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Cilnidipine Nanocrystals, Formulation and Evaluation for Optimization of Solubility and Dissolution Rate

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Abstract

The aim of this study is to formulate and evaluate cilnidipine nanocrystals (CLD NCs) using solvent anti-solvent technology. Cilnidipine has a very low solubility (BCS Class-II drug low solubility high permeability), cilnidipine (CLD) as a fourth generation Ca^{+2} channel blockers and extremely low medication compliance, it has been used to treat hypertension and hypertensive associated vascular disorders, cilnidipine can be prepared as nanocrystals (NCs) using solvent-anti-solvent technique with ratio 1:10 as solvent to anti solvent volume, which can improve the solubility and bioavailability. The prepared CLD NCs were evaluated for particle size, polydispersity index (PDI), dissolution study and differential scanning calorimetry (DSC). Two different stabilizers (poloxamer 188 and Tween20) were utilized to prepare nine formulas with different drug to stabilizer ratio as (1:0.25, 1:0.5 and 1:1), F4 was the smallest mean size 152 nm ,PDI (0.161)and the saturated solubility was increased about ten folds, this formula was subjected for freeze drying by adding 3 % mannitol as cryoprotectant .A complete dissolution of F4 was established in about 20 minutes which confer the DSC and PXRD results in conversion from crystalline into amorphous state .It can conclude that tween 20 was a best stabilizer to be used and solvent-anti-solvent technique was a successful method in preparation of nanocrystals of CLD .

Keywords: Cilnidipine, Nanocrystals, Solvent/ Anti- Solvent, Tween20

تصييغ وتقييم بلورات الساندبين النانوية لتحسين الذوبانية ومعدل الاذابة

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#المؤتمر العلمي الثاني لطلبة الدراسات العليا
١ وزارة الصحة والبيئة ، دائرة صحة الانبار ، الانبار ، العراق
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الخلاصة

تم استخدام السلندبين وتعد من حاصرات قنوات الكالسيوم من الجيل الرابع لعلاج ارتفاع ضغط الدم واضطرابات الأوعية الدموية المرتبطة بارتفاع ضغط الدم ، حيث يمتاز بقابلية ذوبان منخفضة جدًا (عقار BCS Class-II قابلية منخفضة للذوبان عالية النفاذية) والامتثال للدواء دائمًا ضعيف جدًا لذا يمكن صياغة السلندبين على شكل بلورات نانوية باستخدام تقنية المذيب / المذيب المضادة التي يمكن أن تحسن قابلية الذوبان والتوافر البيولوجي. تم استخدام اثنين من المثبتات المختلفة (poloxamer 188 و Tween20) تم اعداد تسعة صيغ بنسب مختلفة ١: ٠,٢٥ ، ١: ٠,٥ و ١: ١ . حيث تم دراسة وتقييم عوامل الصياغة التي قد تؤثر على حجم الجسيمات ومؤشر التشتت المتعدد PDI.

تم تقييم حجم الجسيمات ودراسة الذوبانية لبلورات السلندبين المحضرة ، حيث كانت F4 أصغر حجم ١٥٢ نانومتر ، (0.161) PDI ,حيث زادت قابلية الذوبان المشبعة حوالي سبعةعشرة ضعفا ، هذه الصيغة خضعت للتجفيف بالتجميد مع إضافة ٣٪ وزن من المانيتول كواقي للتجميد. تم تحقيق الذوبان الكامل في حوالي ٢٠ دقيقة. واجريت عليها اختبارات اخرى مثل مسعر المسح التباييني، واختبار حيود المسحوق. وتؤكد نتائج مسعر المسح التباييني، واختبار حيود المسحوق ان هناك دليل على التحول من الحالة البلورية إلى حالة غير متبلورة. ويمكن أن نستنتج أن تقنية المذيبات المضادة للمذيبات كانت مفيدة في تحضير معلق البلورات النانوية.

كلمات مفتاحية: السلندبين ، الكرستالات النانوية،المذيب / مضاد المذيب،Twen20

Introduction

Hypertension is the most frequent modifiable risk factor for death and disability including stroke، heart failure, chronic kidney disease CDK, accelerated coronary and systemic atherosclerosis [(1)]. Blood pressure can be corrected with antihypertensive medications. The incidence of cardiovascular disease and target organ damage were minimized by administration of calcium channel blockers such as cilnidipine which is a calcium channel blocker that display a reduction in cardiovascular outcomes [(2)]. Cilnidipine is a BCS Class-II substance with a very low solubility and a high permeability [(3)], and due to drastically insufficient medical care, cilnidipine can be manufactured as nanoparticles in the form of orodispersible Tablets, which can improve the solubility and bioavailability [(4)]. Cilnidipine (CLD)

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nanocrystals were prepared by the precipitation technique which is also called solvent-anti-solvent method all these terms referred to bottom-up technology. The term "Bottom-up technology" means that one starts from the molecular level, and goes via molecular association to the formation of a solid particle. Precipitation is a classical technique in pharmaceutical chemistry and technology. The simple, low-cost equipment and higher saturation solubility is the advantage for precipitation compared to other methods of nanosuspension preparation. The drug needs to be soluble in at least one solvent (thus excluding all new drugs that are simultaneously poorly soluble in aqueous and in organic media), the solvent needs to be miscible with at least one non-solvent, solvent residues need to be removed, thus increasing production costs and it is a little bit tricky to preserve the particle character (i.e. size, especially the amorphous fraction) all these may consider as disadvantages for the precipitation method. In general, it is recommended that a second consecutive process has to be performed for particle preservation that is spraydrying or lyophilisation [(5)]. Cilnidipine was dissolved in a methanol (solvent) 5 ml at room temperature; organic solution was dropped slowly by means of a syringe onto 50 ml of DW (anti-solvent) containing surfactant and subsequently stirred at agitation speed of about 1000 round per minute (rpm) on magnetic stirrer for 1 hour to allow the volatile solvent (methanol)to evaporate[(6)]. Pharmaceutical applications have been reported for nanoparticle engineering methods that accelerate drug solubility and dissolution rates [(7)]. For instance, drug surface area has been increased through the use of nanosizing methods to speed up drug dissolution and increase the oral bioavailability of drugs that are not easily soluble in water. A huge surface area allows for increased contact with the solvent which in turn increasing solubility. Nanoparticles are solid particulates or particulate dispersions that range in size from 10 to 1000 nm [(8)].

Stabilization of nanoparticles is essential to ensuring their efficacy. A huge surface energy is produced by the significant increase in surface area, which is unfavorable thermodynamically. In order to decrease excess energy on the surface, particle agglomeration is accelerated by the rise in surface energy. The long-term effectiveness of nanoparticle formulation tends to be affected via agglomeration [(**9**)].

Nanoparticles (NCs) have been stabilized by polymers comprising Poloxamers® (338), Hydroxy propyl methyl cellulose HPMC (E5), poly vinyl pyrolidone PVP (K25), and others through surface binding and the steric mass of their three-dimensional structure [(10)].

Nanosuspensions are submicron colloidal dispersions of pure drug particles in an outer liquid phase. Nanoparticle engineering enables poorly soluble drugs to be formulated as nanosuspensions either alone or with a combination of pharmaceutical excipients. Precipitation, high-pressure homogenization, and pearl milling, either in water or in mixtures of water and water-miscible liquids or in non-aqueous media, are the current nanosuspension engineering methods used. The bioavailability of active pharmaceutical ingredient (API) is closely correlated with its solubility and dissolution [(11)].

The drugs administration by oral route has wide acceptance up to 50-60% of total dosage forms [(12)]. The acceptability of the drugs given via oral were a consequence of its simplicity in administration, dose accuracy, self-medication, better patient compliance and ease in manufacturing so that the Tablets are the most popular dosage type, [(13,14)]. Cilnidipine with half-life (2.1-2.5 h) is a brand-new and distinctive 1, 4-dihydropyridine derivative calcium antagonist that has strong inhibiting effects on both L- and N-type voltage-dependent calcium channels. The N-type voltage-dependent calcium channel controls norepinephrine release from sympathetic nerve terminals and is crucial for sympathetic neurotransmission. CLD (pKa = 11.39, ClogP=5.54) belongs to class II of the Biopharmaceutics Classification System (BCS) [(15)]. It is a yellow, odorless crystalline powder with a recommended dose of 10 mg orally; it has insufficient dissolution and restricted oral bioavailability owing to its low aqueous solubility [(16, 17)]. According to studies, once-daily administration of cilnidipine reduced essential hypertension's blood pressure safely and more effectively than once-daily administration of nifedipine did without causing an abnormal drop in blood pressure or reflex tachycardia [(18)].

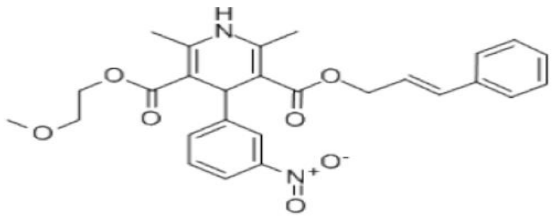

Figure 1. Chemical structure of cilnidipine [(19)]

Materials and Methods

Cilnidipine powder (CLD), sodium poloxamer (188) and Tween20 were purchase from Hyperchem Chemical Co., Ltd (China). All other chemicals and solvent were of analytical reagent grade.

Preparation of Cilnidipine Nanocrystals

A total of five milliliters of methanol, an organic liquid, were used to dissolve ten milligrams of cilnidipine. On the other hand, the anti-solvent system is composed of 50 mL of deionized water that has stabilizers (poloxamer 188 and Tween20) in a ratio of 1:10. The next stage is to gently add an organic solvent to an aqueous solution using a syringe pump, while mechanical agitation is carried

out at a speed of 1000 rpm with the help of a hotplate magnetic stirrer at room temperature [20].After that stirring the sample slowly for an hour at a temperature of 25 °C to obtain the desired results, the organic liquid was evaporated [21]. Each of samples was treated with an ultrasonic probe with power input 75 watt for 6 minutes (time on 2minutes and 1minute off). The probe (tip diameter, 8 mm) was immersed about 10-12 mm in the liquid by which waves was travelled downwards and reflected upwards, during ultra-sonication the temperature was also controlled by using ice water bath. Change in solvent and anti-solvent ratio was completed to create the formulations for the various CLD nanocrystal preparations shown in Table (1).

Table 1. CLD Nanocrystals Prepared Formulas

Formula no.	CLD mg	Poloxamer 188 mg	Tween20 mg	DW ml	Methanol ml
1	10	2.5		50	5
2	10	5		50	5
3	10	10		50	5
4	10		2.5	50	5
5	10		5	50	5
6	10		10	50	5
7	10		2.5	5	5
8	10		2.5	30	5
9	10		2.5	60	5

Characterization of the prepared nanocrystals: Polydispersity Index (PDI) and Particle Size

Malvern Mastersizer 2000 MS was used to measure or analyze the particle size and polydispersity index. (Worcestershire, Great Britain). Which involves measuring the amount of light that is dynamically dispersed by the sample's molecules as a function of time, at a scattering angle of 90 degrees, and at a constant temperature of 25 °C. A brief ultrasonication is sometimes used in conjunction with made diluted suspensions to help separate loosely held agglomerates, samples of 2 or 3 mL nanosuspension were selected for computation of particle size and polydispersity index [22].

Nanosuspension freeze-drying

The best formula F4 was frozen and then dried to create dry powder for subsequent testing. Cryoprotectant mannitol used at 3% w/v. A dry powder was created for testing by freeze drying about 100 mL of the optimized selected formula. For 24 hours, four containers were frozen at -60°C in a deep freezer. Four flasks, each holding 100mL of nanosuspension, were attached to the vacuum port of the apparatus after the frozen flasks, and the instrument was operated until dry powder was produced. Solvent sublimation from frozen samples required 48 hours [23].

Evaluation of lyophilized powder
Lyophilized CLD powder and pure CLD's saturation solubility

The saturation solubility of the pure drug and lyophilized formula were examined using three dissolving solvents: water, 0.1 N HCl with pH 1.2, and phosphate buffer pH 6.8. Each test tube holding the aforementioned solvents received an excess amount of the drug, which then added. The test tubes were then shaken for at least 48 hours at 25 °C in a water bath shaker. For every sample, clean with a filter syringe after which read. At 6000 rpm for 15 minutes, sample test containers were centrifuged. To calculate how much drug was dissolved in a particular volume of each dissolving medium, the absorbance of the supernatant layer of specimen in the container was measured spectrophotometrically by UV–spectrophotometer and a calibration curve was done [24]. The solubility factor (Sf) was then calculated using the equation.

$$Sf = Sncs/Sw \text{- - - - - - - - } 1$$

Where:
Sf=Solubility factor
Sncs=Solubility of CLD nanocrystals
Sw=Solubility of CLD pure drug
The in-vitro dissolution profile of lyophilized cilnidipine nanocrystals

Utilizing type II dissolving test equipment, an in-vitro dissolution test of lyophilized cilnidipine powder was performed, 900 ml of phosphate buffer pH 6.8 as dissolution medium was placed on and rotated at 100 rpm at 37 °C with precisely weighed lyophilized powder equal to 10 mg of Cilnidipine. To maintain the constant volume, an aliquot of 5-milliliter samples was taken out at regular intervals (1, 2, 5, 10, 15, 20, 30, 60, 90 and 120minutes) and replenished again with new dissolution medium. After that, samples were filtered through a 0.45 µm filter syringe and spectrophotometrically measured using a UV spectrometer and the experiment was repeated in triplicate. The same aforementioned steps were applied, whereas pH 1.2 buffer as dissolution media was utilized instead. The results acquired from the dissolution studies were statistically validated using a similarity factor (f2). The f2 was used to consider similar dissolution profiles (equation No.2 below).

$$f2 = 50 \cdot \log\left\{100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5}\right\} \; 2$$

Where (n) is the number of dissolution time points. (Rt), (Tt) are the reference and test dissolution

values at time t respectively. The two dissolution profiles consider similar when f2 values greater than 50 (50– 100); otherwise, the profiles are not similar [25].

Impact of changing the solvent/antisolvent mixture on the particle size of cilnidipine nanocrystals

Evaluate the impact of changing in the proportion of solvents to anti-solvents in nanocrystals, where the anti-solvent (deionized water) the quantity is changed from 50 mL to 5,30and 60mL. Formulas (F7-F9) were used [26].

Differential scanning calorimetry (DSC) study

Evaluating the crystalline form of the drug, particularly when converted to nanocrystals, and determining the compatibility between CLD and excipients DSC was used. Precise weighed samples (5 mg) were put in non-hermetic aluminum pans, and the temperature was increased at a rate of 20 °C/minute against an empty aluminum pan as a reference over the range of 50 °C to 300 °C [27].

X-ray powder diffraction (XRPD) analysis

The XRD-6000, Shimadzu-Japan was used to examine the patterns of pure cilnidipine and its nanocrystal form. 5-80 degrees are covered by the constant scan. Operating voltage was set at 40 (kV), current was set at 30 mA, scan step size was set at 0.050° (2θ), and scan step duration was set at 60 sec. [28].

Results and Discussion

Examination of the prepared Cilnidipine NCs

Particle size and polydispersity index PDI evaluation

The particle size Malvern Panalytical was used to examine all of the CLD NCs samples, and the Table 2 below shows the results of that analysis. A parameter to describe the particle size distribution of nanoparticles acquired from a particle analyzer is the polydispersity index. An indicator of the long-term stability of nanosuspension, the PDI measures the width, spread, or variance within the particle size distribution. Higher PDI values denote a broader particle size dispersing and the sample's polydisperse nature, whereas monodisperse samples have a smaller PDI value, 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) [29], Tween 20 was adsorbed on its positions on the outer layer of newly formed drug particles. As a result, it inhibits subsequent growth by inhibiting the inclusion of drug molecules from solution into crystal lattices, resulted in the production of nanosized particles ranged from (152,292 and 311 nm), F4, F5 and F6 respectively as shown below in Table 2 and Figure 3 with optimum particle size in F4 as shown in Figure 2.

Table 2. The Particle Size and PDI of the Prepared Cilnidipine NCs N=3

Formula name	Particle size (nm)±SD	PDI±SD
F1	423±3	0.853± 0.030
F2	750±2	1.226±0.15
F3	992±5	1.477±0.27
F4	152±1	0.161±0.003
F5	292.6±2.8	0.294±0.02
F6	311±3.3	0.257±0.006
F7	276±2	0.114±0.014
F8	198±1.5	0.189±0.004
F9	242±4	0.321±0.009

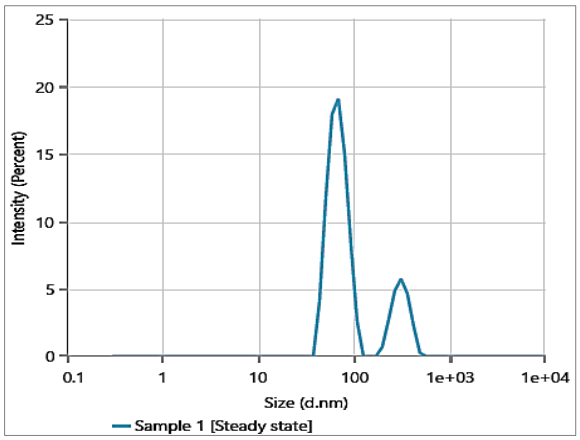

Figure 2. Chart of Particle Size of Selected Formula F4 CLD NCs

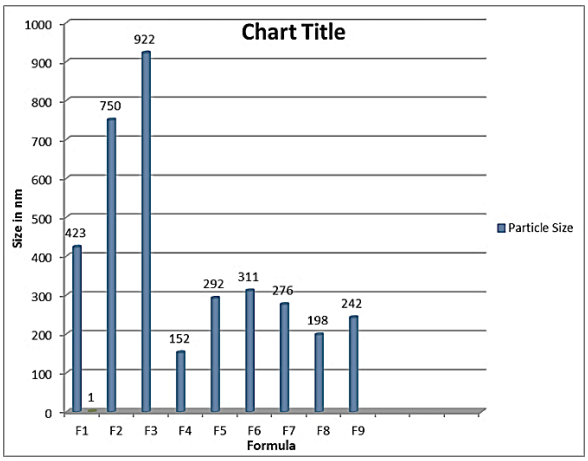

Figure 3. Represent Particle sizes of CLD NCs with Different Polymers

Saturation solubility of pure drug and lyophilized powder

Identifying the purified CLD and cilnidipine NCs F4 saturation solubility Pure CLD and CLD NCs F4 were investigated for solubility in D.W., 0.1 N HCl (pH 1.2), and (pH 6.8). As illustrated by Table (3) and Figure 4, CLD NCs' F4 solubility was raised clearly. According to the Ostwald-Freundlich equation, the saturation solubility of CLD rises as

particle size approaches the nanoscale region, which accounts for the enhanced solubility.

However, according to Ostwald–Freundlich equation (Eq.3, in apposition to microparticles, the saturation solubility and equilibrium solubility of spherical particles with size of smaller than 1000 nm can influence the particle size.

$$Log\frac{C_s}{C_\infty}=\frac{2\sigma v}{2.33RT_{\rho r}} \qquad 3$$

That Cs is solubility,

C∞ is solubility of the solid which consist of large particles,

σ is interfacial tension substance

ρ is the solid density.

Also, the formation of nanosuspensions not only increases the surface area but also enhances the saturation solubility of the solute in medium, resulting in better bioavailability [30].

When compared to bulk CLD, the saturation solubility of CLD NCs F4 as shown in Figure 4 was improved, which was primarily due to the smaller particle size of CLD NCs F4 and the solubilization impact of Tween20.The disruption of the drug microparticles' ideal structure into nanoparticles is another reason for the solubility improvement. High interfacial tension energy is produced by this disturbance, which improves the solubility of nanoparticles [31, 32].

Table 3. Saturated Solubility of Pure CLD and CLD NCs at Different Media N=3

Media	Saturated solubility of pure CLD (µg/ml)	Saturated solubility of CLD NCs F4 (µg/ml)	Solubility Factor Sf
DW	0.334±0.07	11.192 ± 0.4	33.5
Buffer 6.8	1.098±0.12	19.558 ± 0.7	17.8
Buffer 1.2	0.535±0.11	5.23±0.16	9.7

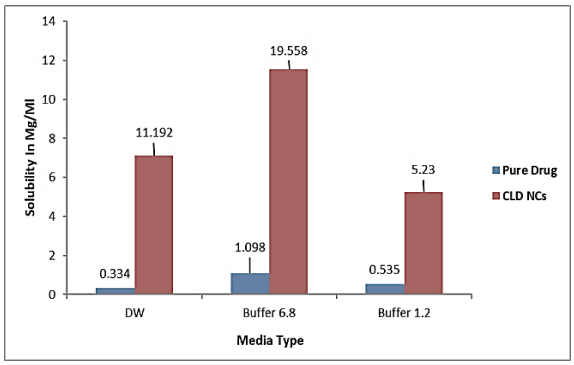

Figure 4. Represent Solubility of CLD NCs F4 and Pure CLD in µg/ml in Three Different media.

In vitro dissolution study

The dissolution profile in phosphate buffer 6.8 for pure CLD shows 22% of drug released compared with 11.8% of drug released in pH 1.2 buffer, while 100% of CLD NCs F4 was released at 20 minutes in phosphate buffer 6.8 compared with 29% released in pH 1.2 buffer as shown in Figure 5 and 6 respectively; it's conceivable that excipients (tween 20) had improved particle wettability and dissolution rate, were present. The CLD-NCs had significantly higher disintegration rates. In the nanosuspension, more than 66% of the substance was released within 5 minutes, and approximately 85% was released after 15 minutes, as depicted in Figure 5. It was concluded as a result that the change in the dissolution rate of CLD-NCs was mainly caused by the increased surface area of CLD nanocrystals and the decrease in particle size to the nanometer range. As an amorphous drug with high internal energy and molecular motion is advantageous in increasing the dissolution rate, the existence of amorphous CLD also played a significant role in raising dissolution [33, 34, 35]. According to statistical analysis by similarity factor (f2), it was shown that CLD NCs F4 (*f*2 =7.3) with better release profile than pure CLD.

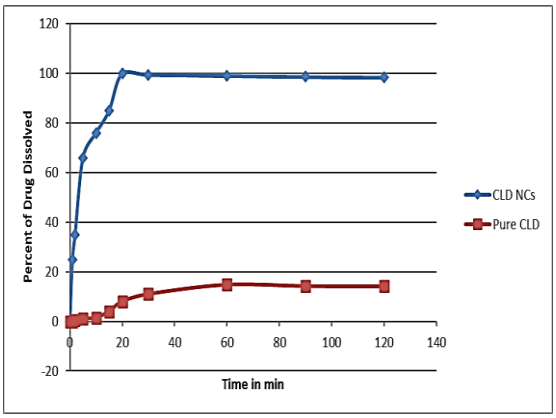

Figure 5. In-Vitro Dissolution Profile of Prepared CLD NCs F4 and Pure CLD in Phosphate Buffer 6.8

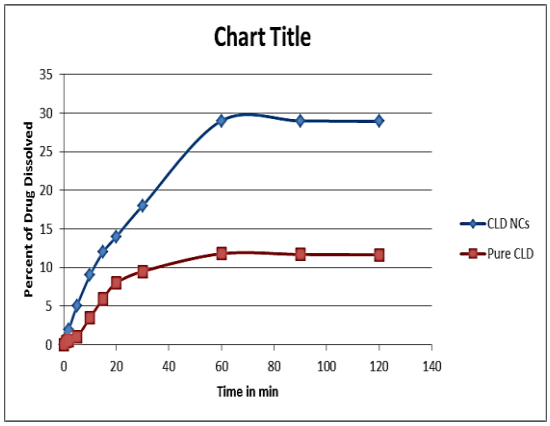

Figure 6. In-vitro dissolution profile of prepared CLD NCs F4 and pure CLD in pH 1.2

The Effect of Type of Stabilizer

Tween 20 was effectively more efficient over poloxamer 188 in that the former as a stabilizer, a mechanical barrier which was created by adsorbed materials on the hydrophobic drug CLD's surface, inhibiting crystal development and agglomeration [(36)]. After crystallization process, the stabilizer took up the adsorption sites on the surface of newly created drug crystals. As a consequence, it prevents the incorporation of drug molecules from solution into crystal lattices, as has already been seen for other drugs like felodipine and folic acid [(37)]. This prevents further growth. Additionally, Tween 20 produced nanosized particles as in F4 in (Table 2) due to its nonionic surfactant characteristics, which include tiny particle size and low MW [(38)].

The Effect of solvent to anti-solvent ratio

It was determined that the solvent-anti-solvent volume ratio of 1:10 gave the lowest mean of particle size in comparison to other ratios, which may be the result of the best molecular distribution of drug and polymer for stabilization. The results of the study on the impact of this ratio on the size of the formulated CLD NCs are summarized in Table (3). The same outcome has been observed by Dong and coworkers in the formulation of spironolactone nanoparticles using 1:10 ratio [(39)].

This can be explained as the volume of anti-solvent increased the particle size decreased. It could be explicated by two theories; (i) when drug solution was injected into anti-solvent, drug concentration reduced rapidly with an increased part of anti-solvent which leads to proliferative precipitation of the drug into nanoparticles, (ii) larger volume of anti-solvent (water) headed to fastened nucleation rate and generates smaller nuclei, at the same time the growth will rise [(40,41)].

Table 3: Represent the effect of solvent to anti-solvent ratio

Formula No.	Solvent: Anti-solvent	Particle size nm
4	1:10	152
7	1:1	276
8	1:6	198
9	1:12	242

Differential scanning calorimetry (DSC)

It's noticed from Figure 7 that displays DSC thermograms of the materials examined. At 111.2 °C, a pronounced endothermic peak was recorded for the melting point of the pure CLD crystals, which also confirmed their purity. CLD NCs F4 showed an additional peak of mannitol (added as a cryoprotectant) at 169 °C, but there was no chemical interaction between the drug and the excipients. Figure 8 of the DSC thermogram of CLD NCs lyophilized powder of F4 shows CLD broad endothermic peak shifted at 158 ºC. This outcome can be ascribed to the prepared formulas' conversion from the crystalline state to the amorphous state. Thermogram of CLD NCs did not show the typical endothermic peak of pure CLD, suggesting that the drug undergoes conversion to amorphous form during formulation [(42)].

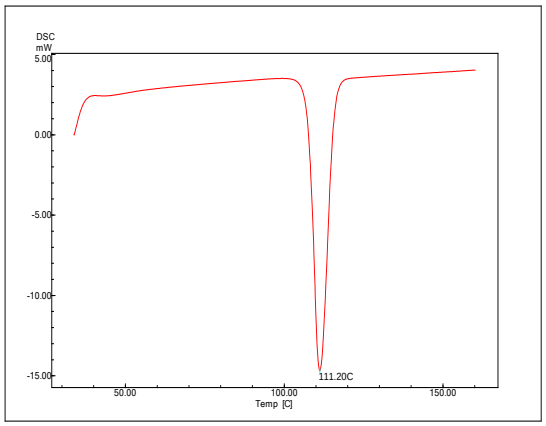

Figure 7. DSC thermogram for Pure CLD Powder

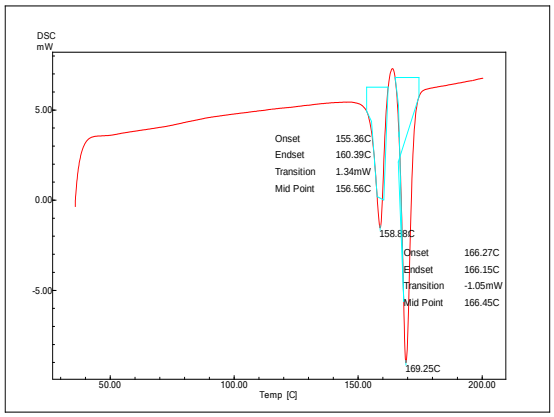

Figure 8. DSC thermogram for CLD NCs lyophilized powder F4

X-ray powder diffractometry (XRPD)

The results obtained from the XRPD studies are shown in Figure 9 the XRD of pure CLD showed sharp characteristic peaks at 2θ scattered angles of 11.8°, 16.43°, 19.77°, 21.72°, and 23.21° indicating its crystalline nature. While in the case of CLD NCs F4 XRD chart displayed the position of most distinct crystalline peaks remained unchanged compared to pure CLD, but with lower peak intensity and relatively rough amorphous patterns, which may have been due to the reduced particle size after preparation and gave an indication about the conversion of CLD into amorphous state in a form of nanocrystals as appeared in Figure 10[42].

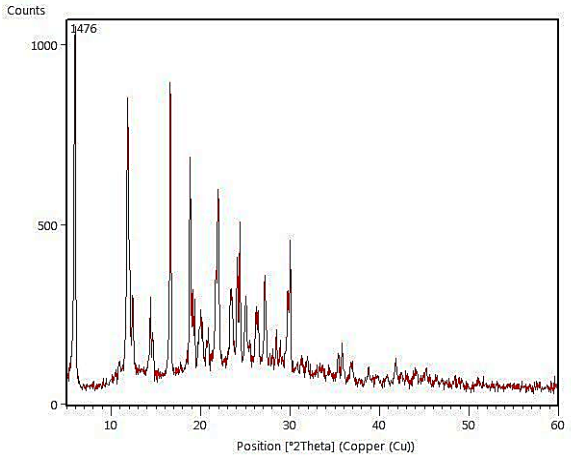

Figure 9. PXRD for pure CLD

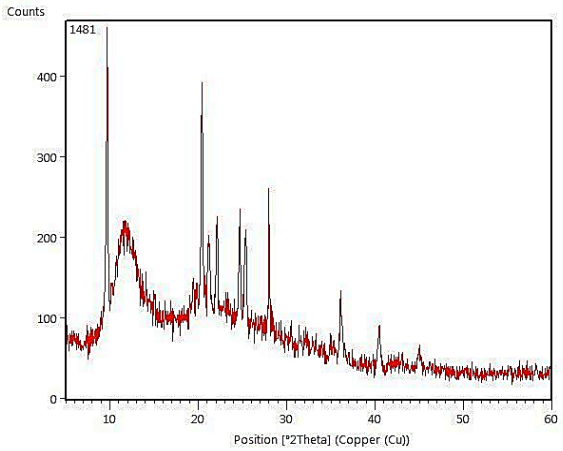

Figure 10. PXRD of Prepared CLD NCs F4

Conclusion

Precipitation technique was successfully used to prepare CLD NCs whereas the nanocrystals provide great potentials with accepTable particle size and PDI which so that optimizing the saturation solubility and the dissolution profile of poorly soluble Cilnidipine which in turn may improve the bioavailability.

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Ethics Statements

This article was approved by the ethical committee of the College of Pharmacy/University of Baghdad**.**

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

The authors confirm contribution to the paper as follows: performed data analysis and interpretation of the results and writing : Suray Abed Hazzaa. Study conception , design,Validation,review and editing:Nawal Ayash Rajab.

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