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Research Article

Carvedilol-loaded polymeric nanoparticles for treatment of hypertension: formulation and development

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ABSTRACT

Carvedilol nanoparticles were intended to be manufactured and evaluated using various hydrophilic polymers. Carvedilol was selected as an effective pharmaceutical agent for gastro-retentive nanoparticles due to its absorptive nature in the upper gastrointestinal tract and stomach, frequent dosing requirements, and limited bioavailability. In order to produce nanoparticles that are non-toxic to the body, the nanoprecipitation method was utilized to eliminate the need for surfactants or chlorinated solvents. The carvedilol nanoparticulate formulations prepared with various polymers in a 1:1 ratio exhibited particle sizes ranging from 214.09 to 744.09 nm, a polydispersity index (PDI) ranging from 0.82 to 1.1, zeta potential values ranging from -15.2 to +35.6 mV, loading efficiency ranging from 9.47% to 18.45%, and entrapment efficiency ranging from 54.17% to 76.4%. The nanoparticulate formulation prepared using gelatin in a 1:1 ratio yielded good results. The average particle size was 744.09 nm, the polydispersity index (PDI) was 0.82, the zeta potential was 15.2 mV, the loading efficiency was 9.47%, and the entrapment efficiency was 74.44%.

KEYWORDS: Nanoparticles, Nano-precipitation, Gastroretension, Carvediol, Formulation.

INTRODUCTION

Oral drug administration is the most practical and widely used way to give drugs because it has many therapeutic benefits, such as being easy for patients to follow, and allowing for more formulation options (Attia, *et al.,* 2023). However, this method comes with some physiological problems, such as the fact that the rate at which the stomach fills and moves can change without warning (Amarachinta, *et al.,* 2021). This makes it harder to keep the controlled drug delivery system in one place in the GI tract. Also, the stomach usually empties in two to three hours in the primary absorption area, which is made up of the stomach and upper intestine (Akhilesh, *et al.,* 2012). This can cause drugs to be released partially from the drug delivery system, which lowers the effectiveness of the dose that was delivered. Because of these issues, scientists have come up with a way to give drugs that can stay in the stomach for a long time and stay effective (Aboud, *et al.,* 2016). A controlled drug delivery system is being made to keep changes in plasma drug levels to a minimum and cut down on how often doses need to be given (Sabareesh, *et al.,* 2020). We are able to do this by giving the drug in a steady and controlled way and keeping the medically effective plasma drug concentration for a long time. There are a number of science papers that talk about ways to make medicines stay in the stomach longer (Suryawanshi, *et al.,* 2021). The aforementioned examples comprise hydrodynamically balanced systems that float within the stomach. Subsequent storage in the stomach improves the solubility of medications that exhibit poor solubility under alkaline conditions. This cuts down on drug waste and improves bioavailability (Sharma, *et al.,* 2018). Gastro retention makes it easier for people to get new medicines that work as well as they should and have big benefits for patients (Ahire, *et al.,*

2020). The study's goal was to create carvedilol gastro-retentive nanoparticles that would allow controlled release of the drug at the site of absorption, making it easier for the body to use (figure 1). Mucoadhesive materials like chitosan, gelatin, and bovine serum albumin were used to make gastroretentive nanoparticles. These polymers were chosen because they improve the interaction between the dosage form and the absorption site (Sharma, *et al.,* 2016). This lowers the drug's luminal diffusion pathway (bioadhesion) and makes oral drug administration much better (Sahoo, *et al.*, 2014).

This medicine is used to treat high blood pressure. One big problem with making new drug forms that make it more bioavailable is that it doesn't dissolve well in water (Ramkanth, *et al.,* 2018). People have tried changing Carvedilol's chemical and physical qualities, among other things, to get around the drug's limited ability to dissolve in water (Behera, *et al.,* 2010). The drug carvedilol works by blocking both α1 and β-adrenergic receptors, so it doesn't just work on one type. In addition, if your heart doesn't pump blood well during a heart attack, it can increase your chances of living (Surana and Mahajan, 2022). Getting rid of high blood pressure can help stop heart attacks, strokes, and problems with the kidneys (Reddy and Gandla, 2022).

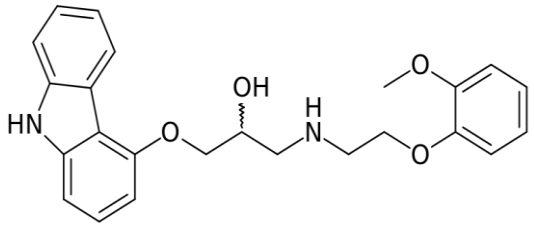

Figure 1: Structure of Carvediol

There are several benefits to having mucoadhesive polymeric nanoparticles in the stomach. For example, they will make the dosage form stay on the stomach's mucosal cells for longer. This will increase the drug's bioavailability and improve its absorption (Yeola, *et al.,* 2023). Higher drug concentration at the absorption site will enhance the passive uptake of the medication by the cells. The bioadhesive drug delivery system allows for direct passage of the drug without any dilution or risk of degradation in the luminal fluids prior to reaching its target (Pawar, *et al.,* 2023).

MATERIALS AND METHODS

Formulation of Nanoparticles:

With a few small changes, the nanoprecipitation method was used to successfully make nanoparticles. To sum up, 200 mg of polymer was mixed with 25 ml of acetone one at a time. 100 mg of carvedilol was mixed with 2 mL of DMSO to make a solution. Stirring the mixture vigorously for thirty minutes. The acetone was evaporated using a low-pressure rotary flash evaporator, resulting in a 10 milliliter suspension volume. The suspension was then centrifuged at a temperature of 4°C for 30 minutes at a speed of 15,000 revolutions per minute. Following the removal of the liquid portion atop the solid, the solid underwent three rinses using distilled water. To dry the nanoparticles, they were subjected to a 24-hour exposure in an oven set at 60°C. They were subsequently placed in a desiccator to maintain their dryness (Deepika, *et al.,* 2020 and Ahmad, *et al.,* 2017).

Evaluation of Nanoparticles of Carvedilol:

Evaluation of Loading Efficiency:

Utilizing 0.1M hydrochloric acid, the drug was extracted from the nanoparticles and the concentration of the drug in the mixture was determined. Fifty milliliters of a 0.1 M hydrochloric acid solution were combined with fifty milligrams of nanoparticles until the nanoparticles were completely dispersed. The resulting solution was subsequently filtered via a Millipore filter, and the drug concentration was assessed at 254 nm via UV spectrophotometry subsequent to the appropriate dilution (Gandra, 2020).

Entrapment Efficiency:

A certain number of nanoparticles that had been ground up into a powder were mixed with 100 milliliters of clean water. There were 92 hours of storage time for the mixture. A UV spectrophotometer set to a frequency of 262 nm was used to measure the absorbance of the filtered mixture and figure out the drug concentration (Kakar, *et al.,* 2010 and Sonawane, *et al.,* 2023).

Evaluation of Particle Size Distribution, Particle Size, and Zeta Potential:

The photocorrelation spectroscopy technique was utilized in order to determine the formulation's particle size distribution. To dilute each sample, a zeta master outfitted with the software was employed. To ascertain the surface charge of the nanoparticles, a zeta sizer was employed to evaluate their electrophoretic mobility. In order to prepare the samples, refined water was utilized (Govindarajan, *et al.,* 2022 and Aher, *et al.,* 2023).

Polydispersity Index:

The range of particle sizes in a nanoparticle sample is quantified using the polydispersity index, which is derived from the analysis of photon correlation spectroscopy. As determined by the autocorrelation function, the dimensionless number for monodispersed particles can range from 0.01% to between 0.5 and 0.7%. Samples exhibiting a broad spectrum of dimensions possess polydispersity indices surpassing 0.7 (Surana, *et al.,* 2022 and Keservani, *et al.,* 2010).

RESULTS AND DISCUSSION

The nanoprecipitation approach was utilized to prevent the use of surfactants and chlorinated solvents, which can have detrimental effects on the body. Three duplicates of each determination were created.

Drug loading efficiency and entrapment efficiency

The ratio of the physical mass of the active constituent to the mass of the nanoparticles is referred to as drug loading. On the contrary, the calculation of entrapment efficiency involves dividing the empirically ascertained drug content percentage by the theoretical or actual mass of the drug utilized in the synthesis of the nanoparticles. The specific polymer-drug combination and the chosen procedure determine the efficacy of injection. Hydrophobic polymers have the capacity to enclose greater quantities of hydrophobic pharmaceuticals, while hydrophilic polymers have a tendency to capture greater quantities of hydrophilic pharmaceuticals. Numerous formulation parameters can influence the quantity of drug delivered, such as the proportion of organic to aqueous phase, the weight ratio of polymer to drug, and the type of emulsifier utilized. The influence of polymer composition on the efficiency of drug loading and entrapment is depicted in Table 1. The corresponding effects are also depicted in Figures 2 and 3. The corresponding percentages were as follows: 54.17% to 76.4% and 9.47% to 18.45%. The

results indicated that chitosan nanoparticles exhibited a significantly high loading efficiency in comparison to gelatin and HPMC nanoparticles. The investigation found that whereas the entrapment effectiveness of the formulations containing gelatin and chitosan was significantly high, that of the formulation containing bovine serum albumin was noticeably poor. By making sure there is enough polymer to trap the drug in the solution, increasing the polymer ratio can improve loading efficiency. On the other hand, carvedilol's hydrophilic properties might lead to decreased entrapment efficiency.

Table 1: Evaluation of loading efficiency of drug

Sr. No.	Formulation code	Drug and Polymer ratio	Loading efficiency of drug ± SD
1	F01	1.0:2.0	12.34 ± 0.3
2	F02	1.0:2.0	18.45 ± 0.4
3	F03	1.0:2.0	17.23 ± 0.3
4	F04	1.0:2.0	16.21 ± 0.2
5	F05	1.0:2.0	09.47 ± 0.4

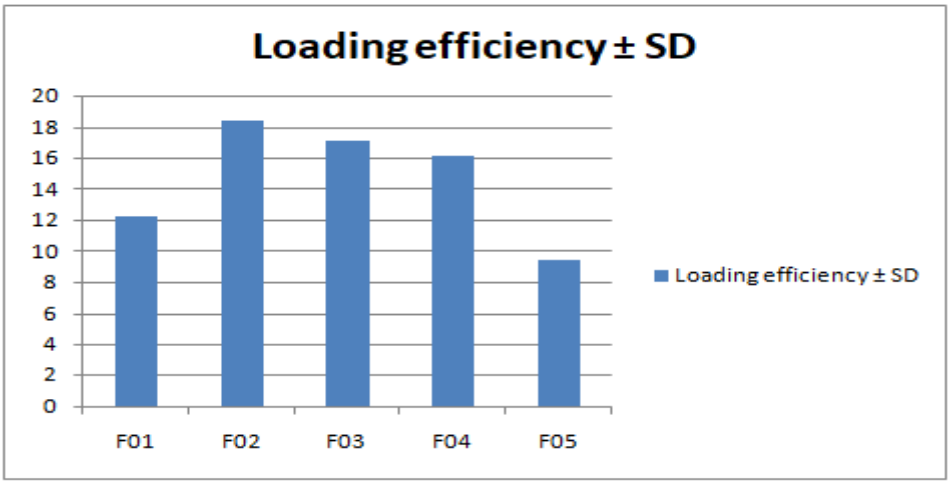

Figure 2: Loading efficiency polymer effect.

Table 2: Entrapment efficiency of drug

Sr. No.	Formulation code	Drug and Polymer ratio	Entrapment efficiency of drug ± SD
1	F01	1.0:2.0	54.17 ± 0.7
2	F02	1.0:2.0	76.4 ± 0.9
3	F03	1.0:2.0	74.52 ± 0.8

4	F04	1.0:2.0	72.12 ± 0.7
5	F05	1.0:2.0	74.44 ± 1.1

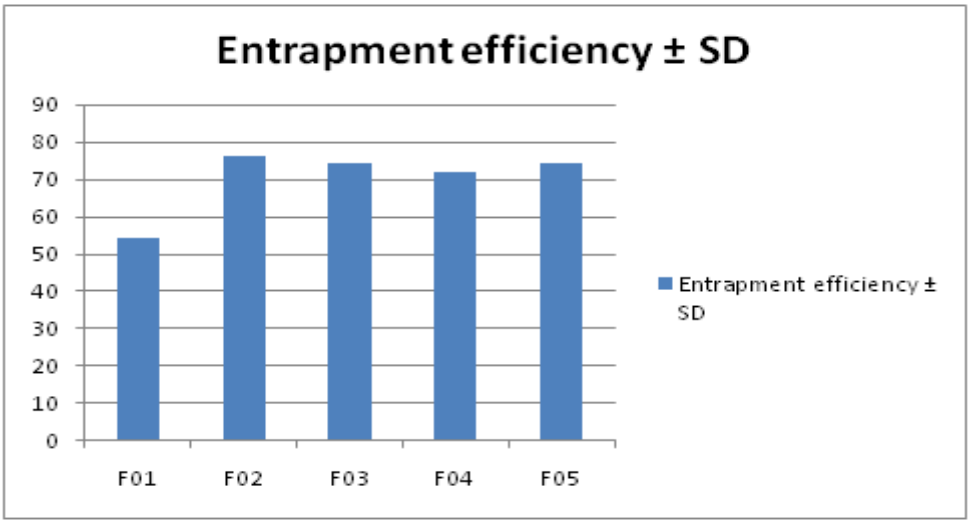

Figure 3: Entrapment efficiency of polymer

Particle Size Distribution (PSD) and Polydispersity Index (PDI)

The effectiveness of nanoparticles depends a lot on their size and where they are spread out. Changing speeds. Different batches with a wide range of particle sizes have very different drug loading, drug release, absorption, and effectiveness. In addition to light scattering, transmission and scanning electron microscopy can also be used to find out how big particles are and where they are located. Nanoparticles are taken in by cells through a process called endocytosis, which means that increasing their size may make it harder for the body to absorb drugs.

How much endocytosis happens depends on the target cell. Table 2 and Figure 3 show the outcomes of nanoparticle formulations of carvedilol that use different polymers. There was a very high polydispersity index (PDI) for the formulas, which was between 0.8 and 1.1. Based on the information about particle size distribution, most of the HPMC nanoparticles had a mean width of 250.12 nm. On the other hand, most of the chitosan nanoparticles had a mean width of 312.04 nm, with most of them being between 200 and 400 nm. Most of the gelatin nanoparticles were between 480 and 1200 nanometers in size, with 744.09 nanometers being the average particle width. Despite this, only a small number of nanoparticles were found across a much narrower range that covered all of the formulations. When the highest polydispersity scores were seen, they were in formulations that were made by minority groups.

To enhance the production of particles in the lower size range and achieve smaller nanoparticles with a more uniform size distribution, we are now studying the process variables that affect the proportions of different particle populations. Efficient methods such as filtering facilitate the extraction of these nanoparticles from the larger population.

Table 3: Particle size distribution and zeta of formulation

Formulation Code	**Polymer used**	**Mean Particle Size (nm)±SD**	**PSD**	**PDI±SD**	**Zeta Potential (mV)±SD**
F01	Chitosan	251.21 ± 16	11.10% (15-30 nm) 88.19 % (200-400 nm)	0.9 ±0.13	22.6± 1.5
F02	Ethyl cellulose	313.05 ± 31	8.9% (48-90 nm) 91.5% (200-525 nm)	0.86 ±0.14	34.1±1.9
F03	PLA	252.23 ± 15	12.11% (15-30 nm) 78.8 % (200-400 nm)	1.1 ±0.13	18.6± 1.1
F04	PLGA	214.05 ± 28	9.5% (48-90 nm) 87.5% (200-525 nm)	0.88 ±0.15	35.6±1.9
F05	Gelatin	744.09 ± 36	15.3% (70-160 nm) 87.5% (480-1200 nm)	0.82±0.15	15.2±1.2

The provided evidence clearly indicates that the average size and distribution of nanoparticles produced using chitosan and HPMC were decreased. Nevertheless, the presence of large particles in the nanoparticle population occurred when gelatin was employed as the polymer during the nanoparticles' formation. It's possible that the bigger particle size and polydispersity index are because there wasn't an emulsifier present. Emulsifiers lower the surface tension between the watery phase and the organic phase (acetone), which makes smaller solvent drops and, in turn, smaller particles. Prior research indicates that it additionally stabilizes recently produced surfaces and prevents the particles from clumping together. Hence, the results of this investigation could be improved by employing a greater drug to polymer ratio, employing an alternative formulation technique such as desolvation or counter-ion-induced aggregation, incorporating a cross-linking agent and subsequently neutralizing any remaining cross-linkers with cysteine, and employing vigorous agitation.

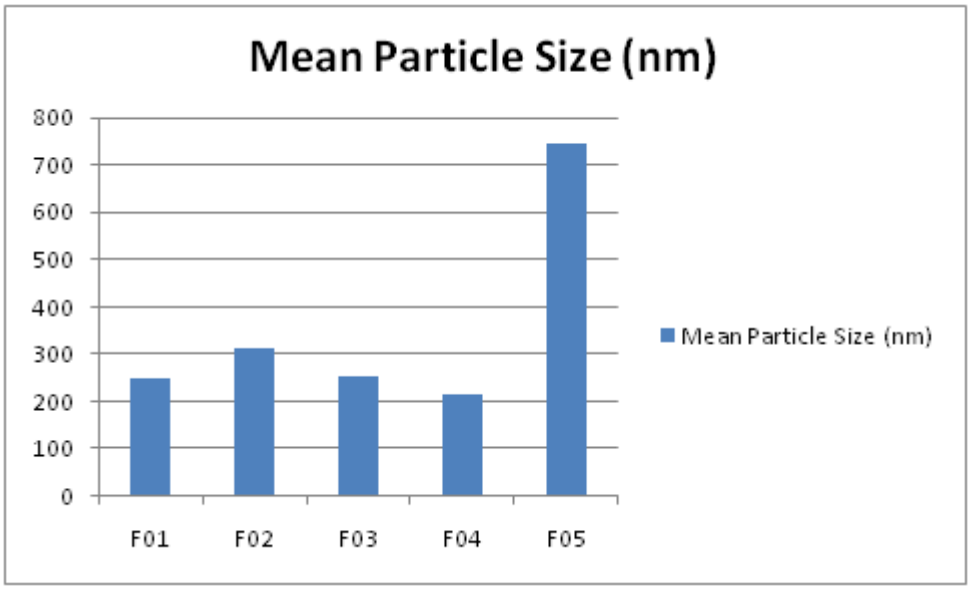

Figure 4: Mean particle size polymer effect

It is possible to estimate the storage stability of colloidal dispersions using the zeta potential. The phenomenon of electrostatic repulsion reduces the probability of adhesion between charged particles possessing a high zeta potential. Soils of nanocapsules possessing Zeta potentials exceeding 30 mV exhibit enhanced stability due to the intermolecular forces generated by the particles. This holds true irrespective of the positive or negative Zeta potential. Electrostatic repulsion, also known as a decrease in zeta potential, was hypothesized to be the cause of the particles' adhesion. Where the nanospheres adhere to substances and how cells absorb them are both influenced by their surface charge. Electrostatic forces enhance the adhesion of positively charged nanoparticles to cell walls that are negatively charged. Consequently, the functionality of cationic or neutral nanoparticles can be enhanced through the introduction of a positive charge onto their surface. The colloidal solution exhibited a zeta potential range of -15.2 to +35.6 mV, indicating the possibility of instability and aggregation. Altering the zeta potential values can be achieved, among other things, by adjusting the pH and ionic strength of the dispersing phase.

CONCLUSION

The objective of this inquiry was to produce and assess carvedilol nanoparticles through the utilization of a range of hydrophilic polymers. Carvedilol was chosen as an appropriate medication for gastro-retentive nanoparticles due to its short half-life, limited absorption in the upper gastrointestinal tract and stomach, requirement for frequent administration, and low bioavailability. Formulation F05, which was generated via the nanoprecipitation technique, demonstrated desirable characteristics with respect to its average particle size (744.09 nm), whereby the majority of particles belonged to the range of 200–525 nm. Furthermore, the material exhibited the following characteristics: a loading efficiency of 9.47%, an entrapment efficiency of 74.44%, and a polydispersity index of 0.82.

DECLARATIONS:

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

All the authors approved the manuscript for publication.

Availability of data and material:

All required data is available.

Competing interests:

All authors declare no competing interests.

Funding:

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