

A SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS) FOR NISOLDIPINE: CHARACTERIZATION, DISSOLUTION AND CONVERSION INTO SOLID SEDDS

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ABSTRACT

Poorly soluble drugs such as nisoldipine offer challenges in developing a drug product with adequate bioavailability. The objective of present study was to improve solubility and dissolution rate of nisoldipine by developing and characterizing self emulsifying drug delivery system (SEDDS) of nisoldipine. Solubility of nisoldipine was carried out in various oils, surfactants and co-surfactants. Six self emulsifying formulations were prepared using various proportions of oil, surfactants and co-surfactants in which solubility of nisoldipine was high. The stability studies after introduction of nisoldipine into different combinations provided the optimized liquid SEDDS comprising of capmul MCM EP, labrasol, tween 60 and polyethylene glycol 400, which was then evaluated for droplet size, percentage transmittance and coalescence studies. Liquid SEDDS was then converted into free flowing powder by adsorbing onto solid carriers. Solid state characterization of solid SEDDS was performed by scanning electron microscopy (SEM) and differential scanning calorimetric (DSC) measurements. The comparative dissolution studies with nisoldipine and SEDDS proved the efficiency of self emulsifying formulations in improving dissolution rate. The permeability studies as non everted sac method gave higher permeation rate for SEDDS. This solid SEDDS may provide a useful solid dosage form for oral poorly soluble drugs.

Key words: *Nisoldipine; Self emulsifying drug delivery system; Labrasol; Capmul MCM EP*

INTRODUCTION

The use of high throughput screening in drug discovery has led to large proportions of new drug candidates having poor aqueous solubility & hence poor bioavailability¹. There is various formulation strategies reported to overcome these problems which include micronization, cyclodextrins, solid dispersions, lipids etc. In recent years, self-emulsifying drug delivery systems (SEDDS) have gained importance as promising technology to improve oral bioavailability of many lipophilic drugs. SEDDS are isotropic mixtures of lipid, surfactant, co-surfactant and drug substance that spontaneously form a fine oil-in-water emulsion when exposed to aqueous media under gentle stirring. The digestive motility of stomach & intestine provide the agitation required for self emulsification *in vivo*. The spontaneous formation of emulsion presents the drug in a dissolved form and the resultant small droplet size provide a large interfacial area for diffusion²⁻⁵.

SEDDS are normally prepared either as liquids or encapsulated in soft gelatin capsules which have some shortcomings as in manufacturing process, leading to high production costs. Also, these dosage forms may be inconvenient to use and incompatibility problems may occur with the shells of soft gelatin capsules. The liquid self- emulsifying formulation can be incorporated into solid dosage form to overcome the disadvantages of liquid formulation⁶⁻⁸.

In this study, an attempt was made to improve the solubility and *in vitro* dissolution of nisoldipine by formulating it as SEDDS. Nisoldipine, O5-methyl O3-(2-methylpropyl) 2, 6-dimethyl-4-(2- nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate⁹, has poor aqueous solubility resulting in low and often irregular bioavailability. Nisoldipine is used to treat high blood pressure. Nisoldipine is also used to treat patients with angina and is being studied in patients with congestive heart failure¹⁰. It may be used alone or in combination with other agents¹¹. Nisoldipine is available as extended release tablet under the brand name 'Sular'¹². Other controlled release solid oral dosage formulation comprising nisoldipine were also developed to improve bioavailability wherein the formulation comprises a core or central layer comprising nisoldipine and one or more barrier layers comprising one or more swellable, erodible, or gellable polymers, delaying release to a region within the gastrointestinal tract and providing greater uptake of the nisoldipine¹³. The present work provided four folds improvement in dissolution rate for nisoldipine when formulated as self emulsifying drug delivery systems. Self emulsifying mixture that combines good self emulsifying properties, acceptable solubilization of nisoldipine and optimum surfactant, co-surfactant composition was selected, evaluated for droplet size, stability, dissolution, permeability and a Solid SEDDS was prepared using Magnesium

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Aluminium Silicate as adsorbent. The solid SEDDS was further evaluated by *in-vitro* dissolution studies, non everted sac permeability studies and characterized by Scanning electron microscopy (SEM) and Differential scanning calorimetry (DSC).

EXPERIMENTAL

Nisoldipine was supplied by Shri Ram Chemicals, Ghaziabad. Corn oil was obtained from Acros Organics, New Jersey, USA. Tween 80, Tween 60, Polyethylene glycol (PEG) 400 and Magnesium aluminium silicate were obtained from CDH, New Delhi. Propylene glycol was obtained from Qualikems Fine Chemicals Pvt. Limited, New Delhi. Labrasol, Transcutol P, Lauroglycol 90, Labrafil M 1944 Cs and Capryol 90 were gift samples from Gattefosse India Pvt. Limited, Mumbai. Capmul MCM EP and Captex 100 were gift samples from Abitec Corporation, Janesville, WI. All the reagents and solvents used were of analytical grade.

Excipient Screening—Saturation Solubility Studies

The saturation solubility of nisoldipine was evaluated in various oils, surfactants, and cosurfactants. In this study, an excess amount of nisoldipine was added to 5 ml of each of vehicle in amber colored volumetric flasks and mixed using a vortex mixer (Hicon) to facilitate drug solubilization. The mixture heated to 40°C in a water bath shaker (Hicon) under continuous stirring for 6 hours. The mixture was then kept at ambient temperature for 24 h to attain equilibrium. The equilibrated sample was centrifuged (Remi RM 12C Centrifuge) at 4,000 rpm for 10 min to remove the undissolved drug which was then filtered off and the liquid was assayed through UV spectrophotometer^{9,14} (Shimadzu UV-1700) at 298 nm. (Fig.1)

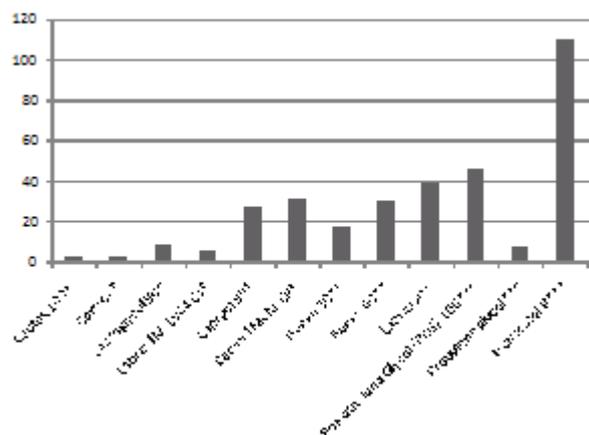


Fig. 1: Solubility of Nisoldipine in various oils*, surfactants** and cosurfactants/ cosolvents***

Determination of optimized composition of liquid SEDDS (Preformulation isotropicity test)

For the determination of optimized composition of SEDDS, different ratios of the components i.e. oil, surfactant and co surfactant, were tested for self

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emulsification i.e. ability to form SEDDS in that particular ratios. The region of self emulsification was assessed by visual examination. Appearance of bluish transparent color gave the indication of self-micro emulsification. The combinations (0.1 ml) were introduced into 100 ml water in a glass beaker at 37°C and the contents were blended gently using a magnetic stirrer (Remi Equipments Ltd) bar. The tendency to emulsify spontaneously and also the development of emulsion droplets were monitored. The tendency to form an emulsion was judged as 'good' when droplets spread easily in water and formed a fine emulsion that was clear or slightly opaque in appearance, and it was judged 'bad' when poor emulsion formed. The liquid SEDDS were optimized on two parameters, fixed ratio of surfactant and co surfactant in combination with varying amount of oil and fixed amount of oil and varying ratios of surfactant and co surfactant. All the trials were carried out in duplicate, with similar observations being made between repeats.

The use of single surfactant did not give satisfactory results so the SEDDS were developed using combination of surfactants (Table 1 & Fig. 2). Percentage transmittance of SEDDS was obtained by using distilled water as blank at 650 nm by UV spectrophotometer (ShimadzuUV-1700).

Table 1: Preformulation isotropicity test

Batch Code	Oil Code	Labrafil M 1944 Cs (% w/w)	Transcutol P (% w/w)	PEG 400 (% w/w)	Capmul MCM EP (% w/w)	Capryol 90 (% w/w)	% Transmittance
A	1:1	2:2:56:22:5	-	15	10	-	98.2
B	1:2	1:5:15	50	-	10	-	98.4
C	2:1	3:10:30	50	-	10	-	99.5
D	1:1	2:2:56:22:5	-	15	-	10	99.5
E	1:2	1:5:15	50	-	-	10	99.7
F	2:1	3:10:30	50	-	-	10	99.9



Fig. 2: Formulations obtained after preformulation isotropicity test (Vials numbered 1 to 6 denote batch numbers A to F)

Preparation of nisoldipine liquid SEDDS

In the SEDDS, the content of Nisoldipine was maintained constant (10 mg dose). Components of the SEDDS i.e. oil, surfactant and co surfactant, were weighed into a glass vial and vortexed using vortex mixer until unit dose (10 mg) of Nisoldipine got dissolved completely and a transparent and monophasic solution formed (Fig. 3).

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Fig. 3: Nisoldipine liquid SEDDS (left) and Nisoldipine emulsion (right) obtained by dilution

Evaluation of SEDDS²⁻⁴

The prepared SEDDS were evaluated by following methods:

Stability studies

The physical stability of a lipid based formulation can be adversely affected by precipitation of drug in excipient matrix. Poor formulation physical stability can lead to phase separation of excipient and affect formulation performance. So following stability studies were performed on prepared SEDDS.

Phase separation studies

1 ml of SEDDS was added to 5 ml distilled water at 25°C. The mixture was vortexed for 2 min and then stored for 2 hrs and any phase separation was visually observed.

Heating cooling cycles

Only batch A passed phase separation studies so it was further studied. Six cycles between refrigerator temperature (4°C) and elevated temperature of 45°C with storage at each temperature of not less than 48 hrs was studied. The formulation was stable at these temperatures and then subjected to centrifugation test.

Centrifugation studies

The formulation was centrifuged (Remi RM 12C Centrifuge) for 3500 rpm for 30 minutes and it was found to be stable.

Droplet size determination

SEDDS was diluted with double distilled water. The average globule size and polydispersibility index of Nisoldipine microemulsion were determined by the zeta

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sizer (Malvern instruments) from IIT, New Delhi. The average droplet size (nanometers) was found to be 253.9 nm (Fig. 4).

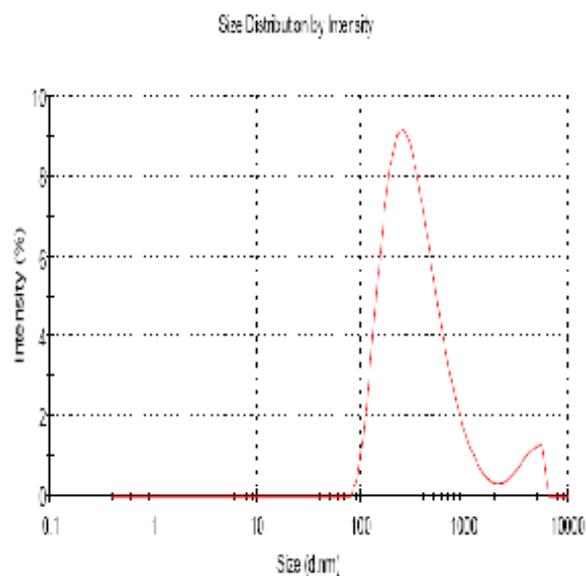


Fig. 4: Particle size analysis

Drug content

Drug content analysis was done by dissolving samples equivalent to 10 mg of Nisoldipine in 10ml of methanol. This solution was then kept for one hour. After one hour, the solution was filtered and a 10 µg/ml solution was prepared from this solution by dilution with methanol. The solution was assayed through UV Spectro photometric method at 298 nm. The drug content was found to be 99.53%.

Percentage Transmittance studies

Percentage Transmittance was found to be 98.5%.

Coalescence studies

In-vitro dissolution of SEDDS was carried in distilled water (500 ml, temperature 37± 0.5°C) using USP 2 apparatus (Hicon) at 50rpm for 24 hrs and SEDDS were observed visually at different time intervals for clarity or turbidity. The SEDDS emulsified readily and transparency was maintained for 24 hours.

Conversion to Solid Intermediates of Self Emulsifying Formulation⁶⁻⁸

The optimized liquid SEDDS was converted into free flowing powder by adsorption of liquid SEDDS onto solid carriers^{5,6}. The solid carrier used was Magnesium Aluminium Silicate which has high surface area, good adsorption & high disintegration characteristic. SEDDS was adsorbed uniformly till it formed free flowing powder. Adsorbed SEDDS was sifted through mesh # 44 and weighed amount of blend for unit dose (10 mg) was filled in size "00" capsule.

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Solid state characterization of solid SEDDS

Differential Scanning Calorimetry (DSC)¹⁵

Thermograms of Nisoldipine and Solid SEDDS were obtained using DSC at IIT New Delhi.

Morphological Analysis of Solid SEDDS

Scanning Electron Microscopy (SEM)

The outer macroscopic structure of the Nisoldipine and solid SEDDS were investigated by SEM at IIT New Delhi.

Stability studies with SEDDS

The ageing studies¹⁶ were helpful in finding out the physico-chemical stability of SEDDS. The stability studies of nisoldipine loaded SEDDS was assessed by keeping them at ambient temperature for 90 days. Samples were removed at 0, 30, 60 and 90 days interval and checked for appearance and drug content.

In-Vitro release

The release of drug from liquid SEDDS formulation and solid intermediates filled in capsules was determined using USP apparatus 2 at 37±0.5°C at 50 rpm¹⁷. The dissolution medium used was 0.1 N HCl. Samples equivalent to 10 mg of Nisoldipine were taken and filled in "size 00" capsules. At specified times, 5ml samples were withdrawn, filtered, suitably diluted and assayed by the UV Spectrophotometric method at 298 nm.

Non Everted Sac Permeability studies¹⁸

The permeation studies were done by using chicken intestinal segment obtained from slaughter house. For the study, intestinal segment of 5 centimeters was chosen and separated. It was rinsed with isotonic saline (37°C) until the outlet solution was clear. Using the aeration pump, the intestinal segments were perfused at a flow rate of 1-2 bubbles/min in Tyrode's solution. 1.5 milliliters of tyrode's solutions (0.1mg/ml) of nisoldipine, liquid and solid SEDDS were filled in the normal sac (mucosal side) and both ends of sac were ligated tightly. These sacs were then immersed in 40 ml of tyrode's solution in conical flasks. The medium was prewarmed and preoxygenated. The conical flasks were kept in water bath shaker at 37°C and bubbled with CO₂/O₂ mixture gas periodically. The transport of nisoldipine from mucosal to serosal surface across the intestine was measured by sampling 5 ml and replenishing with fresh tyrode's solution. The nisoldipine transported was measured using UV Spectrophotometric method at 298 nm.

The apparent permeability (P_{app}), in cm/sec can be calculated as

$$P_{app} = (V_A / \text{Area} \times \text{Time}) \cdot [(\text{drug})_{\text{acceptor}} / (\text{drug})_{\text{donor}}]$$

Where V_A is Volume of acceptor well, area is surface area of intestinal membrane ($2\delta rh + 2\delta r^2$) and time is total transport time i.e. 4500 seconds

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RESULTS AND DISCUSSION

The objective of solubility studies is to identify the suitable oil, surfactants and co-surfactants which have good solubilizing capacity for nisoldipine. Based on the results of solubility studies various combinations of oil, surfactant and co-surfactant were prepared which were tested through isotropicity studies. Only those formulations in which a surfactant combination was used passed this test. The percentage transmittance was greater than 99% (Table 1) in all the cases which indicated the microemulsion region. The effect of drug incorporation on all the combinations was observed and liquid SEDDS thus prepared were evaluated. Only batch A passed phase separation studies which was then evaluated for heating cooling cycles and centrifugation studies. The formulation found stable under these studies gave average particle size 253.9 nm. The optimized Liquid SEDDS was then converted into solid SEDDS.

The DSC thermograms of pure drug and solid SEDDS are shown in Fig. 5 and 6 respectively. Pure drug substance showed sharp endothermic peaks at 150.68°C indicating the drug is highly crystalline. The absence of drug peaks in the solid SEDDS formulation indicates change in melting behavior of drug and inhibition of crystallization following granulation using lipid, surfactants and granulating materials. The SEM of pure drug nisoldipine and solid SEDDS are shown in Fig. 7. The SEM images of solid SEDDS show well separated spherical particles. Stability studies (Table 2) of liquid and solid SEDDS indicated no decline in nisoldipine content at the end of three months.

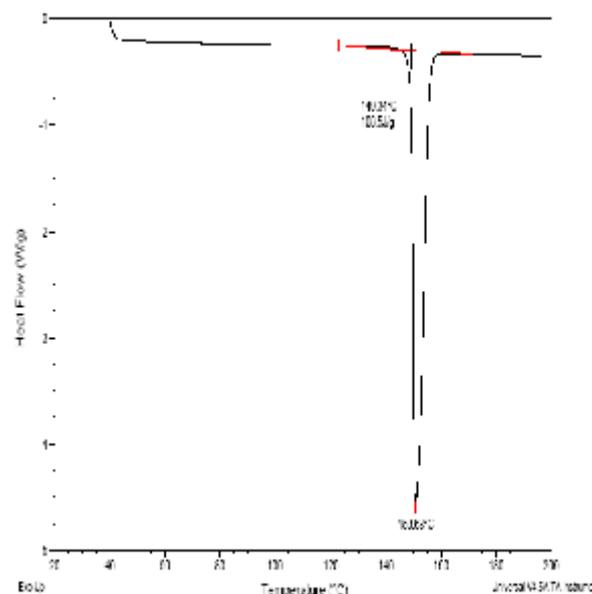


Fig. 5: DSC curve of Nisoldipine

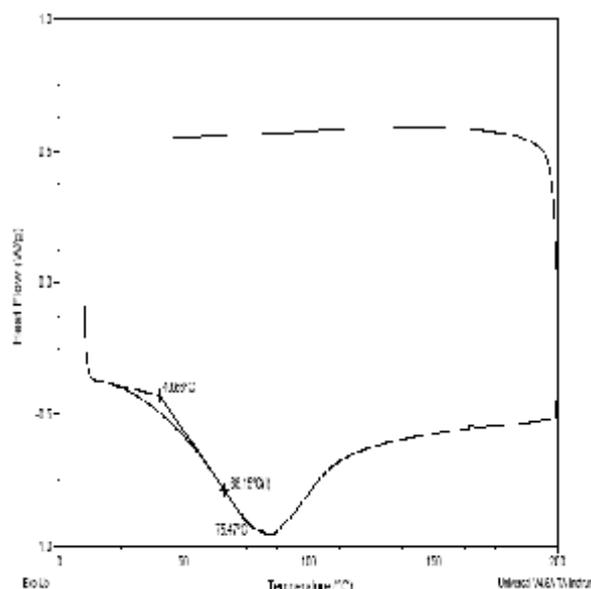


Fig. 6: DSC curve of Nisoldipine SEDDS

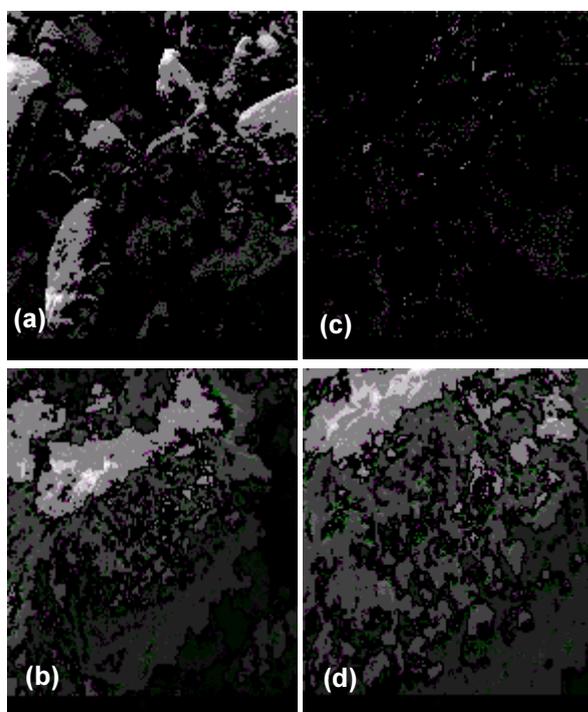


Fig.7: SEM images of Nisoldipine (a and c) and solid SEDDS (b and d)

Table 2: Stability study

Days	Liquid SEDDS		Solid SEDDS	
	Appearance	Drug content (%)	Appearance	Drug content (%)
0	Clear	99.53	Light yellow	98.70
30	Clear	99.53	No change	98.70
60	Clear	99.23	No change	98.45
90	Clear	99.23	No change	98.42

The *in vitro* dissolution comparisons of pure drug, liquid SEDDS and solid SEDDS in 0.1 N HCl are shown in Fig. 8. The faster dissolution from SEDDS indicates that the drug is in solubilized form and upon exposure to dissolution medium results in small droplets that can dissolve rapidly in dissolution medium. More than 45% of drug released within five minutes from liquid and solid SEDDS as compared to only 6% dissolution from pure drug. The similarities between dissolution patterns of liquid and solid SEDDS showed that self emulsifying properties of SEDDS are unaffected following conversion into solid SEDDS. The permeability studies gave P_{app} (cm/sec) of 1.26×10^{-4} , 5.63×10^{-4} and 4.97×10^{-4} for nisoldipine, liquid and solid SEDDS respectively. Thus, after incorporation into SEDDS, nisoldipine showed better permeation rate (Fig. 9).

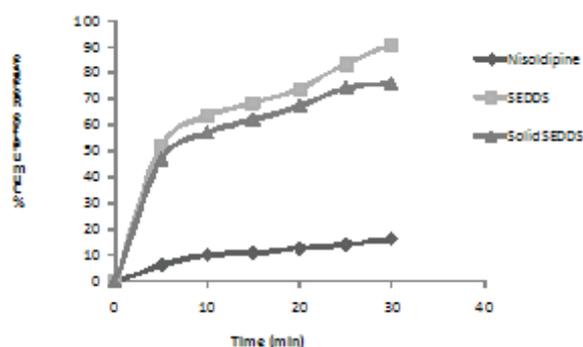


Fig. 8: Percentage drug release

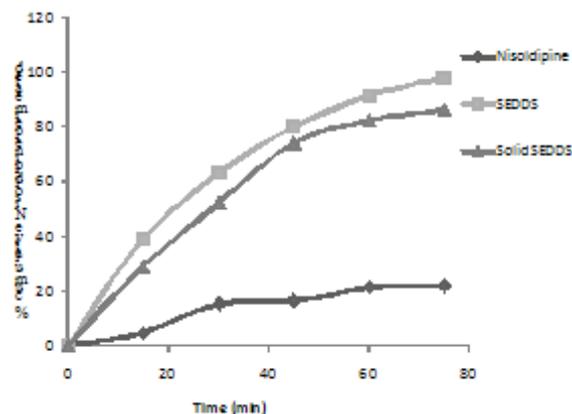


Fig. 9: Percentage Permeation

CONCLUSION

The optimum formulation of Nisoldipine SEDDS consisted of capmul MCM EP, labrasol, tween 60 and PEG 400 which has sufficient drug loading, rapid emulsification in aqueous media and could produce small mean droplet size. The SEDDS formulation and solid intermediates for capsule filling both showed faster dissolution when compared with nisoldipine. The solid SEDDS consisted of well separated spherical particles. DSC measurements suggested that nisoldipine in

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SEDDS was in amorphous or molecular dispersion state. Thus, the solid self emulsifying drug delivery systems may provide a useful solid dosage form for poorly soluble drug such as Nisoldipine to improve its solubility and dissolution rate.

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