Review Article

Review on Formulation of Mucoadhesive Anti-Migrane Nasal Microsphere of Rizatriptan

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ABSTRACT

The aim of this investigation was to develop a mucoadhesive sustained release nasal drug delivery system of RIZA for direct nose to brain delivery and to release the drug across nasal mucosa in a controlled manner such that once a day therapy can be achieved by increasing the residence time of drug in to the nasal mucosa. The present investigation was to develop mucoadhesive sustained release microspheres for treatment of migraine which releases the drug up to 8 hrs. The starch microspheres were prepared with Span80 as surfactant & sodium-di-hydrogen orthophosphate as crosslinking agent through W/O emulsification – crosslinking method at 50˚C. Microspheres obtained were evaluated for size distribution, sphericity, drug loading, release properties, mucoadhesion etc. The microspheres obtained were of good sphericity and narrow size distribution. The drug entrapment was found to be 53% and invitro release was 89% .Furthermore, the release profile showed an initial burst release followed by sustained swelling-controlled release. Thus starch microspheres seem to be promising carriers for the selected antimigrain drug.

Keywords: mocoadhesive microsphere, nasal microsphere, starch based nasal microsphere.

INTRODUCTION

A Migraine is a very painful form of vascular headache. During a migraine attack,Enlargement of the temporal artery stretches the nerves that coil around the artery and cause the nerves to release chemicals, which cause inflammation, pain, and further enlargement of the artery. The increasing enlargement of the artery magnifies the pain. Sympathetic activity also delays emptying of the stomach into the small intestine and thereby prevents oral medications from entering the intestine and being absorbed. The impaired absorption of oral medications is a common reason for the ineffectiveness of medications taken to treat migraine headaches. The nasal mucosa presents an ideal site for Bioadhesive drug delivery systems. Microspheres of natural polymer presents ideal carrier system. Rizatriptan benzoate(RIZA) is an antimigrain 5HT1 receptor agonist. The conventional tablet of Rizatriptan has poor oral bioavailability and frequency of dosing is 3-4 times a day .Thus, nasal route was chosen to avoid first pass metabolism.

Drug : Rizatriptan benzoate
Polymer : Starch
Cross linking agent : Sodium-di-hyd-orthophosphate & sodium-tri-polyphosphate
Emulsifiers : Span 80, Tween 80
External Phase : Heavy Liquid Paraffin

The microspheres were prepared by singlestep emulsification and crosslinking method. Briefly, span 80 was added to liquid paraffin solution and heated at 50˚C, assembly was maintained. To it the aqueous solution of starch and sodium di hydrogen orthophosphate, containing drug was added. Stirring was continued for 4 hours at constant temperature. Later microspheres were washed and dried and stored in desicator for further analysis.

Microspheres obtained were evaluated for size distribution, sphericity, entrapment, drug release and mucoadhesion etc.

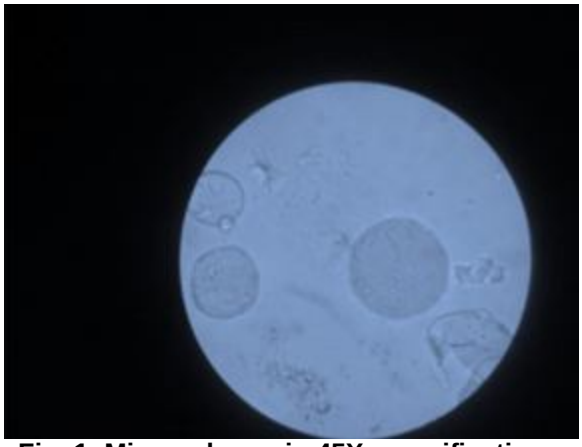

Fig. 1: Microspheres in 45X magnification

Evaluation Parameters for Microspheres
Particle Size and Size Distribution
The particle size was carried out by projection microscope.

Span factor = (d90-d10)/d50

The mean particle size was found to be 18.11µm. The SPAN Factor was found to be 0.8.
The particle greater than 10 µm are usually deposited in the nasal cavity. Particles that are in between 2 to 10 µm can be retained in the lungs.
The particle size distribution shows the suitability of the microspheres for nasal delivery.
The higher the SPAN value wider is the particle size distribution. The low SPAN value indicates the narrow distribution.

In-Vitro Mucoadhesion Testing
Percent mucoadhesion was determined by in vitro wash-off test. The assembly for the test is shown in the figure.

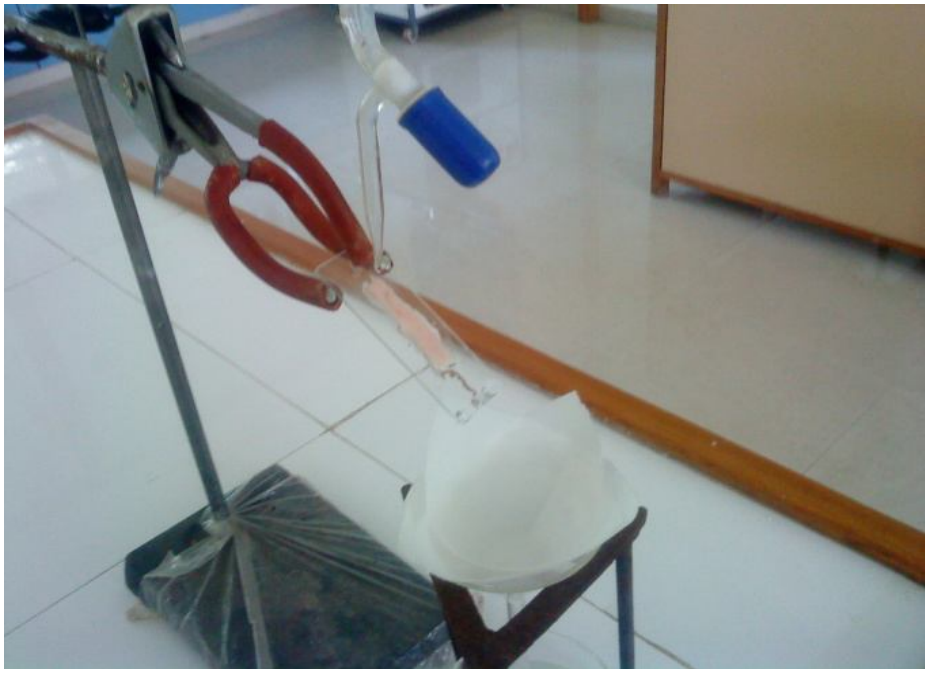

Fig. 2: In-Vitro Mucoadhesion Testing

The % mucoadheshion was calculated from the following formula:

$$\%\text{mucoadhesion} = \frac{\text{amount of microspheres retained in the tissue} * 100}{\text{Amount of microspheres taken}}$$

The percent mucoadhesive of the best batch was found to be 69 % at the end of the 5 hrs. Starch polymer is able to interact strongly with the nasal mucosa and other epithelial and other cells and the overlying mucus layer thereby providing a longer contact time for drug transport across the nasal membrane, before the formulation is cleared by the mucociliary clearance mechanism.Therefore the retention time of the drug can be enhanced by formulating it in a microsphere form.

% Drug Loading
Drug Entrapment Efficiency
Swelling Index
Swelling index was calculated by determining Mean particle size before as well as after swelling.

$$\text{Swelling index: } \frac{(Ds - Dd)}{Ds}$$

The swelling index of the best batch was found to be 0.134.
Starch polymer is able to absorb water from the site of application. The mucoadhesive and viscosity enhancing properties of starch may both increase the residence time and intimate contact of drug and nasal mucosa.

In-Vitro Drug Release Study

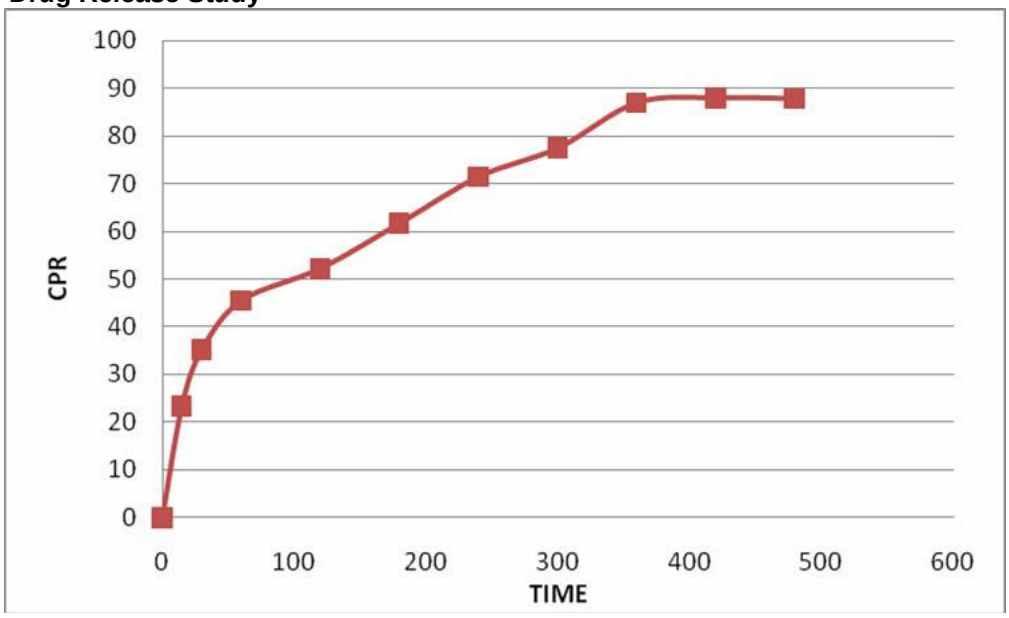

Fig. 3: In-Vitro Drug Release Study

In-Vitro Drug Permeability Study

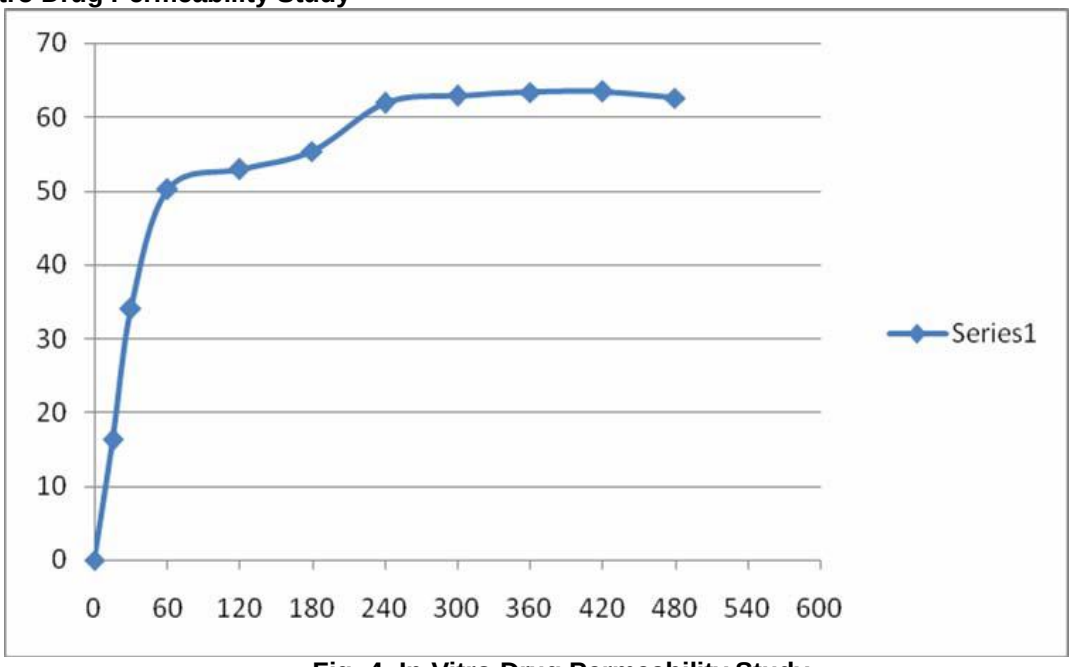

Fig. 4: In-Vitro Drug Permeability Study

Scanning Electron Microscopy (SEM)

It can be clearly shown that the microspheres are spherical in shape and there is minimum aggregation and size is within range.

Sphericity and aggregation of the microspheres is usually affected by the presence of the surfactant and concentration of the polymer solution. The SEM picture of microspheres indicates the proper optimization of the formulation parameters.

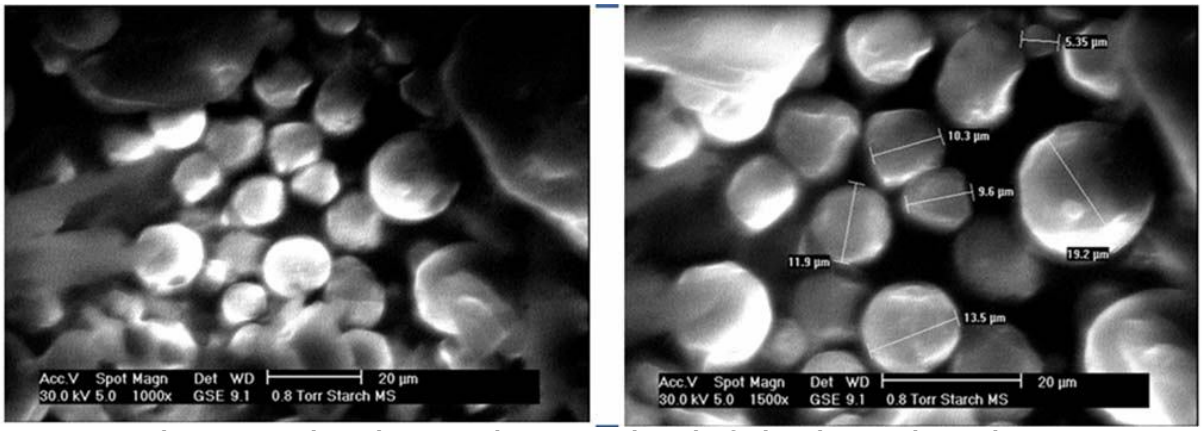

Fig. 5: Scanning Electron Microscopy (SEM) of Rizatriptan microsphere

Initially trials were done to obtain the desired formulation for microspheres with sustained drug release and least aggregation and to achieve the particle size between 10 to 50 µ, so as to accomplish the nose to brain delivery of RIZA. Further optimization was done for several parameters .including concentration of polymer, drug to polymer ratio amount of surfactant, crosslinking agent, stirring time ,stirring speed, temperature were optimized. The results indicated that microspheres with drug to polymer ratio of batch 1:5 were having good release and higher entrapment values.

CONCLUSION

The microspheres obtained were of good sphericity and appropriate size within the range with little aggregation. They showed 53% entrapment and 89% drug release and 65% drug permeability, and good mucoadhesion, Thus they seem to be promising carriers for selected antimigrain drug.

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