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FORMULATION AND EVALUATION OF NEBIVILOL MICROSPHERES

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ABSTRACT

Nebivilol a non-selective beta blocker was formulated as microspheres by using ethyl cellulose as carrier. These ethylcellulose microspheres were prepared by the solvent evaporation method. The prepared microspheres were subjected to various evaluation and in vitro release studies. Highest percentage of entrapment was obtained by increasing the amount of polymer with respect to drug. The particle sizes of the prepared microspheres were determined by optical microscopy and SEM analysis. The prepared microspheres had good spherical geometry with smooth surface as evidence by SEM. The study showed that nebivilol microspheres of 1:2(F_3 batch) ratios showed better sustained effect over a period of 12 hours.

KEYWORDS: Nebivilol, Drug profile, Ethylcellulose, Entrapment efficiency, In vitro profile, Microspheres.

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. Nebivilol 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 thes most extensively studied methods is microsphere.[3] The overall aim and objective of project was the formulation of nebivilol microspheres and their evaluation of microspheres with their release kinetics.

MATERIALS AND METHODS

Drugs and Chemicals Nebivilol 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 Nebivilol 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/nm2. 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]

Nebivilol microspheres were prepared by solvent evaporation technique. For this nebivilol 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 800 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[8-10]

Microspheres equivalent to 5 mg of Nebivilol 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 281 nm. The drug entrapment efficiency was calculated using the following formula.

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

Table: 1. Formulation table of Nebivilol microspheres

S.NO	Ingredients	Batches of Nebivilol microspheres prepared		
		F_1	F_2	F_3
1	Nebivilol	250mg	250mg	250mg
2	Ethyl cellulose	250mg	375mg	500mg
3	Dichloromethane	10ml	10ml	10ml
4	Ethanol	10ml	10ml	10ml
5	Poly vinyl alcohol	750mg	750mg	750mg
6.	Distilled water	100 ml	100 ml	100 ml

EVALUATION OF MICROSPHERES

Drug and Excipients Compatibility Studies

a. Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer had occurred. The wave numbers of final formulation and individual ingredients were compared, Hence it was concluded that no chemical interactions were found between drug and polymer.[12-13]

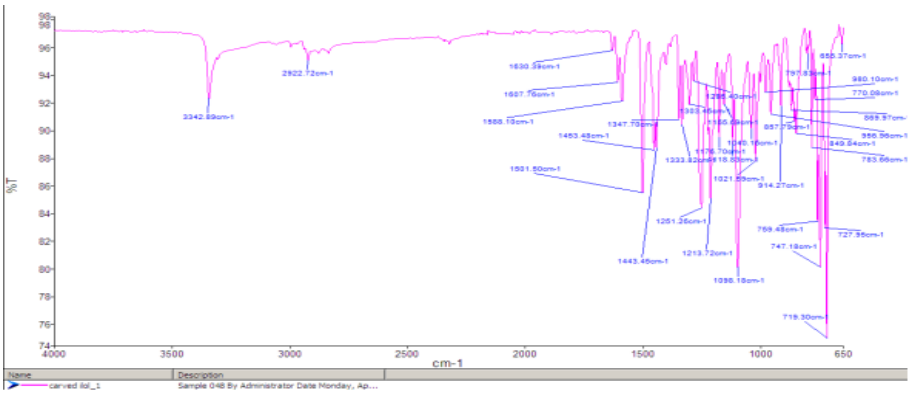


Fig: 1 FTIR of Nebivilol

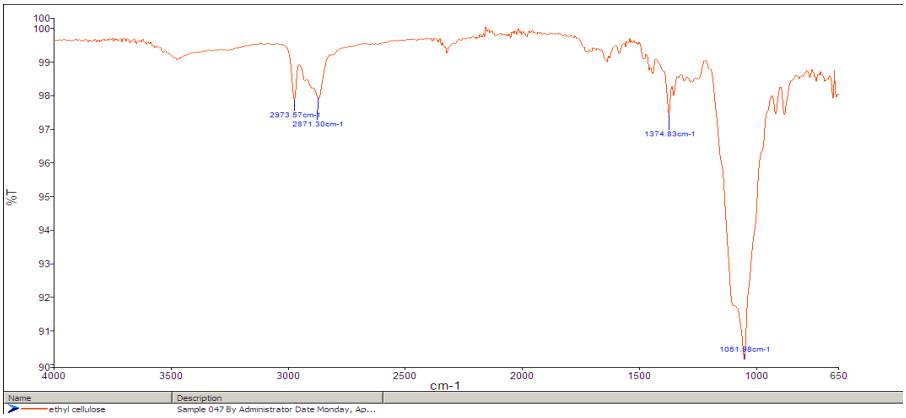


Fig: 2 FTIR of Ethyl cellulose

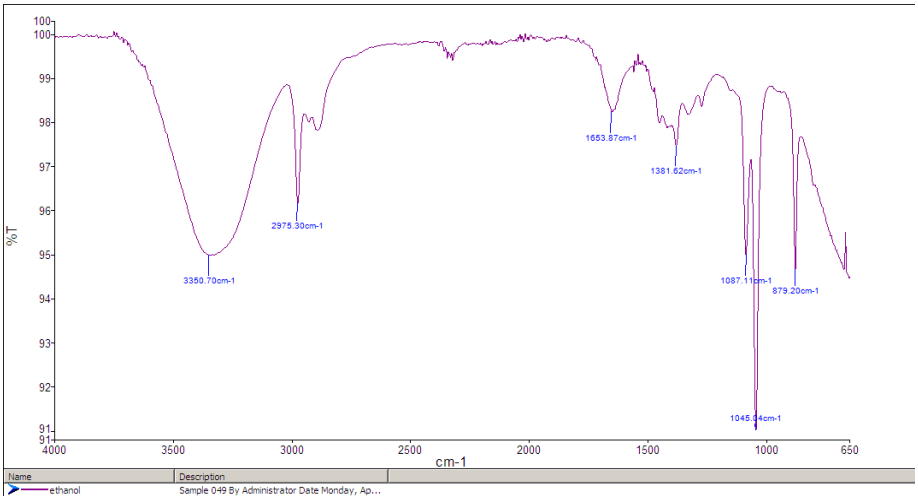


Fig: 3 FTIR of Ethanol

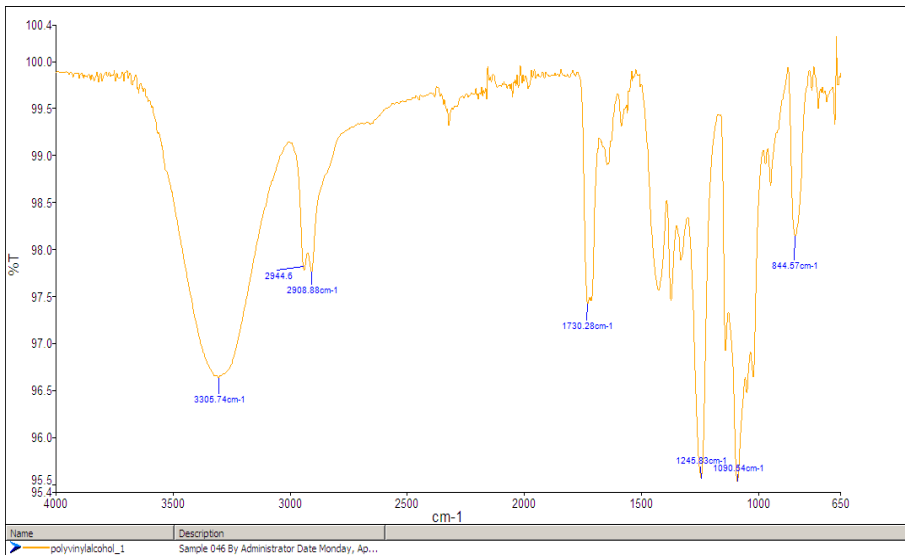


Fig: 4 FTIR of Poly vinyl alcohol

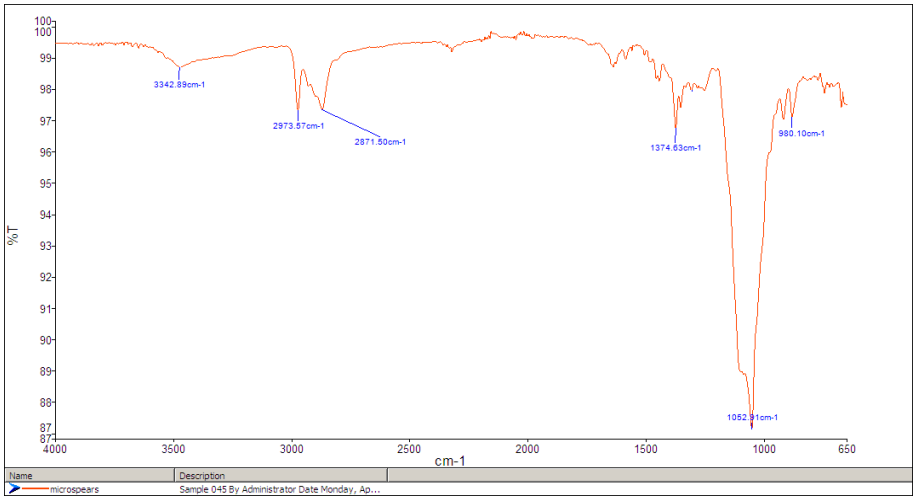


Fig-5: FTIR of Microspheres

Evaluation of Microspheres

Linearity plot of Nebivilol in dichloromethane

The solutions of Nebivilol were prepared and the absorbance of resulting solutions was measured in UV spectrophotometer at 281 nm. The standard graph between concentration Vs absorbance was given in figure no-6.

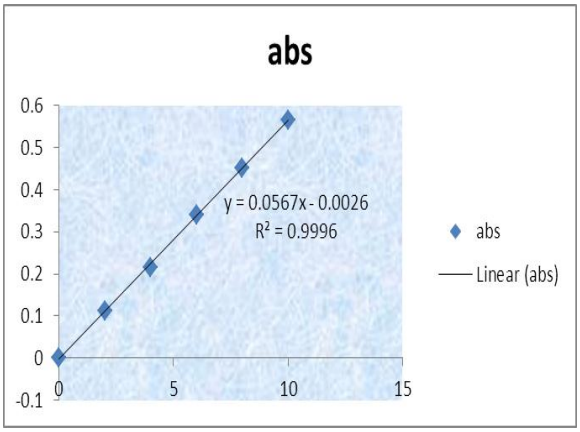


Fig: 6 linearity plot of Nebivilol.

Percentage yield, entrapment efficiency, drug loading of microspheres (Table:2.)

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

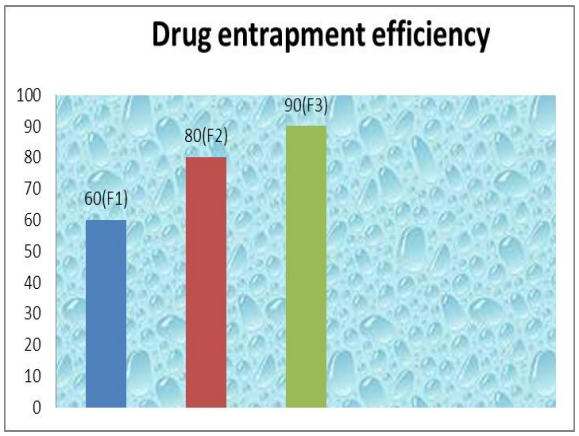


Fig: 7: Drug entrapment efficiency of microspheres

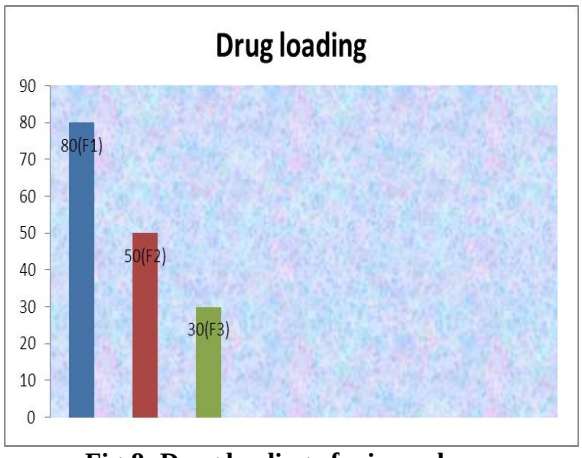


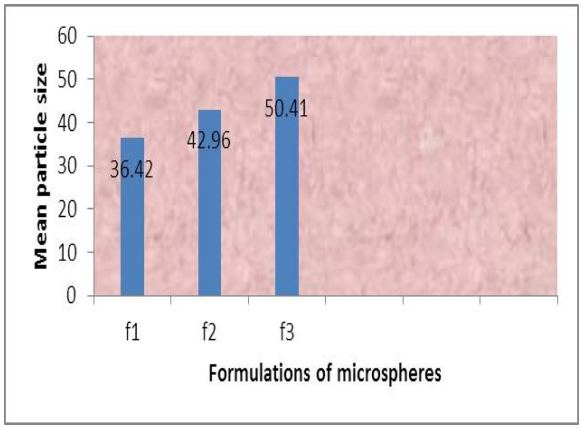
Fig-8: Drug loading of microspheres

Mean Particle Size

Mean particle size was determined by optical microscopy and the average particle size was calculated .The results were shown in table-3 and figure -9.

Table: 3. Mean particle size of Nebivilol microspheres

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



Fig; 9 mean particle size of microspheres

Scanning Electron Microscopy

The microspheres prepared by solvent evaporation method showed a good sphericity, with smooth surface and the particles were distributed uniformly without any lumps.

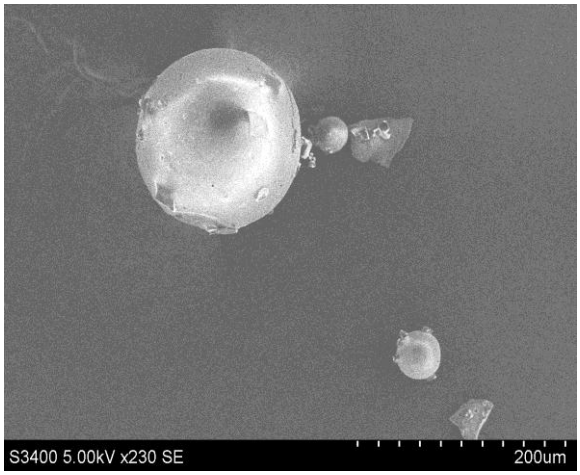


Fig: 10 SEM photograph of Nebivilol microspheres.

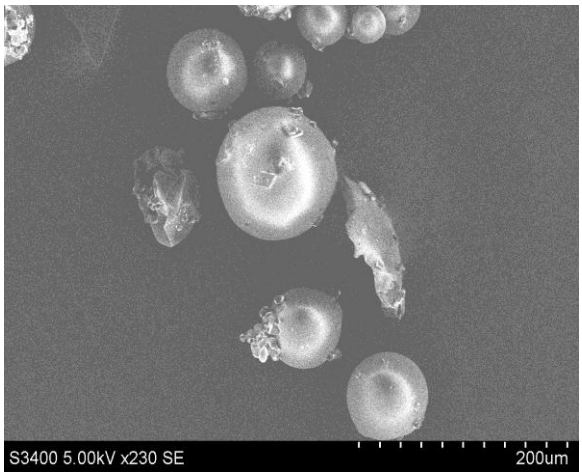


Fig: 11 SEM photograph of Nebivilol microspheres.

In-vitro release studies

Table: 4. Cumulative drug release of Nebivilol microspheres

Time (hrs)	% Cumulative drug release		
	$F_{1\pm SD}$	$F_{2\pm SD}$	$F_{3\pm SD}$
0	0	0	0
1	18.14±0.012	14.5±0.102	13.67±0.01528
2	20.25±0.005	17.3±0.085	15.85±0.02517
3	24.35±0.068	19.28±0.342	17.25±0.03055
4	36.29±0.305	21.65±0.0643	19.54±0.03512
5	44.56±0.512	24.38±0.921	24.86±0.03055
6	52.72±0.482	32.59±0.007	27.62±0.1101
7	75.29±0.053	41.26±0.0181	33.86±0.09713
8	81.23±0.810	53.69±0.146	39.02±0.09849
9	82.45±0.035	71.34±0.0273	42.94±0.1
10	83.52±0.612	83.64±0.0471	54.37±0.283
11	-	84.5±0.0513	75.3±0.429
12	-	-	86.43±0.245

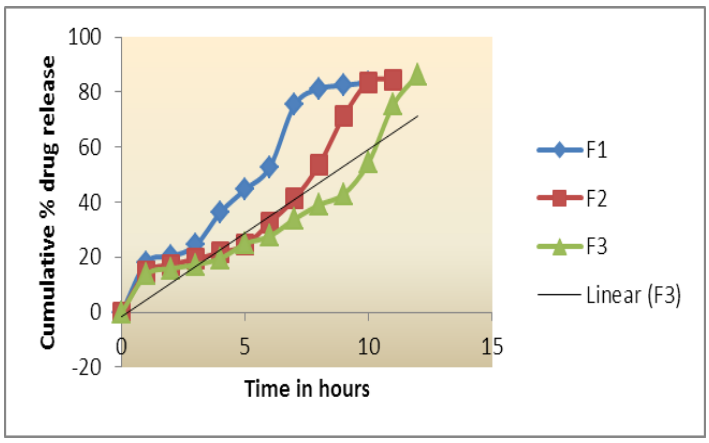


Fig -11: in vitro drug release of Nebivilol microspheres.

Release Kinetics Plots For Ethyl Cellulose Microspheres Containing Nebivilol.

The dissolution of microspheres formulation follows Zero order and Higuchi models.

Table: 5. Drug release kinetics of Nebivilol microspheres

Formulations	Zero order	First order	Higuchi plot	Peppas plot(Korsmeyer)	
	R^2	R^2	R^2	R^2	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 ethylcellulose microspheres of Nebivilol were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing Nebivilol loaded microspheres from its higher percentage yield. The formulation F3 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 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 and all the batches of microspheres show uniform size distribution. The Mean particle size were found to be F_1 36.42,F_2 42.96,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 Nebivilol microspheres formulation F3 showed better sustained effect over a period of 12hours.Dissolution results of formulations were found to be $F_1$83.52,$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.It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, 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 release Vs time was plotted. From all the parameters mentioned above were taken, including surface characteristics of the formulation, drug polymer ratio and time F3 Shows the reliable results.

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