DESIGN AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF SALBUTAMOL SULPHATE

Anita Desai*, jayadev Hiremath. and Prabhu Halakatti.
Hanagal shri kumareshwar College of Pharmacy, Bagalkot, Karnataka ,india

ABSTRACT

Mucoadhesive buccal films of Salbutamol sulphate were prepared by solvent casting technique using hyrdoxy propyl methyl cellulose as main polymer and eudragit RL100, carbapol-934 and poly vinyl pyrrolidone as co-polymers. The prepared films were evaluated for, surface texture, appearance, folding endurance, drug content, swelling studies, *In vitro* studies bioadhesion test, surface pH , % elongation test and stability studies.

The films exhibited controlled release over more than 6 hours .From the study it was concluded that the films containing 60 mg of Salbutamol sulphate in 450 mg of hydroxyl propyl methyl cellulose and 350 mg hydroxyl propyl methyl cellulose incorporated with 100 mg carbopal-934 exhibited satisfactory swelling, index an optimum residence time, and promising drug release of about 87% (F1) and 82% (F4) by using diffusion cell at 37°C using pH 6.6 phosphate buffer. The formulation was found to be suitable candidate for the development of buccal films for therapeutic use.

Keywords: Salbutamol sulphate, Buccal patches, *In vitro* studies, HPMC, Carbapol-934.

1.Introduction

Drug delivery via buccal mucosa using bioadhesive dosage form, offers such a novel route of administration, the route has successively been tried for systemic delivery of a number of drug candidates and excellent site for the absorption of the drugs(Harris,1992).

Amongst the various routes of drug delivery, oral route is perhaps the most preferred route to patients and clinical alike, within the oral cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has rich blood supply and is relatively permeable. The buccal route of drug delivery is a good alternate (Pramod Kumar,2002)over the last two decades mucoadhesion has become of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within gastrointestinal tract) or systemic delivery, by retaining the formulation in intimate contact with the absorption site. Mucoadhesion may be defined as a state in which two materials, one of which is mucus or a mucus membrane, is held for extended period of time (Smart,2005). Recently, Jasti, Salamat-miller has reviewed the use of mucoadhesive polymers in buccal drug delivery and highlighted the use of novel mucoadhesive polymers (Jasti,2003;Salamat-miller,2005) attempts have been made to formulate various mucoadhesive devices including tablets (Ali,1998), films (Kodha,1997), patches (Nair,1996;Perioli ,2004), disks (Prodi,1996), strips (Ali,2002), ointments (Ilango,1997) and gels (Bremackar,1984), after inhalation most of an inhaled is swallowed and enters the lungs with positive intermitted breathing, than by aerosol. It is subjected to first pass metabolism (Shin,2000) currently buccal patches have been used to deliver a variety of drugs to dogs, including buprenorphine, heparin, melatonin, theophylline, nitroglycerine, digoxine, propranolol, miconazole, insulin, morphine, fentanyl and estrodiol.(Shojaei,1998;Hoogstraate,1996; Vincent ,2001;Hussain,1988;Streisand,1995).

Salbutamol sulphate is used in treatment of asthma, chronic bronchitis and other pulmonary disorders. The drug is well absorbed from gastrointestinal tract. But buccal mucoadhesive drug delivery system has advantage like avoiding the first pass metabolism and gastrointestinal side effects of delayed release system (Alka Gupta,1992).The development of technology for release of drug at controlled rate and systemic circulation using buccal cavity as part of entry has become popular.

In the study an attempt was made to design the mucoadhesive buccal films of Salbutamol sulphate with various polymers like hyrdoxy propyl methyl cellulose as main polymer and Eudragit RL100, Carbopol-934 and poly vinyl pyrrolidone as co-polymers. The films

***Correspondence address:**
itsmeanitard@rediffmail.com

were characterized by keeping uniformity, flexibility, clarity and homogeneity as a tools.

2.Materials

Salbutamol sulphate I.P was obtained from Neuland Lab, Hyderabad and the polymers such as carbapol-934, HPMC by Zydus Cadila Ltd, Ahmedabad, poly vinyl pyrrolidone by Loba chemicals,Bombay and Eudragit RL-100 on Top pharmaceuticals,Bangalore.

Methods

Preparation of Patches

A series of buccal patches containing 60mg of Salbutamol sulphate in an area of 1 cm^2 were prepared by solvent casting technique (Sierra ,1972;Devi,1998) taking mercury substrate (table no.1). Hydroxy propyl methyl cellulose soaked in 4 ml ethanol, salbutamol sulphate dissolved in 1 ml of water. Then 1.5ml methanol, 1.5ml dichloromethane, are added methanol is used to get transparent films, it will totally evaporate when we stir it for 30 min and dry for over night so small amount of methanol will not give any fatal effect . Ethanol is used as a solvent and glycerol as a plasticizer and sweetener. Then the whole drug polymer mixtures are stirred for 30 minutes at magnetic stirrer. The polymer drug solution (3ml) poured over mercury substrate in a petridish within a bangle (4.5 cm). After 12 hours dried patches were collected and stored in desiccators until further use. In the same manner F_2, F_3, F_4 patches were prepared using co-polymers. Eudragit RL100, Carbapol-934 and Poly vinyl pyrrolidone (Raghuraman,2002).

An apparatus was used for in vitro release study. A 250 ml glass beaker was filled with isotonic phosphate buffer. After stabilizing 1cm^2 Salbutmol sulphate film was fixed in buffer (IPB, pH 6.6) in the study, procine buccal mucosa was used as barrier membrane. The buccal pouch of freshly sacrificed animal was procured from local slaughter house. The mucosa was excised and trimmed evenly from the sides. It is then washed in isotonic phosphate buffer (pH 6.6) and used immediately. Mucosa was tied with a thread to diffusion cell of size +1 cm^2. The patch attached to the mucosa was dipped into the buffer solution into a flask in a position just below the diffusion fluid. The flask was kept on magnetic stirrer. The whole assembly was maintained at 37° C. Samples were collected at fixed time intervals by replacing same volume of diffusion fluid. Samples with suitable dilutions were analysed by using UV spectrometer at 276 nm.

The in vitro bioadhesion test is an index of adhesive strength of a film to the buccal mucosa till the complete drug releases. Bioadhesion strength of the patch was measured using a modified double beam balance described by Chowdary,2000. Percentage elongation at break, stability study was determined as Pandya,1995.

Folding endurance was measured as Raghuraman,2002, the films of each formulation of (2x2 cms) were cut by using sharp blade. Folding endurance was determined by repeatedly folding the stripes till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance, thickness and size, drug content (Raghuraman,2002). Thickness was measured by micrometer screw gauge. Drug content was determined by taking films and placed in 100ml phosphate buffer and stirred and then the drug content was measured by UV spectrophotometer at 276nm. Swelling studies as Lalla,2002 the surface pH was measured as similar to Nafee,2003. A combined glass electrode of pH meter was used on previously swallowed films. (The patches kept in contact with 0.5 ml of distilled water for 1 hour on an agar plate) pH was noted by bringing the electrode near the surface of the patch and allowing it to equilibrate for 1 minute.

3.Results and Discussion

Mucoadhesive buccal films of Salbutamol sulphate were prepared by using mucoadhesive polymers like hydroxyl propyl methyl cellulose E-15, Eudragit RL-100, poly vinyl pyrrolidone and carbapol 934. The drug delivery system was formulated as a matrix.The films were characterized for their physical characteristics, bioadhesive performance, release characteristics, surface pH thickness, drug content and % elongation, folding endurance (table-2) and swelling index (table-3).

The film thickness were observed to be in the range of 0.51 ± 0.03 to 0.76 ± 0.07mm and weight was found in the range of 129 ± 1.0 mg to 168 ± 0.09 mg

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymers. The surface pH of the buccal films was determined to optimize both drug

permeation and mucoadhesion. Attempts were made to keep the surface pH as close to buccal/salivary pH as possible. The surface pH of all the films was within the range of salivary pH (6.2 to 6.4). No significant difference was found in surface pH of different films. The hydration is required for a mucoadhesive polymer to expand and create a proper macromolecular mesh of sufficient size, the optimum swelling index was calculated by using the formula, Swelling index =final weight of the patch - initial weight of the patch/initial weight of the patch) X 100 and found as F4 has given more swelling index than F3, F1 and F2 and the order was F4>F3>F1>F2.

The bioadhesion strength of hydroxy propyl methyl cellulose containing carbopol was more than hydroxy propyl methyl cellulose alone, because combination of two hydrophilic polymers would result in better bioadhesion than combination of hydrophilic and hydrophobic polymers. The order of bioadhesion was in an order $F_4>F_3>F_2>F_1$.

All the formulations show the folding endurance in the range of 70 to 200. Folding endurance was found to be highest for F4 (200) and lowest F2 (73). The order was (F4>F3>F1>F2). The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties

The drug content in formulation was uniform. It was found that drug was dispersed uniformly throughout the film. *In vitro* release studies performed using pH 6.6 phosphate buffer as diffusion medium and measured drug concentration spectrophotometrically at 276nm distinguishable difference was observed in the release of Salbutamol sulphate films. Addition of co-polymers in hydroxy propyl methyl cellulose has retarded the drug release and the order was F1>F4>F3>F2. Formulation F1 showed 87%, F4 (82.1%), F3 (78.3%) and F2 (72%) release at the end of 12 hrs.

Films gave good % elongation and tensile strength essential. F4 showed maximum % elongation and minimum. The order was F4>F3>F1>F2. All the formulation found stable at 30 °C.

The present study indicates a good potential of erodible. Mucoadhesive buccal films of salbutamol sulphate for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The results of salbutamol sulphate can be delivered buccally.

It may be concluded that the films containing salbutamol sulphate in hydroxy propyl methyl cellulose (F1) and films with hydroxy propyl methyl cellulose incorporated with carbapol-934 has shown good swelling, convenient bioadhesion and promising controlled drug release. Thus seems to be a potential candidate for the development of buccal films for effective therapeutic use.

4.Acknowledgements

I am thankful to Dr.T.S Muchandi, Principal, HSK College of Pharmacy Bagalkot, for providing me the basic facilities to carry out my research work. I am also thankful to Zydus Cadilla Ltd, Ahmedabad, for providing the gift sample.

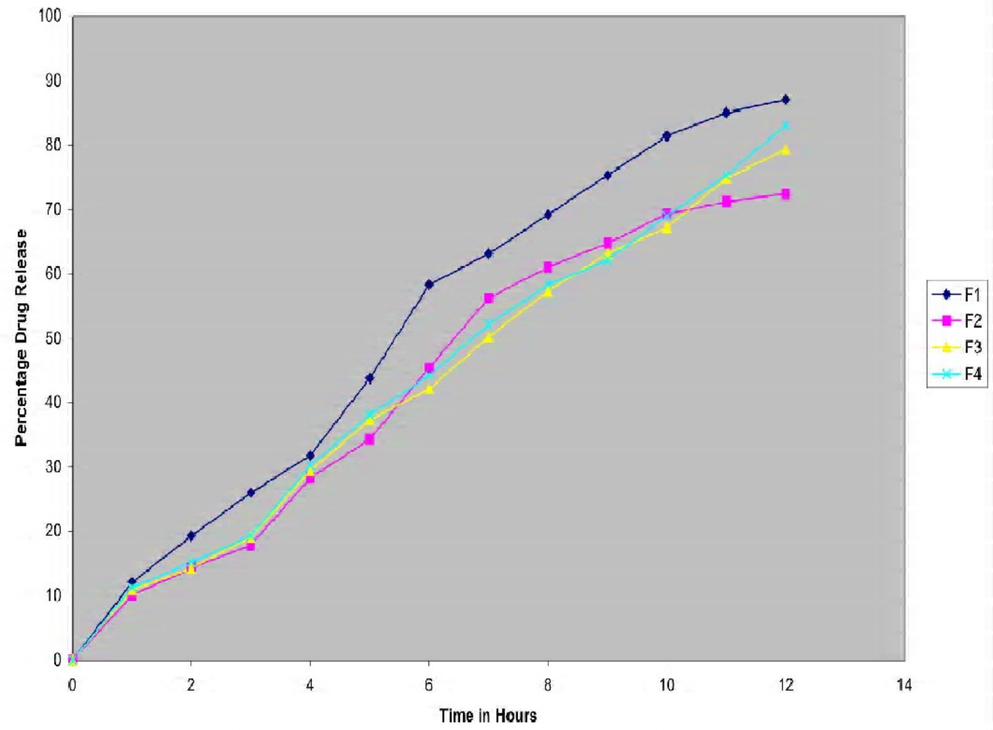

Figure1. *In vitro* release of buccal films showing the release with different polymers and copolymers in F1 (HPMC), F2 (Eudragit RL 100), F3 (PVP) and F4 (carbopol-934).

Table 1. Formulae of different mucoadhesive buccal films containing Salbutamol sulphate

Ingredients (mg or ml)	FORMULATION CODE			
	F1	F2	F3	F4
Salbutamol sulphate	60	60	60	60
HPMC E-15	450	350	350	350
Eudragit RL-100	-	100	-	-
PVP	-	-	100	-
Carbopol-934	-	-	-	100
Ethanol	6	6	6	6
Dicholoromethane	1.5	1.5	1.5	1.5
Methanol	1.5	1.5	1.5	1.5
Water	1	1	1	1
Glycerol	0.05	0.05	0.05	0.05

The formula given above is to produce a film of area 15.896 sq.cm

Table 2. Physical characteristics of buccal films Of Salbutamol Sulphate.

Formulation code	Colour	Surface texture	Folding endurance (no's)	Thickness (mm)		Average* Wt (mg)	Surface PH	Drug content(%)	% Elongation	Bioadhesion strength*
				Mean	SD					
F1	+	VERY SMOOTH	133	0.51	0.03	132±1.414	6.2	98.10	26.5	28.1(0.08)
F2	-	SMOOTH	73	0.64	0.03	129±1.0	6.3	99.02	15.0	14.8(0.01)
F3	+	VERY SMOOTH	150	0.76	0.07	165±0.9	6.4	99.06	30.5	19.3(0.13)
F4	-	SMOOTH	200	0.73	0.02	168±0.9	6.2	99.07	77.5	29.1(0.05)

* Each value represents the average of three and five determinations.

\+ Transparent

\- Opaque

Table 3. Swelling characteristics of prepared patches

Time in hours	Swelling index			
	F_1	F2	F3	F4
0	0	0	0	0
5	4.78	1.69	7.13	9.34
10	3.20	4.1	5.81	7.46

The swelling index was calculated by using the formula S = (final weight of the patch-initial weight of the patch/ initial weight of the patch) X 100

References

Ahuja A, Khar RK, Ali.J. Mucoadhesive Drug Delivery Systems. Drug Dev. Ind. Pharmacy. 43,1997,489.

Ali J, Kha RK, Ahuja A. Formulation and characterization of a buccoadhesive erodible tablet for the treatment of oral lesions. Pharmazie.53,1998,329-34.

Ali J, Kha, RK, Ahuja A, Kalra R. Buccoadhesive erodible disk for treatment of oro-dental infection: Design and characterization. Int J Pharm,238,2002,93-103.

Alka Gupta, Sanjay Garg and R.K. Khar. Mucoadhesive buccal drug delivery system; a review. Indian drugs,(Oct) 29,13,1992,586-592.

Bottenberd, Cleymact P, Muyhek R , Remon CD,Cooman JP, Michotte SD. Development and testing of bioadhesive ,fluoride-containing slow-release tablets for oral use. J.Pharmacol.43,1991,457.

Bremackar KD, Strempel H, Klein G. Novel concept for a mucosal adhesive ointment. J Pharm Sci,73,1984,548-52.

Chowdary KPR and Srinivas L. Mucoadhesive drug delivery systems. A review of current status, Indian drugs.(Sep) 37,9,2000,400-409.

Devi K., Paranjothy Kl., development and evaluation of true film and transdermal patches of ketorolac tromethamine using polymers and pressure sensitve adhesives. Eastern Pharmacist. 48,1998,97.

Harris D and Robinson, J.R., Drug delivery via the mucous membranes of the oral cavity. J. Pharm Sci. 81,1992,1.

Hoogstraate AJ, Coos Verhoef JC, Van Leengoed LA, Verheijden JH,et al. In Vivo Buccal delivery of the peptide drug buserelin with glycodeoxycholate as an absorption enhancer in pigs. Pharm Res,13,1996,1233-1237.

Hussain MA, Aungst BJ, Koval CA, Shefter E. Improved Buccal delivery of opoid analgesics and antagonists with bitterless prodrugs. Pharm Res,5,1988,615-618.

Ilango R, Kavimani S, Mullaicharam AR, Jayakar B. In vitro studies on buccal stripes of glibenclamide using chitoson. Indian J Pharm Sci,59,1997,232-5.

Jasti B, Li X, Cleary G. Recent advances in mucoadhesive drug delivery system . Bus Briefing Pharma tech 2003,194-6

Kodha Y, Kobayashi H, Baba Y,Yuasa H,Ozeki T,Kanaya Y,et al. Controlled release of Lidocaine hydrochloride from buccal mucosa adhesive films with solid dispersion. Int J Pharm. 158,1997,147-55.

Lalla JK, Rita. Permeation of Diclofenac through buccal mucosa. Indian J. Pharma. Sci. (July),2002,372-377.

Nafee NA, Ismail FA, Boraie NA ,Mortada LM. Mucoadhesive buccal patches of miconiazole: In vitro/ in vivo performance and effect of ageing. Int J Pharm,264,2003,1-14.

Nair MK, Chien YW. Development of anticandidal delivery system (II) Mucoadhesive devices for prolonged drug delivery in oral cavity. Drug Dev Ind Pharm,22,1996,243-53.

Pandya S, Pai M. Singh UV and Udupa N. Mucoadhesive formulation of thiophylline. Indian J.Pharma. Sci.(July),1995,241-243.

Perioli L, Ambrogi V ,Rubini D , Giovagnoli S, Ricci M, Blasi P , et al . Novel mucoadhesive buccal formulation containing metranidazole for the treatment of periodontal disease. J Control Release,95,2004,521-33.

Pramod Kumar T.M., Kashappa Goud Desai and Shivakumar H.G. Mechanism of buccal permeation enhancers. Indian J. Pharm. Edu . (July) 36 (3),2002,147-151.

Prodi B, Russo E, Caviglioli G, Cafaggi S, Bignardi G. Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride, Drug Dev Ind Pharm,22,1996,445-50

Raghuraman S., Velrajan G., Ravi R.,Jeyavalan B., Benito Johnson D. Design and evaluation of propranolol HCl buccal films" The Indian J. Phama. Sci. 64(1),2002,32-36.

Salamat-miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev.57,2005,1666-91.

Shin SC, Bum JP, Choi JS. Enhanced bioavailability by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits. Int J Pharm,209,2000,37-43.

Shojaei AH, Berner B, Xiaoling. Transbuccal delivery of acyclovir: In Vitro Determination of routes of buccal transport. Pharm Res.15,1998,1182-1188.

Sierra JJ and Gidwani RN. Evalution of selected physical constants of polymeric films and proposed kinetics of drug release. J.Pharm.Sci,61,1972,754.

Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 57,2005,1556-68.

Streisand JB, Ahang J, Niu S, McJames S, Natte R,et al. Buccal Absorption of fentanyl is PH- dependent in dogs. Anaesthesiology. 1995;82,1995,759-764.

Vincent H. L Lee. Mucosal drug delivery. Journal of the National Cancer Institute Monographas No 29, 2001;41-44.