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Using ionic Liquids-Based Surfactant in formulating Nimodipine Polymeric Nanoparticles: A Promising Approach for Improved Performance

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Abstract

According to definition, polymeric nanoparticles exist as tiny, solid, colloidal particles ranging from 1-1000 nm in size, manufactured from biodegradable and biocompatible polymers, lipids, or metals. Polymeric nanoparticles have attracted substantial attention in various fields, including imaging, and diagnostics, and are considered as interesting choices for drug delivery and targeting. The synthesis and stabilization of nanoparticles are crucial for their successful application. Ionic liquid-based surfactants (ILBS) have emerged as promising solvents and stabilizers owing to their distinct features, like minimal volatility, high thermal stability, and customizable physicochemical properties. It is distinguished from commercially available surfactants by outstanding features such as low critical micelle concentration (CMC), improved wetting and foaming capabilities, in addition to strong solubilization ability. The present work aimed to formulate polymeric nanoparticles using ILBS, 1-tetradecyl-3-methylimmidazolium bromide (TDMB) as a stabilizer to improve Nimodipin's poor solubility and dissolution rate. They were produced using the nanoprecipitation method. Results show that most of the prepared NID-PNP formulations exhibited particle sizes in the nanoscale range. The optimized formula (F5), stabilized with ionic liquid 0.5% and soluplus prepared under a stirring speed of 1000 rpm, exhibited a particle size (64.33nm) and PDI (0.067). Moreover, it displayed an enhanced dissolution rate 96% in phosphate buffer pH 7.4 with 0.5%Brij-35 within 20 minutes, compared to the pure NID 15.4 % in the identical media. Collectively, Nimodipine polymeric Nanoparticle significantly enhanced the solubility and dissolution velocity of NID and offered an encouraging nano platform for hydrophobic drug delivery.

Keywords: Ionic Liquids-Based Surfactant, Nanoparticles, Nanoprecipitation, Nimodipine

Introduction

Enhancing the solubility and dissolution rate of poorly water-soluble drugs is of significant importance. Several techniques are used such as salt formation, pH adjustment, complexation, solid dispersions, and particle size reduction via micronization and nanonization[(2)]. Nanotechnology is a technique that produces materials at ananoscale level and has a crucial role in optimizing the potential of nanoparticles and their respective applications. Polymeric nanoparticles (PNPs) and microspheres, as well as liposomes, have emerged as versatile drug delivery platforms and have shown considerable promise in improving therapeutic effects. Particles with at least one dimension smaller than 100 nm are included in the large class of materials known as PNPs [(2)]. Based on their size, shape, and chemical composition, NPs can be broken down into several distinct categories such as carbon NPs, metal NPs, polymeric NPs, and lipid NPs[(3, 4)]. Two methods employed for the preparation of PNP can be categorized into bottom-up approaches such as precipitation and top-down approaches including media milling [(5)], emulsion solvent diffusion, high-pressure homogenization, and Nano-Edge technology [(6)].The PNPs are either nanocapsules, whereby the solid mass is entirely encapsulated within the particle [(7)], or nanospheres, where the whole mass is usually solid and the other molecules are adsorbed at the outside border of the spherical surface [(8)]. The success of these NPs hinges on their ability to efficiently encapsulate and deliver therapeutic agents, as well as their stability and biocompatibility. To address these challenges, researchers have turned to novel surfactants, such as ionic liquids, to enhance the formulation and performance of PNP [(9-11)].Ionic liquid-based surfactants (ILBS), have been known for over 100 year and has grown significant attention recently due to their potential to be used in PNP formulation and improve drug delivery systems. It is distinguished

from commercially available surfactants by outstanding properties such as high thermal stability low vapor pressure, non-flammability, low critical micelle concentration (CMC), improved wetting and foaming capabilities, strong solubilization ability, and biocompatibility, making them promising alternatives and attractive candidates as surfactants in NPs formulation[12].The ILBS can stabilize and control the size and morphology of PNP[13]. They can act as emulsifiers, preventing aggregation and aiding in the homogenous dispersion of hydrophobic drugs. Furthermore, the tunable nature of IL allows for the tailoring of their structures to achieve specific interactions with polymeric materials, thereby influencing drug loading capacity, release kinetics, and overall NP stability[14] . Various techniques, such as emulsion polymerization, nanoprecipitation, and microfluidic synthesis were employed to obtain NPs with controlled sizes and properties. Additionally, they can modify the surface chemistry of NPs, imparting stealth properties to evade the immune system and enabling targeted drug delivery to specific tissues or cells[15, 16].

An effective calcium channel blocker (NID) which acts via its influence on vascular smooth muscle cells, by maintaining the inactive conformation of voltage-gated L-type calcium channels. By obstructing the influx of calcium into smooth muscle cells, NID reduces calcium-dependent smooth muscle contraction and resultant vasoconstriction [18-20]. The impact of NID is more pronounced on cerebral circulation than on peripheral circulation. It is employed as an adjunctive therapy to enhance the neurological outcomes of individuals suffering from subarachnoid hemorrhage caused by ruptured intracranial aneurysms. Nevertheless, its limited solubility which is contingent upon dissolution, reduced NID oral bioavailability[21].The purpose of this work was headed for preparing NID-loaded NPs using ILBS to improve solubility and dissolution rate and study the effects of variables on particle size such as polymer and stabilizer type and ratio. To overcome short storage life, NID-PNP were freeze-dried to be evaluated through DSC, FTIR, XRD, FE-SEM, AFM and comparative drug release from PNP was also considered.

Materials and Methods

Materials

Nimodipine was purchased from Zhejiang Shenzhou pharmaceutical Co., LTD, China. Ethanol was purchased from Honeywell International Inc., USA. Soluplus® was purchased from BASF, Germany. Poloxamer 188 from Hyper Chem, China, PVA from Central Drug House, India. 1-tetradecyl-3-methylimidazolium bromide (TDMB) from Hyper Chem, China. Brij® -35 from Central drug house, India. Dialysis bag 8-14 kDa Lab Pvt. Ltd USA. Amicon ultrafilter with a (MWCO 3kDa. Merck(sigma-Aldrich). All other chemicals were of analytical grade

Methods

Preformulation studies were done by determining the saturated solubility of the pure NID utilizing shake-flask method by dissolving excess quantity of NID in 10 ml tubes containing either water or phosphate buffer solution (PBS) pH 7.4 both with 0.5% brij® -35(polyoxy ethylene lauryl ether)[22]. The drug was shaken at 25±0.5˚C in water and 37±0.5˚C in PBS for 72 hr. with regular agitation. At equilibrium, solutions were filtered and examined using a Shimadzu UV-spectrophotometer at a wavelength of maximum absorbance [23, 24].The thermal behavior of pure NID was investigated using Differential Scanning Calorimetry (DSC) with DSC-60, Shimadzu, Japan. Nitrogen gas was employed as the purge gas in the DSC cell, with a flow rate of 50 ml/min and 100 ml/min through the cooling unit. A representative portion (5-10 mg) of the sample was subjected to thermal treatment using aluminum pans. The heating process for each sample was initiated at 40°C and gradually increased to 300°C at a rate of 10°C per minute[25, 26]. Additionally, Fourier-transform infrared spectroscopy (FTIR) by (FTIR-8300 Shimadzu, Japan) was studied for pure drug, by grinding NID with potassium bromide (KBr) and pressing it into a thin disc using a specific process and scanning at waves number (4000-400 cm^{-1}) to compare and identify any potential interactions and chemical changes between NID and excipients employed during NPs formulation[27, 28].Solvent - antisolvent precipitation method (nanoprecipitation) was utilized for preparing PNPs, where precisely weighed amounts(30 mg) of NID and polymer such as poloxamer 188(p-188) and polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®), in different weight ratio (1:1,1:2,1:4, 1:8) were dissolved simultaneously in 3 ml of ethanol, as organic phase, and by using syringe needles to inject dropwise into aqueous phase, in volume ratio (1:9), that containing ionic liquid based surfactant (1-tetradecyl-3-methylimidazolium bromide –TDMB 0.5%) (Figure.1), polyvinylalcohol (PVA 1%) as stabilizer. The resultant solution was prepared using magnetic stirrer at a speed of 1000 rpm at 25°C at a rate of 0.5 ml/min, mixing for one hr. to allow the organic solvent to be evaporated. The composition of prepared NID-PNP formulas is listed in Table 1[29, 30]

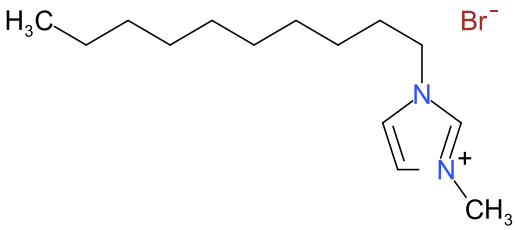


Figure 1. Structure of 1-tetradecyl-3-methylimidazolium bromide

Characterization of NID -PNPs

Particle Size and Polydispersity Index

The determination of PS of all NID-PNP formulations was conducted at ambient temperature through the application of a dynamic light scattering (DLS) approach, utilizing a Malvern zetasizer particle size analyzer (Uitra Red, USA) model. The measurements were taken at a scattering angle of 90°. The aforementioned methodology quantifies the dispersion of particles undergoing Brownian motion, subsequently translating it into dimensions size distribution [29, 32, 33]. Additionally, the impact of polymer and stabilizer type and concentration on PS plus entrapment efficiency (EE) were studied.

Entrapment Efficiency

The (%EE) was determined by subjecting 4 ml dispersion to centrifugation at 3000 rpm for 15 min using an Amicon ultrafilter with a molecular weight cut-off (MWCO) of 10 kDa. This procedure allowed for the quantification of drug content encapsulated inside the PNPs. The quantity of unbound drug was assessed using spectrophotometry, specifically by measuring the UV absorbance at a wavelength of 237 nm. The amount of drug trapped within the system was then computed using Equation (1) [34].

$$\%\mathbf{EE} = \frac{\mathbf{A(total)-A(free)}}{\mathbf{A(total)}} \mathbf{x\ 100} \quad \mathbf{Eq(1)}$$

Where

% EE: refers to the entrapment efficiency percentage

$A_{(total)}$: The overall amount of drug.

$A_{(free)}$: The free amount of drug.

***Solubility Determination*:**

A volume (1.5ml) of selected NID-PNP was dissolved in 2 ml of distilled water and shaken for 24 hr. Tubes were centrifuged and the clear supernatant was filtered through 0.45µ filter syringe, properly diluted, and spectrophotometrically measured at 238 nm to be compared with pure NID solubility, Triplicates of each experiment were conducted [27, 33-35].

Table 1. Composition of prepared NID-PNP formulations

F	NID (mg)	polymer type	NID: polymer ratio w/w	Ethanol ml	stabilizer type	Stabilizer conc. %w/v	O/A* volume ratio	Speed (rpm)
F1	30	p- 188*	1:1	3	PVA*	1%	1:9	1000
F2	30	p- 188	1:2	3	PVA	1%	1:9	1000
F3	30	p- 188	1:4	3	PVA	1%	1:9	1000
F4	30	p- 188	1:8	3	PVA	1%	1:9	1000
F5	30	Soluplus	1:1	3	TDMB*	0.5%	1:9	1000
F6	30	Soluplus	1:2	3	TDMB	0.5%	1:9	1000
F7	30	Soluplus	1:4	3	TDMB	0.5%	1:9	1000
F8	30	Soluplus	1:8	3	TDMB	0.5%	1:9	1000

P-188* (poloxamer-188), PVA (polyvinyl alcohol), TDMB* (1-tetradecyl-3-methylimidazolium bromide) O/A* (Organic/aqueous volume ratio)

In- vitro NID Release

To accomplish a more thorough examination, the release behavior of selected NID-PNP formulas was studied. Three milliliters mL of dispersion, (equivalent to 3.3 mg NID) using a USP Type II dissolution apparatus with a dialysis bag (MWCO 8000-14000 Da) that was pre-soaked with dissolution medium overnight through which sample was placed inside. The membrane was attached to the paddle and immersed in °00 ml of PBS, pH 7.4 with 0.5% brij-35 at 37 ± 0.1°C and 100 rpm. At regular intervals of 5, 10, 15, 30, 45, 60, and 90 minutes, 5ml of the sample were collected, filtered through 0.45 µm syringe filter, and subsequently analyzed spectrophotometrically, to keep the sink condition, five milliliters of fresh buffer solution was added after each withdrawn. All samples were analyzed three times (n = 3). The percent release was plotted against time [32, 35, 36].

The NID-PNPs formulas were optimized and lyophilized. The sample was prefrozen and 2% w/v mannitol was added as a cryoprotectant using an Alpha 1-2 LD plus-CRIST lyophilizer, Germany, at -45°C and 380 mT pressure for 48 hr. to yield dry NPs. Furthermore, after reconstitution, PS and PDI

were examined for the lyophilized formulations in order to detect any change in PS that affects PNP stability [24, 25, 37, 38].

Zeta Potential Measurement:

The electrophoretic mobility of a chosen formula was determined using the Malvern Zetasizer Nano ZS instrument (Malvern instrument, Worcestershire, UK). This measurement was then converted to zeta potential, which provides information about the degree of repulsion among charged particles and assesses the stability of the prepared dispersion. The sample was introduced into an electrophoretic cell by subjecting them to an electrical field with a strength of 15.2 V/cm [39, 40]

Compatibility and Identification of the Crystalline Pattern

were studied via FTIR and XRD respectively, for optimized NID-PNP formula and compared with pure drug[25].

Atomic Force Microscopy

A NaioAFM2022, Nanosurf, Switzerland was used to examine the morphology of NID-PNPs by scanning surface solid objects under controlled circumstances. In a nutshell, a few drops of nanodispersion were applied to a glass slide and allowed to dry for the entire night to create a thin coating that could be examined by AFM. Particle size, a three-dimensional image, and a histogram of the distribution of particle sizes were obtained[33].

Field Emission-Scanning Electron Microscope

A model Inspect 50 FEI, Germany with different magnifications were used to study the morphology of NID-PNP. The specimens of NID-PNP were evenly dispersed onto double-sided adhesive carbon tapes, which were then affixed to FE-SEM specimen mounts. Prior to imaging, a 2-min sputter-coating operation was carried out to establish a homogeneous coating on the samples. This procedure entailed coating the samples with a thin layer to improve conductivity and enable better imaging [22].

Statistical Analysis

The experiment's outcomes were presented as mean and standard deviation (SD) of samples taken in triplicate using one-way analysis of variance (ANOVA) to find significant variances among the related data. When using Microsoft Excel 2010, at a p-value less than 0.05, the outcome was considered significantly different.

Results and Discussion

Saturated solubility results of pure NID and the prepared formula (F5) showed that plain NID had a saturation solubility of (99.49±0.21) µg/ml in PBS at pH 7.4, and a solubility of (31.89± 1.84) µg/ml in distilled water. Based on the provided solubility values, NID has limited solubility in the specified circumstances in both aqueous medium and PBS[21, 22]. Saturation solubility of the prepared NID-PNP (F5) in water was (114.1±0.23) µg/ml. Thus, there is a larger increase 3.6 times in the saturation solubility of NID when it is formulated as a PNP which is attributed to the dual role of surfactant and smaller PS, and subsequent increase in surface area according to (Noyes–Whitney equation)[41].

Characterization of NID-PNP

Particle Size (PS) Analysis and PDI

Table 2 reveals the average PS of prepared NID-PNPs. Most of the formulations exhibited nanoscale PS ranging from 64.33 nm to 449.5 nm. The PDI of each formulation was determined and ranged from low 0.067to high value 0.687 depending on surfactant type and concentration and techniques such as, sonication, homogenization which are being employed to control the size and size distribution of drug carrier systems[32] Markedly, the inclusion of soluplus and TDMB as stabilizers (in F5) resulted in smaller PS representing the effective role of IL- TDMB as stabilizers by preventing the aggregation of NPs that tend to adsorb onto the surface of PNPs, creating a protective layer that avoids their coalescence owing to the formation of intermolecular H- bonds between NPs plus ILBS on numerous positions.[42] Additionally, various interactions such as van der Waals, electrostatic, and steric interactions are well established for ILBS with long side chains which provide steric stabilization in addition to solvation forces which dictate PNPs stability [43, 44].Also, ILBS can modify the surface properties of PNPs through specific functionalities such as hydrophobicity or hydrophilicity, which can influence their interactions with other molecules or surfaces. This can be advantageous for tailoring the properties of PNPs for specific applications[45].Furthermore, ILBS can enhance the reactivity of NPs in certain chemical reactions owing to their unique solvent properties and ability to solvate reactants, they can facilitate chemical reactions involving NPs, such as catalysis or synthesis[46].Overall, the use of ILBS in NPs formulation can provide numerous benefits, including improved stability, dispersion, solubility, surface modification, and reactivity. These effects can be harnessed to optimize the properties and performance of NPs in various applications, such as drug delivery[47].

Table 2. The Particle Size, PDI, and %EE of NID-PNP Formulations

Formula no.	Particle size (nm)*	PDI ±SD*	EE%±SD*
F1	401.8 ±1.5	0.687 ±0.02	75.89 ±2.60
F2	449.5 ±4.4	0.223 ±0.043	87.99 ±0.97
F3	263.1 ±1.7	0.63 ±0.015	91.02 ±0.51
F4	295.8 ±1.2	0.317 ±0.008	92.19 ±0.46
F5	64.33 ±1.6	0.067 ±0.019	95.46 ±0.401
F6	81.49 ±2.7	0.164 ±0.002	96.25 ±0.561
F7	95.16 ±2.6	0.190 ±0.037	88.8 ±1.62
F8	102.3 ±6.07	0.176 ±0.002	96.66 ± 2.60

*mean ± standard deviation (SD), n=3

The Impact of Types and Concentrations of Polymers

Studying the impact of polymer, two types in different ratios, soluplus (F5-F8) and p-188 (F1-F4) were employed in preparing NID-PNPs. The PS obtained was presented in (figure 2). For P-188, the mean PS obtained was (401.8, 449.5, 263.1,295.8nm) while for soluplus was (64.33,81.49, 95.16,102.3 nm) for the same ratio. Soluplus has a bifunctional character as a matrix polymer for solids and an active solubilizer via micelle formation in water. it contains polyethylene glycol backbone as a hydrophilic moiety and vinyl caprolactam/vinyl acetate side chain as a lipophilic part that provides an amphiphilic nature which makes it an admirable surface-active and wetting agent in dropping the interfacial tension among the hydrophobic surface of NID particles and the aqueous antisolvent. Thus preventing aggregation of the NP due to the effect of steric hindrance leads to produce a uniform NPs with a narrower size distribution[27,48].Regarding the impact of concentration of polymer, increasing concentration of soluplus (F5-F8) results in reducing PS significantly (P <0.05),while increasing P-188 concentration (F1-F4) will cause an increase in PS significantly (P <0.05).This observation is consistent with the findings reportedby **Nasef and Ullah F.et al**. in studying the impact of stabilizer. The aggregation may result from the high concentration of the polymer leading to increased adsorption of the hydrophobic part of the chains on the surface of NPs forming multiple layers and the increased thickness of the coat may lead to aggregation of particles causing thermodynamic instability of the PNP system (Figure 2) [49-52]

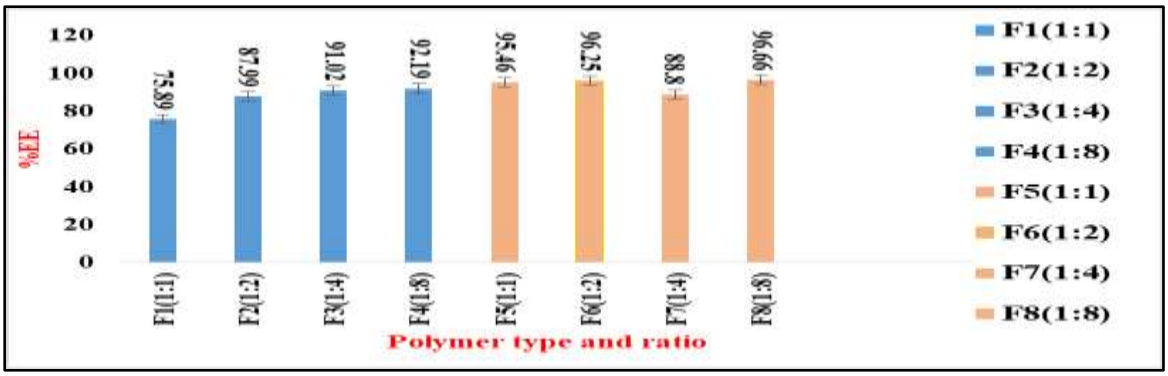


Figure 2. Effect of polymer ratio on the particle size of NID-PNP formulas

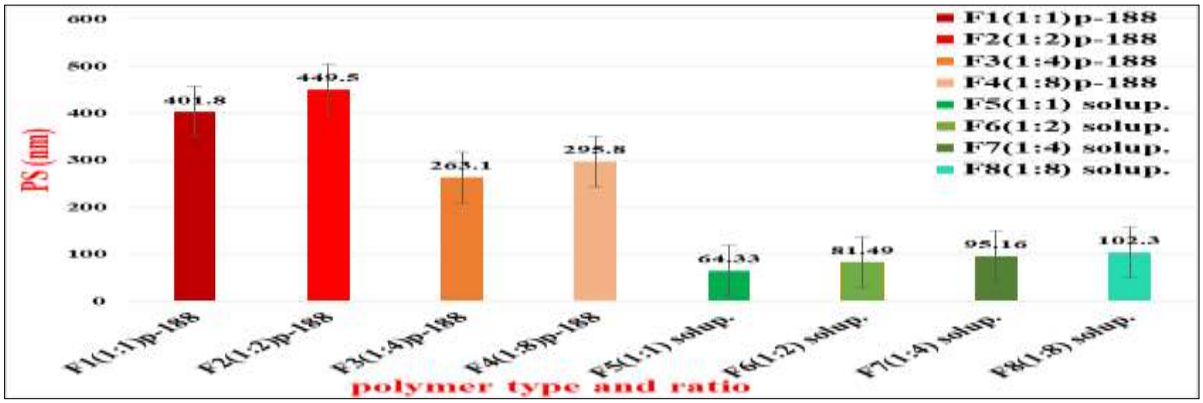


Figure 3. Effect of polymer type and ratio on the %EE of NID-PNP formulations Effect of Stabilizer Type and Ratio.

Have been investigated by employing two different types of stabilizers (PVA and TDMB). As shown in (Table 2) the formulations containing TDMB (F5-F8) as stabilizers had small particle size (64.33 nm) paralleling to formulations enclosing PVA (F1-F4) (310.5 nm) respectively[53] .The observed results can be attributed to the effect of PVA as stabilizers that results in a reduction of polymer-solvent interactions and an increase in polymer-polymer interactions, such an attractive forces give rise to regions where polymeric chains develop a coiled shape, rendering them incapable of generate monodispersions.[52] Due to the limited molecular mobility, the intermolecular interactions were affected. The increase in friction has the potential to generate larger particles while TDMB has the ability to wet the surface of the drug particles and provide a steric or ionic barrier to prevent forming aggregates of NPs[54]. Due to smaller PS and PDI and higher %EE resulted, F5selected as optimized formula to be lyophilized. Moreover, the PS of lyophilized NID-PNP (F5) was measured to be (79.21±1.05 nm), and PDI was 0.28±0.16 indicating that there was nonsignificant (P> 0.05) increase in both the PS and PDI.

Zeta Potential (ZP):

For optimized formula (F5) was found (22.78 ± 1.01) mV confirming that there would be no instability issues with the developed formulation.[52]

Entrapment Efficiency (%EE)

The %EE of NID depends on the high solubility of the drug as well as on the amount of polymer and surfactant may have either reduction or increase in %EE. Generally, %EE of NID increased on increasing the amounts of p-188 plus PVA (F1-F4) due to increasing polymer concentration as shown in (Figure 3)[52]. With the exception for (F7) in which %EE reduced due to the creation of micelles caused by an excess of surfactants enhancing the solubilization of NID in the aqueous phase by reducing its adsorption on the surface of NP. Hence, NID partitioned in aqueous phase during washing in ultrafiltration of NP, thus reducing %EE of NID on the surface of NP which agreed with results obtained by Preeti Singh. et al. in formulated satranidazole NS and by Abbas HK.et al. in formulated Ketoprofen NPs [55, 56]

In-vitro Release

Cumulative percent drug release profile of NID from optimized PNP-formulation (F5) and lyophilized F5 exhibited a significantly higher release paralleled with pure NID over 90 min. Formula F5 exhibited a release percentage of 96% within 20 min. compared to the pure drug achieved a release of 15.4 % in the same media which indicates the poor solubility of pure NID, while NID-PNP formulation effectively enhanced drug release as shown in (Figure 4)due to reduction of PS and increasing surface area [57].

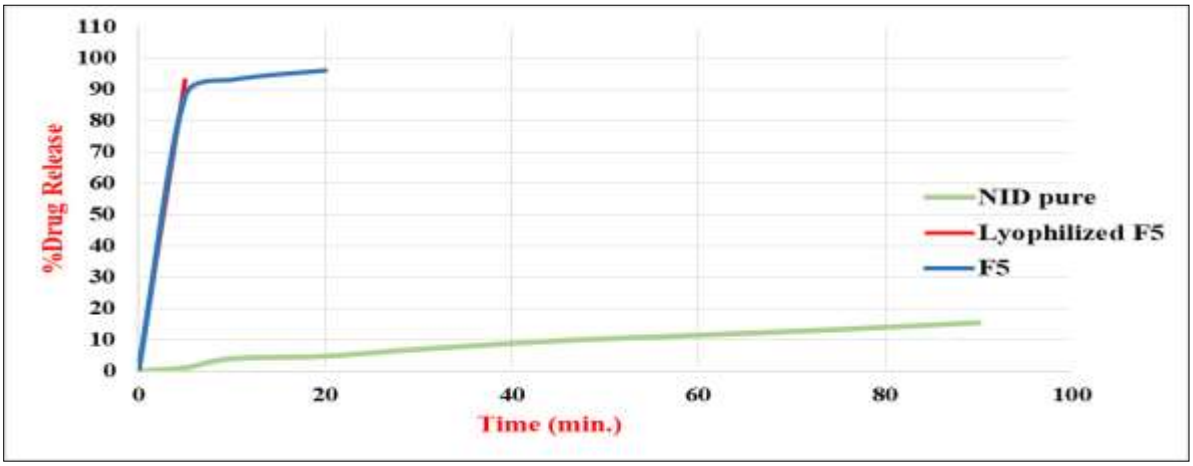


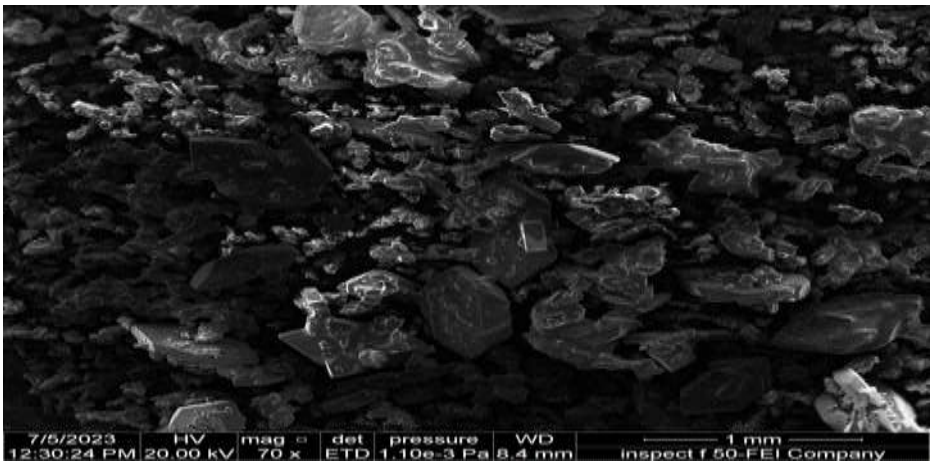
Figure 4. *In-vitro* drug release of pure NID, NID-PNP (F5) and lyophilized F5 in BPS pH 7.4 with 0.5%Brij-35

Field Emission-Scanning Electron Microscope (FE-SEM)

Was done to study morphologies of both pure NID and optimized NID-PNP (F5). The pure NID displayed crystalline, irregular shapes and a non-uniform PS distribution whereas the NID-PNP (F5) analysis revealed that the particles of NID incorporated into the polymer and exhibited a nearlyspherical morphology within the nanoscale size range (Figure 5).

Differential Scanning Calorimetry (DSC)

Figure 6 (a, b, c, and d) depicts the DSC thermograms of pure NID, ILBS, physical mixture, and lyophilized NID-PNP powder of optimized formula (F5). Sharp endothermic peak was seen for pure NID at 128.63°C, which parallels to its melting crystallinity. Moreover, the peak of NID was reduced (100°C) of the lyophilized NID-PNP(F5), which indicated that the NID was entrapped into the PNP and existed in solubilized state due to the solubilizing effect of surfactants[29].



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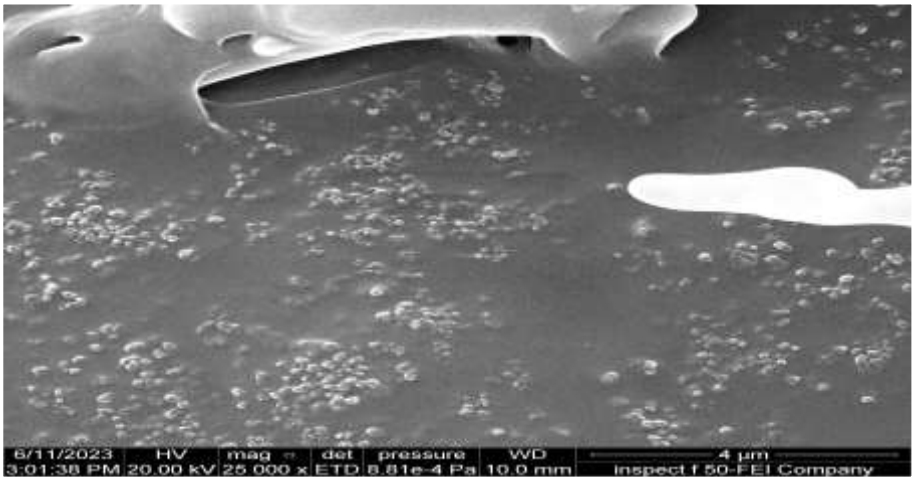

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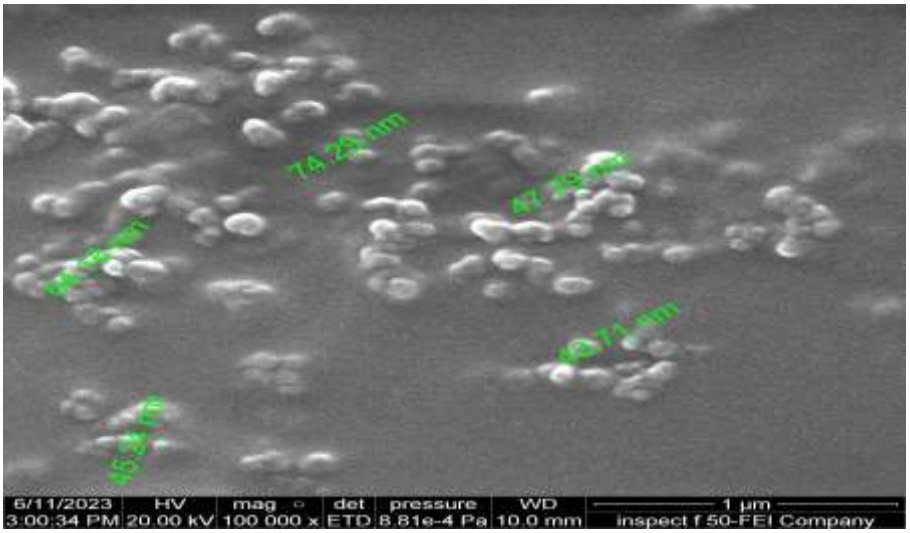

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Figure 5. FE-SEM of (a) pure NID (b, c) NID-PNP (F5)

Compatibility Study

The drug-excipient's compatibility was studied via FTIR for pure NID, physical mixture, and optimized F5 as shown in (Figure 7). Pure NID spectrum shows characteristic peaks; (3271 cm^{-1}) NH stretching, (3086 cm^{-1}) C–H aromatic stretching, C–H aliphatic stretching (2947cm^{-1}). Carbonyl stretching of ester (1701 cm^{-1}), C=N Stretching(1624 cm^{-1}), −C–CH3(1381 cm^{-1}),

aromatic C=C stretching (1621cm^{-1}), pyridine NH(1648.84cm^{-1}), and NO_2 stretching(1531 , 1309.43 cm^{-1}) and C-H bending (1130 cm^{-1}) [58].

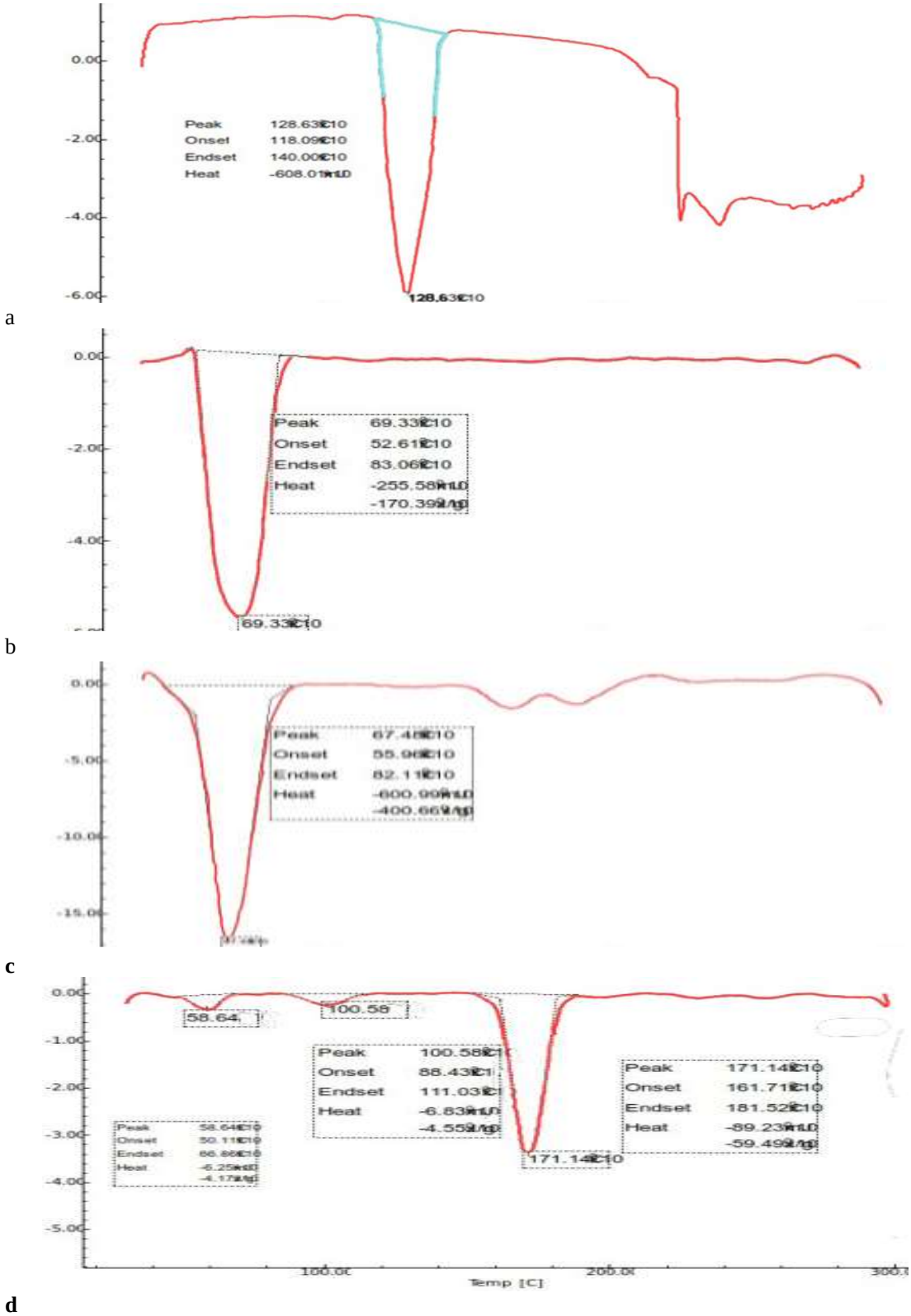
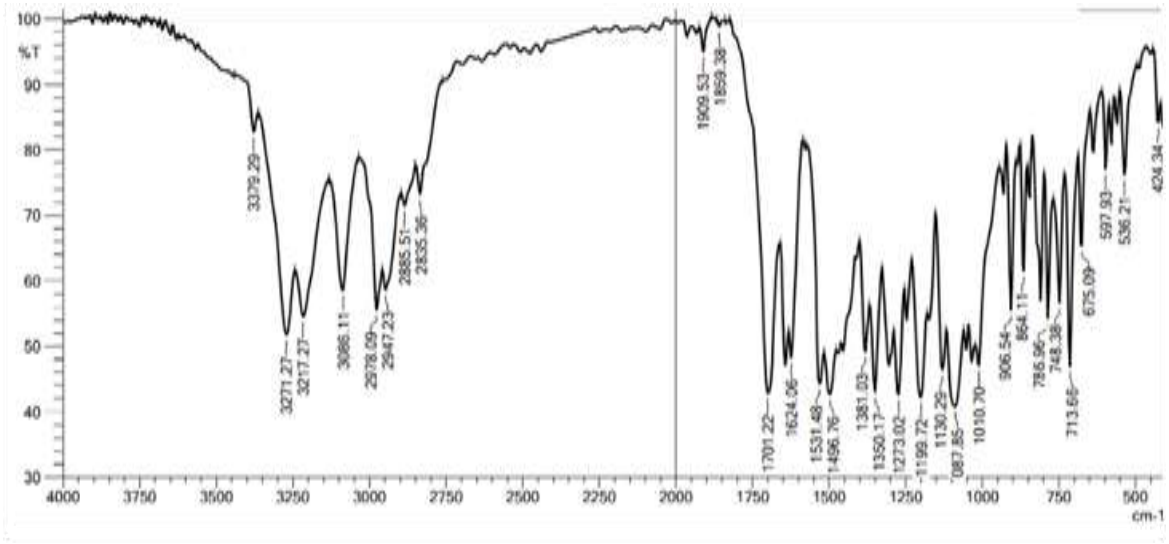


Figure 6. DSC thermogram of a) pure NID, b) ILBS, c) physical mixture, and d) lyophilized F5

However, the peaks of C=O and NO_2 were shown to move and reduce intensity owing to the formation of hydrogen bonds between the hydrophilic group included on excipients like soluplus, ILBS, and NID. Broad peak was seen in the formulation's spectra in the region of 3275 cm^{-1}.In summary, the analysis revealed that there are no known chemical interactions, and we may deduce that the improved solubility of the medicine is caused by the formation of hydrogen bonds [59].

X-ray Thermogram

X-ray thermogram of pure NID, physical mixture, ILBS, and optimized NID-PNP (F5) are depicted in (Figure. 8). X-ray thermogram exhibited characteristics sharp peaks at 2Ɵ value for pure NID at 12.520, 13.000, 17.310, 20.310 and 26.210, representing a crystalline nature of NID. Although, the XRD of the developed formulation showed peaks with lower intensity compared to pure NID which may be due to the presence of NID linking with ILBS and soloplus in solubilized state. Hence the lyophilized (F5) is predicted to be more stable as well as the improved solubility and dissolution rate were attributed to the reduction in the size and presence of the surfacta



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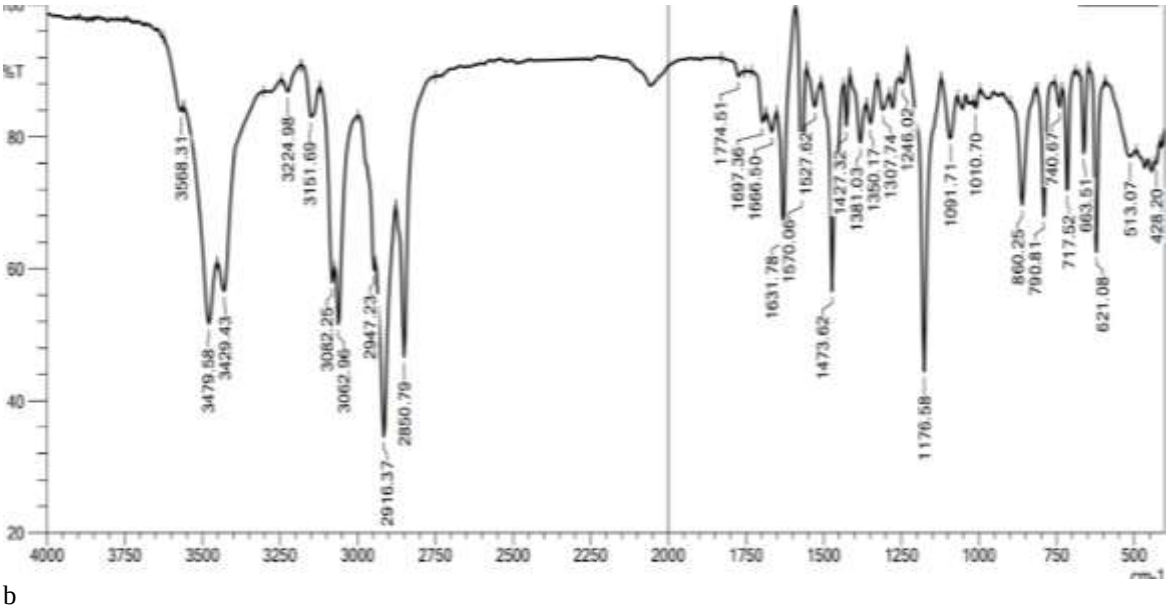

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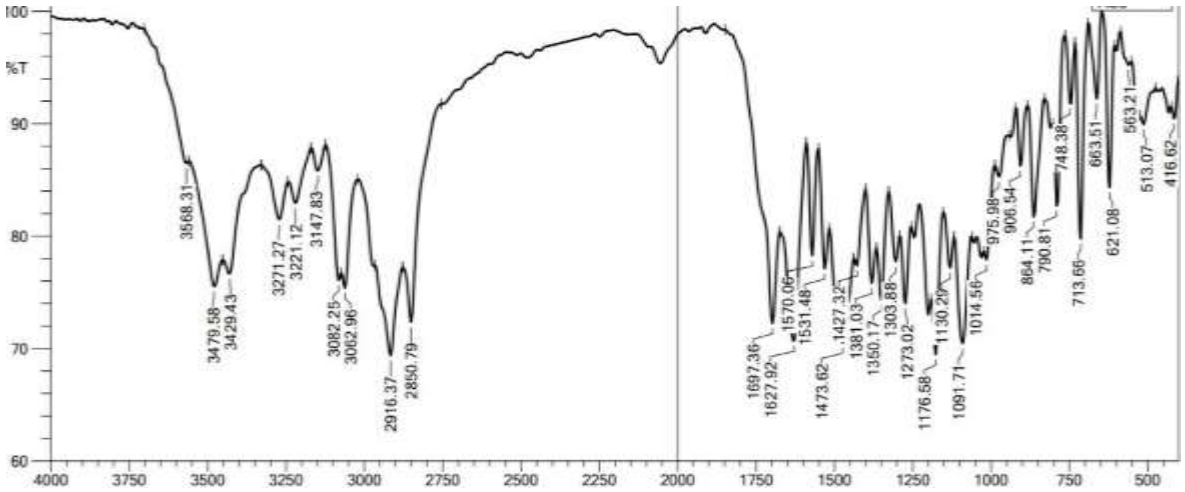

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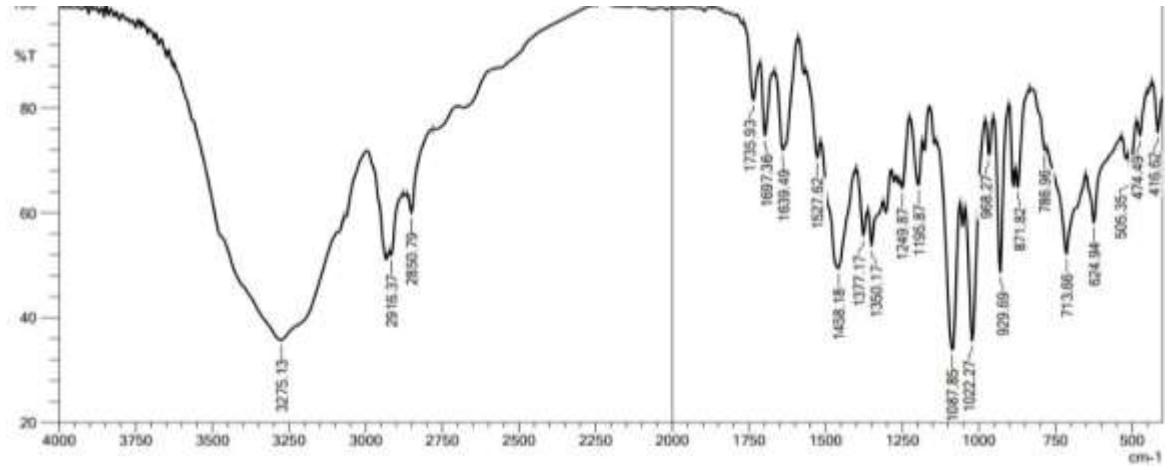

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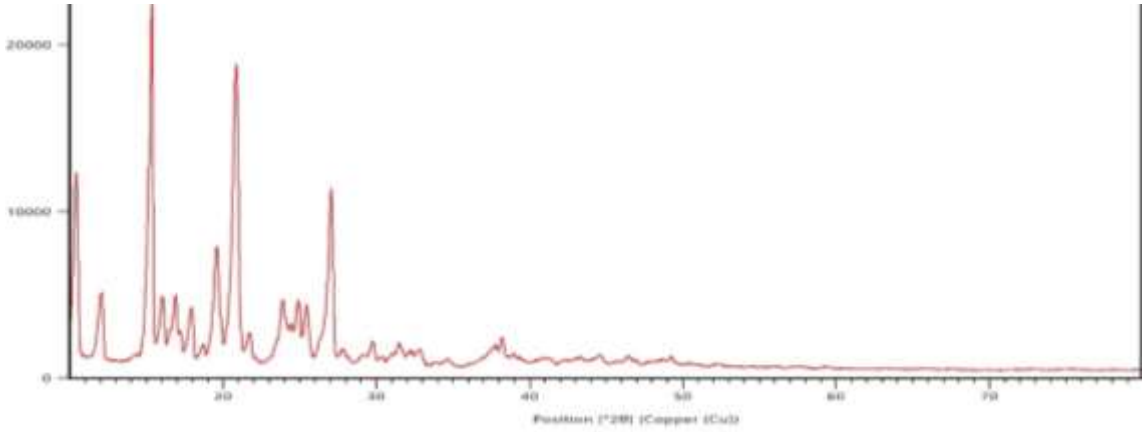
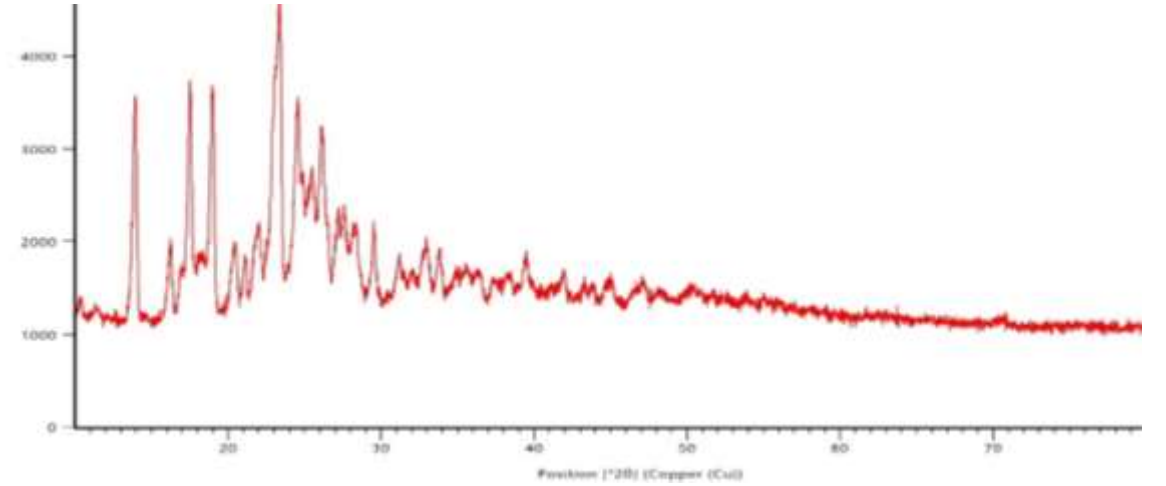
Figure 7. FTIR of (a)pure NID,(b) ILBS, (c)physical mixture, and (d)lyophilized (F5)

Atomic Force Microscopy (AFM)

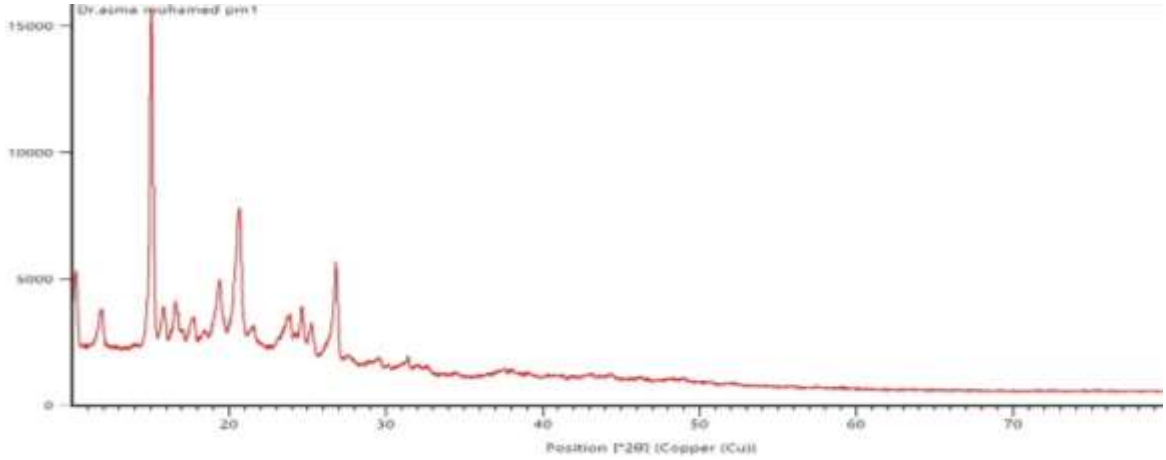
It's employed to scan surfaces and accurately measure their properties under controlled environmental circumstances. Additionally, AFM is utilized to identify the size of (NPs) with a high level of precision (Figure.9). AFM enables the observation of samples with high resolution in three spatial dimensions, specifically in the x-, y-, and z-directions. AFM reveals a consistent morphology and evenly dispersed particle dimensions, confirming an alignment between the measured PS and the desired size distribution, leading to the stability of optimized F5[33].



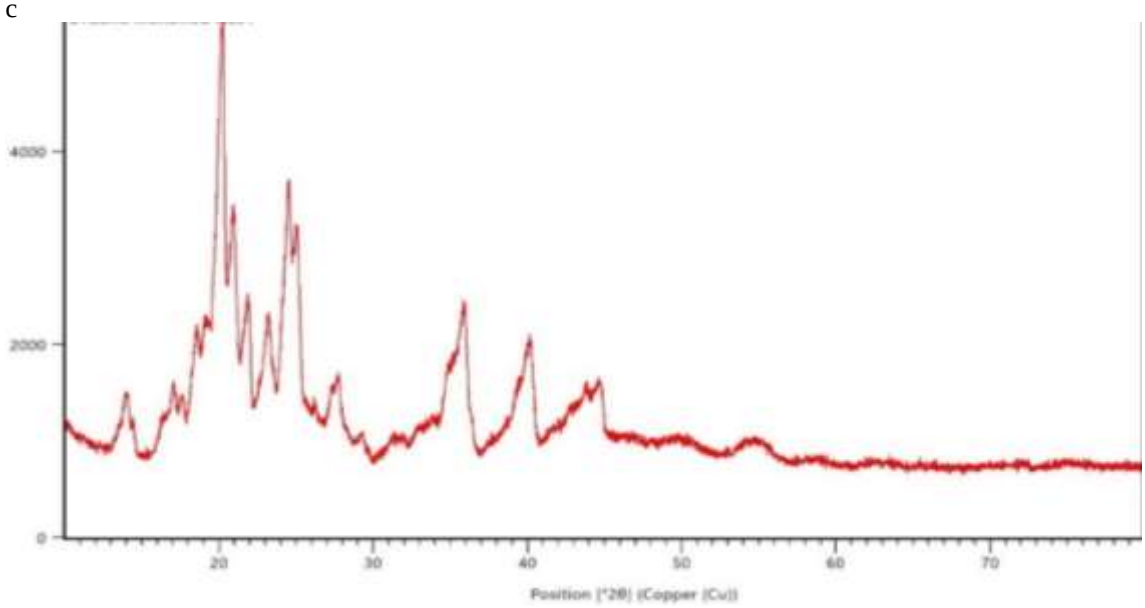
a



b



c



d

Figure 8. XRD of (a)pure NID, (b)ILBS, (c)physical mixture and(d) lyophilized (F5)

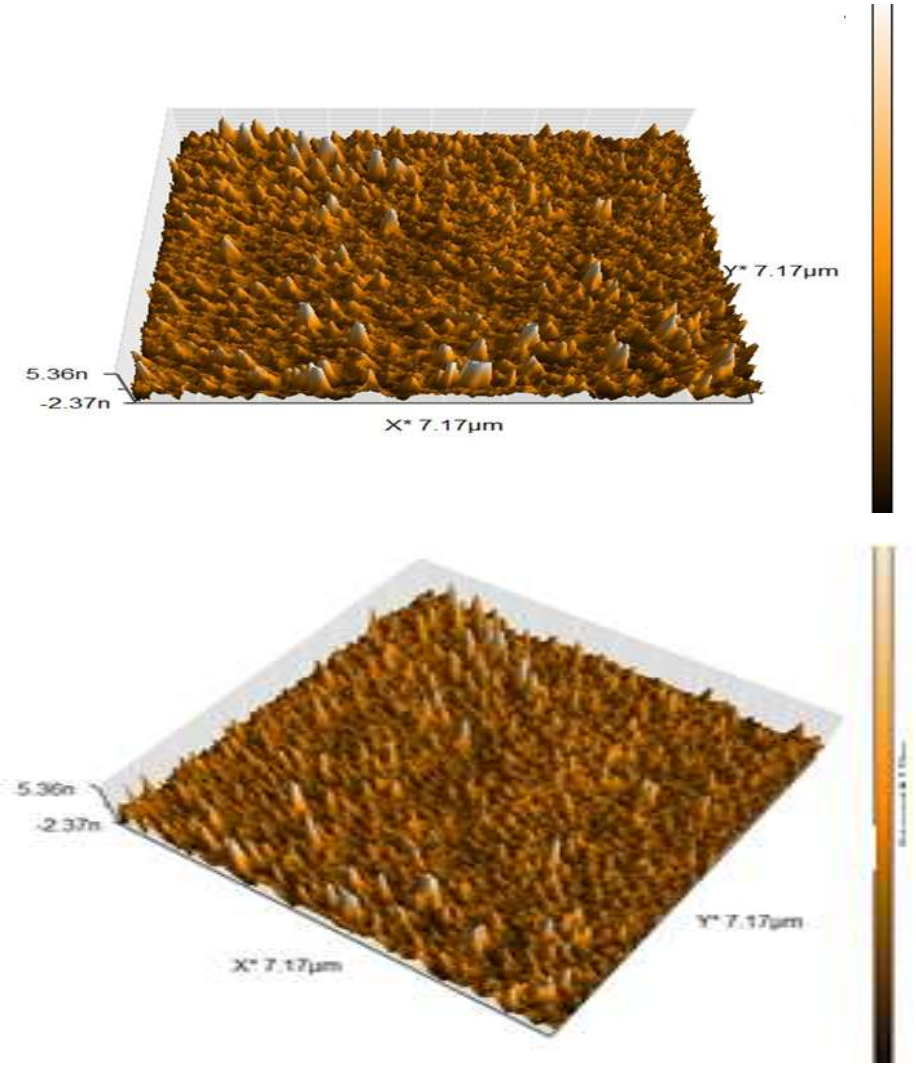


Figure 9. AFM of optimized formula (F5)

Conclusion

The outcomes demonstrated that the incorporation of ionic liquid-based surfactants (ILBS) for PNPs offers promising opportunities to develop highly stable, soluble, and efficient nanoscale systems with enhanced properties and controllable release behavior. Nanoprecipitation technique was more efficient to give small PS with relatively good entrapping efficiency. The type and ratio of polymer, stabilizer type, and ratio show an effect on the nanoparticle size. The prepared NID-PNP will be introduced in transdermal microneedle patches in part two of this research.

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Conflicts of Interest

The authors declare that there is no conflict of interest

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Ethics Statements

This study was in vitro and does not need ethical approval from an ethics committee.

Author Contribution

A.M.R. Data collection, Investigation, Methodology, Writing –Original Draft Preparation. M.M. G. Project Administration, Supervision, Writing –Review and approve the final version of the manuscript.

References

1. Teng Z, Yu M, Ding Y, Zhang H, Shen Y, Jiang M, et al. Preparation and characterization of nimodipine-loaded nanostructured lipid systems for enhanced solubility and bioavailability.

International journal of nanomedicine. 2019:119-33.
2. Thorat YS, Gonjari ID, Hosmani AH. Solubility enhancement techniques: a review on conventional and novel approaches. International journal of pharmaceutical sciences and research. 2011;2(10):2501.
3. . Leong MY, Kong YL, Burgess K, Wong WF, Sethi G, Looi CY. Recent Development of Nanomaterials for Transdermal Drug Delivery. Biomedicines. 2023;11(4):1124.
4. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arabian journal of chemistry. 2019;12(7):908-31.
5. Moribe K, Ueda K, Limwikrant W, Higashi K, Yamamoto K. Nano-sized crystalline drug production by milling technology. Current pharmaceutical design. 2013;19(35):6246-58.
6. Du J, Li X, Zhao H, Zhou Y, Wang L, Tian S, et al. Nanosuspensions of poorly water-soluble drugs prepared by bottom-up technologies. International journal of pharmaceutics. 2015;495(2):738-49.
7. Mansha M, Qurashi A, Ullah N, Bakare FO, Khan I, Yamani ZH. Synthesis of In2O3/graphene heterostructure and their hydrogen gas sensing properties. Ceramics International. 2016;42(9):11490-5.
8. Rao JP, Geckeler KE. Polymer nanoparticles: Preparation techniques and size-control parameters. Progress in polymer science. 2011;36(7):887-913.
9. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, et al. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. Chemical reviews. 2008;108(6):2064-110.
10. Lu S-D, Sian H-W, Wang M-H, Liao R-M. Application of extension neural network with discrete wavelet transform and Parseval's theorem for power quality analysis. Applied Sciences. 2019;9(11):2228.
11. Pan J, Rostamizadeh K, Filipczak N, Torchilin VP. Polymeric co-delivery systems in cancer treatment: an overview on component drugs' dosage ratio effect. Molecules. 2019;24(6):1035.
12. Amaral M, Pereiro AB, Gaspar MM, Reis CP. Recent advances in ionic liquids and nanotechnology for drug delivery. Nanomedicine. 2020;16(1):63-80.
13. El Seoud OA, Keppeler N, Malek NI, Galgano PD. Ionic liquid-based surfactants: Recent advances in their syntheses, solution properties, and applications. Polymers. 2021;13(7):1100.
14. Wang L, Chen G, Zhao J, Cai N. Catalase immobilization on amino-activated Fe3O4@ SiO2 nanoparticles: loading density affected activity recovery of catalase. Journal of Molecular Catalysis B: Enzymatic. 2016;133:S468-S74.
15. Moshikur RM, Ali MK, Moniruzzaman M, Goto M. Recent advances in surface-active ionic liquid-assisted self-assembly systems for drug delivery. Current Opinion in Colloid & Interface Science. 2021;56:101515.
16. Wu Z, Huang Z, Yin G, Wang L, Gao F. Fabrication of Gd/Eu-codoped SmPO4 nanorods for dual-modal magnetic resonance and bio-optical imaging. Journal of colloid and interface science. 2016;466:1-11.
17. Asasutjarit R, Sorrachaitawatwong C, Tipchuwong N, Pouthai S. Effect of formulation compositions on particle size and zeta potential of diclofenac sodium-loaded chitosan nanoparticles. International Journal of Pharmacological and Pharmaceutical Sciences. 2013;7(9):568-70.
18. Li J, Fu Q, Liu X, Li M, Wang Y. Formulation of nimodipine nanocrystals for oral administration. Archives of pharmacal research. 2016;39:202-12.
19. Jadhav RS, Jagdish VB. Analytical Method Development and Validation for estimation of Bisoprolol Fumarate in bulk and tablet dosage form by UV spectroscopic method. International Journal of Universal Science and Technology. 2018; 4 (1)008-17.
20. Jadhav RS, Jagdish VB. Development and Validation of Analytical method for estimation of Nimodipine content by UV spectroscopic method. World Journal of Pharmaceutical Research. 2018;7(5):1075-84.
21. Al-Omar MA. Nimodipine: Physical profile. Profiles of Drug Substances, Excipients and Related Methodology. 31: Elsevier; 2005. p. 337-54.
22. Gorajana A, Rajendran A, Rao NK. Preperation and in vitro evaluation of solid dispersions of nimodipine using PEG 4000 and PVP K30. Asian Journal of Pharmaceutical Research and Health Care. 2010;2(2):163-9.
23. Patil J, Pandya N, Marapur S, Shiralashetti S. Influence of method of preparation on physico-chemical properties and in-vitro drug release profile of nimodipine-cyclodextrin inclusion complexes: a comparative study. Int J Pharmacy Pharmaceutical Sci. 2010;2:71-81.
24. Zu Y, Li N, Zhao X, Li Y, Ge Y, Wang W, et al. In vitro dissolution enhancement of micronized l-nimodipine by antisolvent re-crystallization from its crystal form H. International journal of pharmaceutics. 2014;464(1-2):1-9.
25. Guan T, Miao Y, Xu L, Yang S, Wang J, He H, et al. Injectable nimodipine-loaded nanoliposomes: preparation, lyophilization and characteristics. International journal of pharmaceutics. 2011;410(1-2):180-7.

26. Prajapat MD, Butani SB, Gohel MC. Liquisolid: A promising technique to improve dissolution efficiency and bioavailability of poorly water soluble nimodipine. Journal of Drug Delivery Science and Technology. 2019;53:101135.
27. Ghareeb MM. Formulation and characterization of isradipine as oral nanoemulsion. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2020;29(1):143-53.
28. Alkufi HK, Kassab HJ. Formulation and evaluation of sustained release sumatriptan mucoadhesive intranasal in-situ gel. Iraqi J Pharm Sci. 2019;28(2):95-104.
29. Shelake S, Patil S, Patil S, Sangave P. Formulation and evaluation of fenofibrate-loaded nanoparticles by precipitation method. Indian J Pharm Sci. 2018;80(3):420-7.
30. Fayyad MS, Ghareeb MM, Kassab HJ. Study of Some Variables Affecting Product Properties of Felodipine Nano Precipitation. Int J Pharm Sci Rev Res. 2017;42:265-8.
31. Aleksa V. Raman stpectroscopy of vibrational and rotational relaxation of acetonitrile molecules dissolved in ionic liquids. Lithuanian Journal of Physics and Technical Sciences. 2007;47(4):435-41.
32. Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018;10(2):57.
33. Noor AH, Ghareeb MM. Formulation and evaluation of ondansetron HCl nanoparticles for transdermal delivery. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2020;29(2):70-9.
34. Rashid AM, Abd-Alhammid SN. Formulation and characterization of itraconazole as nanosuspension dosage form for enhancement of solubility. Iraqi Journal of Pharmaceutical Sciences. 2019;28(2):124-33.
35. Alhagiesa AW, Ghareeb MM. The Formulation and Characterization of Nimodipine Nanoparticles for the Enhancement of solubility and dissolution rate. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2021;30(2):143-52. Elsayed I, Abdelbary AA, Elshafeey AH. Nanosizing of a poorly soluble drug: technique optimization, factorial analysis, and pharmacokinetic study in healthy human volunteers. International journal of nanomedicine. 2014:2943-53
36. Mohsen K, Azzazy HM, Allam NK, Basalious EB. Intranasal lipid nanocapsules for systemic delivery of nimodipine into the brain: In vitro optimization and in vivo pharmacokinetic study. Materials Science and Engineering: C. 2020;116:111236.
37. Dawood NM, Abdul-Hammid S, Hussein A. Formulation and characterization of lafutidine nanosuspension for oral drug delivery system. Int J App Pharm. 2018;10(2):20-30.
38. Alobaidy RAR, Rajab NA. Preparation And In-Vitro Evaluation of Darifenacin Hbr as Nanoparticles Prepared as Nanosuspension. Clinical Schizophrenia and Related Psychoses. 2021;15(6).
39. Ghareeb MM, Neamah AJ. Formulation and characterization of nimodipine nanoemulsion as ampoule for oral route. International Journal of Pharmaceutical Sciences and Research. 2017;8(2):591.
40. Jakubowska E, Milanowski B, Lulek J. A systematic approach to the development of cilostazol nanosuspension by liquid antisolvent precipitation (LASP) and its combination with ultrasound. International Journal of Molecular Sciences. 2021;22(22):12406.
41. Kharazi M. Interfacial Tension Reduction with Ionic Liquid Surfactants. Available at SSRN 4158928. 2022.
42. He Z, Alexandridis P. Nanoparticles in ionic liquids: interactions and organization. Physical Chemistry Chemical Physics. 2015;17(28):18238-61.
43. Chen S, Zhang S, Liu X, Wang J, Wang J, Dong K, et al. Ionic liquid clusters: structure, formation mechanism, and effect on the behavior of ionic liquids. Physical Chemistry Chemical Physics. 2014;16(13):5893-906.
44. Hulsbosch J, De Vos DE, Binnemans K, Ameloot R. Biobased ionic liquids: solvents for a green processing industry? ACS Sustainable Chemistry & Engineering. 2016;4(6):2917-31.
45. Chen D, Zhuang X, Zhai J, Zheng Y, Lu H, Chen L. Preparation of highly sensitive Pt nanoparticles-carbon quantum dots/ionic liquid functionalized graphene oxide nanocomposites and application for H2O2 detection. Sensors and Actuators B: Chemical. 2018;255:1500-6.
46. Welton T. Ionic liquids: a brief history. Biophysical reviews. 2018;10(3):691-706.Shamma RN, Basha M. Soluplus®: a novel polymeric solubilizer for optimization of carvedilol solid dispersions: formulation design and effect of method of preparation. Powder technology. 2013;237:406-14.
47. Nasef AM, Gardouh AR, Ghorab MM. Polymeric nanoparticles: influence of polymer, surfactant and composition of manufacturing vehicle on particle size. World Journal of Pharmaceutical Sciences. 2015:2308-22.
48. Sanjula B, Shah FM, Javed A, Alka A. Effect of poloxamer 188 on lymphatic uptake of carvedilol-loaded solid lipid nanoparticles for

bioavailability enhancement. Journal of drug targeting. 2009;17(3):249-56.
49. Mahmood HS, Ghareeb MM, Hamzah ZO, Kadhim ZM. Formulation and characterization of Flurbiprofen nanoparticles loaded microneedles. Kerbala J Pharm Sci. 2021;1:90-107.
50. Ullah F, Iqbal Z, Khan A, Khan SA, Ahmad L, Alotaibi A, et al. Formulation Development and Characterization of pH Responsive Polymeric Nano-Pharmaceuticals for Targeted Delivery of Anti-Cancer Drug (Methotrexate). Frontiers in Pharmacology. 2022;13:911771.
51. Thakkar HP, Patel BV, Thakkar SP. Development and characterization of nanosuspensions of olmesartan medoxomil for bioavailability enhancement. Journal of Pharmacy and Bioallied Sciences. 2011;3(3):426.
52. Sahoo SS, Rao CB, Mehta AK. Formulation development and optimization of nanosuspension of simvastatin for improved solubility by nanomilling. J PharmaSciTech. 2015;5:78-86.
53. Abbas HK, Wais FMH, Abood AN. Preparation and evaluation of ketoprofen nanosuspension using solvent evaporation technique. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2017:41-55.
54. Hamed HE, Hussein AA. Preparation, in vitro and ex-vivo evaluation of mirtazapine nanosuspension and nanoparticles incorporated in orodispersible tablets. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2020;29(1):62-75.
55. Atyabi F, Mohammadi A, Dinarvand R. Preparation of nimodipine loaded microspheres: evaluation of parameters. 2005.
56. Kothawade S, Biyani S, Harne C, Wakure R, Bagul U, Gattani S. EFFECT OF CO-PROCESSED SUPERDISINTIGRANT ON NIMODIPINE ORODISPERSIBLE TABLETS USING 2 3 FACTORIAL DESIGN APPROACH.
57. AlSheyyab RY, Obaidat RM, Altall YR, Abuhuwaij RT, Ghanma RR, Ailabouni AS, et al. Solubility enhancement of nimodipine through preparation of Soluplus® dispersions. Journal of Applied Pharmaceutical Science. 2019;9(9):030-7.

استخدام المواد الخافضة للشد السطحي القائم على السوائل الأيونية في صياغة الجسيمات النانوية البوليمرية لعقار نيموديبين: نهج واعد لتحسين الأداء

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الخلاصة

تعرف الجسيمات النانوية البوليمرية على انها جزيئات صغيرة وصلبة وغروية يتراوح حجمها بين ١-١٠٠٠ نانومتر، ويتم تصنيعها من بوليمرات أو دهون أو معادن قابلة للتحلل ومتوافقة حيويًا. لقد اجتذبت الجسيمات النانوية البوليمرية اهتمامًا كبيرًا في مختلف المجالات، بما في ذلك التصوير والتشخيص، وتعتبر خيارات مثيرة للاهتمام لتوصيل الأدوية واستهدافها. يعد تخليق واستقرار الجسيمات النانوية أمرًا بالغ الأهمية لتطبيقها الناجح. حديثا حيث برزت المواد الخافضة للتوتر السطحي والقائمة على السوائل الأيونية (ILBS) كمذيبات ومثبتات واعدة نظرًا لصفاتها المميزة، مثل قلة التطاير ، والثبات الحراري العالي، والخصائص الفيزيائية والكيميائية القابلة للتعديل . وتتميز هذه المواد عن المواد الخافضة للتوتر السطحي الاعتيادية والمتوفرة تجاريًا بميزات رائعة مثل تركيز المذيلة الحرج المنخفض (CMC)، وقدراتها العالية في عملية الترطيب والرغوة ، بالإضافة إلى قدرة الذوبان القوية. يهدف العمل الحالي إلى صياغة جسيمات بوليمرية نانوية باستخدام الخافض للتوتر السطحي القائم على السوائل الأيونية (ILBS) ١-تتراديسيل-٣-ميثيل ميدازوليوم بروميد (TDMB) كمثبت لتحسين قابلية الذوبان الضعيفة ومعدل االنحلال لعقار النيموديبين باستخدام طريقة الترسيب النانوي حيث أظهرت النتائج أن معظم تركيبات النيمودبين البوليمرية النانوية المحضرة تمتلك أحجام جسيمات تقع ضمن النطاق النانوي. أظهرت الصيغة (F5)، المحضرة بالسائل الأيوني بنسبة ٠,٥٪ والمحضر باستخدام سرعة تبلغ ١٠٠٠ دورة في الدقيقة لها حجم (٦٤,٣٣ نانومتر) وPDI (٠,٠٦٧) علاوة على ذلك، فقد أظهر معدل الانحلال في محلول الفوسفات بفر pH 7.4 تحررا للدواء بنسبة ٩٦٪ خلال 20 دقائق، مقارنة بتحرر النيمودبين النقي ١٥,٤٪ ولنفس الوسط. لذلك وبصورة عامة فان تحضير العقار بشكل NID-PNP قد عزز و بشكل كبير قابلية الذوبان وسرعة انحلال NID ومنح قاعدة نانوية مشجعة تستخدم لتوصيل الأدوية الكارهة للماء.

الكلمات المفتاحية: مخفض الشد السطحي القائم على السوائل الايونية, جسيمات نانوية,الترسيب النانوي, نيمودبين

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