INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

FORMULATION AND EVALUATION OF BISOPROLOL FUMARATE BUCCAL PATCHES BY USING SELECTED POLYMERS

Sarath chandran C*, KV. Shijith, KV . Vipin and Ann Rose Augusthy

Department of Pharmaceutics, Academy of Pharmaceutical Sciences,

Pariyaram- 670 503, Kannur, Kerala, India.

ABSTRACT

This investigation mainly focused on the ability of polymer to release the Bisoprolol fumarate in a controlled pre determined manner. The polymers selected for the investigation include chitosan. HPMC, and sodium CMC. The polymers were selected on the basis of their property. The muco adhesive buccal patches were prepared by solvent casting method with appropriate modification. The prepared patches were subjected to physical evaluations, invitro diffusion study, and stability study. The result obtained was satisfactory with all the formulation, but, the patches prepared with 2% chitosan showed a better invitro diffusion result as it can diffuse 96% of drug within 12 hour of the therapy. The result of physical evaluation and stability study indicating that the Bisoprolol buccal patches with 2% chitosan could effectively treat the possible anginal attack and hypertension.

Keywords: buccal patches, mucoadhesion, chitosan, HPMC, sodium CMC.

INTRODUCTION

Extensive effort has been made to focused on targeting a drug or drug delivery system in a particular region of the body not only for targeting of drug, but also for better systemic delivery. One amongst the best was mucoadhesive buccal drug delivery. Mucoadhesive are synthetic or natural polymer that can effectively interact with the mucin layer, thus offers better results. Various polymers are under investigation as carrier for buccal drug delivery.

In this investigation three polymers, chitosan, HPMC and sodium CMC, were selected on the basis of their property. Chitosan is a natural bio compatable and bio degradable polymer, extensively used in the devolopement of mucoadhesive buccal drug delivery. Chitosan has a an excellent filim 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. Appart from this chitosan has a cell binding and membrane permeation activity[21].

HPMC is a semisynthetic cellulose derivative, biocompatable, has a variety of application in novel drug delivery systems including mucoadhesive property. The property of HPMC to form a strong, flexible filim, made the polymer to use in this investigation. It is stable over a pH range of 3 to 11. Apart from this HPMC has the ability to absorb water and swell, there by enhancing the thickness of the filim, thus an ideal candidate for mucoadhesive buccal systems[1,2,21].

The other polymer used in this investigation is sodium CMC, other cellulose derivative, biocompatable polymer, already proven its ability to form better mucoadhesive buccal drug delivery system. It is an anionic polymer made by swelling cellulose with NaOH and then reacting it with monochloroacetic acid. It is stable over a pH range of 4 to 10. The thixotropic behaviour of the

CMC solution made this polymer as an ideal candidature for this study[1,2,21].

This investigation mainly focused on the ability of polymer to release the Bisoprolol fumarate (BPL) in a controlled pre-determined manner. Bisoprolol fumarate is a beta adrenergic blocking agent, used to treat cardiac disease. Bisoprolol 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 percentage. 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.

MATERIALS AND METHODS

Bisoprololfumarate (BPL) was obtained as a gift sample from Chethana Pharmaceuticals, Kerala, chitosan and sodium CMC were obtained from Balaji chemicals, Gujarat, HPMC was obtained from Otto kemi, Mumbai. 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. The desired percentage of polymer (chitosan, HPMC or sodium CMC) 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.
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^{0}C 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^{0}C), room temperature(30±2^{0}C) and oven temperature (45$\pm$2°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
Buccal patch is a category of controlled DDS in which the release of drug was controlled in a pre-determined rate by using suitable polymeric systems. All the selected polymers were well established for designing various novel drug delivery systems. 1% acetic acid (AA) was used as solvent for developing the formulations. The concentrations for selected polymers and AA were optimized during the investigation (Table No.1). 10% ethanol was incorporated as the permeation enhancer for all the developed patches and glycerin was selected as plasticizer. Developed patches were cut in to suitable size and packed in aluminum foil and used for further evaluations.
The visual inspection confirmed that the prepared patches had satisfactory physical attributes in terms of color and clarity. Patches developed using chitosan had pale yellow in color, whereas the HPMC and sodium CMC based patches had white colour. In spite of the application of heat during the development of the formulations, colour of developed patches were almost same as that of pure polymers incorporated[22]. The results of physical characteristics were satisfactory for a buccal patches developed using selected polymers.
Folding endurance for developed buccal patches were ranging between 165-255 for all the developed patches (Table No.2). Lowest folding endurance was calculated for the patches prepared using sodium CMC, where highest folding endurance of 255 was obtained for HPMC based patches. All the patches, irrespective of polymers used, showed good folding endurance and ensured good flexibility[23].
All the developed patches had a thickness in between 0.5-0.7mm (Table No.2). Data for patch thickness were matching with the desired level of thickness for buccal patches. The average weight of drug loaded patches was calculated to ensure the weight uniformity[24]. Data obtained during evaluation of weight variation proved the uniformity of contents in the developed formulations. Higher the weight variation, higher will be the variation in contents which make the formulation therapeutically unacceptable[25]. The average weight obtained for the patches were ranging between 9.8-10.8 mg. The patches prepared using sodium CMC (F3) had the lowest average weight in comparison with patches developed using other two polymers, this may be due to the lower molecular weight of sodium CMC in comparison with HPMC and chitosan.

The surface pH for the developed formulations were approximately 7.0(Table No.2). The pH at mucosal surface is approximately 6.8. The pH between 6.5-6.7 of the developed patches indicates that the patches may be safe enough for the regular application in the mucosal region. The % swelling index were calculated after 5 hours and recorded highest for sodium CMC and lowest for chitosan. Since chitosan is a natural bio degradable polymer, which takes much time to swell in the AA medium and erode slowly which might have reflected through low swelling index value. The swelling property of chitosan may contributes to its improved release profile as a controlled release formulation. No significant difference was found between the patches in terms of moisture content.

Tensile strength value of chitosan based formulations were 2.87-2.95 kg/cm^2 which was highest in comparison with other formulations. Tensile strength proves the resistance power of the patch from breaking apart. The high tensile strength of chitosan may be due to the nature of polymeric chain present in the structure of chitosan. Lowest average tensile strength was recorded for sodium CMC based buccal patches. Drug content of more than 90% in the formulation shows the high amount of drug present in the formulation, without causing any change in the ideal property of buccal patches Highest % drug content was calculated for formulation F1 which was chitosan based, lowest %Drug content was obtained for HPMC based formulation F2. The high % Drug content of chitosan may be due to the high molecular weight of the chitosan as compared to HPMC and sodium CMC which results in high entrapment efficiency of drug within the polymer structure of chitosan.

The in vitro diffusion study may be used as an indirect measurement of drug solubility, especially in the preliminary assessment of formulation factors and manufacturing methods that are likely to influence the bioavailability. In vitro diffusion study was carried out using modified franz diffusion cell across cellophane membrane using PBS of pH6.8 as medium. When the diffusion profile for F1,F2 and F3 were cross compared, the diffusion profile of F2,ie 2% chitosan buccal patches showed much improved results in comparison to F4 and F6. During the initial stages of the diffusion study ,ie within 1 hour, 25% of drug has been diffused from F2. % Drug diffused from F2 after 1hour was much higher than the % diffusion of drug from formulation F4 and F6. This data proves that BPL may experience good initial burst release when formulated as buccal patch with 2% chitosan. The diffusion data obtained was impressive when compared with % drug release profile of US patented multiparticulate tablet of BPL which is already existing in US market[26]. After the good initial burst release, the formulation F1 showed a controlled release profile upto a period of 12 hour. At the end of 12th hour of the diffusion study, the % drug diffused from F1 was 93.96, at the same period of study, F2 and F3 had 87.09% and 78.77% drug diffused (Table No.3) & (Fig No.1). Since HPMC and sodium CMC, being a semisynthetic derivative of cellulose, when these polymers comes in contact with saliva forms a gelatinous barrier layer at the surface of patches, which may result in its lower rate of diffusion in comparison with chitosan based buccal patch[27,28]. Apart from this, chitosan possess inherent permeation enhancing property[29], which might have resulted in a synergistic effect with 10% ethanol incorporated in formulation for improved release properties of chitosan based buccal patch.

There was no significant change reported in colour, thickness, and pH of all the developed formulations at the end of one month period irrespective of the temperature difference (Table No.4). The % drug content calculated for formulation F1 was 84.5± 0.04% which was much better than the other formulations during the study hence chitosan may be the best suitable polymer to design and develop a stable buccal patche containing BPL. Based on available results, these developed buccal patches may be more stable between a temperature range of 0-30^{0}C, whereas higher temperature may cause deleterious effect on patches.

Table 1: Composition of formulation

Ingredients	Formulation code		
	F1	F2	F3
Bisoprololfumarate	100	100	100
Chitosan(%) in acetic acid 1%	2%	-	-
HPMC(%) in acetic acid 1%	-	2%	-
Sodium CMC(%) in acetic acid 1%	-	-	2%
Ethanol 10%	1	1	1
Glycerine	0.5	0.5	0.5

Table 2: Characterization of developed formulations

FORMULATION CODE	F1	F2	F3
Appearance	Smooth	Smooth	Smooth
Texture	Flexible	Flexible	Flexible
Folding endurance	210±2	255±3	185±2
Thickness(mm)	0.7±0.2	0.6±0.2	0.6±0.2
Average weight (mg)	11.3	10.8	10.1
Surface Ph	6.7	6.6	6.6
%Swelling index (after 5 hours)	36	34	35
% Moisture content	1.7	3.3	2.5
Tensile strength (Kg/cm^2)	2.95±0.03	2.65±0.03	2.61±0.02
% Drug content	98.79	94.52	95.01

Table 3: In vitro diffusion data of developed formulations

TIME (Hrs)	% Drug diffused		
	F2	F4	F6
0	0	0	0
0.5	11.95	8.35	7.47
1	25.5	16.07	14.95
2	33.4	28.68	21.66
3	40.36	36.48	27.13
4	49.91	45.58	38.4
5	62	55.43	45.99
6	74.73	60.63	61.1
8	89.17	81.52	72.24
12	93.96	87.09	78.77

Table 4: Stability data of all formulation

Formulation code	Physical appearance			% Drug content		
	4±2⁰C	30±2⁰C	45±2⁰C	4±2⁰C	30±2⁰C	45±2⁰C
F1	+	+	++	98.60	98.75	84.5
F2	++	+	+++	93.58	93.95	71.11
F3	++	+	+++	94.35	94.85	72.95

+ - no change, ++ - marginal change, +++ - significant change.

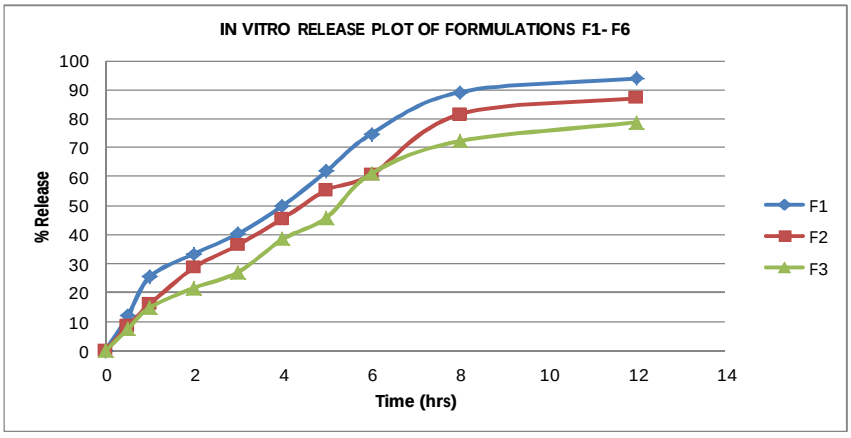

Fig. 1: In vitro diffusion plot of developed formulation F1- F3

CONCLUSION

The above investigation reveals that the property of developed patches greatly depends on the nature of the selected polymer use in the formulations. From overall investigation data, it can be concluded that 2% chitosan may be the best polymer to develop a stable mucoadhesive patches to deliver Bisoprololfumarate. 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 at bed time may assure maximum concentration of Bisoprolol fumarate in the early mornings, which can avoid the possible angina attack for hypertensive patients.

REFERENCES

1. Sarathchandran.C, Shijith.k.v, A conscise insight on mucoadhesivebuccal drug delivery system, Lamb.Acad.Pub.2012: 1-65
2. KV. Shijith, SarathChandran C, KV. Vipin, Ann Rose Augusty, K. Premaletha, A review on basics behind development of muco adhesive buccal drug delivery systems, IJAPBC.2013; 2(2): 310-317.
3. S. Roy, K. Pal, A. Anis, K. Pramanik and B.Prabhakar, Polymers in mucoadhesive drug delivery system, A brief note, designed monomers and polymers.2009; 12: 483-495.
4. Y Indira Muzib, K SrujanaKumari, Mucoadhesivebuccal films of glibenclamide: Development and evaluation, Int. J. Pharma. Ivn.2011; 1(1):42-47
5. Vinod R, Ashok kumar P, SomeswaraRao B, Suresh V. kulkarni and Shankar MS, Design and evaluation of miconazole nitrate buccalmucoadhesive patches, J. Pharmacy Res.2010; 3 (6): 1338-1341
6. G. A. Khairnar, F. J. Sayyad, Development of buccal drug delivery system based on mucoadhesive polymers, Int.J. PharmTech Res.2010; 2(1): 719-735
7. N.K. Jain, Controlled and novel drug delivery, CBS Publishers and Distributors, 1st Edition.2010:52-81
8. RaghavendraRao N. G. and Suryakar V. B, Formulation and evaluation of montelukast sodium mucoadhesivebuccal patches for chronic asthma attacks,Int.J. Pharma and Bio Sci.2010: 1(2)
9. M. Balamurugan, V.S. Saravanan, P. Ganesh, S.P. Senthil, P.V. Hemalatha and SudhirPandya, Development and In-vitro Evaluation of MucoadhesiveBuccal Tablets of Domperidone, Res.J Pharmacy and Tech.2008; 1(4).
10. A Semalty, Mona Semalty, and U Nautiyal, Formulation and evaluation of mucoadhesivebuccal films of Enalapril maleate, Ind. J.Pharma. Sci.2010; 72(5): 571–575
11. M Nappinnai, R chandanbala, R Balajirajan, Formulation and evaluation of nitrendipinebuccal films, Ind.J. Pharm. Sci.2008;70 (5): 631-635.
12. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragitbuccal patches. Int J Pharm. 1999 Feb 1; 178(1): 11-22.
13. Balamurugan K, Pandit JK, Choudary PK, Balasubramaniam J. Systemic absorption of Propranolol Hydrochloride from buccoadhesive films. Ind J Pharm Sci. 2001; 63(6): 473-480.
14. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesivebuccal patches of Miconazole nitrate: in vitro/in vivo performance and effect of ageing. Int J Pharm. 2003 Oct; 264(1-2): 1-14.
15. Panigrahi L, Pattnaik S, Ghosal SK. Design and characterization of mucoadhesivebuccal patches of Diclofenac Sodium. Ind J Pharm Sci. 2005; 67(3): 319-326.
16. Pavankumar GV, Ramakrishna V, William GJ, Konde A. Formulation and evaluation of buccal films of Salbutamol Sulphate. Ind J Pharm Sci. 2005; 67(2): 160-164.
17. Chinna Reddy Palem, Ramesh Gannu, Vamshi Vishnu Yamsani, Shravan Kumar Yamsani and MadhusudanRaoYamsani, Development of bilayeredmucoadhesive patches for buccal delivery of felodipine: in vitro and ex vivo characterization, Cur. trends in Biotech. and Pharmacy. 2010 April; 4(2).
18. J. Thimmasetty, G. S. Pandey, P. R. SatheshBabu, Design and evaluation of carvidilolbuccalmucoadhesive patches, Pak.J.Pharm. Sci. 2008 July;21(3): 241-248.
19. Garry Kerch, VadimKorkhov, Effect of storage time and temperature on structure, mechanical and barrier properties of chitosan-based films, Euro. Food Res. and Tech.2012; 232(1):17-22.
20. Kristine Romøren, Astrid Aaberge, GroSmistad, Beate J Thu, OysteinEvensen, Long-term stability of chitosan-based

polyplexes, PubMed- Pharm. Res.2005;21(12):2340-2346
21. Punitha S, Girish Y, Polymers in mucoadhesive buccal drug delivery system – A review, Int. J. Res. Pharm. Sci. 2010;1(2): 170-186.
22. J. Varshosaz, Z. Dehghan, Development and characterization of buccoadhesiveNifedipine tablets, Eur. J. of Pharma. and Biopharm.2002; 54: 135–141.
23. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragitbuccal patches. Int J Pharm. 1999 Feb 1; 178(1): 11-22.
24. Subhash V. Deshmane, Madhuri A. Channawar, Anil V. Chandewar1, UnmeshM.Joshi, Kailash R. Biyani, Chitosan based sustained release mucoadhesivebuccal patches containing verapamil HCl, Int.J. Pharmacy and Pharma. Sci.(Nov.-Dec. 2009); 1(1)
25. Liji Jacob, C. I. Sajeeth, K. Santhi, Design, Development and Evaluation of the Mucoadhesive Patches of Nifedipine for Buccal Delivery, Int. J. of Pharmacy and Techn.2012;4 (1): 3883-3900.
26. Stark etal, multiparticulate Bisoprolol formulation, United state patent, patent no.US 6733789B1, patented date. May 11, 2004.
27. VipinBansal, Pramod Kumar Sharma, Nitin Sharma, Om Prakash Pal, RishabhaMalviya, Applications of Chitosan and Chitosan Derivatives in Drug Delivery, Adv. in Biolog. Res.2011; 5 (1): 28-37.
28. InampudiAjit, AdimoolanSemthil, Bhosale Rahul, V.B.NarayanaSwamy, Formulation and evaluation of VelnafaxineHClbuccal tablet, Int.Res. J. of Pharmacy.2012;3(1): 226-231.
29. Muralikrishna K, Nagaraju T, Gowthami R, Rajashekar M, Sandeep S, Himabindu S, ShravankumarYamsani, Comprehensive review on buccal delivery, . Int J Pharm. 2012; 2(1): 205-217.