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Research Article

Development Of Carvedilol Nanoparticles As Antihypertensive Agent

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ABSTRACT

In the present work, an attempt was made to formulate nanoparticles of carvedilol, to increase the bioavailability of Carvedilol. Carvedilol is an antihypertensive agent, nonselective ß-blocker of low molecular weight 406.47 gm/mol BCS class II undergoes extensive hepatic first-pass metabolism (75% - 80%), with an oral bioavailability of 20 to 25% and a half-life of 7 hrs. The dosage for hypertension is 3.25 to 12.5 mg twice daily for the first 2 days and can then be increased if necessary to 50 mg daily. The prepared nanoparticles were formulated using Eudragit RL100 as the rate-controlling polymer at different concentrations. Nanoparticles of carvedilol were prepared by using Eudragit RL, Tween 80 and Mannitol. The prepared formulations were then characterized for loading efficiency, encapsulation efficiency and drug-excipient compatibility. The prepared nano-particulate formulations of carvedilol with different polymers in 1:2, 1:3, and 1:4 ratio have shown entrapment efficiency in the range of 76.44%-84.03%. In FTIR study no major interaction occurred between the drug and polymers used in formulation. The surface morphology of the formulations were studied by scanning electron microscopy which confirmed the formation of nanoparticles. From prepared formulation in 1:2 ratio showed satisfactory results of dissolution for 10 hrs. with cumulative release of 88.16% compare to other formulations. This study confirmed that solubility of carvedilol was improved by formulation of nanoparticles by nanoprecipitation method.

INTRODUCTION

During the last decades, alternative ways of medication administration have gained attention. There are numerous studies on novel drug delivery approaches. But oral administration remains the most effective and easiest to administer, and it induces minimal side effects. However, the main disadvantage of oral administration is poor bioavailability. To overcome these problems, the use of Nano-carriers as drug delivery systems by oral route has become well known. Numerous studies have shown that nanoparticles can improve

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the oral bioavailability of hydrophobic, hydrophilic and biologic drugs via various mechanisms1. Nanoparticles (NPs) are capable of functioning as pharmaceutical carriers for a variety of delivery systems. Studies have shown that NPs have been applicable for use in the pharmaceutical and biomedical sectors to treat illnesses including diabetes, hypertension, cancer, and HIV. NPs have been developed to increase therapeutic limitations and membrane permeability, and with the development of personalized therapies, their therapeutic efficacy has been improved.2 Polymeric NPs, such as the chitosan, ethyl cellulose, HPMC are commonly 10–1000 nm in dimension and, being formulated from polymers, have a natural bio adaptability, biocompatibility, and biodegradability. Chitosan NPs have the benefit of slowing and controlling the release of drugs, improving their solubility and stability, and decreasing their toxicity.3-4 Carvedilol is a β-blocker Antihypertensive drug, lipophilic in nature and has low bioavailability. Hence, a higher daily dose 25 mg twice a day is necessary to maintain therapeutic effectiveness. The absorption of drugs through the oral mucosa depends on the concentration gradient.5 Thus, their solubility can be improved by formulation of nanoparticles. Eudragit RL100 a positively charged polymer, displays unique pH-independent changes, enabling it to remain intact during pH variations in the stomach.6-8 Thus this study involves formulation of carvedilol nanoparticles for the treatment of hypertension.

MATERIALS AND METHODS

Materials:

Drug: Carvedilol, Polymers: Eudragit RL100, Methanol, Potassium hydrogen phosphate, Eudragit-RL100, and Tween-80 were purchased from Loba chemie labs, Mumbai. All chemicals used were of analytical grade and obtained commercially.

METHODS:

Pre-formulation studies: 9-11

A complete evaluation of physicochemical properties carvedilol was carried out.

Identification tests: Determination of melting point: The melting point of carvedilol was determined by using a melting point apparatus.

Drug excipient interaction study by FTIR spectroscopy: A physical mixture of drug and polymer (1:1) were prepared and mixed by triturating with a suitable quantity of potassium bromide. Approximately 100 mg of this mixture was compressed to form a transparent pellet. The sample was scanned from 4000 to 400 cm-1. The IR spectrum of the physical mixture was compared with those of the pure drug and polymers, and matching was performed to detect any appearance or disappearance of the peak.

Preparation of the standard calibration curve of carvedilol in pH 6.8 phosphate buffer: Accurately100 mg of carvedilol was dissolved in 10 ml of methanol, the volume was adjusted to 100 ml with pH 6.8 phosphate buffer, from this stock solution, serial dilutions of 1 to 7 µg/ml carvedilol were prepared using pH 6.8 phosphate buffer. The prepared solutions of carvedilol were analyzed by UV–visible spectrophotometer by measuring the absorbance at 241 nm.

Preparation of Carvedilol-Loaded Eudragit RL 100 Polymeric Nanoparticles: 12-13 Carvedilol loaded Eudragit RL100 polymeric nanoparticles were prepared by a nanoprecipitation method. Three formulations, NP1, NP2 and NP3, were prepared by changing the drug: polymer ratio to 1:2, 1:3 and 1:4, respectively. The exact amounts of polymer and drug used for the preparations are depicted in Table 2.

Table 1: Formulation of carvedilol-loaded Eudragit RL100 nanoparticles.

Ingredients	Formulations		
	NP1	NP2	NP3

Carvedilol (mg)	1000	1000	1000
Eudragit RL100 (mg)	2000	3000	4000
Methanol (ml)	30	30	30
Ethanol (ml)	12	12	12
Tween 80 (2% w/v) (Qty. in ml)	1.2	1.2	1.2
Purified water (ml)	58.8	58.8	58.8
Mannitol	150	200	250

Carvedilol was first dissolved in methanol, and the polymer was dissolved in ethanol. Finally, both the polymer and drug solutions were mixed. In 100 ml of measuring cylinder, 1.2 ml of Tween 80 was taken, and the volume was made up to 60 ml with purified water. This solution was transferred to a beaker and kept under magnetic stirring with continuous stirring to form a vertex. The organic phase was added at a rate using a 1 cc syringe to 60 ml of aqueous phase containing 2% w/v Tween 80 under continuous stirring. The formulation was then subjected to size reduction using a high-speed homogenizer at 10000 rpm for 10 minutes. Continuous evaporation of the organic phase under stirring ensures the precipitation of polymeric nanoparticles. The resulting formulation was sonicated for 5 minutes and lyophilized to obtain free-flowing carvedilol-loaded Eudragit nanoparticles using mannitol as cryoprotectant, which was added prior to lyophilization. The nanoparticles were collected and stored in a cool, dark place.

Characterization of the Eudragit RL100 nanoparticles:[14-16]

Percentage yield: Percentage yield was calculated using the following formula:

$$\textit{Percentage yield} = \frac{\textit{Weight of nanoparticles obtained}}{\textit{Weight of drug+Polymer+Tween 80+Mannitol}} \textit{ X 100}$$

Percentage entrapment efficiency: The entrapment efficiency was determined by the dialysis method. A weighed quantity of nanoparticles was placed inside the dialysis tube and suspended in a beaker containing 1000 ml diffusion medium (pH 6.8 phosphate buffer), which was constantly stirred at 37°±1 °C on a magnetic stirrer for 5 min and then transferred to the next beaker containing the same medium maintained under similar conditions. Each sample was diluted suitably and assayed spectrophotometrically at 241 nm using a Shimadzu UV-1800. The same procedure was followed to separate unentrapped drugs until negligible readings were obtained. The sum of each release gives the total amount of unentrapped drug. The time required to release the unentrapped drug was noted. After suitable dilutions, the encapsulated drug was analysed by triturating the retained nanoparticles and then assayed spectrophotometrically at 241 nm.

The percentage entrapment efficiency (%EE) was calculated using the following equation:

$$\%EE = \frac{\text{Assay value}}{\text{Theorotical amount of drug}} \text{ X } 100$$

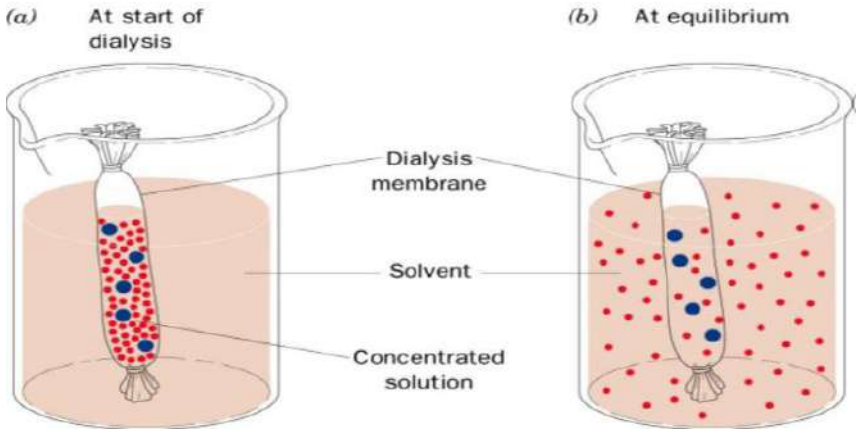

Fig 1: The entrapment efficiency was determined by the dialysis method

Drug content: The formulation was triturated in a mortar, and 100 mg of powder was transferred to a 100 ml volumetric flask. To this, 20 ml of methanol was added to the flask. The mixture was shaken well, and then the volume was made up to 100 ml with phosphate buffer (pH 7.4). 1.0 ml of this solution was diluted to 100 ml in volumetric flask. The absorbance of the solution was measured with UV–visible spectrophotometer at 241 nm. The amount of carvedilol was calculated. The drug content was calculated using the following equation:

$$\text{Drug content} = \frac{\text{Analyzed weight of drug in nanoparticles}}{\text{theoretical weight of drug in nanoparticles}} \text{ X } 100$$

Solubility studies in pH 6.8 phosphate buffer:17
Excess (equivalent to 50 mg of carvedilol) carvedilol nanoparticles and pure carvedilol powder (50 mg) were added to 30 ml of pH 6.8 phosphate buffer solution in two different 50 ml beakers. The mixtures were stirred on a magnetic stirrer for 12 h at 37±0.5 °C. Visual inspection was performed to ensure that there was an excess sample in the solid state, indicating that saturation had been reached. The mixtures were filtered, and the filtrates were diluted to determine the solubility of carvedilol using UV–visible spectrophotometer.

Scanning electron microscopy (SEM):
The size and surface morphology of the nanoparticles were observed using scanning electron microscopy. The sample was placed in a scanning electron microscope (JEOL-JSM-6360, Japan) chamber (at a pressure of 0.6 mm Hg) at an acceleration voltage of 20 kV, and photographs were taken41.

RESULTS AND DISCUSSION

Pre-formulation studies of pure drug:

Determination of the melting point: The melting point of carvedilol was 115 °C.

FT-IR spectroscopy: The FT-IR spectra of pure carvedilol, carvedilol with Eudragit RL 100 and carvedilol with other excipients were obtained. It was clear from the spectra that all the characteristic peaks were present and that the drug and excipients were compatible with each other (Fig. 2 to 4).

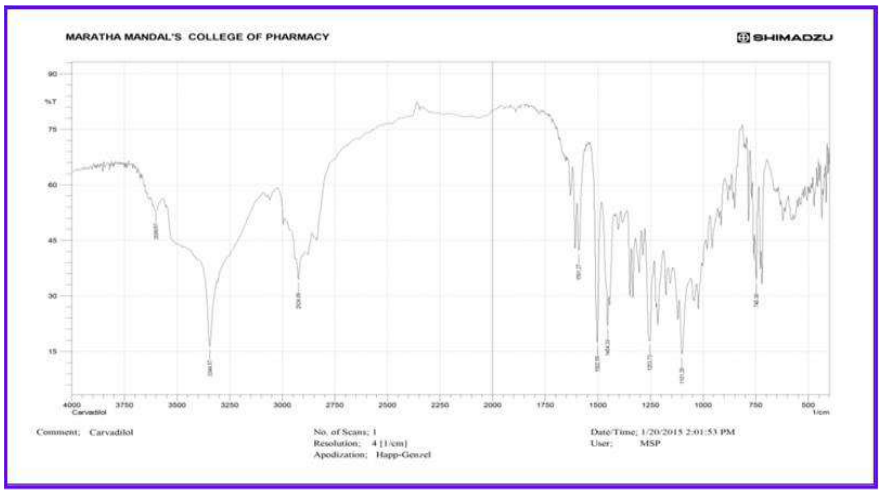

Fig 2: FT-IR spectra of carvedilol.

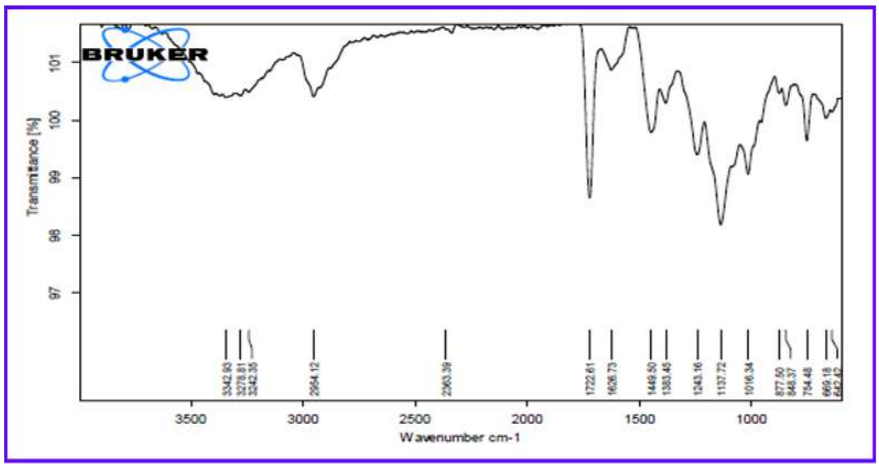

Fig 3: FT-IR spectra of carvedilol + Eudragit RL100

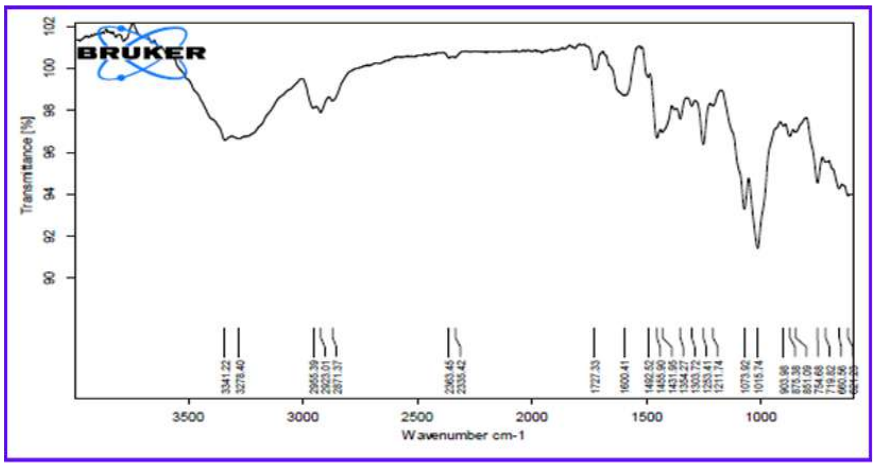

Fig 4: FT-IR spectra of carvedilol + excipients.

Determination of the λ_{max} of carvedilol: The λ_{max} was observed at 241 nm, as shown in Fig. 5.

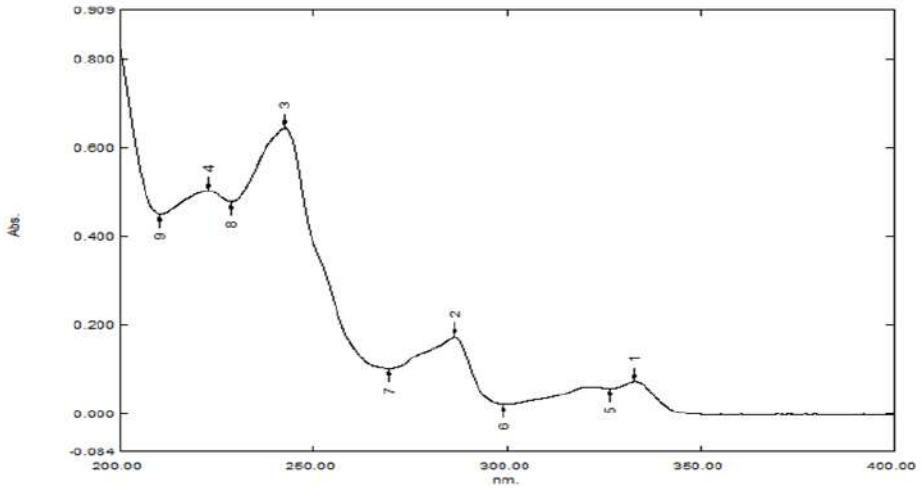

Fig. 5: The λmax of carvedilol in pH 6.8 phosphate buffer.

Standard calibration curve of carvedilol: The standard calibration curve was found to be accurate and precise between the concentration of 1-6 mcg/ml, with a regression coefficient of 0.999 (Table 7).

Table 7: Calibration curve of carvedilol in pH 6.8 phosphate buffer.

Concentration (µg/ml)	Average absorbance
0	0
1	0.145±0.003
2	0.285±0.009
3	0.424±0.012
4	0.562±0.011
5	0.718±0.013
6	0.848±0.004

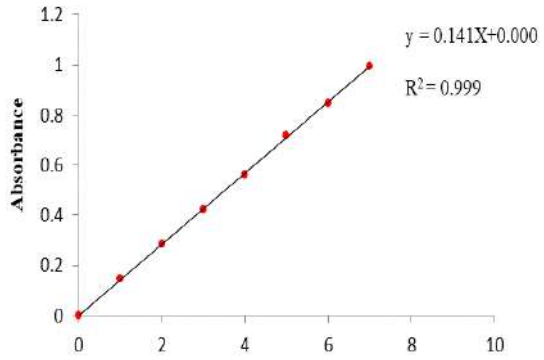

Fig 6: Calibration curve of carvedilol in pH 6.8 phosphate buffer

Evaluation of nanoparticles:

Percentage yield: The percentage yield obtained in all three formulations was good and in the range of 61.2% to 72.55% (Table 8). The loss of material during the preparation of nanoparticles is due to process parameters as well as during the recovery of nanoparticles.

Table 8: Percentage yield.

Formulation code	% yield
NP1	61.21%
NP2	67.93%
NP3	72.55%

Percentage entrapment efficiency: The entrapment efficiency was determined after separating the unentrapped drug from the entrapped drug. Compared with the other formulations, formulation NP3 showed maximum entrapment of carvedilol (Table 9).

Table 9: % Entrapment efficiency of carvedilol nanoparticles.

Formulation	% Entrapment efficiency
NP1	76.44±0.75
NP2	81.11±0.86
NP3	84.03±0.47

Drug content: The percentage of carvedilol in the nanoparticles was evaluated in pH 6.8 phosphate

buffer. The drug content was between 83.48 to 87.65%. Compared with the other formulations, formulation NP3 had the maximum drug content (Table 10).

Table 10: Drug content in pH 6.8 phosphate buffer.

Formulation code	Drug content (%)
NP1	85.43±0.4
NP2	83.48±0.6
NP3	87.65±1.2

Solubility studies in pH 6.8 phosphate buffer: The observed solubility of the pure drug was 0.461 µg/ml, and the observed solubility of the nanoparticles was 0.764 µg/ml; i.e., the solubility increased by 40 to 32% (see Table 11).

Table 11: Solubility study of carvedilol nanoparticles.

Sample	Drug soluble (µg/ml)
Carvedilol pure form	0.461
Carvedilol nanoparticles	0.659

Scanning electron microscopy (SEM): The surface morphology of the NP1 formulation was studied by scanning electron microscopy at 20 kV with a magnification of 20000X, and images were obtained. The particle is irregular in shape, and its size is nanometers. The surface of the nanoparticles was planar, as shown in Fig. 7. This confirms the formation of nanoparticles.

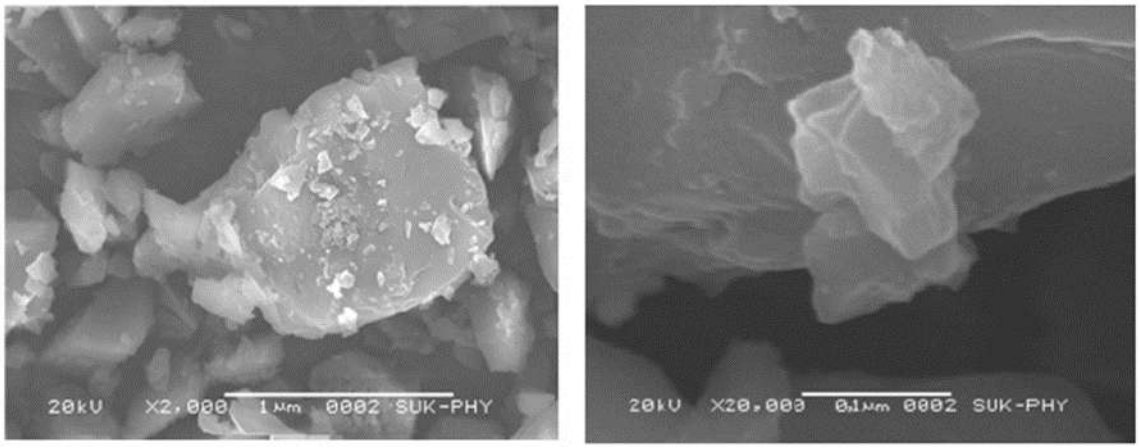

Fig. 7: SEM image of the size and surface morphology of NP1.

***In vitro* dissolution study:**

The percentage cumulative drug release at the 10th hr. was ranging between 79.91 to 86.16 Among the 3 formulations, NP1 and NP2 showed good drug release at the end of 10 hr (Table 12). Hence, formulations NP1 and NP2 were selected for further studies. A plot of the % cumulative drug release versus time for the different formulations is shown in Figs. 8

Table 12: Cumulative % drug release of carvedilol from Nanoparticles

Time	Cumulative % drug release of carvedilol		
	NP1	NP2	NP3
0	0	0	0
5	6.03±0.22	5.58±0.22	5.96±0.21
15	9.58±0.46	10.33±0.97	9.28±0.32
30	15.64±0.68	15.94±1.57	14.92±0.89
60	21.70±0.34	25.37±1.73	22.92±1.74
120	33.68±0.77	36.98±1.81	33.06±0.86

180	44.61±1.18	47.16±0.38	46.34±0.44
240	56.34±1.27	55.69±0.81	52.21±0.98
300	62.65±1.91	63.33±0.59	61.05±1.11
360	69.76±2.14	69.54±1.78	68.05±1.42
420	76.28±2.04	74.55±2.89	72.41±1.77
480	80.99±2.58	78.45±1.56	75.83±1.56
540	84.66±1.59	82.12±1.68	78.55±1.96
600	88.16±1.68	83.30±1.72	79.91±1.07

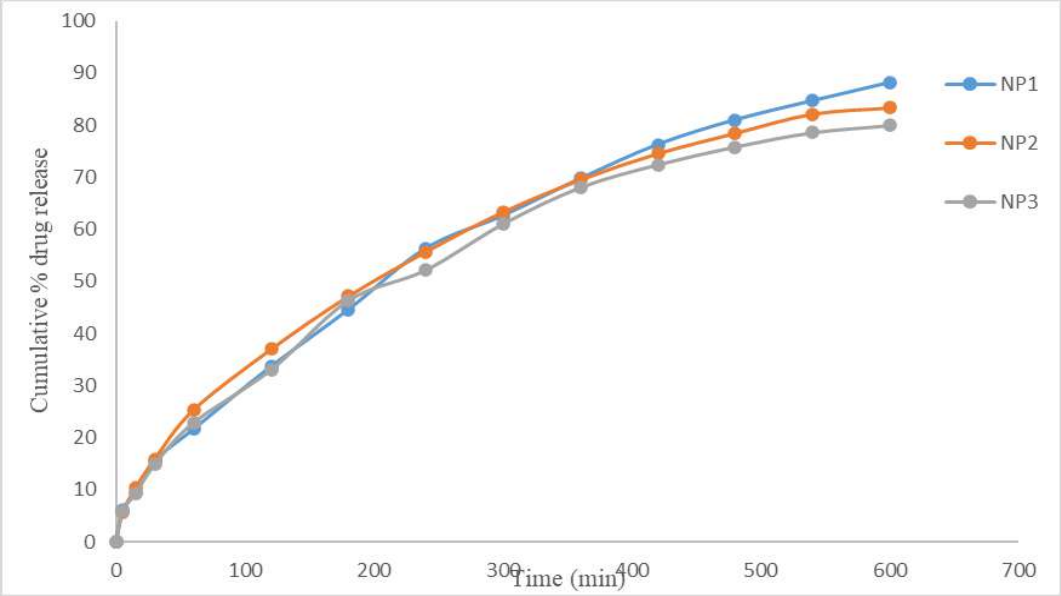

Fig. 8: %CDR vs. time of formulations NP1 to NP3 for the dissolution study.

CONCLUSION

Polymeric nanoparticles possess various beneficial characteristics for the oral administration of drugs. These nanoparticles facilitate the achievement of the appropriate properties of prolonged release and protection from proteinaceous enzymatic environment. This study showed that the solubility of carvedilol can be improved by nanoprecipitation method. Among different nanoparticulate formulations prepared by nanoprecipitation method NP1, formulation with Eudragit RL 100 in 1:2 drug: polymer ratio, showed satisfactory results. Entrapment efficiency of formulations was between 76-84%. Cumulative drug release at the 10^{th} hr. was ranging between 79.91 to 88.16%. FTIR study concluded that no major interaction occurred between the drug and polymers used in the present study. The major advantages of the polymeric nanoparticles are the simple method of preparation, minimizing of the dose and high therapeutic efficiency.

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