Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2015; 5(4); 132-137

ISSN: 0975-4415

Research Article

Formulation and Evaluation of Self Nanoemulsifying Drug Delivery System of Nifedipine

Dinesh Kaushik*, Jyoti Malik, Satish Sardana

Department of Pharmaceutics, Hindu College of Pharmacy, Sonepat (Haryana) India

Available Online:25th November, 2015

ABSTRACT

Oral route is the most preferred route of drug administration due to its easy accessibility, intake, and wide range of choices making it economical. Currently, greater than 60% of marketed drugs are oral products**.** Over 90% of therapeutic compounds given orally areknown to possess oral bioavailability limitations**.** Therefore, there is a need to explore various approaches that can be used to improve oral drug bioavailability besides using physical and chemical means. The objective of this study is to prepare a formulation i.e. self microemulsifying drug delivery system (SMEDDS) of nifedipine with the intention to improve the increase dissolution rate (solubility). This will ensure the quick absorption and uniform bioavailability of nifedipine. Selection of oils, surfactants and co-surfactants was done by determining % transparency and on the basis of compatibility studies by FTIR spectra analysis. Different SMEDDS formulation were prepared of different ratio of oil:surfactantmix (1:9,2:8,3:7,4:6,5:5,6:4,7:3,8:2,9:1) and different ratio of surfactants : cosurfactants. Pseudo ternary phase diagram were constructed by water titration method to obtain a particle micro-emulsion region (on the basis of clarity and transparency). The formulation B-I was optimized because of maximum transparency (87.35%) and maximum % drug entrapment (95.32%). The average droplet size and zeta potential was found 86.05 and -0.189. The solubility of nifedipine increase in SMEDDS formulation upto72.17%.From in vitro dissolution study it was proved that SMEDDS formulation releases drug at faster rate, thus the objective of increase solubility and hence the better dissolution rate for uniform bioavailability via SMEDDS formulation of nifedipine was successfully achieved.

Keywords: Self microemulsifying drug delivery system (SMEDDS), nifedipine, *in vitro* release, transmission electron microscopy, transparency and bioavailability.

INTRODUCTION

Oral delivery is the most favorable and preferred route of drug administration due toconvenience, possibility of self-administration and improved patient compliance. Oral products have greater stability and are easy to scale up. Majority of the formulations available in the market are oral drug delivery systems.[1-5] The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, and the patient, the length of the therapy and the properties of the drug.A poor oral bioavailability can result in low efficacy and higher inter-individual variability and therefore can lead to unpredictable response to a drug. Efforts are going on to enhance the oral bioavailability of such lipophilic drugs in order to increase their clinical efficacy.[6-8] Oral bioavailability of drugs is affected by various factors, which influence their absorption from gastrointestinal tract. One determined factor for absorption is drug dissolution, which isinfluenced by solubility of drug in GI fluid. A variety of methods have been developed to improve the release and dissolution of such drugs. Self-microemulsifying drug delivery sytems (SEDDS) are isotropic mixtures of oil, surfactant and cosurfactant with the solubilized drug. These formulations can rapidly form oil in water (o/w) fine emulsions when dispersed in aqueous phase (gastric medium) under mildagitation (peristaltic movement).[9-15] The rapid emulsification of these formulations in the gastrointestinal tract can provide both improved oral bioavailability and a reproducible plasma concentration profile for lipophilic drugs. The droplet size of the emulsion would influence the extent of absorption of the orally administered drugs.[16-20]

With a large variety of liquid or waxy excipient available, ranging from oils through biological liquids, hydrophobic and hydrophilic surfactants, to water-soluble cosurfactant/co-solvent, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions.[21-24]

MATERIALS AND METHOD

Nifedipine was obtained as a gift sample from Belco Pvt. Ltd., India. Ethyl Oleate, Tween 80, PEG 400 and Ethanol werepurchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Determination of solubility in various solvents (oils, surfactants and co surfactants)

To find out the appropriate oils, surfactants and co-

*Author for Correspondence

Table 1: Solubility of Nifedipine in various oils

S.No	Oil	Solubility(mg/ml)(mean ±SD)
1	Ethyl oleate	8.5±0.023
2	Olive oil	1.5±0.032
3	Castor oil	6.19±0.012
4	Iso propyl myristate	3±0.042
5	Sunflower oil	0.4±0.035
6	Linseed oil	6.8±0.025

Table 2: Solubility of Nifedipine in various surfactants

S.No	Oil	Solubility(mg/ml)(mean±SD)
1	Tween 80	9.8±0.015
2	Span 80	8.78±0.019
3	Span 20	5.65±0.021

Table 3: Solubility of Nifedipine in various co-surfactants

S.No	Oil	Solubility(mg/ml)(mean±SD)
1	Polyethylene glycol 400	5.14±0.025
2	Propylene glycol	3.4±0.035
3	Ethanol	7.8±0.027

surfactants of SMEDDS the solubility ofnifedipine in various oils (ethyl oleate, castor oil, sunflower oil, isopropylene myristate,Linseed oil), surfactant (span 80, tween 80, span 20) and co-surfactants (propylene glycol, ethanol, polyethylene glycol 400) was determined by using shake flask method. Briefly, an excess amount of nifedipine (50mg) was added to each vial containing 5 ml of the selected vehicle, i.e., oil, co-surfactant and surfactant. After sealing, the mixture was vortexed for 10 min and sonicated by using bath sonicator for 8 mins in order to facilities proper mixing of nifedipine with the vehicles and reduces the particle size of drug. Mixtures were shaken for 72 hrs. in an shaker, maintained at 37±1˚C, and afterwards, mixtures were centrifuged at 1200 rpm for 10 min and then supernatant was filtered through membrane filter (0.45 µm) to remove the remaining insoluble nifedipine in the filtrate was determined at 238nm by UVSpectrophotometer and solubility of nifedipine in different oils, surfactants and cosurfactantswas calculated with the help of standard calibration curve. On the basis of solubility studies and compatibility studies oil (ethyl oleate), surfactant (Tween 80) and co-surfactants (PEG, Ethanol) were selected for SMEEDS formulationbecause of absence of any type of incompatibility[25-30]

Determination of %transparency between different components

On the basis of solubility studies the oils, surfactant and co-surfactant (that have maximumsolubility) were selected and % transparency was determined to find out the maximumtransparency between oil, surfactant and co-surfactant because SMEEDS is a clear transparent system when diluted with distilled water.[31-32]

Structural Compatibility studies between drug and polymers:

On the basis of % transparency the oil (ethyl oleate), surfactant (tween 80) and co-surfactant
(PEG) were selected because of maximum transparency (property of microemulsion)between them. Drug polymers compatibility was studied using FTIR and the spectra wererecorded in the wavelength region of 900-3500 cm-1. Samples of pure drug, pure polymer,and the physical mixtures containing both the drug and polymer were scanned in thementioned wavelength region.[33-37]

Construction of pseudo-ternary phase diagram

On the basis of the solubility and compatibility testing pseudo-ternary phase diagrams were constructed by using water titration method to obtain the o/w micro-emulsion region, and theconcentration range of the components (oil, surfactant and co-surfactant) was identified. Theweight ratio of surfactant (tween 80) to co-surfactant (Km) was varied as 1:1 and 2:1 and theratio of oil: surfactant/co-surfactant was varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1.The oil, surfactant and co-surfactant were mixed in a glass vial and water was added drop bydrop to each oily mixture under proper magnetic string at 370C until the mixture becameclear and transparent at a certain point. Then the concentration of the components wererecorded in order to complete the pseudo-ternary phase diagrams, and then the contents ofoil, surfactant, co-surfactant and water at appropriate weight ratios were selected based onthese results. The percentage of water, oil and surfactant-cosurfactant mix in which nano emulsion formedwere selected and plotted on ternary phase diagram with one axis representing the aqueousphase, the other representing the oil and third representing the Smix. The observations were made for each Smix ratio separately. All formulations contain 1% of Nifedipine.[38-41]

Preparation of SMEDDS formulation

With the help of pseudo-ternary phase diagram existing micro emulsion region was foundand concentration of oil, surfactant and co-surfactant at appropriate weight ratios wereselected for SMEEDS formulation (at which clear and transparent micro emulsion wasobtained). A series of SMEEDS formulation (A-1, B-1, B-2) were prepared using ethyloleate as oily phase and Tween, polyethylene glycol and ethanol were used as surfactant andco-surfactant. Accurately weighed nifedipine was placed in a glass vial and oil, surfactant,co-surfactant were added. After adding all the components the mixture was sonicated for 3min. using bath sonicator and then glass vial (containing mixture) kept at 30-400C for 1 minthen all the mixture in a glass vial were vortexed for using vortex shaker until nifedipine was perfectly dissolved. Then mixture (SMEDDS) was stored at room temperature for further use.[42-45]

Characterization of SMEDDS

Determination of percent drug entrapment efficiency

Accurately weighed Nifedipine (100mg) was taken in a glass vial and then oil (ethyl oleate),surfactant (Tween 80), co-surfactant (PEG) and cosolvent (Ethanol) were added in a glassvial. Then the glass vial was sonicated for

Morphology (TEM)

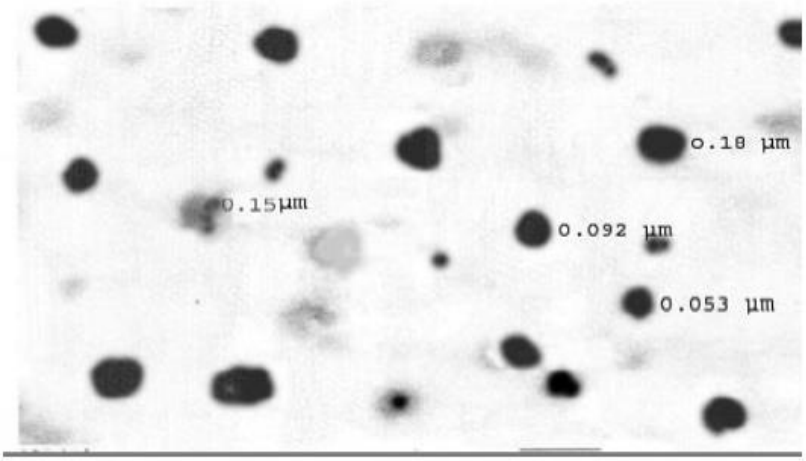

Figure 1 : TEM of Microemulsion

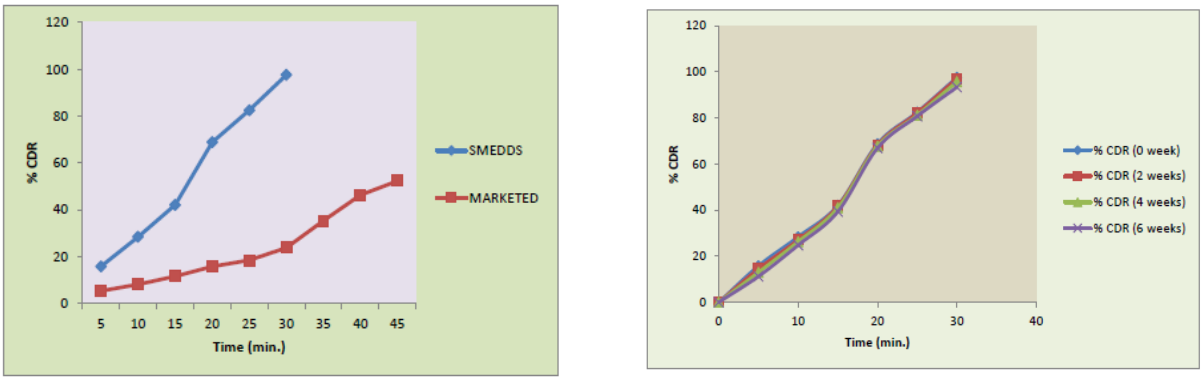

Figure 2: In vitro release of nifedipine loaded SMEDDS in HCL and PBS (pH 7.4)

3 minutes and then mixture (SMEEDS) wasshaken for 72 hours at 370C using isothermal shaker. Then the mixture (SMEDDS) wascentrifuged at 12000 rpm for 10 minutes and 1 ml of supernatant was taken and diluted withmethanol (if necessary) and absorbance was measured at 238 nm by UV Spectrophotometer.Then the concentration of nifedipine was determined using standard curve equation and %drug entrapment was calculated using formula:-

% Drug Entrapment = Practical value/ Theoretical value x 100

Determination of solubility of nifedipine loaded SMEDDS in water:

The solubility of nifedipine loaded SMEDDS in water was determined by shaking Flaskmethod.

Transmission Electron Microscopy (TEM)

Only freshly prepared SMEDDS containingnifedipine was examined for TEM images, because this one shows most expected results among the other formulations.

Measurements of micro-emulsion droplet size and zeta potential

Droplets size of the formulation is measured by using the Malvern Zetasizer Nano (1000 HS,Malvern Instruments, U.K.) The Zetasizer systems determined the size by first measuring the Brownian motion of the particles in a sample using Dynamic Light Scattering (DLS).

Viscosity

SMEDDS formulation quantity more than 300 ml was taken in beaker. Viscosity of the initial SMEDDS was measured using Brookfield viscometer. The needle (spindle) was introduced in the specimen sideways to avoid trapped bubbles at the bottom, when inside, center it in such a way that the wave produced by it be the same atall points around the spindle. Turn the viscometer on and let it work freely for a minimum of 30 seconds to a maximum of one minute, in the case the dial was went beyond 100, turn the viscometer off, place the another suitable spindle number. When this time was over, press the lever to stop the dial and write down the reading of it Digital viscometer: Viscosity at 250C =Direct reading.

Self emulsification studies

SMEDDS formulation wasanalyzed for self emulsifying property on the basis of clarity (clear transparent liquid). 1 ml of SMEDDS formulation was added (drop wisely) into 100, 250 and 1000 ml of distilled water, 0.1 N HCl and phosphate buffer of pH 6.8. This was done in glass beaker at room temperature and the contents were gently stirred with a glass rod. Precipitation was evaluated by visual inspections of the resulting emulsion after 24hours. The formulation then categorized as stable (clear transparent liquid) or unstable (non clear turbid liquid or show precipitation).

In-vitro drug release

The dissolution study was performed using USP dissolution apparatus II paddle assembly at50 rpm at

37±0.50C. The formulation was tested individually in 0.1 HCl (pH 1.2) and in phosphate buffer (pH 6.8). These media were selected to mimic the conditions in stomach, small intestine respectively. Aliquot samples were withdrawn at specified time intervals and were analyzed spectrophotometrically at 237 and 238 nm respectively. The volume of the sample withdrawn each time was replaced with the same volume of the respective solutions.

RESULTS AND DISCUSSION

Pseudoternary phase diagram

Pseudo-ternary phase diagrams were constructed by using water titration method to obtain the o/w micro-emulsion region, within which the concentration range of the components (oil, surfactant and co-surfactant) was identified. The weight ratio of surfactant (tween 80) to co surfactant (Km) was varied as 1:1 and 2:1 and the ratio of oil: surfactant/co surfactant was varied 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1It represents a three components system (oil, water and cos (surfactant+ co surfactant)). The * point represents micro emulsion (transparent and clear) reason and other points are of coarse emulsion (turbid). The * point depends upon appearance of the simple after titration with water (0.05 ml water was added at a time).[46-47]

Preparation of optimized SMEDDS formulation

B-1 formulation was optimized because of maximum % transparency (87.35%) and maximum % drug content (95.32%) and it is prepared successfully.

Determination of solubility of nifedipine

The solubility of nifedipine in SMEDDS formulation was determined using shaking flask method. Solubility of nifedipine in SMEDDS formulation was found to be 20.21 mg/ml. Solubility of nifedipine in aqueous was 0.28 mg/ml but in SMEDDS formulation this was found that 20.21mg/ml hence solubility increases 72.17% via SMEDDS formulation (Table 1-3).

Surface topography

TEM study indicated that microemulsion generated from optimized formulation, appeared as black spots on a white background. The emulsion drops generated were spherical having average size 86.05nm (Figure 1).

Measurement of size and zeta potential

The droplet of micro-emulsion having negative charge and no aggregation of globule wereformed. Zeta-potential of the resulting micro-emulsion was determined using the Zetasizer.(Malvern Instrument)The negative value (-0.1891) of zeta potential indicates that SMEDDS formulation have anegative charge. Due to negative charge on micro emulsion droplets there is a repulsive forcebetween droplets due to which there is no aggregation of micro emulsion droplet and hencebetter micro emulsion will form.

Viscosity determination

Viscosity of SMEDDS was measured by using the Brookfield Viscometer and spindle no. 2was used for the particular study. Viscosity of SMEDDS was found to be (362cps), which was suitable for filling of SMEDDSin hard gelatin capsule without risk of leaking problem.When SMEDDS (1ml) was diluted 100 times with water, Viscosity of the system wasdecreased, which indicates that when SMEDDS formulation will be diluted with the stomachfluid its viscosity will be decreased and therefore absorption from stomach will be fast.

Self emulsification

SMEDDS formulations were analyzed for self emulsifying property on the basis of clarity(clear transparent liquid). 1 ml of SMEDDS formulation was added (drop wisely) into 100,250 and 1000ml of distilled water, 0.1 N HCL and phosphate buffer of pH 6.8. Theformulation then after 24 hours categorized as stable (Clear transparent liquid) or unstable (turbid liquid or show precipitation). In the self emulsification study it was found that there was no phase separation (turbid) solution all the dilution were clear and transparent liquid which indicates that micro emulsion will formed easily in stomach (0.1N HCl) and intestine (phosphate buffer 6.8 pH) under mildagitation means faster dissolution and hence absorption.

In-vitro drug release

The dissolution study was performed using USP dissolution apparatus II paddle assembly in

900 ml of 0.1 N HCl and phosphate buffer (6.8 pH) at 100 rpm at 37±1oC (Figure 2).

CONCLUSION

Nifedipine showed a good absorption from gastrointestinal tract but due to poor solubility or dissolution rate in gastrointestinal tract it shows low bioavailability. Being a poorly water soluble drug, there exist a lag time between dosage administration and eliction of pharmacological response. Hence to get a uniform bioavailability with immediate pharmacological response the solubility and dissolution rate of Nifedipine enhanced by SMEDDS formulation. The solubility of nifedipine increase in SMEDDS formulation upto 72.17%. From in vitro dissolution study it was proved that SMEDDS formulation releases drug at faster rate, thus the objective of increase solubility and hence the better dissolution rate for uniform bioavailability via SMEDDS formulation of nifedipine was successfully achieved.[48-50]

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