



# FORMULATION AND EVALUATION OF GASTRORETENTIVE-NANOPARTICLES OF BCS CLASS – II DRUG

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## ABSTRACT:

The current study was focus on to the formulation of nanoparticles of carvedilol by using different polymers. Carvedilol was selected because it is under the BCS classII i. e, it having the low solubility and high permeability, and also it having the short half life (7 to 10 hours), due to the short half life the frequency of administration is high, and narrow absorption window in stomach and upper part of GIT so that it having low bioavailability that's why the carvedilol is a suitable for gastro- retentive nanoparticles drug delivery system. The nanoparticles was prepared by using nano-precipitation method, so as to avoid both chlorinated solvents and surfactants to prevent their toxic effect on the body. Nanoparticles was prepared by using hydrophilic polymers such as chitosan, HPMC K100M, Polyox WSR Coagulant and gelatin. The zeta potential, particle size, polydispersity index, loading efficiency, encapsulation efficiency and drug-excipient compatibility test carry out for to evaluate the nanoparticles of carvedilol . The 1:1 ratio of polymer is used to prepare the nanoparticles that shows the good results. The Drug-Excipient compatibility study was carry out and its shows the drug any interaction between drug and polymer (excipient) it is compatible with each other.

**Keywords:** Nanoparticles, gastro-retentive, zeta potential, bioadhesive , particle size, polydispersity index, zeta potential; entrapment efficiency.

## INTRODUCTION :

The oral route of drug administration is that the most convenient and commonly used method of drug delivery thanks to their considerable therapeutic advantages like simple administration, patient compliance, and adaptability in formulation. However, this route has several physiological problems, like inability to restrain and locate the controlled drug delivery system within the specified region of the alimentary canal thanks to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans, which normally means 2-3 hours through the main absorption zone, i.e., stomach and upper a part of the intestine, may result in incomplete drug release from the drug delivery system resulting in reduced efficacy of the

administered dose 1-6. These difficulties have prompted researchers to style a drug delivery system which may stay within the stomach for prolonged and predictable period. Several attempts are being made to develop a controlled drug delivery system, which may provide therapeutically effective plasma drug concentration for a extended period, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady-state by delivering the drug during a controlled and reproducible manner. Different methodologies are reported within the literature to extend the gastric retention of medicine , like intra-gastric floating systems, hydro dynamically balanced systems, extendable or expandable, micro porous compartment system, microballons, bio-adhesive systems, highdensity systems, and super porous biodegradable hydro gel systems. After oral administration, such a dosage form would be retained within the stomach for several hours and would release the drug there during a controlled and prolonged manner, in order that the drug might be supplied continuously to its absorption sites within the upper alimentary canal 7-12. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of medicine that are less soluble during a high pH environment. it's also suitable for local drug delivery to the stomach and proximal intestine . Gastro retention helps to supply better availability of latest products with suitable therapeutic activity and substantial benefits for patients. The aim of this study was to formulate gastro retentive nanoparticles of carvedilol to deliver the drug at a controlled rate to its absorption site in order that its oral bioavailability are often enhanced. Mucoadhesive polymers, like bovine albumin , chitosan, and gelatin, were selected to organize gastroretentive nanoparticles as they intensify the contact between dosage form and therefore the site of absorption, thereby reducing the luminal diffusion pathway of the drug (bioadhesion) and cause significant improvements in oral drug delivery 13-18. Carvedilol is an antihypertensive characterized by itslow aqueous solubility, a serious obstacle in drug formulation development to enhance its bioavailability. to beat problem of poor aqueous solubility of Carvedilol, various approaches are investigated including physical and chemical modifications of the drug. <sup>19</sup>

These mucoadhesive polymeric nanoparticles within the stomach will offer various advantages like (i) Longer duration of the dosage form on mucosal tissues within the stomach. this may improve absorption of the drug and increase the drug bioavailability. (ii) Higher drug concentration at the location of adhesion absorption, which can create a drive for the paracellular passive uptake. (iii) Immediate absorption from the bioadhesive drug delivery system without previous dilution and possible degradation within the luminal fluids. <sup>20-23</sup>

## 2. MATERIALS AND METHODS:

S.No.	INGREDIENTS	SUPPLIER
1	Carvedilol	Shodhana Labs from India
2	Polyox WSR Coagulant	Colorcorn
3	Hydroxyl propyl methyl cellulose K100M	VladaChem GmbH, Malsch, DE
4	Gelatin	AEGIS-LIFESCIENCES, Ahmedabad
5	Dimethylsulfoxie	Shilpa Chemspec International Pvt. Ltd., Mumbai
6	Chitin	Marine Hydrocolloids, Kerala

**Table 1: List of Materials used for the study**

## PREPARATION OF NANOPARTICLES<sup>20-22</sup>

Nanoparticles were prepared consistent with the nanoprecipitation method with slight modification. Briefly, 200 mg of polymer (Polyox, HPMC, gelatin and chitosan) was dissolved in 25 ml of acetone separately. The carvedilol 100 mg was dissolved in 2 ml of dimethylsulfoxide. Both solutions were mixed then 50 ml of water was added and stirred for a half hour. Acetone was eliminated by evaporation under reduced pressure using rotary flash evaporator and therefore the final volume of the suspension was adjusted to 10 ml. Then this suspension was centrifuged at 15000 rpm at 40°C for half an hour. The supernatant was discarded and precipitate was washed 3 times with water. Then the nanoparticles was dried for 12 hours in oven at 60°C and stored during a desiccator. The prepared formulations were characterized for loading efficiency, entrapment efficiency, particle size, particle size distribution, polydispersity index, zeta potential and drug excipient compatibility studies.

### 3. Characterization of Carvedilol Loaded Nanoparticles<sup>19- 22</sup>

#### 1. Loading Efficiency

Drug content within the preparation decided by extracting the drug from the nanoparticles with 0.1 M acid. during this method, the nanoparticles (50 mg) were stirred in 50 ml of 0.1 M acid until dissolved; it had been filtered through a Millipore filter and therefore the drug content decided, after suitable dilution, at 254 nm by UV spectrophotometry.

The loading efficiency (L) of the nanoparticles was calculated consistent with Equation 1

$$L (\%) = (Q_n / W_n) \times 100 \dots(1)$$

Where, **W<sub>n</sub>** is that the weight of the nanoparticles and **Q<sub>n</sub>** is that the amount of drug present within the nanoparticles.

#### 2. Entrapment Efficiency

For determination of drug entrapment, the amount (quantity) of Carvedilol present within the clear supernatant after centrifugation was determined by UV spectrophotometer at 254 nm. a typical calibration curve of drug was plotted for this purpose. the quantity of drug in supernatant was then subtracted from the entire amount of drug added during the preparation (W). Effectively, (W-w) will give the quantity of drug entrapped within the particles.

Then percentage entrapment of a drug was calculated consistent with Equation 2

$$\% \text{ Drug Entrapment} = (W-w/W) \times 100 \dots(2)$$

#### 3. Particle Size, Particle Size Distribution, and Zeta Potential

The particle size and particle size distribution of the formulation decided by photo correlation spectroscopy with a zeta master (Malvern Instruments, UK) equipped with the Malvern PCS software. Every sample was diluted with water. The surface charge (Zeta potential) decided by measuring the electrophoretic mobility of the nanoparticles employing a Malvern zeta sizer (Malvern Instruments, UK). Samples were prepared by diluting with water.

#### 4. Polydispersity Index

Polydispersity index may be a parameter to define the particle size distribution of nanoparticles obtained from photon correlation spectroscopy. it's a dimensionless number extrapolated from the autocorrelation function and ranges from a worth of 0.01 for mono dispersed phase and up to values of 0.5-0.7. Samples with very broad size distribution have polydispersity index values  $> 0.7$ .

#### 5. Drug-Excipient Compatibility Studies

The drug excipient compatibility studies were performed by using FT-IR spectrophotometer (Perkin Elmer). The FT-IR spectra of drug, polymers, and formulations were analyzed separately then correlated for incompatibility.

### 3.0. RESULTS AND DISCUSSION

The method of nanoprecipitation was used so on avoid both chlorinated solvents and surfactants to stop their toxic effect on the body. All the determinations were wiped out triplicate.

#### 1. Drug-loading and entrapment efficiency

Although drug loading expresses the percent weight of active ingredient encapsulated to the load of nanoparticles, entrapment efficiency is that 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 polymer-drug combination and therefore the method used. Hydrophobic polymers encapsulate larger amounts of hydro phobic drugs, whereas hydrophilic polymers entrap greater amounts of more hydrophilic drugs. Several formulation parameters, like 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 and shown in Figure 1. The values were within the range of 8.74%-18.54% and 56.7%-76.3%, respectively. Loading efficiency was low for gelatin and HPMC nanoparticles (8.74% and 13.54% respectively) while high for chitosan nanoparticles (18.54%). it had been found that the entrapment efficiency were high for the formulations containing chitosan and gelatin (73.4% and 76.3% respectively) while low for the formulation containing bovine albumin (55.7%). Loading efficiency could also be increased by increasing polymer ratio, in order that sufficient quantity of polymer are going to be available to entrap the drug present within the solution, while less entrapment efficiency could also be thanks to hydrophilic nature of carvedilol.

Sr. no.	Formulation no.	Drug: Polymer	Loading efficiency $\pm$ SD	Entrapment efficiency $\pm$ SD
1	F1	1:2	12.23 $\pm$ 0.2	56.7 $\pm$ 0.8
2	F2	1:2	13.54 $\pm$ 0.3	72.3 $\pm$ 1.0
3	F3	1:2	8.74 $\pm$ 0.3	73.4 $\pm$ 1.0
4	F4	1:2	18.54 $\pm$ 0.3	76.3 $\pm$ 1.0

**Table 2: Drug loading and Entrapment efficiency**

## 2. Particle Size Distribution and Polydispersity Index

The particle size and particle size distribution area unit crucial factors within the performance of nanoparticles, as batches with wide particle size distribution show vital variations in drug loading, drug unharness, bioavailability, and effectiveness. Particle size and particle size distribution is determined victimization light-weight scattering techniques and by scanning or transmission microscopy. Formulation of nanoparticles with a slender size distribution are going to be a challenge if emulsion can not be created with a slender drop size distribution. As nanoparticles area unit internalized into cells by endocytosis, a rise in particle size can decrease uptake and doubtless, have an effect on bioavailability of the drug. The extent of endocytosis relies on the sort of the target cell. The results of ready nanoparticulate formulations of beta-adrenergic blocking agent with completely different polymers area unit given in Table two and shown in Figure two. The formulations had terribly high polydispersity index (PDI) within the vary of zero.681-1.0. From the particle size distribution knowledge, it's evident that just in case of HPMC nanoparticles, mean particle diameter was 250.12 nm and major portion of the particles were within the vary of 200-400 nm, for chitosan nanoparticles mean particle diameter was 312.04 nm; and major portion of the particles were in vary of 200-525 nm. just in case of gelatin nanoparticles mean particle diameter was 743.07 nm and most of the particles were within the vary of 480-1200 nm. However, all told the formulations contained a minority population of nanoparticles in abundant smaller vary. For HPMC, about 10.1% of the particles were within the vary 15-30 nm, for chitosan concerning seven.1% of the particles were within the vary 48-90 nm and for gelatin fourteen.1% of the particles were within the vary 70-160 nm. These minority populations area unit to blame for larger over all polydispersity indices of the formulations. we have a tendency to area unit presently exploring the method variables moving the relative amounts of various populations with AN objective to extend the yield of the particles within the smaller vary to urge abundant smaller nanoparticles, that have bigger degree of monodispersity. Such nanoparticles is simply separated from the larger sized population by easy ways like filtration.

Formulation No.	Polymer	Mean Particle Size (nm) $\pm$ SD	Size Distribution	PDI $\pm$ SD	Zeta Potential (mV) $\pm$ SD
F1	Polyox	250.12 $\pm$ 18	10.1% (15-30 nm) 89.9 % (200-400 nm)	1.0 $\pm$ 0.12	21.7 $\pm$ 1.4
F2	HMPC	279.53 $\pm$ 28	8.1 % (45-60 nm) 90.12% (200-400)	0.82 $\pm$ 0.13	26.5 $\pm$ 1.9
F3	Gelatin	743.07 $\pm$ 45	14.2% (70-160 nm) 85.8% (480-1200 nm)	0.77 $\pm$ 0.14	14.2 $\pm$ 1.3
F4	Chitosen	312.04 $\pm$ 32	7.8% (48-90 nm) 92.2% (200-525 nm)	0.68 $\pm$ 0.15	33.2 $\pm$ 2.1

**Table 3: Drug polymer ratio, mean particle size, particle size distribution, poly dispersity index (PDI) and zeta potential.**

From the higher than knowledge it's clear that nanoparticles ready by exploitation chitosan and HPMC exhibited reduction in mean nanoparticulate diameter and narrower granulometric distribution. however the nanoparticles ready exploitation gelatin as a chemical compound resulted in nanoparticulate population of huge particles. the upper particle size and polydispersity index is also owing to absence of surface-active agent because the use of surface-active agent decreases the physical phenomenon between organic section resolvent and liquid section and results in the formation of smaller solvent droplets, that successively causes decrease in particle size. It additionally stabilizes fresh generated surfaces and prevents aggregation of the particles as reportable by previous researchers. so results that were

obtained during this study is also improved by exploitation exaggerated drug:polymer magnitude relation, exploitation totally different formulation strategy like desolvation (for gelatin and albumin) or counter particle elicited aggregation (for chitosan and metallic element alginate), using cross linking agent followed by neutralizing residual cross linking agent with aminoalkanoic acid and high speed stirring.

**3. Zeta Potential** The measure of the Zeta Potential permits predictions concerning the storage stability of mixture dispersions. In general, particle aggregation is a smaller amount probably to occur for charged particles (i.e. high Zeta Potential) thanks to electrical repulsion. Generally, Zeta Potential values higher than thirty mV (positive or negative values) cause a lot of stable nanocapsule suspensions as a result of repulsion between the particles prevented their aggregation. A decrease in Zeta Potential, i.e. static repulsion, was thought of because the cause for the aggregation method. The charge on the surface of the nanospheres can influence their distribution within the body and also the extent of uptake into the cells. as a result of cell membranes are charged, there's bigger static affinity for charged nanoparticles. Therefore, the surface of ion or neutral nanoparticles is also changed to confer a charge to reinforce effectuality. The Zeta Potential values that were within the vary of  $-14.2$  -  $+21.7$  mV, indicates that the sol might not be stable and will cause aggregation. Zeta Potential values are often altered by modifying the most important parts like surfactants, polymer, and surface composition of the nanoparticles, the presence or the absence of adsorbable compounds, composition of the phase, chiefly the ionic strength, and the pH.

**4. Drug-Excipient Compatibility Studies** From the IR knowledge it's clear that functionalities of drug have remained unchanged, as well as intensities of the height. this implies that in the method of formulation chemical compound has not reacted with the drug to provide rise to chemical merchandise. therefore it's solely physical mixture and there's no interaction between them that is in choose to proceed for formulation.

## CONCLUSION

Among totally different nanoparticulate formulations prepared by nanoprecipitation methodology formulation NP a pair of, with chitosan in 1:1 drug: polymer ratio, showed satisfactory results; i.e. mean particle size of 312.04 nm (majority of the particles were within the vary of 200-525 nm), polydispersity index of 0.681, Zeta Potential 33.2 and loading potency of 18.54%, and entrapment efficiency of 76.4%. FTIR study all over that no major interaction occurred between the drug and polymers utilized in this study.

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