RESEARCH ARTICLE

Formulation and Evaluation of Nimodipine Nanoparticles Incorporated within Orodispersible Tablets

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ABSTRACT

Nimodipine (NMD) is a Dihydropyridine calcium channel blocker with some selectivity to the cerebral vasculature administered to minimize the neural deficit for patients with subarachnoid hemorrhage. The NMD is characterized by low bioavailability because of its low water solubility and extensive first-pass metabolism. This research aims to improve bioavailability by enhancing the solubility via the formulation of nanoparticles (NPs) and decreasing the first-pass metabolism by incorporation the prepared NMD NPs in orodispersible tablets (ODTs). The preparation of NMDNPs was done by solvent antisolvent precipitation technique using three different stabilizers (TPGS, Soluplus®, and PXM 407) in two drugs: stabilizer ratios (1:2 and 1:3) and two different injection speed (30 and 60 mL/hr) of the solvent to the antisolvent phase. The optimized formula is composed of 30 mg NMD, 60 mg Soluplus® and 1% w/w mannitol as cryoprotectant. The degree of crystallinity of pure NMD and NMD NPs was examined by X-ray diffraction. It was established that the degree of crystallinity had been reduced, which is an indication of converting the crystalline NMD into a more amorphous form. ODTs incorporating NMD NPs show a complete dissolution after forty minutes in SSF with 0.5 % Brij-35 compared with ODT incorporating pure NMD, which reaches only 50% in the same duration. It is concluded that formulation NMD as NPs to be incorporated in ODT is an excellent technique to enhance the dissolution rate and promoting pre-gastric absorption.

Keywords: Biopharmaceutical classification system, Nimodipine, Nanoparticles, Orodispersible tablets.

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INTRODUCTION

Nimodipine (NMD) is a dihydropyridine calcium channel blocker with a selectivity to the cerebrovascular circulation. It shows a potent dilation effect on the cerebral arterioles, which makes it essential in the prevention and treatment of delayed ischemic effects due to cerebral vasospasm and subarachnoid hemorrhage.[1]

NMD belongs to class II drugs of the biopharmaceutical classification system (BCS), which is characterized by low solubility and high permeability. It has low bioavailability (around 13%) because of its low water solubility and extensive first-pass metabolism.[2]

This research aims to enhance the bioavailability of NMD by improving its solubility through the formulation of NMD as NPs and reduce the extensive first-pass metabolism through the formulation of ODTs by promoting pre-gastric absorption.

Nanoparticles (NP) are solid colloidal particles that usually lie in the 100 nm size range.[3] The NPs are made to be biodegradable or non-biodegradable polymers. Decreasing the particle size to the nanometer range will increase the specific surface area (which is the surface area to mass ratio), hence improving the low water solubility drugs' dissolution rate and their bioavailability.[4]

An ODT is a dosage form designed to be placed in the mouth cavity to be dissolved or dispersed in a short time ranged from a few seconds to three minutes. The primary purpose of the production of this dosage form was to improve patient compliance, especially for the ones having swallowing difficulties because this tablet doesn't require water or chewing.[5]

MATERIALS

Nimodipine (NMD) pure powder, tocopheryl polyethylene glycol succinate (TPGS) and poloxamer 407 (PXM 407)were purchased from Hyperchem, China. Soluplus® was obtained from Basf, Germany. Brij-35 was bought from Himedia, India. Disodium hydrogen phosphate (Na_2HPO_4) and (Potassium dihydrogen phosphate (KH_2PO_4) were obtained from Thomas baker, India. Sodium chloride (NaCl) was purchased from LAD, India. Hydrochloric acid (HCl) was obtained from Chem limited, India. Dialysis membrane; MWCO 12000 -14000

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Da was obtained from (USA), ethanol was purchased from Chemlab, Belgium. Mannitol was bought from England.

METHODS

Formulation of Nimodipine Nanoparticles

The NMD NPs were prepared by a solvent – antisolvent precipitation method (nanoprecipitation method). This method involves dissolving 30 mg of NMD in 3 mL ethanol (solvent) and allowed to be added dropwise using a syringe pump at a speed of 30 and 60 mL/hr into a beaker containing 27 mL distilled water (antisolvent) with different ratios of the following stabilizers (TPGS, Soluplus®, and poloxamer 407) on a magnetic stirrer at a speed of 300 rpm. Precipitation of solid NPs occurred immediately. The resultant nanosuspension is left for one hour under a magnetic stirrer to allow the organic solvent to evaporate. Then nanosuspensions with the smallest particle size were lyophilized using Labconco freeze dryer (USA) after the addition of 1% w/w mannitol as a cryoprotectant to obtain the nanoparticle powder.[6]

Measurement of the Particle Size and Polydispersity Index of Nimodipine Nanosuspension

Samples of all prepared nanosuspensions were analyzed using the ABT-9000 nanolaser particle size analyzer, which acts by a dynamic light scattering technique. This device measures the particle size of dispersed molecules by measuring the intensity of light scattering as a function of time at a scattering angle of 90° and a constant temperature of 25°C. The device also measures the polydispersity index (PDI), which indicates the particle distribution within the prepared samples. Particle size and PDI were recorded for each sample made.[7]

Measurement of the Particle Size and Polydispersity Index After Drying

The dried powder's particle size was done by dispersing an equivalent amount of 10 mg of NMD as dried NPs in 9 mL distilled water then sonicated for two minutes. This procedure was done so that the drug's concentration in the redispersed suspension is the same as the concentration of the drug in the nanosuspension before lyophilization. The particle size and PDI were measured using the ABT-9000 nanolaser particle size analyzer, and the results were recorded for the formulas with the smallest particle size.[8]

In vitro Dissolution of the Prepared Nanoparticles

In vitro dissolution was done for the prepared NMD NPs with the smallest particle size and pure NMD. It was performed using dissolution apparatus 2 (paddle type) containing SSF with 0.5% Brij-35 as a dissolution media, the rotation speed was 75 rpm, and the temperature was 37°C ± 0.1. The dissolution was done by placing an NMD NPs equivalent to 30 mg and 30 mg pure NMD separately in a dialysis membrane with a molecular weight cutoff of 12000–14000 dalton. 5 mL samples were withdrawn for analysis and substituted with an equal volume of fresh media to maintain constant volume from 5 to 120 min. The samples were filtered using 0.45 µm and analyzed using UV-spectrophotometer at the specified λmax (238.8 nm). The experiments were performed in triplicate, and the average value was calculated. The accumulative percentage of drug dissolved was calculated and drawn against time.[9,10]

Determination of Degree of Crystallinity

Powder X-ray diffraction (XRD) is used to study the atomic and molecular structure of crystalline substances such as drugs and excipients. The study was done for pure NMD, and the prepared NMD NPs by powder X-ray diffraction (XRD-6000, Shimadzu, Japan 220V/50Hz) at a continuous scanning range of 2θ = 5–50°, the operating voltage and current were 40 (kV) and 30 (mA) respectively.

Incorporation of Nimodipine Nanoparticles in the Orodispersible Tablets

Nimodipine (NMD) dried NPs equivalent to 30 mg NMD were mixed with 25 mg cross carmellose (super disintegrant) and mannitol as a diluent up to 250 mg for each ODTs.

A powder blend of 20 tablets was mixed in a dry and clean mortar for 15 minutes and then passed through sieve number 60(250 µm pore size). Finally, magnesium stearate was added to the powder blend (1 mg for each tablet) as a lubricant, mixed for further 5 minutes, then the powder blend was compressed into a tablet weighing 250 mg to a hardness about 3–4 kg/cm^2 by a 10 mm single punch tablet machine and 20 tablets were made in every batch. The prepared tablets were further evaluated.[11]

In vitro Dissolution Study of ODTs Incorporating NMDNPs[9,12]

The dissolution study was done for the ODT containing NMD NPs and for the ODT containing pure NMD. These studies were done in USP apparatus 2 (paddle type). The

Table 1: The Composition and variables of the prepared NMD NPs

Formula name	*NMD amount (mg)*	*Polymer name*	*Polymer amount (mg)*	*Injection speed (mL/hr)*
F1	30	TPGS	60	60
F2	30	TPGS	90	60
F3	30	Soluplus®	60	60
F4	30	Soluplus®	90	60
F5	30	PXM 407	60	60
F6	30	PXM 407	90	60
F7	30	TPGS	60	30
F8	30	Soluplus®	60	30
F9	30	PXM 407	60	30

dissolution media were 900 mL SSF with 0.5 % Brij-35 and 0.1 N HCl with 0.5% Brij-35(incorporation of Brij-35 was to maintain sink conditions). The device was adjusted to 75 rpm and at a temperature of 37 ± 0.1°C. Samples of 5 mL were withdrawn at different times and replenished with 5 mL of fresh media to maintain a constant volume. The samples were filtered using a 0.45 µm syringe filter, and they were assayed spectrophotometrically at their λmax. The concentration of the samples was calculated by using NMD calibration curves in SSF and 0.1 N HCl (Table 1). Each reading was converted to an accumulative drug dissolved as a percentage and drawn versus time to show the dissolution study of the active constituent NMD versus time. Each reading was repeated in triplicate, and the mean was calculated.

RESULTS AND DISCUSSION

Measurement of the Particle Size and Polydispersity Index

The ABT-9000 nanolaser particle size analyzer analyzed all the samples of NMD nanosuspension, and the particle size distribution of all formulas was recorded, as shown in Table 2.

The particle size distribution was measured using surface area mean diameter D,[3,2] which is also called Sauter mean diameter. This analysis is the weighted average surface diameter, and it is most useful where specific surface area is essential as in bioavailability, reactivity, and dissolution behavior.[13]

The polydispersity index (PDI) was measured for all the nanosuspension formulas, as shown in Table 2. PDI is an essential means to evaluate the particle size distribution within the sample. It is crucial in determining the uniformity of particle size, which is valuable in the stability of a nanosuspension. Monodisperse samples have low PDI values than the polydisperse samples.

PDI values in the range of (0-0.05) are considered to be (monodisperse standard), (0.05-0.08) is (nearly monodisperse), (0.08 -0.7) is (mid-range polydispersity), and more than 0.7 is (very polydisperse).[14]

The Effect of Polymer Type on Particle Size

Three different polymers (TPGS, Soluplus®, and PXM 407) were used in two different ratios 1:2 and 1:3 to prepare the formulas (F1-F6), as shown in Figure 1.

Table 2: The particle size and PDI of the prepared NMD nanosuspension

Formula name	*Particle size (nm)*	*PDI*
F1	533 ± 12.6	0.004±0.005
F2	652 ± 7.5	0.008±0.001
F3	44 ± 6.5	0.008±0.0005
F4	78 ± 7.5	0.008±0.0005
F5	534 ± 15.2	0.003±0.001
F6	452 ± 6.8	0.008±0.0005
F7	1263 ± 15	0.008±0.0005
F8	51.6 ± 7.6	0.013±0.005
F9	771 ± 20.1	0.007±0.0005

It was established that Soluplus®, which was used as a stabilizer, is the best in reducing the particle size of the prepared NS below 100 nm. Soluplus® is a graft copolymer with amphiphilic properties. The hydrophilic part is represented by the polyethylene glycol backbone and the hydrophobic part by vinyl caprolactam/ vinyl acetate side chain.[15] This amphipathic nature makes it an excellent surface-active and wetting agent that reduces the interfacial tension between the hydrophobic surface of NMD particles and the aqueous antisolvent. Soluplus® allows the surface- water interaction and maintains the small particle size of the prepared nanosuspension.

TPGS and PXM 407 show a fair particle size reduction (452–652 nm). TPGS is a water-soluble analog of vitamin E; it can stabilize the NS by hydrophobic (Vander Waals) interaction between the particles.[16] While PXM 407 is a hydrophilic non-ionic surfactant, and it has been widely used as a coating agent for the NPs.[17]

The Effect of Polymer Concentration on Particle Size

Two different ratios (1:2 and 1:3) of three different stabilizers (TPGS, Soluplus®, and PXM 407) were used to prepare the formulas (F1-F6) as illustrated in Figure 2.

It was found that increasing the polymer concentration in TPGS and Soluplus® increases the particle size. This increment in the PS may be due to the increased viscosity,

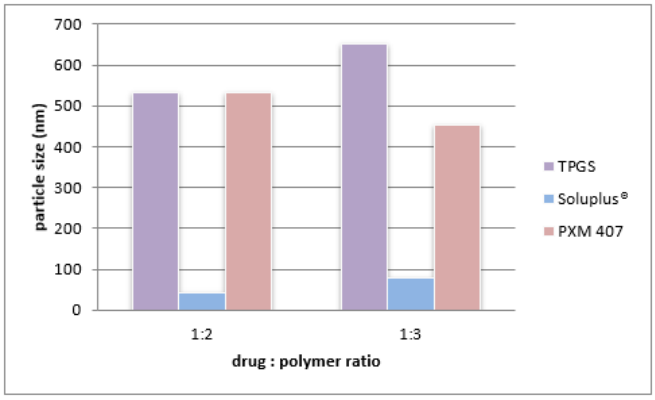

Figure 1: The effect of polymer type on the PS of the prepared NMD NPs

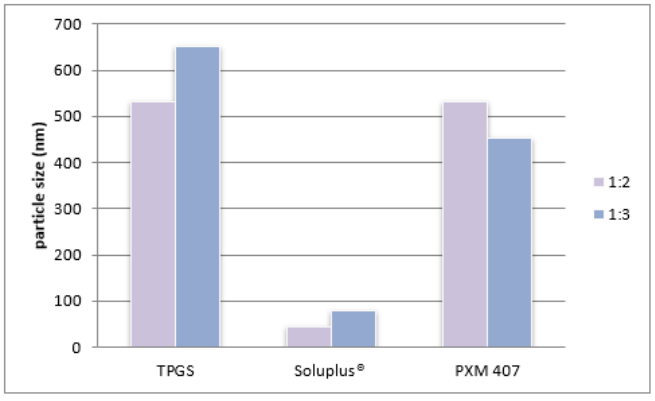

Figure 2: The effect of polymer concentration on the PS of the prepared NMD NPs

which hinders the particles' movement in the solution and prevents good coverage of the newly forme NPs. Also, high stabilizer concentration may increase the thickness of the coating enveloping the NPs and prevent the diffusion between the solvent and the antisolvent phase during NPs precipitation.[18]

On the other hand, as the PXM 407 concentration increases, the particle size decreases. The concentration of a stabilizer is so essential to maintain the particle size. At a low ratio (1:2), the stabilizer level was not enough to fully envelope the newly formed NPs hence they aggregate. As the concentration of PXM 407 increases, better coating, and coverage for the particles, thus maintain the small PS (452 nm).[19]

The Effect of Injection Speed on Particle Size

Formulas (F7-F9) were prepared to illustrate the effect of the injection speed of the solvent phase to the anti-solvent phase, as shown in Figure 3.

The particle size of the prepared NPs increases as the injection speed decreases because, at a lower rate (30 mL/hr), the mixing efficiency between the solvent and the anti-solvent will be reduced, which promotes crystal growth and results in the formation of larger particles.[20]

Particle size and PDI after Lyophilization

The particle size of the lyophilized powder was measured using the ABT-9000 nanolaser particle size analyzer, and the results are shown in Figure 4.

The particle size after lyophilization varies considerably because the drying process has a profound effect on the aggregation of the NPs. This aggregation is affected substantially by the process parameters as the freezing rate, freezing temperature, and the presence of cryoprotectant.[21]

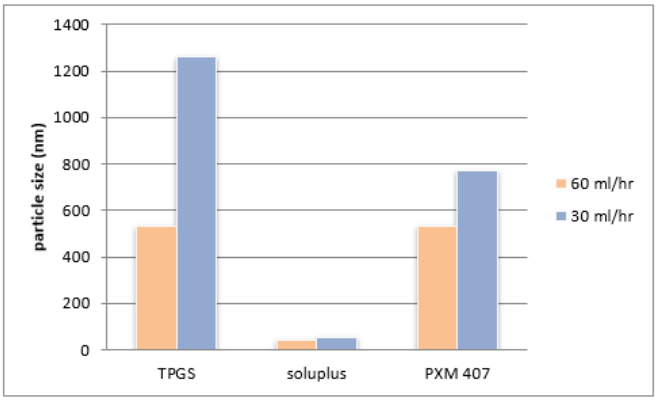

Figure 3: The effect of injection speed on PS of the prepared NMD NPs

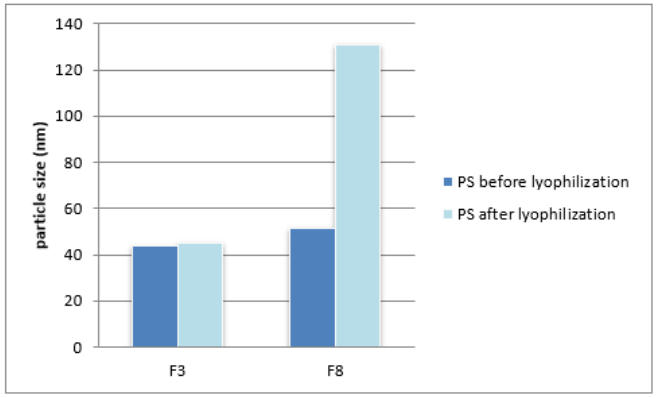

Figure 4: PS of the prepared NMD NPs before and after lyophilization

In vitro Dissolution of NMD NPs

The dissolution profiles of the prepared NMD NPs and pure NMD are shown in Figure 5.

It was found the F3 reaches a complete dissolution after 90 minutes from the starting of the dissolution study, and it was the fastest formula that reaches 100 % dissolution of NMD compared with other nanoparticle's formulas and pure NMD.

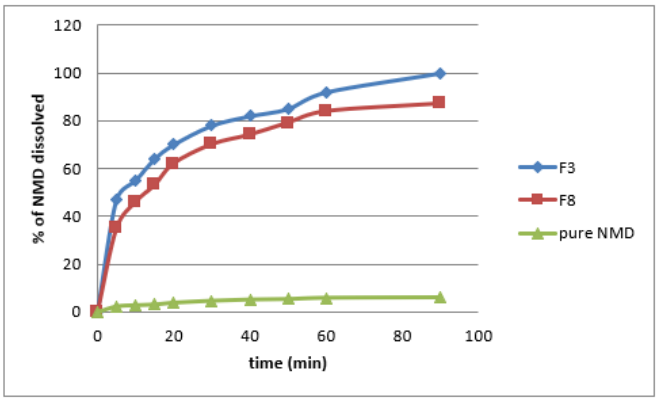

Figure 5: The dissolution profile of pure NMD and NMD NPs

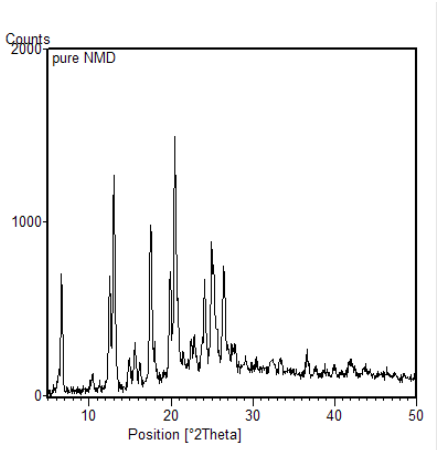

Figure 6: XRD pattern of pure NMD

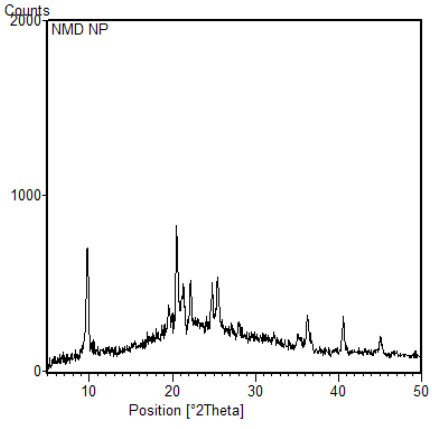

Figure 7: XRD pattern of NMD NPs

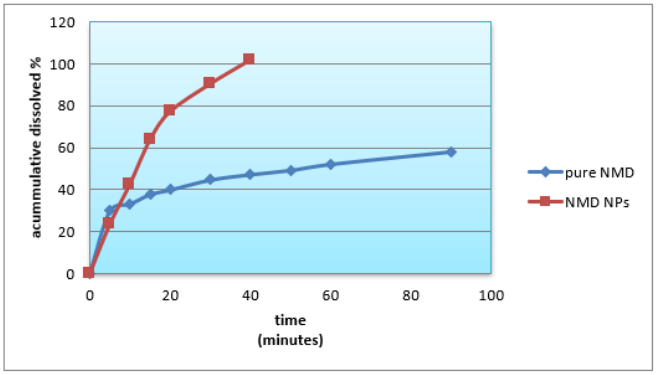

Figure 8: *In vitro* dissolution of ODT containing pure NMD and NMD NPs in SSF with 0.5 % Brij-35

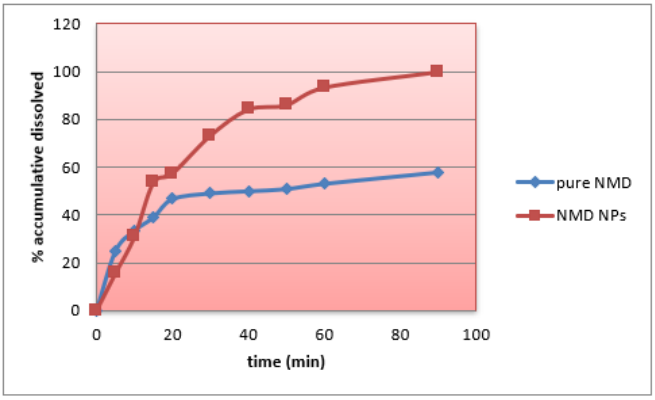

Figure 9: *In vitro* dissolution of ODT containing pure NMD and NMD NPs in 0.1 N HCl with 0.5 % Brij-35

This formula has the smallest particle size; hence it has a faster dissolution rate according to Noyes -Whitney equation because it has a higher surface area.

Powder X-ray Diffraction

XRD study was done for pure NMD and NMD NPs, as shown in Figures 6 and 7, respectively.

XRD can provide information about the arrangement of atoms within a crystalline material. The scattering of X-ray is much weaker for the NPs, as confirmed by the XRD pattern of NMD NPs, because of the small volume of the particles and limited coherence due to their small size.[22]

In-vitro dissolution study of ODTs incorporating NMD NPs

In vitro dissolution study was done to the ODTs containing NMD NPs and pure NMD in SSF containing 0.5 % Brij-35 (pH 6.8) and 0.1 N HCl (pH 1.2) containing 0.5 % Brij-35 to simulate the physiological condition of the oral cavity and the stomach as shown in Figures 8 and 9 respectively.

The dissolution of NMD in SSF was enhanced profoundly since ODT contains NMD NPs that reaches a complete dissolution of the drug after forty minutes, while the ODT containing pure NMD reaches only 60 % of the total amount after two hours. Also, the dissolution of ODT holding NMD NPs was much faster than the ODT holding pure NMD in 0.1 N HCl. These results coincide with the dissolution of ODT containing Meloxicam nanoparticle prepared by *Winarti et al.*[23]

CONCLUSIONS

From this research, it was found that the formulation of NMD as NPs is an excellent technique for enhancement of the dissolution rate. Also, the incorporation of NMD NPs in ODTs is a suitable method for enhancing bioavailability via improving the pre gastric absorption.

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