphate, dibasic sodium phosphate, hydroxypropyl methylcellulose, microcrystalline cellulose, and magnesium stearate were obtained from Himedia Laboratories, Mumbai.

Methods

Preformulation studies

The investigation of any possible interactions between the drug and the excipients was performed by Fourier transform-infrared (FT-IR) spectroscopy. The IR spectra of pure drug felodipine, with mixtures isopropyl myristate, labrasol, and capmul MCM-C8, were carried out using FT-IR Shimadzu Spectrophotometer. The samples were prepared as potassium bromide disks compressed under a pressure 6 ton/nm^2. The IR spectrum of the physical mixture was compared with those of drug, and excipients matching were done to detect any appearance or disappearance of peaks.

Solubility studies

About 2 ml of each solvent was transferred into a 5-ml glass vial, and an excess quantity of drug was added to the vial. The solubility of the drug samples was also analyzed by adding excess amount (150 mg) of the drug to 2 ml of various oils, surfactants, and cosurfactants in screw-capped glass vials, followed by vortex mixing for 30 s using vortex mixer (Sphinx, Japan). The mixtures were shaken for 48 h at 30°C in a thermostatically controlled shaking water bath, followed by equilibrium for 24 h. The sample mixtures were then centrifuged at 3000 rpm for 10 min, and the supernatant liquid was filtered through a millipore membrane filter (0.45 μ). Samples were suitably diluted with methanol, followed by sonication for 10 min and finally diluted with the same solvent. The final drug concentration was quantified by ultraviolet (UV)–visible spectrophotometer at λmax 364 nm.

Construction of ternary phase diagram[6]

To evaluate the effect of drug on the robustness/stability of the SNEDDS, phase diagrams were constructed in the absence and presence of drug. A dose equivalent of 5 mg of Felodipine were added to the preconcentrate of snedds formulations. The oil concentration was varied from 10% to 80% (w/w); the above mixture was diluted to 20 ml with distilled water and observed for nanoemulsion formation. The nanoemulsions were kept under observation for 24 h. Nanoemulsions which showed precipitation of the drug or cracking were rejected. The area of nanoemulsion formation was identified for respective systems, and the phase diagram was plotted using CHEMIX ternary Plot software (Chemix School Ver. 3.6, pub. Arne Standnes , Bergen, Norway. The mean globule size of most stable nanoemulsion was recorded.

Preparation of liquid SNEDDS

Self-nanoemulsifying system was prepared by dissolving felodipine (5 mg) in the mixture of oil, surfactant, and cosurfactant at room temperature by stirring using cyclomixer until a clear solution was obtained. The size reduction was aided by probe sonication for 1 min using sonics probe sonicator till a clear solution was obtained. The composition of SNEDDS formulations was given in Table 1.

Preparation of self-nanoemulsifying system liquisolid compacts

The prepared liquid self-nanoemulsifying system was solidified using adsorbents as solid carriers. The 1 ml of liquid SNEDDS was placed in a small bowl, and the solid carrier colloidal silicon dioxide (Aerosol 200) was added slowly and mixed vigorously to get the granular mass, and it is freeze dried using Yodel freeze dryer at the temperature of –40°C.

Evaluation Parameters for SNEDDS

Dilution studies[7]

Dilution of the vehicle has considerable effect on the phase separation of the spontaneously emulsifying systems in view of this, selected felodipine SNEDDS was diluted (20 times and 100 times) with deionized water. The diluted nanoemulsions were stored for 24 h at room temperature and observed for any signs of phase separation or drug precipitation.

Table 1: Composition of self-nanoemulsifying drug delivery system from F1-F9

Formulation code	Isopropyl myristate (%)	Labrasol (%)	Capmul. MCM-c8 (%)
F 1	10	70	20
F2	10	60	30
F3	20	70	10
F4	30	60	10
F5	30	40	30
F6	30	50	20
F7	60	30	10
F8	70	20	10
F9	70	30	-

Droplet size determination

SNEDDS formulations (1 ml) were diluted with 20 mL deionized water in a beaker with constant stirring on a magnetic stirrer. The droplet size distribution resultant nanoemulsions were determined by phase-contrast microscope (Leica). After equilibrium, the droplet size was recorded.

Particle size distribution[8]

Laser diffractometry was employed to determine the particle size of the nanoemulsion laser diffractometry yields a volume distribution. The size distribution of the particles in the nanoemulsion was determined by laser diffraction (LD) method using Microtrac particle size analyzer (Blue wave model S4521).

In vitro drug release study

Self-nanoemulsifying granules equivalent to 5 mg of felodipine were studied for drug release profiles in 500 ml, 1% (w/v) sodium lauryl sulfate solution using Type II apparatus (Electrolab, Mumbai, India) rotating at 50 rpm by powder dispersion technique. Samples were withdrawn at pre-determined time intervals and analyzed spectrophotometrically using Shimadzu 160A UV-visible spectrophotometer at 364 nm.

RESULTS AND DISCUSSION

FT-IR Spectral Analysis

Compatibility studies of felodipine, isopropyl myristate (IPM), labrasol, and capmul MCM –C8 were carried out using FT-IR. The IR spectra obtained are given in Figure 1. In felodipine IR spectrum, intense peaks were noticed at 1445 cm^{-1} (-CH_2), 2970 cm^{-1} (C-H stretching), 1270 cm^{-1} (-CO- stretching), 3080 cm^{-1} (C-H pyridine), and 3371 cm^{-1} (N-H pyridine). The prepared FT-IR spectra did not show any significant differences from those obtained for pure sample. These obtained results indicate that there was no positive evidence for the interaction between the drug and excipient as indicated in Figure 2 and Table 2.

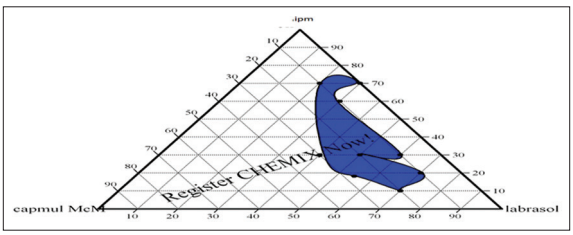

Figure 1: Ternary phase diagram

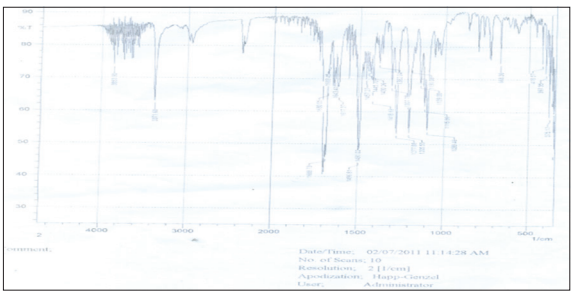

Figure 2: Fourier transform-infrared spectroscopy study of felodipine with excipients

Solubility Study

Self-emulsifying formulation consists of oil, surfactant, and cosurfactant, and it should have good solvent properties to allow appropriate solubility of the drug in the formulation. Drug incorporated in the formulation should also be readily dissolved as clear and monophonic liquid at ambient temperature when introduced to aqueous phase. The solubility of felodipine in various vehicles is presented in Figure 2. Among the vehicles tested, IPM showed highest solubility of felodipine with 41.17 mg/ml, followed by labrasol and capmul MCM-C8 with 252.17 mg/ml, and 35.59 mg/ml, respectively, as indicated in Table 3.

Phase Diagram Study of Felodipine SNEDDS

Based on the results of solubility studies, nine different ratios of oil, surfactant, and cosurfactant were used for the phase diagram study. Corresponding ternary phase diagram of each ratio is represented in Figure 1, the shaded portion indicates the nanoemulsion region. No distinct conversion from w/o to o/w nanoemulsion was observed.

Dilution Studies

The preconcentrate of Snedds formulations were evaluated for dilution studies (1:20 and 1:100) with deionized water and larger dilutions may be considered

Table 2: Fourier transform-infrared spectroscopy spectrum of felodipine

Functional groups	Felodipine
CH_2	1445.7
CH_3	1430.26
C-H stretching	2970
-CO- stretching	1270
C-H (pyridine	3080
N-H (pyridine)	3371.98
-C-Cal	868.36

Table 3: Solubility studies of felodipine in various vehicles

Vehicles	Solubility (mg/ml)
Isopropyl myristate	41.17±0.33
Soya oil	1.1±0.35
Cottonseed oil	2.41±0.35
Sunflower oil	1.29±0.95
Span 20	4.49±0.64
Span 80	2.16±0.34
Labrasol	252.17mg
Tween 80	7.08±0.15
PEG400	10.0±0.34
Propylene glycol	2.43±0.25
Capmul MCM-C8	35.59±0.23

Table 4: Visual assessment of self-nanoemulsifying drug delivery system after dilution

After dilution with water	Dilution (1:20) grade	Time h (24)	Dilution (1:100) grade	Time h (24)
F1	II	III	II	III
F2	I	I	I	I
F3	II	III	II	III
F4	II	II	II	II
F5	IV	V	IV	V
F6	II	III	II	III
F7	II	II	II	II
F8	I	I	I	I
F9	I	I	I	I

Table 5: *In vitro* release data for F2, F4,F7, F8, and F9

Time in min	Percentage release				
	F2	F4	F7	F8	F9
0	0	0	0	0	0
5	23.12±0.36	25.06±0.55	25.04±0.53	26.5±0.35	30.4±0.23
15	37.12±0.27	37.12±0.67	55.16±0.86	51.28±0.19	51.26±0.38
30	55.10±0.55	65.3±0.75	71.29±0.75	75.04±0.59	64.3±0.65
45	75.06±0.80	72.5±0.27	81.06±0.34	85.2±0.32	76.9±0.46
60	95.02±0.39	78.24±0.25	84.7±0.27	90.24±0.46	83.12±0.75

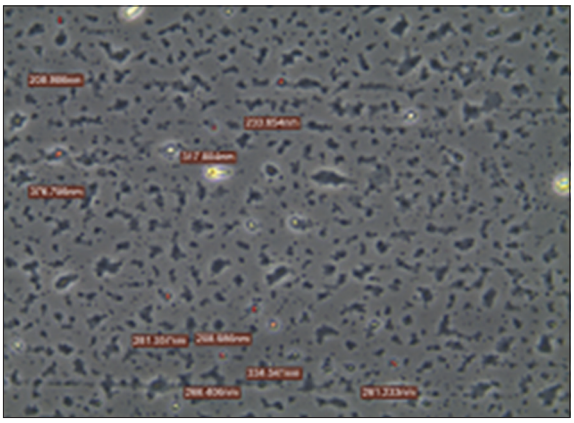

Figure 3: Phase contrast microscope image for formulation-2

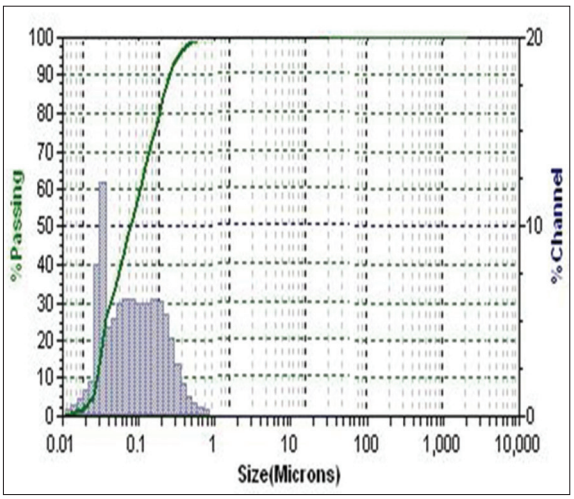

Figure 4: Particle size distribution for F2

due to the of presence of higher concentrations of surfactant included in Snedds which may cause irritation in stomach. Dilution with deionized water

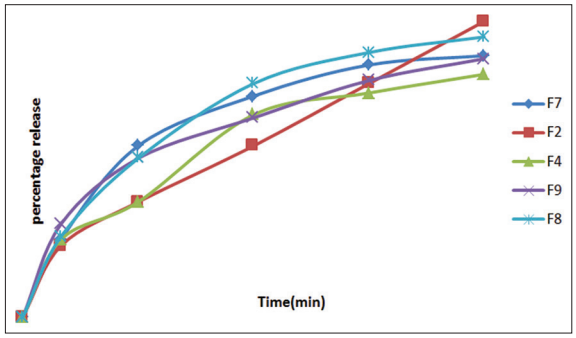

Figure 5: *In- vitro* drug release profile F2, F4, F7, F8, and F9

shows no change in the visual clarity. This was observed after 24 h at room temperature for F2, F8, and F9 formulations. However, formulations F1, F3, F4, F5, F6, and F7 turned hazy after 24 h of dilution as indicated in Table 4.

Droplet Size Analysis

SNEDDS formulations (1 ml) were diluted with 20-ml deionized water in a beaker with constant stirring on a magnetic stirrer.[9,10] The droplet size distribution resultant nanoemulsions were determined by phase-contrast microscope (Leica). The formulation F2 containing 60% surfactant showed the droplet size <200 nm [Figure 3] when compared with the other formulations. The formulations F1, F3, F6, F7, F8, F4, and F5 showed the size range of 600–900 nm.

Particle Size Distribution

The particle size distribution of the nanoemulsion was determined by LD technique with a wet sampling system, and diameter was calculated by volume of distribution, and the mean volume of large particle d (v: 0.5) reported to be 0.186 µm. The formulation F2 containing 60% of surfactant, 10% oil, and 30%

cosurfactant showed the lowest particle size range among all the formulations as indicated in Figure 4.

In vitro Drug Release Studies

The release patterns of the formulation of the *in vitro* release rate studies (F2) containing 60% surfactant, 10% oil, and 30% cosurfactant showed the least emulsification time and maximum drug release of 95% within 1 h. When compared with other formulations, the pattern reveals that release from F1, F7, F8, and F9 formulations was significantly less than that of F2 formulation; due to the larger globule size formed which would eventually lead to slower drug release as indicated in Table 5 and Figure 5.

CONCLUSION

Self-nanoemulsified liquisolid compacts serve as an ideal carrier for the delivery of drugs belonging to BCS Classes II and IV. The present study has clearly demonstrated the potential utility of self-emulsified liquisolid compacts for formulating felodipine with improved aqueous solubility and dissolution. The optimum formulation of felodipine liquisoild system comprising of IPM, labrasol, and capmul MCM-C8 was formulated, and this formulation was evaluated for post-compression parameters. Thus, it was concluded that the prepared self-emulsified liquisolid compacts with promising *in vitro* characteristics hope to solve the oral delivery problems encountered for highly potent lipophilic drugs.

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