



Change in Site of Release Offers Advantages for Candesartan Cilexetil

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ABSTRACT

Candesartan cilexetil is a poorly soluble antihypertensive agent with solubility limited bioavailability (15%). It is a prodrug which converts into active drug candesartan with hydrolysis in GIT. Apart from having low solubility, candesartan cilexetil also shows pH dependent solubility. Solubility of said drug increases with rise in pH. To check the advantage of controlling the release till intestinal pH, nanoencapsulates of said drug with eudragit L100 were prepared and evaluated for particle size, surface morphology, saturation solubility and multimedia dissolution. The technique was found to be effective for candesartan cilexetil with particle size in the range of 551-1234 nm as D90% with a smooth surface and % entrapment efficiency was 18-23%. Considerable rise in solubility and dissolution as compared to pure drug was seen in multimedia dissolution offering advantage of improved dissolution with change in site of release in intestine.

Keywords: Candesartan, Controlled release, Dissolution enhancement, Eudragit L100, Nano encapsulation, Nanoparticles, Solubility enhancement.

INTRODUCTION

Candesartan cilexetil is a low soluble antihypertensive drug with solubility limited bioavailability (15%). It is a prodrug which gets convert into active drug candesartan by hydrolysis in gastrointestinal tract.

Various methods are reported to enhance the solubility of a poorly soluble drugs including complexation,¹⁻³ nanoparticles,⁴⁻⁶ self micro emulsifying systems⁷⁻⁹ and have shown beneficial results on various categories of drugs as well as on candesartan cilexetil.¹⁰⁻¹²

Apart from having low aqueous solubility candesartan shows a pH dependent solubility profile with more in solubility with increased pH.¹³ Surprisingly the dosage forms which are available for candesartan cilexetil and the research carried out is for release of drug in stomach, the pH in which the drug is least soluble.

Present research attempts to control the release of candesartan cilexetil for release at intestinal pH and checking the improvement in solubility as well as dissolution.

As reported before the aim of preparing nanoparticles by nano encapsulation was to retard the release in stomach. Various polymers are available which are used as enteric coated polymers. Eudragit polymers are also a group of polymers which are repeatedly reported to be used in the formulation of nanoparticles as well as controlled or sustained release per oral systems. Many nanoparticles are used for targeted as well as in ocular therapy. Various grades of eudragits are available but most commonly used are E100, RL100, RS 100, EPO, RSPO and RLPO.

Various grades of eudragits are used for various purposes such as Eudragit 100 and eudragit E 12.5 are yellow in color, are soluble in gastric fluid up to pH 5 and are used for film coating. Eudragit NE 30 is a swellable grade yellow in color and used for sustained release. Eudragit L100, L 12.5 and L 12.5 P are a white free flowing powder, soluble in intestinal fluid from pH 6 and used for enteric coatings. Eudragit L 30 D-55, L100-55, Eastacryl 30D, Kollicoat MAE 30 D, Kollicoat MAE 30 DP are white or milky white in color, soluble in intestinal pH from pH 5.5 which are used for enteric coatings. Eudragit S100, S12.5, S12.5 P are white free flowing powders, soluble in intestinal fluid from pH 7 are used for the purpose of enteric coatings.

As release of this formulation was expected in intestine, it was decided to use Eudragit L 100 because it was reported to enhance the solubility and bioavailability of many poorly soluble drugs.¹⁴⁻¹⁹

MATERIALS AND METHODS

Candesartan cilexetil was obtained as a gift sample from Alembic Ltd., Baroda. Eudragit L100 was obtained as a gift sample from Evonik, Mumbai. All solvents used in this research were purchased from s.d.fine chemicals Ltd., Mumbai.

Preparation of nanoparticles by nano encapsulation

Nanoparticles were prepared by using o/w emulsification solvent evaporation technique.

Polymer was dissolved in a 5 ml mixture of methylene chloride: ethanol (3:1). After dissolving polymer, drug was added in the mixture and dissolved by using ultra sonicator. This solution was poured in 1% w/w PVA

solution by keeping different ratio's of phase to volume. An o/w emulsion was formed with extensive stirring with a magnetic stirrer. System was kept on stirring until methylene chloride was evaporated. System was centrifuged at 12000 rpm for 1 hour and resultant nanoparticles were collected and lyophilized. Total 9 systems were prepared, out of that best system was evaluated particle size, polydispersity index, zeta potential, drug loading efficiency, drug content, percentage yield, drug content, Saturation solubility testing, in vitro multimedia study and surface morphology.

Evaluation²⁰

Prepared nanoparticles were evaluated for particle size analysis, drug content, drug loading efficiency, in-vitro release study and morphological analysis.

Measurement of particle size and zeta potential

Particle size was measured by photon correlation spectroscopy using a zetasizer.

Drug loading efficiency

Drug loading efficiency was calculated by analyzing amount of drug present in supernatant by UV spectroscopic analysis by using following formula

$$\text{DLE} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \times 100 \dots\dots\dots \text{Eq.1}$$

Table 1: Formulation design for preparation of nanoparticles

Sr. No.	Drug: Polymer	Organic phase: Aqueous phase
NE 1	1:10	1:2
NE 2	1:10	1:3
NE 3	1:10	1:4
NE 4	1:20	1:2
NE 5	1:20	1:3
NE 6	1:20	1:4
NE 7	1:30	1:2
NE 8	1:30	1:3
NE 9	1:30	1:4

Percentage yield

Percentage yield was calculated using following formula -
% yield=

$$\frac{\text{Amount in grams of nanoparticles obtained}}{\text{Total amount of drug + polymers added}} \times 100 \text{ Eq.2}$$

Total amount of drug + polymers added

Drug content

Drug content was analyzed by taking amount of drug equivalent to 10 mg and diluting suitably with acetonitrile and analyzing the drug content by UV spectroscopic analysis.

Solubility studies

Nanoparticles containing a fixed amount of drug was added to vials containing 5 ml each of 0.1 N HCl, phosphate buffer pH 6.8 and water and rotated in rotary shaker for 48 hours at 37°C. Solutions were then centrifuged at 12000 rpm for 30 minutes and supernatant was analyzed for drug content using UV spectroscopic analysis.

In-vitro release study

Release was checked in all previously mentioned medias for 1 hour and subsequently for 2, 4 and 8 hours in phosphate buffer pH 6.8 and drug release was analyzed using UV spectroscopic analysis.

Morphological analysis

Surface morphology was studied by using SEM analysis.

RESULTS AND DISCUSSION

Preparation of nanoparticles

Total 9 systems were prepared as described in previous section. Amongst all prepared systems, only systems NE3, NE6 and NE9 were having comparative clear appearance and were chosen for further studies.

Evaluation of nanoparticles using nano encapsulation technique

For measurement of entrapment efficiency, supernatant was suitably diluted with methanol and analyzed at 254 nm and amount of an entrapped drug was calculated. Percentage drug entrapment was calculated by dissolving nanoparticles equivalent to 8 mg drug were dissolved in methanol. Drug loading efficiency was found to vary between 18 to 23 % with system NE3 showing maximum drug loading efficiency of 23.18%. Percentage yield was calculated by the formula described Eq.2

Particle size, polydispersity index and zeta potential of the given systems was calculated using photon correlation spectroscopy and electrophoretic light scattering using Delsa Nano instrument. Particle size was found to range from 551 nm-1234 nm of the selected systems It was found that lower the ratio of drug: polymer, lower the size of particles. In the same way higher the drug present, higher the drug loading efficiency was seen.

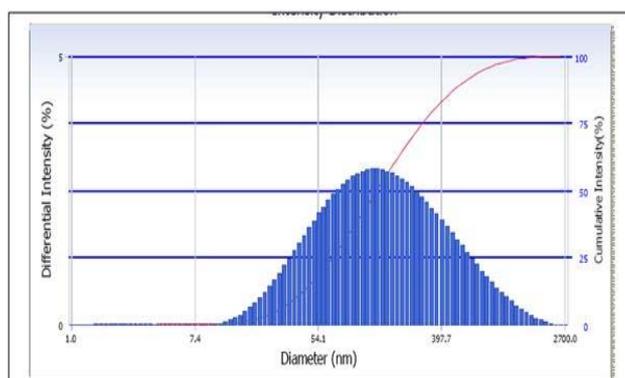
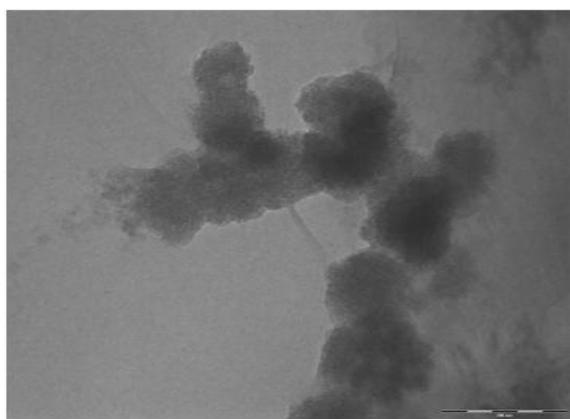


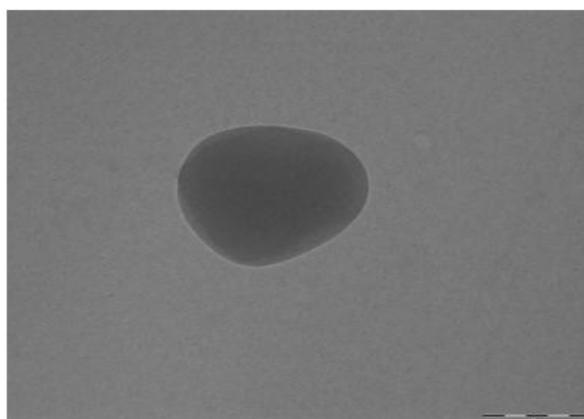
Figure 1: Particle size distribution curve of NE 3

Table 2: Evaluation of selected nanoparticle systems

Formulation code	Encapsulation efficiency (%) n=3	DLE (%), n=3	Drug content (%), n=3	Polydispersity index	Zeta Potential	Percentage yield (%W/W) n=3	Particle size D (90%)
NE3	44.24	23.18	95.16	0.239	21.62	60	551.4
NE6	34.33	20.06	96.14	0.173	24.36	48	624
NE9	29.45	18.17	95.48	0.28	22.17	55	1234



(a)



(b)

Figure 2: TEM images of nanoparticles prepared by nanoencapsulation technique (a = Clusture of particles, b=Individual particle)

From particle size, polydispersity index and drug loading efficiency as shown in table 2 and figure 1, NE3 was chosen for further analysis of morphology saturation solubility and in vitro multimedia dissolution.

TEM images revealed smooth surfaces and formation of spherical particles. Though the particles are seen together in first image, they are well separated as shown in second image.

The saturation solubility testing and multimedia dissolution study of the selected system was carried out in all media's mentioned above. There was a drastic increase in saturation solubility as compared to pure drug in all medias, as shown in Figure 3 and 4.

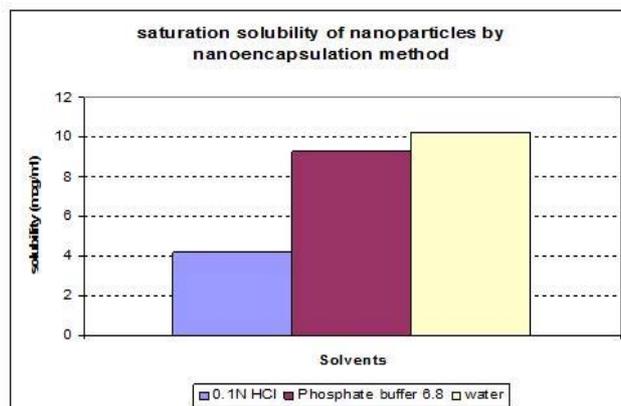


Figure 4: Saturation solubility of nanoparticles

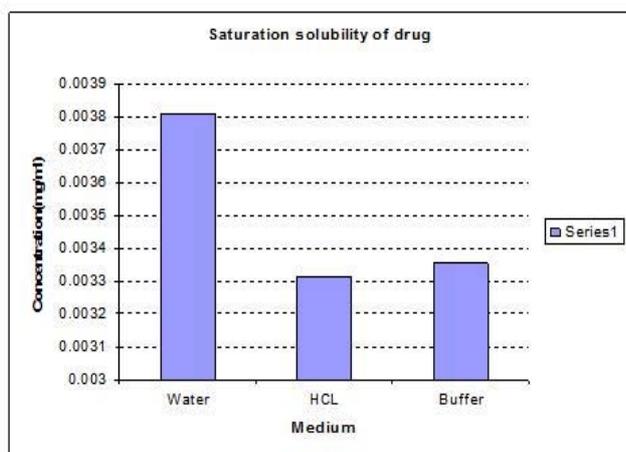


Figure 3: Saturation solubility of drug

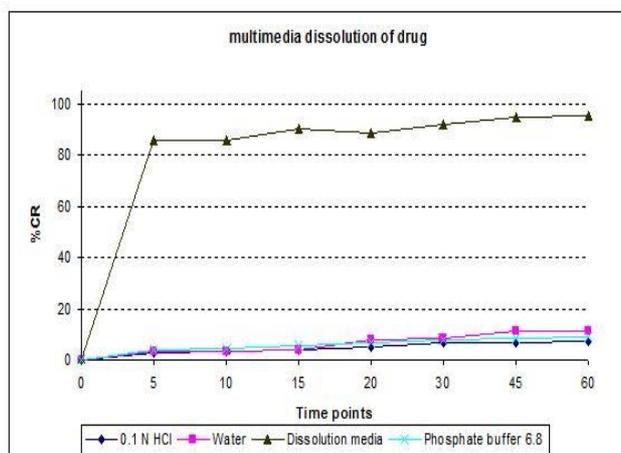


Figure 5: Multimedia dissolution of drug

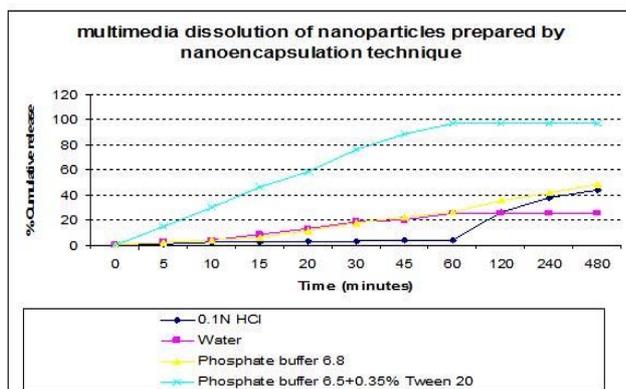


Figure 6: Multimedia dissolution of nanoparticles

In-vitro multimedia dissolution of prepared nanoparticles was carried out. It was seen that in acidic pH, the release up to one hour was only 4% because of low solubility of drug as well as polymer in that pH. In water and phosphate buffer pH 6.8, initial slow release followed by a burst release at the end of 10 minutes was seen might be due to solubilization of polymer and release of drug. A total drug release of around 25% and 26% was seen in water and phosphate buffer pH 6.8 respectively as compared to 11% and 9% of pure drug as shown in figure 5 and 6. When dissolution was continued in phosphate buffer pH 6.8, maximum release of 48% was seen at the end of 8 hours. No further enhancement in total release of drug was seen when dissolution in acidic media was continued for three hours in phosphate buffer pH 6.8.

CONCLUSION

Change in site of release has shown promising advantage in solubility and multimedia dissolution of candesartan cilexetil owing to pH dependent solubility of drug. *In-vivo* studies of the said system can confirm biopharmaceutical advantage of the same.

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