Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 4, 2014

Original Article

FORMULATION AND IN VITRO STUDIES OF CARVEDILOL MICROSPHERES WITH ITS CHARACTERIZATION

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Received: 24 Feb. 2014 Revised and Accepted: 10 Mar 2014

ABSTRACT

Objective: Carvedilol is a non-selective beta blocker was formulated as microspheres by using Ethyl cellulose as a carrier.

Methods: These ethyl cellulose microspheres were prepared by the solvent evaporation method. The prepared microspheres were subjected to various evaluation parameters and in vitro release studies. Highest percentage of entrapment was obtained by increasing the amount of polymer with respect to uniformity of drug. The particle sizes of the prepared microspheres were determined by optical microscopy method and morphology by SEM analysis.

Results: The prepared microspheres have gained good spherical geometry with smooth surface as evidence by SEM studies. The entrapment efficiency for f_3 was found to be 97.5±0.1527 % with maximum drug loading of 45.26 around. The best-fit release kinetics was achieved with Korsmeyer-Peppas plot followed by zero order and first order kinetics. The release of drug was influenced by the drug to polymer ratio and particle size and was found to be both diffusion and dissolution controlled.

Conclusion: The study showed that Carvedilol microspheres of 1:2 (F_3 batch) ratios got better sustained effect over a period of 12 hours. Finding of all this investigation conclusively demonstrate prolongation of drug release at a constant and controlled rate.

Keywords: Carvedilol, Ethyl cellulose, Entrapment efficiency, SEM, *in vitro*-profile.

INTRODUCTION

The primary objective of zero-order release is to up-hold constant drug concentration in blood for a prolonged period of time. Microspheres have played a vital role in the development of controlled/sustained release drug delivery systems [1-2].

It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors. Carvedilol is a non-selective beta blocker indicated in the treatment of mild to moderate congestive heart failure (CHF).

Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release. Different kinds of controlled drug delivery systems have been developed for various routes of administration, since they require less frequent drug administration, provide more efficient therapeutic effects, and reduce the incidence of side effects. To develop a drug delivery system for oral administration, the preferred route of administration, it is necessary to optimize the release rate of an active ingredient from the system. One of the most extensively studied methods is microsphere [3].

The overall aim and objective of project was the formulation of carvedilol microspheres and their evaluation of microspheres with their release kinetics.

MATERIALS AND METHODS

Drugs and Chemicals

Carvedilol was a gift sample obtained from Chandra labs, Hyderabad, Ethyl cellulose, Dichloro methane, Poly vinyl alcohol was supplied from Research Fine Chem. Industries, Mumbai.

Drug and excipients compatibility studies

To investigate any possible interactions between the drug and excipients used, the FTIR spectra of Carvedilol and its physical mixture with ethyl cellulose, ethanol, dichloromethane and polyvinyl alcohol were carried out using Bomem FTIR MB-II spectro photometer. The samples were prepared as KBr (potassium bromide) discs compressed under a pressure of 10 Ton/nm^2. The wave number selected ranged between 400 and 4800 cm^{-1}. The results were summarized in and discussion made in table 1. The Fourier Transform Infra red analysis was conducted for the structure characterization. FTIR spectra of the formulated microspheres and drug were recorded. Microspheres were taken in a KBr pellet using Bomem FTIR MB-II instrument. Approximately 5mg samples were mixed with 50mg of spectroscopic grade KBr, samples were scanned in the IR range from 500-3500cm^{-1}, with a resolution of 4cm^{-1}.

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer has occurred. The wave numbers of final formulation and individual ingredients were compared, hence it was conclude that there was no chemical interactions were found among excipients and the drug.

Solvent Evaporation Method [4-7]

Carvedilol microspheres were prepared by solvent evaporation technique. For this carvedilol was dissolved in dichloromethane and then polymer was dissolved in ethanolic solution. Both drug and polymer solutions were mixed well to form a uniform solution. The obtained drug and polymer solution was added drop wise to the PVA solution under constant stirring at 1500 rpm by using homogenizer. The beaker and its content were heated to 80^0 c with constant stirring for 1hr until the aqueous phase was completely removed by evaporation. The microspheres formed were collected by whattman filter paper and washed 3 times with distilled water and dried at a room temperature for one day.

Surface morphology

The surface morphology and structure were visualized by scanning electron microscopy (SEM).The samples were prepared by lightly

sprinkling the microspheres powder on a double side adhesive tape which already shucked to on aluminum stubs. The stubs were then placed into fine coat ion sputter for gold coating. After gold coating, samples were randomly scanned for particle size and surface morphology.

Drug entrapment efficiency

Microspheres equivalent to 5 mg of Carvedilol were crushed using a glass mortar and pestle and the powdered microspheres were suspended in 25 ml of phosphate buffer pH 6.8. After 24 hrs, the solution was filtered, 1 ml of the filtrate was pipette out and diluted to 10 ml and analyzed for the drug content by using Elico SL- 159 UV Visible Spectrophotometer at 242 nm.

The drug entrapment efficiency was calculated using the following formula.

Entrapment efficiency = (Actual drug content/theoretical drug content) ×100.

Table 1: FT-IR Spectra data of Carvedilol and polymer

S. No	Functional group	Characteristic peak cm^{-1}	Observed peak for drug cm^{-1}	Peaks for Microspheres formulation
1	N-H	3500-3300	3342.89	3342.89
2	C-H	2950-2800	2922.72	2973.57
3	C-O	1260-1000	1098.28	1052.91
4	O-H	1250-970	980.10	980.10

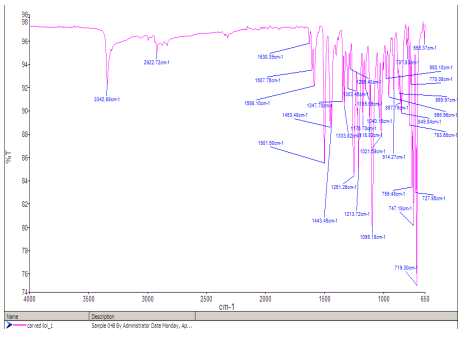
Table 2: Formulation of Carvedilol microspheres

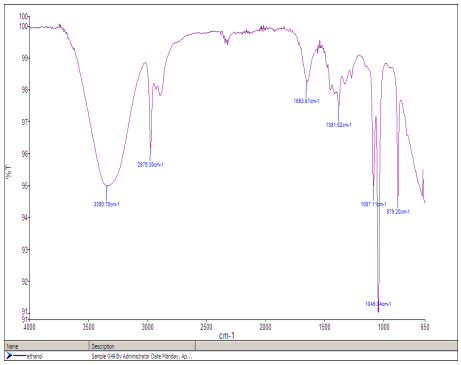
S. No.	Ingredients	Batches of Carvedilol microspheres prepared		
		F_1	F_2	F_3
1	Carvedilol	250mg	250mg	250mg
2	Ethyl Cellulose	250mg	375mg	500mg
3	Dichloro Methane	10ml	10ml	10ml
4	Ethanol	10ml	10ml	10ml
5	Poly vinyl Alcohol	750mg	750mg	750mg
6.	Distilled water	100 ml	100 ml	100 ml

Table 3: Percentage yield, entrapment efficiency, drug loading of microspheres [8]

Formulations	Percentage yield (%)	Entrapment efficiency(%)±SD	Drug loading±SD
F_1	61.6	62.6±0.378	81.14±0.0208
F_2	71.5	88.6±0.208	51.75±0.0152
F_3	73.6	97.5±0.1527	45.26±0.114

Values are represented as mean± standard deviation (n=3)





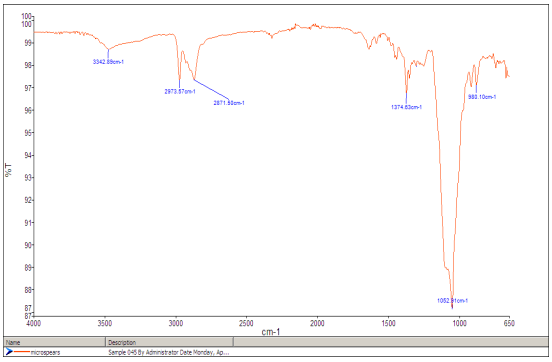


Fig. 1: FTIR Spectra of Ethyl cellulose, Ethanol, Poly vinyl alcohol and mixture.

RESULTS AND DISCUSSIONS

Evaluation of Microspheres

The experiments were carried out and the results of percentage yield of microspheres were 61.6% to maximum of 73.6%. The maximum yield was obtained with formulation F_3. The entrapment efficiency was found to be between 62.6% - 97.2%. As the polymer concentration increases the drug encapsulation was found to be increasing in microspheres. The results of percentage yield and drug entrapment were shown in table 3.

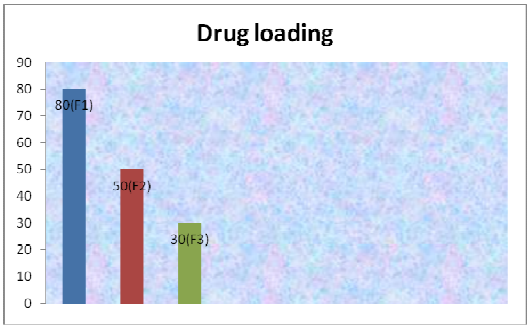


Fig. 2: Drug loading of microspheres

Mean Particle Size [9]

Mean particle size was determined by optical microscopy method [10-11] and the average particle size was calculated.The results were shown in table – 4.

Table 4: Mean particle size of Carvedilol microspheres.

S. No.	Batches	Mean Particle Size(µm)
1	F_1	36.42
2	F_2	42.96
3	F_3	50.41

Scanning Electron Microscopy [12]

The microspheres prepared by solvent evaporation method and results have proved a good sphericity with smooth surface in its morphology with SEM studies based, and the particles were distributed uniformly without forming any clumps.

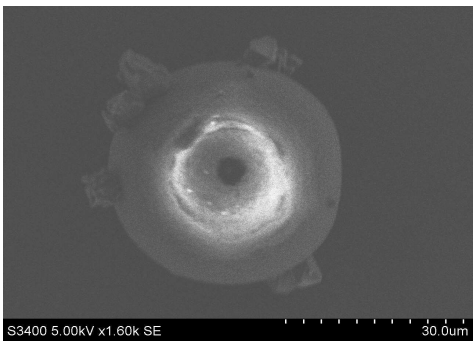


Fig. 3: SEM photograph of Carvedilol microspheres

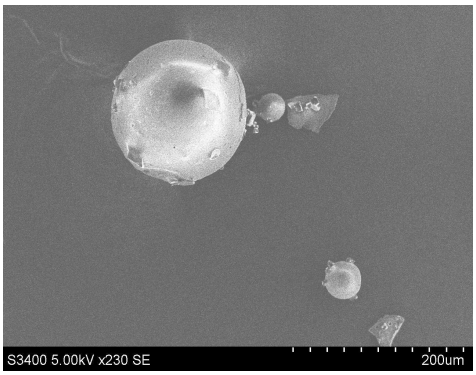


Fig. 4: SEM photograph of Carvedilol microspheres

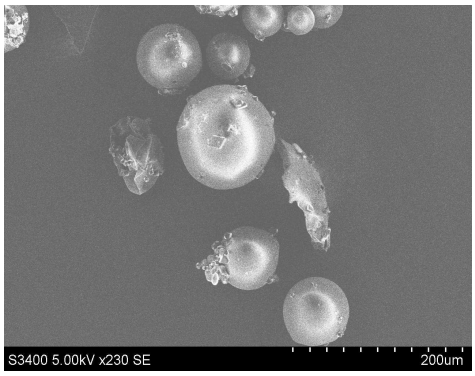


Fig. 5: SEM photograph of Carvedilol microspheres

The results profiles of in-vitro studies profile were displayed in given following figure No 6.

In-vitro release studies

The in-vitro release profile of carvedilol microspheres were conducted in a pH 6.8 buffers for 12 hrs. with 60 RPM by using Dissolution apparatus USP I Basket type at temperature of 37˚.0 ±0.5ºC. The sampling was withdrawn for every one hour up to 12 hrs. At different time intervals various aliquots were withdrawn and replaced by an equal volume of dissolution medium in order to maintain constant volume. After suitable dilution, samples were analyzed spectro photometrically at 242 nm. All the experimental units were analyzed in triplicate (n=3). Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

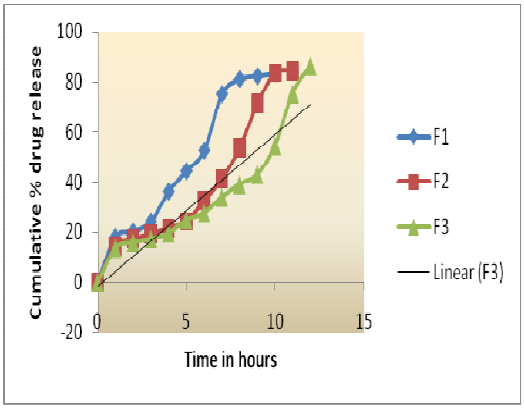


Fig. 6: in vitro drug release of Carvedilol microspheres

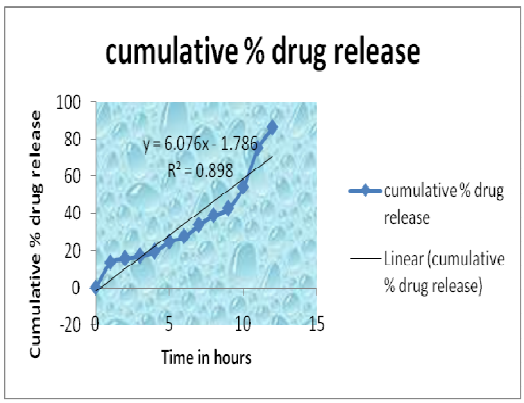


Fig. 7: Zero order release of carvedilol microspheres

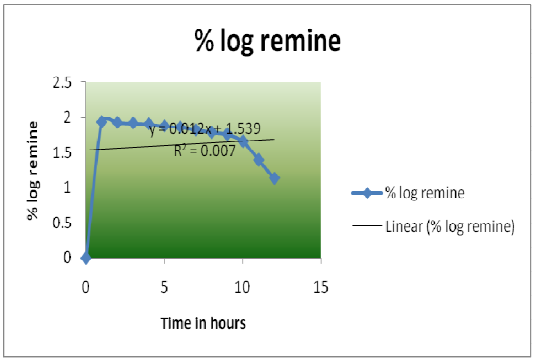


Fig. 8: First order release of Carvedilol microspheres.

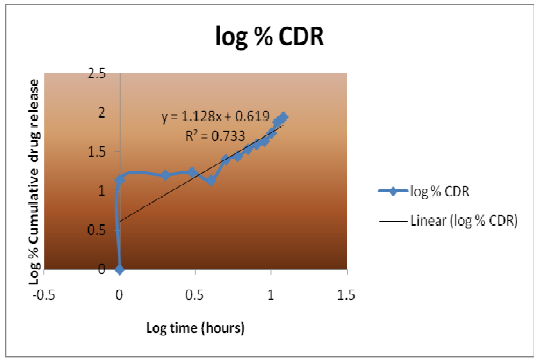


Fig. 9: Peppas plot of Carvedilol microspheres.

Table 5: Drug release kinetics [13- 14] of Carvedilol microspheres

Formulation Code	Zero order R^2	First order R^2	Higuchi plot R^2	Peppas plot(Korsmeyer) R^2 And **n**	
F_1	0.963	0.000	0.897	0.719	0.400
F_2	0.927	0.001	0.907	0.742	0.336
F_3	0.898	0.007	0.889	0.733	0.269

CONCLUSION

The ethyl-cellulose microspheres of Carvedilol were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing carvedilol loaded microspheres from its higher percentage yield. The formulation F_3 has highest milligram of drug content followed by other formulations. The drug entrapment efficiency of three formulations were found to be F_1 62.6, F_2 88.6,F_3 97.5 percentages and the percentage yield of three formulations were found to be F_1 61.6,F_2 71.55 and F_3 73.6.

The particle size of a microsphere was determined by optical microscopy technique and all the batches of microspheres have given uniform size distribution. The Mean particle size was found to be F_1 36.42, F_2 42.96, and F_3 50.41. The prepared microspheres had good spherical geometry with smooth as evidenced by the scanning electron microscopy. The *in vitro dissolution* studies showed that Carvedilol microspheres formulation F_3 showed better sustained effect over a period of 12 hours. Dissolution results of different formulations were found to be $F_1$83%, $F_2$84.5% and $F_3$86.43% in which F_1 formulation shows maximum drug release at 10^{th} hour, F_2 at 11^{th} hour and F_3 at 12^{th} hour. Hence the drug release of F_3 formulation gets sustained than other formulations for a period of 12 hrs.

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, Korsmeyer Peppas and finding the R^2 values of the release profile corresponding to each model. It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, in which the drug molecules have to traverse so, the drug release of F_3 formulation takes long time than other formulations.

For all the formulations dissolution profile graph and percentage of drug releases versus time was plotted. From basis of all the parameters which mentioned above and taken into consideration of parameters including surface characteristics of the formulation, drug- polymer ratio and time,F_3 shows the good reliable results.

ACKNOWLEDGMENTS

The author is thankful to Osmania University, Hyderabad for providing spectras of FTIR and SEM studies as a part of research work and grateful to Sree Dattha Institute of pharmacy, Hyderabad for provision of making research at their college premises.

REFERENCES

1. Mahajan BV, Deore HS, U.V. 2004; Int. J Chem. Tech Research, 1(3), 634-642.
2. Tamer Guneri.,Mesut Arici., Gokhan Ertan. 2004; Fabad j. pharm. Sci, 29, 177-184.
3. Rajput G,Majumdar F,Patel JThakor R,Rajgor NB,Stomach Specific muco adhesive microspheres as a controlled drug delivery system. Sys Rev Pharm, 2010 ; 1(1): 70-78.
4. Hosney, E.A.AL- suwaych.s Mahrous G M,effect of spheres size, polymer to drug ratio and plastisizer concentration on the release of theophyllin from ethyl cellulose microspheres. Saudi pharm Journal, 2007; 15: 213-216.
5. Jaspreet kaur vasir, Kaustubh Tambwekar,Sanjay Gang,Bio adhesive microspheres as controlled drug delivery system. International journal of pharmaceutics, 2003; 255:13-32.
6. Woo BH, Jiang G, Jo YW, DeLuca PP. Preparation and characterization of a composite PLGA and poly (acryloyl hydroxymethyl starch) microsphere system for protein delivery. Pharm. Res. 2001; 18(11): 1600-1606.
7. Capan Y, Jiang G, Giovagnoli S, DeLuca PP.Preparation and characterization of poly (D,L-lactide-co-glycolide) microsphere for controlled release of human growth hormone. AAPS Pharm Sci Tech. 2003; 4(2).
8. Gohel MC,Amin AF.Formulation optimization of controlled release diclofenac sodium microspheres using factorial design. J. Control. Release. 1998; 51: 115-122.
9. Thompson.C.J, Hansford.D, Higgins.S, Rostron.C, Hutcheon, Munday.D.L, and Evaluation of ibuprofen-loaded microspheres prepared from novel co-polyesters. Int.J.Pharm, 2007; 329: 53-61.
10. Shivakumar HN, Sarasija Suresh,Desai BG.Design and Evaluation of controlled onset extended release multiparticulate systems for chrono therapeutic delivery of ketoprofen.Indian J Pharm Sci, 2006;68(1):76-82.
11. Eugene L.Milling. In:Lachman L, Liberman HA. The theory and practice of industrial pharmacy, 2nd ed. Varghese publishing house, Mumbai; 1991; 26-2712.S.
12. Dashora K, Saraf S, Effect of processing variables on micro particulate system of aceclofenac. Pak. J Pharm Sci. 2006; 19: 6-10.
13. Freiberg, XX. Zhu polymer microspheres for controlled drug release. International journal of pharmaceutics 2004; 282: 1-18.
14. Barhate1 Shashikant D, Rupnar Yogesh S, Sonvane Rupesh M.,Pawar Kapil R. and Rahane Rahul kumar D, Formulation and Evaluation of Floating Microspheres of Ketorolac Trometamol. International Journal of Pharmaceutical Research and Development, 2009;1(9): 1-8.