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Design and In-vitro Evaluation of Gelatin Microspheres of Salbutamol Sulphate

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Abstract

In the present study, gelatin microspheres containing Salbutamol sulphate were prepared by coacervation phase separation method and characterized by optical microscopy and scanning electron microscopy. The microspheres were analyzed for drug entrapment, and in vitro release pattern. The different batches of microspheres were prepared by altering drug : polymer ratio and cross linking with glutaraldehyde The size of microspheres was in the range of 5.6μ- 22.4 μ and the average diameter was found to be 12.34 μ. They were spherical in shape as evidenced by scanning electron microscopic photographs. The percent drug entrapment was up to 80% and they could sustain drug release over a period of 8 ½ hours.

Keywords: Salbutamol sulphate, microspheres, gelatin, glutaraldehyde.

Introduction

Micro encapsulation is a process by which solids, liquids, or even gases may be encapsulated in to microscopic size particles through the formation of thin coatings of "**wall**" material around the substance being encapsulated. Microspheres are usually solid, approximately spherical particles with size varies from 50nm to 2mm containing a core substance (dispersed drug). Microspheres serve as a carrier for the drug. Microspheres consist of a biodegradable carrier in which drug is entrapped. Drug release from microsphere is controlled by dissolution and by diffusion of drug through the microsphere matrix or the microcapsule wall.

Salbutamol sulphate is a short acting $_2$ – adrenergic agonist with more bronchodilatory $_2$ effect and less cardiac stimulatory $_1$ effect and useful in the treatment of bronchial asthma. Salbutamol sulphate is readily absorbed from gastrointestinal tract. The plasma half-life of Salbutamol sulphate varies from 2 to 7 hours. In the treatment of asthma, it is given in the dose of 2-4mg, three to four times a day orally[1]. Gelatin is proteinaceous biodegradable polymer obtained from partial hydrolysis of the collagen derived from skin, connective tissues and bones of animals. Gelatin microspheres are prepared by cross-linking gelatin in water in oil emulsion with glutaraldehyde by coacervation phase separation method. The shape of the microspheres prepared by this method is spherical.[2] The aim of this work was to prepare sustained release microcapsules of Salbutamol sulphate by Thermal Change method and evaluation of the prepared microcapsules[3].

Materials and Methods

Salbutamol sulphate IP was a gift sample from Cabstab Pharma, Cochin, Kerala, Gelatin [E. Merck (India) Limited, Mumbai], Glutaraldehyde [Merck Specialities Private Limited, Mumbai] and Sunflower oil of food grade was purchased from local market. All other reagents were of analytical grade. Magnetic stirrer [Rolex], UV-1700 Pharmaspec, UV-Spectrophotometer SHIMADZU, Double Beam UV-Visible Spectrophotometer [ELICO SL164], Microscope [Olympus OIC], and Dissolution apparatus [Electrolab Tablet Dissolution Tester Model No.TDT-06T] were the equipments used in this study.

Preparation of Gelatin Microspheres Containing Salbutamol Sulphate

Gelatin microspheres containing Salbutamol sulphate were prepared by coacervation phase separation method utilizing temperature change. Gelatin was dissolved in 10ml water previously heated to 50^0 C. The drug was dispersed with stirring in this solution and the dispersion was then poured drop wise in to the oil phase, which was also heated to 50^0C. the oil phase contained 0.5ml Span 20, which acted as an emulsifier. The mixture was stirred for 5minute to ensure uniform dispersion. The temperature of the system was lowered down to 10^0C by placing in ice bath with continuous stirring to effect phase separation. The dispersion was stirred for 1.5 hours in ice bath at 10^0C. At the

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end of first hour, 1.5ml of Glutaraldehyde was added to the dispersion and stirring continued for next 30 minutes. After 1.5 hours, stirring was stopped; beaker was covered and refrigerated at 0^0 C for 2 hours to ensure rigidisation of microspheres. After 2 hours, beaker was removed and slurry was filtered. Microspheres collected were washed with ice-cold acetone to make the free of oil. The solvent also acted as hardening agent. The washed microspheres were then collected and stored in a desiccator until used for further studies [3,4].

Characterization of Prepared Microspheres:

Particle size analysis
The sample of prepared microspheres was randomly selected and their size was determined using an optical microscope.

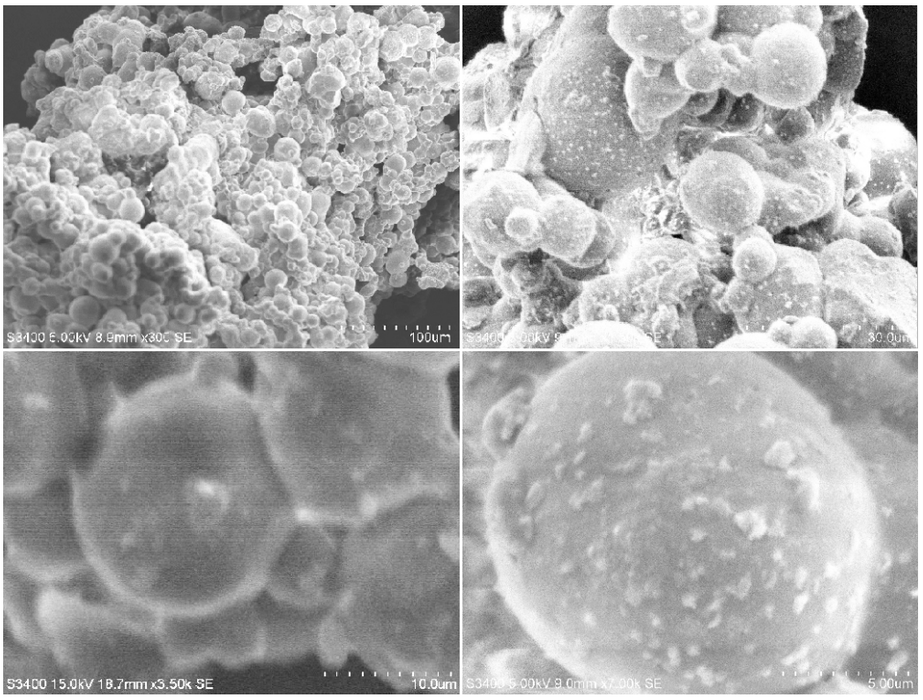
Scanning electron microscopy
Scanning electron microscopy was carried out to study the shape of the microspheres and micrographs were also taken.

Percentage entrapment of Salbutamol sulphate in microsphere:
50mg of the microspheres was digested in 50ml 0.1M Hydrochloric acid. The suspension was then warmed for 5 minutes. It was then cooled to room temperature and filtered. Suitable dilution of the filtrate was prepared and the solution was analyzed at 276nm to determine amount of Salbutamol sulphate entrapped in microspheres.

In vitro release study
The in-vitro dissolution studies was carried out using Dissolution apparatus [Electrolab Tablet Dissolution Tester Model No.TDT-06T] in simulated gastro intestinal fluid of pH 1.2 up to 2hours, in pH 5.6 up to 2-3 hours, in pH 6.8 up to 3-5 hours and in pH 7.4 up to 5-10 hours. A sample of microspheres equivalent to 15mg of Salbutamol sulphate was taken in a hard gelatin capsules. The dissolution medium was maintained at 37 ± 2°C. The shaft of the apparatus to which the basket is fixed was rotated at a speed of 100rpm. 5ml samples were withdrawn periodically at intervals of half an hour and same volume of fresh medium was replaced into the beaker. The dissolution was carried out for a period of 10 hours. The percent of drug released at various time intervals was calculated and plotted against time.

Results and Discussion
Particle size analysis
The size of microspheres ranged between 5.6µm to 22.4 µm with an average diameter of 12.34 µm.

Scanning electron microscopy:
The shape of the prepared microspheres was spherical, surface shows roughness due to the presence of drug particles on the surface as evidenced from the photomicrograph



Scanning Electron Micrographs of Gelatin Microspheres of Salbutamol sulphate

Percentage entrapment of Salbutamol sulphate in microsphere:
It was found that percent entrapment of Salbutamol sulphate was between 75% – 80% depending on the drug: carrier ratio (Table. I).

Drug to carrier ratio	Percentage yield (*)
0.25:1	70
0.5:1	85
1:1	79

* Average of 3 preparations.

In vitro release study
The release of Salbutamol sulphate from the microspheres was only 6.2% -19.6% at pH 1.2 for 2 hours. At pH 5.6 there was a slight increase in the release i.e., 26.53%-28% for a period of 1 hour. The release was found to be significant at pH 6.8 i.e., 32.27% - 57.53% for 2 hours followed by pH 7.4 i.e., 62.4%-96%. The maximum concentration of Salbutamol sulphate was released from the microsphere and marketed sustained release product at 8 ½ hours.

The release pattern of the microspheres of Salbutamol sulphate was found to be comparable with the release pattern of marketed sustained release product [Plate -II].

Salbutamol sulphate is released from the microspheres at a constant rate following zero order pattern[3,4,5,6].

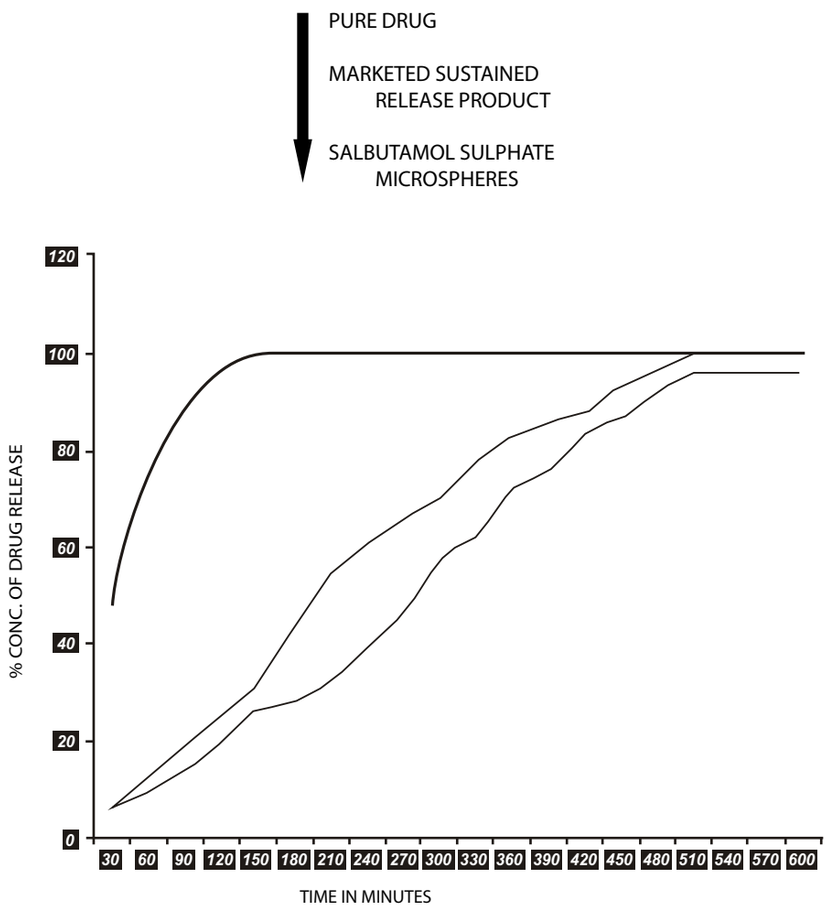


PLATE- II DISSOLUTION RATE PROFILE OF PURE SALBUTAMOL SULPHATE, MARKETED SUSTAINED RELEASE PRODUCT OF SALBUTAMOL SULPHATE AND SALBUTAMOL SULPHATE MICROSPHERS IN pH 1.2, 5.6, 6.8 AND 7.4 MEDIA

Conclusion

Gelatin micro spheres of Salbutamol sulphate of 0.5:1 drug to carrier ratio sustained the release of drug appreciably. The drug release from the microspheres is at constant rate i.e., zero-order release. The results of the dissolution studies of Salbutamol sulphate microspheres are more encouraging since the release property is almost similar to the marketed sustained release product.

This method of preparation of gelatin microspheres is found to be simple and reproducible and gelatin that is used as the carrier is biocompatible, easily available and the gelatin microspheres being susceptible to the macrophage recognition can be used as the carrier. Thus, encapsulation with gelatin by coacervation phase separation with temperature change and cross-linking with glutaraldehyde was able to sustain the drug release effectively.

Acknowledgement

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