Research Article

Formulation and Evaluation for Solid Lipid Microparticles of Efonidipine

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ABSTRACT

Design a dosing frequency level for efonidipine and examine its pharmacokinetics and dynamics. Solid Lipid Microparticles were made using efonidipine. ATR-FTIR research 4000 to 400cm^{-1}, SEM analysis, Diffrantional Scanning Calorimetry, Power X-ray diffraction. The current state of *in vitro* drug release research is discussed. Then we'll look at the ingredients and procedures for making solid lipid microparticles. It is possible to prepare and use microparticles in many ways. Hypotensive solid lipid microparticles with efonidipine showed promise. They all survived three months at 4°C. Oral administration is the most usual technique. Many pharmacological dosage forms are intended to delay drug release. Its systemic circulation and plasma profile are prolonged.

Keywords: Efonidipine, Solid Lipid Microparticles, Efonidipine, Stearic acid, Glyceryl Trilaurate and Egg lecithin.

INTRODUCTION

Solid Lipid Microparticles (SLMs) are solid lipid particles that are spherical in shape and range in size from 1 to 1000 um. They're made up of biodegradable synthetic polymers and modified natural products, including starches, gums, proteins, lipids, waxes, polymeric, waxy, or other protective elements. In recent years, biocompatible lipid microparticles have been presented as a potential drug carrier system and as an alternative to the polymer. In comparison to liposomes, they are physiologically compatible, physicochemically stable, and allow for large-scale development at a low production cost. Efonidipine is an antihypertensive pill that has been around for an extended period. It was originally developed to treat angina pectoris, hypertension, and atherosclerosis as a dihydropyridine calcium channel antagonist. The immediate drug release from the dose form avoids the liver's metabolism of efonidipine, providing rapid relief from anginal pain and hypertension, which is helpful in such cases, Emulsification in a hot melt, Evaporation of the solvent, Homogenization under high pressure, Emulsification of membranes, Congealing/cooling spray.[1-2] some Advantages are the Possibility of drug targeting and controlled drug release, Chemical degradation of the integrated labile drug is prevented, Chemical and physical storage stability is present (for both drug and carrier systems), Biodegradable lipids are used and it allows for the incorporation of hydrophilic and hydrophobic drugs. Some Disadvantages are particle growth is a possibility, The safety profile may be ambiguous, The water content of SLM dispersions is high and they alter the integrated drug's release profile.

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MATERIALS AND METHODS

Materials

Efonidipine, Stearic acid, Glyceryl Trilaurate, Egg lecithin, Poloxamer, Chloroform, Carbinol, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Distilled water.

Preparation of Solid Lipid Microparticles by Hot Homogenization Method[3]

The lyophilized drug-loaded SLMs were made using a procedure of hot homogenization, ultrasonication, and freeze-drying. The drug, solid lipid, and emulsifier (egg lecithin) were dissolved in a 10ml mixture of carbinol and chloroform (1:1). The organic solvents were extracted extensively using a rotary flash evaporator. The drug-incorporated lipid layer was melted at a temperature of 5°C above the melting point of the lipid. Simultaneously, in distilled water, a 1.5 percent w/v aqueous solution of the stabilizer, Poloxamer 188, was prepared and heated to the same temperature as the oil phase. The aqueous phase was then added to the oil phase, and the mixture was homogenized for 4 min at 12000 rpm in a homogenizer (DIAX 900, Germany). Using a probe sonicator, the oil-aqueous emulsion mixture was homogenized before being sonicated for 20 min (Vibracell, USA; 12T-probe). Drug-loaded SLMs were created after allowing the heated micro-emulsion to cool to room temperature. To get lyophilized SLM powdered product, frozen samples were transferred and dried using a freeze-dryer, followed by vacuum suction for roughly 48 hr.

The preparation ingredients are shown in Table 1- 2.

Table 1: Composition of ENS-SLM with different surfactants at various concentrations.

Ingredients	mg/ml					
	ENS1	ENS2	ENS3	ENS4	ENS5	ENS6
Efonidipine (mg)	10	10	10	10	10	10
Stearic Acid (mg)	---	---	150	150	---	---
Glyceryl Trilautrate (mg)	---	---	---	---	150	150
Egg Lecithin (mg)	75	100	75	100	75	100
Poloxamer-188 (in ml)	1.5	1.5	1.5	1.5	1.5	1.5
Dis.Water (ml)	10	10	10	10	10	10
Chloroform:Methanol (1:1)(ml)	10	10	10	10	10	10

Table 2: Composition of ENS-SLMs with different surfactants at carrying concentrations.

Ingredients	mg/ml			
	ENS1	ENS2	ENS3	ENS4
Efonidipine (mg)	10	10	10	10
Stearic Acid (mg)	100	150	---	---
Glyceryl Trilautrate (mg)	---	---	100	150
EGG Lecithin (mg)	100	100	100	100
Poloxamer-188 (in ml)	1.5	1.5	1.5	1.5
Dis. Water (ml)	10	10	10	10
Chloroform: Methanol (1:1) (ml)	10	10	10	10

EVALUATION STUDIES

UV Spectral Analysis[4]

Preparation of Standard stock solution of the drug

In a 100 ml volumetric flask, 10 mg of efonidipine was dissolved in carbinol solution. To make a stock solution with a concentration of 1000 g/ml (1 mL g/mL), the volume was raised to 100 mL using carbinol. To generate a 100 g/mL (0.1 mg/mL) solution, 10 mL of this stock solution was transferred to a 100 mL volumetric flask and diluted with carbinol.

Standard Calibration curve preparation for Pure drug

From both the standard stock solutions prepared, Aliquots of 1 to 10 ml of each standard stock solution were deposited in a 10 ml volumetric flask separately, yielding solutions with working concentrations of 1,2,3,4,5,6,7,8,9,10 g/ml of drug and carbinol, respectively. Using a twin beam U.V. spectrophotometer, the absorbance of these solutions was measured up to 238nm (1601 UV spectrophotometer Shimadzu, Japan). The absorbance measurements against concentration (in g/ml) were plotted on the standard calibration curve. The results are shown in the Figure 1, 2.

Compatibility Studies[5]

The spectrum was captured between the wavelengths of 4000 and 400cm^{-1}. An IR spectrum was obtained using an ATR-FTIR spectrophotometer after a homogenous mixture of the drug and Lipids was put into the die cavity of the sample holder and the spectrum. The results are shown in the Figure 3.

Differential Scanning Calorimeter[6]

One of the most often used procedures for assessing drug-excipient compatibility is differential scanning calorimetry (DSC). DSC of pure medicine, pure lipids, and the lyophilized optimal formulation was performed using the Mettler-SToledo DSC 821e (Columbus, OH,

UV Spectroscopy

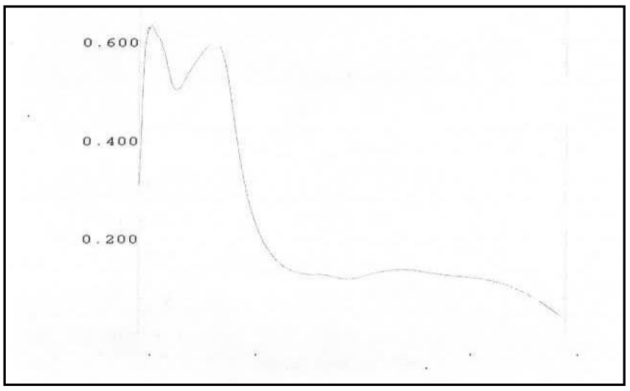

Figure 1: UV Spectroscopy.

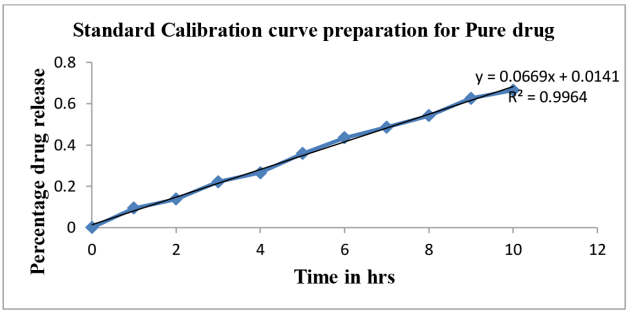

Figure 2: Standard Calibration curve preparation for Pure drug.

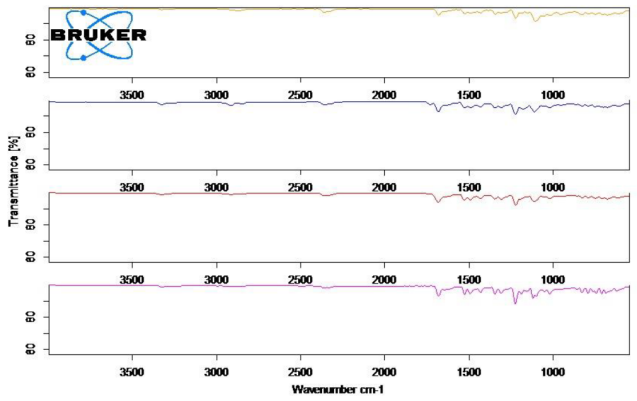

Figure 3: IR spectra analysis of Efonidipine.

USA) equipment at a heating rate of 10°C/min in the temperature range of 60-300°C. The results are shown in the Figure 4.

Powder X-Ray Diffraction[7]

A powder X-ray diffraction (Multiflex, M/s. Rigaku, Japan) was used to conduct the diffraction investigation. For powder XRD studies, the sample substances were subjected to nickel-filtered CuK radiation (40kV, 30mA) and scanned from 2 to 70, 2 with a step size of 0.045

Evaluation Studies for Solid Lipid Microparticles

Differential Scanning Calorimetry

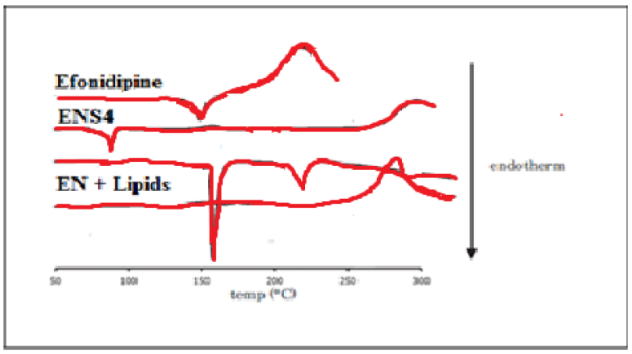

Figure 4: Differential Scanning Calorimetry.

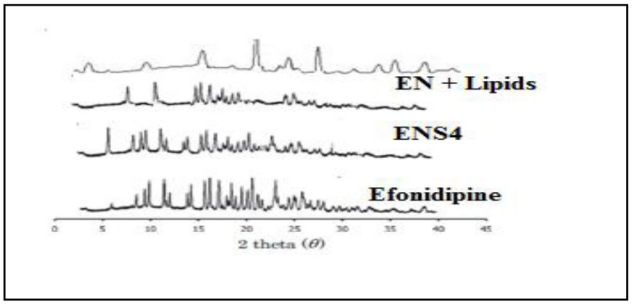

Figure 5: Powder X-ray diffraction.

Table 3: Drug Loaded Efficiency.

Formulation Code	Drug-loaded efficiency of solid lipid microparticles %
ENS1	90.01%
ENS2	90.69%
ENS3	91.84%
ENS4	91.87%

and a step time of 0.5sec. Drugs, lipids, physical mixes of drug and lipid, and lyophilized drug-loaded solid lipid microparticles were all subjected to separate XRD tests. The results are shown in Figure 5.

Drug Load Efficiency[8]

100 mg of crushed Solid Lipid Microparticles were added to a 100 ml volumetric flask and dissolved with a tiny amount of ethanol before being filled with phosphate buffer pH 7.4 and swirled for 12 hr. The results are shown in the Table 3.

$$\text{load efficiency} = \frac{\text{the actual drug content in Solid Liquid Microparticles}}{\text{theoretical drug content}} \times 100$$

Morphological Analysis

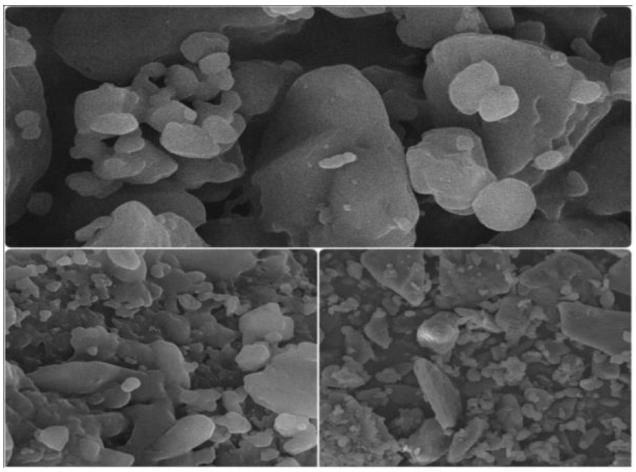

Figure 6: SEM analysis of Solid Lipid Microparticles.

Surface Morphology Study by Scanning Electron Microscopy[9-10]

Scanning Electron Microscope analysis was used to examine the particle size and shape of solid lipid microparticles. The drug's lyophilized SLMs were diluted with double distilled water (1/100 dilution), and the dispersion of microparticles was scanned with an electron beam under-regulated vacuum settings. The results are shown in the Figure 6.

In vitro Drug Release Studies[11]

In vitro release studies were conducted using a dialysis membrane with a pore size of 2.4 nm and a molecular weight cut-off capacity of 12,000-14,000 kDa that had been soaked overnight in Phosphate buffer pH 6.8 12 hr before the release study (Narendar D and Kishan V, 2014). Phosphate buffer pH 7.4 was used as the study medium. One end of the aperture was connected to the dialysis membrane, while the other was left open for sample entry in the experimental unit with donor and receptor compartments. The donor compartment had a 1 mg/mL reconstituted SLM formulation, whereas the receptor compartment had a 100 mL dialysis medium. A steady temperature of 37.5°C was maintained throughout the experiment. To maintain a constant volume of the release medium, aliquots of 2 ml of the sample were removed from the receptor compartment and replaced with fresh medium at time intervals of 0, 0.5, 1, 3, 5, 7, 9, and 12. UV Spectroscopy at a maximum wavelength of 238 nm was used to examine the materials acquired using a UV Visible Spectrophotometer. The results are shown in the Table 4, 5 and Figure 7, 8.

Determination of Short-term Stability Studies for Solid Lipid Microparticles[12]

The optimized formulation of solid lipid microparticles for the stability determination accelerated stability conditions at (40°C/75%RH). It's taken and examined for load efficiency and *in-vitro* drug release studied every 30 days for three months. These factors are compared to the initial sample and evaluated to see whether it

In vitro Release Studies

Table 4: *In vitro* Composition of ENS-SLM with different surfactant at various concentrations.

Time(hr)	ENS1	ENS2	ENS3	ENS4	ENS5	ENS6
0	0	0	0	0	0	0
0.5	9.78	10.74	13.91	15.61	18.91	21.03
1	12.31	19.83	21.09	24.91	26.91	30.90
3	20.31	27.54	32.89	37.45	39.60	44.06
5	34.08	36.01	45.74	50.09	54.56	57.67
7	41.41	44.73	53.08	62.51	68.45	69.21
9	47.21	58.91	61.80	65.91	70.91	75.94
12	53.83	65.83	67.90	69.09	74.82	82.03

Table 5: *In vitro* Composition of ENS-SLMs with different surfactants at carrying concentrations.

Time(hr)	ENS7	ENS8	ENS9	ENS10
0	0	0	0	0
0.5	9.21	11.46	14.88	20.85
1	18.45	24.88	26.73	29.54
3	33.67	36.94	38.92	35.88
5	45.08	48.85	53.89	47.89
7	51.27	53.82	57.93	59.67
9	62.91	66.63	69.86	73.88
12	71.82	74.82	75.72	85.54

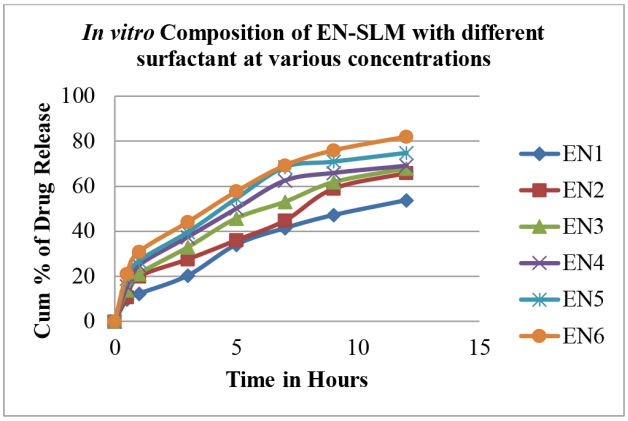

Figure 7: *In vitro* Composition of ENS-SLM with different surfactants at various concentrations.

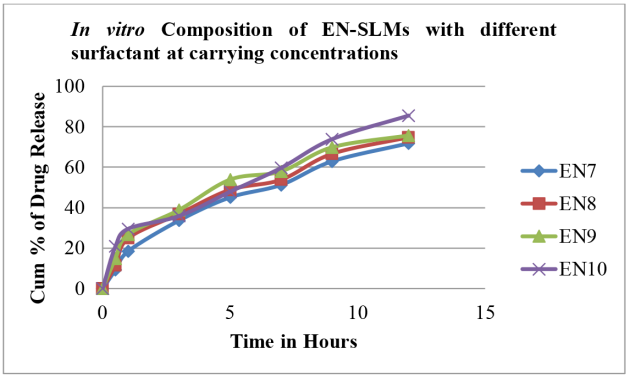

Figure 8: *In vitro* Composition of ENS-SLMs with different surfactants at carrying concentrations.

Table 6: Determination of prepared Solid Lipid Microparticles.

Parameters	Initial	After one month 40/75 (°C/ Rh)	After the second month 40/75 (°C/ Rh)	After the third month 40/75 (°C/ Rh)
Drug load efficiency (%)	91.87	91.64	91.23	90.89
In vitro drug release (%)	85.54	85.17	84.95	84.82

meets the specifications. If it does, the batch passes the test. The results are shown in the Table 6.

RESULTS AND DISCUSSION[13-14]

UV Spectroscopy

The wavelength at which the drug's highest absorbance occurs was obtained using a UV spectrophotometer. Carbinol was chosen as the preferred solvent due to its solubility. The UV spectra of Active Pharmaceutical Ingredients. When compared to a standard API (238 nm).

Compatibility Studies

The ATR-FTIR spectrophotometer was used to perform a chemical compatibility analysis of the medicine and excipients, and the spectra were obtained in the wavenumber range of 4000 to 400cm^{-1}. The peaks in the physical combination spectrum are associated with the peaks in the pure drug spectrum. This means the medicine is compatible with the other ingredients in the formulation.

Evaluation Studies for Solid Lipid Microparticles

Differential Scanning Calorimetry

Differential Scanning Calorimetry thermograms of Efonidipine drug with lipids, an optimized formulation of ENS4 Solid Lipid Microparticles were investigated. The result indicates the decomposition of lipids without melting.

Powder X-ray Diffraction

The peak size and shape of X-Ray Diffraction help determine the crystallinity of Efonidipine, Efonidipine with lipids, and optimized formulation ENS4 Solid Lipid Microparticles. From the below graph, a reduction in the crystalline nature of drug and lipids in Solid Lipid Microparticles generally improves the solubility and release of drug from Solid Lipid Microparticles.

Drug Load Efficiency

The loading efficiency was performed for drug-loaded solid lipid microparticles for all formulations, ranging from 90.01% to 91.84%. The results indicated that the EN10 formulation exhibited the maximum entrapment efficiency percentage with maximum drug content loaded.

Morphological Analysis

SEM analysis was studied for the optimized drug-loaded solid lipid microparticle formulation (ENS4). The pure drug was evaluated for the surface morphology of the prepared SLM at magnifications of 250X, 20.00 K X, and 30.00 K X. The surface morphological study results confirmed that prepared solid lipid microparticles were formed well and confirmed under various magnifications in scanned electron microscopy.

In vitro Release Studies

In vitro drug release kinetic studies were performed by dialysis method for all the formulations of solid lipid microparticles. It was observed that the EN10 formulation showed 91.87% maximum drug release efficiency during the study period. Based on the release studies mentioned above, the EN10 formulation was concluded to be the best optimized solid lipid microparticle formulation. From the result of *in-vitro* drug release kinetic, optimized EN10 formulation was further subjected for stability studies.

Determination of Short-term Stability Studies for Solid Lipid Microparticles

The stability studies for optimized EN10 formulation were conducted for three months. Minor variations in load efficiency and *in vitro* drug release were identified in the research, showing vulnerability to stability issues

during storage at room temperature, and 40°C/75 % RH was observed.

SUMMARY AND CONCLUSION

This research work was carried out to develop and evaluate the solid lipid microparticle formulations for Efonidipine. Efonidipine, a poorly water-soluble drug with high first-pass metabolism, is available as conventional tablets. As a result, an effort was undertaken to manufacture drug-loaded solid lipid microparticles to bypass first-pass metabolism and boost efonidipine bioavailability. Following the initial preformulation studies, various drug-loaded solid lipid microparticle formulations, EN1 to EN10, were prepared using the Hot homogenization method and then tested for drug loading capacity using DSC, Power X-Ray Diffraction, Surface morphology analysis by SEM, and *in vitro* drug release dialysis. For the optimal formulation of SLM, DSC and Power X-Ray Diffraction experiments were carried out; the size and shape of the curve indicate the crystalline substance. From these studies, the reduction in the crystalline nature of drugs and lipids generally improves the drug's solubility and release.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

API: Active Pharmaceutical Ingredient; **ATR-FTIR:** Attenated Total Reflectance- Fourier Transform Infrared; **DSC:** Differential Scanning Calorimetry; **EN:** Efonidipine; **SLMs:** Solid Lipid Microparticles; **EN-SLMs:** Efonidipine-Solid Lipid Microparticles.

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