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Formulation and evaluation of polymeric nanoparticles of an antihypetensive drug for gastroretention

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ABSTRACT

The aim of present study was to formulate and evaluate nanoparticles of carvedilol by using different hydrophilic polymers. Carvedilol was selected as a suitable drug for gastro- retentive nanoparticles due to its short half life, low bioavailability, high frequency of administration, and narrow absorption window in stomach and upper part of GIT. The nano-precipitation method was used to prepare nanoparticles so as to avoid both chlorinated solvents and surfactants to prevent their toxic effect on the body. Nanoparticles of carvedilol were prepared by using hydrophilic polymers such as HPMC K100M, chitosan, and gelatin. The prepared formulations were then characterized for particle size, polydispersity index, zeta potential, loading efficiency, encapsulation efficiency and drug-excipient compatibility. The prepared nanoparticulate formulations of carvedilol with different polymers in 1:1 ratio have shown particle size in the range of 250.12-743.07 nm, polydispersity index (PDI) in the range of 0.681-1.0, zeta potential in the range of -14.2 to +33.2 mV, loading efficiency in the range of 8.74-17.54%, and entrapment efficiency in the range of 55.7%-74.2%. Nanoparticulate formulation prepared with chitosan in 1:1 ratio showed satisfactory results i.e. average particle size 312.04 nm, polydispersity index 0.681, zeta potential 33.2 mV, loading efficiency 17.54%, and entrapment efficiency 73.4%. FTIR study concluded that no major interaction occurred between the drug and polymers used in the present study.

Keywords: Nanoparticles; gastro-retentive; nano-precipitation, polydispersity index, zeta potential; entrapment efficiency.

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INTRODUCTION

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 [1-6]. These 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 longer 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. After oral administration, such a dosage form would be retained in the stomach for several hours and would release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract [7-12]. Prolonged gastric retention improves bioavailability, reduces drug waste, and

improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. 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 gastroretentive 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[13-18].

Carvedilol is an antihypertensive drug characterized by **i***t*slow aqueous solubility, a major obstacle in drug formulation development to improve its bioavailability. To overcome problem of poor aqueous solubility of Carvedilol, various approaches have been investigated including physical and chemical modifications of the drug. [19]

These mucoadhesive polymeric nanoparticles in the stomach will offer various advantages such as (i) Longer residence time of the dosage form on mucosal tissues in the stomach. This will improve absorption of the drug and increase the drug bioavailability. (ii) Higher drug concentration at the site of adhesion absorption, which will create a driving force for the paracellular passive uptake. (iii) Immediate absorption from the bioadhesive drug delivery system without previous dilution and possible degradation in the luminal fluids. [20-23]

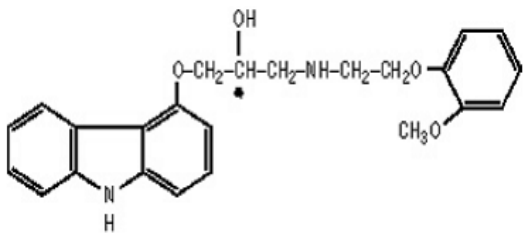
MATERIALS AND METHODS

Table 1: List of Materials used for the study

S.No.	INGREDIENTS	SUPPLIER
1	Carvedilol	Yarrow Chem, Mumbai
2	Hydroxyl propyl methyl cellulose K100M	Ozone International, Mumbai.
3	Gelatin	Ozone International, Mumbai.
4	Chitin	Loba Chemie Pvt Ltd., Mumbai.
5	Dimethylsulfoxie	Sd Fine-Chem Limited, Mumbai.

Drug Profile

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity. It is Carvedilol 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:



Structural formula of Carvedilol

Mechanism of action: Carvedilol is a racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity[19].

Preparation of Nanoparticles[20-22]

Nanoparticles were prepared according to the nanoprecipitation method with slight modification. Briefly, 200 mg of polymer (HPMC, chitosan, and gelatin) was dissolved in 25 ml of acetone separately. The carvedilol 100 mg was dissolved in 2 ml of dimethylsulfoxide. Both solutions were mixed and 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 the final volume of the suspension was adjusted to 10 ml. Then this suspension was centrifuged at 15000 rpm at 4^{O}C for half an hour. The supernatant was discarded and precipitate was washed 3 times with distilled water. The nanoparticles thus obtained were dried overnight in oven at 60ºC and stored in 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.

Characterization of Carvedilol Loaded Nanoparticles[19-22]

Loading Efficiency

Drug content in the preparation was determined by extracting the drug from the nanoparticles with 0.1 M hydrochloric acid. In this method, the nanoparticles (50 mg) were stirred in 50 ml of 0.1 M hydrochloric acid until dissolved; it was filtered through a Millipore filter and the drug content was determined, after suitable dilution, at 254 nm by UV spectrophotometry. The loading efficiency (L) of the nanoparticles was calculated according to Equation 1

$$L\ (\%) = (Qn / Wn) \times 100 \quad \text{.....(1)}$$

Where Wn is the weight of the nanoparticles and Qn is the amount of drug present in the nanoparticles.

Entrapment Efficiency

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

Then percentage entrapment of a drug was calculated according to Equation 2

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

Particle Size, Particle Size Distribution, and Zeta Potential

The particle size and particle size distribution of the formulation was determined by photo correlation spectroscopy with a zeta master (Malvern Instruments, UK) equipped with the Malvern PCS software. Every sample was diluted with distilled water. The surface charge (Zeta potential) was determined by measuring the electrophoretic mobility of the nanoparticles using a

Malvern zeta sizer (Malvern Instruments, UK). Samples were prepared by diluting with distilled water.

Polydispersity Index

Polydispersity index is a parameter to define the particle size distribution of nanoparticles obtained from photon correlation spectroscopic analysis. It is a dimensionless number extrapolated from the autocorrelation function and ranges from a value of 0.01 for mono dispersed particles and up to values of 0.5-0.7. Samples with very broad size distribution have polydispersity index values > 0.7.

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 and then correlated for incompatibility.

RESULTS AND 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 polymer-drug combination and 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, 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 and shown in Figure 1. 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: Drug loading and Entrapment efficiency

S.No.	Formulation code	Drug : Polymer	Loading efficiency ± SD	Entrapment efficiency ± SD
1	NP 1	1:2	11.43 ± 0.2	55.7 ± 0.8
2	NP 2	1:2	17.54 ± 0.3	75.3 ± 1.0
3	NP 3	1:2	8.74 ± 0.3	73.4 ± 1.0

* = Average of three determinations

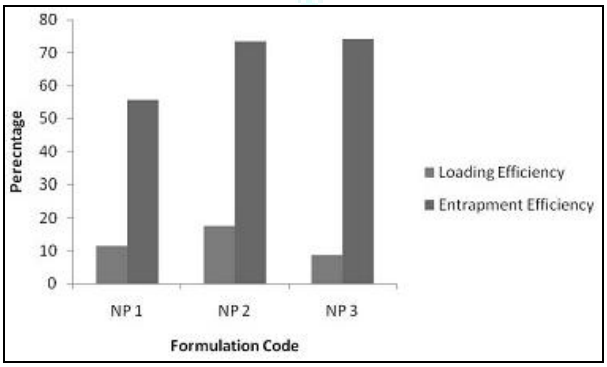


Figure 1: Effect of polymer on loading and entrapment efficiency.

Particle Size Distribution and Polydispersity Index

The particle size and particle size distribution are critical factors in the performance of nanoparticles, as batches with wide particle size distribution show significant variations in drug loading, drug release, bioavailability, and efficacy. Particle size and particle size distribution can be determined using light scattering techniques and by scanning or transmission electron microscopy. Formulation of nanoparticles with a narrow size distribution will be a challenge if emulsion cannot be produced with a narrow droplet size distribution. As nanoparticles are internalized into cells by endocytosis, an increase in particle size will decrease uptake and potentially, affect bioavailability of the drug. The extent of endocytosis is dependent on the type of the target cell.

The results of prepared nanoparticulate formulations of carvedilol with different polymers are given in Table 2 and shown in Figure 2. The formulations had very high polydispersity index (PDI) in the range of 0.681-1.0. From the particle size distribution data, it is evident that in case of HPMC nanoparticles, mean particle diameter was 250.12 nm and major portion of the particles were in the range of 200-400 nm, for chitosan nanoparticles mean particle diameter was 312.04 nm; and major portion of the particles were in range of 200-525 nm. In case of gelatin nanoparticles mean particle diameter was 743.07 nm and most of the particles were in the

range of 480-1200 nm. However, in all the formulations contained a minority population of nanoparticles in much smaller range. For HPMC, about 10.1% of the particles were in the range 15-30 nm, for chitosan about 7.1% of the particles were in the range 48-90 nm and for gelatin 14.1% of the particles were in the range 70-160 nm. These minority populations are responsible for larger over all polydispersity indices of the formulations. We are currently exploring the process variables affecting the relative amounts of different populations with an objective to increase the yield of the particles in the smaller range to get much smaller nanoparticles, which have greater degree of monodispersity. Such nanoparticles can be easily separated from the larger sized population by simple methods like filtration.

Table 2: Drug polymer ratio, mean particle size, particle size distribution, poly dispersity index (PDI) and zeta potential.

F. Code	Polymer	Mean Particle Size (nm) ± SD	Size Distribution	PDI ± SD	Zeta Potential (mV) ± SD
NP 1	Ethyl cellulose	250.12 ± 18	10.1% (15-30 nm) 89.9 % (200-400 nm)	1.0 ±0.12	21.7± 1.4
NP 2	Chitosan	312.04 ± 32	7.8% (48-90 nm) 92.2% (200-525 nm)	0.68 ±0.15	33.2±2.1
NP 3	Gelatin	743.07 ± 45	14.2% (70-160 nm) 85.8% (480-1200 nm)	0.77±0.14	14.2±1.3

* = Average of three determination

From the above data it is clear that nanoparticles prepared by using chitosan and HPMC exhibited reduction in mean nanoparticulate diameter and narrower granulometric distribution. But the nanoparticles prepared using gelatin as a polymer resulted in nanoparticulate population of large particles. The higher particle size and polydispersity index may be because of absence of emulsifier as the use of emulsifier decreases the surface tension between organic phase acetone and aqueous phase and leads to the formation of smaller solvent droplets, which in turn causes decrease in particle size. It also stabilizes newly generated surfaces and prevents aggregation of the particles as reported by previous researchers. Therefore results which were obtained in this study may be improved by using increased drug:polymer ratio, using different formulation strategy such as desolvation (for gelatin and albumin) or counter ion induced aggregation (for chitosan and sodium alginate), employing cross linking agent followed by neutralizing residual cross linking agent with cysteine and high speed stirring.

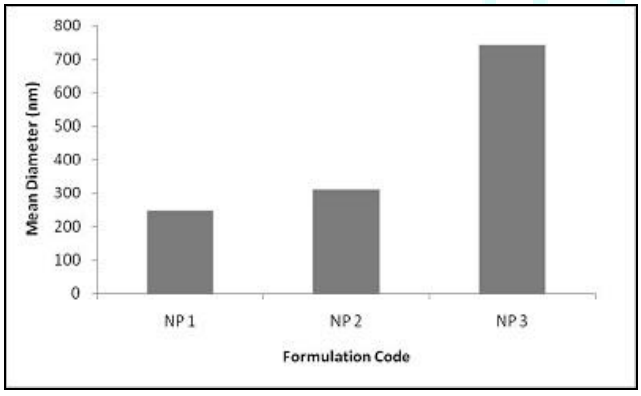


Figure 2: Effect of polymer on mean particle size.

Zeta Potential

The measurement of the zeta potential allows predictions about the storage stability of colloidal dispersions. In general, particle aggregation is less likely to occur for charged particles (i.e. high zeta potential) due to electric repulsion. Generally, Zeta potential values above 30 mV (positive or negative values) lead to more stable nanocapsule suspensions because repulsion between the particles prevented their aggregation. A decrease in zeta potential, i.e. electrostatic repulsion, was considered as the cause for the aggregation process. The charge on the surface of the nanospheres will influence their distribution in the body and the extent of uptake into the cells. Because cell membranes are negatively charged, there is greater electrostatic affinity for positively charged nanoparticles. Therefore, the surface of cationic or neutral nanoparticles may be modified to confer a positive charge to enhance efficacy. The zeta potential values which were in the range of –14.2 - +21.7 mV, indicates that the colloidal suspension may not be stable and may lead to aggregation. Zeta potential values can be altered by modifying the major components such as surfactants, polymer, and surface composition of the nanoparticles, the presence or the absence of adsorbed compounds, composition of the dispersing phase, mainly the ionic strength, and the pH.

Drug-Excipient Compatibility Studies

From the IR data it is clear that functionalities of drug have remained unchanged, including intensities of the peak. This suggests that during the process of formulation polymer has not reacted with the drug to give rise to reactant products. So it is only physical mixture and there is no interaction between them which is in favor to proceed for formulation.

CONCLUSION

Among different nanoparticulate formulations prepared by nanoprecipitation method formulation NP 2, 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 in the range of 200-525 nm), polydispersity index of 0.681, zeta potential of 33.2 and loading efficiency of 17.54%, and entrapment efficiency of 73.4%. FTIR study concluded that no major interaction occurred between the drug and polymers used in the present study.

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