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Design, Development and Characterization of Self-Microemulsifying Drug Delivery System of Nitrendipin

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Abstract: The objective of the present work was to formulate a self-microemulsifying drug delivery system (SMEDDS) for Nitrendipin, which is widely used in the treatment of hypertension. Nitrendipin SMEDDS were formulated using a mixture of Ethyl oleate as oil, cremaphore RH40 as surfactant and PEG 400 as co-surfactant. The developed SMEDDS were evaluated for droplet size, zeta potential, self micro emulsification time and drug content determination and in vitro diffusion profiles. The cumulative percentage release of optimized batch was observed 98.33%. The optimized batch of mean droplet size, polydispersity index, zeta potential and drug content were showed 67nm, 0.247, -38.2 and 99.85±0.024 respectively. The stability studies of solid SMEDDS, reveals that there was no significant decrease in drug release and drug content, hence the all the prepared formulation were found to be stable. The comparative in vitro release study of optimized batch and marketed formulation showed that the formulation of solid SMEDDS of nitrendipine showed more than 90% drug release in 60 min, where as marketed preparation shows <80% drug release. The study illustrated the self micro emulsifying drug delivery system of Nitrendipine, owing to nanosize, has potential to enhance its absorption and solubility, dissolution, and consequently oral bioavailability.

Keywords: Nitrendipine, SMEDDS, Ternary phase diagram, bioavailability, Solubility.

INTRODUCTION:

For the therapeutic delivery of lipophilic active moieties (Class II drugs), lipid based formulations are inviting increasing attention. Amongst many such delivery options, like incorporation of drug in oils [1], surfactant dispersions [2], emulsions [3] and liposomes [4], one of the most popular approaches are the self-microemulsifying drug delivery systems (SMEDDS). Poor aqueous solubility of lipophilic drugs creates problems in formulation as well as in oral administration. [5] It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability.

As oral route for drug administration is most commonly used among all the routes of administration due to its convenience, non-invasiveness and cost effectiveness it becomes necessary that drug should have aqueous as well as lipid solubility for their absorption. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for drug absorption [6, 7]. Many researchers have reported various rational applications of SMEDDS for delivering and targeting lipophilic drugs, e.g., coenzyme Q10 [8], vitamin E [9], halofantrine [10] and cyclosporin A [11]. Potential advantages of these systems include enhanced oral bioavailability (enabling dose reduction), more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the

hostile environment in the gut [12, 13]. For selecting a suitable self-emulsifying vehicle, drug solubility in various components, identification of emulsifying regions and resultant droplet size distribution need careful monitoring, since these are drug-specific systems.[14 -16]

Thus, Solid-SMEDDS will have combined advantages over the SMEDDS such as enhanced solubility, bioavailability, with those of solid dosage forms, such as low production cost, convenience of process control, high stability and reproducibility, better patient compliance.[17-18]

Nitrendipine is a lipophilic drug used for the management of mild to moderate essential hypertension. It possesses low oral bioavailability (20 %) due to hepatic first pass metabolism after oral administration. Nitrendipine, a dihydropyridine calcium channel antagonist is a typical poorly water-soluble drug. For such biopharmaceutical classification system (BCS) II type compounds, the rate and degree of absorption from the gastrointestinal tract are usually controlled and limited by the dissolution process. These all parameter of NTD matches the suitable criteria of SMEDDS there for it selected as a model drug to improve the solubility, dissolution rate and bioavailability.[19-21]

Various attempts to enhance the dissolution rate and bioavailability of nitredipin have been reported (22, 23). In the present study, SMEDDS formulations containing nitredipin were developed using different proportions of oils and surfactant systems for oral administration. Isotropic systems were evaluated for the quality of emulsion produced, mean droplet size and in vitro drug diffusion. [24-25] Optimized formulation was further evaluated for its droplet size, zeta potential, self micro emulsification time and drug content determination and in vitro diffusion profiles.

MATERIAL AND METHODS:

Material:

Nitrendipine and Cremophor RH40, Cremophor EL was obtained as a gift sample from US Vitamin Ltd. Mumbai, India, & Libra Pharma, New Delhi. PEG 400, Tween 80, Captex 8000, Labrafil, Labrasol, and Maltodextrin were purchased from Loba Chem. Mumbai, India. All other solvents and reagents in this work were of analytical/HPLC grade and used as provided.

Method:

Preliminary studies:

Apparent solubilities of nitredipin were determined in different oils at ambient temperature. Based on these results, the oils selected were formulated in SMEDDS using different surfactant systems (with varying ratios of surfactant to co-surfactant) by mixing the components in sealed glass vials. These systems were titrated with water and phase clarity and quality of emulsion produced were visually observed. The melting point was determined by capillary tube method.

Compatibility Studies:

FTIR studies:

FTIR studies were done to assess whether any possible interaction among drug, oil, surfactant, co-surfactant and maltodextrin. This is done by FTIR spectrophotometer (Jasco-4100). Infrared spectrums of pure drug, physical mixture of ingredients of the formulation, and batches were recorded in the wavelength region of 4000 to 400 cm-1.

Determination of the saturation solubility of Nitrendipine in oils and surfactants:

In order to find out appropriate solvents with good solubilizing capacity of nitrendipine, the saturation solubility of nitrendipine was investigated in some oils such as isopropyl myristate, Capryol 90, Labrafil 1944CS, castor oil, olive oil and some surfactants including Labrasol, Tween 80, Cremophor RH40, PEG 400, transcutol and labrafac by shake flask method.[26]

Construction of pseudoternary phase diagram:

From the result of solubility studies and screening of excipients; ethyl oleate, Cremaphore and PEG 400 were selected as oily phase, surfactant and co-surfactant respectively.[27] A ratio of surfactant over co-surfactant (Km) i.e. S/Co was chosen and the corresponding mixture (S_{mix}) was made. At desired Km value (1:1, 2:1, 3:1, and 4:1) S_{mix} and oil were mixed at ratio of 1:1, 1.5:1, 2:1, 2.5:1, 3:1, 3.5:1, 4:1, 4.5:1 and 5:1 in pre-weighed test tube. To the resultant mixtures, double distilled water was added dropwise till the first sign of turbidity in order to identify the end point and after equilibrium; if the system became clear then the water addition was continued. After complete equilibrium was reached, the mixtures were checked visually for phase clarity and flowability.

Formulation of SMEDDS:

Maltodextrin 10 gm was dissolved in 100 ml distilled water by magnetic stirring and sonicated for 5 min to completely dissolve. This solution is filtered through whatman filter paper to remove any undissolved particles. The liquid SMEDDS (10.0 gm) was then added with constant stirring, and the solution was kept at 50 ºC to obtain good O/W microemulsion. The microemulsion was spray dried with lab scale spray dryer.[27]

Characterization of SMEDDS:

Drug content determination:

The powder was taken in the 100 ml volumetric flask. To this sufficient quantity of SGF (without enzyme) was added and the flask was shaken for 10 min. Then the volume was made with SGF. This was then filtered through nylon filter paper (0.45 µm), and from filtrate exactly 1 ml was transferred to another volumetric flask of 10 ml and volume was made with SGF. The UV absorbance of this was taken at 236 nm λ_{max}. Drug content was then calculated by using calibration curve of pure drug in SGF.

Dilution and Self Emulsification Study:

Dilution and self emulsification time study was done for checking out the dispersibility of microemulsion and after reconstituted with water and SGF. Dilution study was done to access the effect of dilution on SMEDDS pre-concentrates. In this study selected formulations were subjected to various dilutions (i.e.1: 10, 1:50 & 1:100) with distilled water and formulations are visually assessed by using the following grading system.

Globule Size Determination:

Solid SMEDDS formulations (10 mg) were diluted with 10 ml double distilled water in a beaker with constant stirring on a magnetic stirrer. The average droplet size, size distribution and polydispersity index of microemulsion from solid SMEDDS were assessed by lesser light scattering technique using Malvern zetasizer (Nano-ZS, Malvern Instruments, UK).

Zeta Potential Analysis:

Measurement of Zeta potential is also a prerequisite to know the stability of microemulsion. The zeta potential of the microemulsion droplet surface was determined by electrophoretic mobility in an apparatus such as a Malvern Zetasizer (Malvern Instruments, UK) equipped with suitable software and calibrated with the supplied standard.

In vitro dissolution Study:

The dissolution test was performed in USP type I dissolution apparatus I (Electrolab) according to United State Pharmacopoeia dissolution procedure. The solid SMEDDS containing 10 mg of nitrendipine were filled into hard gelatin capsules (capsule no. 00). Solid SMEDDS hard gelatin capsule put into basket was loaded with 900 ml of simulated gastric fluid with 0.5% SDS at 37 ± 0.5 ºC with paddle speed of 100 rpm. Each sample (5 ml) was withdrawn at 5, 10, 15, 20, and 25 up to 60 min with replacement by an equal volume of temperature-equilibrated media and filtered through 0.45 µm pore size nylon filter. The amount of drug dissolved determined by UV spectroscopy at λ_{max} of 236 nm for simulated gastric fluid.

Differential scanning calorimetry:

Thermograms of pure drug, solid SMEDDS batches and physical mixtures were obtained using Differential Scanning Calorimetry instrument (TA Instruments SDT-2960, USA) equipped with an intracooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale.

Powder X-ray diffraction studies:

To obtain the changes in the Crystallinity of the components of formulation prepared, the PXRD study was carried out by using X ray diffractometer (Philips PW-3710, Holland). For this the samples of pure drug, prepared batch and physical mixture of the same batch was taken and was irradiated with monochromatised CuKα radiation and analyzed between from 20 º to 80 º **(**2θ).

Scanning electron microscopy:

The outer macroscopic structure (morphology) of the solid SMEDDS was investigated by SEM (JEOL, Japan), operating at 20 kV. The sample was fixed on SEM stub and then coated with thin layer of gold or platinum.

Comparative *in vitro* release study of optimised batch and marketed preparation:

In vitro dissolution studies were performed for the solid SMEDDS formulation and conventional tablet formulation Nitrepin®.

Stability study:

The developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. The SMEDDS formulations were put into empty hard gelatin capsules (size 00) and subjected to stability studies at 40°C ±2 and 75% ±5 RH.

RESULTS AND DISCUSSION:

Compatibility Study:

From the FTIR studies, it can be seen that the principal peaks of the Nitrendipine were retained in the spray dried batches, and the FTIR of the physical mixture and that of treated batches were almost identical. The fundamental peaks retained in all batches. The overlain of IR results showed in figure 1, there was no chemical interaction or changes during spray drying of liquid microemulsion and nitrendipine was stable in all spray dried formulation. The intensity of the peaks was reduced and peaks were slightly broadened in formulation batches.

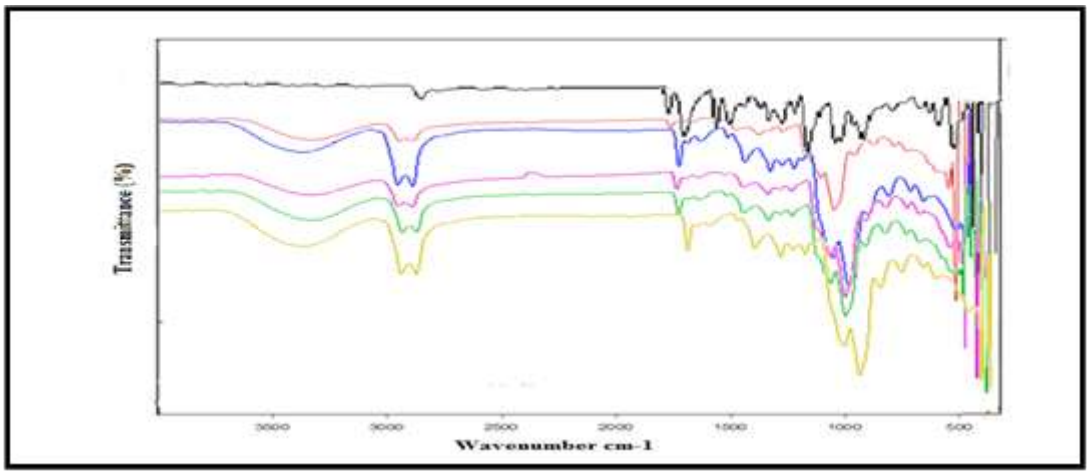

Figure 1: Overlain IR spectra of pure drug (black), physical mixture (red), formulation batches NM1 (blue), NM2 (pink), NM3 (green), NM4 (yellow)

Solubility of Nitrendipine in various excipients:

Solubility studies were carried in different surfactant, co-surfactant and oils. The results of these studies were shown in table1. On the basis of solubility studies, amongst the different oils, surfactant and co-surfactant the drug has high solubility in ethyl oleate, Cremaphore & PEG 400 were selected as oily phase, surfactant and co-surfactant respectively.

Table.1. Solubility of nitrendipine in different vehicles

Sr. No.	Oils	Solubility (mg/ml)*

1	Ethyl oleate	73.48±0.012
2	Cremaphore	87.89±0.012
3	PEG 400	94.94±0.014

***Indicates average triplicates ±SD (n=3)**

Determination of microemulsion existence region & construction of Pseudo-ternary phase diagram:

Based on results of solubility studies of oil, surfactant and co-surfactant were selected for microemulsion formulation. Nine different potential combination of surfactant mixture to oil at different K_m values (1, 2, 3 and 4) were used for the phase diagram study of NTD SMEDDS. No distinct conversion of water-in-oil (w/o) to oil-in-water (o/w) was observed.

The boundary layer of o/w microemulsion was determined in each phase diagram. Components used for construction of pseudoternary phase diagram are Ethyl oleate (oil phase), Cremaphore RH40 (surfactant), PEG 400 (co-surfactant) and bi-distilled water (aqueous phase).

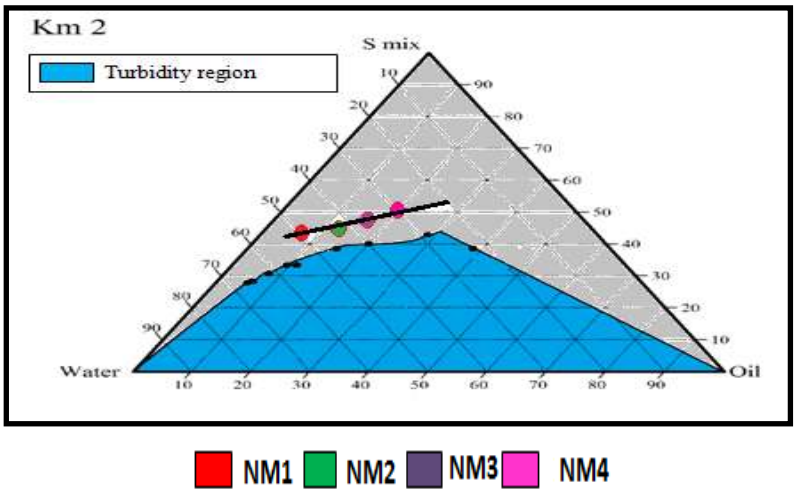

Figure 2: Selected composition of formulation NM1 to NM4

Preparation of optimized solid SMEDDS:

The four formulations were selected from phase diagram at K_m value 2, named as NM1, NM2, NM3 and NM4 as shown in figure 2. Quantitative unit compositions of selected formulation of SMEDDS are presented in table 2.

Table 2: Composition of formulation

Sr. No.	Formulation Batches	Drug (mg)/ 10 gm	% Composition (w/w)		
			Ethyl Oleate	Cremaphore RH 40	PEG 400
1.	NM1	500	9	60.6	30.3
2.	NM2	500	12	58.7	44
3.	NM3	500	15	56	28
4.	NM4	500	20	54.7	26.3

Characterization of Solid SMEDDS:

Drug Content Determination:

Drug content of nitrendipine solid SMEDDS batches were determined by UV spectroscopy method to evaluate uniformity of formulation. The drug content of different nitrendipine solid SMEDDS batches were given in following table 3. According to drug content, saturation solubility the NM1 batch was selected as optimized batch.

Table 3: Drug content and drug recovery of solid SMEDDS batches

Batch code	% Drug content
NM1	99.85 ±0.024
NM2	99.03±0.014
NM3	97.89±0.028
NM4	99.28±0.035

***Indicates average triplicates ±SD (n=3)**

Dilution & self-micro emulsification time study:

A visual test was carried out to assess self emulsification of solid SMEDDS in 100 ml double distilled water at 37ºC under gentle agitation. All solid SMEDDS batches showed spontaneous microemulsification and there was no sign of phase separation or phase inversion of microemulsion after storage of 2 hr shown in table 4. Optimised batch showed grade I which means rapid forming microemulsion, which was clear and time to form self microemulsion was 38 seconds.

Table 4: Dilution & self microemulsification time study of solid SMEDDS batches

Sr. no.	Batch code	Dilution Study		Emulsification time
		1:10	1:50	
1.	NM1	I	I	38 sec.
2.	NM2	I	II	44 sec.
3.	NM3	II	II	1.4 min.
4.	NM4	II	II	1.7min

Globule size determination, Polydispersity Index (PI) and Zeta potential analysis:

The mean droplet size of all reconstituted solid SMEDDS were very low and all were found to be in the nanometric range (<100 nm). Globule size in nano or micron range gives good transparency and increase surface area for partitioning of drug between oil and water. Mean particle size, polydispersity index & Zeta Potential were carried out, it was found that 67nm, 0.247 & -38.2 respectively for optimized batch NM1, which shown in figure 3 & 4 and table 5. All formulations shows polydispersity index less than 1, indicating uniform distribution of globules throughout formulation. The zeta potential value of all SMEDDS batches were found to be in between -19 to -38 mV, optimised batch NM1 showed -38.2 mV mean zeta potential which means the optimised batch having more stability than other batches.

Table 5: Globule size of solid SMEDDS formulation, PI & Zeta potential

Batch Code	Mean Particle Size (nm)	Polydispersity Index (PI)	Mean Zeta Potential (mV)
NM1	67	0.247	-38.2
NM2	71	0.549	-25.1
NM3	79	0.851	-19.3
NM4	84.12	0.946	-20.5

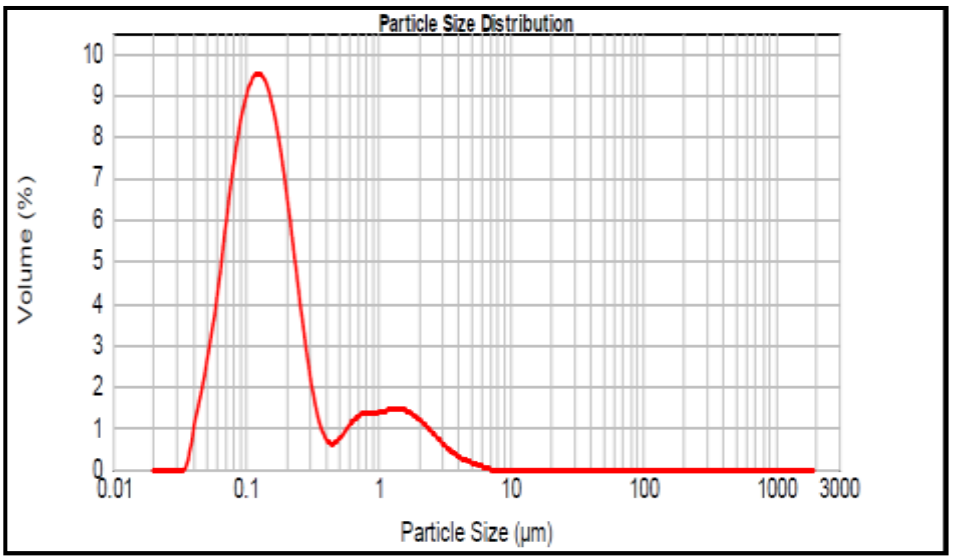

Figure 3: Particle size distribution of optimized batch NM1

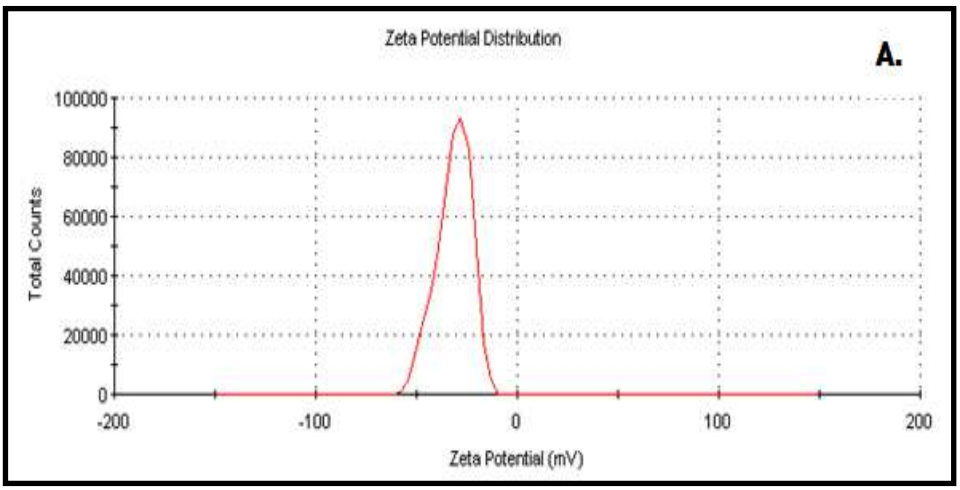

Figure 4: Zeta potential of solid SMEDDS formulation NM1

In vitro dissolution studies:

The in vitro release profile of solid SMEDDS formulations in dissolution media SGF pH 1.2 shown in figure 5. Solid SMEDDS formulation batch NM1 was showed significantly higher % release of drug as compared with that of all remaining batches. The cumulative percentage release of optimised batch NM1 was observed 98.33%. It could be suggested that the solid SMEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase than that of other batches.

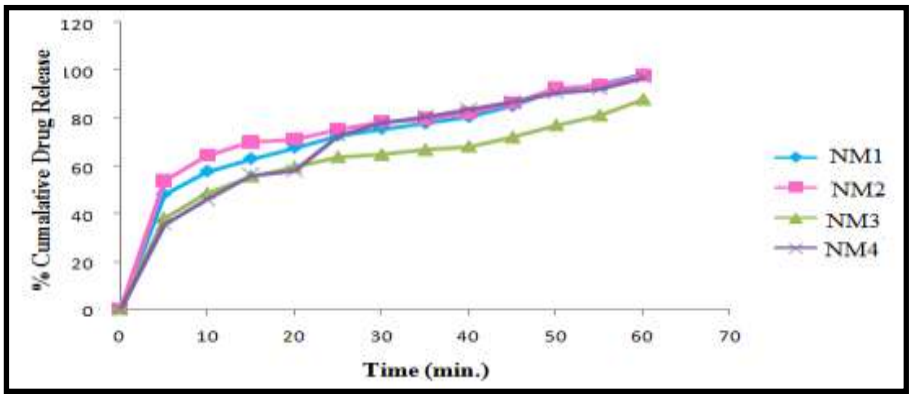

Figure 5: In-vitro release profile of solid SMEDDS formulation in SGF

Differential Scanning Calorimetry (DSC):

DSC curve of pure drug exhibited a sharp endothermic peak at 160.12°C indicating the melting point of nitrendipine. Physical mixture showed a less intense melting point peak at 157.67°C. Spray dried optimized formulation batch were shown in figure 6(C) that thermogram showed reduction in peak height as compared to pure drug and physical mixture which indicating NTD in Solid SMEDDS was present either in an amorphous form or in a disordered crystalline form of a molecular dispersion.

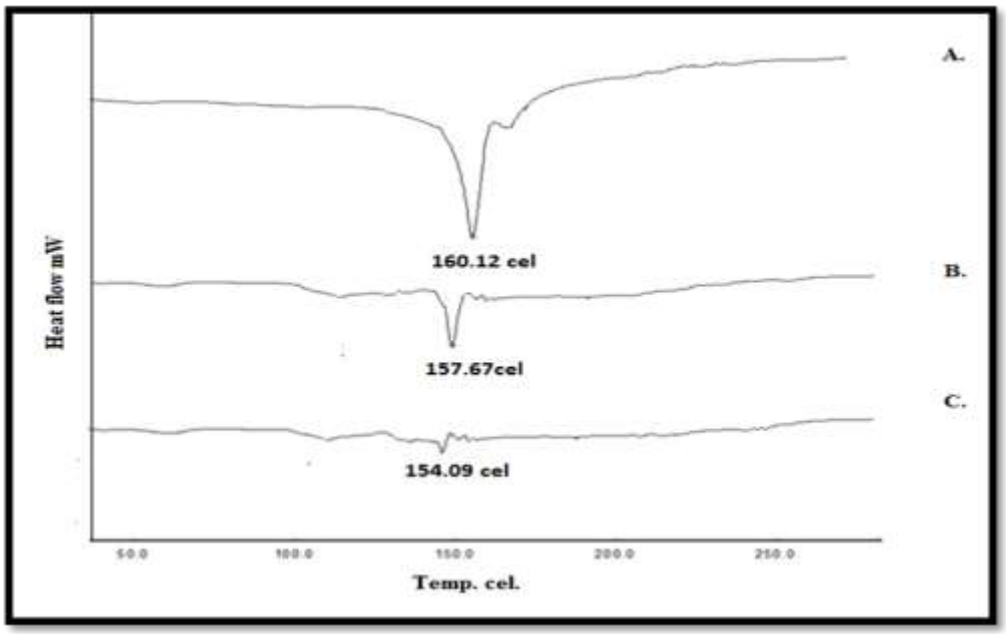

Figure 6: Thermogram of NTD (A), physical mixture (B) and optimised batch (C)

Powder X-ray diffraction studies:

In the powder X-ray diffraction studies, the diffractograms of the representative batches were taken to find out the effect on the crystallanity of the drug and excipients. The major peaks in the diffractogram of the pure drug, physical mixture and formulation batch NM1 were shown in figure 7.

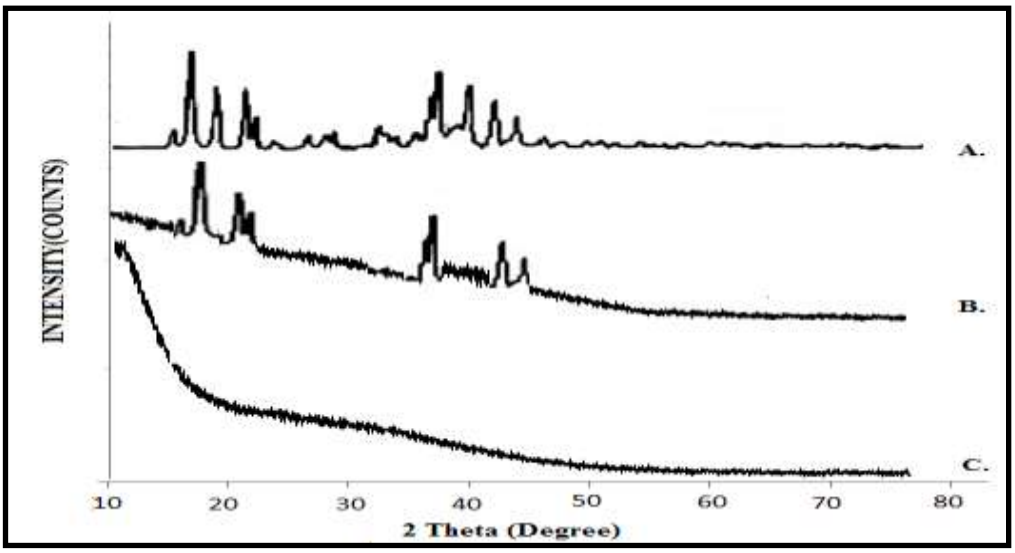

Figure 7: PXRD data for NTD(A), physical mixture(B) and formulation NM1(C)

From the diffractogram of physical mixture and formulation batches, complete amorphism of drug along with excipients occurred. No intense peak was observed which revealed solubilization of drug in the formulation batches as shown in figure 7. Maximum peak intensities were observed at 18, 20, 21, 23, 39, 42 and 43º for NTD.

Scanning electron microscopy (SEM):

Nitrendipine appeared as smooth irregular crystalline structures. Similar observations of micrographs were also made by other researchers. **(**Peng Quan et al., 2011). The SEM images of solid SMEDDS of batch NM_1 were shown in figure 8(C). According to SEM images, the solid SMEDDS of nitrendipine consisted of well separated particles with no agglomeration. Moreover, the particles showed a satisfactory regular spherical shape with shallow dents and it also shows that, drug present is completely soluble in solid SMEDDS. It is suggested that maltodextrin has ability to diminish the agglomeration of particles.

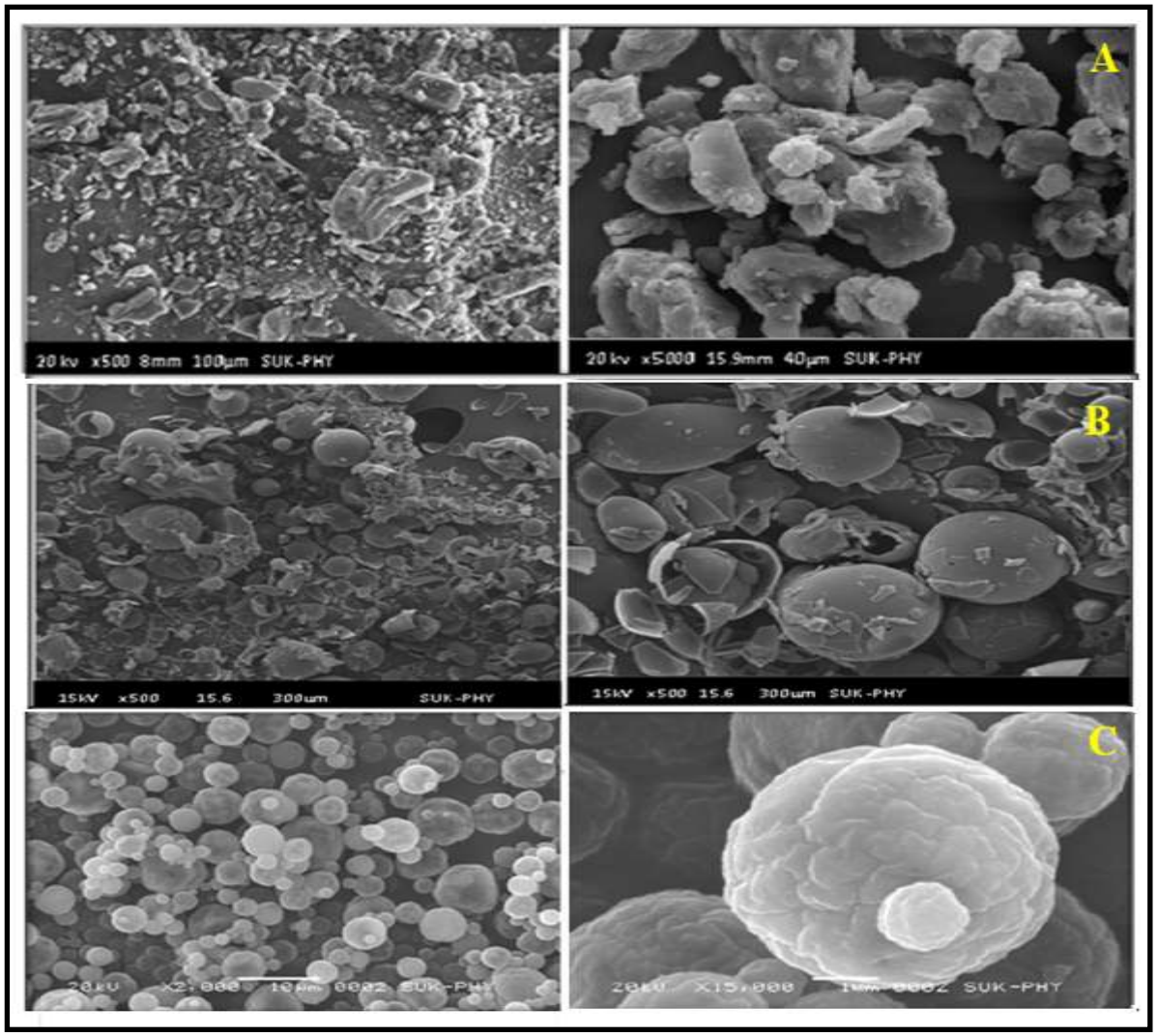

Figure 8: Scanning electron photomicrograph of NTD (A), maltodextrin (B) and optimised batch NM1 (C) at 500 X and 5000X

Comparative *in vitro* release study of optimised batch and Marketed formulation:

In vitro drug releases from solid SMEDDS formulations were observed significantly higher as compared with that of conventional nitrendipine tablet (nitrepin®). It could be suggested that the solid SMEDDS formulation resulted in spontaneous formation of a microemulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase than that of conventional nitrendipine tablet. Thus, this greater availability of dissolved NTD from the solid SMEDDS formulations could lead to higher absorption and higher oral bioavailability. Invitro drug releases, clearly observed that solid SMEDDS formulations shows more than 90% drug release in 60 min in SGF where as marketed preparation shows <80% drug release in SGF shown in figure 9. This observation showed that the formulation of solid SMEDDS of nitrendipine shows better dissolution than marketed tablet formulation Nitrepin®

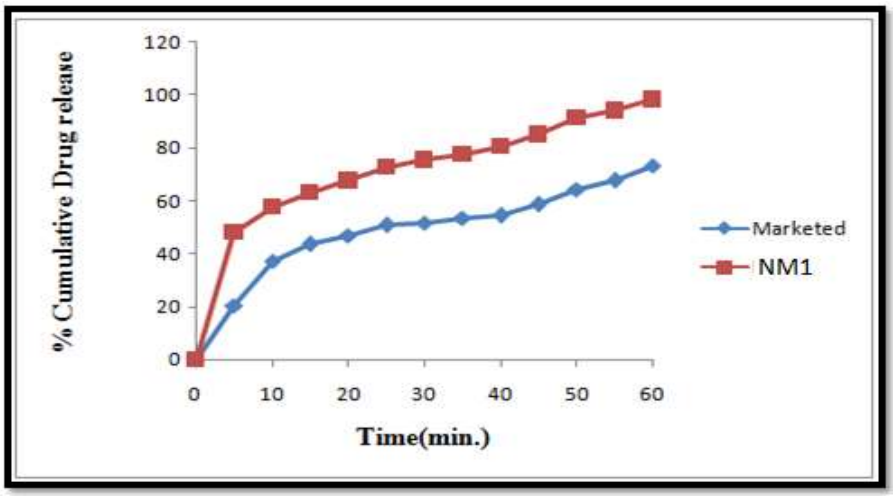

Figure 9: In-vitro release profile of optimised batch NM1 and Marketed Preparation Nitrepin®

Stability Study:

The developed formulation was subjected to stability studies to evaluate its stability and the integrity of the dosage form. The cumulative percentage release of optimised batch NM1 after its stability period 30days, 60 days and after 90 days was observed 95.07%, 93.63% and 90.43% respectively. Release profile was shown in figure 10 at different time intervals during stability period. There was slight decrease in percentage release but not much significant therefore it suggested that, the final formulation confirm its stability.

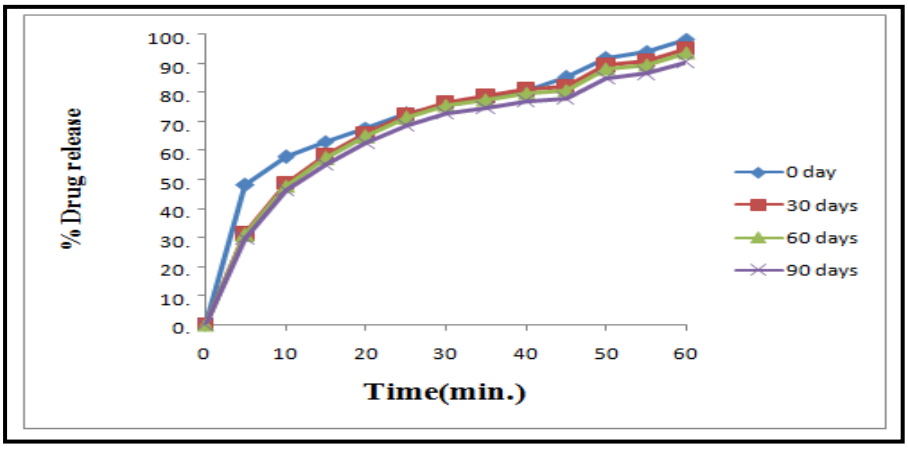

Figure 10: In-vitro stability studies of optimised batch NM1

The formulation was found to be stable for 3 months at intermediate and accelerated conditions. There was no significant change in the drug content, drug release. It was also seen that the formulation was compatible with the hard gelatin capsule shells, as there was no sign of capsule shell deformation. Thus, these studies confirmed the stability of the developed formulation and its compatibility with hard gelatin capsules shown in table 6.

Table 6: % cumulative drug release & % drug content of NM 1 batch after stability study

Sampling done at	% Drug content	% cumulative release
0 day	99.85±0.0224	98.33±0.147
30 day	99.54±0.208	95.07±0.059
60 day	97.73±0.02494	93.63±0.057
90 day	96.46±0.0329	90.43±0.002

***Indicates average triplicates ±SD (n=3)**

CONCLUSION:

In the present work, solid SMEDDS of nitrendipine was prepared by spray drying, for direct filling into hard gelatin capsule for oral administration. The four batches of SMEDDS were prepared and NM1 was found to be the optimized batch showed 74.30 mg/ml saturation solubility. DSC measurements and X-ray diffraction analysis suggested that nitrendipine in the solid SMEDDS was in the amorphous or molecular dispersion state. In vitro dissolution test showed that the solid SMEDDS (NM1) had a faster release rate than the conventional tablet in phosphate buffer pH 1.2. From the stability studies of solid SMEDDS, there was no significant decrease in drug release and drug content, hence the formulation is found to be stable. Thus, prepared nitrendipine solid SMEDDS provided a useful solid dosage form for oral poorly water-soluble drug for enhance solubility and dissolution rate, which may improve therapeutic performance. SMEDDS appear to be unique and industrially feasible approach to overcome the problem of low oral bioavailability associated with the lipophillic drugs.

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