International Journal of Advances in Pharmaceutics
ISSN: 2320–4923; DOI: 10.7439/ijap
Volume 4 Issue 4 [2015]
Journal home page: http://ssjournals.com/index.php/ijap

Research Article

Preparation and evaluation of mucoadhasive microspheres of Propranolol HCl for nasal delivery

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Keywords:
Mucoadhesion;
Migraine;
Propranolol HCL;
Microsphere;
Bioavailability

Abstract

In the recent decades, the interest in intranasal route for drug delivery is increased as the nasal mucosa offers numerous benefits such as rapid systemic drug absorption and fast onset of action. Additionally, intranasal absorption avoids the hepatic presystemic metabolism and enhances drug bioavailability in comparison to that obtained after oral administration. Also, it offers patient ease being non invasive, offers favourable tolerability profile and it is also pharmaceutically economic as don't require sterilization. Propranolol HCl is the most commonly used β blocker drug for the prophylaxis of migraine. The problem with the oral route is low bioavailability (26%) due to pre-systemic metabolism. So, the aim of the work is to formulate and evaluate mucoadhesive microsphere of Propranolol HCl to increase its bioavailability and reduce its dose. Mucoadhesive microspheres increase the residence time of the drug by gel formation mechanism and hence improve bioavailability as compared to powder and liquid formulations. The prepared formulation was evaluated for particle size, shape and morphology, mucoadhesive strength, micrometric properties, *in vitro* drug diffusion study, entrapment efficiency and stability studies.

1. Introduction

Mucoadhesion is a topic of current interest in the design of drug delivery systems. The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer [1]. Microspheres can be described as small particles (in 1-1000 µm size range) for use as carriers of drugs and other therapeutic agents consisting of proteins or synthetic polymers which are biodegradable in nature. The term microsphere describes a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix or encapsulated [2]. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bioadhesion. Microspheres exhibit a prolonged residence time by intimate contact with the absorption site and produce better therapeutic action [3]. Generally microspheres possess potential to be employed for targeted and controlled release of drug, but incorporating mucoadhesive properties to microspheres will furthermore improve absorption and bioavailability of the drugs [4-7]. Mucoadhesive microspheres used in nasal drug delivery absorb water into sphere matrix, resulting in swelling of sphere and formation of gel.

The gel formation improves the nasal residential time and hence, improves bioavailability. Another mechanism stated for improving nasal bioavailability is improving the nasal permeation by opening the tight junction of nasal epithelium. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect [8,9].

Advantages of Mucoadhesive Microspheres [10]:

1. Provide sustained therapeutic effect.
2. Reduces the frequency of drug administration and thus improve patient compliance.
3. Improve the bioavailability of drug by improving absorption.

4. As drug dose is reduced, the chance of adverse effects also decreased.

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4-48 hr. There are dismal statistics that indicate that migraines are quite common. 25-30% of women and 15-20% of men occasionally get migraines. It is of two major types-

1. Classical migraine (migraine with aura)-headache is preceded by visual or other neurological symptoms.
2. Common migraine (migraine without aura)-it is not accompanied by any visual symptoms [11].

Propranolol is the first choice of drug for the prophylaxis of migraine. Propranolol, a beta blocking drug, seems to be an effective prophylactic for common and classic migraine. Antimigraine effect results from inhibition of vasodilation, the presence of β-adrenergic receptors in pial vessels of the brain [12].

The problem with the oral delivery of Propranolol is its low bioavailability (26%) due to pre-systemic metabolism. To overcome this problem, propranolol can be delivered via nasal route. Propranolol has been showed to be absorbed effectively via the nasal route with bioavailability comparable to those for the intravenous route of administration [13-15].

In this work an attempt was made to formulate mucoadhesive microsphere of Propranolol HCL for nasal delivery.

2. Material and Methods

Propranolol HCl was obtained as a gift sample. *Sodium tripolyphosphate*, Chitosan were obtained from Central Drug House, Delhi. All the reagents and chemicals used were of analytical grade.

2.1 Preparation of mucoadhesive microsphere of propranolol HCl

Mucoadhesive microspheres of Propranolol HCl were formulated using Ionotropic gelation method. STPP solution (25 ml) of different concentrations (1- 4 % w/v) was prepared in distilled water and taken in the beaker (250 ml). Drug was dissolved in Chitosan solution in 1:1 proportion. Drug polymer mixture (10 ml) was added dropwise to the *Sodium tripolyphosphate* solution (using 22 guage needle) with continuous stirring using mechanical stirrer at 1000 rpm for 1 hr at room temperature. The prepared microspheres were decanted, washed with distilled water to remove excess of STPP, filtered and dried at room temperature for 24 hrs, as shown in Table no.1

Table no. 1: Preparation of Different batches of Mucoadhesive microspheres of Propranolol hydrochloride

Formulation no.	Chitosan concentration in 1.5 % v/v acetic acid (%w/v)	STPP in distilled water (%w/v)	Drug : Polymer
F1	1	3	1:1
F2	1	4	1:1
F3	1.5	1	1:1
F4	1.5	2	1:1

2.2 Evaluation of prepared mucoadhesive microspheres

2.2.1. Particle Size

The prepared slide of microspheres was examined by an optical microscope and size of the microsphere was measured using the pre-calibrated occular micrometer (at 40x magnification). About 25 microspheres of each formulation were observed and average particle size was determined. Higher STPP conc. leads to the formation of small size particles upto a certain limit which may be due to high anionic concentration. as shown in Table no.2.

2.2.2. Shape and surface morphology

Shape and surface morphology of prepared microspheres were observed in Leica EC 3. The prepared slide was observed at 4x and 40x magnification, as shown in Figure no.1and 2.

2.2.3. Percentage Yield

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch divided by the sum of the initial weight of polymer and drug. The percentage yield of F4 was found out to be maximum, followed by F2, F3 and F1. Formulation F4 showed best yield of 69.48%. The loss of material during preparation of microspheres was due to process parameters. as shown in Table no.3

2.2.4. Entrapment Efficiency

20 mg microspheres of Propranolol hydrochloride were crushed in a glass mortar and pestle and the powdered microspheres were suspended in 25 ml of phosphate buffer saline pH 6.4. After 24 hours, the solution was centrifuged at 4000 rpm for 10 min. and filtered. 0.2 ml of the filtrate was pipette out and further diluted to 25 ml and analyzed for the drug content using UV spectrophotometer at 290 nm. Entrapment efficiency of the formulations containing 1.5%w/v of

chitosan (i.e, F3 and F4) were higher than that of the formulations having 1%w/v of chitosan (i.e, F1 and F2), as shown in Table no.4

2.2.5. Swelling index

20 mg microspheres (W) were weighed and placed in phosphate buffer saline pH 6.4. At every 1 hour interval, the microspheres were collected and blotted to remove excess of water and their weight (Wt) was noted. It was noticed that with respect to time, formulations F3 and F4 with higher polymer concentration (1.5%w/v) showed higher swelling and maintained their integrity till 4 hrs unlike formulations F1 and F2 with 1% w/v polymer concentration which lost their integrity after 3 hrs. This may be because the density of former was greater and so the rate of solvent penetration was less in it but for longer duration as compared to the later. The swelling index was also found to be dependent on the surface area of particle. As the particle surface area increased, the swelling index was also found to be increased as shown in Table no.5.

2.2.6. Mucoadhesive Test

The *in vitro* mucoadhesion study of microspheres was assessed using falling liquid film technique. A strip of goat nasal mucosa was mounted on a glass slide and 25 mg of accurately weighed microspheres were sprinkled on the nasal mucosa. This glass slide was incubated for 15 min to allow the polymer to interact with the membrane and finally placed at an angle of 45°. Phosphate buffer saline pH 6.4 was allowed to flow over the membrane at the rate of 1 ml/min for 5 min with the help of a burette. The effluent was collected on a watch glass. At the end of this process, the detached particles collected, were dried and weighed the mucoadhesion was also found to be dependent on the surface area of particle. As the particle surface area increased, the mucoadhesion was also found to be increased as shown in Table no.6.

2.2.7. *In- vitro* Drug Release study

Drug release from the microspheres was carried out using modified diffusion cell. 50 ml Phosphate buffer solution pH 6.4 was taken in 250 ml beaker and used as the release medium. The semi permeable membrane (cellulose nitrate membrane, pore size 0.45µm and 47 mm in diameter) was soaked in a buffer for 6-8 hours for activation. A weighed amount of microspheres containing equivalent to 20 mg of Propranolol HCl, were suspended using pre-activated semipermeable membrane in the release media. The release media was stirred on a magnetic stirrer at 50 rpm and was maintained at 37±2ºC. 1 ml sample was withdrawn at every 1 hr interval and diluted upto 10 ml using 6.4 pH buffer solution and absorbance of the resulting solution was measured at 290 nm in a double-beam UV spectrophotometer using the release medium as blank. The volume of the release medium was adjusted every time by adding 1 ml of buffer to it. The study was carried out for 7 hrs.

In vitro drug release of F4 was more than F3 irrespective of high entrapment efficiency of F3. This may be due to high surface area and high swelling index of F4 than F3. F4 showed maximum release of 71.42 % in 7 hrs as shown in Table no.7. The drug release kinetic was studied using different kinetic models (Zero order, First order, Higuchi and Korsemeyer peppas kinetic model)

The regression value of each of these release kinetics were calculated and compared. The data revealed that the release pattern of formulation best fitted for Higuchi release kinetic as shown in Table no.8.

3. Result and Discussion

3.1 Particle size

The microspheres were in the size range of 29.87±1.17 to 47.09±1.17 µm. The particle size was found to be more dependent on the crosslinking agent concentration than on polymer concentration. Higher STPP conc. leads to the formation of small size particles upto a certain limit which may be due to high anionic concentration. Particle size of formulations is shown in Table no. 10. Formulation F4 among different formulations was most appropriate formulation with particle size of 38.91±0.98 µm, which is appropriate for nasal administration.

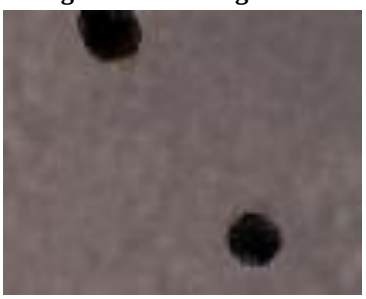
Table no. 2: Particle size of different formulations

Formulation Code	Particle size (µm)
F1	34.09±1.32
F2	29.87±1.77
F3	47.09±1.17
F4	38.91±0.98

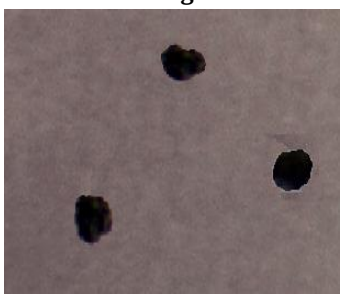
3.2 Shape and surface morphology

The images of different formulations (F1, F2, F3 and F4) were taken from Leica at 4x. F4 formulation was observed to be more uniform in shape (Figure no. 1 and 2).

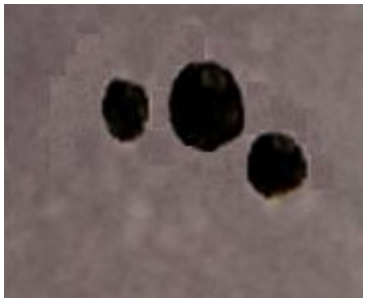
Figure no. 1: Images of formulation F1, F2, F3 and F4 at 4x magnification



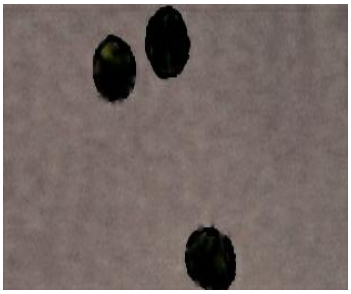
F1



F2

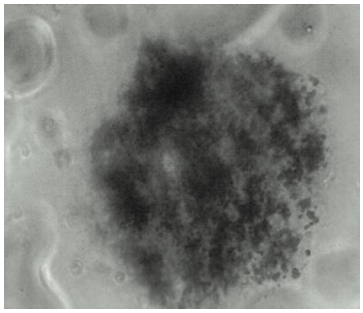


F3



F4

Figure no.2: F4 at 40X magnification



3.3 Percentage yield

It was observed that an optimum concentration of polymer and crosslinking agent is required, below or above this concentration microspheres are not formed. The percentage yield of different formulations is shown in Table no.3. The percentage yield of F4 was found out to be maximum, followed by F2, F3 and F1. The percentage yield was found to be in the range of 54.71% - 69.48%. Formulation F4 showed best yield of 69.48%. The loss of material during preparation of microspheres was due to process parameters.

Table no. 3: Percentage yield of Propranolol HCl formulations

Formulation Code	Percentage Yield (%)
F1	54.71 %
F2	63.67 %
F3	59.02 %
F4	69.48 %

3.4 Entrapment efficiency

The values obtained for entrapment efficiency of the formulations is shown in Table no. 4. It may be roughly concluded that the entrapment efficiency is affected by polymer concentration. Entrapment efficiency of the formulations containing 1.5%w/v of chitosan (i.e, F3 and F4) were higher than that of the formulations having 1%w/v of chitosan (i.e, F1 and F2). It was observed that with the increase in polymer concentration the entrapment efficiency.

Table no.4: Entrapment efficiency of all formulations

Formulation code	Entrapment efficiency (%)
F1	60.46
F2	58.15
F3	71.88
F4	69.06

3.5 Swelling property

Swelling Index of the formulations are given in Table no. 5. It was noticed that with respect to time, formulations F3 and F4 with higher polymer concentration (1.5%w/v) showed higher swelling and maintained their integrity till 4 hrs unlike formulations F1 and F2 with 1% w/v polymer concentration which lost their integrity after 3 hrs. This may be because the density of former was greater and so the rate of solvent penetration was less in it but for longer duration as compared to the later. The swelling index was also found to be dependent on the surface area of particle. As the particle surface area increased, the swelling index was also found to be increased.

Table no. 5: Swelling index of prepared formulations

Formulation code	Swelling Index (%)			
	1 hr	2hr	3hr	4hr
F1	22.15	36.81	44.96	-
F2	25.66	38.94	47.28	-
F3	19.26	32.58	43.91	65.85
F4	20.78	34.42	46.83	68.74

3.6 Mucoadhesion test

The result of mucoadhesion test is shown in Table no. 6. The result observed indicate that the mucoadhesive strength increases with increase in the polymer concentration. Mucoadhesive strength was more in formulations containing 1.5 % w/v polymer concentration (i.e. F3 and F4) than in formulations with 1% w/v polymer concentration (i.e. F1and F2). The mucoadhesion was also found to be dependent on the surface area of particle. As the particle surface area increased, the mucoadhesion was also found to be increased.

Table no. 6: Mucoadhesion properties of formulations

Formulation code	Mucoadhesion (%)
F1	71.57
F2	72.24
F3	78.48
F4	81.62

3.7 *In vitro* drug release study

In vitro drug release study was carried out for F3 and F4 formulation (Table 7) as their entrapment efficiency, swelling index and mucoadhesion was better than F1 and F2. F4 showed maximum release of 71.42 % in 7 hrs and so its drug release was studied using different kinetic models (Zero order, First order, Higuchi and Korsemeyer peppas kinetic model) shown in Table no. 8. *In vitro* drug release of F4 was more than F3 irrespective of high entrapment efficiency of F3. This may be due to high surface area and high swelling index of F4 than F3.

From the drug release study of F4, release kinetics was studied using Zero order, First order, Higuchi release kinetic and Korsemeyer peppas kinetic model. The regression value of each of these release kinetics were calculated and compared. The data revealed that the release pattern of formulation best fitted for Higuchi release kinetic.

Table no. 7: *In vitro* percentage drug release profile of mucoadhesive microspheres of Propranolol HCl formulation code F3 and F4.

Time (hours)	% Drug release	
	F3	F4
1	5	5.29
2	14.9	19.58
3	25.57	34.05
4	31.78	42.66
5	36.8	53.45
6	45.94	63.95
7	50.44	71.42

Table no. 8: Regression co-efficient (r^2) values of different kinetic models for formulation F4.

Release kinetics Model	Regression value (r^2)
Zero order	0.992
First order	0.981
Higuchi	0.997
Peppas	0.968

4. Conclusion

Mucoadhesive microspheres of Propranolol hydrochloride for intranasal systemic delivery were developed by using ionotropic gelation method with the aim to avoid first pass metabolism, to improve the patient compliance, to use an alternative therapy to conventional dosage form, to achieve controlled blood level profile of drug and to improve the therapeutic efficacy of propranolol hydrochloride as a prophylactic for migraine.

Chitosan was the mucoadhesive polymer used and Sodium tripolyphosphate was used as the polyanionic solution. The prepared microspheres were evaluated for different parameters.

Formulation F4 showed best results among the formulations made. Particle size of formulation F4 was found to be 38.91±0.98µm, which is appropriate for nasal administration. Percentage yield of F4 was 69.48%. The entrapment efficiency, swelling index and mucoadhesion values for formulation F4 were 69.06 %, 68.74 % and 81.62 % respectively. Formulation F4 showed maximum *in vitro* drug release of 71.42 % in 7 hrs. The release kinetics best fitted Higuchi model. From the interaction study of formulation using FTIR, no interaction was found between the drug and excipients. The characteristic peak of STPP and chitosan were found to be shifted, which showed the interaction between chitosan and STPP.

From the studies, it can be concluded that the nasoadhesive microspheres present a better alternative for the controlled delivery of Propranolol HCl.

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