Research Article

Enhancement of solubility of candesartan by nanotechnology application.

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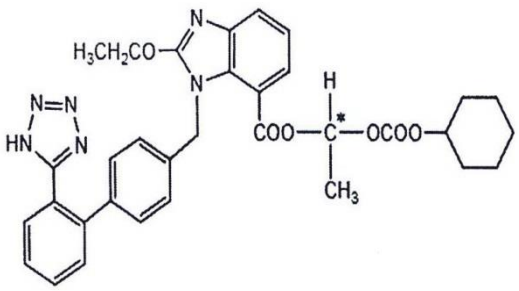
Abstract
Candesartan cilexetil (CC) belongs to the class Angiotensin II Receptor antagonist which is used in the treatment of hypertension. Candesartan cilexetil is included in Biopharmaceutical Classification System (BCS) Class II which is practically insoluble in water. This poor aqueous solubility of drug leads to difficulties in the phannaceutical formulation. To overcome this drawbacks there are many strategies to enhance the solubility and bioavailability. So the objective of these studies was to improve the solubility and dissolution rate of Candesartan by employing nanoteclmology.
Keywords: Candesartan, Nanoparticles and Pharmacokinetics.

Introduction
The progress in treatment of diseases has been evident within upsurge in development of new drugs. An estimated 40% of new chemical entities discovered by the phannaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development[1]. Candesartan is a tetrazole derivative (five-membered heterocyclic ring with 4 nitrogen atoms). Clinically it is used in the form of an ester prodrug Candesartan cilexetil. Candesatian cilexetil is chemically 2-ethoxy-3-[21-(lH-tetrazol-5-yl) biphenyl-4-yl methyl]-3H-benzimidazole-4-carboxilic acid 1 cyclohexyloxy ethyl ester (structure 1) with chemical formula $C_{33}H_{34}N_6O_6$ and molecular weight 610.67. It is white to off white powder with melting point 157-160° C. It is practically insoluble in water and sparingly soluble in methanol Candesartan Cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to Candesartan[2].



Structure l: Candesartan cilexetil (chiral center is marked by*).

Nanotechnology offers drugs in the nanometer size range which enhances the performance in a variety of dosage forms. Nano word is originated from Latin word, which means dwarf. Ideal size range offered by nanotechnology refers to one thousand millionth of a particular unit Recent advancement in nanotechnology has proven that nanoparticles acquire a great potential as drug carriers. Size reduction methods and technologies yields different types of nanostructures that exhibit unique physicochemical and

biological properties. These methods make the nanostructures favorable material for biomedical applications and thus acquire the significance importance in pharmaceutical sciences In addition these methods help in reducing toxicity, enhancing release, improving solubility and bioavailability and provide better formulation opportunities for drugs.

Materials and Methods

Materials

- Candesartan cilexetil (CC) is a gift sample provided by pharaonia pharmaceutical, Poly ethylene glycol 8000 (PEG 8000) and hydroxypropylmethylcellulose (HPMC) were purchased from El-Nasr pharm. Co., Egypt. Poly vinyl pyrolidone k30 (PVP K30) and Poly vinyl pyrolidone k90 (PVP K90) are purchased from sigma chemical Co.St, Louis (USA)

Preparation of Candesartan cilexetil (CC) **nanoparticles**

1- Preparation of Candesartan cilexetil (CC) **nanoparticles (NP) using solvent evaporation method;**

In this method the polymer was dissolved in aqueous solution using stirrer at 750 rpm and CC was dissolved in acetone and CC was injected drop wise to aqueous solution which standed in ice bath and 1 ml of a bar of prop sonicator was immersed under the surface of aqueous solution and a sonication was allowed for 5 minutes. Then a final system was allowed for homogenization for 15 minutes at 25000 rpm- and standed on stirrer at 750 rpm over night to remove the organic solvent (acetone) Finally this system was dried by freeze dryer for further characterization.
Polymers used in this method are PVP K30, PVP K90, PEG8000 and HPMC

General Procedure for Preparation of Nanoparticles

Polyvinylpyrolidone (PVP K90), macrogol 8000 (PEG), and Hydroypropylmethylcellulose (HPMC) were used as excipients. Each excipient (0.5 g or 1.0 g) was dissolved in water (10 mL), and two solutions with concentrations 5% and 10% were prepared. Candesartan cilexetil (0.2 g) was dissolved in acetone (10 ml), i.e. 2% solution was prepared. The solution of the substance in acetone was slowly dropped (2 mL/min) to the aqueous solutions of excipients that were stirred (600 rpm). Then the system was stirred (600 rpm) for 10 min at 35 °C, after which the mixtures were transferred to an ultrasonic bath in the fume chamber, where they were mixed again for 40 min, and simultaneously organic solvent was evaporated. The final volume of the aqueous sample was 10 mL. The particle size of nanonized substances in samples was evaluated by means of Nanosizer. All samples were dispersed by ultrasonic directly before the measurement.[3] All polymers used and it is ratios are reported in table (1).

Table (1) method and polymer concentration used in nanoparticle preparation

Polymer used	Method	Polymer cone.	Sample code
PVPK90	SEM		NP1
PVP K30	SEM		NP2
PEG 8000	SEM		NP3
HPMC	SEM		NP4
PVPK-90	General	10%	NP5
PEG8000	General	10%	NP6
HPMC	General	10%	NP7
PVPK-90	General	5%	NP8
PEG8000	General	5%	NP9
HPMC	General	5%	NP10

Characterization of the prepared samples

1. Particle size determination of nano-particles by Nano sizer

The mean particle size and particle size distribution of CC nanoparticles was determined by Nano Malvern Nano sizer at room temperature. All the samples were diluted with double distilled water to get a suitable concentration for examination and every sample was measured in triplicate[4].

2. In Vitro Release study of CC from different samples

USP type II dissolution test apparatus (Paddle) was used for in vitro dissolution studies of CC in different samples.[?] 16 mg of the CC equivalent of each sample was placed in 900 ml phosphate buffer (pH 6.8) stirred at 50 rpm and the temperature was kept at 37°C ± 0.5°C At predetermined time interval, 5 ml samples were pulled out and substituted with an equal volume of fresh buffer.

The concentration in the pulled out samples was determined spectrophotometrically at 256 nm. Each sample was implemented in three times and expressed as mean values ± standard deviation.

3. Kinetic data

The dissolution profile of each sample was fitted to various models such as zero order kinetics, first order kinetics and Higuchi, to assess the kinetics of drug release from prepared samples.

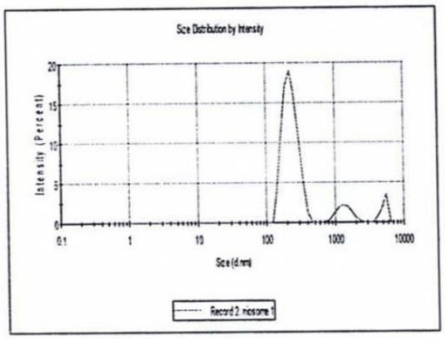
Results and discussion

1. Particle size determination of nano-particles by Nano sizer

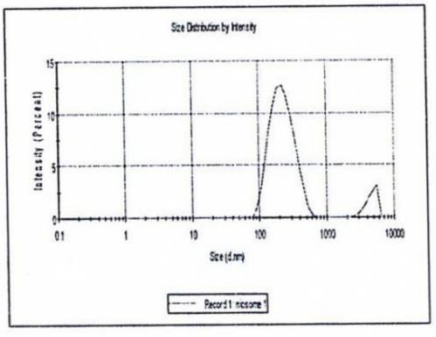
The average size of the prepared samples is recorded in table (2).as illustrated in figures (1-10) from the table the best results obtained in samples S1 and S2. So these two results were allowed only for further characterization. Also (S3) and (S4) contain good nanoparticles but their PDI not good. Also (S10) contains nearly good nanoparticles.

Table (2): Average particle size of CC nanoparticles

Sample	Mean particle size (nm)± SD	PDI
S1	291.5 ± 20.19	0.418
S2	238.9 ± 19.25	0.320
S3	483 ± 71.5	0.892
S4	699 ± 29.19	0.288
S5	1156± 100.50	0.703
S6	4652 ± 200	0.069
S7	5125 ± 150.9	0.127
S8	1156 ± 70.17	0.594
S9	1033 ± 48.90	0.505
S10	741 ± 17.80	0.447



Figures (1) Size of S1



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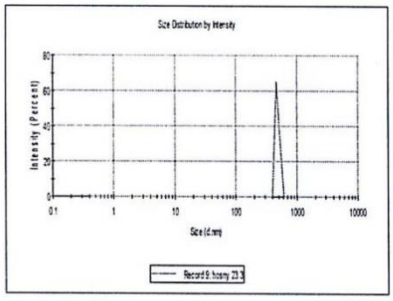
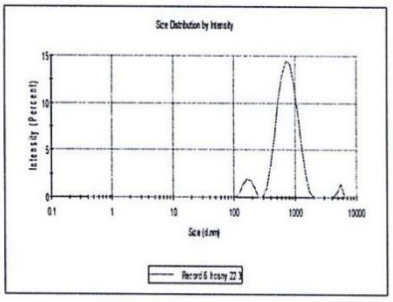
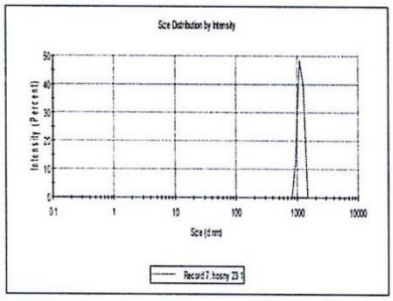


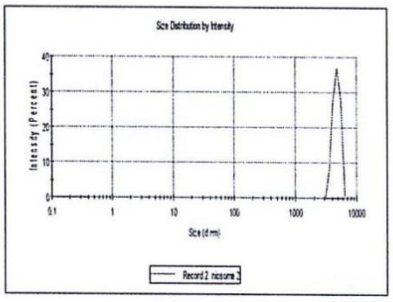
Figures (3) Size of S3



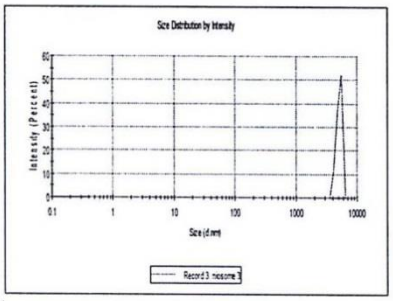
Figures (4) size of S4



Figures (5) Size of S5



Figures (6) size of S6



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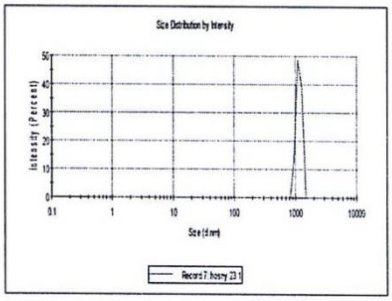

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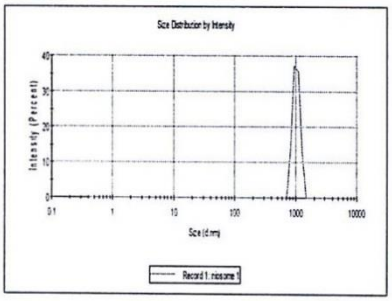
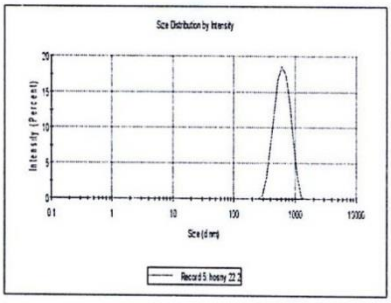


Figures (9) Size of S9



Figures (10) size of S10

2. In vitro release study

In vitro release of CC alone and different samples was illustrated in figure (11). All samples of CC nanoparticles modified the release of CC when compared to the drug itself. This improvement may be due to higher wettability and dispensability, while co precipitation of drug with hydrophilic carrier resulted in greater wetting and increase surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media.

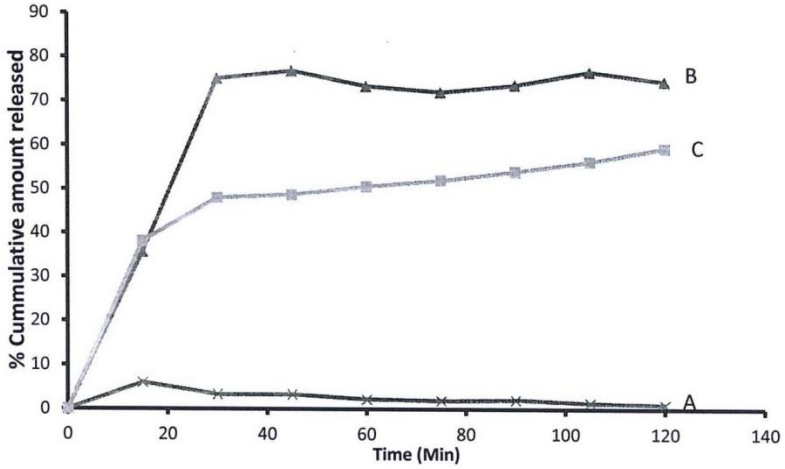


Figure (11) In vitro release ofCC-nanoparticles (A) CC alone (B) Nano with PVP K30 and (C) Nano with PVP K90

3. Kinetic analysis of release profiles

The release patterns were fitted on various kinetic models such zero, first and Higuchi. The correlation coefficient of the straight line that has the highest value was used to compare between different models. Table (3) listed the correlation coefficients (r) of all samples. The obtained data revealed that the release profiles of all samples follow Higuchi diffusion model except samples SD2 and SD6 release profiles follow first order kinetics.

Table (3): The kinetics parameter correlation coefficient (r) of zero, first and Higushi models for different samples.

Sample code	zero	first	Higushi
	r^2	r^2	r^2
NP1	0.6562	0.7578	0.8829
NP2	0.726	0.8448	0.9135
NP3	0.846	0.790	0.889
NP4	0.783	0.819	0.916
NP5	0.834	0.798	0.898
NP6	0.781	0.832	0.952
NP7	0.882	0.825	0.911
NP8	0.789	0.792	0.832
NP9	0.698	0.779	0.893
NP10	0.803	0.881	0.912

Conclusion

From the previous results, it was possible to conclude that dissolution rate of Candesartan were considerably improved when formulated as nanoparticles by solvent evaporation method and this method may be considered ideal method for preparation of candesartan nanoparticles.

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