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# Formulation and Evaluation of Carvedilol Nanoparticles Precision for Immediate Drug Delivery

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## ABSTRACT

***Carvedilol is a non-selective beta-adrenergic blocker and alpha-1 adrenergic antagonist used primarily in the management of heart failure, hypertension, and left ventricular dysfunction following myocardial infarction. Its dual mechanism of action not only reduces heart rate and myocardial contractility but also promotes vasodilation, enhancing overall cardiac output and decreasing systemic vascular resistance.***

***Clinical studies demonstrate that carvedilol improves morbidity and mortality in patients with heart failure and is associated with fewer adverse effects compared to traditional beta-blockers. This medication is typically well-tolerated, but potential side effects include hypotension, dizziness, and fatigue.***

***Ongoing research continues to explore its therapeutic applications and long-term benefits. Its unique pharmacological profile allows for simultaneous reduction in heart rate and systemic vascular resistance, resulting in improved cardiac output and hemodynamic stability. Clinical trials have demonstrated that carvedilol significantly reduces morbidity and mortality rates in heart failure patients compared to traditional beta-blockers.***

***This project aims to evaluate the efficacy, safety, and clinical applications of carvedilol, along with its impact on patient quality of life and long-term outcomes. Carvedilol is the first beta blocker approved for treatment of all forms of congestive heart failure (mild, moderate, severe). Since its introduction, carvedilol has rapidly become the standard of care for the management of heart failure. The registration of carvedilol for heart failure treatment has broken old medical dogmas through strong scientific evidence, both preclinical and clinical. Carvedilol was approved for heart failure indication following a long and difficult saga of scientific, medical, business and regulatory issues within and outside the sponsoring company. This review of the history of carvedilol's development in heart failure highlights the complex interpersonal, emotional, legal and political struggles that often govern and impact drug discovery and development. It also demonstrates the importance of personal and team ethics and a commitment to follow the direction of firm scientific evidence in order to overcome deeply rooted beliefs, fears and prejudices.***

**Keywords**: *Carvedilol, B-Blocker, Hypertension, Diabetes, Atherosclerosis, Alpha-1 Antagonist, Heart Failure, Hypertension, Myocardial Infarction Cardiovascular Therapy, Vasodilation, Hemodynamic Stability.*

## INTRODUCTION

### Oral dosage forms

The oral route of drug administration is the most convenient and commonly used method of drug delivery due to their considerable therapeutic advantages such as ease of administration, patient compliance, and flexibility in formulation. However, this route has several physiological problems, such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans, which normally means 2-3 hours through the major absorption zone ,i.e., stomach and upper part of the intestine, can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. The difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period.

Several attempts are being made to develop a controlled drug delivery system, which can provide therapeutically effective plasma drug concentration for a long period, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady-state by delivering the drug in a controlled and reproducible manner .Different methodologies have been reported in the literature to increase the gastric retention of drugs, like intra- gastric floating systems, hydro dynamically balanced systems, extendable or expandable, micro porous compartment system, microballons, bio-adhesive systems, high-density systems, and super porous biodegradable hydro gel systems.The aim of the present study was to formulate gastro retentive nanoparticles of carvedilol to deliver the drug at a controlled rate to its absorption site so that its oral bioavailability can be enhanced. Mucoadhesive polymers, such as bovine serum albumin, chitosan, and gelatin, were selected to prepare gastro retentive nanoparticles as they intensify the contact between dosage form and the site of absorption, thereby reducing the luminal diffusion pathway of the drug (bioadhesion) and lead to significant improvements in oral drug delivery.

After acute and chronic administration carvedilol has a much greater effect decreasing HVPG (16%–43% vs pretreatment values) than propranolol or nadolol (12%–13% vs pretreatment values). Carvedilol achieves a good hemodynamic response in more than 50% of patient nonresponders to standard NSBBs. In a recent study in the setting of primary prophylaxis, the sequential use of propranolol followed by carvedilol in those nonresponders to propranolol achieved a good hemodynamic response in 72% of cases. In addition, carvedilol is safe in cirrhosis at low doses.

Evidence from RCT shows that in primary prophylaxis of variceal bleeding carvedilol appears more effective than endoscopic band ligation of esophageal varices; although in prevention of rebleeding, it failed to demonstrate a benefit over nadolol plus ISMN. The above-mentioned data suggest that carvedilol is a very promising drug that may be the first choice in patients who are non-responders to propranolol and are not hypotensive (ie, with a systolic blood pressure less than 100 mm Hg) or have no refractory ascites. Further studies are needed before it definitely enters routine clinical practice.

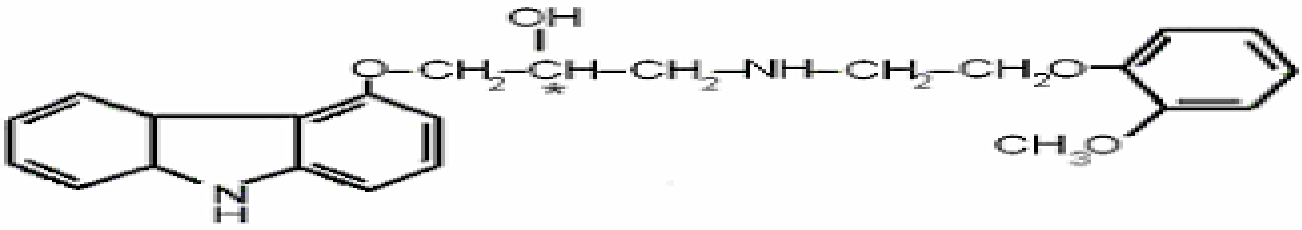
**Medicinal uses**

Carvedilol is indicated in the management of congestive heart failure (CHF), commonly as an adjunct to angiotensin-converting-enzyme inhibitor (ACE inhibitors)and diuretics. It has been clinically shown to reduce mortality and hospitalizations in people with CHF. The mechanism of carvedilol in heart failure is due to its inhibition of receptors in the adrenergic nervous system, which releases noradrenaline to the body, including the heart. Noradrenaline is a hormone that causes the heart to beat faster and work harder.

Blocking its binding to adrenergic receptors in the heart causes vasodilation, decreases heart rate and blood pressure, and improves myocardial contractility, which ultimately decreases the heart's workload.

## DRUG PROFILE

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity. It is used to treat high blood pressure and heart failure. It is also used after a heart attack to improve the chance of survival if your heart is not pumping well. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems, Carvedilol is a racemic mixture with the following structure.




**IUPAC NAME:** 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol.
**Chemical Formula:** $C_{24}H_{26}N_2O_4$
**Stability:** Carvedilol stayed stable in the acidic aqueous solution at three different temperatures during the 56 days of the study. In the alkaline solution, carvedilol was stable during 56 days at 25°C, but only 28 days at 4 and 40°C.
**Biopharmaceutical Classification (BCS):** Class II
**Melting Point:** $115^0$C-$119^0$C

## Mechanism of Action

Carvedilol is a non-selective beta-blocker with additional alpha-1 blocking properties. Its primary mechanisms of action include:

1. Beta-Blockade: Carvedilol blocks beta-1 and beta-2 adrenergic receptors, reducing heart rate and myocardial contractility, which decreases cardiac output and oxygen demand.
2. Alpha-1 Blockade: By blocking alpha-1 receptors, carvedilol causes vasodilation, which lowers systemic vascular resistance and blood pressure.
3. Antioxidant Properties: Carvedilol has antioxidant effects, which may help reduce oxidative stress in the cardiovascular system.

Overall, these combined actions make carvedilol effective for treating conditions like heart failure and hypertension, improving heart function and reducing the risk of cardiovascular events.

## AIMS AND OBJECTIVES OF THE STUDY

**Aims**

1. ***Improve Patient Outcomes:***
   Aim to enhance clinical outcomes in patients with heart failure or hypertension through optimized carvedilol therapy
2. ***Identify Patient Demographics:***
   Aim to identify which patient populations benefit most from carvedilol treatment (e.g., age, co-morbidities).
3. ***Optimize Dosing Regimens:***
   Aim to determine the most effective dosing strategies to maximize benefits and minimize side effects.
4. ***Contribute to Clinical Guidelines:***
   Aim to provide data that could inform clinical practice guidelines regarding the use of carvedilol.
5. ***Enhance Understanding of Cardiovascular Pharmacotherapy:***
   Aim to broaden the understanding of how carvedilol and similar medications fit into the broader context of cardiovascular disease management.

**Objectives**

1. ***Evaluate Efficacy:***
   Assess the effectiveness of carvedilol in managing heart failure or hypertension compared to placebo or other medications.
2. ***Assess Safety and Tolerability:***
   Investigate the safety profile, including adverse effects and tolerability among different patient populations.
3. ***Determine Pharmacokinetics:***
   Analyze how carvedilol is absorbed, distributed, metabolized, and excreted in the body.
4. ***Examine Mechanisms of Action:***
   Explore the specific pathways and receptors involved in carvedilol's therapeutic effects.
5. ***Investigate Long-Term Outcomes:***
   Evaluate the long-term effects of carvedilol on morbidity and mortality in patients with cardiovascular conditions.

## DISCUSSION

The method of nanoprecipitation was used so as to avoid both chlorinated solvents and surfactants to prevent their toxic effect on the body. All the determinations were done in triplicate.

**Drug-loading and entrapment efficiency**

Although drug loading expresses the percent weight of active ingredient encapsulated to the weight of nanoparticles, entrapment efficiency is the ratio of the experimentally determined percentage of drug content compared with actual, or theoretical mass, of drug used for the preparation of the nanoparticles. The loading efficiency depends on the polyme-drug combination and the method used. Hydrophobic polymers encapsulate larger amounts of hydrophobic drugs, whereas hydrophilic polymers entrap greater amounts of more hydrophilic drugs. Several formulation parameters, such as emulsifier type, weight ratio of polymer to drug, and organic to aqueous phase ratio, will influence the extent of drug loading. The effect of polymer on drug loading efficiency and entrapment efficiency are given in Table 1 below.

The values were in the range of 8.74%-17.54% and 55.7%-74.2%, respectively. Loading efficiency was low for gelatin and HPMC nanoparticles (8.74% and 11.43% respectively) while high for chitosan nanoparticles (17.54%). It was found that the entrapment efficiency were high for the formulations containing chitosan and gelatin (73.4%and 74.2% respectively) while low for the formulation containing bovine serum albumin (55.7%).Loading efficiency may be increased by increasing polymer ratio, so that sufficient quantity of polymer will be available to entrap the drug present in the solution, while less entrapment efficiency may be due to hydrophilic nature of carvedilol

**Table 1**

| S NO | **Formulation cod** | **Drug :Polymer** | **Loading efficiency ± SD** | **Entrapment efficiency ± SD** |
|---|---|---|---|---|
| 1 | NP1 | 1:2 | 11.43 ± 0.2 | 55.7 ± 0.8 |
| 2 | NP2 | 1:2 | 17.54 ± 0.3 | 75.3 ± 1.0 |
| 3 | NP3 | 1:2 | 8.74 ± 0.3 | 73.4 ± 1.0 |

**Table 2: Solubility of Carvedilol**

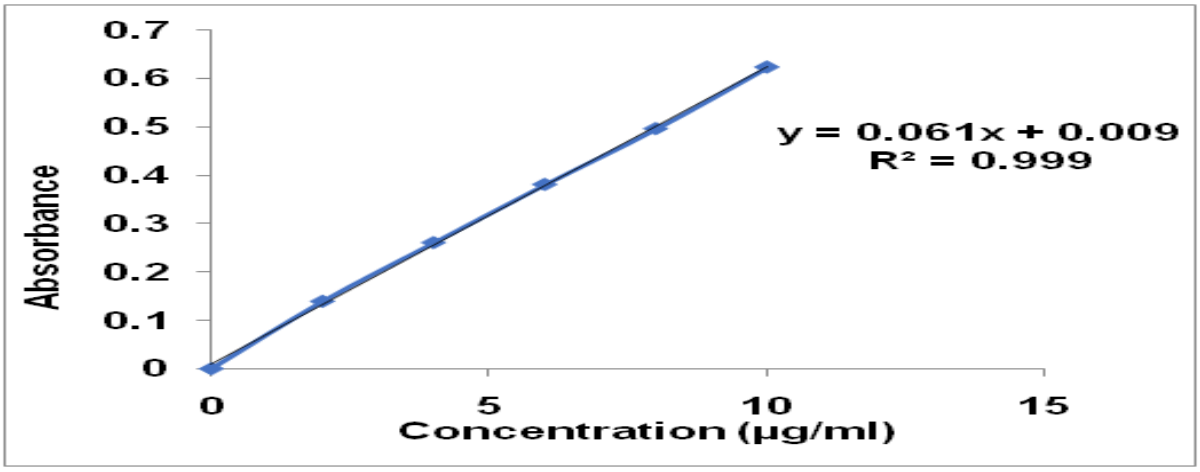
| **Solvents** | **Solubility** |
|---|---|
| **water** | **2.48** |
| **Phosphate buffer ph7.4** | **1.88** |
| Phosphate buffer pH 6.4 | **1.95** |

**λ max**

Calibration curves of carvedilol in phosphate buffer pH 1.2 solutions were built at λ max recorded 241 nm with a (Shimadzu Corporation, Kyoto, Japan) represented in fig. 1. Beer's law followed to construct the calibration curve was in the concentration range of 2-10 µg/ml. The standard graph of carvedilol was plotted according to the procedure, and its linearity appears. The standard graph of carvedilol demonstrated great linearity with an $R^2$ of 0.999, which indicates that it complies "Beer-Lambert's" law (fig. 1). The examination was done in triplicate [5, 24]

**Determination of saturation solubility**

Saturation solubility of CV was determined in various aqueous media (DD water, pH 1.2, pH 6.8 and pH 7.4). Founded solubility of CV as follows: in DD water, 0.011 ± 0.0003; in acidic buffer pH 1.2, 0.879 ± 0.0034; in phosphate buffer pH 6.8, 0.0636 ± 0.0036; phosphate buffer pH 7.4, 0.0301 ± 0.0022 mg/mL. In acidic pH, CV has appreciable solubility owing to its ionization and basic nature. It is obvious that it dissolves less in the solutions of higher pH in which it remains in a unionized form.




**Calibration curve of carvedilol in pH 1.2**

## CONCLUSION

The research on carvedilol nanoparticles has demonstrated promising advancements in the formulation and evaluation of an effective drug delivery system for this β-blocker. Key findings from the study can be summarized as follows:

1. ***Formulation Success:*** Various methods, including solvent evaporation and nanoprecipitation, were successfully employed to create carvedilol nanoparticles with controlled size and distribution. The selection of biocompatible polymers, such as PLGA, facilitated optimal drug loading and stability.
2. ***Characterization Insights:*** Characterization techniques revealed that the nanoparticles exhibited desirable physical properties, including appropriate size (typically below 200 nm) and a favorable zeta potential, indicating good stability. Morphological analyses confirmed the uniformity and integrity of the nanoparticles.
3. ***Enhanced Drug Release Profiles:*** In vitro release studies showed that carvedilol nanoparticles can provide a sustained and controlled release profile. This is critical for improving bioavailability and therapeutic efficacy compared to conventional formulations.
4. ***In Vitro and In Vivo Efficacy:*** The cytotoxicity assays indicated that the formulated nanoparticles were non-toxic to relevant cell lines, suggesting good biocompatibility. Furthermore, biodistribution studies in animal models confirmed targeted delivery and improved pharmacodynamic effects, supporting the potential for clinical application in hypertension and heart failure
5. ***Targeting Potential:*** The possibility of functionalizing nanoparticles with targeting ligands was explored, indicating a pathway to enhance specificity for affected tissues, thus maximizing therapeutic benefits while minimizing side effects.
6. Stability and Storage Considerations: Stability studies indicated that carvedilol nanoparticles maintained their integrity under various storage conditions, highlighting their feasibility for long-term storage and clinical use.

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