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FORMULATION AND EVALUATION OF METOPROLOL TARTRATE NASAL MUCOADHESIVE MICROSPHERES

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Abstract

Solid biodegradable mucoadhesive microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of the drug. Solid biodegradable mucoadhesive microspheres of chitosan containing metoprolol tartrate were prepared by ionic precipitation method. The aim of present work is to provide quick relief and sustained action of drug for prolong period of time by administration through nasal route as suspension which is beneficial over conventional enteric coated tablet system because it protect the drug from gastric environment and releases drug in systemic circulation at controlled rate. The effects of different factors (chitosan concentration, acetic acid concentration, stirring rate, gluteraldehyde concentration and tween 80 concentration) on microsphere size and encapsulation efficiency were studied. The prepared microspheres were evaluated for particle size distribution, surface morphology and entrapment efficiency. Maximum entrapment was found to be 94.19±0.015 %. The maximum release was 97.88±0.02 % within 18 hr for optimized formulation in phosphate buffer solution (pH 7.0) which shows sustained release of dosage form. So microsphere of chitosan can be successfully prepared and delivered by nasal route.

Keywords Metoprolol Tartrate, Nasal drug delivery, Bioadhesive Microspheres, Chitosan Microsphere

Introduction

Hypertension, also called silent killer, is a well established risk factor for coronary artery disease. In the year 2001, hypertension was the most common primary diagnosis made by the office based physicians in USA and it has been estimated to cause 4.5 % of the current global disease burden.

Metoprolol is a selective β_1 receptor blocker used in treatment of several diseases, especially hypertension. The active substance metoprolol is employed either as metoprolol succinate or as metoprolol tartrate. The tartrate is an immediate-release and the succinate is an extended-release formulation.[1] Metoprolol is used for a number of conditions including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches.[2] Common side effects include: trouble sleeping, fatigue, feeling faint, abdominal discomfort. It needs to be used carefully in those with liver problem.[2, 3] Metoprolol was first made in 1969.[2]

Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). [4]

In medicine, it may be useful in bandages to reduce bleeding and as an antibacterial agent; it can also be used to help deliver drugs through the skin. [5]

Chitosan's properties also allow it to be used in transdermal drug delivery; it is mucoadhesive in nature, reactive and most importantly, has a positive charge under acidic conditions. Lack of a positive charge means chitosan is insoluble in neutral and basic environments. [6] However, in acidic environments, protonation of the amino groups leads to an increase in solubility. The implications of this are very important to biomedical applications.

Among mucosal sites, the nasal route of administration has gained in interest. The large absorptive surface and high vascularity of the nasal mucosa ensure a rapid absorption of compounds under circumvention of the hepatic first pass elimination. Particles less than 1μm will escape to the lungs, whereas particles larger than 10μm will deposit in the nasal mucus membrane, with larger ones depositing more anteriorly.

The aim of this work was to develop bioadhesive microspheres for nasal delivery of hydrophilic model drug Metoprolol tartrate. The purpose of work is to apply

theory and practice of microspheres in pharmaceutical controlled drug delivery system, to enhance the activity of drug in comparison to available other marketed formulation.

Experimental

Materials

Metoprolol Tartrate and Chitosan were obtained as gift samples from Aristo Pharmaceutical Ltd, Bhopal and Central Institute of Fisheries Technology, Kochi respectively**.** All other chemicals used were of analytical grade.

Method

The microsphere system was prepared by ionic precipitation and chemical cross linking method. [7] A specific amount of chitosan was dissolved in 100 ml of 2% v/v acetic acid solution. To the above solution 1% v/v Tween-80 was added with constants stirring. Then sodium sulphate (20% w/v) solution was added drop wise during the stirring process, until uniform turbidity was observed. To this, 1% w/v cross linking agent, glutaraldehyde was added and solution was homogenized for additional 1.0 hour to stabilize the microspheres. Now the microsphere suspension was centrifuged at 3000 rpm for 15 minutes and microspheres were collected. The microspheres were washed twice with distilled water and freeze-dried.

Characterization

Particle size and particle size distribution

The particle size and surface morphology were determined with the help of optical microscope and particle size analyzer. The drug loaded microspheres were suspended in distilled water for size distribution analysis with the help of Malvern instrument Ltd U.K, Zeta sizer ZS-90.

Surface Morphology

The morphology of the microspheres was determined by observation on a fluorescent microscope. The samples were prepared in distill water and mounted on glass slide to determine the morphology of microspheres with the help of Fluorescent microscope, Radical Rx Lr 3T.

Entrapment Efficiency

The entrapment efficiency of microsphere prepared by ionic precipitation technique was determined by using cooling centrifuge. The microsphere dispersions were centrifuged at 3,000 × *g* for 30 min in acetic acid solution. The clear supernatant was analyzed for metoprolol tartrate by UV-spectrophotometric method at 274 nm gives the amount of entrapped drug. The drug-loading efficiency was determined as the ratio between the analytical and theoretical drugs [8]

$$\% \text{ Drug entrapment} = \frac{\text{Mass of drug obtained in particles}}{\text{Mass of the drug used in formulation}} \times 100$$

In Vitro Drug Release studies

In vitro drug release of the microsphere was performed in phosphate buffer solution (pH 7.0). For determination of drug release behavior of Chitosan microspheres, 10 mg of microspheres where suspended in small amount of PBS 7.0 solution. This suspension was placed in an egg membrane; suspend in beaker filled with 50 ml of PBS 7.0 release media (PBS). This solution was stirred at 100 rpm with magnetic stirrer at 37±1^{0}C. Sink conditions were maintained during the drug dissolution study. Sampling was done at specific interval. At each sampling, 3 ml of the solution withdrawn and was replaced with fresh media .The drug concentration was measured at 274 nm using "Shimadzu 1700 UV/visible spectrophotometer" The analyses were performed in triplicate. The results are expressed as mean ± standard deviation (S.D.). The above drug release procedure was applied on the formulation for 18 hours.

Optimization of process variables

The preparation procedure was then optimized and validated. The preparation of chitosan microspheres involves following various process variables:

Effect of Acetic acid concentration

The concentration of acetic acid was varied from 1 % to 2.5 % and the effect of acetic acid concentration on entrapment efficiency was then studied.

Effect of Drug:Polymer ratio

Drug concentration was kept constant while its ratio with polymer was varied in the range of 0.5 to 2. The effect of drug polymer ratio on entrapment efficiency was then studied.

Effect of stirring speed

The stirring speed was varied from 2000 to 3500 rpm and the effect of stirring speed on entrapment efficiency was studied.

Effect of Glutaraldehyde

Similarly the effect of Glutaraldehyde concentration on entrapment efficiency was studied by varying the concentration in the range 0.8 % to 1.4 %.

Effect of Tween 80 concentration

The effect of Tween 80 concentration on entrapment efficiency was studied by varying the concentration in the range 0.8 % to 1.4 %.

Result

Spherical shaped microspheres of chitosan were observed with optical microscope.

The entrapment efficiency was estimated after freeze-drying. On the basis of entrapment efficiency, acetic acid concentration, drug polymer ratio, stirring speed, gluteraldehide concentration, and Tween 80 concentrations were optimized as in table 1, 2, 3, 4, and 5 respectively.

Table 1: Effect of Acetic Acid Concentration on the entrapment efficiency

Formulation code	Acetic acid concentration (%)	% drug entrapment
F1	1.0	57.89±0.36
F2	1.5	69.41±0.54
F3	2.0	77.28±0.42
F4	2.5	73.65±0.46

Table 2: Effect of Drug : Polymer Ratio on the entrapment efficiency

Formulation code	Drug : Polymer Ratio	% drug entrapment
F5	1: 0.5	47.47±0.89
F6	1: 1.0	75.83±1.37
F7	1: 1.5	79.29±0.53
F8	1: 2.0	64.84±0.37

Table 3: Effect of Stirring Speed on the entrapment efficiency

Formulation code	Stirring speed (rpm)	% drug entrapment
F9	2000	63.24±0.14
F10	2500	70.14±0.17
F11	3000	77.28±0.43
F12	3500	80.74±0.26

Table 4: Effect of Glutaraldehyde Concentration on the entrapment efficiency

Formulation code	Concentration of Glutaraldehyde (%)	% drug entrapment
F13	0.8	66.05±0.18
F14	1.0	77.29±0.42
F15	1.2	81.37±0.16
F16	1.4	75.05±0.18

Table 5: Effect of Tween 80 Concentrations on the Entrapment efficiency

Formulation code	Concentration of Tween 80 (%)	% drug entrapment
F17	0.8	74.87±0.14
F18	1.0	81.01±0.04
F19	1.2	86.71±0.84
F20	1.4	94.19±0.015

So the maximum entrapment of drug was found to be 94.19±0.015 %. The average particle size of optimized formulation was found to be 1.897mm (Fig 1). Table 6 shows, the optimized formula for the final formulation.

Table 6: Optimized batch formula

Drug to polymer ratio	1:1.5
Concentration of acetic acid	2.0% v/v
Speed of mechanical stirrer	3500rpm
Glutaraldehyde Concentration	1.2% w/v
Surfactant (Tween-80) Concentration	1.4 %v/v

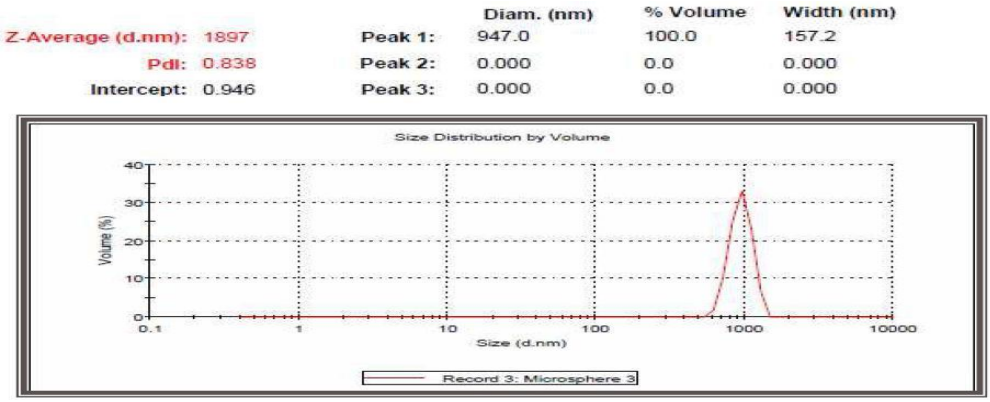

Figure 1: Particle size analysis of formulation

The *in vitro* drug release observations were continuously made for 18 hr in PBS (Phosphate Buffer Saline) 7.0 medium. The maximum drug release of optimized formulation was found to be 97.88±0.02 % (Fig 2).

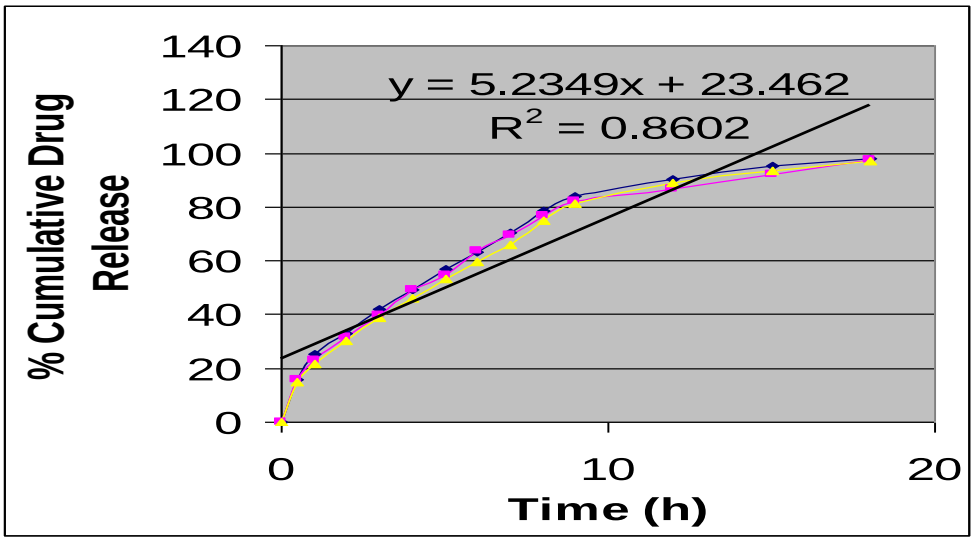

Figure 2: Cumulative % drug release of formulation

Discussion

The change in particle size was observed with some processing variables like concentration of chitosan, stirring speed and the concentration of emulsifier. It was shown that microsphere size decreased with increasing stirring rate since increased stirring results in the formation of smaller particle. In chitosan microspheres formulation, the increase in stirring rate will rapidly disperse the precipitating agent in solution. As shearing force increases, the size of microspheres decreases and the % drug entrapment increases.

Glutaraldehyde differently influenced the microparticle sizes. Glutaraldehyde is probably able to interact with the amine groups of metoprolol tartrate, forming a complex that forms the microspheres.

But the maximum influence was found to be with surfactant concentration. On increasing the concentration of surfactant, there was an increase in entrapment of drug. This was may be due to decrease in interfacial surface tension. 1.4 % v/v concentration of Tween-80 is suitable for maximum entrapment of drug.

On increasing the concentration of polymer the rate of release of drug from chitosan microspheres decreased, because the thickness of polymer was increased and diffusion distance for drug to diffuse out from microspheres was increased.

Conclusion

Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. Chitosan microspheres have excellent mucoadhesive properties. The electrostatic attraction between the positively charged mucoadhesive chitosan microspheres and negatively charged mucus glycoprotein plays an important role in the adsorption of mucin on chitosan microspheres and vice versa. Factors causing the reduction of this attraction would lead to a reduction in the adsorption. The utility and potential of microsphere drug delivery systems have been demonstrated and it has been shown that tailored delivery is possible.

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Conflict of Interest

None

Reference

1. Cupp M. Alternatives for Metoprolol Succinate, Pharmacist's Letter / Prescriber's Letter 2009; 25 (250302).
2. Carlsson, edited by Bo, Technological systems and industrial dynamics,

Dordrecht: Kluwer Academic. 1997: 106.

3. Geffner DL, Hershman JM. β-Adrenergic blockade for the treatment of hyperthyroidism, The American Journal of Medicine. 1992;93(1): 61–8.

4. Shahidi F, Synowiecki J. Isolation and characterization of nutrients and value-added products from snow crab (Chionoecetes opilio) and shrimp (Pandalus borealis) processing discards, J of Agri & Food Chem. 1991;39(8):1527–32.

5. Agnihotri S, Mallikarjuna A, Nadagouda N, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery, J of Cont Rel. 2004;100 (1):5–28.

6. Sadigh-Eteghad S, Talebi M, Farhoudi M, Mahmoudi J, Reyhani B. Effects of Levodopa loaded chitosan nanoparticles on cell viability and caspase-3 expression in PC12 neural like cells, Neurosciences, 2009;18(3):281–283.

7. Berthold A, Cremer K, Kreuter J. Preparation and characterization of chitosan microspheres as drug carrier for prednisolone sodium phosphate as model for anti-inflammatory drugs. J. Control Rel. 1996; 39:17-25.

8. Krisnamoorthy R, Mitra AK, Mucoadhesive polymers inocular drug delivery, in: Ophthalmic Drug Delivery Systems, Marcel Dekker, New York, 1993: 199–221.

9. Junior AA, Matos J.R. Thermal behavior and stability of biodegradable spray-dried microparticles containing triamcinolone, Int. J. Pharm. 2009;368:45–55.

10. Gavini E, Hegge AB, Nasal administration of Carbamazepine using Chitosan microspheres: In vitro/in vivo studies, Int. J. of Pharm. 2006;307:9–15.

11. Jameela SR, Kumary TV, Lal AV, Jayakrishnan A. Progesterone-loaded chitosan microspheres: a long acting biodegradable controlled delivery system. J. Control Rel. 1998;52:17-24.

12. Dini E, Alexandridou S, Kiparissides C. Synthesis and characterization of cross-linked chitosan microspheres for drug delivery applications. J. Microencapsul. 2003;20:375-385.

13. Shiraishi S, Arahira M, Imai T et al. Enhancement of dissolution rates of several drugs by low-molecular weight chitosan and alginate. Chem. Pharm. Bull. 1990;38:185-187.

14. Lohiya NK, Pathak N, Mishra PK, Manivannan B. Contraceptive evaluation and toxicological study of aqueous extract of the seeds of *Carica papaya* in male rabbits. J Ethnopharmacol2000;70:17-27.