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Design and Evaluation of Chitosan Microspheres of Metoprolol Tartrate for Sustained Release

A. R. SHABARAYA* AND R. NARAYANACHARYULU
N.G.S.M. Institute of Pharmaceutical Sciences, Mangalore-575 005

Metoprolol tartrate was formulated as biodegradable microspheres using chitosan by the phase separation emulsification technique. Microspheres of 1:0.5, 1:1 and 1:2 drugs to carrier ratios were prepared and thermally cross-linked. Drug to carrier ratio 1:1 showed maximum percentage yield and highest drug entrapment. The size range of the microspheres varies from 3.5 to 31.5 μm. UV and DSC studies were carried out to confirm the presence and stability of the drug in the microspheres. Short-term stability studies were carried out at different temperatures. *In vitro* release studies were carried out at different pH for a period of 10 h and compared with the pure drug. The release of metoprolol tartrate from the chitosan microspheres was found to be sustained.

The main objective of any drug therapy is to achieve a desired concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for an extended period of time. This goal can be achieved by proper design of the sustained release dosage regimen[1]. Microspheres, which are matrix systems containing drug throughout (either in solution or microcrystalline form) the structure are potential candidates for oral sustained release. Of the various biodegradable polymers used for the development of sustained release formulations, chitosan has been reported to be advantageous since it is a natural product that is biocompatible[2]. It has been also reported that chitosan microspheres provide a potentially useful means of delivering drugs because they are stable, both physically and chemically amenable to preparation in large batches, non-antigenic, metabolize within the body and capable of accommodating a wide variety of drug molecules in a relatively non-specific fashion[3,4].

Metoprolol tartrate is used as a selective β1 receptor blocker in the treatment of several cardiovascular disorders such as hypertension, angina pectoris, disturbances of cardiac rhythm, myocardial infraction and functional heart disorders. It has a short plasma half-life of 2-3 h. The total oral daily dose is 100 mg to 300 mg in divided doses. The present study deals with the design and evaluations of chitosan microspheres of metoprolol tartrate for sustained release.

*For correspondence
Huruli Majal House, Post Kokkada, Pin-574 198.
Belthangady Taluk, Mangalore District.
E-mail: rkokkada@rediffmail.com

MATERIALS AND METHODS

Metoprolol tartrate was a gift sample from Astral IDL, Bangalore. Chitosan was obtained from Fisheries College, Matsyapuri, Cochin. All other chemicals and solvents used were of analytical reagent grade and double distilled water was used throughout the study.

Preparation of microspheres:

Chitosan microspheres containing metoprolol tartrate were prepared in three different drug to carrier ratios (1:0.5, 1:1and 1:2) by phase separation emulsification technique as reported by Seheffel *et al.*[5]. Two percent solution of chitosan was prepared in 1 % acetic acid and used in required volume for the preparation of the microspheres. Arachis oil containing sodium lauryl sulphate (0.5% in n-heptane) was taken in a large beaker and stirred at 1500 rpm. The metoprolol tartrate was dissolved in distilled water in a

test tube, then chitosan was added into the test tube and dispersed and immediately added to the oil being stirred. The test tube was further rinsed with water and transferred to the beaker. An emulsion was obtained and stirring was continued for a period of 45 min. To the above emulsion 0.1 ml of 25% formaldehyde was added and stirring was continued.

Same quantity of arachis oil was heated to temperatures of 80-90° in another beaker with continuous stirring. The emulsion that was stirred for 45 min was then added to the oil and the temperatures was maintained at 80-90° with continuous stirring at 500 rpm speed. The stirring was continued for another 45 min during which period microspheres were formed. The suspension of microspheres in oil was cooled and then it was mixed with n-hexane and filleted through suction. The microspheres were washed with diethyl ether. The washings were analysed for the presence of the drug and the washing was continued until the oil was removed completely. Then the microspheres were dried under vacuum and stored in a desiccator until used for further studies.

Analysis of microspheres:

Differential scanning calorimetric and UV spectrophotometric methods were employed to verify the presence of drug in the microspheres and its chemical stability. The differential scanning calorimeter (Shimadzu. DT-50) was used to obtain the thermograms of various formulations[6]. A study was performed on the percentage of yield of microspheres when drug polymer ratios were changed. Drug was extracted from the microspheres with water and absorbance was measured using Chemato 2500 UV/Vis spectrophotometer at 276 nm, The amount of metoprolol tartrate in the microspheres was estimated with help of standard graph.

Determination of the shape and size of the microspheres:

To study the shape of the microspheres, the microspheres were dispersed in liquid paraffin and observed under 200X magnification using an optical microscope. The size distribution was carried out by optical microscopy. An average of about 300 particles were counted and determined[7].

Stability studies:

The microspheres were placed in screw capped glass containers and stored at ambient humidity conditions, at room temperatures (27±2°), oven temperature (40±2°) and in refrigerator (5-8°) for a period of 60 d. The samples were assayed for drug content at regular intervals of two weeks[8,9].

***In vitro* drug release:**

In vitro release profile of metoprolol tartrate from microspheres was examined in pH 1.2 buffer from 0 to 2 h, in pH 5.8 buffer from 2 to 3 h and in phosphate buffer of pH 7.4 from 3 to 10 h using the rotating basket method specified in USP XXI at 100 rpm. Microspheres equivalent to 50 mg of drug were suspended in the dissolution medium and the medium was maintained at 37±2°. Five millilitres of samples were withdrawn periodically at intervals of half an hour and same volume of fresh medium was replaced in to the beaker. The concentration of the drug released at different time intervals was then determined by measuring the absorbence using Chemato 2500 UV/Vis spectrophotometer at 276 nm and with the help of standard graph[8,9].

RESULTS AND DISCUSSION

Among the three drug to carrier ratios, 1:1 ratio showed maximum percentage yield of 88.1% and 1:2 ratio showed highest drug entrapment of 72.1 % w/w as shown in the Table 1. The shape of chitosan microspheres was found to be spherical by microscopic studies. The size of the microspheres was found to be ranging between 3.5-31.5 μm and the average diameter was 8.99 μm.

The presence of peak at 276 nm in the UV absorption spectra of chitosan microspheres of metoprolol tartrate confirmed the presence of drug in the microspheres. In UV absorption spectra only one peak was obtained at 276 nm. This indicates that there was no chemical interaction between the drug and carrier.

The compiled thermograms of DSC for the pure drug, drug-loaded microspheres and plain microspheres indicated that pure sample of metoprolol tartrate showed an endothermic peak by melting at 121.6° whereas, the plain chitosan

TABLE 1: YIELD AND DRUG ENTRAPMENT IN CHITOSAN MICROSPHERES OF METOPROLOL TARTRATE.

Drug to carrier ratio	Percentage yield *	Drug entrapment (% w/w)
1:0.5	79.9	38.9
1:1	88.1	56.0
1:2	85.4	72.1

*Average of three preparations.

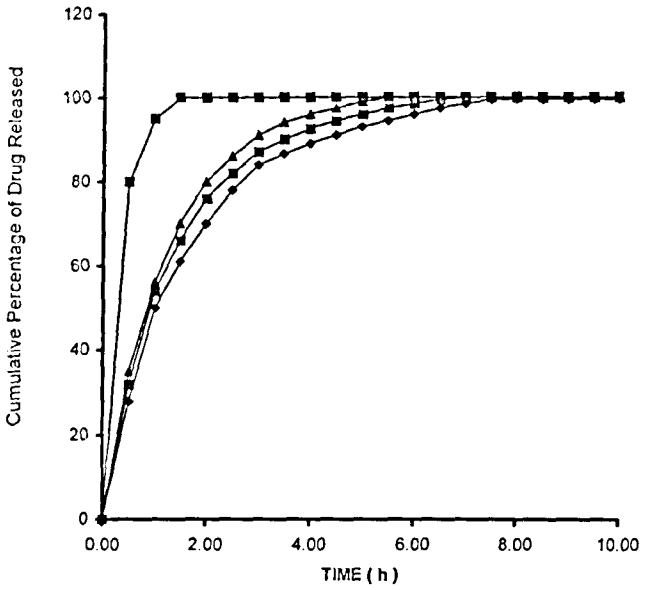

Fig. 1: Dissolution profile of chitosan microspheres.

Dissolution profile of chitosan microspheres of different drug to polymer ratios of 1:0.5 (-◆-), 1:1 (-■-), 1:2 (-△-) and pure drug (-□-).

microspheres showed an endothermic peak at 60° and 280°, the first one corresponds to water of evaporation and the second peak corresponds to melting of the polymer. The drug-loaded chitosan microspheres showed two peaks, one corresponding to drug at 121.6° and other corresponding to chitosan at 280°. This indicates that there was no significant interaction between chitosan and metoprolol tartrate (figure not shown). It was further confirmed that the DSC values of chitosan were complying with the values reported in literature[10,11].

No appreciable difference was observed in the extent of degradation of products during 60 d in the microspheres, which were stored at various temperatures. In the *in vitro* drug release studies, it was found that the drug was released by diffusion from the matrix after hydration and swelling of the microspheres in the dissolution medium. As shown in fig. 1, when the release of the pure drug and the microspheres were compared, the pure drug was entirely released within 1.5 h, whereas in case of microspheres the release pattern was in the following order, 1:0.5 drug to carrier ratio showed maximum release within 6.5 h, 1:1 ratio showed within 7.0 h and 1:2 ratio showed within 8.5 h. It is inferred from the above data that 1:2 ratio showed a better-sustained release. In case of 1:2 ratio, 38% of the drug was released at pH 1.2 after 2 h. At pH 5.8, there was a slight decrease in the release rate i.e., 16% for a period of 1 h. The release was much decreased and more sustained at pH 7.4 for 5.5 h. It was observed that the rate of release decreased as the concentration of the carrier was increased.

The method of preparation of chitosan microspheres of metoprolol tartrate was found to be simple and reproducible. Chitosan, which is used as a carrier is easily available, biocompatible and biodegradable. The microspheres were found to be effective in sustaining the drug release up to 8.5 h. From the above data, it may be concluded that drug-loaded microspheres are a suitable delivery system for metoprolol tartrate, and may help to reduce the dose of the drug and frequency of administration.

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