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OPTIMIZATION OF PRODUCT VARIABLES IN FORMULATION OF METOPROLOL TARTARATE MICROBEADS

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ABSTRACT

The objective of this study the effect of product variables like polymer and cross linking agent in Formulation and Evaluation microbeads containing Metoprolol tartarate for the treatment of Hypertension. Five formulation of microbeads are prepared by Ionotrophic gelation method by using different concentration of sodium alginate natural polymer and calcium chloride cross linking agent. The CaCl_2 was used as a cross linking agent to stabilize the microbeads and to enhance the drug entrapment efficiency and matrix formation of microbeads while processing the formulation. In process optimization techniques are followed to select an optimized concentration of polymer and cross linking agent in the formulation of Microbeads. The formulated microbeads are inspected for surface morphology by SEM studies, Drug content, entrapment efficiency, and Invitro drug release studies etc.

Keywords: Microbeads, Metoprolol tartarate, Ionotrophic gelation method, calcium chloride, Sodium alginate.

INTRODUCTION

Microbeads are uniform polymer particles, typically 0.5 to 500 micrometers in diameter. Bio-reactive molecules can be adsorbed or coupled to their surface, and used to separate biological materials such as cells, proteins, or nucleic acids. Microbeads are used for isolation and handling of specific material or molecules, as well as for analyzing sensitive molecules, or those that are in low abundance, e.g. in miniaturized and automated settings [1].

A range of patented processes and applications have been developed based on the use of microbeads in academic and industrial research. Microbeads are pre-coupled with a ligands; a biomolecule such as antibody, streptavidin, protein, antigen, DNA/RNA or other molecule [2].

The aim of the present study, which was to develop sustained release oral product namely microbeads of metoprolol tartarate using sodium alginate as the hydrophilic carrier in combination with cross linking agent like calcium chloride. Also improve its bioavailability by bypassing the first pass metabolism because alginate beads shrink but unable to swell at acidic environment and the encapsulated drugs are not released where as they easily

swell in an alkaline environment and release the drug in an sustained manner.

MATERIALS AND METHODS

Metoprolol Tartarate and Atorvastatin calcium was gift sample from Orchid Pvt ltd., Chennai. Sodium alginate and Calcium chloride were purchased from Chem. Scientifics, Bangalore. All the chemicals were of analytical grade and double distilled water used throughout the experiment.

Preparation of Micro beads

The microbeads were prepared by the Ionotrophic gelation technique. The sodium alginate solution was prepared by dispersing the sodium alginate in de-ionized water under continuous stirring for 30 minutes. The weighed amount of the drug was thoroughly mixed with sodium alginate dispersion. By following the same procedure the alginate beads of different ratios of drug: polymer were prepared. The resulted homogeneous dispersion was extruded in to the 5% calcium chloride solution through hypodermic syringe with flat tip needle (20G) and stirred for 15 minutes at 100rpm using magnetic

stirrer. The formed micro beads were allowed to cure for 30 minutes in the calcium chloride solution to complete the gelation reaction. The microbeads were then filtered and dried in hot air oven at 60°C for 3 hr [3,4].

EVALUATION OF MICROBEADS

Preformulation studies:

Compatibility study by using FT-IR

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of Metoprolol tartarate, polymer and physical mixtures of samples were weighed and mixed properly with KBr to a uniform mixture. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR spectrum of the pellet from 450-4000cm⁻¹ was recorded taking air as the reference and compared to study any interference [5].

Post formulation studies:

Particle size evaluated by scanning electron microscopy

Morphological details of the specimen were determined by using a scanning electron microscope (SEM).

Granulometric studies

Particle size distribution pattern was determined by sieve analysis on mechanical sieve shaker, using different meshes like (12, 16, 20 and 30) of American society of testing materials.

Micrometric properties of the beads

The mean particle size of the alginate microbeads was determined by optical microscopic method using a pre-calibrated stage micrometer.

Flow properties of Beads

The flow properties of prepared microbeads were investigated by measuring the Angle of Repose by using fixed funnel method. Depends upon these values, the flow properties of the microbeads can be assumed. The Angle of Repose Values was mentioned in the Table-3. The value of angle of repose was calculated by using the following formula,

$$\text{Angle of repose } (\theta) = \tan^{-1} h/r$$

h = cone height,

r = radius of circular base

The bulk and tapped densities were measured in a 10ml graduated cylinder as a measure of pack ability of the microbeads. Each experiment was carried out in triplicate [6,7].

Drug content (mg)

100 mg microbeads were powdered and transferred into a 100 ml volumetric flask and the volume was made upto the mark with 6.8 pH phosphate buffer and kept aside for 12 hrs with occasional shaking. Then the absorbance was analyzed spectrophotometrically at 274 nm. Three determinations were carried out for each

formulation. The drug content was calculated by using the formula; [8]

$$\text{Drug content} = \frac{\text{Concentration} \times \text{dilution factor} \times \text{conversion factor}}{\text{amt. of stock sol.}}$$

Drug entrapment efficiency

Metoprolol tartarate content in the microbeads was estimated by a UV-spectrophotometric method. Accurately weighed 100mg of microbeads (100 mg) were powdered and suspended in 6.8 pH phosphate buffer. The resulting solution was kept for 24hrs. Next day it was stirred for 20min using ultra sonicator. The solution was filtered through a 0.45 µm membrane filter, after suitable dilution if required, Metoprolol tartarate content in the filtrate was analysed at 274 nm using UV-Visible spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Calculating this concentration with dilution factor the percentage of actual drug encapsulated in microbeads was calculated. The drug entrapment efficiency was determined using following relationship. The yield was calculated [9].

$$\text{Percentage yield} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

In-vitro release studies

In-vitro release studies of prepared micro beads were carried out using phosphate buffer (pH 6.8) using USP- basket type apparatus. Accurately weighed quantity of 50 mg of prepared micro beads put into the basket rotated at a constant speed at 100rpm and maintained temperature 37±5°C in 900ml of the dissolution medium (phosphate buffer pH6.8).The sample was withdrawn at 0.5hrs, 1hrs, 2hrs, 3hrs, 4hrs, 5hrs, 6hrs, 7hrs, 8hrs, 9hrs, 10hrs, 11hrs, 12hrs, 13hrs,14hrs, 15hrs and 16hrs. Each time interval 10 ml of sample was withdrawn, at the same time 10 ml of fresh dissolution media was added to maintain sink condition. The withdrawn samples were suitably diluted and measure the absorbance at 274 nm spectrophotometrically. Then calculate the cumulative percentage drug release at regular time intervals [10].

RESULTS AND DISCUSSION

Compatibility Studies for Drug and Polymer - FTIR

The IR Spectrum of Pure drug and the spectrum of drug and the polymer was taken and studied for the compatibility of drug and the polymer. While comparing the spectrum of both pure drug and the mixture it shows that there was no any interaction of drug and polymer. So both are compatible for formulation.

Physical properties of Metoprolol Micro beads:

Particle size

The particle size and surface morphology was determined with the help of scanning electron microscopy (SEM). Spherical shaped microbeads were observed. Among the five formulations of microbeads F2 possess

small particle size 100.52 μm in size and also uniform particle size distribution was seen in formulation F2. The particle size ranges of formulations were shown in (Table 2)

Drug Entrapment Efficient

On increasing the concentration the gelatin, the amount of drug entrapment increased as it was observed maximum 95.31% in F2 and less 78.92 in F4 where the gelatin concentration is less gelatin with respectively. This shows that increased concentration of controlling agent leads to greater degree of cross linking of CaCl_2 . The rank order of entrapment efficiency is $\text{F2} > \text{F5} > \text{F1} > \text{F4} > \text{F3}$. The results of drug entrapment efficiency for all the batches were shown in (Table no 2).

Product yield

The percentage yield of Microbeads was more than 75%. Among the prepared batches, batch F2 show highest percentage yield of 89.34%. The results of production yield for all the batches were shown in (Table no 2).

Drug content

The drug content in the micro beads was found to be in the range of 79.85 ± 2.25 to 98.59 ± 1.15 mg. The formulation F2 shows maximum drug content and the values are given in (Table no 2).

In-vitro drug release

These studies show the effect of environment of the body on the drug release pattern from the prepared Microbeads. The in vitro release was not observed in simulated gastric fluid for 3 hrs. The *in-vitro* drug release was observed after 3 hrs up to 16 hrs. It was found the release rate from the all formulations was found to be different for the polymer proportion and conc. of cross linking agent used in the all formulations. 97.86 ± 1.2 , 98.05 ± 2.5 , 85.13 ± 2.8 , 82.59 ± 2.5 & 79.2 ± 1.3 . F2 with polymer Sodium alginate concentration and cross linking agent showed maximum Sustained release pattern i.e., 98.25 ± 0.5 in 16th hr, as shown (Graph no 1).

Graph 1. Cumulative % drug release profile for metoprolol Microbeads F1 – F5

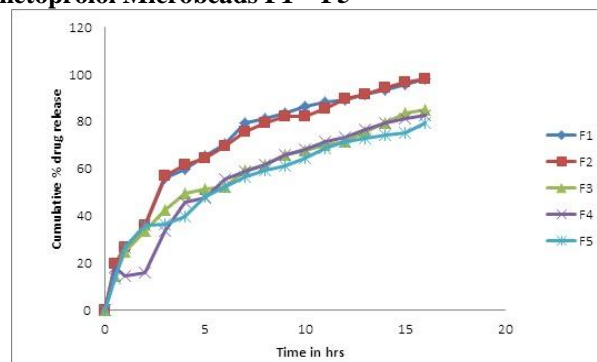


Table 1. Formulation of Microbeads

Formulation code	Amount of Metoprolol tartarate (mg)	Amount of sodium alginate	Amount of calcium chloride
F1	50	1%	3%
F2	50	2%	4%
F3	50	3%	5%
F4	50	1%	5%
F5	50	2%	6%

Table 2. Physical evaluation of Microbeads F1-F5

Formulation code	Particle size (μm)	Product yield in %	Drug content in %	% drug entrapment
F1	105.15 ± 7.0	77.59	86.15 ± 1.12	79.16 ± 2.18
F2	100.52 ± 1.2	89.34	98.59 ± 1.15	95.31 ± 1.25
F3	107.89 ± 3.0	75.32	89.66 ± 1.96	78.23 ± 1.89
F4	109.45 ± 4.2	72.53	79.85 ± 2.25	78.92 ± 1.45
F5	110.52 ± 6.2	61.52	86.45 ± 1.85	81.58 ± 1.75

CONCLUSION

From the results and discussion it was concluded that the formulation containing 2% Sodium alginate and 4% CaCl_2 i.e., formulation F2 was an optimized one that formulated by Ionotrophic gelation method. So it can be

concluded that the sustained release microbeads containing Metoprolol tartarate may overcome all the disadvantages of conventional dosage form of metoprolol tartarate available in market.

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