Original Article

ETHYL CELLULOSE BASED TIMOLOL MALEATE MICROSPHERES FOR SUSTAINED DRUG DELIVERY

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Abstract

Timolol Maleate is a non-selective adrenergic receptor blocking agent and it is used the treatment of hypertension. It requires multiple administration of drug, leading to fluctuation in plasma concentration. The aim of the present study is to formulate for sustained drug release Timolol Maleate microspheres (TM), by using ethyl cellulose using different drug: polymer ratios. Six formulations were prepared by using multiple solvent evaporation technique. TM were evaluated for parameters like angle of repose, bulk density, particle size, drug content in microspheres, drug loading, encapsulation efficiency, in-vitro drug release studies. The prepared TM showed good flow properties, where spherical in shape with uniform surface morphology TM showed sustained release of the drug from the formulation for a period of 12 hours.

Keywords: Timolol Maleate, Ethyl cellulose, Microspheres.

Introduction

Microspheres are matrix system that contain drug throughout their structure and are potential candidates for oral controlled release. Microspheres can be defined as solid spherical particles ranging from 1 to 1000µm in size[1-4]. These particles consist of drug which is the core material and a coating material. The coating material can be of various types ranging natural polymers such as albumin, gelatin, chitosan, ethyl cellulose and synthetic polymers such as sodium carboxymethylcellulose and carbopo[5,6]. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethyl cellulose to inhibit oxidation[7].

Materials and Methods

Timolol Maleate and ethyl cellulose obtained as gift sample from Signet Chemicals; Mumbai, India. All other reagents used were of analytical grade belongs to Loba Chemicals, Mumbai.

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Method

Ethyl cellulose microspheres containing Timolol maleate were prepared in six different drug to polymer ratios (1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1: 3.5) by emulsification and organic solvent evaporation technique. Dissolve specific amount of ethyl cellulose in 20ml of dichloromethane and add slowly 100mg of Timolol maleate to form uniform solution. Add gradually ethyl cellulose solution containing the drug to beaker containing distilled water and 50ml of 0.5% gelatin solution. The beaker is heated in a water bath at 40^0 C. The dispersed phase was then added and stirred with using stainless steel mechanical propeller at 2000rpm. Continue mixing (45 min to 60 min) so that all the dichloromethane evaporates[7]. Separate microspheres by filtration using whatman filter paper and the microspheres thus obtained can be washed four times with 20ml of distilled water and dry in a desiccator. The prepared microspheres were dried in dessicator at 45^0C.

Determination of Percentage Drug Entrapment

A weighed quantity of the microspheres was crushed and suspended in phosphate buffer, pH 7.4 to extract the drug from microspheres. After 24 hrs the filtrate was assayed from spectrophotometrically at 243 nm for drug content (UV-Spectro 2060 plus)[8].

Corresponding drug concentration in the sample were calculated from the calibration plot and drug entrapment efficiency was calculated using the following formula,

$$\text{Entrapment efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

Particle size determination

Optical microscope was used to determine the size of the particle that lies within a range from 0.2 µm to 100 equal divisions and hence, each division is equal to 10 µm and the particles are measured along an arbitrarily chosen fixed line across the center of the particle. The particle size is a factor to be considered important in formulation of microspheres[9, 10].

Stability studies of Microspheres

All the formulations were studied for stability profile for 1 month at different environmental conditions such as 4°C, 25°C and 45° C. The microspheres were placed in screw capped glass containers and stored at ambient temperatures by keeping the microspheres in refrigerator to produce 4°C environment, 45°C environment was produced by keeping the microspheres in hot air oven. From the above samples every week upto one-month period suitable representative samples were taken and it is analyzed for drug content[11-13]. Change in average drug content was noted.

In vitro release study

The drug release study was performed using USP type II dissolution test apparatus, paddle model and at 100 rpm using 900ml of phosphate buffer saline 7.4pH as a dissolution medium. The medium temperature was maintained at 37±0.5°C. Periodically 1 ml of the samples were withdrawn and diluted to 10 ml by using phosphate buffer pH 7.4. After each withdrawal the same quantity of the fresh medium was replaced immediately. Then the samples were assayed spectrophotometrically, Spectro-2060 plus spectro--photometer at 496 nm using medium as blank.

Result and Discussion

Timolol Maleate microspheres with varying proportions of ethyl cellulose were prepared by multiple solvent evaporation technique.

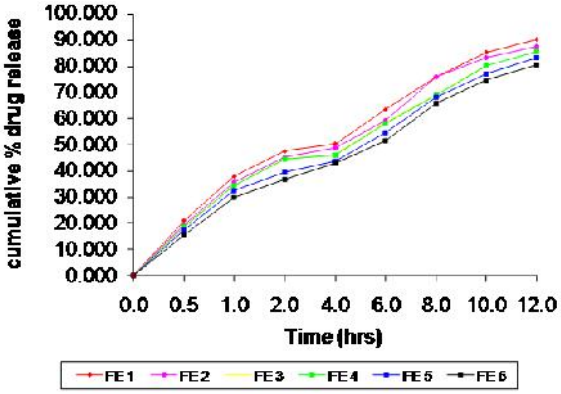

Figure 1: In vitro Release profile of Timolol Maleate microspheres

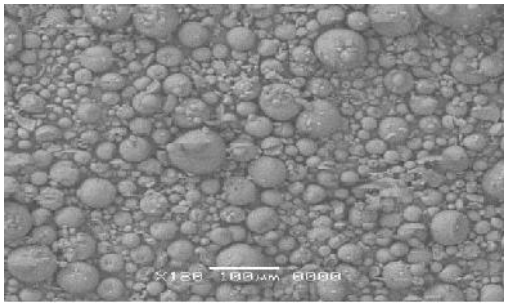

Figure 2: Scanning Electron Microscopy of FE 6

Table 1: Yield, drug entrapment and average particle size of Timolol Maleate ethyl cellulose microspheres

Formulation code	Drug: Polymer	Percentage yield (%)	Drug Entrapment (% w/w)	Average particle size (µm)	% of Encapsulation
FE 1	1:1	90.0	27.3	58.9	68.3
FE 2	1:1.5	93.6	65.2	80.6	69.7
FE 3	1:2	95.6	68.2	96.1	71.3
FE 4	1:2.5	94.8	68.7	116.2	72.5
FE 5	1:3	96.0	71.3	153.7	73.9
FE 6	1: 3.5	97.3	72.8	205.1	74.8

The particle size was determined by optical microscopy and was found to increase with increase in concentration. The mean particle size of microspheres is shown in the table 1. The stability studies did not reveal any remarkable change in the drug content. This proves the stability of the formulation.

The in- vitro release profiles of all the formulations have been shown in figure 1. The in-vitro release profiles of microspheres in phosphate buffer ph 7.4 at 37°c confirmed the sustained release of microspheres. the increasing concentration of polymer is decreased

the release rate. By the end of 12th hour, formulations FE 1, FE 2, FE 3, FE 4, FE5 & FE 6 were found to release 90.42%, 87.39%, 85.56%, 84.35%, 83.13% and 80.50 %. The scanning electron microscopy of the microspheres was shown in fig.1. The most of the microspheres were spherical in shape and size ranges from 50-100 µm. only some spheres were in large size. The size distribution of the microspheres was found to be normal in all the batches.

Conclusion

The present method of Timolol maleate microspheres by using ethyl cellulose in different ratio was found to be simple, reproducible and the carrier used is also proved that it is biocompatible. From the above data, we may conclude that drug loaded microspheres appear to be a suitable delivery system for Timolol maleate and may help to reduce dose of drug and frequency of administration.

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