ejpmr, 2023, 10(5), 321-331

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

DESIGN & CHARACTERIZATION OF PEGYLATED NIFEDIPINE LOADED LIPOSPHERE

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Article Received on 28/02/2023 **Article Revised on 20/03/2023** **Article Accepted on 10/04/2023**

ABSTRACT

Lipospheres are lipid-based dispersion systems in which drug is dispersed in lipidic core, the surface of which is embedded with emulsifier layer. Particle size of such lipid particles ranges from 0.2-100 micrometer. Nifedipine (NI) is a high potent calcium channel blocker, used for the treatment of Hypertension & angina, is poorly soluble and undergo extensive first pass metabolism, which lead to poor bioavailability (about 50%). The aim of the research work is to develop the optimized formulation of PEGylated Nifedipine liposphere with a goal of improving the solubility and giving a prolonged release of drug. Nifedipine liposphere were prepared by melt dispersion techniques using stearic acid, and paraffin wax as lipid matrix and PEG 4000(Poly Ethylene Glycol) as surfactants. Formulation was optimized by using Central composite design where particle size, entrapment efficiency and drug release were dependent variables and lipid and surfactant concentration were independent variables. Optimized formulation of nifedipine shows 95.33% entrapment efficiency and particle size was found to be 77.72 µm with spherical shaped. In vitro release was carried out using dissolution apparatus in phosphate buffer and optimized formulation shows 95.23% drug release within 12 hrs which follows non-fickian type of transport. Developed liposphere formulation was able to sustain the drug release and entrap the nifedipine at high level. The findings of this study suggest that issue of nifedipine stability and poor solubility can be remedied by tactical engineering of lipid drug delivery systems such as liposphere.

KEYWORDS: Nifedipine, Liposphere, Drug release, Poly ethylene glycol.

1. INTRODUCTION

In recent times, formulation scientists have discovered that the poor aqueous solubility and dissolution rate of active pharmaceutical ingredients (APIs) is one of the biggest challenges in pharmaceutical development. The poor solubility often results in low bioavailability of orally administered drugs, and thus results in poor therapeutic efficacy. Therefore, one of the major tasks that the pharmaceutical industry need to overcome is how to develop strategies that could improve the dissolution and/or apparent solubility of these drugs/compounds into orally bioavailable and therapeutically effective drugs for the benefit of patients in clinical settings.[1]

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of water insoluble drug. Solid dispersion, drug micronization, lyophilization, microencapsulation, inclusion of the drug solution or liquid drug into soft gelatin capsules are some of the methods that have been used to enhance dissolution characteristics of water insoluble drugs. Among them, lipospheres are amongst the promising particulate drug delivery systems for improving dissolution rate of water insoluble drugs that were initially reported as a particulate dispersion of solid spherical particles between 0.2-100µm in diameter consisting of solid hydrophobic fat core such as triglycerides or fatty acids derivatives, stabilized by monolayer of phospholipids. Benefits of liposphere drug delivery system are Improving drug stability, possibility for controlled drug release, controlled particle size, and high drug loading. In addition, use of lipospheres for oral administration, it can protect the drug from hydrolysis, as well as improve drug bioavailability.[2]

Nifedipine (Dihydropyridine derivative) is a calcium channel blocker. It is also a peripheral arterial vasodilator which acts on smooth muscle. It is used in the treatment of angina pectoris and systemic hypertension. Nifedipine is a BCS class II drug with elimination half-life of about 2-4hrs. It shows 45-56% of oral bioavailability because of hepatic first pass metabolism. Rate limiting step in absorption of Nifedipine from gastrointestinal tract is the dissolution rate because it is a poorly soluble drug.[3]

The purpose of this research work was to design the optimized formulation of PEGylated Nifedipine loaded liposphere with improved solubility and giving a prolonged release of drug. Nifedipine loaded liposphere was prepared by melt dispersion method using stearic acid, and paraffin wax as lipids and PEG 4000 as surfactant.

2. MATERIAL AND METHODS

Materials

2.1 Chemicals used

Nifedipine (Yarrow Chem Products, Mumbai), PEG 4000, Paraffin wax, Lecithin, Stearic acid (Sisco research laboratories, Maharashtra)

2.2 Instruments used

Double beam UV Spectrometer, Electronic weighing balance (Price scale industries, Ahmedabad), Bruker alpha-Attenuated Total Reflectance, Dissolution apparatus (Electrolab, Mumbai), Magnetic stirrer (Rotek; B & C industries, Kerala).

Methods

2.3 Preformulation study

Preformulation study is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physical and chemical properties a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable & bioavailable dosage forms which can be mass produced. Obviously, the type of information needed depend on the dosage form to be developed.[4]

2.3.1 Organoleptic properties

The organoleptic character of the drug like color, odor and appearance play an important role in the identification of the sample, and hence they should be recorded in a descriptive terminology.[5]

2.3.2 Solubility studies

It is important to know about solubility characteristics of a drug in aqueous systems, since they must possess some limited aqueous solubility to elicit a therapeutic response. Solubility was carried out in water, methanol 0.1N HCl, 7.4 pH phosphate buffer.[5]

2.3.3 Determination of melting point

Melting point of the drug was determined by capillary tube method. Take a small amount of the drug in a capillary tube closed at one end and was placed in Thieles melting point apparatus and the temperature at which the drug melts were noted. Average of triplicate readings was taken.[5]

2.3.4 Determination of UV λ max

Standard stock solution of drug (100µg/ml) was prepared in 7.4 pH phosphate buffer. For the selection of analytical wavelength, solution of nifedipine of concentration 30µg/ml was prepared by appropriate dilution of standard stock solution with phosphate buffer pH 7.4 and scanned in the spectrum range from 200 to 400nm. From this overlain spectrum of the drug, the wavelength with maximum absorbance was chosen for further analysis.[5]

2.3.5 Preparation of standard calibration curve of Nifedipine in 7.4 pH phosphate buffer

1st Stock: 1000µg/ml solution of nifedipine was prepared by dissolving 100 mg of nifedipine in 10ml methanol and the volume was made up to 100ml with 7.4 pH phosphate buffer.

2nd Stock: Pipette 10ml of above solution into another 100ml of volumetric flask and the volume was made up to mark with the 7.4 pH phosphate buffer. (i.e.: 100µg/ml in 7.4 pH buffer).

The above second stock solution was serially diluted with 7.4 pH phosphate buffer to get the final concentrations of 10, 20, 30, 40, 50 and 60µg/ml. The absorbance of each concentration was measured 254nm using UV-Visible spectrophotometer and graph was plotted against the concentration and absorbance.[5]

2.3.6 Drug and Excipients compatibility study

FTIR spectroscopy method was used to carry out drug-excipients compatibility study. FTIR spectra of pure drug, PEG 4000, stearic acid, paraffin wax and their physical mixture were taken by KBr pellet technique between 400- 4000cm^{-1}. Once spectra were recorded, the peaks of pure drug, polymer and physical mixtures of polymers and drug were compared for incompatibility.[4]

2.4 Preparation of nifedipine encapsulated liposphere

Drug encapsulated Liposphere were developed by melt dispersion technique. The formulation of different batches is depicted in Table.1 Briefly, the lipid core was melted on a water bath maintained at 70-72°C. Finely powdered drug was dispersed into the molten lipidic phase. The aqueous phase was prepared by heating a blend of water and surfactant to 70-72°C with a stabilizer. The molten lipidic phase was slowly transferred to the hot aqueous phase (o/w emulsion) and the emulsification was assisted by stirring the content with a magnetic stirrer continuously. The milky dispersion was then rapidly cooled to 20°C by immersing the formulation in an ice bath without stopping the agitation to yield a uniform dispersion of lipospheres. The obtained lipospheres were then washed with water and isolated by filtration.[4]

Table No. 1: Formulation table of nifedipine liposphere.

Formulation Code	Drug (mg)	Lipidic Core		PEG 4000 as Surfactant (%w/w)	Lecithin as Stabilizer (mg)	Water (ml)
		Paraffin Wax (mg)	Stearic Acid (mg)			
F1	20	250	250	0.25%	5	100
F2	20	250	100	0.4%	5	100
F3	20	250	400	0.4%	5	100
F4	20	250	400	0.25%	5	100
F5	20	250	250	0.25%	5	100
F6	20	250	250	0.25%	5	100
F7	20	250	250	0.1%	5	100
F8	20	250	250	0.25%	5	100
F9	20	250	100	0.25%	5	100
F10	20	250	400	0.1%	5	100
F11	20	250	250	0.4%	5	100
F12	20	250	100	0.1%	5	100
F13	20	250	250	0.25%	5	100

2.5 Characterization of nifedipine encapsulated liposphere

2.5.1 Particle size determination

Particle size analysis of glipizide-loaded lipospheres was performed by optical microscopy using a compound microscope. A small amount of dry lipospheres was suspended in purified water (10ml). The suspension was shaking for 10 seconds. A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing lipospheres was mounted on the stage of the microscope and 100 particles were measured using a calibrated micrometer.[6]

2.5.2 Drug entrapment efficiency

Accurately weighed 100mg of Lipospheres were dissolved in 100ml of Phosphate buffer pH 7.4. The solution was kept overnight and was filtered through whatman filter. The drug concentration was determined by UV spectrometer at maximum wavelength of 254 nm. The following equation was used to calculate drug entrapment efficiency.[7]

$$\%\text{Drug Entrapment} = \frac{\text{Calculated Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

2.5.3 *In-vitro* drug release study

The drug release study of Nifedipine lipospheres was studied using USP type I Basket dissolution apparatus in phosphate buffer (pH-7.4). Capsules were filled by lipospheres equivalent to that of 20 mg drug. The capsules were maintained at 37°C ± 0.5°C, under stirring at 100 rpm in dissolution apparatus. Samples were withdrawn periodically (0 min, 1 hrs. upto 12 hr.) and the same volume was replaced immediately by fresh medium. Sample solutions were filtered, diluted appropriately and analyzed by measuring absorbance at 254nm on UV-Visible spectrophotometer. Capsules were of blue white colored and size no. 5 was used.[8]

2.5.4. Optimization by design expert stat ease software

Statistical design of experiments, a computer-aided optimization technique, was used to identify critical factors, their interactions and ideal process conditions that accomplish the targeted response. The best formulation was determined using Design Expert Stat Ease Software. Central composite design was used for the optimization. In this study, stearic acid and PEG 4000 were selected as the two factors and particle size, entrapment efficiency and *in vitro* drug release were considered as the three responses. Hence, thirteen experimental trials were done. Contour plots were drawn and optimum formulation was selected by optimization criteria.[9]

Table 2: Factor combination by CCD for the formulation of nifedipine liposphere.

Formulation Code	Point type	Coded factor level	
		X_1	X_2
F1	Center	0	0
F2	Factorial	-1	+1
F3	Factorial	+1	+1
F4	Axial	+1	0
F5	Center	0	0
F6	Center	0	0
F7	Axial	0	-1

F8	Center	0	0
F9	Axial	-1	0
F10	Factorial	+1	-1
F11	Axial	0	+1
F12	Factorial	-1	-1
F13	Center	0	0

X1-Stearic acid X2-PEG 4000

2.5.5 Drug release kinetics

In order to understand the exact mechanism of drug release from the dosage form, the data of *in vitro* dissolution study of optimized formulation was fitted in to various kinetics equations (zero order, first order, Higuchi model and Korsmeyer Peppa's model).[5]

2.5.6 Surface morphology

The morphology of the optimized batch of lipospheres was investigated using Scanning Electron Microscopy (SEM). The samples were prepared by sprinkling the formulation on double-adhesive tape stuck to aluminum stub. The stub was placed in high-vacuum evaporator. The samples were then randomly scanned and photomicrographs were taken with a Scanning Electron Microscope.[7]

2.5.7 Stability testing of batches

Stability study of Nifedipine lipospheres optimized batch was carried out according to ICH and WHO guidelines. Optimized formulation was packed in aluminium foil and exposed this to different thermal conditions i.e., 5°C ± 3°C, 25 ± 2°C/ 60 ± 5% RH and 40 ± 2°C/ 75 ± 5% RH for a period of 3 months. The sample were withdrawn at different time intervals over a period of 3 months and evaluated for particle size, entrapment efficiency, and drug release.[10]

3. RESULT AND DISCUSSIONS

3.1 Preformulation study

3.1.1 Organoleptic properties

Organoleptic properties of Nifedipine was studied and it was concluded that, Nifedipine is a yellow crystalline powder, odorless and tasteless

3.1.2 Melting point

Melting point of Nifedipine was found to be 173°C (n=3)

3.1.3 Solubility studies

Table no. 3: Solubility of nifedipine in different media.

Name of the media	Saturation solubility of drug
Distilled Water	Insoluble
Methanol	Soluble
pH 7.4 Phosphate Buffer	Slightly soluble

3.1.4 Determination of UV λ max

The pure drug of Nifedipine was scanned by UV spectroscopy and λmax was found to be 254 nm.

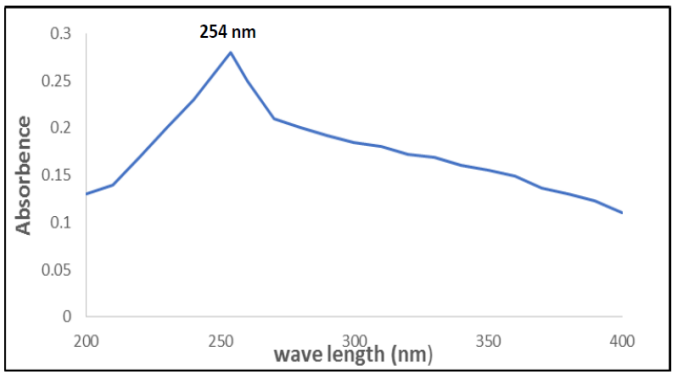

Fig. No. 1: Uv Spectrum of nifedipine in phosphate buffer (pH 7.4).

3.1.5. Standard calibration curve of nifedipine in 7.4 pH phosphate buffer

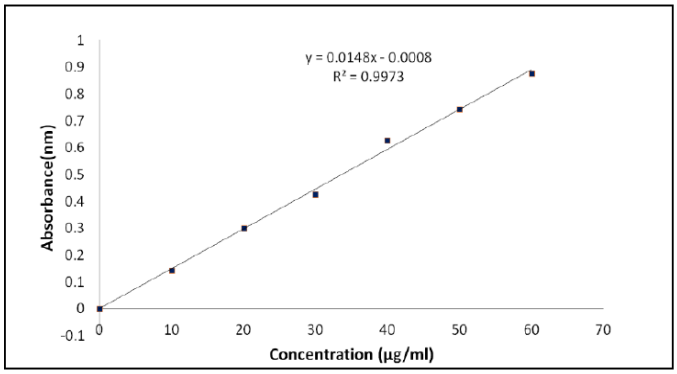

Fig. No. 2: Standard calibration curve of nifedipine in pH 7.4 Phosphate Buffer.

3.1.6 Drug and Excipients compatibility study

FTIR studies were conducted in pure Nifedipine and physical mixture of drug with stearic acid and PEG 4000. The FTIR spectrum is shown below.

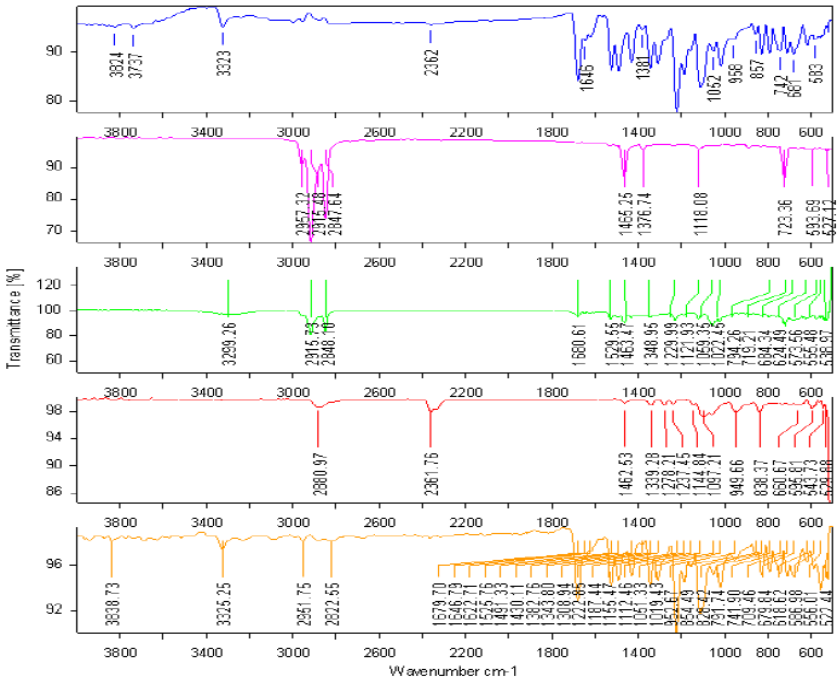

Fig. no. 3: FTIR spectrum of Nifedipine, Paraffin wax, Stearic acid, PEG 4000, and physical mixture (Nifedipine + Paraffin wax + Stearic acid + PEG 4000).

FT-IR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer had occurred. During FT-IR studies, the peaks of Nifedipine was obtained at 3323cm^{-1} due to N-H Symmetric Stretching, 1679cm^{-1}(N=O)$_2$ due to Asymmetric Stretching, 1187cm^{1} (N=O)$_2$ due to Symmetric Stretching etc. There is no significant change in the peak of the pure drug in the FTIR spectrum of physical mixture of pure drug with the polymers, i.e., stearic acid and PEG 4000. It indicates that there is no chemical interaction between the drug and the polymers. This shows that Nifedipine was compatible with both the polymers.

3.2 Characterization of nifedipine encapsulated lipospheres

3.2.1 Particle size determination

Particle size may be a function of either one or more of the following: formulation excipients, degree of homogenization, homogenization pressure, rate of particle size growth, crystalline habit of the particle, etc.[11] Here the particle size ranged from 67.45 ± 1.24 µm to 83.85 ± 1.36 µm. From the result, it was observed that increase in PEG 4000 reduced the particle size. From the result shown in table 4 the maximum particle size was found in formulation F10.

Table No. 4: Particle size.

Formulation code	Particle size(µm)
F1	77.79 ± 1.75
F2	67.45 ± 1.24
F3	80.9 ± 1.78
F4	82.69 ± 1.37
F5	77.79 ± 1.75
F6	77.79 ± 1.75
F7	78.76 ± 1.39
F8	77.79 ± 1.75
F9	69.67 ± 1.54
F10	83.85 ± 1.36
F11	73.45 ± 1.41
F12	71.56 ± 1.32
F 13	77.79 ± 1.75

All values are expressed as mean ± SD, n=3

3.2.2 Drug entrapment efficiency

The role of the formulated liposphere is to deliver the API (Active Pharmaceutical Ingredient) to the target tissues intact. Thus, the ability of the liposphere to accommodate active molecules is an important property. It can be expressed by the entrapment efficiency (EE%).[11]

As could be seen in Table 5, the EE% ranged from 64.2±0.43% to 96.7 ± 0.32% for liposphere. The varied EE% may be as a result of API and matrix physicochemical properties. All the same, higher EE% values were obtained for F7 compared with other formulations. The EE% increased as the amount of the polymer (PEG 4000) in the lipid matrix decreased. The reason for this is uncertain, but may be related to increase in crystallinity of the liposphere with increase in PEG 4000 concentration that resulted in difficulty in encapsulation of Nifedipine. For example, when added at high levels, PEG lipids induce the formation of mixed micelles.

Table No. 5: Entrapment efficiency.

Formulation code	Entrapment efficiency (%)
F1	84.4 ± 0.62
F2	75.9 ± 0.55
F3	64.2 ± 0.43
F4	74.3 ± 0.56
F5	84.4 ± 0.62
F6	84.4 ± 0.62
F7	96.7 ± 0.32
F8	84.4 ± 0.62
F9	81.45 ± 0.22
F10	86.58 ± 0.23
F11	78.5 ± 0.45
F12	90.8 ± 0.46
F 13	84.4 ± 0.62

All values are expressed as mean ± SD, n=3

3.2.3. *In-vitro* drug release study

The drug release from liposphere in phosphate buffer pH in 7.4 has been shown in figure 4. All of the drug release could last to 12hrs. Drug release of Nifedipine liposphere varied in range of 81.2±0.31% to 95.3±0.18%. All the formulation showed a prolonged release profile and showed higher drug release for F7 were 95.3±0.18%.

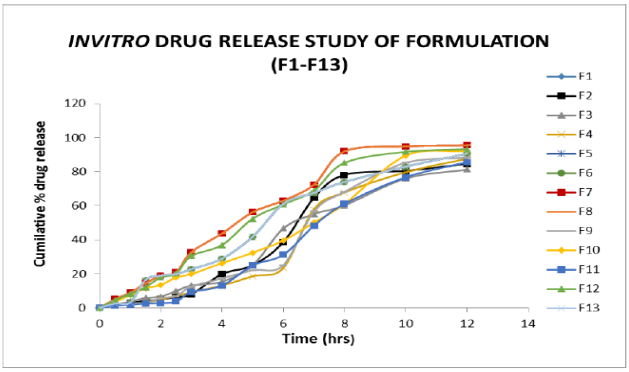

Fig. No. 4: *Invitro* drug release study.

3.2.4. Optimization by design expert stat ease software

Optimization was done by Design Expert Stat Ease Software version 13.0.7.0. Two factors were selected for optimizing the formulation. The factor selected were stearic acid and PEG 4000. Central composite design was used for optimization. To determine the best formulation, 3 responses that is particle size, entrapment efficiency and drug release were considered. 13 formulation were suggested by the software. The average values were submitted to multiple regression analysis using Design Expert Software. Polynomial models were generated or all response variables. The best fitting mathematical model was selected based on the comparisons of several statistical parameters including the coefficient variation (CV), the multiple correlation coefficient (adjusted R^2) and predicted residual sum of square (Table 6).

Table 6: Numerical test result of model adequacy checking for influence of independent variables on response variable.

Response	Model	Sequential P Value	Adjusted R^2	Predicted R^2	Adequate Precision	% CV
Particle size	linear	<0.0001	0.8237	0.9625	13.7501	2.76
Entrapment efficiency	Quadratic	<0.0001	0.9949	0.9984	81.2452	0.6943
% drug release	Quadratic	<0.0001	0.9921	0.9528	60.2094	0.3794

The fit of the model was evaluated using R^2-values. Here the predicted R^2 value was in good agreement with the adjusted R^2 value (the difference is less than 0.2), indicating the reliability of the models.

Based on the fit summary linear model was selected as best fit model for particle size and the Quadratic model was selected as best fit for entrapment efficiency, and % drug release as suggested by the software. Adequate precision (which measures signal to noise ratio) was greater than 4 for all responses showing that the proposed models can be used to navigate the design space.

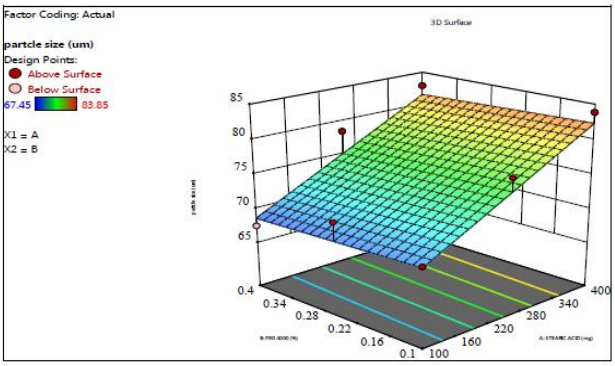

Fig. 5: Response surface plots for the effect of amount of stearic acid and PEG 4000 on Particle size.

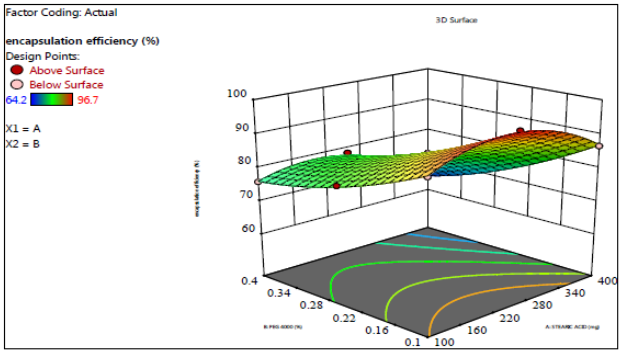

Fig. 6: Response surface plots for the effect of amount of stearic acid and PEG 4000 on % entrapment efficiency.

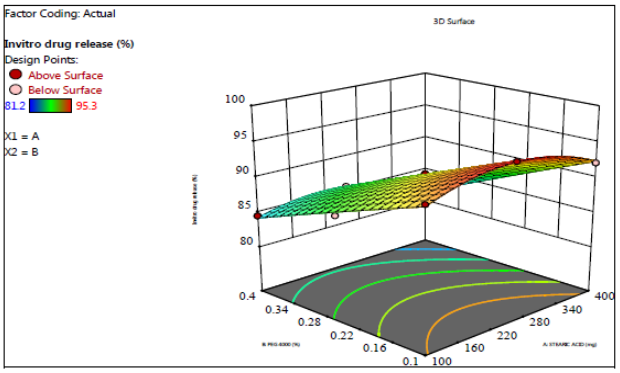

Fig. 7: Response surface plots for the effect of amount of stearic acid and PEG 4000 on % invitro drug release.

The desirability function approach is one the most widely used method for optimization of multiple responses. Overall desirability function is a measure of how well the combined goals for all responses are satisfied. Desirability function ranges from 0 to 1, with value closer to 1 indicating a higher satisfaction of response goal. The numerical optimization tool provides 2 set of optimal solution (table 7) among which 289.979 mg of stearic acid and 0.1% of PEG 4000 was selected (by the software) as optimized concentration with desirability of 0.978. The area of optimized formulation was also ratified using overlay plot as shown in fig:8 in which the yellow region represents the area satisfying the imposed criteria.

Table 7: Desirability table.

Number	Stearic Acid	PEG 4000	Partcle size	Encapsulation efficiency	Invitro drug release	Desirability	
1	289.979	0.100	77.600	95.210	95.037	0.978	Selected
2	270.191	0.100	76.748	95.860	95.211	0.961	

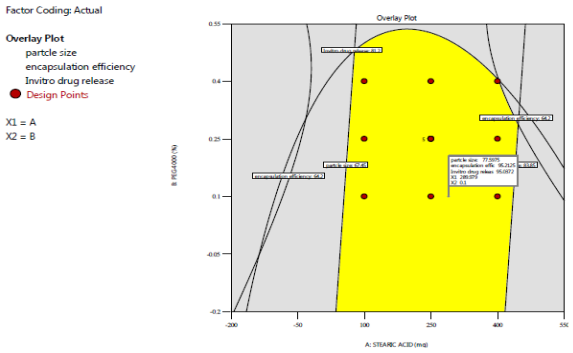

Fig. 8: Overlay plot of optimized formulation of nifedipine loaded liposphere.

The experiment were carried out in triplicate at the selected optimum concentrations (289.979mg of stearic acid and 0.1% of PEG 4000) and the resulting liposphere were evaluated for particle size, entrapment efficiency, and invitro drug release. The result shown in table 8.

Table 8: Predicted and observed responses for optimized formulation.

Solution 1 of 1 Response	Predicted	Observed	%Error
Particle size	77.600	77.72	0.1544
Entrapment efficiency	95.210	95.33	0.1258
In-vito Drug Release	95.037	95.23	0.2026

3.2.5. Scanning electron microscopy examination

The surface morphology of the liposphere prepared by melt technique was studied and has been depicted in Fig. 9. The SEM showed uniformly sized spherical liposphere with minimum evidence of the crystals of Nifedipine.

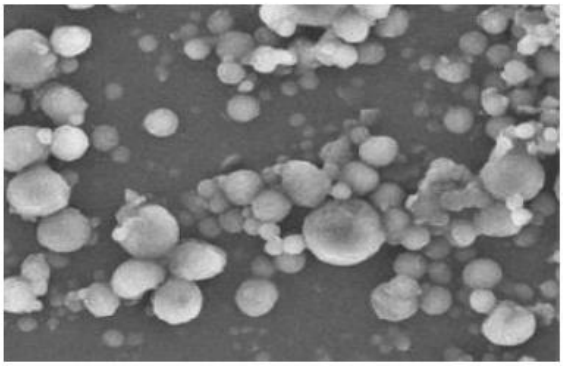

Fig. 9: Scanning electron image of optimized formulation.

3.2.6. Drug release kinetics

In optimized formulation, correlation coefficient of zero order kinetics was found to be 0.8888, first order release kinetics was 0.9753 and Higuchi plot was found to be 0.897. Hence the formulation follows first order kinetics. To confirm the exact mechanism of drug release from the liposphere, data was fitted according to Korsmeyer Peppa's plot. The value of slope of plot n gives indication of release mechanism. When n=1, release is independent of time that is zero order.

If n=0.5, then release is fickian diffusion. If n=0.5-1, diffusion is non-fickian and n>1then it is super case transport. The 'n' exponent value of best batch was 0.77. Hence it **s**hows non-fickian transport.

Table 9: Drug release kinetics of optimized formulation.

Zero order	First order	Higuchi	Korsmeyer-Peppas	
R^2	R^2	R^2	R^2	n
0.8888	0.9753	0.9377	0.9513	0.77

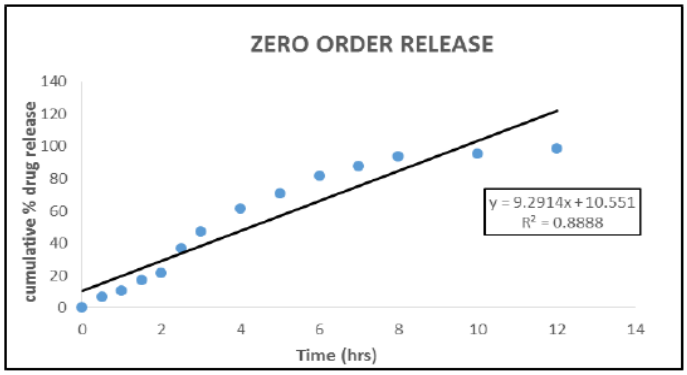

Fig. 10: Zero order release plot.

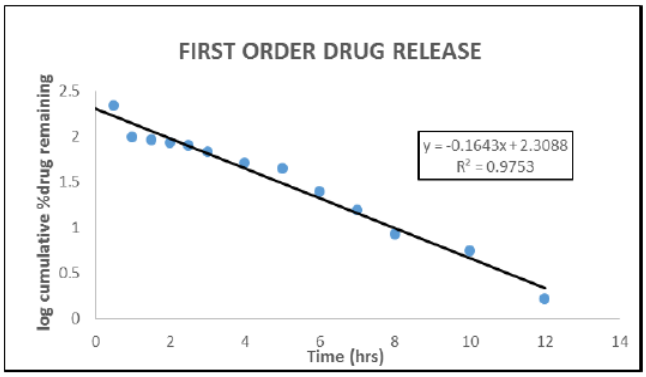

Fig. 11: First order release plot.

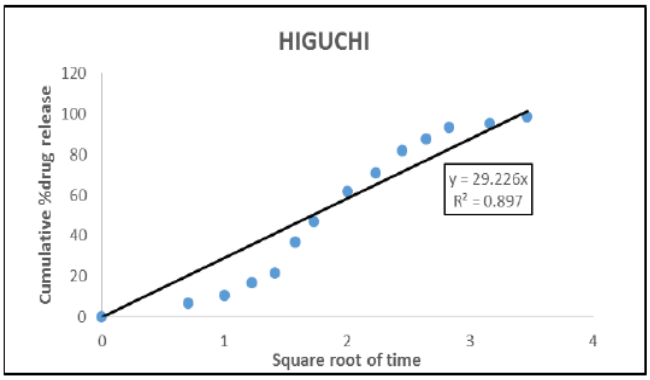

Fig. 12: Higuchi plot.

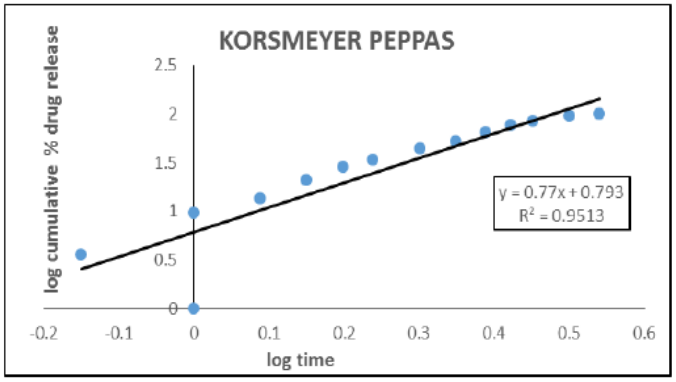

Fig. 13: Korsmeyer peppas plot.

3.2.7 Stability studies

The optimized formulation was used for stability studies as per the ICH guidelines for 3 months. It shows that prepared liposphere pass stability studies with not much significant changes in the particle size, entrapment efficiency and in vitro drug release (Table 10)

Table 10: Stability data of optimized formulation.

Storage Condition	Sampling Interval	Particle Size (µm)	Entrapment Efficiency (%)	Invitro Drug Release
40ºC ± 2ºC at 75%± 5%RH	Initial study	77.72± 1.39	95.33± 0.32	95.23±0.21
	30 days	77.08± 1.21	94.63± 0.14	95.03±0.97
	90 days	76.46± 1.30	93.85 ± 0.11	94.13±0.45
25ºC ± 2ºC at 60%±5% RH	Initial study	77.72± 1.39	95.33± 0.32	95.23±0.21
	30 days	77.22± 1.11	95.10± 0.69	95.10±0.56
	90 days	76.92± 1.17	94.93± 0.91	94.68±0.35
5ºC ± 3ºC	Initial study	77.72 ± 1.39	95.33±0.31	95.23±0.21

	30 days	77.44 ± 1.26	95.23±0.21	95.13±0.11
	90 days	77.16 ± 1.03	95.16±0.61	94.53±0.78

CONCLUSION

The novel approach was developed for liposphere formulation by selecting optimum blends of lipids, surfactants using systematic "DoE" methodology of central composite design. The optimized formulation showed high drug entrapment efficiency, proper particle size and exhibited a sustained release property for oral use in the form of capsules.

Findings of this investigation suggest that liposphere were able to entrap the drug at very high levels and sustain its release over a prolonged time. So it can be concluded that liposphere might be a promising lipid based colloidal carrier system to enhance the absorption of nifedipine.

Acknowledgement

It gives us great pleasure to express our gratitude to the college management of Crescent College of Pharmaceutical Sciences, Payangadi, for providing the facilities for the successful completion of our project work.

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