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Formulation and Evaluation of Carvedilol loaded Eudragit e 100 Nanoparticles

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Abstract: The aim of this work was to prepare Eudragit E 100 Nanoparticles of Carvedilol and to characterize them. Nanoparticles of Carvedilol with Eudragit E 100 were prepared by the Nanoprecipitation method using Polymeric stabilizer Poloxamer 407. Nanoparticles of Carvedilol were obtained with high encapsulation efficiency. The particles were characterized for particle size by photon correlation spectroscopy and transmission electron microscopy. The in vitro release studies were carried out by USP Type II apparatus in SGF without enzyme (pH 1.2).The particle size of the prepared nanoparticles ranged from 190 nm – 270 nm. Nanoparicles of Carvedilol were obtained with high encapsulation efficiency (85-91%). The drug release from the carvedilol nanoparticles showed within 5 minutes. These studies suggest that the feasibility of formulating carvedilol – loaded Eudragit E 100 nanoparticles for the treatment of hypertension.

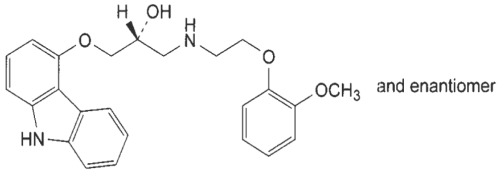
Keywords: Carvedilol, Nanoparticles, Particle size, Zeta potential, TEM, in vitro release studies.

Introduction:

Carvedilol is a nonselective β-adrenergic blocking agent with α_1-blocking activity.

Carvedilol is (2 RS)-1-(9H-Carbazol-4yloxy)-3-[[2-(2-methoxy phenoxy)ethyl]amino] propan-2-ol. (Fig.1).

Figure .1 Chemical structure of Carvedilol



It antagonizes the actions of catecholamine more potently at β receptors than at α receptors. It is β_1 and β_2 blocker; α_1-blocker. It is a racemic mixture in which non cardio selective β-adrenergic receptor blocking activity is present in the S(-) enantiomer and selective α_1-adrenergic receptor blocking activity is present in both R(+) and S(-) enantiomers at equal potency. In higher concentrations it blocks the entry of Ca^{++} into the vascular smooth muscle. It also has antioxidant activity. The ratio of α_1- to β adrenergic receptor antagonist potency for carvedilol is 1:10.

Carvedilol is a lipid soluble compound, practically insoluble in water and poorly absorbed from the gastrointestinal tract. The slow absorption of Carvedilol was attributed to its poor water solubility. It has absolute bioavailability 25-35%. Therefore Nanotechnology can be used to improve the bioavailability of Carvedilol by improving the dissolution characteristics and other physico-chemical characterization.

Nanoparticles are one of the multiparticulate delivery systems and are prepared to improve bioavailability or stability and to target drug to specific sites. Nanoparticles can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance[1]. Haznder and Dortune reported controlled release Eudragit microspheres of acetazolamide[2], whereas Dai et al studied Eudragit Nanoparticles as a carrier for enhancing oral bioavailability of cyclosporine[3]. Tzu-Hui Wu et al reported novel quercetin nanoparticles system prepared by a simple nanoprecipitation technology with Eudragit E (EE) and polyvinylalcohol as carriers[4]. Bingbing Jiang, Ling Hu, Changyou Gao et al. developed a co-precipitation method to fabricate nano-scale core-shell particles of ibuprofen stabilized by DEAE dextran[5]. O.Kayser, et al. were developed Formulation of amphotericin B as nanosuspension for oral

administration[6]. The object of the study was to formulate and characterize Eudragit Nanoparticles containing carvedilol by determining their size, their external morphology and encapsulation efficiency.

Material and methods

Carvedilol was obtained from Torrent Phrmaceuticals (Ahmedabad,India) as a gift sample. Eudragit E 100 (Rohm Pharma) was kindly provided by Degussa (India), Poloxamer 407 was procured from BASF, and sodium alginate was procured from Loba chemie. Pvt ltd. All other chemicals were of analytical grade.

Preparation of Nanoparticles

Nanoparticles (nanospheres) were prepared by Nanoprecipitation according to the method developed by Fessi and colleagues[7].Eudragit E 100 was dissolved in methanol then Carvedilol was added and dissolved. The organic solution was injected at a rate of 48ml/min in distilled water containing Poloxamer 407 under magnetic stirring at room temperature. Methanol and some proportion of water were eliminated under reduced pressure. The final Nanosuspension was used for further characterization. Nanosuspension formulae were established (Table1) with different polymer concentration levels to obtain higher encapsulation efficiency, desired particle size. A placebo Nanosupension (with out drug) was prepared for comparison studies.

Table No 1. Formulae of Nanosuspensions

Batches	Carvedilol (mg)	Eudragit E 100 (mg)	Poloxamer (mg)	Sodium Alginate (mg)	Methanol (ml)	Water (ml)
CNS – A	0	200	200	50	20	40
CNS – B	100	200	200	50	20	40
CNS – C	100	400	200	50	20	40
CNS – D	100	200	400	50	20	40
CNS – E	100	400	400	50	20	40
CNS – F	100	200	400	0	20	40

Table No 2. Particle size, polydispersity and Zeta potential and Encapsulation efficiency of carvedilol nanoparticles.

Batches	Particle size	Polydispersity index	Zeta Potential	Encapsulation efficiency (%)
CNS – A	190 nm	0.309	- 32.6 mv	-
CNS – B	210 nm	0.386	- 32.8 mv	85.29
CNS – C	244 nm	0.334	- 34.4 mv	91.85
CNS – D	240 nm	0.463	- 28.3 mv	86.48
CNS – E	270 nm	0.492	- 34.5 mv	90.87
CNS – F	215 nm	0.583	+15.5 mv	87.57

Nanoparticle characterization

Particle size analysis

Particle size analysis of Nanoparticles was performed by photon correlation spectroscopy (PCS).This technique yields the mean particle diameter and particle size distribution. Samples were analyzed using Mastersizer 2000(Malvern Instruments, Malvern, UK), which allows sample measurement in the range of 0.020 – 2000.00 µm.

Polydispersity was determined according to the equation:

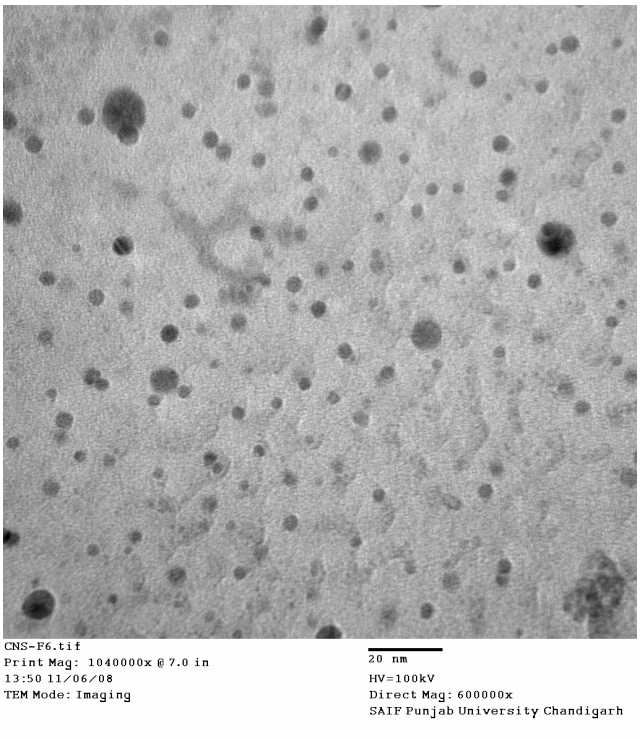
$$\text{Polydispersity} = \frac{D(0.9) - D(0.1)}{D(0.5)}$$

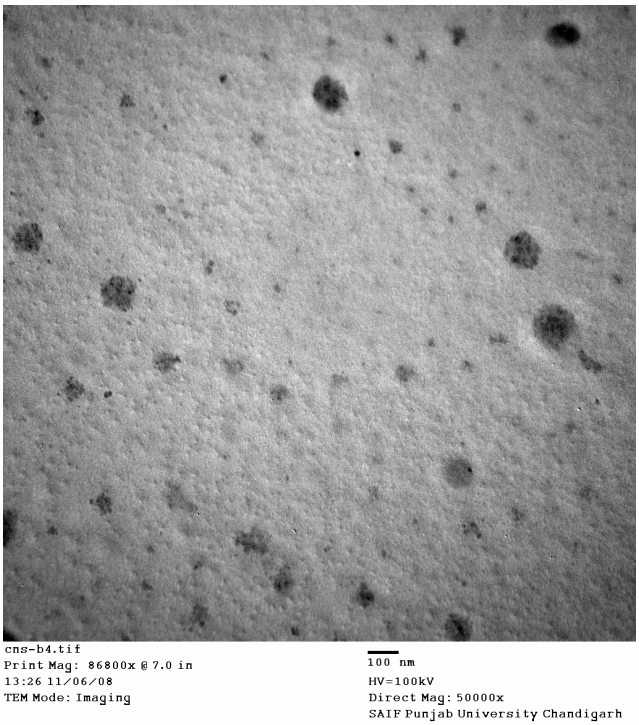
Where D(0.9) corresponds to particle size immediately above 90% of the sample, D(0.5) corresponds to particle size immediately above 5% of the sample, D(0.1)corresponds to particle size immediately above 10 of the sample[8].

External morphological study

External morphology of Nanoparticles was determined using Transmission electron microscopy (TEM). Samples of Nanoparticles (drug– loaded and placebo Nanoparticles) were prepared by placing one drop on a copper grid, before being examined using TEM without being stained.

Figure 2: TEM micrographs of Eudragit E 100 nanoparticles (CNS-F6) Carvedilol-loaded Eudragit E 100 nanoparticles magnified 6,00,000 x and (CNS-B4) Placebo nanoparticles magnified 50,000 x



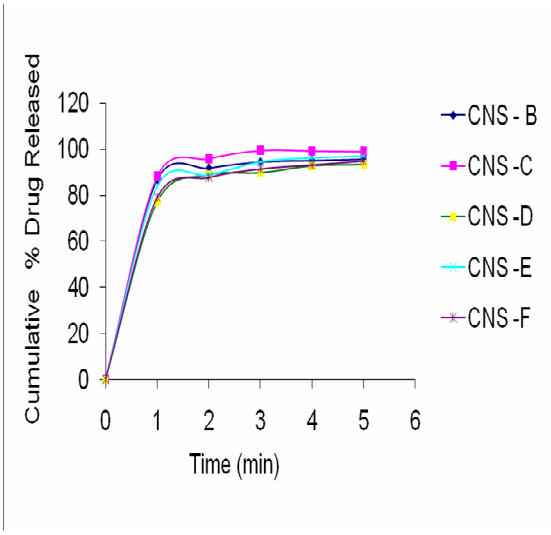


Encapsulation efficiency of Nanoparticles

Total Carvedilol was determined after full dissolution of a specific amount (1 ml) of carvedilol- loaded Eudragit E 100 Nanoparticle suspension in 20 ml of SGF[8].Free carvedilol was determined after centrifugation of the samples at 9000 rpm for 30 minutes.

$$\text{Encapsulation efficiency} = \frac{\text{Total drug} - \text{Free dissolved drug content}}{\text{Drug amount used}} \times 100$$

Figure 3: Cumulative percent drug released in SGF (pH 1.2) Mean ± SD, n=3



Invitro drug release studies

The in vitro drug release from carvedilol nanosuspension was carried out using USP Padddle apparatus at 50 rpm and 37±0.5°c; simulated gastric fluid with out enzyme[9] (pH 1.2) was used as the dissolution medium. Briefly, Carvedilol loaded Eudragit Nanoparticles (Equivalent to 10 mg) were suspended in 900 ml of simulated gastric fluid with out enzyme[10]. The samples were withdrawn at regular intervals and replaced with fresh media and analyzed by UV spectrophotometer (Shimadzu UV/VIS) at 240 nm for the presence of drug. Dissolution test were performed in triplicate.

Results :

Particle size analysis:

The mean particle size of carvedilol – loaded Nanoparticles is shown in Table 2. The particle size distribution curves for all the samples are unimodel. Nanoparticle sizes were 210 nm, 244 nm, 240 nm, 270 nm and 215 nm for Batches CNS-B, CNS-C, CNS-D, CNS-E, and CNS-F, respectively. The nanoparticle size depended directly on Eudragit E-100 amount. The smallest particles of 210 nm were found in batch CNS-B (200mg Eudragit content) and the largest particles of 270 nm were seen in batch CNS-E (400 Eudragit content) (Table2). The data in Table2 suggest that an increase in polymer concentration increases the size of the Nanoparticles.

The Zeta potential of nanosuspension were - 32.6 mV, - 32.4 mV, - 34.4 mV, - 28.3 mV, - 34.5 mV, and + 15.5 mV for Batches CNS-B, CNS-C, CNS-D, CNS-E, and CNS-F, respectively. Negative zeta potential value was observed due to the presence of Sodium alginate, in the absence of sodium alginate in batch CNS- F + 15.5 mV positive zeta potential was observed.

External morphological study

The external morphological study revealed that all Nanoparticles were spherical in shape. Placebo Nanoparticles (with out drug) showed an absence of matrix.(Figure 2). The Nanoparticles size, as observed by TEM, correlated well with size measured by PCS.

Encapsulation efficiency of Nanoparticles.

The amount of free dissolved drug in the nanosuspensions ranged from 14.71 %(CNS-B), 8.15 %(CNS –C), 13.52 %(CNS-D) and 9.13 %(CNS-E) and 12.43 %(CNS-F), respectively. Free dissolved drug in the nanosuspension decreased with an increase in the Eudragit concentration. Encapsulation efficiency was inversely related to free dissolved drug and it was directly related to the amount of Eudragit used. Although encapsulation efficiency increased with an increase in the Eudragit amount.

Invitro drug - release studies

Figure 3 show the percentage release of carvedilol from different batches (CNS B-F) in SGF without enzyme. The drug release from the carvedilol nanoparticles showed with in 5 minutes. The data indicate that the rate of release of carvedilol from the nanoparticles were faster and almost similar in all formulations.

Conclusion :

This study confirms that the nanoprecipitation technique is suitable for the preparation of carvedilol nanoparticles with high encapsulation efficiency. This formulation approach can be used to improve the therapeutic efficacy of poorly soluble drugs. The changes in nanoparticle size and drug encapsulation efficiency were affected by changes in polymer concentration.

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