DOI : https://doi.org/10.31351/vol32issSuppl.pp235-243

Factors Affecting the Preparation of Cilnidipine Nanoparticles

Ruaa A. Alzalzalee*,[1] and Hanan J. Kassab [2]

#2nd Scientific Conference for Postgraduate Students Researches.
[1]Ministry of Health and Environment, Al-Kut Hospital, Directorate, Wassit, Iraq
[2]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Abstract

Cilnidipine is a dihydropyridine calcium channel blocker used to improve the neurological outcome following subarachnoid hemorrhage. It belongs to BCS class II drugs that have a low oral bioavailability of 13%, thus preparation as nanoparticles would be expected to improve bioavailability.

The aim of the study is to prepare Cilnidipine as nanoparticles using different carriers and co-carriers, concentrations, and types.

Cilnidipine nanoparticles were prepared by a solvent anti-solvent method using different carriers (Soloplus®, Poloxamer 188, PVA cold) with co-stabilizers (PEG200, glycerol) at different ratios.

Based on the obtained results, formula N4, which included Soloplus in a 5:5:1.19 weight ratio of drug to the polymer to co-stabilizer, exhibited a particle size of 88.89 nm when stirred at 1000 rpm with an injection speed of 1 ml/min. The polydispersity index (PDI) for this formula was measured at 0.2413. Furthermore, formula N4 demonstrated an impressive 92.2% drug content and an entrapment efficiency (EE) of 95.8%, giving 100% release in 30 min.

Keywords: Cilnidipine, Soloplus®, PVA cold, Poloxamers 188, PEG200, Glycerol.

العوامل المؤثرة على تحضير جزيئات سيلنيديبين النانوية

رؤى عبدالله الزلزلي*[1] و حنان جلال كساب[2]

#المؤتمر العلمي الثاني لطلبة الدراسات العليا
[1]مستشفى الكوت، دائره صحه واسط، واسط ،العراق.
[2]فرع الصيدلانيات ، كلية الصيدلة، جامعة بغداد، بغداد،العراق.

الخلاصه

يعتبر سيلنيديبين مانعًا لقنوات الكالسيوم من مشتقات الديهيدروبيريدين المستخدم لتحسين النتيجة العصبية بعد نزف تحت العنكبوتية. ينتمي إلى الفئة الثانية من العقاقير الفئوية التي تمتلك امتصاصًا فمويًا منخفضًا بنسبة ١٣٪، ومن المتوقع أن تعزز التحضيرات النانوية منه الامتصاص البيولوجي. تهدف الدراسة إلى تحضير سيلنيديبين كجزيئات نانوية باستخدام أنواع وأحمال مختلفة من الناقلات والمساعدين.

تم تحضير جزيئات سيلنيديبين النانوية باستخدام طريقة المذيب المضاد للمذيب باستخدام ناقلات مختلفة (سولوبلس، بولوكسامر ١٨٨، بيفا كولد) مع مثبطات مشتتة (PEG200، الجلسرين) بنسب مختلفة.

بناءً على النتائج المحصل عليها، فإن التركيبة N4 التي تحتوي على سولوبلس بنسبة وزنية ١:١:١ من الدواء إلى البوليمر إلى المثبط المشتت، أظهرت حجم جزيئات يبلغ ٨٨,٨٩ نانومتر عند التحريك بسرعة ١٠٠٠ دورة في الدقيقة بسرعة حقن تبلغ ١ مل/دقيقة. تم قياس مؤشر التشتت البوليمري (PDI) لهذه التركيبة عند ٠,٢٤١٣. علاوة على ذلك، أظهرت التركيبة N4 محتوى دوائيًا بنسبة ٩٢,٢٪ وكفاءة احتباس (EE) بنسبة ٩٥,٨٪، مما أدى إلى تحرر الدواء بنسبة ١٠٠٪ في ٣٠ دقيقه

الكلمات المفتاحية : سيلنيديبين، سولوبلس، بي في أيه الباردة، بولوكسامير ١٨٨، بي إي جي ٢٠٠، الجلسرين

Introduction

The pharmaceutical industry has faced significant hurdles in formulating drugs with low water solubility, which remains a critical issue in developing dosage forms with optimal efficacy. The solubility characteristics of a drug profoundly impact its dissolution rate, absorption, and bioavailability. The principal challenge encountered in utilizing Cilnidipine, a Class II drug exhibiting low water solubility and high permeability, pertains to its inadequate aqueous solubility. In recent times, nanotechnology has emerged as a highly promising and efficient approach to overcome such formulation difficulties and enable the effective delivery of lipophilic compounds. Nanoparticles small particle size results in a large surface area, which increases drug absorption, and bioavailability; therefore, the increased effectiveness of the drug is due to enhanced drug penetration through blood capillaries. It also offers the ability to safeguard drugs from degradation in the gastrointestinal tract and facilitate targeted drug delivery to various regions of the body. By passing the liver and delivering drugs that are not particularly water-soluble, this technology makes it possible to avoid first-pass metabolism. thereby enhancing the oral bioavailability of pharmaceuticals. This is due to their unique properties, including improved dissolution rate, improve stability in chemical reactions, and a significantly larger surface area to volume [(1,2)].

[1]Corresponding author E-mail: ruaa.abd2100m@copharm.uobaghdad.edu.iq
Received: 29/5 /2023
Accepted: 18/7 /2023

But the main setbacks are physical instability due to the small size of the particles, causing them to aggregate with each other [3].

Nanoparticles can be prepared using two methods: bottom-up and top-down. These methods are used to synthesize nanoparticles that yield more physically stable products [4]. Particle-size reduction is one of the most commonly used processes in the formulation development. Due to the size reduction, the surface area of the particles increases, allowing a greater interaction with the solvent and improving the dissolution. nanonization can affect both the solubility and the dissolution rate, The enhancement in oral bioavailability[5].

Cilnidipine is a novel and unique 1,4-dihydropyridine derivative calcium antagonist that inhibits both L-type and N-type voltage-dependent calcium channels. Studies have shown that once-daily administration of Cilnidipine is safer and more effective in decreasing blood pressure in essential hypertension without causing excessive blood pressure reduction or reflex tachycardia compared to similar administration of nifedipine [6], since it has slow-onset, and long-lasting vasodilation effect [7], despite having a half-life of 2.1-2.5 hours. Cilnidipine belongs to Class II of the Biopharmaceutics Classification System (BCS), due to its poor aqueous solubility, and poor dissolution, it has low oral bioavailability (6-30%) from an effective oral dose of 10mg [8,9]. Cilnidipine is a yellow, odorless crystalline powder with a pKa of 11.39, log P of 5.54, and melting point of approximately 110°C [10]

It is freely soluble in acetonitrile, sparingly soluble in methanol and in ethanol (99.5), and practically insoluble in water[9] ,and has very low crystalline solubility (0.03–0.06 μg/mL) and amorphous solubility (0.3–2.3 μg/mL) in buffer or other biologically relevant media at different pH values [11].

The objective of the study is to establish the most appropriate carrier type and co–stabilizer type and ratio, to produce Cilnidipine nanoparticles.

Materials and Methods

Materials

Cilnidipine (CLD) was supplied by Hyperchem. China. Poloxamer 188 (P188) was purchased from Eastman chemical company, USA. Sodium lauryl sulfate (SLS) was purchased from BDH Chemical Ltd, UK. Soloplus ® (SL)Basf SE, Germany. Methanol and Ethanol were purchased from Sigma-Aldrich, Germany. Glycerol (GL), PEG200 was purchased from BDH, England. Polyvinyl alcohol cold (PVA c) was purchased from Pancreac Quimica SA. Spain

Determination the saturated solubility of Cilnidipine

One approach for assessing the solubility of the substance entails agitating an excessive quantity of the drug in a 10 mL plastic tube within a water bath shaker for 48 hours. The drug powder underwent agitation with 10 mL of Buffer 6.8 containing 0.5% SLS in a 10 mL plastic tube. After 48 hours, the solution was filtered and analyzed using UV spectroscopy at its maximum wavelength. The solubility of the substance was then calculated based on the obtained results [12] .

Preparation of Cilnidipine nanoparticles

To prepare Cilnidipine nanoparticles, a bottom-up technique called the solvent anti-solvent method was used. The organic phase was prepared by dissolving 5 mg of the drug in 3 mL of Ethanol, while the aqueous phase was prepared by dissolving different types of carriers (Soloplus ®, Poloxamers188, and PVA Cold) in water (5mg of polymer + 10 mL of distilled water) with different co-stabilizers (PEG 200, glycerol)at different ratios 50% and 30% of the weight of the carrier, as seen in Table 1. The organic phase was then placed in a syringe with a needle gauge of 0.6 mm and placed on a syringe pump (Kelly Med, Germany). The organic phase was added drop by drop to the aqueous phase at a speed of 1 mL/min while being on a magnetic stirrer (Joan lab, China)at a speed of 1000 rpm (except N37) for 20 minutes to evaporate the organic solvent [12] .The prepared nanoparticle suspensions were covered and placed overnight in a cool place.

Characterization of Cilnidipine nanoparticles CLD NP

Determination of the particle size and polydispersity index of CLD NP

The size and distribution of Cilnidipine nanoparticles in all formulations were determined using dynamic light scattering (DLS) technique with a particle size analyzer nano Laser (Malvern zeta sizer, Ultra rate Company, USA) at room temperature. The measurements include particle size (PS) and polydispersity index (PDI) [13].

Factors affecting the particle size and PDI of prepared of CLD NP

Several factors influence the formulation of the drug.

The effect of carrier polymer type and concentration

In this study, various types of polymers, including PVA Cold, Poloxamers 188, and Soloplus®, were utilized at different ratios depicted in Table 1. The particle size and polydispersity index were measured and recorded.

The effect of co-stabilizer type and concentration

Table (1) was constructed to investigate the impact of incorporating co-stabilizers such as PEG200, and Glycerol at 50% and 30% w/w of the carrier weight on the particles size and PDI of the developed nanoparticles.

The effect of the stirring rate

The impact of stirring rate 500 rpm(N37) vs 1000 rpm (N4) on particle size was studied.

Initial selection of the optimized formula of CLD NP

The process of selecting the optimal nanoparticle formulas involved considering various factors such as particle size, polydispersity index (PDI). The top-performing formula, based on these criteria, was then chosen for further use.

Entrapment efficiency measurement

The percentage of drug that is enclosed within the nanoparticle's matrix is referred to as the entrapment efficiency (%EE). To determine the %EE, 2 mL of nanosuspension is placed in an Eppendorf tube. The tube was then centrifuged at 16000 rpm at 4°C for 20 minutes, after which 1mL of supernatant was taken and the concentration of free drug was measured using a UV spectrophotometer. The %EE was calculated using the following equation:[14].

$$\%EE = (C\ initial - C\ free)\ \times 100 \ldots\ldots (Eq\ 2)$$

Where; %EE = Percentage of entrapment efficiency.

$C_{initial}$ = Initial drug concentration or the theoretical drug content

C_{free} = Free drug concentration (unentrapped drug in the supernatant).

In-vitro dissolution of the selected Cilnidipine nanoparticles

The dissolution of the selected Cilnidipine nanoparticles was evaluated using the USP type II dissolution apparatus, where a dialysis membrane (MWCO 12000-14000 Da) was attached to the paddle and placed in 900 mL of phosphate buffer pH 6.8 containing 0.05% w/v SLS at 37°C and 50 rpm to maintain the sink condition. To assess the release of the drug, 5 mL of the sample was withdrawn and replaced with fresh buffer at regular intervals of 5, 10, 15, 20, 25, 30, 45, and 60 minutes. The amount of Cilnidipine released was measured spectrophotometrically at the maximum wavelength (241nm) of the drug in the buffer containing SLS. The cumulative percent release of the drug was calculated and plotted against time [12].

Selection of the optimum formula

Based on the drug content and %EE and in vitro release profile the optimum formula was selected

Lyophilization of the optimum formula

The selected formulas were mixed with 2% mannitol and subjected to dry ice for 1 hour then placed in a lyophilizer (Christ, Germany) for 24 h The collected lyophilized powder was stored in a cool place.

Table 1. Composition of Cilnidipine Loaded Nanoparticles CLD NP.

	CLD mg	SL mg	PVAc mg	P188 mg	PEG200 (µl)	GL (µl)	EtOH mL	DW mL	Speed rpm
N1	5	5			2.21 (50%)		3	10	1000
N2	5	5			1.32 (30%)		3	10	1000
N3	5	5				1.98(50%)	3	10	1000
N4	5	5				1.19 (30%)	3	10	1000
N5	5	10			4.43 (50%)		3	10	1000
N6	5	10			2.65 (30%)		3	10	1000
N7	5	10				3.96 (50%)	3	10	1000
N8	5	10				2.38 (30%)	3	10	1000
N9	5	20			8.86 (50%)		3	10	1000
N10	5	20			5.31 (30%)		3	10	1000
N11	5	20				7.93 (50%)	3	10	1000
N12	5	20				4.76 (30%)	3	10	1000
N13	5		5		2.21 (50%)		3	10	1000
N14	5		5		1.32 (30%)		3	10	1000
N15	5		5			1.98(50%)	3	10	1000
N16	5		5			1.19 (30%)	3	10	1000
N17	5		10		4.43 (50%)		3	10	1000
N18	5		10		2.65 (30%)		3	10	1000
N19	5		10			3.96 (50%)	3	10	1000
N20	5		10			2.38 (30%)	3	10	1000
N21	5		20		8.86 (50%)		3	10	1000
N22	5		20		5.31 (30%)		3	10	1000
N23	5		20			7.93 (50%)	3	10	1000
N24	5		20			4.76 (30%)	3	10	1000
N25	5			5	2.21 (50%)		3	10	1000
N26	5			5	1.32 (30%)		3	10	1000
N27	5			5		1.98(50%)	3	10	1000
N28	5			5		1.19 (30%)	3	10	1000

Continued table1.

	CLD mg	SL mg	PVAc mg	P188 mg	PEG200 (µl)	GL (µl)	EtOH mL	DW mL	Speed rpm
N29	5			10	4.43 (50%)		3	10	1000
N30	5			10	2.65 (30%)		3	10	1000
N31	5			10		3.96 (50%)	3	10	1000
N32	5			10		2.38 (30%)	3	10	1000
N33	5			20	8.86 (50%)		3	10	1000
N34	5			20	5.31 (30%)		3	10	1000
N35	5			20		7.93 (50%)	3	10	1000
N36	5			20		4.76 (30%)	3	10	1000
N37	5	5				1.19 (30%)	3	10	500

Characterization of Cilnidipine NPs optimized formula.

Determination of Fourier Transform Infrared Spectroscopy (FTIR)

The Fourier transform infrared (FTIR) spectra of Cilnidipine pure drug, and the nanosuspension of the selected formula were obtained using an FTIR spectrometer (FTIR-8300 Shimadzu, Japan), and then scanned in the wave numbers range from 4000 to 400 cm^{-1}. The FTIR analysis was conducted to detect any evidence of interaction or complexation between Cilnidipine and the excipients used in the nanoparticle formulation [15].

Differential Scanning Calorimetry (DSC)

This instrument is commonly used to assess the crystalline state of a drug, particularly when it is in the form of a lyophilized powder. It can also be utilized to examine the physical compatibility between the drug and excipients used in the formulation. In this study, non-hermetically sealed aluminum pans were used for all samples. A total of 8-10 mg of pure Cilnidipine, stabilizer, and lyophilized powder from selected formulations were added to the pan and heated at a rate of 10 ºC/min. The measurement was conducted under a flow of dry nitrogen gas at 100 ml/min, and the temperature was set between 30 to 300 ºC. An empty aluminum pan was used as a reference, and the measurement was performed using the(DSC-Shimadzu 60 plus, Japan)[16][17].

Atomic force microscope (AFM)

The best formulation liquid sample was adsorbed on the surface of silicon wafer and allowed to dry at room temperature. The sample was examined using multimode scanning probe microscope (NTMOT, NTEGRA Prima, Russia) in semi-conduct mode with a force constant range of 0.35–6.06 N/m and a resonating range of 47–150 kHz. The phase image was used to determine the morphology of Cilnidipine nanosuspension.[18] .

Results and Discussion

The solubility of Cilnidipine

Cilnidipine is practically insoluble in water with a mean solubility of 0.024583 ± **0.000556 mg/mL**, and in Buffer 6.8 is **0.011152±0.0002** However, the addition of a surfactant such as SLS has been observed to enhance its solubility [19][20].

The Particle size and polydispersity index of CLD nanoparticles suspension

The particle size measurement for all formulas was shown in the table (2).

Table 2. Particle size and PDI data of prepared Cilnidipine nanoparticle suspension

C:P	Formula	P.S nm	PDI	Formula	P.S nm	PDI	Formula	P.S nm	PDI
1:1	**N1**	149.1	0.3154	**N13**	1850	0.8083	**N25**	2626	1.695
	N2	145.9	0.1209	**N14**	267.6	0.242	**N26**	1706	1.35
	N3	143.9	0.0066	**N15**	355.1	0.556	**N27**	682.5	0.4508
	N4	88.89	0.2413	**N16**	103.7	0.05016	**N28**	79.02	0.707
1:2	**N5**	162	0.025	**N17**	3951	1.703	**N29**	3992	1.436
	N6	143.2	0.2	**N18**	567	0.474	**N30**	617.9	0.897
	N7	155.4	1.106	**N19**	1118	1.411	**N31**	510.5	0.377
	N8	38.92	0.404	**N20**	152.8	0.262	**N32**	401.4	0.545
1:4	**N9**	4416	0.808	**N21**	4672	0.459	**N33**	8123	1.819
	N10	378.5	0.3588	**N22**	1809	1.043	**N34**	3826	1.388
	N11	3468	0.928	**N23**	1543	1.35	**N35**	1361	0.23
	N12	194.4	0.518	**N24**	197.3	0.4103	**N36**	696.3	0.805
	N37	823.8	1.07						

The Effect of carrier type on particle size and PDI

Table (2) shows the particle size analysis results for all formulations. The polydispersity index is a crucial factor for understanding the distribution of nanoparticle sizes obtained from the particle size analyzer [(21)].

These carriers gave different particle sizes because of the lipophilicity, hydrophilicity and molecular weight, also physicochemical properties of the drug itself, to be completely enveloped by the carrier.

The molecular weight of the polymer or carrier and hydrophobic nature will greatly affect the formation of nanoparticles. The NP shows an increase in particle size when concentration of polymer increase meaning that aggregation and accumulation occur because of increased viscosity of solution.

Comparing different carriers SL gave the smaller particle size in contrast to PVA c and P188, Soloplus is amphipathic nature water soluble polymer solubilize poorly water-soluble materials also soothe nano suspension. Soloplus composed from polyvinyl caprolactam and polyvinyl acetate, which represent the hydrophobic moiety.

Soloplus has surface-active and wetting agent commonly used to provide equilibrium and provide thermodynamic barrier that prevent particle from agglomerate. Also, it has a lower viscosity score than other polymers [(22)].

Soloplus in a formulation that the best nano-size particles in comparison with others meaning that this polymer type is enough to envelop nanoparticles formed [(23),] as seen when comparing formula N1-N12(SL) vs. N13-N24 (PVC c) and N25-N36(P188).

When the drug: carrier polymer ratio is 1:1 in formulations N1- N4(SL), N13-N16 (PVA c), N25-N28(P188), the particle size was lower than higher ratios indicating that these formulations achieved better nano size reduction at this ratio and reached lower particle size than other ratios. This could be attributed to the amount of stabilizer being adequate to coat particles and maintain the stability of nanoparticles at their low size, as well as prevent aggregation.

However, as the drug: carrier ratio increased to 1:2, in the formulas N5-N8 (SL), N17-N20 (PVA c), N29- N32(P188), and at 1:4 ratio in N9-N12(SL), N21-N24(PVA c) and N33-N36(P188) larger particle size range was obtained. These results may be due to increased polymer concentration which deposit on the drug particles and the urge to increase particle size. This could be explained by an increase in the viscosity of the anti-solvent solution that might obstruct particle movement and cause more coating of drug particles. These results were in agreement with Dora, et al [(24)].

Effect of co-stabilizer type and concentration

In all the formulas using PEG as co-stabilizer at different concentration, particle size was larger Thus the higher viscosity of the co-stabilizer may prevent transportation from an organic solvent to an aqueous anti-solvent, resulting in poor stabilization and particle accumulation So, this combination is inappropriate for CLD nanoparticles. While when glycerol was used as co-stabilizer smaller particle size was obtained as seen in table 2

Glycerol is a hygroscopic compound with humectant properties and has a lower molecular weight than PEG 200. It has the ability to attract and retain water, which can help in the dispersion and reduction of particle size in certain applications. Glycerol can act as a solvent or dispersing agent, aiding in breaking down larger particles and promoting their dispersion into smaller sizes.

Effect of stirring speed on particle size

By using magnetic stirring nanoparticle measure at speed 500 revolution per minute at formula N37 at the ratio 1:1 of drug to polymer gave particle size 823.8 nm in comparison to same formula at speed 1000 rpm which gave particle size 88.89 nm as in table (2), meaning that at low speed, particle will aggregate when increase speed from 500 to 1000 rpm increase shear mixing and thus more rapid diffusion of the organic solvent into the water phase and evaporation. It will induce the fast nucleation of drug particles and produce very small drug particles [(25).]

Initial selection of the CLD NP formulas

The additives can help in achieving and maintaining a desired particle size in which SL was the best carrier and Glycerol was the best co-stabilizer : formulas containing SL(N4) when adding co stabilizer 30%glycerol in ratio 1:1 drug :stabilizer the particle size was 88.89nm with PDI 0.2413, and formula containing SL (N8) when adding co stabilizer 30%glycerol in ratio 1:2 drug :stabilizer the particle size is 38.92nm and PDI 0.404, as seen in table 3

Table 3. Particle size, PDI and %EE data of intial selection of Cilnidipine nanoparticle suspension

Formula	P.S nm	PDI	% EE
N4	88.89	0.2413	95.84667 ± 0.159478%
N8	38.92	0.404	65.74± 1.292904%

Entrapment efficiency measurement of CLD nanoparticles

The entrapment efficiency (%EE) of (N4) was better than N8; **95.84667% ± 0.159478 (N4) vs** 65.74%± 1.292904 (N8), due to the higher availability of surfactant of SL led to smaller micelles which can accommodate or encapsulate the drug [26] .

In vitro drug release for CLD nanoparticles

The release profile of N4(5mg CLD/10ml D.w) gave 100% release in 30 min while N8 gave 66% release. In contrast to the pure drug powder N* gave only 26% release at 30 min, as shown in figure (1). Although according to Noyes Whitney N8 excepted to have faster release because small particle size but opposite was obtained .

Fourier transform infrared spectroscopy of Cilindipine (FTIR)

The infrared (IR) spectrum was obtained in the range of 4000-400 cm^{-1}. The IR spectrum of pure Cilindipine powder was compared to a reference spectrum and found to be similar, as depicted in Figure 2 for the pure Cilnidipine and CLD NP.

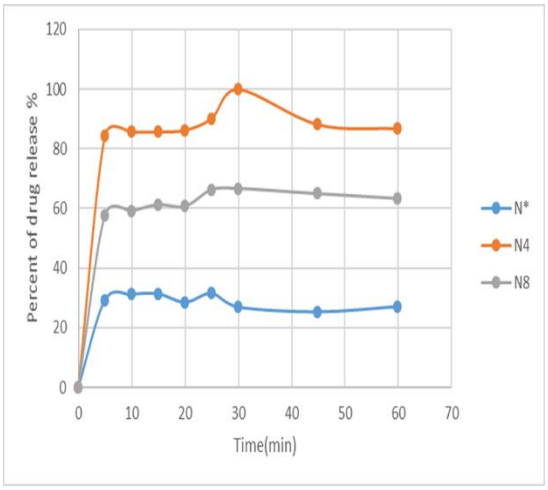

Figure 1.In vitro dissolution profile of CLD pure drug N* and prepared CLD NPs N4, N8

Table 3. FTIR peak for Cilindipine pure drug and reference drug

Functional Group	**CLD Nanoparticle (cm^{-1})**	**Pure drug [27] (cm^{-1})**
O-H stretch	3439	3379.29
C-H stretch	2958	2943.37
C=O stretch	1684	1697.36,1647.21
C=C stretch	1602	1600-1523
O-C-O	1117	1203.58
NO2	1462	1381..03

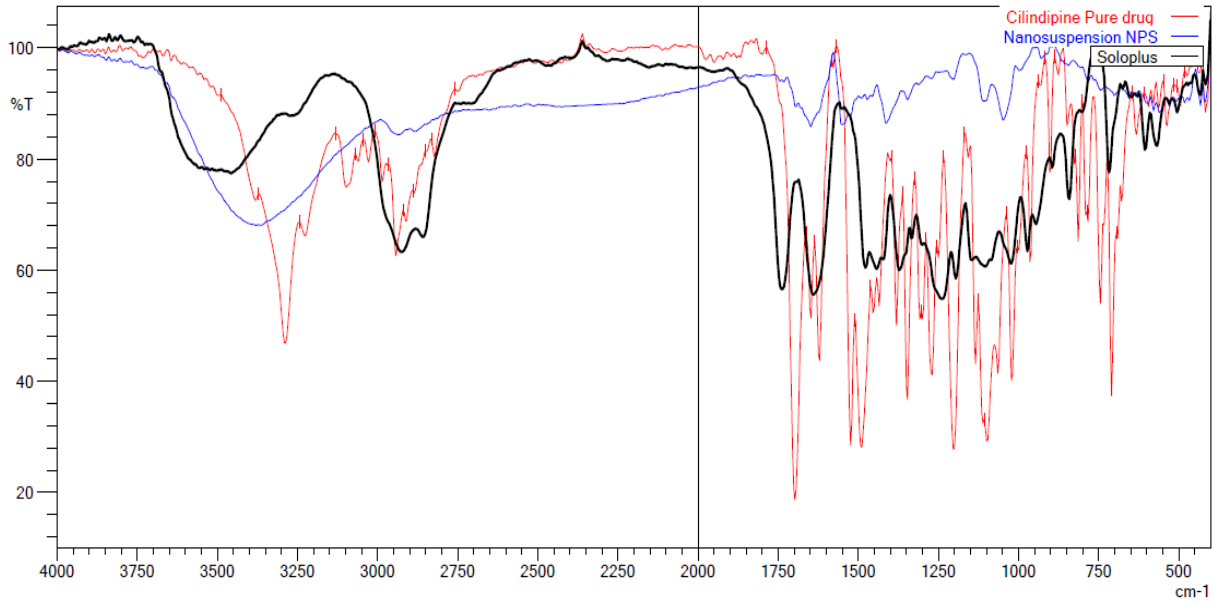

Figure 2. FTIR spectrum of comparison between CLD pure drug and Cilnidipine nanoparticle and Soloplus

Differential scanning calorimetry (DSC)

DSC of Cilindipine showed an endothermic peak corresponding to the temperature 115.02°C. Its sharp peak indicates that Cilindipine existed in a crystalline structure with high purity (28) , and complete amphorous nature of N4 as complete disappearance of the peaks as seen in figure 3

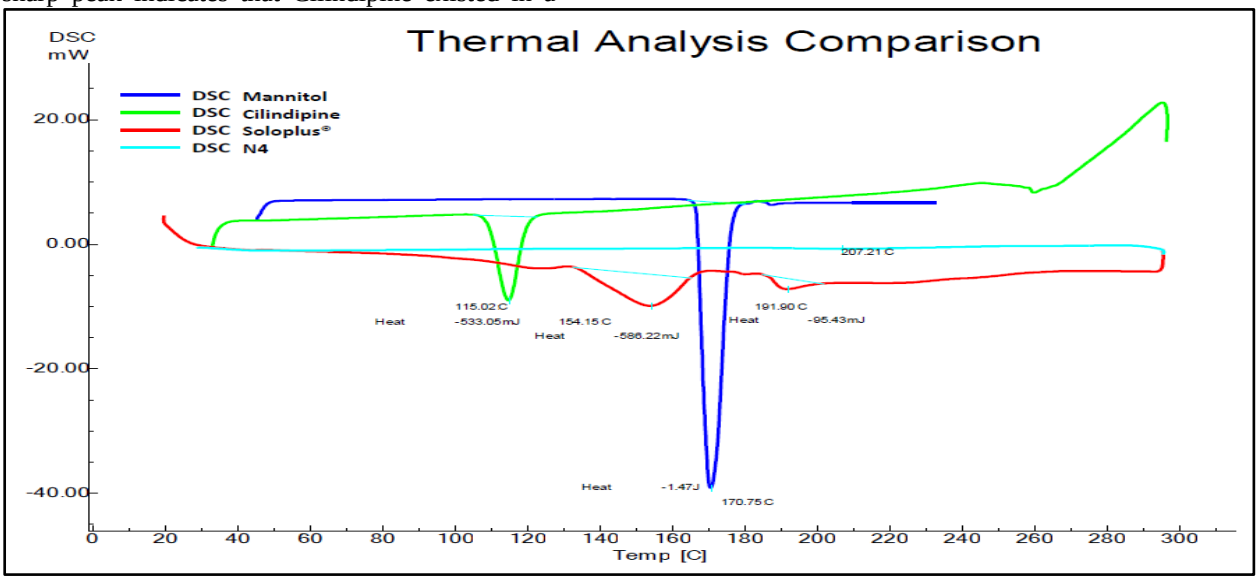

Figure3.Differential scanning calorimetry of Cilnidipine

Atomic force microscope (AFM)

AFM is capable of scanning and measures the properties and characteristics of the surfaces. With the high accuracy of the AFM, it is possible to determine the dimensions of nanoparticles with high reliability.

AFM allows the visualization of samples with design in three dimensions.

This method provides direct information about particle aggregation and therefore, a useful method to support the development and optimization of nanosuspension formulations. AFM done for optimum formula N4,its surface was found to be smooth with no aggregation which indicated particle size distribution and stability of formula. As shown in figure (4).

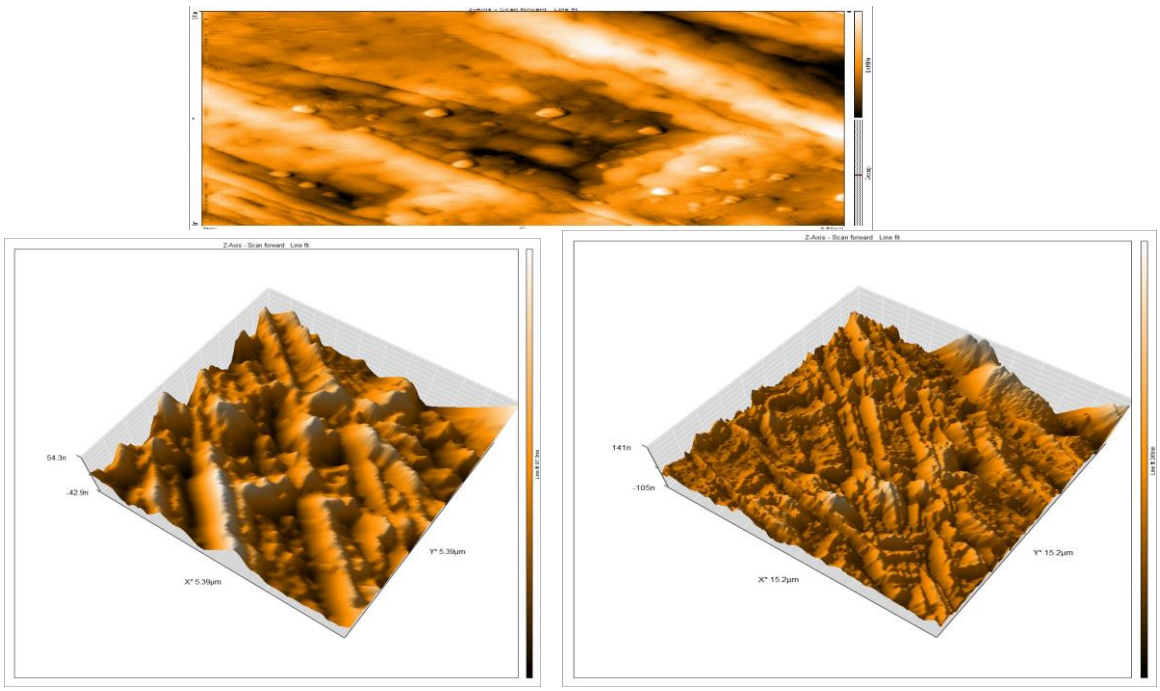

Figure 4. AFM of surface of the best formula N4 of CLD

Conclusions

Based on the obtained results of this study, it can be concluded that the solvent anti solvent precipitation method is the most effective process for the preparation of Cilnidipine nanoparticles, and the best polymer was Soloplus® at 1:1 Drug : carrier weight ratio which gave the smallest particle size and agreeable PDI and the best stabilizer was glycerol at 30% of the carrier weight which gave good EE%. The FTIR study revealed no chemical interaction between Cilnidipine, and the polymer used.

Funding

This research did not receive any specific fund.

Ethics Statements

This work didn't require an ethical approval ,no animal or human was involved.

Conflict of interest:

The authors declare that there is no conflict of interest

Author contributions

Ruaa A. Alzalzalee and Hanan J. Kassab conceived and designed the study. Ruaa A. Alzalzalee performed the data collection. Ruaa A. Alzalzalee and Hanan J. Kassab performed data analysis and interpretation of the results. Ruaa A. Alzalzalee wrote the initial draft of the manuscript. Ruaa A. Alzalzalee and Hanan J. Kassab wrote and revised the full paper. All authors have read and agreed to the published version of the manuscript

Reference

1. Saadh MJ, Jadullah RK. Nanotechnology in Drug Delivery. Pharmacologyonline. 2021;3:1129–35.
2. Konwar R, Ahmed AB. Nanoparticle: an Overview of Preparation, Characterization and Application. Int Res J Pharm. 2016;4(4):47–57.
3. Jafari M, Yousefi M, Baniyaghoub S. Original paper Green Synthesis and Characterization of AgCl Nanoparticle Using Onopordum acanthium Extract. 2022;1(3):154–8.
4. Shid RL, Dhole SN, Kulkarni N, Shid SL. Nanosuspension: A review. Int J Pharm Sci Rev Res. 2013;22(1):98–106.
5. Ainurofiq, A.; Putro, D.S.; Ramadhani, D.A.; Putra, G.M.; Santo, L.D.D. A review on solubility enhancement methods for poorly water-soluble drugs. *J. Rep. Pharm. Sci.* **2021**, *10*, 137–147.
6. Hoshide S, Kario K, Ishikawa J, Eguchi K, Shimada K. Comparison of the Effects of Cilnidipine and Amlodipine on Ambulatory Blood Pressure. 2005;28(12):1003–8.
7. Kokilambigai KS, Lakshmi KS. Innovare Academic Sciences Review Article Analytical Methodologies For Determination Of Cilnidipine : An Overview. 2014;6(6).
8. Mishra R, Mir SR, Amin S. Polymeric Nanoparticles For Improved Bioavailability of Cilnidipine. 2017;9(4).
9. Ministerial W, No N, Paragraph P, Law A, No L. The Ministry of Health , Labour and. Powder Diffr. 2007;2007(285):1–1654.
10. Upadhay M. Preparation and evaluation of cilnidipine microemulsion. In: Journal of Pharmacy and Bioallied Sciences. 2012. p. 114–5.

Liu Q, Mai Y, Gu X, Zhao Y, Di X, Ma X, Yang J. A wet-milling method for the preparation of cilnidipine nanosuspension with enhanced dissolution and oral bioavailability. Journal of Drug Delivery Science and Technology. 2020 Feb 1;55:101371.

11. Nagar SK, Soniwala MM. Optimization of Cilnidipine Nanosuspension Using a Center Composite Design. Int J Pharm Sci Drug Res. 2017;9(04):149–59.
12. Sh H, Rajab NA. Polymeric nanoparticle of Ebastine: Formulation, Characterization and in vitro Evaluation. Journal of Complementary Medicine Research. 2023 Feb 10;14(1):16-.
13. Jassim ZE, Hussein AA. Formulation and evaluation of clopidogrel tablet incorporating drug nanoparticles. IJPS. 2014:838-51.
14. Hazzaa SA, Abd-Alhameed SN. Formulation and Evaluation of Optimized Zaltoprofen Lyophilized Tablets by Zydis Technique. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2017 Jul 12;26(1):40-9.
15. Hussein ZA, Rajab NA. Formulation and characterization of bromocriptine mesylate as liquid self-nano emulsifying drug delivery system. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2018 Dec 6:93-101.
16. Ghareeb MM. Formulation and characterization of isradipine as oral nanoemulsion. Iraqi Journal of Pharmaceutical Sciences (P-ISSN 1683-3597 E-ISSN 2521-3512). 2020 Jun 25;29(1):143-53.
17. Rajab NA, Jassem NA. A Design and In vitro Evaluation of Azilsartan Medoxomil as A Self-Dispersible Dry Nanosuspension. Der Pharm Sin. 2018;9(1):12-32.
18. Rao S, Song Y, Peddie F, Evans AM. Particle size reduction to the nanometer range: a promising approach to improve buccal absorption of poorly water-soluble drugs. Int J Nanomedicine. 2011;6:1245–51.
19. Daebis N, Abdallah OY, El-Massik M, Abdelkader H. Formulation and Characterization of Itraconazole Oral Nanosuspension: Methyl Cellulose as Promising Stabilizer. J Drug Dev Clin Trials. 2015;1(1):1–8.
20. Jassem NA, Rajab NA. Formulation and in vitro

evaluation of azilsartan medoxomil nanosuspension. Int J Pharm Pharm Sci. 2017;9(7):110.

21. Kim, M. S., Song, H. S., Park, H. J. and Hwang, S. J. Effect of solvent type on the nanoparticle formation of atorvastatin calcium by the supercritical antisolvent process. Chemical and Pharmaceutical Bulletin,2012; 60(4).

22. Alwan, R. M. and Rajab, N. A. Nanosuspensions of Selexipag: Formulation, Characterization, and in vitro Evaluation. Iraqi Journal of Pharmaceutical Sciences,2021; 30(1).

23. Dora CP, Singh SK, Datusalia AK, Deep A. Development and characterization of nanoparticles of glibenclamide by solvent displacement method. 2010; Acta Poloniae Pharmaceutica -Drug Research.2010; 67(3): 283-290.

24. 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.

25. Rashid AM, Abd-Alhammid SN. Formulation and characterization of itraconazole as nanosuspension dosage form for enhancement of solubility. Iraqi J Pharm Sci. 2019;28(2):124–33.

26. Shaikh F, Patel M, Patel V, Patel A, Shinde G, Shelke S, Pathan I. Formulation and optimization of Cilnidipine loaded nanosuspension for the enhancement of solubility, dissolution and bioavailability. Journal of Drug Delivery

27. Prajapati ST, Maheshwari PD, Patel CN. Formulation and Evaluation of Orodispersible Tablets of Cilnidipine By Spray Drying Technique. Shailesh al World J Pharm Pharm Sci. 2015;4(05):1526–39.