DOI: https://doi.org/10.31351/vol30iss2pp143-152

Formulation and Characterization of Nimodipine Nanoparticles for the Enhancement of solubility and dissolution rate

Areej W. Alhagiesa[*,1] and Mowafaq M. Ghareeb[**]

[*]Department of Pharmaceutics, College of Pharmacy, University of Kufa, Najaf, Iraq
[**]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Abstract

Nimodipine (NMD) is a dihydropyridine calcium channel blocker useful for the prevention and treatment of delayed ischemic effects. It belongs to class II drugs, which is characterized by low solubility and high permeability. This research aimed to prepare Nimodipine nanoparticles (NMD NPs) for the enhancement of solubility and dissolution rate. The formulation of nanoparticles was done by the solvent anti-solvent technique using either magnetic stirrer or bath sonicator for maintaining the motion of the antisolvent phase. Five different stabilizers were used to prepare NMD NPs(TPGS, Soluplus®, HPMC E5, PVP K90, and poloxamer 407). The selected formula F2, in which Soluplus® has been utilized as a stabilizer, has a particle size (77 nm) and polydispersity index (PDI) (0.016). The formulas with the smallest particle size were freeze dried with the addition of 1 % w/w mannitol as cryoprotectant. The saturation solubility of NMD in the prepared nanoparticles was increased twenty four-folds, and the complete dissolution was achieved at 90 minutes compared with pure NMD, which reaches only 6%. The formation of hydrogen bonding between NMD and the polymer or the cryoprotectant, as confirmed by the FTIR study. In conclusion, the preparation of NMD as polymeric nanoparticles is a useful technique for enhancing the solubility and dissolution rate.

Keywords: Nimodipine nanoparticles, Solvent antisolvent precipitation, Solubility enhancement.

تصييغ وتقييم الجسيمات النانوية لعقار النيمودبين لتحسين الذوبانية

اريج وهاب الحاج عيسى [*،١] و موفق محمد غريب[**]

[*] فرع الصيدلانيات ،كلية الصيدلة ، جامعة النهرين ، بغداد ، العراق .
[**]فرع الصيدلانيات ، كلية الصيدلة، جامعة بغداد، بغداد،العراق .

الخلاصة

النيمودبين هو ديهيدروبيريدين مغلق قناة الكالسيوم مفيد للوقاية والعلاج من الآثار الإقفارية المتأخرة في الدماغ .
هو ينتمي إلى عقاقير من النوع الثاني التي تتميز بانخفاض قابلية الذوبان ونفاذية عالية. يهدف هذا البحث إلى إعداد الجسيمات النانوية النيموديبينية لتعزيز الذوبانية ومعدل الذوبان. تم تكوين الجسيمات النانوية باستخدام تقنية الترسيب للمذيب ومضاد المذيب باستخدام إما جهاز الدوران المغناطيسي أوالحمام المائي ذو الموجات الصوتية للحفاظ على حركة الطور المضاد. تم استخدام خمسة مثبتات مختلفة لأعداد الجسيمات النانوية وتتضمن هذه المثبتات
.(TPGS, Soluplus®, HPMC E5, PVP K90, and poloxamer 407)
اظهرت النتائج ان سوليوبلس هو الافضل بتقليل حجم الجسيمات حيث كانت افضل صيغة وهي (الصيغة الثانية) لها حجم جسيمي (٧٧ نانوميتر) . ازدادت الذوبانية بمقدار اربع وعشرين مرة وتم تحقيق الذوبان الكامل بعد تسعين دقيقة للجسيمات النانوية بينما النيمودبين الخام قد وصل الى ٦ % فقط خلال هذه المدة. كما اظهرت النتائج بالاشعة تحت الحمراء تكوين الاواصر الهيدروجينية بين النيمودبين والبوليمر وبذلك يمكن ان نستنتج ان الجسيمات النانوية قد حسنت من ذوبانية ومعدل ذوبان النيمودبين.

الكلمات المفتاحية : الجسيمات النانوية للنيمودبين ، تقنية الترسيب بالمذيب ومضاد المذيب ، تحسين الذوبانية .

Introduction

Many new pharmaceutical entities, approximately 40 % of them, are lipophilic compounds which have low water solubility and raise a clinical issue regarding their dissolution and absorption from their administration sites[(1)].

The solubility of drugs in aqueous media is an essential consideration to be dealt with early in the drug discovery process , and several formulation strategies have been proposed to enhance the solubility, such as complexation, pH adjustment, and using co-solvents[(2)].

Nanoparticles (NPs) are solid colloidal particles that usually lie in the 100 nm size range[(3)]. They exhibit many advantages of better stability, tremendous enhancement in solubility and dissolution rate of poorly soluble drugs, high drug loading, targeting different organs and tissues, and they can be incorporated in various dosage forms[(4)]. Nanoparticles can be prepared from liquid nanosuspension (NS) after drying by a suitable method like spray drying, vacuum drying, and the most widely used freeze-drying.

[1]Corresponding author E-mail: areej.w.alhagiesa@uokufa.edu.iq
Received: 18/7/2020
Accepted:11 /4 /2021
Published Online First: 2021-12-11

The transformation of liquid NS into solid NPs may provoke stressful conditions on the prepared NPs. It may cause aggregation and agglomeration into larger particles and lose its unique property of nano range particle size. Freeze-drying is the process of removing water by sublimation and desorption under a high vacuum. It is better to mention that the solidification process is dependent mainly on the surface hydrophobicity and cohesive energy of the drug to produce a stable, dried NS. A cryoprotectant may be added to preserve the dispersibility of a NS[6].

NMD is a dihydropyridine calcium channel blocker useful for the prevention and treatment of delayed ischemic effects due to cerebral vasospasm and subarachnoid hemorrhage[7]. It has a low bioavailability of around 13 % because of its low water solubility (4.14 µg/ml) and extensive first-pass metabolism. It belongs to class II drugs (low solubility and high permeability) in the Biopharmaceutical Classification System[8]. Many attempts have been applied to enhance its bioavailability like solid dispersion[9][10], cyclodextrin complexation[11], and nanotechnology approaches like nanoemulsion[12][13], solid lipid nanoparticles[14], nanoliposomes[15], and nanocrystals[16].

NMD is chemically described as (3-(2-methoxyethyl) 5-propan-2-yl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) . Its chemical structure is shown in figure (1).

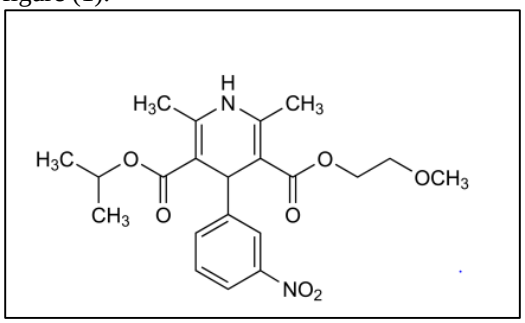

Figure 1. The chemical structure of Nimodipine

NMD is a yellow crystalline powder with a melting point of 125℃, pKa 5.4, and a partition coefficient (log p) 3.05. It has a molecular formula and weight of $C_{21}H_{26}N_2O_7$ and 418.4 gm/mol, respectively[8].

This research aims to enhance the solubility and dissolution rate of the poorly water soluble drug Nimodipine.

Materials

Nimodipine pure powder, tocopheryl polyethylene glycol succinate (TPGS) poloxamer 407 (PXM 407), Hydroxypropyl methylcellulose (HPMC E5) and Polyvinyl povidone (PVP K90) were purchased from Hyperchem, China. Soluplus® was bought from Basf, Germany. Brij-35 was obtained from Himedia, India. Disodium hydrogen phosphate (Na_2HPO_4) and (Potassium dihydrogen phosphate (KH_2PO_4)were bought 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 Da was puechased from (USA), ethanol was brought from Chemlab, Belgium. Mannitol was obtained from England.

Method

Preparation of nimodipine nanoparticles

Nimodipine 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 syringe pump as shown in figure(2) at a speed of 1 ml/min into a beaker containing 27 ml distilled water (antisolvent in presence of (60 mg) of the following stabilizers (TPGS, Soluplus, HPMC E5, PVP K90, poloxamer 407) and this process was done using either magnetic stirrer at a speed of 300 rpm or bath sonicator[17]. Precipitation of solid nanoparticles occurred immediately. The resultant nanosuspension is left for one hour under magnetic stirrer to allow the organic solvent to evaporate. 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[18].

Figure 2. Preparation of Nimodipine nanoparticles using a syringe pump

The composition and the variables of the prepared NMD NPs are listed in the table(1)

Table 1.The Composition of The prepared NMD Nanoparticles.

Formula name	Polymer name	NMD: polymer ration	Magnetic stirrer	Bath sonicator
F1	TPGS	1:2	300 rpm	-
F2	Soluplus®	1:2	300 rpm	-
F3	PXM 407	1:2	300 rpm	-
F4	HPMC E5	1:2	300 rpm	-
F5	PVP K90	1:2	300 rpm	-
F6	TPGS	1:2	-	3 minutes
F7	Soluplus®	1:2	-	3 minutes
F8	PXM 407	1:2	-	3 minutes
F9	HPMC E5	1:2	-	3 minutes
F10	PVP K90	1:2	-	3 minutes

Measurement of the particle size and polydispersity index of nimodipine nanosuspension

Samples of all prepared nanoparticles were analyzed using ABT-9000 nanolaser particle size analyzer, the average particle size and polydispersity index (PDI) for each sample were recorded[19].

Characterization of the lyophilized powder

Determination of drug content in the lyophilized powder

For the determination of NMD content in the dried nanoparticles, 18 mg (which is equivalent to 3 mg of NMD) of the lyophilized powder for the accepted smallest particle size formula was allowed to dissolve in 100 ml ethanol in a dry volumetric flask and sonicated for 10 minutes, then 2 ml of this solution were taken and diluted with ethanol twenty five times. The solution filtered, and the absorbance was measured using a UV-visible spectrophotometer at a λ_{max} (236.8 nm).[20].

The experiment was performed in triplicate, and the average value was calculated. The percentage of drug content was calculated according to the following equation:

%Drug content = (Actual drug content)/ (Theoretical drug content) x100…. Eq (1).

Measurement of the particle size and polydispersity index after drying

The particle size of the dried powder was done by dispersing an equivalent amount to 10 mg of NMD as dried nanoparticles in 9 ml distilled water then sonicated for two minutes. This procedure was done so that the concentration of the drug 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[21]

In vitro dissolution of the prepared nanoparticles

in vitro dissolution was done for the prepared NMD nanoparticles with the smallest particle size and pure NMD. It was performed using dissolution apparatus 2 (paddle type) containing Simulated Salivary Fluid (SSF) with 0.5% Brij-35 (to maintain sink condition) as a dissolution media, the rotation speed was 75 rpm, and the temperature was 37°C±0.5. 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 for 120 min. The samples were filtered using 0.45 µm and analyzed using UV-spectrophotometer at λ_{max} (238 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 [22].

For the statistical analysis of the dissolution study for the pure NMD and NMD NPs, the similarity factor f_2 was employed. The pure NMD was considered to be the reference, while the NPs were supposed to be the test. The release profiles are considered to be similar when the value of $f2$ is between 50 and 100

f_2 can be calculated from equation 2

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (2)$$

Where;

Rt, *Tt* is the percentage of the drug dissolved of the reference and test profile, respectively, at time *t; n* is the number of sampling [23].

Screening of pure Nimodipine and Nimodipine nanoparticles saturation solubility

Saturation solubility of pure NMD and NMD NPs was measured in 0.1 N HCl (pH 1.2) and SSF (pH 6.8) in a shaking water bath at a temperature of 37±0.5 ˚C for 48 hrs. Their solubility was also screened in distilled water at a temperature of a 25±0.5 ˚C for 48 hrs. Then each sample was filtered, and its absorbance was measured at λ_{max} (238 nm).

Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared spectroscopy (FTIR) spectra were obtained using FTIR Shimadzu 8300 Japan. Samples of pure NMD, Soluplus®, mannitol, and NMD NPs of the selected formula were compressed with potassium bromide. The spectrum obtained was between the wavenumber of 4000-400 cm^{-1}[24].

Results and Discussion

Evaluation of the prepared Nimodipine nanosuspension

Analysis of particle size and polydispersity index

All the samples of NMD NS were analyzed by the ABT-9000 nanolaser particle size analyzer, and the particle size distribution of all formulas was recorded, 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 lower 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 than0.7 is (very polydisperse)[25].

Table 2. The Particle Size and PDI of the Prepared Nimodipine NPs

Formula name	Particle size (nm)	PDI
F1	555± 25	0.008±0.0005
F2	77± 9	0.016±0.002
F3	1070 ± 10	0.003±0.001
F4	702 ± 4.9	0.008±0.0005
F5	872 ± 20	0.015±0.005
F6	367±15.6	0.021±0.01
F7	32.9±18.2	0.3±0.1
F8	305.3±5	0.006±0.001
F9	603±50.6	0.002±0.0005
F10	755±15	0.006±0.0005

The effect of polymer type on the particle size and PDI

Five different stabilizers (TPGS, Soluplus®, PXM 407, HPMC E5, and PVP K90) were used to give the formulas (F1-F5) ,which were prepared by using magnetic stirrer as shown in figure (3).

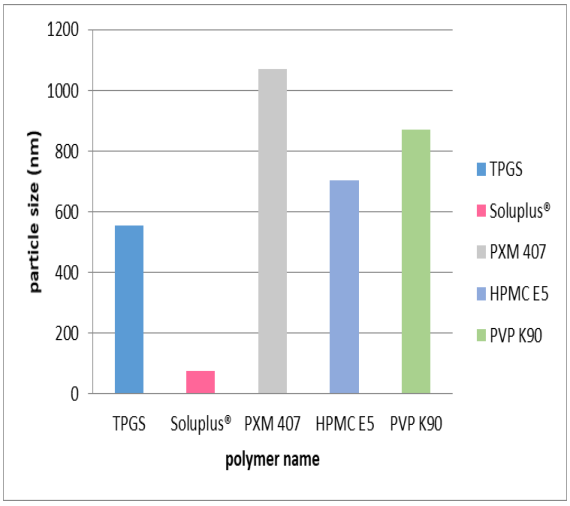

Figure 3. The effect of polymer type on the particle size of the prepared NMD NPs by magnetic stirrer

The smallest particle size was obtained when using Soluplus® as a stabilizer (F2 77 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. 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 NS(26).

The other four polymers show a fair particle size reduction (555- 1070 nm). TPGS is a water-soluble analog of vitamin E; it can stabilize the NS by hydrophobic (Vander Waals) interaction between the particles(27). While PXM 407 is a hydrophilic nonionic surfactant, and it has been widely used as a coating agent for the NPs. HPMC E5 and PVP K90 stabilize the newly formed NMD NPs by a steric mechanism that prevents the freshly formed NPs from aggregation and particle growth(28).

This variation in particle size was due to the efficiency of these different stabilizers to envelop and stabilize the newly formed NMD NPs.

PDI of all these five formulas was in the range of (0.003-0.016), which indicates that NMD nanoparticles are monodispersed standard.

The effect of using a bath sonicator on particle size and PDI

Formulas F6-F10 were prepared to evaluate the effect of using bath sonicator instead of magnetic stirrer on the particle size and PDI of the prepared NMD NPs as shown in figure (4).

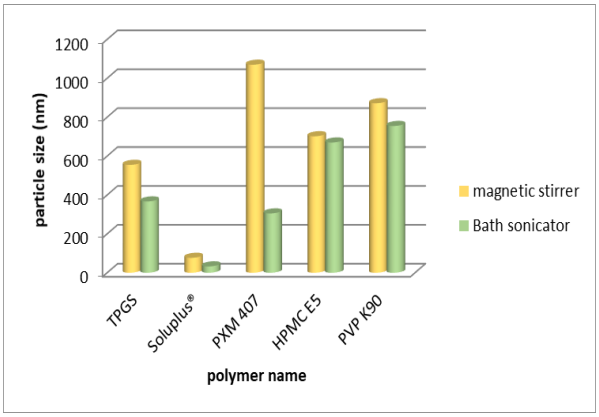

Figure 4. The effect of using Bath sonicator instead of Magnetic stirrer on the particle size of the prepared NMD NPs

The particle size of all formulas prepared by this method was significantly ($p<0.05$) decreased as compared with formulas prepared using a magnetic stirrer and the smallest particle size was obtained by F7 (32.9 nm) in which Soluplus® was used as a stabilizer . The formation of the nanoparticles under the influence of ultrasonic waves is influenced by the higher energy and rapid miscibility of the organic solvent (ethanol) and the aqueous antisolvent, which increases the polarity of ethanol and reduce the solubility of NMD hence the rapid nucleation of NPs.

Also, the sonication process produces high energy, high temperature, and shock waves, which inhibits the growth of newly formed nanoparticles[29].

PDI of the formulas prepared by this method was in the range (0.02-0.006), which indicates that these formulas were in the limit of monodispersed standards except for the F6 in which Soluplus® is the stabilizer; PDI is 0.3 which show mid-range polydispersity of the prepared NPs which is not useful to maintain the stability of the prepared NS.

From the results presented in this study, it appears that Soluplus® is the better stabilizer and the preferred one for reducing the particle size of the prepared NPs.

Characterization of the lyophilized NMD nanoparticles

Determination of drug content in the lyophilized powder

The NMD content of the lyophilized powder for F2 was found to be equal to (102.25±12) % and for F7 is (92.15±10.32) % .The percentage of drug content was ranged from (92-102)%, which is an indication of the excellent and applicable way for loading the NMD into the prepared nanoparticles.

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 table(3), along with PDI.

Table 3.The Particle Size and PDI of NMD NPs After Lyophilization.

Formula name	Particle size	PDI
F2	45±32	0.04±0.04
F7	327±190	0.024±0.007

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[30].

The particle size of F7 increased from 33 nm to 327 nm after drying, as illustrated in figure(5). This increment may be due to the relatively high PDI value (0.3) of the liquid nanosuspension, which indicates the presence of larger particles, and upon drying, these particles aggregate and increased the overall particle size distribution.

On the other hand, the particle size of the formula F2 after drying was close to its original PS, which indicates minimal aggregation of the prepared NMD NPs during lyophilization.

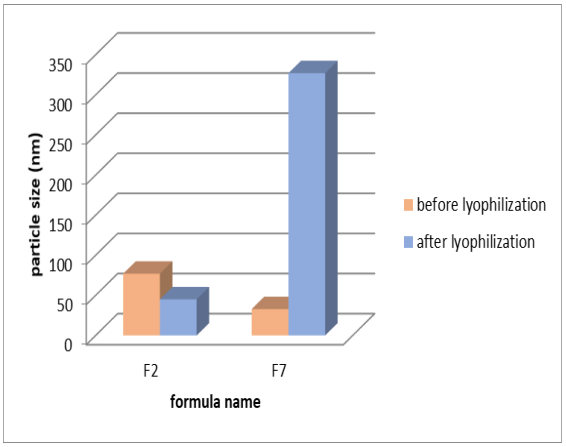

Figure 5. The particle size of the prepared NMD NPs before and after lyophilization

In vitro dissolution of NMD nanoparticles

In vitro dissolution study was done to the formulas (F2, F7) after lyophilization and NMD pure powder using a dialysis membrane with a molecular weight cutoff 12000-14000 dalton. The study was done in a dissolution apparatus type II (paddle type) at a 75 rpm, and the temperature was adjusted at 37±0.5 ℃. The media was simulated salivary fluid (SSF) (pH 6.8) containing 0.5 % Brij-35. The results of the dissolution profile of the dried NMD NPs and pure NMD are shown in figure(6).

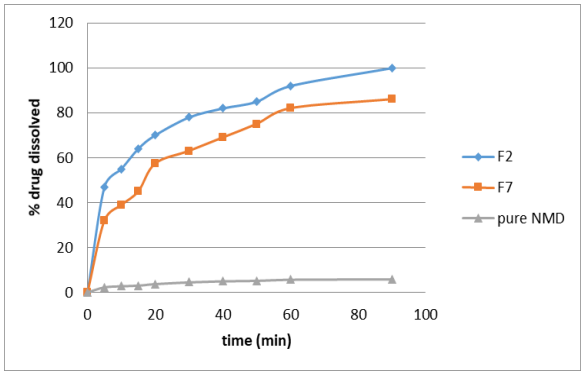

Figure 6. The dissolution profile of the prepared NMD NPs and pure NMD in SSF containing 0.5 % Brij-35.

It was found the F2 (which composed of 30 mg NMD, 60mg Soluplus and 90mg mannitol) reaches a complete dissolution after 90 minutes from the starting of the dissolution study, and it was the fastest formula compared with F7 and pure NMD. 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.

The values of *f2* for the NMD NPs formulas were 7.1 and 11.44 for F2 and F7 respectively.

Screening the saturation solubility of pure Nimodipine and Nimodipine Nanoparticles

The solubility of NMD and NMD NPs was done in D.W., 0.1 N HCl (pH 1.2), and SSF (pH 6.8).The solubility of NMD was increased several folds, as illustrated in the table (4) and figure (7).

Table 4, The Saturation Solubility of NMD Nanoparticles in Different Dissolution Media

Dissolution media	pH	Temperature °C	Saturated solubility of pure NMD (µg/ml)	Saturated solubility of NMD NPs (µg/ml)	Number of increment folds
0.1 N HCl	1.2	37 ± 0.5	10.9	25.6	2.3
SSF	6.8	37 ± 0.5	3.4	46.12	13.56
Water	7-8	25 ± 0.5	4.14	100.7	24.3

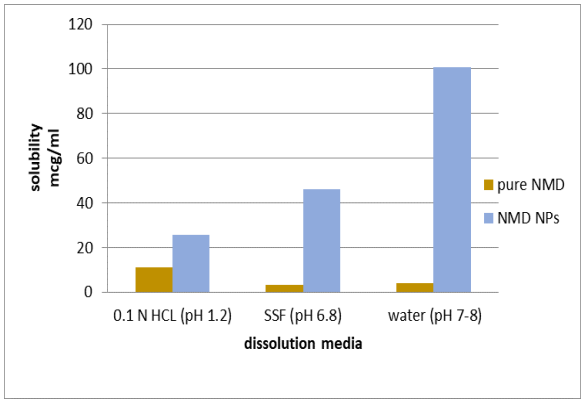

Figure 7. Solubility of pure NMD and NMD nanoparticles in different dissolution media

The enhanced solubility can be explained by Ostwald–Freundlich equation. The saturation solubility of NMD increases as the particle size reaches the nanoscale range.

Another explanation for the solubility enhancement is due to disruption of the ideal structure of the drug microparticles into the nanoparticles. This disruption causes high energy of interfacial tension, which enhances the solubility of nanoparticles [31,32]

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were obtained for pure NMD, Soluplus®, mannitol, and NMD NPs, as shown in figures (8,9,10 and 11 respectively). This study was done to evaluate the compatibility between the drug and the other excipients in the prepared NPs.

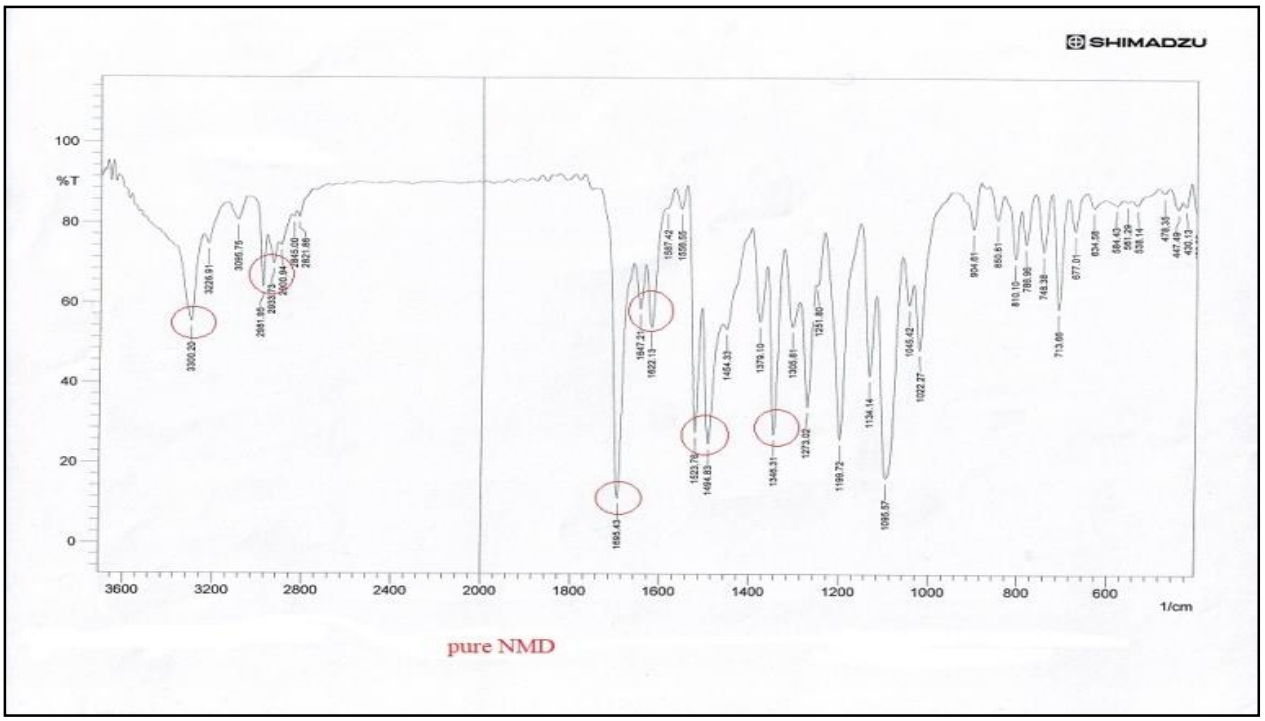

Figure 8. The FTIR spectrum of pure NMD

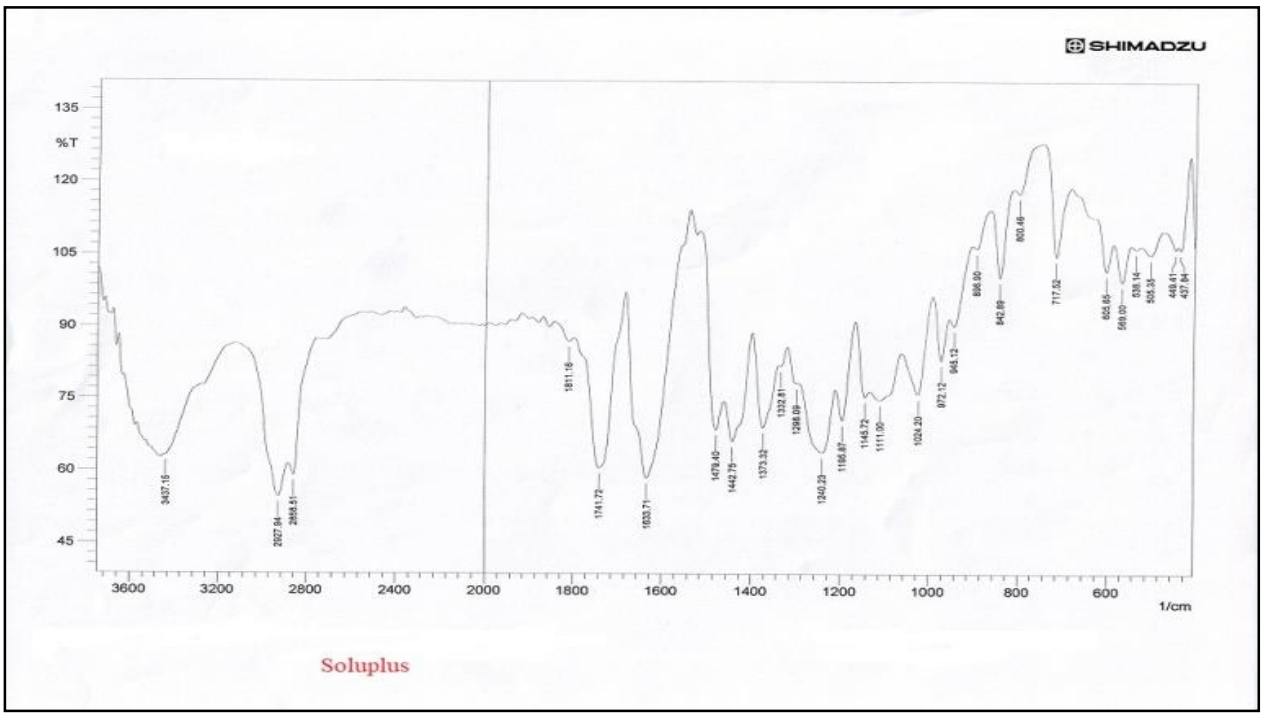

Figure 9. FTIR spectrum of Soluplus®

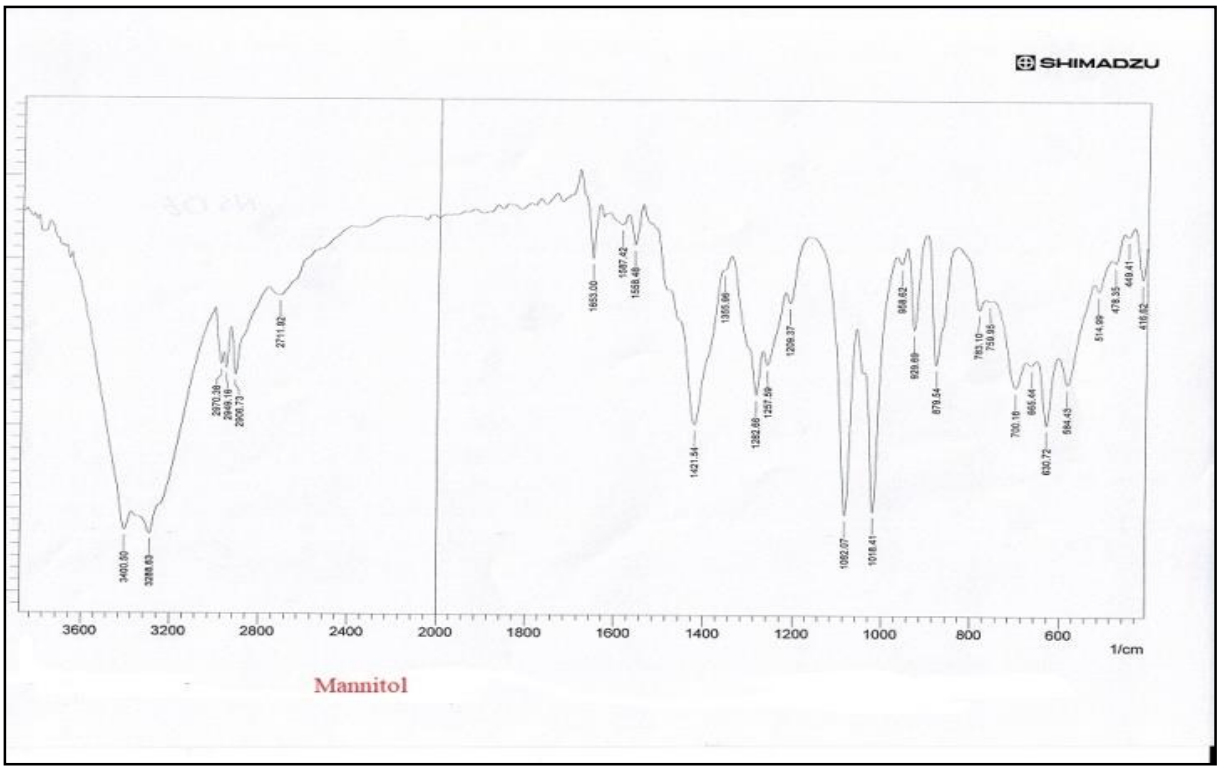

Figure 10. FTIR spectrum of mannitol

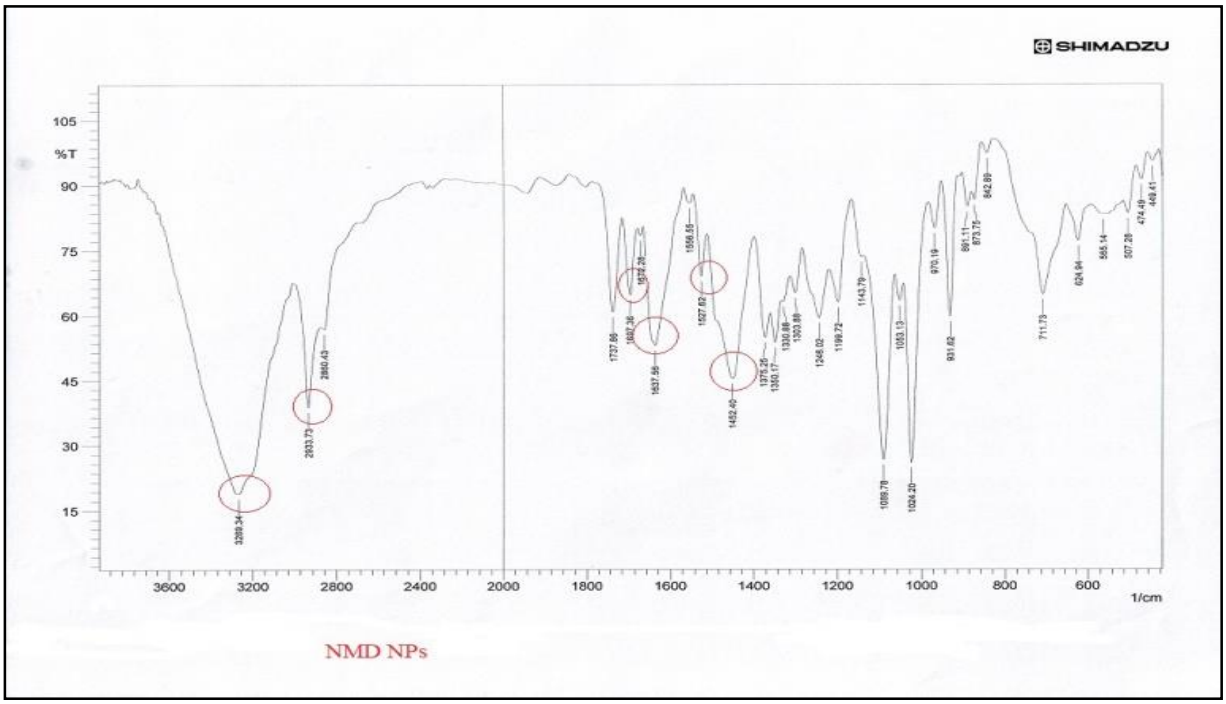

Figure 11. FTIR spectrum of NMD NPs

The FTIR spectrum of NMD shows many main peaks about 3300 cm^{-1} due to N-H stretching, 3226 cm^{-1} and 3095 cm^{-1} due to aromatic C-H stretching, 2981 cm^{-1} due to aliphatic C-H stretching, 1695 cm^{-1} due to C=O stretching in ester, 1647 cm^{-1} due to N-H bending, 1523 cm^{-1} and 1494 cm^{-1} due to C=C ring stretching and 1346 cm^{-1} due to C–C(=O)–O stretching of α,β-unsaturated ester. These peaks are in very close math to the reference peaks[33].

The NMD NPs spectrum also showed the main peaks of Nimodipine (circled in red).

N-H stretching and N-H bending have been broadened, and C=O stretching frequencies have been reduced in intensity, and this is mainly due to the formation of hydrogen bonds between the

hydroxyl group of Soluplus® and Nimodipine. It is well established that the bands could shift to a different wavelength with reduced intensity upon the formation of hydrogen bonding[34].

Conclusion

Nanoprecipitation method using a magnetic stirrer or bath sonicator is an efficient way for the formation of NMD NPs to enhance the saturation solubility and dissolution rate of poorly water-soluble Nimodipine.

References

1. Chen L, Wang Y, Zhang J, Hao L, Guo H, Lou H, et al. Bexarotene nanocrystal - Oral and parenteral formulation development, characterization and pharmacokinetic evaluation. Eur J Pharm Biopharm. 2014;87(1):160–169.
2. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. Int J Pharm Sci Rev Res. 2010;5(1):41–51.
3. Kovalchuk NM, Johnson D, Sobolev V, Hilal N, Starov V. Interactions between nanoparticles in nanosuspension. Adv Colloid Interface Sci. 2019;272:102020.
4. Nagavarma BVN, Yadav HKS, Ayaz A, Vasudha LS, Shivakumar HG. Different techniques for preparation of polymeric nanoparticles- A review. Asian J Pharm Clin Res. 2012;5(SUPPL. 3):16–23.
5. Junghanns JUAH, Müller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008;3(3):295–309.
6. Yue PF, Li Y, Wan J, Yang M, Zhu WF, Wang CH. Study on formability of solid nanosuspensions during nanodispersion and solidification: I. Novel role of stabilizer/drug property. Int J Pharm. 2013;454(1):269–277.
7. MS L, EM S. Nimodipine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in cerebrovascular disease. Drugs. 1989;37(5):669–699.
8. Clarke_s_Analysis_of_Drugs_and_Poisons.
9. Sun Z, Zhang H, He H, Sun L, Zhang X, Wang Q, et al. Cooperative effect of polyvinylpyrrolidone and HPMC E5 on dissolution and bioavailability of nimodipine solid dispersions and tablets. Asian J Pharm Sci. 2019;14(6):668–676.
10. Jijun F, Lishuang X, Xiaoli W, Shu Z, Xiaoguang T, Xingna Z, et al. Nimodipine (NM) tablets with high dissolution containing NM solid dispersions prepared by hot-melt extrusion. Drug Dev Ind Pharm. 2011;37(8):934–944.
11. J. S. Patel , N. R. Pandyl, S.C. Marapurl. Influence of method of preparation on physicochemical properties and in vitro drug release profile of Nimodipine cyclodextrin inclusion complexes. A comparative study. Int J Pharm Pharm Sci. 2016;8(5):404–407.
12. Yadav SA, Poddar SS. Formulation, In-Vitro and In-Vivo evaluation of nanoemulsion gel for transdermal drug delivery of Nimodipine. Asian J Pharm Clin Res. 2015;8(2):119–124.
13. Ghareeb MM, Neamah AJ. Formulation and Characterization of Nimodipine Nanoemulsion As Ampoule for Oral Route. Artic Int J Pharm Sci Res. 2017;8(2):591–602.
14. Chalikwar SS, Belgamwar VS, Talele VR, Surana SJ, Patil MU. Formulation and evaluation of Nimodipine-loaded solid lipid nanoparticles delivered via lymphatic transport system. Colloids Surfaces B Biointerfaces. 2012;97:109–116.
15. Guan T, Miao Y, Xu L, Yang S, Wang J, He H, et al. Injectable nimodipine-loaded nanoliposomes: Preparation, lyophilization and characteristics. Int J Pharm. 2011;410(1–2):180–187.
16. Li J, Fu Q, Liu X, Li M, Wang Y. Formulation of nimodipine nanocrystals for oral administration. Arch Pharm Res. 2016;39(2):202–212.
17. Kathpalia H, Juvekar S, Shidhaye S. Design and In Vitro Evaluation of Atovaquone Nanosuspension Prepared by pH Based and Anti-solvent Based Precipitation Method. Colloids Interface Sci Commun. 2019;29(August 2018):26–32.
18. Mansouri M. Preparation and Characterization of Ibuprofen Nanoparticles by using Solvent/ Antisolvent Precipitation. Open Conf Proc J. 2011;2(1):88–94.
19. Hamed HE, A. Hussein A. Preparation, in vitro and ex-vivo Evaluation of Mirtazapine Nanosuspension and Nanoparticles Incorporated in Orodispersible Tablets. Iraqi J Pharm Sci. 2020;29(1):62–75.
20. Nakarani M, Misra AN, Patel JK, Vaghani SS. Itraconazole nanosuspension for oral delivery: Formulation, characterization and in vitro comparison with marketed formulation. Daru. 2010; " Daru: journal of Faculty of Pharmacy, Tehran University of Medical Sciences 18.2 (2010): 8
21. Dawood N, Abdulhamid S. Formulation and Characterization of Lafutidine as a Nanosuspension A. 2010. Master thesis.
22. Towers M. British Pharmacopoeia 2009. Br Pharmacopia. 2009;
23. Xie F, Ji S, Cheng Z. In vitro dissolution similarity factor (f2) and in vivo bioequivalence criteria, how and when do they match? Using a BCS class II drug as a simulation example. Eur J Pharm Sci. 2015;66(October):163–172.
24. Bharti K, Mittal P, Mishra B. Formulation and characterization of fast dissolving oral films

containing buspirone hydrochloride nanoparticles using design of experiment. J Drug Deliv Sci Technol. 2019;49(November 2018):420–432.
25. Yang H, Teng F, Wang P, Tian B, Lin X, Hu X, et al. Investigation of a nanosuspension stabilized by Soluplus® to improve bioavailability. Int J Pharm. 2014;477(1–2):88–95.
26. Gadad a P, Chandra PS, Dandagi PM, Mastiholimath VS. Moxifloxacin Loaded Polymeric Nanoparticles for Sustained Ocular Drug Delivery. J Pharm Sci. 2012;1727–1734.
27. Ghosh I, Bose S, Vippagunta R, Harmon F. Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. Int J Pharm. 2011;409(1–2):260–268.
28. Kuroiwa Y, Higashi K, Ueda K, Yamamoto K, Moribe K. Nano-scale and molecular-level understanding of wet-milled indomethacin/poloxamer 407 nanosuspension with TEM, suspended-state NMR, and Raman measurements. Int J Pharm. 2018;537(1–2):30–39.
29. Moorthi C, Senthil Kumar C, Mohan S, Kathiresan K. SLS/βCD-curcumin nanosuspension: Preparation, characterization and pharmacological evaluation. J Pharm Res. 2013;7(3):219–223.
30. Yue PF, Li G, Dan JX, Wu ZF, Wang CH, Zhu WF, et al. Study on formability of solid nanosuspensions during solidification: II novel roles of freezing stress and cryoprotectant property. Int J Pharm. 2014;475(1–2):35–48.
31. Xiong R, Lu W, Li J, Wang P, Xu R, Chen T. Preparation and characterization of intravenously injectable nimodipine nanosuspension. Int J Pharm. 2008;350(1–2):338–343.
32. Müller RH, Peters K. Nanosuspensions for the formulation of poorly soluble drugs. I. Preparation by a size-reduction technique. Int J Pharm. 1998;160(2):229–237.
33. AL-Omar MA. Nimodipine: Physical profile. Comptes Rendus l'Academie Sci - Ser IIa Sci la Terre des Planetes. 2004;330(8):581–593.
34. AlSheyyab RY, Obaidat RM, Altall YR, Abuhuwaij RT, Ghanma RR, Ailabouni AS, et al. Solubility enhancement of Nimodipine through preparation of Soluplus® dispersions. J Appl Pharm Sci. 2019;9(9):30–37.