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Effect of Polymer Type and Concentration on Preparation of Cilnidipine Nanoparticle (A Preformulation Study)

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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%.This study aimed to prepare Cilnidipine as nanoparticles using different polymers which would be expected to improve bioavailability. Cilnidipine nanoparticles were prepared by solvent anti-solvent method by using different types of polymers (PVP K30, HPMC E5, Soloplus®, Poloxamers 188, PVA cold) in different ratios. Different formulation variables were changed. Based on the obtained results, formula P1, which included Soloplus in a 1:1 weight ratio of drug to polymer, exhibited a particle size of 140.4 nm when stirred at 1000 rpm with an injection speed of 1 ml/min. The polydispersity index (PDI) for this formula was measured at 0.264. Furthermore, formula P1 demonstrated an impressive 90.12% drug content and an entrapment efficiency (EE) of 92.7%.

Keywords

Cilnidipine, Poloxamers 188, PVA cold, PVP K30, Soloplus®.

In the pursuit of maximizing therapeutic efficacy while minimizing hazards, pharmaceutical researchers seek to employ various methods to improve medication bioavailability and solubility. One such technique is the reduction of drug particle size, which has led to the emergence of nanotechnology as a new field in pharmaceutical research [1]. Nanotechnology is a highly advanced science with its origins dating back to the nineteenth century, and over the past two decades, it has been the focus of many medical researchers. Among the various applications of nanotechnology in medicine, polymeric nanoparticles have shown great potential for targeted drug delivery.

Due to their ability to enhance the pharmacokinetics and pharmacodynamics of drug compounds, nanoparticles have emerged as a promising approach for drug delivery, with the potential to improve bioavailability, sustained release, and intracellular penetration. As the field of nanomedicine continues to advance, drug formulation as nanoparticles has shown great potential for enhancing drug solubility and bioavailability. In this formulation, the drug particles take on an amorphous spherical shape with higher solubility than standard crystalline preparations, resulting in a greater surface area of drug particles. This leads to improvements in the previously low aqueous solubility and bioavailability of drugs [2]

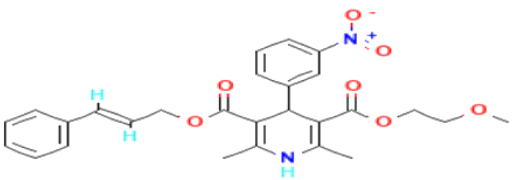

Figure (1) Structure of Cilnidipine [3]

Cilnidipine is a distinctive calcium channel blocker belonging to the dihydropyridine class, with a chemical name of 1, 4-Dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3, 5-pyridine carboxylic acid 2-methoxyethyl (2E)-3-phenyl-propenyl ester. As seen in Figure 1. It is characterized by a slow onset and prolonged vasodilatory effect [3].

Cilnidipine (CLD) has a pKa value of 11.39 and a log P value of 5.54 and is classified as a class II drug according to the Biopharmaceutics Classification System (BCS) [4]. The melting point of CLD is around 110°C, and its oral bioavailability ranges from 6% to 30%. It exists as a yellow, odorless crystalline powder with low aqueous solubility, which results in poor dissolution and consequently leads to low oral bioavailability even at an effective dose of 10 mg taken orally [5,6].

Due to its short half-life of 30.4 minutes and low bioavailability of 13%, it has been proposed to develop nanoparticles of Cilnidipine to ultimately improve bioavailability [7]

The objective of the study is to establish the most appropriate polymer type and concentration for the preparation of Cilnidipine nanoparticles.

Materials and Method

Cilnidipine (CLD) was supplied by Hyperchem. China. PVP K30 was purchased from BDH Chemical LTD, UK Fluka, Germany. Poloxamers 188 was purchased from Eastman chemical company, USA. Soloplus ® Basf SE, Germany. HPMC E5 was purchased from Baoji, China. Methanol was purchased from Sigma-Aldrich, Germany. Glycerol was purchased from BDH, England. Polyvinyl alcohol was purchased from Pancreac Quimica SA. Spain

Characterization of Cilnidipine

Determination of the saturated solubility of Cilnidipine

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 polymers in water (5mg of polymer + 10 mL of distilled water). The polymers used included PVP K30, HPMCE5, Soloplus ®, Poloxamers188, and PVA Cold, as seen in Table 1. The organic phase was then placed in a syringe with a needle gauge of 0.6 mm using a syringe pump (Kelly med, Germany) and added drop by drop to the aqueous phase at a speed of 1 mL/min while being magnetic stirred (Joan lab, China)at a speed of 1000 rpm for 20 minutes to evaporate the volatile solvent [8]. The prepared nanoparticles were covered and placed overnight in a cool place.

Table (1) Composition of Cilnidipine Loaded Nanoparticles

	CLD mg	Soloplus® mg	PVA cold mg	Poloxamer 188 mg	HPMC E5 mg	PVP K30 mg	Ethanol mL	D.W mL
P1	5	5					3	10
P2	5	10					3	10
P3	5	20					3	10
P4	5		5				3	10
P5	5		10				3	10
P6	5		20				3	10
P7	5			5			3	10
P8	5			10			3	10
P9	5			20			3	10
P10	5				5		3	10
P11	5				10		3	10
P12	5				20		3	10
P13	5					5	3	10
P14	5					10	3	10
P15	5					20	3	10

Determination of particle size and polydispersity index

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) [9].

Determining Cilnidipine drug content in Nano suspension

A specific volume of Nano suspension (1 mL) was mixed with methanol in a 10 mL volumetric flask. The sample was then subjected to sonication (Fuyang, China

)for 1 hour and filtered through a 0.45μm filter syringe. The amount of Cilnidipine present in the Nano suspension was quantified using spectrophotometer at (240 nm) [10,11]. The drug content was then calculated using the following equation:

$$\text{Drug content} = (\text{Practical conc} / \text{Theaortical conc}) \times 100\% \quad ..\text{Eq } 1$$

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, the Nano suspension with the smallest particle size was taken (2mL) and 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 removed and the concentration of free drug was measured using a UV spectrophotometer. The %EE was calculated using the following equation:[12].

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

where;

%EE = Percentage of entrapment efficiency.

C initial = Initial drug concentration.

C free= Free drug concentration (un-entrapped drug).

Measurement of Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum of Cilnidipine pure drug and the selected CLD nanoparticles suspension and lyophilized nanoparticles (2% mannitol) which was then subjected to FTIR spectroscopy (Shimadzu, Japan), which involved analyzing the in the 4000-400 cm^{-1} region [13].

Results and discussion

Particle size and PDI of Cilnidipine nanoparticles

Table (2) presents 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 [14,15]. These polymer gave different particle size because it effect on lipophilicity, charge, also physicochemical properties, prevent gathering and coalescence at interface. 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 is reflected a 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 [16,17]. Soloplus in formulation that the best nano size particles in comparison with other ratio meaning that the polymer type is enough to envelop nanoparticles formed [18]. The molecular weight of the polymer and hydrophilicity will greatly affect the formation of nanoparticles. Concentration of polymer, Affinity between the drug and polymer will aid in the formation of nanoparticles. The hydrophobic portion of soluplus and poloxamer will envelop the drug in a more extensive manner,Better than the rest of the other more hydrophilic polymer PVA Cold, HPMC E5.

Show increase in particle size when concentration of polymer increase meaning that aggregation and accumulation occur as a result of increase viscosity of solution. The results indicate the stabilizer concentration was not enough to fully envelope the newly formed CLD NPs. When the stabilizer concentration was increased to a drug: stabilizer ratio 1:1 in formulations (P1,P4,P7,P10,P13) , the particle size ranged from (104.4−349nm), 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, at a drug: stabilizer ratio of 1:2, in the formulas (P2, P5, P8, P11, P14), the largest particle size range (164.2−1041 nm) was obtained. These results may be due to increased stabilizer concentration and 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. [19].

On the other hand PVA cold,PVP K30 , HPMC E15 and PXM 188 have similar behavior as they increase drug : stabilizer ratio from 1:1 to 1:2 lead to increase the particle size of CLD nanoparticles as their stabilizer concentration increases .PVP K30 is a nonionic stabilizer, that creates a protective wall on the surface of CLD NPs and disrupts the intimate particle interaction. Also, it has amphiphilic parts that provide steric stabilization for nanoparticles. So the formulations contain PVA cold and Poloxamer in all three drug: stabilizer ratio gave smaller particle size than the other formulations based on stabilizer HPMC E15 and PVP K30

Polydispersity index (PDI) is a metric used to evaluate the particle size distribution of nanoparticles obtained from a particle size analyzer. A lower PDI value is an indication of a monodisperse sample, meaning that the particle

sizes are uniform, and the sample is stable over time. On the other hand, a higher PDI value is an indication of a polydisperse sample, meaning that the particle sizes vary widely, and the sample is less stable. The PDI values range from 0 to 0.05 for monodisperse systems, 0.05 to 0.08 for nearly monodisperse systems, 0.08 to 0.7 for mid-range polydisperse systems, and greater than 0.7 for very polydisperse samples [20].

Table (2) Particle size and PDI of the prepared Cilnidipine nanoparticles

Formula no.	P.S (nm)	PDI	Drug content (mg)	EE (%)
P1	140.4	0.264	90.93%	92.7%
P2	234	0.102	88.87%	89.5%
P3	243.1	0.206	89.84%	88.5%
P4	281.31	0.2283	88.99	88.56
P5	318.3	0.087	85.67%	84.7%
P6	437	0.446	84..43%	80.67%
P7	164.2	0.2326	90.12%	90.6%
P8	296.1	0.1238	85.45%	81.7%
P9	358.6	0.1425	83.43%	79.5%
P10	349	0.509	83.6%	78.5%
P11	479.2	0.381	82.76%	79.5%
P12	496.8	0.342	80.43%	78.6%
P13	300.3	0.033	84.65%	82.1%
P14	1041	0.3315	70.45%	60.4%
P15	1097	0.518	70.56%	55%

Drug content of Cilnidipine nanoparticle

Drug content of the prepared CLD NPS for formulaP1 and P7were 90.93± 0.725%and 90.12 ± 0.503 % respectively, showed good percent encapsulation efficiency and percent drug loading [21]

Entrapment efficiency measurement of CLD nanoparticles

The entrapment efficiency (%EE) of formula (P1) that had smallest particle size and containing drug: Soloplus® in ratio 1:1 which selected as the optimum formula the EE% was 92.7 % due to the higher availability of surfactant to encapsulate the drug which enables to reduce interfacial tension between the stabilizer and aqueous phase and higher affinity for entrapment of CLD from the outer aqueous layer into the inner surfactant layer. Also, it could be attributed to decreased partitioning of CLD into the external aqueous layer and entrapped in the lipid phase because it is a lipophilic drug [22].

Fourier transform infrared spectroscopy of Cilnidipine (FTIR)

The infrared (IR) spectrum was obtained in the range of 4000-400 cm^{-1}. The IR spectrum of pure Cilnidipine powder was compared to a reference spectrum and found to be similar, as depicted in Figure 2 for the pure Cilnidipine [23]. Figure 3 for the Cilnidipine nanoparticles and Figure (4) of Cilnidipine lyophilized nanoparticles (2% mannitol) powder

Table (3): FTIR peak for Cilnidipine pure drug and reference drug

Functional Group	Pure drug (cm-1)	CLD Nanoparticle (cm -1)	Lyophilized CLD powder (cm-1)
O-H stretch	3379.29	3439	3332.99
C-H stretch	2943.37	2958	2935.66
C=O stretch	1697.36,1647.21	1684	1732.08,1647.21
C=C stretch	1600-1523	1602	1556,1543
O-C-O	1203.58	1117	1195.87
NO2	1381..03	1462	1373.32

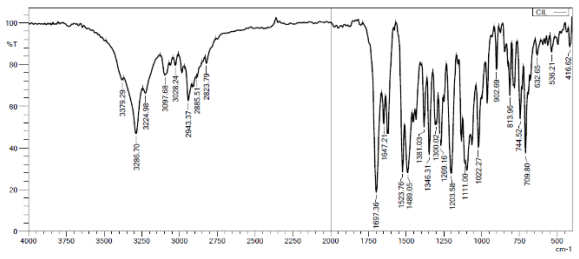

Figure (2) FTIR spectrum of Pure Cilnidipine

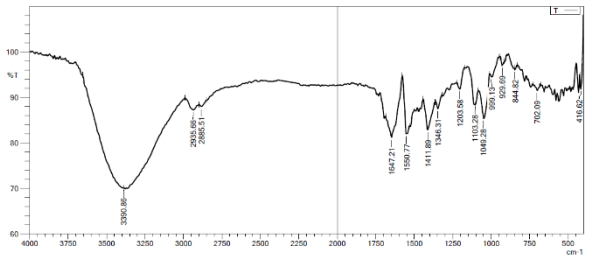

Figure (3) FTIR spectrum of Cilnidipine nanoparticle

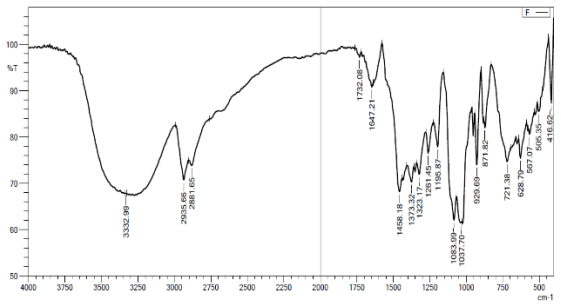

Figure (4) FTIR spectrum of Cilnidipine lyophilized nanoparticles (2% mannitol) powder

Conclusions

Based on the obtained results of this study, can be conclude 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 weight ratio which gave the smallest particle size and agreeable PDI and good EE%. The FTIR study revealed no chemical interaction between Cilnidipine, and the polymer used.

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