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Original Article

# Formulation of Candesartan Cilexetil Nanoparticles by Ionotropic Gelation Method Using Ultrasonication

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## ABSTRACT

**Aim:** Candesartan Cilexetil (CC) is a common drug used by patients suffering from hypertension and heart diseases. However, CC has poor oral bioavailability as it belongs to Biopharmaceutical Classification System (BCS) class II and has low aqueous solubility. This research work is focused to enhance the Bioavailability of CC using nanotechnology. Therefore, CC nanoparticles were developed using the ionic gelation procedure and ultrasonication. **Materials and Methods:** This work is aimed to formulate CC-alginate nanoparticles using the ionic gelation method and to investigate the influence of ultrasonication on the particle size and stability of nanoparticles. This work is also focused on the use of polysaccharides (sodium alginate) for nanoparticle preparation by ionic gelation technique using a cross-linking agent (calcium chloride). The physico-chemical properties, morphology, and effect of ultrasonication on particle size, as well as the effect of polymer concentration on particle size and drug release, of CC nanoparticles, were investigated. **Results and Discussion:** The prepared CC nanoparticles, were stable and have mean particle sizes ranging from 210-538 nm. The encapsulation efficiency of the prepared nanoparticles was reported between 67-83%. The optimized formulation was tested for its physical stability at 8°C and 25°C for 3 months. Pluronic F-68 (PF-68) was also found to have a crucial role in the long-term stability of the formulation. It was observed that sodium alginate played a pivotal role in providing sustained drug release up to 24 hr from the formulation. **Conclusion:** The results suggested that ultrasonication and polymer concentration leads to variation in the particle size and the homogeneity of the system.

**Keywords:** Candesartan cilexetil, Ionic gelation, Ultrasonication, Sodium alginate, Pluronic F-68.

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## INTRODUCTION

Over the past few decades, the field of Polymeric Nanoparticles (PNP) has experienced tremendous growth and assumed an important role in a wide range of fields, including electronics, medicine, photonics, agriculture, conducting materials, sensors, biotechnology, pollution management, and other areas.[1-6] The reduced solubility of most of the active pharmaceutical ingredients is one of the crucial practical obstacles in formulating suitable dosage forms for its most sensitive use.[1] It is unfortunate that more than 40% of newly discovered molecules have poor aqueous solubility.

The BCS system considers solubility, gastrointestinal permeability and dissolution rate as three crucial factors which govern the bioavailability of drugs. The dissolution process is the rate-controlling step in BCS class II drugs due to their low solubility.[2,4,7-10] Hypertension is a dangerous cardiovascular event resulting in an increase in arterial blood pressure. There are many medications available to treat hypertension in conventional dosage forms, but the majority of antihypertensives have low bioavailability because they are poorly water soluble. The best method to overcome the limitations of oral antihypertensive drug administration appears to be nanoparticles. In order to circumvent the oral bioavailability problems with antihypertensive medications, many nanoparticulate formulations, including polymeric nanoparticles and lipid-based nanoparticles have been researched.

The current study revolves around the nanoparticle formulation of Candesartan Cilexetil (CC), a BCS Class II drug. The low solubility of candesartan cilexetil at physiological pH is responsible for its poor intestinal absorption and its reduced bioavailability.[11] Thus, it is an ideal approach to prepare polymeric nanoparticles of CC. Candesartan cilexetil, an angiotensin-II receptor antagonist is predominantly used by the patients suffering from hypertension. It has a half-life of about 5.1 hr and 15-40% bioavailability.[12,13] Natural biopolymers are approached to reduce various adverse effects of the selected drug, and for

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the preparation of nanoparticles. Biopolymers are the materials made chemically from biological basic components such amino acids, carbohydrates, natural fats, or oils and acquired from microorganisms, plants, and animals.[13-17]

Alginate is a naturally occurring polymer. It has huge potential in drug formulations owing to its wide application as a food additive and its well know nontoxic behavior. Alginates are a class of hemocompatible polymers that have been proven to degrade *in vivo* and not accumulate in any significant organs. Alginates exhibit characteristic ion binding for multivalent cations and this is the basis for their gelling properties.[18-20] The covalent bonds resulted due to alginate binding with cations and this cross-linking process hardens the polymer and minimizes swelling in solvents.

This results in the reduction of permeability of different solutes by hindering the release of encapsulated drugs in alginate matrices, and thus permitting these systems to release the drug in a controlled fashion. Insoluble calcium alginate is prepared as a result of the cross-linkage of soluble sodium alginate with calcium chloride. Alginates and calcium ions in combination forms gels, which can delay the release of some medications. The divalent calcium ion interacts with the glucuronic acid residues and forms gels. The ionic gelation process is an easy and uncomplicated technique for the formulation of polymeric nanoparticles. The method depends on interactions between sodium alginate and calcium chloride ion resulting in the formation of a calcium alginate egg-box-like structure.[21-24]

In nanoparticle technology, ultrasonication is a simple, rapid, environmentally friendly, and widely used technique for the preparation and processing of polymer nanoparticles. Achieving a small size and narrow size distribution range is a very tough task using the ionic gelation method. Also, the possibility of the instability of the formulation elevates during their long-term storage in an aqueous medium. To overcome this hindrance, ultrasonication is used as it effectively breaks aggregates and reduces particle size and polydispersity of nanoparticles. Acoustic cavitation, is the primary phenomenon in ultrasonication. It involves the formation, growth, and collapse of bubbles inside the liquid in a period less than a nanosecond. Ultrasonication waves favor the production of very small-sized particles (nanoparticles) with a highly reduced polydispersity index.[25-27]

This work aimed to formulate CC-alginate nanoparticles using the ionic gelation method for the sustained delivery of drug in the gastrointestinal tract. Formulation of the nanoparticles using sodium alginate results in an effective way to get nanoparticles of very small mean diameter. The work also investigates the influence of ultrasonication on particle size and stability of nanoparticles.

## MATERIALS AND METHODS

### Materials

Candesartan Cilexetil (CC) was provided as a gift sample from Microlabs, Bangalore, India. Pluronic F-68 (PF-68) has been purchased from Hi Media Limited., Mumbai. Sodium alginate was procured from Ranbaxy Fine Chemicals Private Limited., Mumbai. All solvents and reagents were of analytical grade and produced commercially.

### Methods

#### *Preparation of CC-sodium alginate nanoparticles*

CC nanoparticles were formulated by ionic gelation method using Sodium alginate as given in Table 1. The foremost step is the preparation of drug solution by dissolving CC in a small amount of ethanol and then adding it dropwise into the Sodium Alginate (SA) solution of different strengths (0.05–0.175%w/v). The dispersion was then stirred continuously for 60 min. After 60 min stirring, a high-intensity probe ultrasonicator (Rivotek, Kenya) was used for ultrasonication at 80 magnitudes. 3 cycles of ultrasonication were done, each for 5 min. To this dispersion, Calcium chloride (18mM) was added slowly and dropwise. The resulting mixture was stirred for at least 1hr. Finally, Pluronic F-68 (stabilizer) solution, was added to the dispersion, and stirred for 30 min. The dispersion was then again treated with 600W ultrasonication using a probe sonicator for 10 min by 2 cycles. The resultant milky colloidal dispersion undergoes centrifugation (Superspin R-V/FA) at 10,000 rpm for 60 min at 4°C to obtain pellets which was then redispersed in distilled water and ultrasonicated (2 cycles, 5 min each). The resultant dispersion of CC nanoparticles was kept at -80°C for its future evaluation.[28]

### Evaluation of Candesartan Cilexetil Nanoparticles

#### *Fourier-Transformed Infrared Spectrophotometry (FT-IR)*

The spectrum of pure drug, sodium alginate, and Pluronic F-68 was analyzed using Fourier-Transformed Infrared Spectrophotometry (FT-IR) (IR Affinity1, Shimadzu, Japan). The purpose of FT-IR is to examine how the medicine interacts chemically with the other excipients incorporated in the formulation. Powdered drug and excipient are used to prepare samples for FT-IR by thoroughly combining them with dry potassium bromide. The combination was maintained on a diffused reflectance sampler, and the spectrum was captured by scanning in the 4000-400 $cm^{-1}$ wavelength range.[9,12]

### Differential Scanning Calorimetry (DSC) Analysis

DSC 60 detector (Shimadzu Co., Japan) was used to perform DSC analysis. Approximately 5 mg of the physical mixture of candesartan cilexetil and sodium alginate was weighed into an aluminium pan and sealed. With a continuous nitrogen purge,

**Table 1: Formulation table for Candesartan cilexetil nanoparticles.**

| Formulation | Drug concentration (mg/mL) | Polymer (%w/v) | $CaCl_2$ (18Mm) (mL) | PF-68 %w/v |
|---|---|---|---|---|
| F1 | 20 | 0.05 | 2.1 | 0.5 |
| F2 | 20 | 0.075 | 2.1 | 0.5 |
| F3 | 20 | 0.1 | 2.1 | 0.5 |
| F4 | 20 | 0.125 | 2.1 | 0.5 |
| F5 | 20 | 0.15 | 2.1 | 0.5 |
| F6 | 20 | 0.175 | 2.1 | 0.5 |

*Data are expressed as Mean± SD ($n$=3).

the scan was conducted from 20 to 200°C using an empty pan as a reference and 10°C/min heating rate.[9]

## Entrapment Efficiency (EE)

Entrapment efficiency was determined using ultracentrifuge which separates drug loaded nanoparticles and unbound CC from the aqueous medium. The formulation was centrifuged at 10,000 rpm 60 min at 4°C. The amount of CC loaded into nanoparticles is determined by subtracting the difference between the total amount of drug used in the preparation of the nanoparticles and the total amount of unbound drug remaining in the supernatant. After a sufficient dilution with phosphate buffer pH 6.8, the amount of free CC in the supernatant was determined using a UV Spectrophotometer (Shimadzu UV-1900I) at 256.5 nm.[13-15] The encapsulation efficiency of CC nanoparticles was analyzed in triplicate manner and calculated from the formula as given below:

$$\% EE = \frac{\text{Total amount of drug} - \text{Total amount of unbound drug}}{\text{Total amount of drug}} \times 100$$

## Zeta Potential (ZP)

The Zeta Potential (ZP) is the difference in potential between the electro-neutral region of the solution and the surface of the firmly bonded layer (shear plane). Zeta potential is used to examine long-term stability of nanoparticles. Since the suspension is positioned between two electrodes with DC voltage, the charge on the potential will move readily, and the velocity will be proportional to the particle's zeta potential, making its measurement simple. Electrophoresis is the technical word for this technique. Zetasizer (Malvern zetasizer) was used to calculate zeta potential. Long term stability of nanoparticles is analyzed by zeta potential.[16,17]

## Transmission Electron Microscopy (TEM)

The morphological investigations of nanoparticles were determined using transmission electron microscopy (Hitachi-H7500). Nanoparticle samples was applied to copper grids that had Formvar coatings. Digital Micrograph and Soft Imaging Viewer software was used to accomplish image capture and study of particle size.[16]

## Polydispersity Index (PDI)

Homogeneity and the stability of the formulation were tested by dynamic light scattering in triplicate using Microtrac Nanotrac A 150, Korea, and Malvern zeta sizer, respectively.[16]

## *In vitro* drug release

The *in vitro* release of drug from different formulations of candesartan cilexetil nanoparticles was determined using the dialysis bag diffusion technique. CC nanoparticle dispersion equivalent to 10 mg of drug was filled in a dialysis bag having a molecular weight cut off 12000-14000 dalton and the bag was sealed. In the USP Type II apparatus (Electrolab, Mumbai) containing 900 mL phosphate buffer pH 6.8, the sealed bag was suspended and rotated at a constant speed of 50 rpm at 37°C ± 0.5°C. Aliquots were withdrawn at a fixed time interval and the same amount was replaced with fresh buffer to maintain sink condition. The amount of drug release was determined using a UV-visible spectrophotometer at a wavelength of 256.5 nm using phosphate buffer pH 6.8 as blank.[16,17]

## Kinetics of drug release

Statistically significant experimental results were compared with the theoretical models to determine a specific release mechanism from the formulation. Model-dependent methods rely on various mathematical functions to describe the dissolution profile of formulation. DD solver software was used in this work to determine the kinetics of drug release from the nanoparticles. The collected experiment data were fitted into the zero-order, first-order, Higuchi matrix, Hixson Crowell, and Korsmeyer-Peppas models in order to examine the mechanism for the release and release rate kinetics of the dosage form. The best-fit model was chosen by comparing the $R^2$ values that were obtained.[15-17]

**Table 2: Effect of ultrasonication on particle size.**

| Time (min) | Particle size (nm) |
|---|---|
| 10 | 540 |
| 12 | 435 |
| 15 | 342 |
| 17 | 250 |
| 20 | 280 |
| 23 | 330 |
| 25 | 380 |

**Table 3: Drug content and entrapment efficiency of Candesartan cilexetil nanoparticles.**

| Formulation | Entrapment efficiency±SD* (%) |
|---|---|
| F1 | 67.47±2.01 |
| F2 | 75.43±1.95 |
| F3 | 83.33±2.81 |
| F4 | 80.32±2.97 |
| F5 | 76.43±3.77 |
| F6 | 73.83±1.28 |

## RESULTS AND DISCUSSION

In the present study, candesartan cilexetil-loaded sodium alginate nanoparticles were prepared by the ionic gelation method followed by the ultrasonication. The sonication time was optimized to 20 min based on particle size and homogeneity of dispersion. Further than this point, no remarkable change in the particle size was noticed. Also, the obtained polydispersity indices for all the formulations were within acceptable limits showing homogeneous particle size.

### Ionic Gelation Method

CC nanoparticles were successfully prepared by the ionic gelation method. The preparation of nanoparticles using sodium alginate and calcium chloride by ionic gelation method includes the complex formation of calcium and alginate. The calcium ion and alginate polymer interaction take place at the oligo polyglucuronic sequence level. Moreover, egg-box structures were the result of parallel packing of oligo polyglucuronic sequences induced by calcium ions and polymer coating formed over the drug particle. The addition of pluronic F-68 as a stabilizer may help to obtain small and well-defined particles and helps in the stability of the formulation.

### Effect of ultrasonication

The nanoparticles were formulated under ideal conditions but they exhibited stability issues on prolonged storage and resulted in the formation of particles agglomerates. To overcome this issue, ultrasonication in the suitable condition is effective in breaking agglomerates. It was found that the ultrasonication time period affects the re-agglomeration of nanoparticles as given in Table 2. The exposure of CC nanoparticles to ultrasonication results in the production of cavitation bubbles which were produced because of sound waves on the suspension. These ultrasound waves produce variable pressure regions when passes through the nanoparticles resulting in the collision of bubbles and generating high-speed liquid jets applying stress on attracting forces between individual particles.[25] The collaborative effect of these events causes the breakage of the agglomerated particles into smaller fragments. If the ultrasonication is continued uninterruptedly, the heating effect becomes more prominent leading to enhanced particle speed and reduced suspension viscosity. This results in an increased probability of the particles colliding with each other and hence a decrease in particle size and their agglomeration.[27]

### Effect of Pluronic F-68

Pluronic F-68, a nonionic block copolymer is made of two hydrophilic polyoxyethylene chains joined by a hydrophobic polyoxypropylene chain that helps in augmentation of aqueous solubility of freely water-soluble drugs.[29,30] The results revealed that addition of hydrophilic carriers enhances the solubility of Candesartan cilexetil which may be the result of the hydrogen bonding interactions between drug and carrier. Elevation in drug solubility may also be the result of enhanced wettability of the drug due to higher aqueous solubility and HLB (hydrophilic lipophilic balance) value of pluronic F-68 (HLB value is 29). Pluronic F-68 also have a crucial effect on the stability of the formulation.[31,32]

### Entrapment Efficiency (EE)

All the formulations showed high entrapment efficiency values that varied from 67.47%±2.01 to 83.33%±2.81 as shown in Table 3. The results depicted that there was elevation in percent entrapment efficiency from formulation F1 to F3 followed by decrease till F6. This may be explained that with the rise in the polymer concentration, entrapment efficiency increases and after a certain concentration, saturation of drug and polymer was attained which leads to reduction in the entrapment efficiency with further increase in the polymer concentration. Such high entrapment efficiency in the resulting nanoparticles is desirable to reduce the administering dose and the frequency in order to give desired therapeutic effect.

### Fourier-Transformed Infrared Spectrophotometry (FT-IR)

The FT-IR spectrum of the pure Candesartan cilexetil was analyzed and compared with standard spectrum of Candesartan cilexetil. From the Figure 1, it can be concluded that the functional group frequencies of Candesartan cilexetil were in the reported range indicating that the obtained sample of Candesartan cilexetil was pure. The characteristics absorption

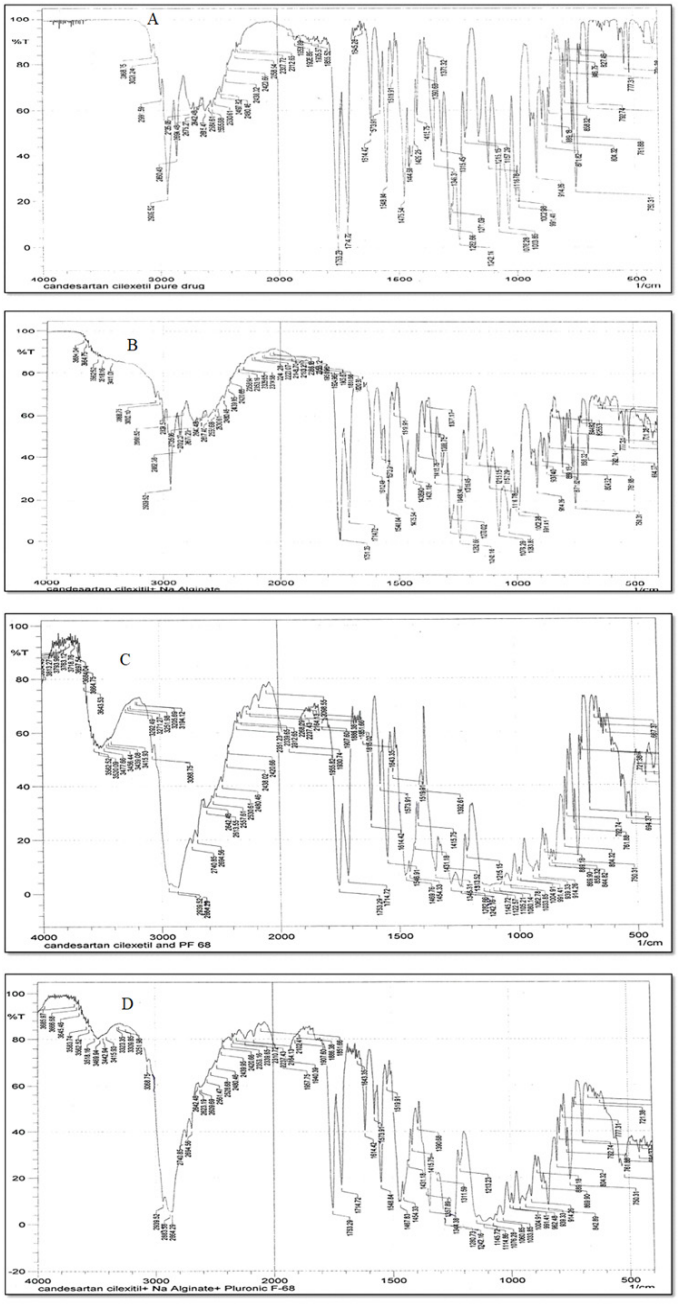


**Figure 1:** (A) FTIR of Candesartan celexetile (B) FTIR of Candesartan celexetile+ Sodium Alginate, (C) FTIR of Candesartan celexetile+ PF-68 (D) FTIR of CC+ Sodium Alginate++ PF-68.

peaks of Candesartan cilexetil were obtained at 1116.78 $cm^{-1}$ (C-N Stretch), 1753.29 $cm^{-1}$ (C=O Stretch), 3068.75 $cm^{-1}$ (Aromatic C-H Stretch) and1424.16 $cm^{-1}$ (C-O-C). Compatibility studies of pure drug with excipients were carried out prior to the preparation of nanoparticles. All the characteristic peaks of Candesartan cilexetil were present in spectra thus indicating compatibility between drug and excipients. This explains that the chemical integrity of drug is maintained and there was no significant change in it.

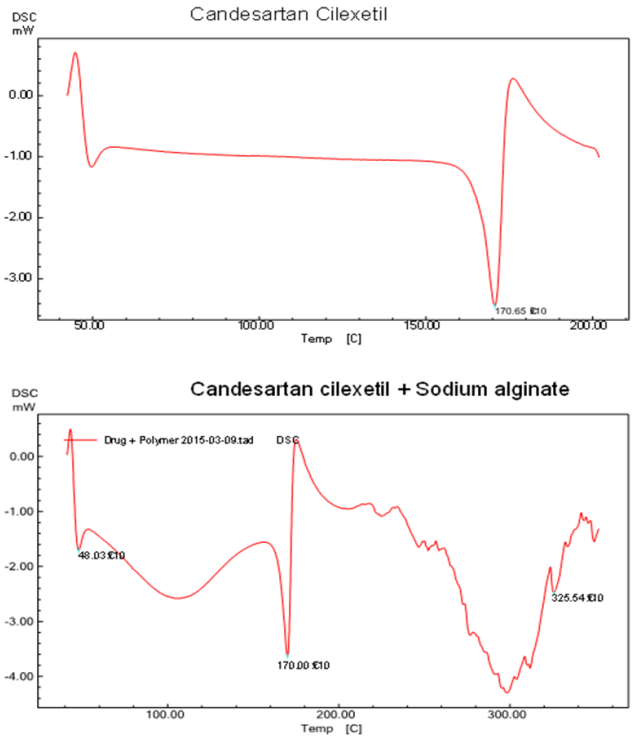


**Figure 2:** DSC of candesartan Cilexetl and physical mixture of pure drug and sodium alginate.

## Differential Scanning Calorimetry (DSC)

The thermogram of pure Candesartan cilexetil showed its characteristic peak at 170.65°C and the physical mixture of Candesartan cilexetil and sodium alginate exhibited peak at 170.00°C, Figure 2. The result suggested that there was no physical interaction between Candesartan cilexetil and sodium alginate.

## Transmission Electron Microscopy (TEM)

TEM of the prepared sample was done and size of the particles of optimized formulation (F3) was found in nanosized range (284.4nm and 300.2 nm) as shown in Figure 3.

## Polydispersity Index (PDI) and Zeta Potential (ZP)

Polydispersity Index ranges from 0 to 1 and indicates the range of the particle size distribution. A monodisperse sample indicates PDI value nearer to 0. However, PDI< 0.2 is considered as narrow size distribution whereas a PDI>0.5 indicates a very broad distribution. Therefore, to confirm size distribution of particles, PDI measurement is essential. The mean PDI values for the CC nanoparticles prepared by ionic gelation method using sodium alginate vary from 0.203-0.490 indicating homo disperse nature of the formulation.

Zeta (ζ) Potential is a vital parameter to evaluate the long-term stability of the nanoparticles. It implies to the particles surface charge. ZP (±) indicates the extent of repulsion among the similarly charged particles in the dispersion that aids inhibition of aggregation of the particles. Therefore, it is a useful parameter to

predict the physical stability of the nanoparticles. Various reports suggested that nanoparticle dispersions having the value of zeta potential less than -30 mV or more than +30 mV predicts good physical stability. The ZP value for the optimized formulation (F3) was found to be -27.1 mV by which it can be deduced that the formulation will exhibit good stability as the repulsive forces check aggregation with aging. Also, this value of zeta potential may be indicative of complete stabilizer coverage on the drug particles and may help to explain the enhanced nanoparticles stability on storage.

## *In vitro* drug release

*In vitro* drug release from the Candesartan cilexetil nanoparticles was carried out in phosphate buffer pH 6.8 using dialysis bag technique.[33] During the study it was found that, in ionic gelation method, polymer concentration and mean particle size exerts a direct effect on the drug release profile as depicted in Figure 4. Formulations F1 with less polymer concentration and least mean particle size showed highest drug release, 96.03%±5.36 at the end

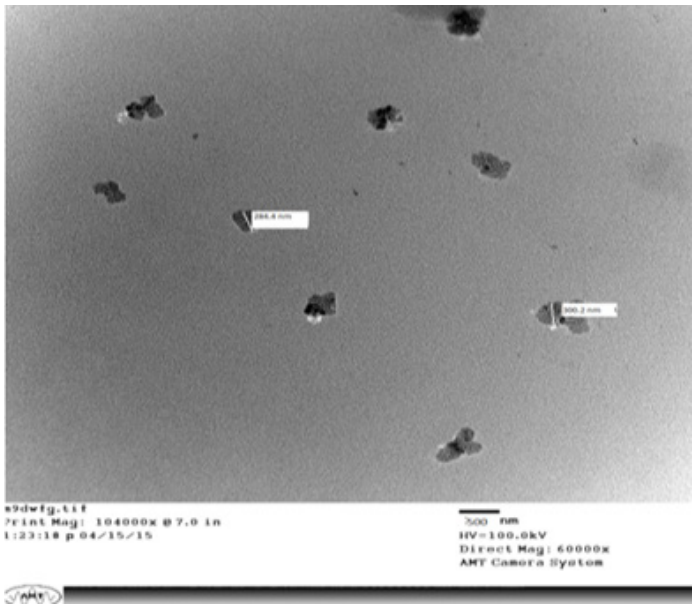


**Figure 3:** TEM of F3.

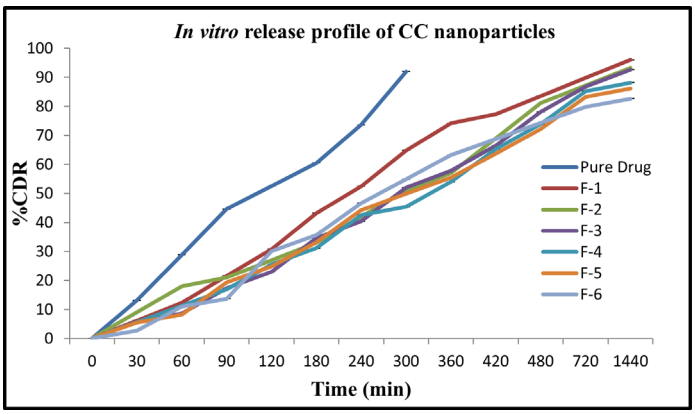


**Figure 4:** *In vitro* drug release profile of Candesartan cilexetil nanoparticles.

of 24 hr. The amount of drug release was reduced in formulations F2, F3, F4, F5 and F6, with the increase in the polymer concentration from 0.05%w/v to 0.175% w/v. This decrease in drug release may be ascribed due to the larger distance that the drug must travel in the nanoparticles as swelling of the polymer may occurs in the phosphate buffer pH 6.8. Therefore, the drug particle takes more time to diffuse from the swelled polymer layer and so there is decrease in the release. Furthermore, it was observed that with the increase in polymer concentration, elevation in particle size was noted, which can also be one more reason for less drug release from F2-F6.

## *In vitro* kinetics of drug release

To evaluate release constant and regression coefficient ($R^2$), the data of drug release was fitted to various kinetic models. From the kinetic study it was found that Korsmeyer-Peppas model was the best fitted model for all the prepared formulations. It was also revealed that that the drug was released from the formulation by diffusion process. All formulations show diffusion exponent (n) values between 0.45 and 0.89, indicating anomalous (Non-fickian diffusion) drug release.

## CONCLUSION

Nanoparticles are novel formulation that are widely used to enhance the bioavailability of drugs with low solubility, target the drugs to the site of action, reduce the unwanted side effects, increase the efficiency of drug, and improve patient compliance. Sodium alginate is a widely used polymer and has been extensively studied by researchers in the formulation of advanced drug delivery system.[34] In this study Candesartan Cilexetil nanoparticles were successfully prepared using sodium alginate and evaluated for the treatment of hypertension. Pluronic F-68 exhibited important role in imparting long-term stability of the formulation by coating the nanoparticles. Also, from the study it was observed that ultrasonication using probe sonicator, gave nanoparticles of small size range and PDI value. Ultrasonication can be used as potent approach for size reduction of particles specially designed for targeted delivery of drug. The results indicated that CC nanoparticles were successfully formulated and evaluated. The Ionic gelation method was found to be easy and low energy requiring process and requires only simple equipment. Thus, it is a promising method for preparing nanoparticles of drugs.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**CC:** Candesartan cilexetil; **PF-68:** Pluronic F-68; **PNP:** Polymeric nanoparticles; **BCS:** Biopharmaceutical Classification System; **SA:** Sodium alginate; **DSC**: Differential scanning calorimetry; **FT-IR:** Fourier-transform infrared spectroscopy; **EE:** Entrapment Efficiency **TEM:** Transmission electron microscopy; **PDI:** Polydispersity index; **ZP:** Zeta Potential (ZP); **HLB:** hydrophilic-lipophilic balance.

## SUMMARY

In the present study, candesartan cilexetil nan-oparticles were preared successfully using the ionic gelation. The nanoparticles were then tested for particle size, shape, surface morphology, *in vitro* release rate, polydispersity index, zeta potential, percentage drug content, percentage entrapment efficiency, and stability studies. From the results obtained by FTIR and DSC studies of Candesartan cilexetil and its physical mixture with polymer and surfactants, it was affirmed that there were no remarkable interactions between them. Sodium alginate and Pluronic F-68 were employed as coating polymer and the stabilizer, respectively. The particle size was affected by the polymer concentration i.e. with the increase in polymer concentration, there was increase in the particle size. So F1 having least polymer concentration have least mean particle size (210 nm) whereas F6 with polymer concentration 0.175% w/v showed maximum mean particle size of 538 nm. Drug encapsulation efficiency was found maximum for F3 i.e., 83.33%±2.81. It was observed that the entrapment efficiency augments with the increase in concentration of polymer (Sodium alginate) to certain level. The dissolution rate depends upon the mean particle size and polymer concentration. Therefore, F1 showed maximum dissolution i.e. 96.03% ± 5.36 while F6 with maximum mean particle size and highest polymer concentration showed least dissolution rate (82.61±3.50). F3 was found to be the optimized formulation, as it showed less particle size (284.4nm), highest entrapment efficiency (83.33%±2.81), high drug content (90.16%±5.53) and 92.64±2.91% drug release at the end of 24 hr and it showed zeta potential value of -27.1mV that indicates good stability of the formulation.

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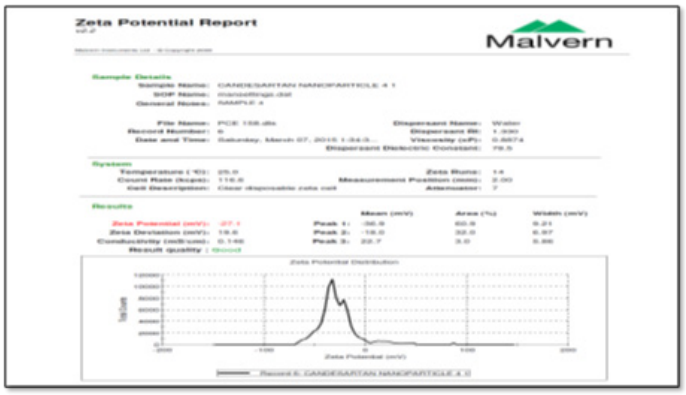


**Figure S6:** Zeta potential of the optimized formulation (F3).