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FORMULATION AND EVALUATION OF CARVEDILOL MICROPARTICLE

Rajan Patel*, Shraddha Saha and Pooja Shah

Pacific College of Pharmacy, Udaipur, Rajasthan, 313003.

***Corresponding Author: Rajan Patel**

Pacific College of Pharmacy, Udaipur, Rajasthan, 313003.

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ABSTRACT

Main aim of this study was to develop carvedilol microparticle by using different polymer.The Carvedilol microparticles were prepared by solvent evaporation method by using different polymer (Ethyl cellulose, cellulose acetate, hydoxy ethyl cellulose) as excipients. Also, it were found to be highly porous and regular in shape. Scanning electron microscopy technique were used to determine chemical interaction between drug and other excipients used in formulation of microparticles.

KEYWORDS: Carvediol, Microparticles, Pharmacokinetic-Biopharmaceutical Properties.

INTRODUCTION

Carvedilol is a competitive adrenoreceptor antagonist that inhibits activity at the β1, β2, and α1adrenergic receptors and exhibits a number of ancillary properties, such as antioxidant effects, inhibition of smooth muscle proliferation, and calcium antagonistic blocking activity. The original formulation of Carvedilol is approved by the US Food and Drug Administration (FDA) to be administered twice daily, but it is also administered four times a day to twice a day and is widely used alone or in combination with other agents for the treatment of essential hypertension, as well as for improving survival in patients with mild-to-severe heart failure and reducing cardiovascular mortality in patients with systolic dysfunction after MI. Sustained release formulation of Carvedilol been developed that may provide levels of exposure to Carvedilol similar to those achieved after administration of the current twice-daily formulation over extended period.[1] Carvedilol is well absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism in the liver. Its absolute bioavailability is considerably low, that is, about 25%, and its plasma half-life is about 6 hours.[2] It is important, especially in the case of antihypertensive agents, to maintain constant blood levels, as otherwise, dose dumping may cause hypotension and subtherapeutic level may cause hypertension. Based on the physicochemical and biopharmaceutical properties carvedilol was selected as a drug candidate for the development of controlled release matrix tablet formulations.

Moreover, it is desirable to develop a formulation that will improve the bioavailability as well as control the release of carvedilol.

Microencapsulation is considered one of the most effective tools in formulating prolonged action dosage forms. It is used to modify drug release by delaying the time during which the drug is available and retard its attack by the gastrointestinal fluids. The preparation of microspheres results by the coating of the individual drug particles with polymeric inert materials, through which the drug would diffuse at a controlled and predictable rate to the surrounding medium. There are several techniques used to produce polymeric microspheres drug delivery systems, which include physicochemical processes such as solvent evaporation method. [3,4,5] (or mechanical processes such as spray drying.[6] and a non-solvent addition process.[7,8] or by cross-linking with glutaraldehyde using poly(vinyl alcohol)-guar gum interpenetrating network microspheres.[9]

MATERIAL AND METHOD

Methods Use of Preparation of Microspheres:[10]

1. Solvent evaporation method,
a) Single emulsion technique.
b) Double emulsion technique.
2. Coacervation phase separation method.
3. Spray drying and spray congealing method.
4. Polymerization method.

Solvent Evaporation

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing

vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion. The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelating prepared by complex coacervation were made.

Preparation of Carvedilol Microparticle

Procedure

Carvedilol microparticles were prepared by solvent evaporation method by using different polymer (Ethyl cellulose, Cellulose acetate, Hydoxy Ethyl Cellulose) as Excipients. Using a solvent evaporation method to make various formulations (f1 to f6). The constant stirring for 3-4 hr until the aqueous phase was completely removed by evaporation. The microspheres were formed were collected by whattman filter paper and washed 3 times with distilled water. The filtered particles were dried at a room temperature for one day and then packed in a sealed bottle for further studies.

Table No. 1: Particles prepared by solvent evaporation method.

Batch Code	Carvedilol (mg)	Ethyl Cellulose (mg)	Cellulose Acetate (mg)	Hydroxy Ethyl Cellulose (mg)	Polyvinyl Alcohol (%)
F1	10	200	-----	------	1
F2	10	400	-----	------	1
F3	10	------	200	------	1
F4	10	------	400	------	1
F5	10	------	-----	200	1
F6	10	------	-----	400	1

Micromeritical Study

(A) Angle of Repose

The angle of repose was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touch the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on the surface. The diameter of the powder cone was measured and angle of repose was then calculated using the following equation.

Tan = h/r

Where, h and r the high and radius of the powder cone respectively.

Table No. 2: Effect of Angle of Repose on Flow Property.

Angle of Repose	Type of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

(B) Bulk density

Bulk density of Carvedilol was determined by using the following method. Carvedilol was weighted 25 gm, which was previously passed through 60 # sieves and transferred in to 100 ml graduated cylinder. Carefully leveled the powder without compacting, and read the unsettled apparent volume (V_0). Bulk density was determined the following formula.

Bulk density = Weight of powder / Bulk volume

(C) Tapped Density

Tapped density of carvedilol was determined. Weighed 25 gm Carvedilol, which was previously passed through 60 # sieved and transfer in 100 ml graduated cylinder. Then tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight. Tap the cylinder for 100 times initially and measured the tapped volume (V_1) to the nearest graduated units and the difference between the two volume is not less than 2 % so that (V_1) is calculated. The tapped density was calculated in gm/ml by the following formula:

Tapped Density = Weight of powder / Tapped volume

(D) Compressibility index (Carr's Index)
It is one of the most important parameter to characteristic the nature of powder and granules. It is simple to test to evaluate the Bulk Density and Tapped Density of the granules and the rate at which it packed down. It can be calculated from the following formula:
Carr's Index (%)= [(Tapped Density – Bulk Density)X 100/ Tapped Density)]

Table No. 3: Standard Curve for Compressibility Index.

Compressibility Index (%)	Flow Chart
<10	Excellent
11-15	Good
16-20	Fair
21-25	Satisfactory
26-31	Poor
32-37	Very poor
>38	Very, very poor

(E) Hausner's Ratio
The Hausner's is a number that is correlated to the flow ability of a granular material. The Hausner's ratio is defined as the ratio of Tapped Density (TD) and Bulk Density (BD).
Hausner's ratio= Tapped Density/ Bulk Density

Solubility Studies
A. Solubility study in water
Drug was added in 20 mg in conical flasks containing 20 ml of distilled water. The flasks were tightly corked and placed in a water bath at 37.0 ± 0.50 C agitated at 100 rpm for at least 12 hrs. Samples were taken at 12 hrs and filtered through 0.45 µm filter, diluted with the medium and the drug concentration in the final sample solutions was determined spectrophotometrically. Each solubility value was determined in triplicate and the results reported are the mean of the three.

B. Solubility study in buffer
Drug was added in 20 mg in six conical flasks each containing pH 1.2 hydrochloric acid, pH 3.0 acid phthalate buffer, pH 4.5 acetate buffer and pH 5.8, 6.8 and 7.2 potassium phosphate buffers were prepared as per IP. The buffers were prepared using distilled water. The solubility of drug in the buffers was measured in the similar manner as in water.

Drug-Excipients Interaction
Infrared spectroscopy & Scanning electron microscopy are useful analytical technique utilized to check the chemical interaction between the drug & other excipients used in the formulation.

Analytical Method Development By Uv Spectroscopy
Determination of absorption maxima (λ_{max})
The solution contacting 10µg/ml of carvedilol in pH 6.8 phosphate buffer was prepared & scanned over the wavelength range of 200 – 400 nm against phosphate buffer as a blank solution using double beam UV spectrophotometer.

Evaluation Parameter of Carvedilol Microparticle
Microparticles are small spherical shape particle, nonporous and uniform mixture.

Optimization of Processing Parameter
Initial formulations were prepared to optimize the procedure and other variables.

Effect of RPM
Formulations with drug polymer ratio were prepared at different RPM and the microspheres were evaluated for size, shape and % yield to optimize the rpm.

Effect of Surfactant
PVA was used in same concentration and the microspheres were evaluated for size, shape and % yield to optimize the PVA.

Effect of Temperature
The formulation was prepared with different temperatures maintained in the continuous phase (1%PVA) and the microspheres were evaluated for size, shape and % yield to optimize the temperature.

RESULTS AND DISCUSSION

Preformulation Studies
Micromeritical Study
Table No. 4: Micromeritical Study of Carvedilol Drug.

Angle of response	39.06
Bulk Density	0.62±0.04 gm/cm^3
Tapped Density	0.78±0.02 gm/cm^3
Compressibility(%)	20.51%
Hausners ratio	1.33

Appearance
Microparticles are small spherical shape particle, nonporous & uniform mixture.

Solubility Test
Carvedilol is a whitish powder it can be easily soluble in methanol & Ethyl acetate and it can partially dissolve in Dichloromethane.

Solubility in distilled water and buffer solutions
The solubility of carvedilol in distilled water was found to be 2.60 µg/ml. Solubility at different pH was in following order: pH 3.0 (380 µg/ml)> pH 4.5 (341 µg/ml) > pH 1.2(290 µg/ml) > pH 5.8 (133.11 µg/ml) > pH 6.8 (80.33 µg/ml) > pH 7.2 (72.11 µg/ml).

Optimization of Processing Parameter
Initial formulations were prepared to optimize the procedure and other variables.

Effect of Homogenization speed

Energy density, which is energy applied per unit total volume has a direct effect on droplet size of the emulsion produced. Increasing the shear stress may result in reduced particle size to produce microparticle.

Therefore, emulsification was performed at same homogenization speeds at 1000 rpm for 15 minutes with evaporation time of organic phase set at 3-4 hours.

Effect of Temperature

If particle where not keep on room temperature then the changes will occured, if the temperature was increase the particle size of microparticles was increase & if the temperature will decrease the particle size will decrease.

Effect of Surfactant

In this investigation, PVA was selected & used as a surfactant. It was observed that, at 1 % PVA concentration the emulsion formed was stable & resulted in particle size 120-145 µm, respectively. If the PVA concentration was change emulsion formed was not stable & phase separation occurred after a few hours of emulsification, resulting in the formulation of polymer aggregates.

Polymer–drug interaction analysis using FTIR spectroscopy

The FT- IR spectra of Carvedilol phosphate, Ethyl cellulose, physical mixture of Drug + Hydroxy Ethyl Cellulose. Ethyl cellulose is shown in the figures 1,4,5 respectively.

There is no significant difference in characteristic peaks of pristine drug and drug-loaded microparticles suggesting drug stability during encapsulation process. This shows the absence of any chemical interactions between drug and polymer.

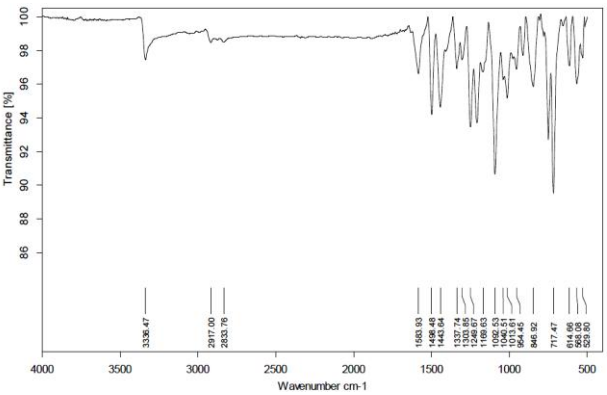

Figure No. 1: FT-IR Spectrum of Carvedilol.

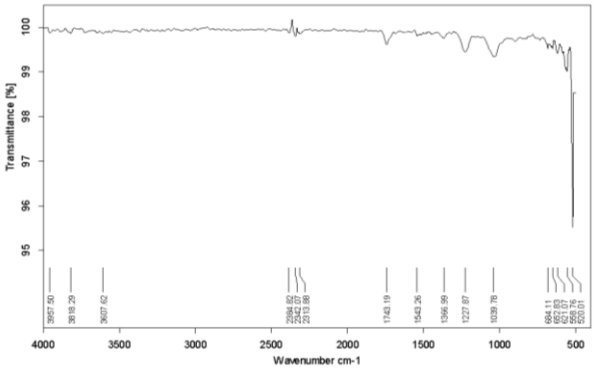

Figure No. 2: FT-IR Spectrum of Cellulose acetate.

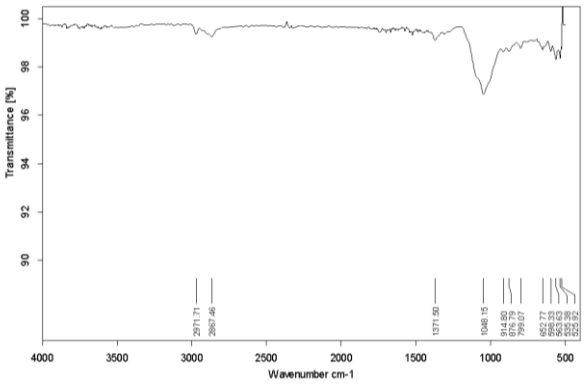

Figure No. 3: FT-IR Spectrum of Hydroxy Ethyl Cellulose.

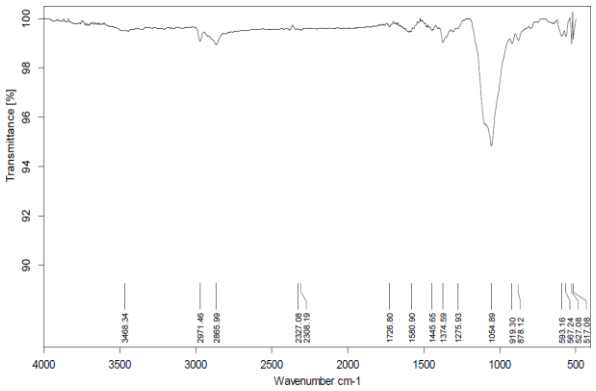

Figure No. 4: FT-IR Spectrum of Ethyl Cellulose.

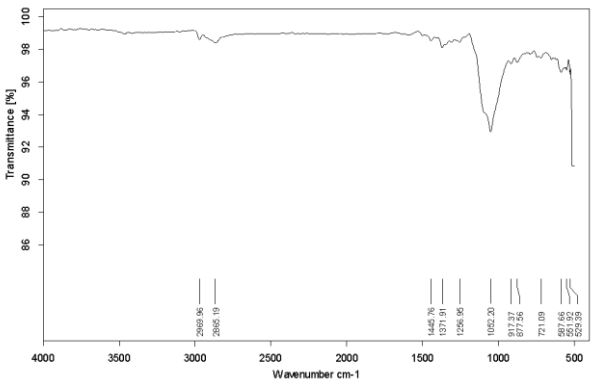

Figure No. 5: FT-IR Spectrum of F6.

Scanning electron microscopy

The SEM of Carvedilol-loaded cellulose derivatives microspheres of batch F2 is shown in Fig.7. It can be seen that microspheres are almost spherical with smooth surface and no drug crystals were found on the microsphere surface which might be attributed to the uniform removal of solvent by evaporation to produce even polymer distribution.

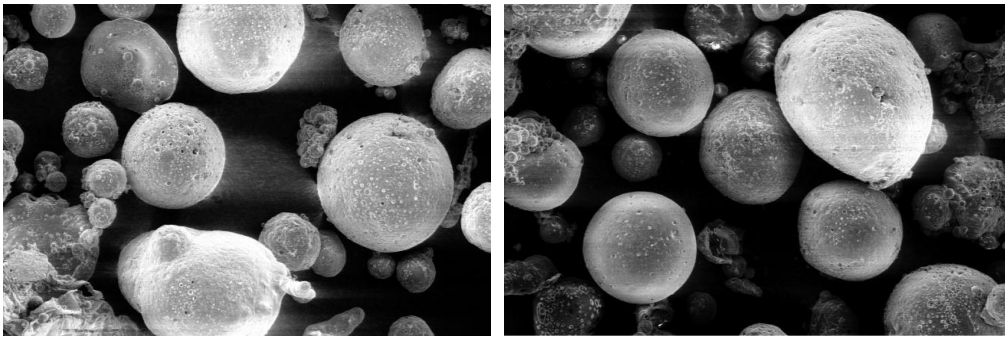

Figure No. 6: SEM of Carvedilol Microspheres prepared with Cellulose Derivatives.

Table No. 5: Results of Particle size for various formulations.

Formulation no.	Drug	Ethyl cellulose	Cellulose acetate	Hydroxy ethyl cellulose	PVA	Particle size
F1	10	200	-	-	1%	120.81±8.64
F2	10	400	-	-	1%	133.04±4.46
F3	10	-	200	-	1%	126.73±9.93
F4	10	-	400	-	1%	140.77±6.67
F5	10	-	-	200	1%	131.34±9.87
F6	10	-	-	400	1%	145.30±6.79

CONCLUSIONS

Morphological analysis by Scanning Electron Microscopy showed that the formulations of Carvedilol-loaded cellulose derivatives microspheres were almost spherical in shape and size Results of Polymer–drug interaction analysis using FTIR spectroscopy There is no significant difference in characteristic peaks of pristine drug and drug-loaded microparticles suggesting drug stability during encapsulation process. This shows the absence of any chemical interactions between drug and polymer. Hence, the results of the present study clearly indicated promising potentials of carvedilol microspheres can be prepared by Solvent Evaporation Method and can be further use for preparing controlled drug prepation.

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