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Research Article

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Formulation Development & Evaluation of Spray Dried Nasal Mucodhesive Microspheres of Atenolol

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ABSTRACT

The object of the study is to prepare and evaluate the formulation of Atenolol for nasal drug delivery system with consideration to parameters require for nasal administration, to get maximum utilization and efficacy of the drug also delivery of drug in case of emergency situation and to see the effect of HPMC K15 on drug release from microspheres. The use of Atenolol in conventional dosage form possesses several disadvantages like the absorption in GI tract is low, hence low bioavailability, require large amount of dose and has to pass first pass metabolism. This encourages us to formulate the dosage form with Atenolol as novel drug delivery which will show maximum potential utilization of the Atenolol. The five formulations of microspheres were formulated with hydroxypropylmethyl cellulose K15 by spray drying technique. The invitro and ex vivo studies of microspheres were performed along with SEM, XRD and Histopathological studies of the formulaiton. The results indicate that Atenolol spray dried microspheres formulated with HPMC K15 is promising nasal delivery system.

KEYWORDS- *Microspheres, Atenolol, HPMC K15, Mucoadhesive*

INTRODUCTION

Atenolol is a selective β_1 receptor antagonist, a drug belonging to the group of beta blockers, a class of drugs used primarily in cardiovascular diseases. The Atenolol is recognized and extensively prescribed as first choice of drugs in the treatment of majority of the hypertension population. The conventional formulation of these drugs is rapidly dissolved in upper gastric intestine and produces peak plasma concentration within 1 to 4 hours and then declines quickly. Consequently, divided doses are recommended for maintaining the effective plasma concentration. However, conventional formulations exhibited drawbacks since they produce peaks and valley time drug plasma concentration on multiple dosing. The multiple dosing results in high and rapid plasma concentrations after each dose, which may be associated with undesirable beta-2 mediated effects like fatigue and bronchospasm. The conventional formulations fail to provide adequate protection against myocardial ischematic episode, which shows circadian pattern. Arterial blood pressure also exhibits circadian rhythm that leads to serious cardiac problems that occurs during early morning hours. The short half-life of the conventional formulations necessitates the multiple dosing which may lead to blood pressure variation over 24-hours and hence may increase target organ damage. Atenolol is subjected to first-pass metabolism[1], which increases the dose size of the drug. All the drawbacks necessitate the development of an even and effective drug

delivery system which could utilizes all the potential of efficacy of the drug atenolol and should maintain the plasma concentration throughout 24 hours in order to achieve maximal cardio protection, improved patient compliance, maximal drug utilization and enhanced bioavailability[2]. Therefore, the development of mucoadhesive microspheres of atenolol could protect drug from first hepatic pass degradation and maintain a constant drug plasma level for extended period of time. This could maximize the drug utilization, improve bioavailability of drug, exhibit better patient compliance and finally applicable in emergency situation.

MATERIALS AND METHODS

Materials

Atenolol was supplied as a gift sample from IPCA Laboratories Ltd, Aurangabad. HPMC K15 was supplied as a gift sample from Colorcon Limited Goa, India. All other chemicals and reagents were of analytical grade. Deionized water was used for all of the experiments. A freshly cut piece, 10 cm long of sheep nasal mucosa was obtained from a local abattoir house.

Method of Microspheres preparation

HPMC K15 microspheres were prepared by spray-drying technique with formulation composition as given in Table 1. Methanol and dichloromethane used in the ratio of (1: 2) as a solvent to prepare different drug/polymer ratio (from 1: 1 to 1:5) microspheres. Feed solution was prepared by dissolving the drug and polymer in the solvent. Atenolol containing microspheres were obtained by spraying the feed solution with a spray dryer (JISL, India) using a standard 0.7 mm nozzle. The process parameters of the spray drying technique were: Inlet temperature 60°C – 750°C, outlet temperature 40°C –55°C, aspirator speed 40–50% and feed pump speed 9–10 ml/min[3].

Table 1: Formulation composition

Polymer	Ratio (drug: polymer)	Formulation code	Drug (mg)	Polymer (mg)	Methanol (ml)	Dichloromethane (ml)
HPMC K15M	1:1	F1	200	200	30	60
	1:2	F2	200	400	50	100
	1:3	F3	200	600	70	140
	1:4	F4	200	800	90	180
	1:5	F5	200	1000	100	200

EVALUATION OF MICROSPHERES

Thermal Analysis (DSC):

The thermal behavior of pure drug, drug loaded microspheres and blank microspheres were studied using a differential scanning calorimeter Shimadzu Japan (DSC 60) at a heating rate of 20°C /min. The measurements were performed at a heating range of 50°–225°C under nitrogen atmospheres

Particle size analysis

The mean particle size of the microspheres was measured using optical microscope (Olympus CX31). The microscope was equipped with the software Magnus pro 3.0 and Olympus master through a camera [5].

Morphology of Microspheres

The morphology of the microspheres was examined by scanning electron microscopy (JSM 6390 India). The sample was mounted on to an aluminum stub and sputter-coated for 120 s with platinum particles in an argon atmosphere[6].

In vitro Release of Atenolol from the microspheres

The drug release test was carried out using a nasal diffusion cell microspheres loaded with Atenolol was placed in the reservoir tube, 100 ml of a release medium is kept and stirred at 50 rpm at 37° C the release media was of pH 6.8 phosphate buffer solutions. An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The samples were analyzed by UV spectrophotometer (UV- 1700 Shimadzu, Japan) at 258 nm [11].

X-Ray Diffraction study (XRD)

The crystallinities of Atenolol, Atenolol loaded microspheres and blank microspheres were evaluated by XRD measurement using an x-ray diffractometer (Brucker Axs, 08 Advance). All samples were measured in the 2ø angle range between 3–80° and 0.010 step sizes[8]

Ex vivo Studies

Histopathological study

The histopathological evaluation of tissue incubated in phosphate buffer (pH 6.8) for 6 h after collection was compared with tissue incubated in diffusion chamber with formulation. Tissue was fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Sections were cut on glass slides and stained with hematoxylin and eosin. Sections were examined under a light microscope to detect and damage to the tissue [10].

Drug release study

The optimized formulation F1 studied for ex vivo release, by using sheep nasal mucosa within 1 hr as that obtained from the local slaughter house. The small section of nasal mucosa is attached to the glass tube of the nasal diffusion cell at the down side and kept the tube in position to just touching the buffer media in the cell. Further procedure of the study is similar to that of in vitro method[11].

Measurement of adhesive force

By falling liquid film technique mucoadhesive microspheres were tested for adhesive force. A freshly cut piece of sheep nasal mucosa (10 cm long) was used. The mucosa was cleaned by washing with isotonic saline solution. A weighed amount of microspheres was placed on mucosal surface, attached over aluminum plate that was fixed in an angle of 45° relative to the horizontal plane. The phosphate buffer pH 6.6 was warmed at 37°C was peristaltically pumped at a rate of 5ml/min. After one hour perfusate was analysed for drug content. The adhered microspheres amount was estimated from the difference between the applied microspheres and the flowed microspheres amount. The ratio of the adhered microparticles was computed as percentage mucoadhesion[9].

RESULTS AND DISCUSSION

Thermal Analysis (DSC)

The thermogram of Atenolol exhibited a sharp endothermic peak at 185.35°C, indicated melting point, which was reported in the literature. The characteristic peak of Atenolol was well recognized in the drug-loaded microspheres. Thus, there was no interaction between Atenolol and HPMC K 15. Further, decrease in peak length and shift of peak of drug loaded microspheres curve revealed encapsulation of drug with some sort of energy minimization (Fig. 1-3).

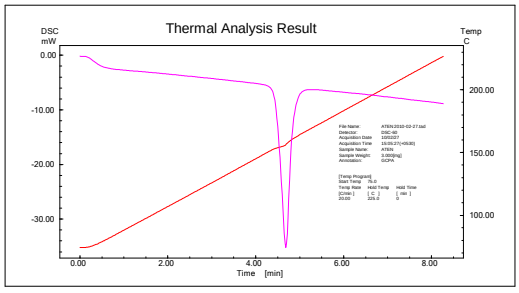

Figure 1: DSC Thermograph of Atenolol Drug

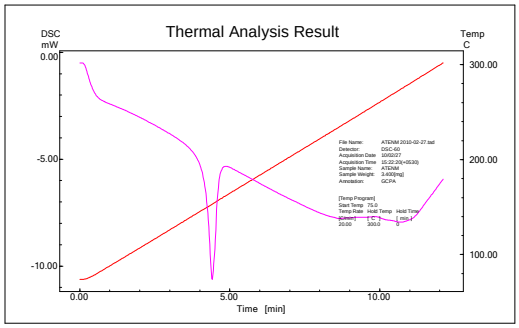

Figure 2: DSC Thermograph of Drug Loaded Microspheres

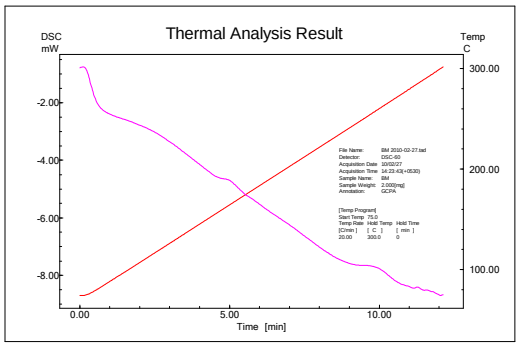

Figure 3: DSC Thermograph of Blank Microspheres

Particle size analysis

A microscopic image analysis technique for determination of particle size is used, the average particle size of microspheres ranged from 20–50 mm, and such particles are considered to be suitable for nasal administration. It was also noted that with the increase in the drug: polymer ratio there was a slight increase in the size of microspheres (Table 2). The images of the scanned field are analyzed by the software. In all measurements at least 100 particles were examined (Fig.4).

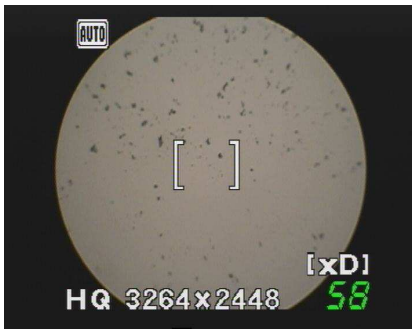

Figure 4: Optical Microscopic Image of Microspheres of Optimized Formulation F1

Morphology

The morphology of the microspheres of optimized formulation F1 was examined by scanning electron microscopy. The SEM revealed a spherical shape with a rough surface morphology (Fig. 5). The inside of the microspheres was completely filled, indicating that the complexation had occurred

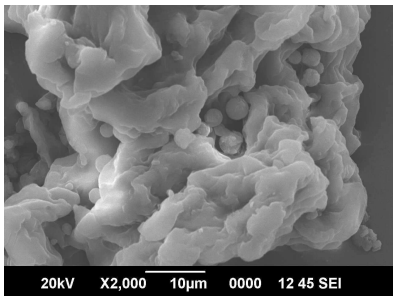

Fig.5 SEM of Microspheres

In vitro drug release

The microspheres bearing HPMC K15 and Atenolol were spherical in shape and in the range of desired particle size. The microspheres swelled when in contact with moisture and released the drug, Fig. 6. Shows the release rates of the HPMC loaded microspheres in phosphate buffer 6.8. After 6 hr study it is found that the release of Atenolol from the HPMC microspheres was in the range of 50-80%

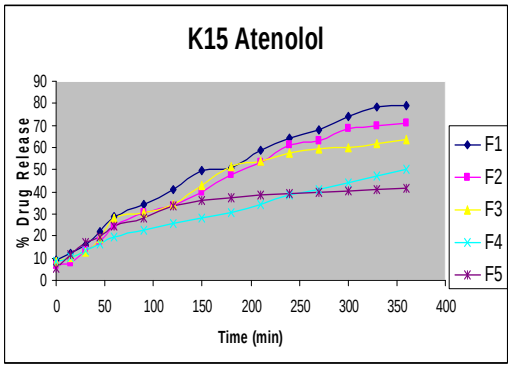

Figure 6: In vitro % Drug Release Study

X-ray Diffraction study (XRD)

The X-ray diffraction spectra's were recorded for Atenolol blank microspheres and drug loaded microspheres for investigating the crystalanity of the drug in the polymeric microspheres. The X-ray diffractogram of Atenolol showed sharp peaks at diffraction angle 8.95° depicting a typical crystalline pattern. Blank microspheres showed less intense peaks, however Atenolol loaded microspheres showed peaks, but of low intensity, indicating that some amount of drug was converted to amorphous form. (Fig.7-9)

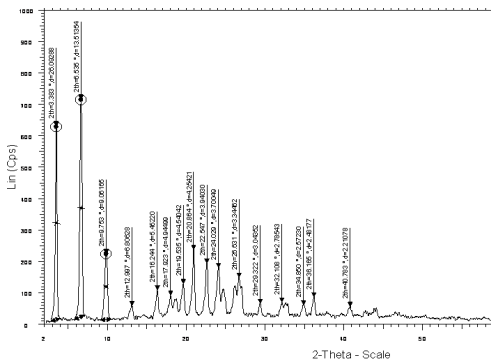

Figure 7: X-ray Diffractogram of Blank Microspheres

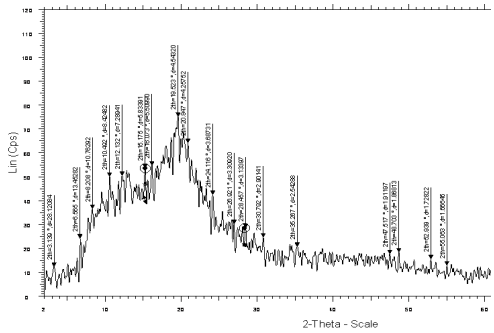

Figure 8: X-ray Diffractogram of Atenolol

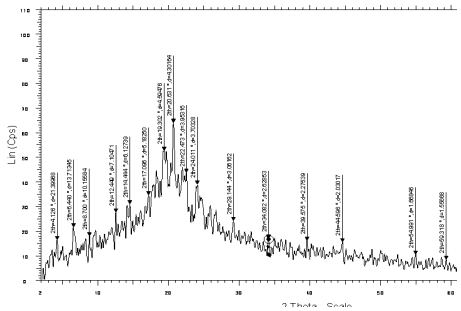

Figure 9: X-ray Diffractogram of Drug loaded Microspheres

Ex vivo Studies

Histopathological study

With histopathological evaluation of the optimized formulation it was concluded that the formulation does not harms the nasal mucosa. The cell linings and the tissues were not destructed by the formulations (Fig.10).

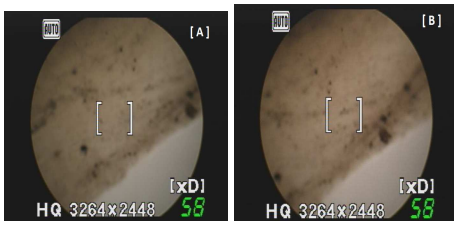

Figure 10: A) Untreated nasal mucosa; B) Nasal mucosa treated with f1 formulation

Table 2: Characterization of microspheres

Formulation code	Mucoadhesion (%) *	Average particle size (µm) #
F1	79.07 ± 0.51	27.21±1.98
F2	81.34 ± 1.51	29.16±2.82
F3	83.76 ± 2.49	35.77±2.41
F4	89.71 ± 2.17	40.47±1.45
F5	93.89 ± 1.41	42.97±2.59

***Denotes ± SD n=3, # Denotes average of 100 particles SD*

Drug release study

The sample obtained was analyzed by UV spectrophotometer at 258nm. The Fig.11 shows the release pattern of optimized formulation F1. The studies revealed a similar pattern of release of formulation performed with sheep nasal mucosa and that with dialysis membrane.

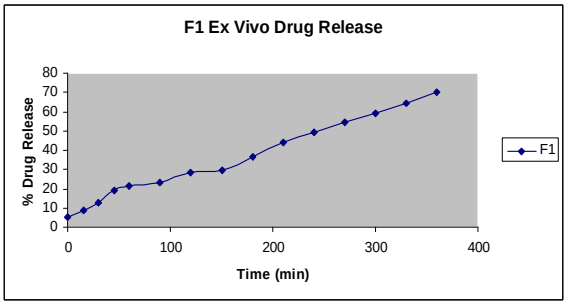

Figure 11: Ex vivo drug release study

Measurement of Adhesive Force

Mucoadhesion studies were carried out to confirm the adhesion of formulation to the nasal mucosa for a prolonged period of time at the site of absorption.

Results showed that the microspheres adequately adhere on nasal mucosa. The ratio of the adhered microspheres was expressed as percentage mucoadhesion. For all batches, percentage of mucoadhesion ranged from 75–95% (Table 2).

CONCLUSION

A mucoadhesive microsphere was prepared by a spray drying technique. The release rate of the complex microspheres was significantly decreased with increase in the drug to polymer ratio. The results of the study indicate that HPMC K15 polymer is suitable for the development of mucoadhesive microspheres as a nasal drug delivery system and shows compatibility in formulation with Atenolol for antihypertensive action. The designed drug and polymer system also holds promise to further study i.e. in vivo studies leading to IVIVC for commercialization.

"Cite this article"

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