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Research Article

Chitosan Based Mucoadhesive Buccal Patches Containing Bisoprolol Fumarate

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ABSTRACT

The aim of the present work is to investigate the formulation of Bisoprolol fumarate buccal patches for controlled release medication in order to treat blood pressure and cardiac diseases. The half life of Bisoprolol fumarate is 10 hrs. Bisoprolol fumarate is used to treat the angina pectoris which required 24hr controlled drug release and to avoid degradation of drug in GIT. The buccal patches were prepared by solvent casting method using chitosan. The patches were found to be smooth in appearance, uniform in thickness, weight uniformity, drug content, swelling index, folding endurance, surface pH and in vitro diffusion study using Franz diffusion cell. The optimized patch of 2% chitosan exhibit in vitro release of 94% through cellophane membrane. The patches were stable at a temperature range of 2-30^{0}C.

Keywords: Bisoprolol fumerate, buccal patch, diffusion, in vitro.

INTRODUCTION

Bisoprololfumarate (BPL) is a beta adrenergic blocking agent, used to treat cardiac disease. BPL is already available in the market as 5mg, 10mg, and 20mg tablet. The drug has a half life of 10 hrs and shows a bio availability of more than 80 percentages. Even though the drug has relatively high bio availability and half-life, the controlled release formulation has its own significance for improving the onset of action, release characteristics and reducing the side effects. The polymer used in this investigation are chitosan. . Chitosan is a natural bio compatible and bio degradable polymer, extensively used in the development of mucoadhesive buccal drug delivery. Chitosan as a biodegradable polymer has proved its ability as the safest and efficient material for the development of novel drug delivery system for various drug molecules. Due to its inherent properties this is one of the preferred polymer for the formulation developers. Chitosan has an excellent film forming ability and better muco adhesive property. the mucoadhesive property of chitosan either due to its ability to form secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged mucin. Apart from this chitosan has a cell binding and membrane permeation activity. So in this investigation, an attempt has been made to develop a mucoadhesive bucal patches of Bisoprolol fumarate by using chitosan, thus expecting a modified release characteristics of the drug for the better treatment for hypertension and angina pectoris.

MATERIALS AND METHODS

Bisoprolol fumarate (BPL) was obtained as a gift sample from Chethana Pharmaceuticals, Kerala, chitosan was obtained from Balaji chemicals, Gujarat.All other reagents and chemicals were of analytical or pharmaceutical grade.

Preparation of bisoprolol fumarate buccal patches[3]

The buccal patches containing BPL were prepared by solvent casting method with required modification (Table No.1). The desired percentage of chitosan was

dissolved in 1% acetic acid by stirring in a mechanical stirrer for 2 hours. This solution was filtered through a muslin cloth to remove debris. The above solution was added with calculated amount of BPL and10 % ethanol and stirred in a mechanical stirrer for 2 hours. This solution was kept overnight to remove air bubbles and poured in to a glass mould having a surface area of 40 cm^2, to which glycerin added as plasticizer. It was dried in an oven at 45^0C, cut in to desired size, and packed in to aluminium foil for further studies.

Folding Endurance[4,5]

Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Patch thickness[6]

The thickness of the buccal patch was measured by using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Weight variation

Ten patches of $1cm^2$ were weighed individually and average of those patches measured.

Surface pH [7,8,9]

Buccal patches were left to swell for 1 hour on the surface of 2% agar plate, it was allowed to stand until it is solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

% Swelling Index[10,11]

The developed buccal patches were cut in to small sizes of 1.5 cm diameter. This patch was placed on the surface of 2% agar plate and the diameter at different time intervals where taken up to 5 hrs and the percentage swelling index was calculated using the formula,

$$\% SD = \frac{Dt - Do}{Do} \times 100$$

Where, % SD = % swelling by diameter method
D_t = diameter of swollen patch after time t
D_o = original patch diameter.

% Moisture content[4,5]

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the patches were taken out and weighed. The moisture content (%) was determined by the formula:

$$\% \text{ Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Tensile Strength[12,13]

The instrument used to measure the tensile strength was designed in pharmaceutics laboratory especially for this project work. The instrument is a modification of chemical balance used in the normal laboratory. One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan as shown in the figure.

$$\text{Tensile strength, } T = \frac{Mxg}{Bxt} \text{ Dynes/cm}^2$$

T= force at break/ initial cross-sectional area of sample.

Where,
M = mass in grams
g = acceleration due to gravity 980 cm/sec^2
B = breadth of the specimen in cm
t = thickness of sample in cm.

%Drug content[14,15,16]

Prepared buccal patch was dissolved in 100ml of Phosphate buffer solution (PBS) of pH 6.8 using a magnetic stirrer for 12 hours and then sonicated for 30 minutes. The solution was centrifuged and then filtered. The drug content determination was done by using UV spectroscopy at 223 nm.

In vitro diffusion study[17.18]

In vitro diffusion study was performed by using modified franz diffusion cell across cellophane membrane. Phosphate buffer solution (PBS) of pH 6.8 was used as medium for diffusion study. Patches of dimension $2x2cm^2$were placed on the membrane, which was placed between donor and receptor compartment of franz diffusion cell. Cellophane membrane was brought in contact with PBS of pH 6.8 filled in receptor compartment. Temperature was maintained at 37^0C with stirring at 50 rpm using magnetic beed stirrer. 1ml of sample was withdrawn from receptor compartment at pre-determined interval and was replaced with fresh PBS of pH 6.8.

With suitable dilution, samples were measured for absorbance at 223nm using UV visible spectrophotometer.

Stability study[19,20]

Stability studies were performed in accordance with ICH guidelines for accelerated stability testing. Patches (2x2 cm^2) were wrapped individually in aluminium foil and maintained at refrigerated temperature(4 ± 2^0C), room temperature(30 ± 2^0C) and oven temperature ($45\pm2°C$) and 75 $\pm$ 5% RH for a period of 1 month. Changes in the appearance and drug content of the stored patches were investigated after storage period.

RESULTS AND DISCUSSION

The results of evaluations were summarized in table (Table No.2). The developed chitosan patches were smooth and flexible. All the characteristics such as folding endurence, thickness average weight, % swelling index, moisture content, tensile strength and % drug content were increased with increase in concentration. The reason behind this is, at higher concentration the more polymer chain with flexible nature may be available, which resulted in higher folding endurence value[22]. It was already proved by the researchers that, the thickness, average weight, % swelling index, moisture content and tensile strength will increases with increase in concentration of polymer[23,24]. The surface pH value indicating that the patches may not produce any irritation to oral mucosa and safer for application[25]. The % drug content was higher with F2, this may be due to higher entrapment efficacy of chitosan polymer at higher concentration[24].

The diffusion data obtained for the buccal patches containing BPL with different concentrations of chitosan were closely assessed. The % drug diffused was plotted against time (Table No.3 and Fig No.1). The % drug diffused from formulation F1 and F2 were found to be 83.66% and 93.96% respectively after 12 hours diffusion (Table No.3). From the data it can be assumed that the %drug diffused from formulation F2 containing 2% chitosan had approximately 13% greater release than formulation F1. Since both the formulation containing equal amount of ethanol (ie, 10%), the role of ethanol as a permeation enhancer cannot be emphasized in this study. But the possibility of ethanol influence on the diffusion pattern may not be neglected. When ethanol combines with the optimum level of polymer, there may be a possibility of good initial burst release as well as better diffusion profile for a drug such as BPL. This may be a possibility for improved release profile of formulation F2. Apart from this, chitosan possess inherent permeation enhancing property, which might have resulted in a synergistic effect with 10% ethanol incorporated in formulation for improved release properties of chitosan based buccal patch[26]. After good initial burst release from F2, good controlled release profile was maintained for the entire duration of investigation. This may be due to the natural polymeric structure of chitosan which might have been reflected in F2 with 2% chitosan.

Accelerated stability studies were performed in accordance with ICH guidelines with necessary modifications. The studies were carried out to verify the changes in physical characteristics such as color, thickness, folding endurance and pH along with changes in % drug content at three different conditions of higher temperature (45 ± 2^0C), room temperature (30 ± 2^0C), and refrigeration temperature (4 ± 2^0C).After the completion of one month, formulation F1 with 1% chitosan had 95.90±0.05% of drug content reported at room temperature, with a minor decrease during the storage at refrigeration temperature of 4 ± 2^0 C. But when the drug content was estimated for F1 at oven temperature, the drug content dropped significantly to 76.30±0.05%. Similar drop in %drug content were observed in case of formulation F2 when kept at higher temperature. Loss in % drug content was found to be minimum in case of formulation of F2 with 2% chitosan. (Table No.4).

Table 1: Composition of formulations

Ingredients	Formulation code	
	F1	F2
Bisoprolol fumarate	100	100
Chitosan(%) in acetic acid 1%	1 %	2%
Ethanol 10%	1	1
Glycerine	0.5	0.5

Table 2: Characterization of developed formulations

FORMULATION CODE	F1	F2
Appearance	mooth	mooth
Texture	exible	exible
Folding endurance	90±2	10±2
Thickness(mm)	6±0.1	7±0.2
Average weight (mg)	10.8	11.3
Surface pH	6.5	6.7
Swelling index(after 5 hours)	30	36
% Moisture content	1.4	1.7
Tensile strength (Kg/cm2)	7±0.02	5±0.03
% Drug content	96.05	98.79

Table 3: Comparison of % drug diffused from formulation F1 and F2

Time (hrs)	% Drug diffused	
	F1	F2
0	0	0
0.5	8.83	11.95
1	16.78	25.5
2	25.41	33.4
3	34.10	40.36
4	42.04	49.91
5	50.31	62
6	61.84	74.73
8	77.15	89.17
12	83.69	93.96

Table 4: Stability study data of developed formulation F1- F6

Formulation code	Physical appearance			% Drug content		
	4 ± 2^0C	30 ± 2^0C	45 ± 2^0C	4 ± 2^0C	30 ± 2^0C	45 ± 2^0C
F1	++	+	+++	95.58	95.90	76.30
F2	+	+	++	98.60	98.75	84.5

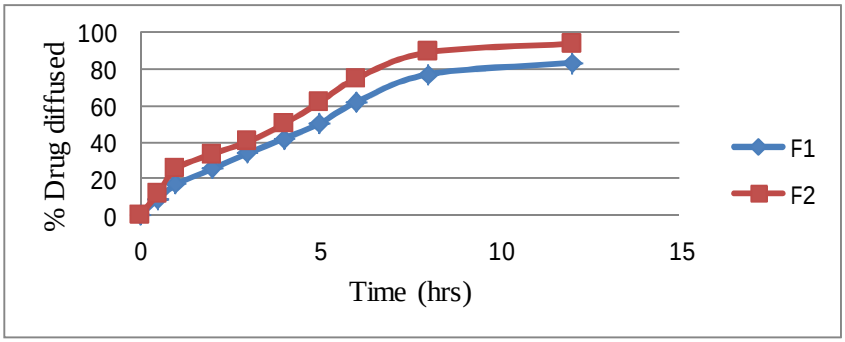

Fig. 1: Comparison of % drug diffused from F1 and F2

CONCLUSION

This investigation established the effectiveness of chitosan as a polymer to develop buccal patches containing bisoprolol fumerate. The results shown that buccal patches developed using chitosan were showing excellent characteristics which was ideally required for buccal patches,. More or less the patches were stable at varying conditions. In vitro diffusion profile of bisoprolol fumerate from chitosan was showing good initial burst release along with excellent controlled release profile for 12 hours duration. Based on investigation results, it may be suggested that 2% is the optimum concentration to develop a good buccal patch containing bisoprolol fumerate. Design and development of such buccal patches may be highly beneficial which can deliver drug up to a period of 12hrs duration. Hence application of buccal patches may ensure sufficient level of Bisoprolol fumarate in the body to avoid the possible angina attack for hypertensive patients. Further clinical investigations may be recommended for Bisoprolol fumarate buccal patches with chitosan to substantially prove its ability as a safe, stable and effective drug delivery system.

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