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Original Research Article

# Formulation and evaluation of mucoadhesive chitosan microspheres of carvedilol for nasal administration

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ABSTRACT

The aim of this study was to develop and characterize chitosan microspheres of Carvedilol (CRV) for nasal delivery to improve bioavailability for treatment of hypertension and angina pectoris. Carvedilol comes under BCS class II, is poorly water soluble drug and highly permeable. Solubility of drug is determined by shaking flask method and lipophilicity of drug is determined by separating funnel method. The nasal route is very convenient for achieving high bioavailability and reduce hepatic first pass metabolism. Chitosan is obtained from chitin of fish, is biodegradable and nontoxic that is suitable for nasal administration. The microspheres were prepared by cross- linking method using glutaraldehyde as cross linking agent and this preparation is evaluated for size, entrapment efficiency (EE), in vitro mucoadhesion, in vitro drug release. The mucoadhesive property was also evaluated by in vitro wash off test. The microspheres were spherical with size of 15-40 micron, which is favorable for intranasal absorption. The EE was observed from 40% to 88% while percentage of mucoadhesion was from 74%to 88%. A strong interaction between mucin and chitosan microspheres was detected explaining absorption with electrostatic interaction. The microspheres released around 80% of drug in 6h. It was concluded that chitosan microspheres could be used to deliver CRV following nasal administration for improving the bioavailability.

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## 1. Introduction

### *1.1. Carvedilol*

Carvedilol is both a non-selective beta adrenergic receptor blocker (ß1, ß2) and an alpha adrenergic receptor blocker (a1). The S (-) enantiomer accounts for the beta blocking activity whereas the S (-) and R (+) enantiomer have alpha blocking activity.[1]

### *1.2. Structure*

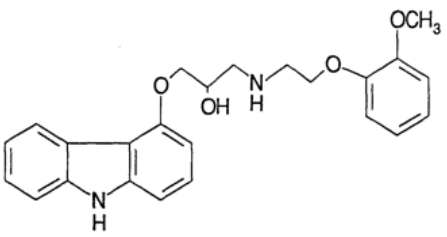


**Fig. 1:** Structure of Carvedilol

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### 1.3. Pharmacokinetics

1. *Absorption:* Carvedilol is about 25% to 35% bioavailable following oral administration due to extensive first-pass metabolism. Absorption is slowed when administered with food, however it does not show significant difference in bioavailability.[2] Taking carvedilol with food decreases the risk of orthostatic hypotension.
2. *Distribution:* Majority of carvedilol is bound to plasma proteins (98%), mainly to albumin. Carvedilol is a basic, hydrophobic compound with a steady-state volume of distribution of 115 L. Plasma clearance ranges from 500 to 700 mL/min.[2]
3. *Metabolism:* The compound is metabolized by liver enzymes, CYP2D6 and CYP2C9 via aromatic ring oxidation and glucuronidation, then further conjugated by glucuronidation and sulfation.Compared with the parent compound, the three active metabolites exhibits only one-tenth of the vasodilating effect of the parent compound.
4. *Excretion:* The mean half-life of Carvedilol following oral administration ranges from 7 to 10 hours.

### 1.4. Chitosan

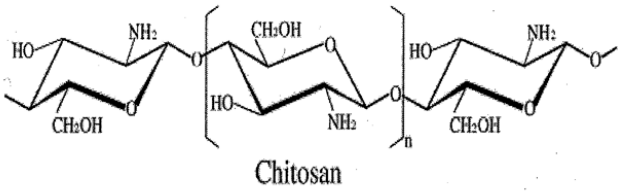


**Fig. 2:** Structure of chitosan

### 1.5. Application of chitosan

Chitosan is a biocompatible, biodegradable, and nontoxic natural polymer with excellent film-forming ability.[3] Being of cationic character, chitosan is able to react with polyamines giving rise to polyelectrolyte complexes.[3] Hence chitosan has become a promising natural polymer for the preparation of microspheres/nano spheres and microcapsules.[4]

### 1.6. Factors effecting chitosan

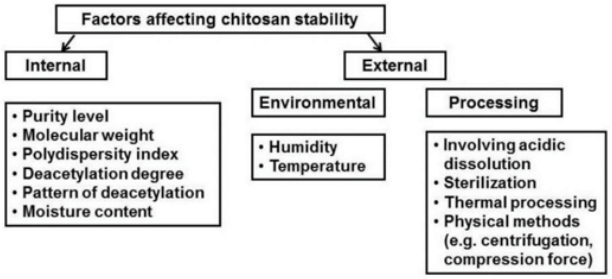


**Fig. 3:** Factors affecting chitosan stability

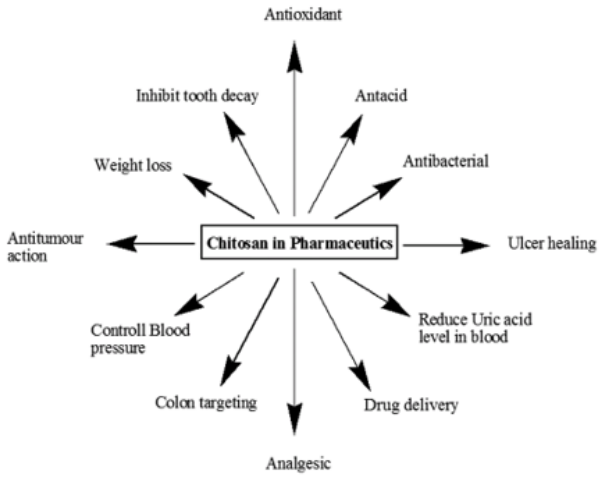


**Fig. 4:** Pharmaceutical properties of chitosan

## 2. Materials and Methods

Carvedilol was a gift sample from GSK, Goa. Chitosan was obtained from Merck. Glutaraldehyde (GA) (25% aqueous solution), Dioctyl sodium sulfosuccinate (DOSS) and other chemicals and reagents used in the study were of analytical grade.

### 2.1. Preparation of chitosan microspheres

Chitosan microspheres were prepared by simple w/o emulsification-cross linking process using liquid paraffin (heavy and light, 1:1) as external phase. Briefly, accurately weighed quantity of chitosan was dissolved in 2% aqueous acetic acid solution by continuously stirring until a homogeneous solution was obtained.[5] The drug was added in chitosan solution and the dispersion was added slowly through syringe to liquid paraffin (heavy and light, 1:1) containing 0.1% w/v of DOSS as stabilizer under constant stirring at 1000 rpm for 30 min using a high speed stirrer. To this W/O emulsion, appropriate quantities of glutaraldehyde (25% solution, as cross-linking agent) were added slowly and stirring was continued for 3 h. The hardened microspheres were separated by vacuum filtration and washed several times with hexane to remove oil.[6] Finally, microspheres were washed with distilled water to remove unreacted glutaraldehyde. The microspheres were

air dried for 24 h and then stored in desiccator.[6]

### 2.2. Formulation table for carvedilol chitosan microspheres

### 2.3. Pre-formulation studies

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre formulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation.[7]

### 2.4. Determination of partition coefficient

Between time that a drug is administered and the time it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid like barriers.[8] A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil / water partition coefficient defined as:

$K = C_O$ / Cw

Where,

Co = Equilibrium concentration of all forms of the drug

Cw = Equilibrium concentration of all forms in aqueous phase.

### 2.5. Determination of solubility

The solubility of drug was determined as per BCS. Carvedilol is poorly water soluble drug and comes under the class II of BCS.[9] Solubility of the drug was determined by shaking flask method.[9] The absorbance is measured by UV spectroscopy and solubility is calculated .The solubility in 0.1N HCl is 545.1($\mu$g/ml) and in 6.8 pH buffer is determined 51.9 ($\mu$g/ml).

### 2.6. Determination of bulk density

Weigh accurately 10g of sample (M), which was previously passed through 20 sieve and transfer in 100 mL graduated cylinder.[10] Carefully level the powder without compacting, and read the unsettled apparent volume ($V_0$). Calculate the apparent bulk density in g/mL by the following formula,

Bulk density = Weight of powder / Bulk volume

### 2.7. Determination of tapped bulk density

Weigh accurately 10g of drug, which was previously passed through 20 sieve and transfer in 100mL graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute.[11] Tap the cylinder for 500 times initially and measure the tapped volume ($V_1$) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume ($V_2$) to the nearest graduated units. If the difference between the two volume is less than 2% then final the volume ($V_2$)

### 2.8. Tapped density = $W / V_F$

Where,

W = weight of the granules

$V_F$ = final volume of the granules.

### 2.9. Carr's compressibility Index ($C_1$) and Hausner's Ratio

The compressibility index and Hausner's ratio are measures of the propensity of powder to be compressed. Carr's compressibility index and Hausner's ratio can be calculated as follows

$C_I \frac{(Tapped\ density - Bulk\ density)}{Tapped\ density} \times 100$

Hausner's ratio = Tapped density / Bulk density

### 2.10. Angle of repose

The frictional force in the powder can be measured by the angle of repose. Angle of repose was calculated by fixed funnel method.

Angle of repose can be calculated by using following formula,

Tan $\theta$ = h / r

$\Theta = \text{Tan}^{-1}\text{h/r}$

Where; h = Height of heap in cm.

r = Radius of heap in cm.

### 2.11. Melting point

Melting point of drug was determined by DSC (Mettler Toledo). Differential scanning calorimetry (DSC) measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature.[12] Quantitative measurement of endothermic and exothermic processes has many applications in Preformulation studies including purity, polymorphism, degradation and excipients compatibility with drugs.[13]

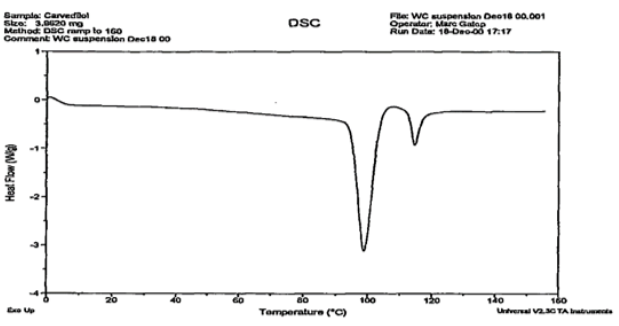


**Fig. 5:** DSC plot of Carvedilol

**Table 1:** Formulation table

| Name of the formulation | Drug(mg) | Polymer(mg) | Quantity of GA after10 min (ml) | Quantity of GA after40 min (ml) | Total amount of cross linking agent(ml) |
|---|---|---|---|---|---|
| F1 | 100 | 200 | 1 | 1 | 2 |
| F2 | 100 | 200 | 1.5 | 1.5 | 3 |
| F3 | 100 | 200 | 2.0 | 2.0 | 4 |
| F4 | 100 | 300 | 1 | 1 | 2 |
| F5 | 100 | 300 | 1.5 | 1.5 | 3 |
| F6 | 100 | 300 | 2.0 | 2.0 | 4 |
| F7 | 100 | 400 | 1 | 1 | 2 |
| F8 | 100mg | 400mg | 1.5ml | 1.5ml | 3ml |
| F9 | 100mg | 400mg | 2.0ml | 2.0ml | 4ml |

**Table 2:** Determination of partition coefficient of the drug

| S.no. | Concentration of drug in octanol ($\mu$g/ml) | Concentration of drug in water ($\mu$g/ml) | P $_{o/w}$ | Average |
|---|---|---|---|---|
| 1 | 0.8113 | 0.225 | 3.605 | |
| 2 | 0.8006 | 0.226 | 3.542 | 3.422 |
| 3 | 0.8299 | 0.226 | 3.119 | |

### *2.12. Drug excipients compatibility study*

API and excipients were to be thoroughly mixed in predetermined ratio given in table and passed through the sieve no. 40. The blend was to be filled in glass vials and were closed with gray rubber stoppers and sealed with aluminum seal and charged in to tress condition 60ºC for 1 and 2 weeks and 40ºC/75% RH 1 month. Similarly API shall also be kept at all condition as per the sample Samples to be withdrawn for analysis within two day of sampling date as per the compatibility study plan.

### *2.13. Determination of $\lambda_{max}$*

The absorption maxima carvedilol were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.[14,15]

### *2.14. Procedure*

Accurately weighed 100mg of drug was dissolved in 100 ml of phosphate buffer pH 6.8 in 100 ml volumetric flasks with aid of sonication in bath sonicator for 20 min. The spectrum of this solution was running 200-400nmrangeinUV spectrophotometer. The spectrum peak point graph of absorbance of carvedilol versus wave length was shown in figure the metformin hydrochloride shows the absorbance maxima at 283nm.in phosphate buffer pH 6.8.[16]

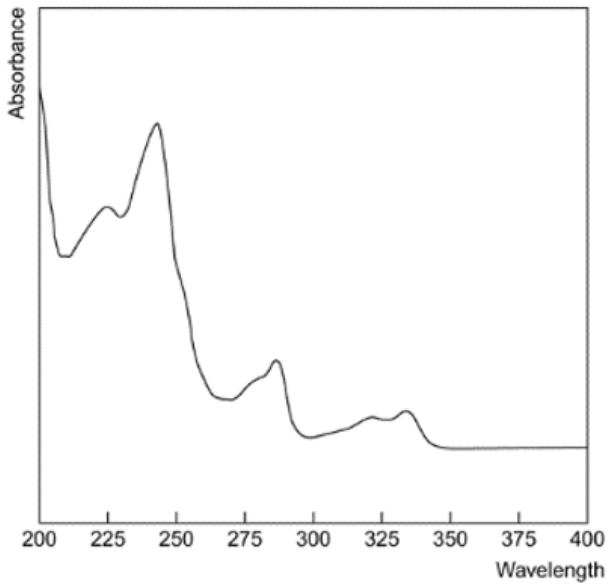


**Fig. 6:** Determination of $\lambda_{max}$ of carvedilol

## 3. Results and Discussion

### *3.1. Particle size determination*

Particle size of the microsphere was in the range of 19.18 -20.55 $\mu$m is favorable for intranasal administration. The microspheres were non aggregated, free flowing powders.[17]

Stage micrometer is simply a microscope slide with a scale etched on the surface

Stage micrometer has scale of stage = 100$\mu$m

Ocular piece covers the stage = 73 $\mu$m

Division covers 1 37 parts of the stage

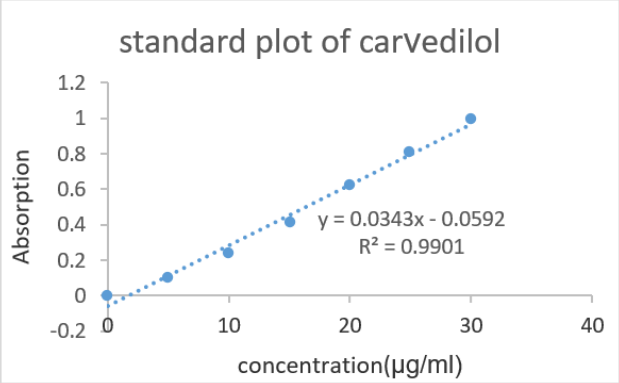


**Fig. 7:** Calibration curve of Carvedilol in pH 6.8 phosphate buffer

**Table 3:** Particle size determination

| Code for formulation | Average size of microspheres ($\mu$m) |
|---|---|
| F1 | 19.18 |
| F2 | 16.44 |
| F3 | 27.40 |
| F4 | 34.25 |
| F5 | 26.25 |
| F6 | 35.62 |
| F7 | 23.29 |
| F8 | 24.66 |
| F9 | 20.55 |

### 3.2. *Determination of % yield*

The dried microspheres were weighed and their percentage yield (w/w) was determined by using the following formula.[18–20]

%yield = practical yield / theoretical yield *100

**Table 4:** Determination of % yield

| Code for formulation | Theoretical yield | Practical yield | %yield |
|---|---|---|---|
| F1 | 300 | 115 | 38.33 |
| F2 | 400 | 125 | 31.25 |
| F3 | 500 | 233 | 46.60 |
| F4 | 300 | 122 | 40.66 |
| F5 | 400 | 152 | 38.00 |
| F6 | 500 | 318 | 63.60 |
| F7 | 300 | 110 | 36.66 |
| F8 | 400 | 200 | 50.00 |
| F9 | 500 | 322 | 64.40 |

### 3.3. *Drug entrapment efficiency*

Drug entrapment Efficiency of drug entrapment for each batch can be calculated in terms of percentage drug entrapment (PDE) as per the following formula:

PDE= (Practical drug loading/theoretical drug loading) ×100

Theoretical drug loading was determined by calculation assuming that the entire drug present in the chitosan solution used gets entrapped in microspheres and no loss occurs at any stage of preparation of microspheres.[21]

Determination of Practical drug loading can be done by taking a weighed quantity of chitosan microspheres (approximately 25 mg) in a 25-ml volumetric flask. Sufficient quantity of methanol is to be added to make the volume 25 ml. After shaking the suspension vigorously it was left for 24 h at room temperature with intermittent shaking.[22] Supernatant was collected by centrifugation and drug content in supernatant was determined by UV spectrophotometer at 283 nm wavelength.

**Table 5:** % Drug entrapmentefficiency

| Code for formulation | % Drug efficiency |
|---|---|
| F1 | 35.50±1.8 |
| F2 | 40.22±1.3 |
| F3 | 38.20±1.4 |
| F4 | 33.89±0.6 |
| F5 | 50.32±0.5 |
| F6 | 42.12±1.4 |
| F7 | 39.60±1.5 |
| F8 | 54.21±0.8 |
| F9 | 37.15±1.3 |

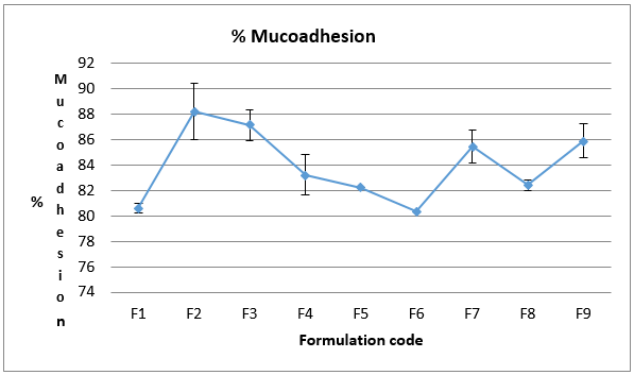


**Fig. 8:** % Adhesion for various formulations of microspheres

### 3.4. *Flow properties of microspheres*

Flow properties of microspheres are determined. There is no aggregation between the microspheres and they are free flowing in nature.

### 3.5. *Measurement of mucoadhesive properties*

The mucoadhesive potential of each formulation was determined by adapting the method called as wash off in

**Table 6:** Micromeritics properties of microspheres

| S.no. | Code of formulation | Bulk density ($g/cm^3$ ) | Tapped density ($g/cm^3$ ) | Angle of repose | Carr's index | Hausner's ratio |
|---|---|---|---|---|---|---|
| 1 | F1 | 0.131 | 0.156 | 24° | 16.02 | 1.19 |
| 2 | F2 | 0.110 | 0.128 | 24° | 14.06 | 1.16 |
| 3 | F3 | 0.121 | 0.150 | 25°.35 | 19.33 | 1.23 |
| 4 | F4 | 0.131 | 0.160 | 24°.5 | 18.12 | 1.22 |
| 5 | F5 | 0.092 | 0.108 | 24°.65 | 14.81 | 1.17 |
| 6 | F6 | 0.113 | 0.133 | 24°.32 | 15.03 | 1.17 |
| 7 | F7 | 0.122 | 0.140 | 25°.35 | 12.85 | 1.14 |
| 8 | F8 | 0.135 | 0.143 | 24°.5 | 12.55 | 1.20 |
| 9 | F9 | 0.123 | 0.152 | 25°.4 | 19.07 | 1.22 |

**Table 7:** Determination of % Mucoadhesion

| Code of formulation | Particle Size In Micron | % Mucoadhesion |
|---|---|---|
| F1 | 19.18 | 80.62±0.36 |
| F2 | 16.44 | 88.22±2.22 |
| F3 | 27.40 | 87.13±1.20 |
| F4 | 34.25 | 83.23±1.58 |
| F5 | 26.25 | 82.22±0.02 |
| F6 | 35.62 | 80.33±0.01 |
| F7 | 23.29 | 85.42±1.30 |
| F8 | 24.66 | 82.42±0.43 |
| F9 | 20.55 | 85.89±1.35 |

**Table 8:** In-vitro wash off test to affectsmucoadhesive properties of the microspheres

| Formulation Code | After 1 HR | After 2 HR | After 3HR | After 4 HR |
|---|---|---|---|---|
| F1 | 70 | 55 | 38 | 30 |
| F2 | 90 | 80 | 75 | 75 |
| F3 | 80 | 75 | 75 | 60 |
| F4 | 54 | 40 | 32 | 32 |
| F5 | 82 | 55 | 52 | 40 |
| F6 | 85 | 65 | 45 | 45 |
| F7 | 85 | 70 | 70 | 65 |
| F8 | 90 | 82 | 75 | 70 |
| F9 | 72 | 62 | 55 | 55 |

**Table 9:** Release kinetics of microspheres

| S.No. | Formulation code$R^2$ value | Zero-order $R^2$ value | First-order$R^2$ value | Higuchi matrix$R^2$ value | Korsemeyer-Peppas$R^2$ value | Diffusion component 'n'value |
|---|---|---|---|---|---|---|
| 1 | F1 | 0.920 | 0.909 | 0.822 | 0.923 | 0.922 |
| 2 | F2 | 0.85 | 0.959 | 0.850 | 0.962 | 0.778 |
| 3 | F3 | 0.902 | 0.945 | 0.902 | 0.955 | 0.825 |
| 4 | F4 | 0.92 | 0.975 | 0.912 | 0.982 | 0.892 |
| 5 | F5 | 0.962 | 0.972 | 0.933 | 0.950 | 0.657 |
| 6 | F6 | 0.977 | 0.966 | 0.962 | 0.933 | 0.852 |
| 7 | F7 | 0.972 | 0.944 | 0.966 | 0.899 | 0.735 |
| 8 | F8 | 0.982 | 0.959 | 0.980 | 0.912 | 0.706 |
| 9 | F9 | 0.988 | 0.935 | 0.978 | 0.989 | 0.650 |

– vitro test. The nasal mucosal tissues of nasal cavity of goat. The tissues were cut into the size of 1*1 cm and were mounted onto the glass slide. About 100 microspheres were spread onto the wet rinsed nasal tissue specimen, then the glass tube hung on one of the grove of USP tablet disintegration test apparatus. The test apparatus was operated where by the nasal tissue was allowed to move upward and downward at a constant speed (20 rpm) in a vessel containi9ng 400ml phosphate buffer of 6.8 maintained at 37o C. Immediately, the time required for complete washing of microspheres from the tissue were noted.

Measurement of adhesive force Mucoadhesion studies were carried out to confirm the adhesion of formulation to the nasal mucosa for a prolonged period of time at the site of absorption. Results showed that the microspheres adequately adhere on nasal mucosa. The ratio of the adhered microspheres was expressed as percentage mucoadhesion. For all batches, percentage of mucoadhesion ranged from 80–90%.

The drug release test was carried out using a nasal diffusion cell microspheres loaded with carvedilol was placed in the reservoir tube, 100 ml of a release medium is kept and stirred at 100 rpm at 37° C the release media was of pH 6.8 phosphate buffer solution. An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The samples were analyzed by UV spectrophotometer at 283 nm.

### *3.6. Kinetic modeling and mechanism of drug release*

The release data obtained were fitted to zero order, first order, Higuchi and korsmeyer peppas equation to determine the corresponding release rate and mechanism of drug release from the mucoadhesive microspheres

## 4. Summary and Conclusion

In the present study chitosan microspheres were prepared by chemical-cross linking method. Various variables such as the drug: polymer ratio, glutaraldehyde concentration and the cross-linking time were optimized by the factorial design. A $3^2$ experimental design was employed to identify optimal formulation parameters for a microsphere preparation with the minimum value of particle size and maximum value of *in vitro* mucoadhesion. Particle size was in the range of 19.18 ±.1.2 to 35.62±0.5 $\mu$m which is considered to be favorable for intranasal absorption. All batches showed good in vitro mucoadhesion (80-90%). Results flow properties study indicated there is no aggregation between drug–polymer in the microspheres. Hence, the results of the present study clearly indicated promising potentials of chitosan microspheres for delivering Carvedilol intranasal and could be viewed as a potential alternative to conventional dosage forms.

## 5. Source of Funding

None.

## 6. Conflict of Interest

None.

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