FORMULATION AND EVALUATION OF NIFEDIPINE LOADED SOLID LIPID NANOPARTICLES

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ABSTRACT

The objective of the research work is to enhance the solubility and dissolution rate of Nifedipine by converting them into suitable solid lipid nanoparticles (SLNs). The method used for formulating solid lipid nanoparticles (SLNs) was high pressure homogenization followed by solvent emulsification- ultrasonication. The evaluation parameters for SLNs were drug content, entrapment efficiency, particle size, solubility study, *in vitro* drug release, etc. Nifedipine loaded solid lipid nanoparticles (SLNs) were characterized for drug content, entrapment efficiency, particle size, solubility study and *in vitro* drug release. Nifedipine loaded SLNs was prepared by using stearic acid and glycerylmonostearate as lipid and Tween 80 as stabilizer. The optimized batch (F4) contained 500mg of Glycerylmonostearate and 300mg of stabilizer. Batch F4 exhibited drug content of $88.75\pm0.510\%$, %EE of $79.31\pm0.119\%$, Particle size of 146 ± 31.2nm, Practical yield of $91\pm1.21\%$, Solubility of 0.011mg/ml and % drug release of 71.17% at 180mins. It was concluded that the solid lipid nanoparticles (SLNs) developed by this method showed increase in solubility and dissolution rate of Nifedipine.

KEYWORDS

Solid lipid nanopartilces (SLNs), High pressure homogenization, Solvent emulsification, Nifedipine, Drug release and Solubility study.

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INTRODUCTON

Nifedipine (Dihydropyridine derivative) is 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[1]. 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[2].

The solid lipid nanoparticles (SLNs) were prepared by using solid lipids instead of liquid lipids to improve the physical stability. SLNs are small colloidal carriers which are made up of biodegradable lipid matrix in the range of 10-1000nm[3]. Solid lipid nanoparticles (SLNs) appears to be a different carrier system to emulsion, liposomes, polymeric nanoparticles, etc. Along with lipids and drug, it contains surfactant as stabilizer. Both lipophilic as well as hydrophilic drugs can be easily incorporated into SLNs[4]. Various advantages of SLNs are large surface area, small size, high drug loading capacity, increased drug stability, etc[5].

Several methods involved in the preparation of solid lipid nanoparticles (SLNs) are: High pressure homogenization, hot homogenization, cold homogenization, ultrasonication, solvent evaporation, double emulsion method, etc[6]. The purpose of this research work was to enhance solubility and dissolution rate of Nifedipine by converting them into suitable Solid lipid nanoparticles (SLNs).

MATERIAL AND METHODS
Materials
Nifedipine, a gift sample was obtained from Nova Chem Drugs Pvt Ltd (Pune, India). Stearic acid, Glyceryl monostearate, Tween 80 and Acetone used in the preparation were of laboratory grade.

Methods
Solid lipid nanoparticles (SLNs) loaded with Nifedipine were prepared by two methods i.e. high pressure homogenization followed by solvent emulsification-ultrsonication. Firstly, the oil phase was prepared by dissolving stearic acid in suitable organic solvent such as acetone. The lipid layer was melted by heating at 70-80ºC i.e. 10ºC above the melting point of the lipid. 20mg of Nifedipine was then dissolved in the oil phase. Secondly, the aqueous phase was prepared by dissolving Tween 80 in 10ml of distilled water and heated at the same temperature as oil phase. Then oil phase was added dropwise to the aqueous phase and homogenization was carried out by using magnetic stirrer at

1500rpm for 2 hrs. The oil in water emulsion was then sonicated for 25mins. Nifedipine loaded SLNs were finally prepared. Various formulations were prepared using different lipid polymer and stabilizer with different composition[7].

Characterization of SLNs
Drug content
About 1ml of SLNs dispersion was taken in a 100ml volumetric flask and volume in the volumetric flask was adjusted with chloroform. This solution was then sonicated for 10mins. The solution was then filtered through Whatmann filter paper with pore size 0.45µ and filtrate was analysed spectrophotometrically at 349nm[8].

Entrapment efficiency
The percentage of Nifedipine entrapped was determined spectrophotometrically at 349nm. The SLNs dispersion was centrifuged at 10000rpm. The amount of free drug was detected from supernatant. The percentage entrapment efficiency was calculated using the following formula:

Entarpment efficiency (%EE)$= \frac{Wt.initial\ drug - Wt.free\ drug}{Wt.initial\ drug} \times 100$

Particle size
The particle size analysis was simply carried out by laser diffraction technique using Malvern Master sizer 2000S. The SLNs dispersion in Milli-Q water was prepared and loaded to determine particle size.

Practical yield
The practical yield of Nifedipine loaded SLNs was determined by taking 10ml of dispersion, which was centrifuged at 12000 rpm for 120min at 4ºC by cooling centrifuge. The supernatant was decanted and remaining part was dissolved in chloroform, sonicated, filtered and analysed using UV visible spectrophotometer at 349nm. Practical yield was calculated as drug analysed in the nanoparticle by the total amount of product obtained and total solid used in the preparation.

Solubility study
Solubility measurement was determined by simly recording absorbance using UV visible spectrophotometer at 349nm. The supersaturate solution of Nifedipine loaded SLNs was stirred by magnetic stirrer for 24 hrs at room temperature. Then the solution was filtered through Whatmann

fiter paper and the concentration of drug was determined spectrophotometrically at 349nm[9].

In vitro drug release study

The *in-vitro* release of Nifedipine loaded SLNs dispersion was determined by using dialysis bag diffusion technique. Accurately weighed amount of Nifedipine loaded SLN dispersion containing drug equivalent to 20mg was transferred ti=o dialysis bag and sealed. The bag was then dipped in a beaker containing 100ml of phosphate buffer pH 7.4 and stirred at constant speed of 50rpm at room temperature. Aliquotes were withdrawn at predetermined intervals and replaced with fresh buffer. Then the drug content was determined spectrophotometrically at 349nm[10].

RESULTS AND DISCUSSION

Drug content

The drug content of all batches of Nifedipine loaded SLNs is tabulated in Table No.2. The drug content for all four batches was found to be 79.09%, 86.30%, 81.89% and 88.75% showing that Nifedipine was evenly distributed in the SLNs dispersion.

Entrapment efficiency (%EE)

From the results given in the table, it has been observed that, the formulation containing high lipid concentration have high entrapment efficiency. It has been observed that F4 batch has higher entrapment efficiency than other three batches. F4 batch has 79.31% entrapment, while F1, F2 and F3 batches has 69.19%, 74.69% and 73.39% entrapment respectively. The percentage of entrapped drug in different batches with different lipid concentration was determined spectrophotometrically.

Particle size

Particle size of Nifedipine loaded SLNs was analysed by simple using a Metasizer 2000 instrument (Malvern). Particle size of all four batches of Nifedipine loaded SLNs was measured. The particle size for F1, F2, F3 and F4 batches was found to be 239nm, 179nm, 191nm and 146nm resp. It was observed that change in concentration of lipid does not much affect the particle size. Nifedipine loaded SLNs were observed to be small in size and spherical in shape. Figure No.1.

Practical yield

It was observed that percentage practical yield increases with increase in concentration of lipid. The percentage practical yield for F1, F2, F3 and F4 batch was found to be 81%, 89%, 86% and 91% resp.

Solubility study

Prepared Nifedipine loaded SLNs showed increased solubility than the pure drug in the water. F4 batch showed increase in solubility i.e. 0.011mg/ml in water whereas the solubility of Nifedipine in water was found to be 0.005mg/ml. The increase in solubility of drug may be due to reduction in particle size[8].

In vitro drug release study

The *in vitro* drug release profile of Nifedipine loaded SLNs is shown in the Table No.4. The *in vitro* release of SLN dispersion was found to be in the range of 62.02 to 71.17% in 180mins resp.

From the dissolution study it was concluded that all formulation batches show more than 50% drug release in120mins. In all batches, F4 batch shows maximum drug release i.e. 71.17% and was selected as the optimized batch. Hence, graph is plotted to determine the drug release of the drug.

Table No.1: Composition of Nifedipine loaded solid lipid nanoparticles (SLNs)

Batch No.	[Drug] Nifedipine (mg)	[Lipid] Stearic acid (mg)	[Lipid] Glycerylmonostearate (mg)	Acetone (ml)	[Stabilizer] Tween 80 (mg)	Distilled water (ml)
F1	20	200	-	5	200	10
F2	20	500	-	5	300	10
F3	20	-	200	5	200	10
F4	20	-	500	5	300	10

Table No.2: Characterization of Nifedipine loaded SLNs

Batches	Drug content	% EE	Particle size (nm)	% Practical yield
F1	79.09 ± 0.460	69.19 ± 0.211	239 ± 11.6	81 ± 1.59
F2	86.30 ± 0.45	74.69 ± 0.461	179 ± 26.1	89 ± 1.01
F3	81.89 ± 0.323	73.39 ± 0.209	191 ± 20.7	86 ± 1.30
F4	88.75 ± 0.510	79.31 ± 0.119	146 ± 31.2	91 ± 1.21

Table No.3: Solubility study of Nifedipine

S.No	Formulation batches	Water solubility In mg/ml
1	Pure drug	0.005
2	F1	0.004
3	F2	0.009
4	F3	0.007
5	F4	0.011

Table No.4: *In vitro* drug release study

| S.No	Time (min)	F1	F2	F3	F4
1	15	17.01 ± 0.652	11.24 ± 0.411	11.04 ± 0.023	14.62 ± 0.133
2	30	27.41 ± 0.112	20.71 ± 0.090	19.05 ± 1.566	26.19 ± 0.442
3	45	36.81 ± 1.422	27.08 ± 0.113	26. 49 ± 0.644	34.15 ± 0.311
4	60	46.04 ± 0.988	33.29 ± 0.843	31.69 ± 0.344	41.71 ± 1.223
5	90	51.97 ± 1.006	47.31 ± 1.276	40.11 ± 0.414	49.07 ± 1.440
6	120	59.09 ± 1.244	54.47 ± 1.221	47.13 ± 1.232	57.18 ± 0.121
7	150	63.29 ± 0.511	60.01 ± 0.832	54.75 ± 1.977	65.14 ± 0.331
8	180	67.02 ± 0.110	63.26 ± 0.754	62.19 ± 0.661	71.17 ± 0.204
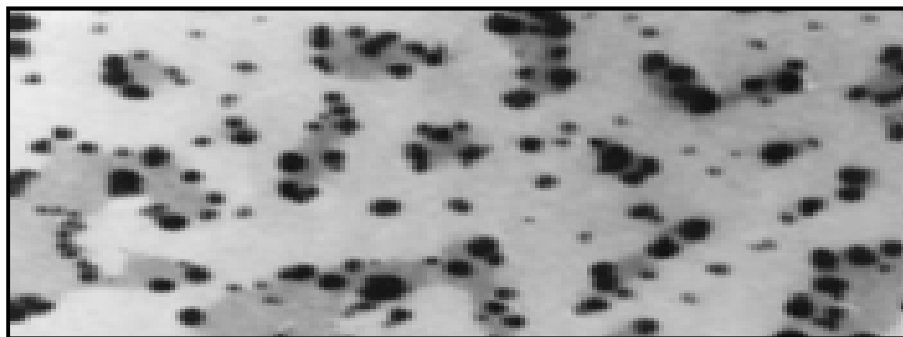
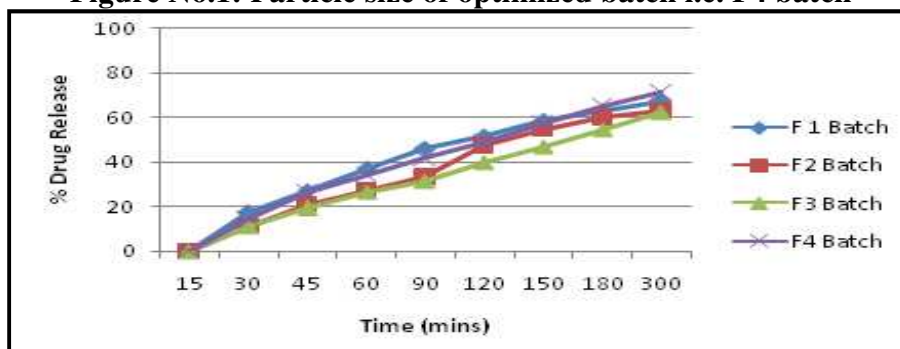**Figure No.1: Particle size of optimized batch i.e. F4 batch**

Figure No.2: *In vitro* drug release of Nifedipine loaded SLNs

CONCLUSION

High pressure homogenization followed by solvent emulsification- ultrasonication method was useful for the incorporation of the poorly water soluble drug i.e. Nifedipine. The particle size of prepared nanoparticles were in nanometer range. The *in vitro* drug release through dialysis membrane from SLNs is much higher than the pure drug. Based on drug content, entrapment efficiency, solubility, drug release study, etc F4 batch was considered as the optimized batch. The results of the above study show that the present work was satisfactory for improved solubility and drug release profile.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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