Mintage Journal of Pharmaceutical & Medical Sciences
RESEARCH ARTICLE

FORMULATION AND EVALUATION OF BUCCAL FILMS OF SALBUTAMOL SULPHATE

NAGAVENI SOMEPALLI*[1], CHANDRA SEKHAR MORU[2], DINESH BABU GOTTIPATI[3], VAMSHI KRISHNA VORUGANTI[3]

[1]M.pharm ,Bellamkonda Institute Of Technology,Podili,Prakasham Dist ,AP ,[2]M.pharm ,Vikas college of B.pharmacy,Suryapet ,AP, [3]Department Of Formulation R&D ,VKT Pharma pvt ltd,Visakhapatnam; **Email:** babu.dinesh89@live.in

Received -18-06-13; Reviewed and accepted -26-06-13

ABSTRACT

For systemic drug delivery, the buccal region offers an attractive route of drug administration. The main objective of the study is to formulate buccal patches of salbutamol sulphate. Salbutamol sulfate is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. It's oral bioavailability is 40% due to extensive first pass metabolism. Salbutamol sulfate patches were prepared using HPMC, SCMC and Carbopol 934 in various proportions and combinations using Glycerol and tween-80 as plasticizers. Patches were laminated on one side with a water impermeable backing layer using ethyl cellulose for unidirectional drug release. The thickness of medicated patches were ranged between 0.402 and 0.431 mm and mass varied between 0.0312 and 0.0352 g. The surface-pH of patches ranged between 6 and 7. All formulations showed good folding endurance. Formulations F9 showed good drug content and Residence time of the tested patches ranged between 108 and 174 min. The maximum in vitro release was found to be 93.89% over a period of 150 min for formulation F9. Data of in vitro release from patches were fitted to different kinetic models such as Higuchi and Korsmeyer–Peppas models to explain the release profile. Formulations F9 were best fitted to the non-Fickian kinetics and zero order release was observed.

Keywords: Buccal patches, Salbutamol, HPMC, Carbopol.

INTRODUCTION

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Buccal mucosa is relatively permeable with a rich blood supply [1].

Additionally, drug delivery via this site avoids extensive enzyme degradation and first-pass metabolism seen with oral administration [2]. Further recent interest in this route has been generated with regard to the non-parenteral delivery of new peptide and protein drugs produced as a result of advances in biotechnology [3].

Beta 2-adrenergic agonists represent an effective for treatment of asthma, bronchospasm and conditions with reversible airways obstruction including chronic obstructive pulmonary disease .Salbutamol sulfate (SS), a selective beta 2-adrenergic agonist and bronchodilator, is one of the widely used drugs for the treatment of the most respiratory diseases arising due to airway obstruction [4] . Salbutamol sulfate is a hydrophilic drug with a dissociation constant of (pKa) 9.2 and a log P value of 0.11. The drug undergoes extensive first-pass metabolism with a plasma half-life of 4–6 h [5].

Salbutamol sulfate has low bio-availability of 40% due to following reasons [6].

- Extensive metabolism via intestinal sulfonation
- First pass metabolism in the liver
- Undergoes degradation in the colon.

To overcome the above reasons and to increase the bio-availability Salbutamol sulfate is given in the form of buccal patches by adhering to the mucosal layer in the buccal cavity. The interest of mucoadhesion is to increase the intimate contact of the dosage form at the adhesion site and to improve the bioavailability of the drug [7].

Buccal route is selected due to following reasons.

- Faster and richer blood supply
- Lesser thickness of the buccal mucosa
- Increased permeability
- Low enzymatic activity

MATERIALS AND METHODS

MATERIALS

Salbutamol sulfate was gift sample from VKT pharma pvt ltd, Visakhapatnam, Hydroxy Propyl Methyl Cellulose K4M, Carbopol 934P were procured from S.D.fine chemicals ,mumbai.Sodium carboxy methyl cellulose, Tween-80,Glycerol,Ethyl cellulose, Ethanol were procured from Karnataka fine chem,Bangalore and Purified water. All solvents used were of analytical grade.

METHODS

The polymers used were listed in table-1 were dissolved in ethanol and water in the ratio of 4:1 and concentrations of HPMC K4M (5%W/V), SCMC (5%W/V), CARBOPOL 934p (3%W/V)were prepared according to table no -1 and mixed well on a magnetic stirrer, at low rpm, for a period of 1 h to get a homogenous clear, bubble free solution. Glycerol 10%V/V and tween-80 were added as a plasticizer and humectant. To this clear mixture drug mixture was added and stirred well on a magnetic stirrer until a clear homogeneous solution was formed. The drug-polymer solution was then poured on a Petri plate (9.6 cm diameter). Which contains ethyl cellulose 10%w/v films which were prepared earlier using ethyl cellulose and ethanol .The ethyl cellulose acts as a backing membrane and helps in uni-directional release from the patch. Patches were then dried at room temperature for 2 h and were further dried for 18 h at 40^{o}C in a hot air oven. Finally, the patches were vacuum dried for 4 h at room temperature in a vacuum desiccator. After careful examination, the dried patches were removed, checked for any imperfections or air bubbles and cut into 4 cm diameter patches using a specially fabricated circular stainless steel cutter. The samples were packed in aluminum foil and stored in a glass container at room temperature.

Table 1: Formulation design for Salbutamol sulphate buccal patches.

S.No	Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Salbutamol	375mg	375mg	375mg	375mg	375mg	375mg	375mg	375mg	375mg
2	HPMC K 4M (5%W/V)	37.5ml	50ml	-	-	-	-	25ml	-	25ml
3	SCMC (5%W/V)	-	-	37.5ml	50ml	-	-	25ml	25ml	
4	CARBOPOL 934p (3%W/V)	-	-	-	-	37.5ml	50ml		25ml	25ml
5	Glycerol	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml
6	Tween-80	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml
7	Ethyl cellulose (backing membrane)	4g	4g	4g	4g	4g	4g	4g	4g	4g
8	Ethanol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S	Q.S.	Q.S.
9	Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S	Q.S.	Q.S.

EVALUATION OF THE PATCHES

Thickness uniformity of the patches

The thickness [8] of each patch was measured using digital vernier callipers at five different positions of the patch and the average was calculated.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. This test was done on five patches.

Uniformity of weight of the patches

Patches sizes of 1x1 cm^2 were cut. The weights of five patches were taken and the weight variation [9] was calculated.

Swelling studies of the patches

A drug-loaded patch of 1x1 cm^2 was weighed on a pre weighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.8 was added. After every five min, the cover slip was removed and weighed after each hour till period of 6 hr. The difference in the weights gives the weight increase due to absorption of water and swelling of patch. The percent swelling[10], %S was calculated using the following equation:

$$\%S = \frac{Xt - Xo}{Xo} \times 100$$

Where

Xt is the weight or area of the swollen patch after time t and Xo is the original patch weight or area at zero time.

Surface pH

Buccal patches were left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.8. The surface pH[11] was measured by means of pH paper placed on the surface of the swollen patch.

Content uniformity

Drug content uniformity[12] was determined by dissolving the patch (backing layer must be removed prior to this) by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 8 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml. The drug content was then determined after proper dilution at 277 nm using a UV-spectrophotometer.

Ex vivo mucoadhesive strength

Fresh sheep buccal mucosa was obtained from a local market and used within 2 h of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. Bioadhesive strength [13] of the patch was measured (n = 3) on a modified physical balance. A piece of buccal mucosa was tied to the open mouth of a glass vial, filled completely with isotonic phosphate buffer pH 6.8. The glass vial was tightly fitted in the center of a glass beaker filled with isotonic phosphate buffer (pH 6.8, 37 ± 1 °C). The patch was stuck to the lower side of the rubber stopper with cyanoacrylate adhesive. The mass, in grams, required to detach the patch from the mucosal surface gave the measure of mucoadhesive strength. The following parameters were calculated from the bioadhesive strength:

$$\text{Force of adhesion (N)} = \frac{\text{Bioadhesive strength} \times 9.81}{1000}$$

$$\text{Bond strength (N m–2)} = \frac{\text{Force of adhesion}}{\text{Disk surface area}}$$

Ex vivo mucoadhesion time

The ex vivo mucoadhesion time [14] was performed (n = 3) after application of the films on freshly cut porcine buccal mucosa. Each film was divided in portions of 0.785 cm^2 and cut a side of each film was wetted with 50 ml of phosphate buffer pH 6.8 and was pasted to the porcine buccal tissue by applying a light force with the finger tip for 20 s. The beaker was filled with 800 ml of the phosphate buffer pH 6.8 and was kept at 370C. After 2 min, a stirring rate was applied to simulate the buccal cavity environment and film adhesion was monitored during 8 h.

In vitro release study from Salbutamol sulphate loaded patches

A standard paddle apparatus was employed to evaluate drug release. A portion of 0.785 cm^2 of patch was used. A side of the patch[15] was attached with double adhesive tape on the inert support and, after 2 min; the vessel was filled with phosphate buffer pH 6.8 and maintained at 370C while stirring at 50 rpm. Five milliliter samples were collected at predetermined time intervals and replaced with an equal volume of simulated saliva fluid. Salbutamol sulphate concentration was determined by a spectrophotometer at λ max = 277 nm and reported as an average of three measurements.

Vapour transmission test (VTR)

Glass-bottle (length= 5 cm, narrow mouth with internal diameter =0.8 cm) filled with 2 g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2 °C. The difference in weight after 24 h, 3rd day and 1 week was calculated. The experiments were carried out in triplicate and vapor transmission rate[16] was obtained as follow:

$$\text{VTR} = \frac{\text{(Amount of moisture transmitted)}}{\text{(Area x Time)}}$$

Statistical and kinetic analysis

The in vitro release [17,18] profiles were tested for their kinetic behavior in order to establish the kind of mechanism possibly involved in Salbutamol sulphate release from the film matrix. Higuchi and cross-meyer peppas and zero order plots were plotted and R^2 value was noted.

RESULTS AND DISCUSSION

Thickness

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated. All the patches have uniform thickness throughout. Average thickness found was about 0.416 mm.

Folding endurance

Folding endurance was satisfactory and films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point.

Weight uniformity

The patches were found uniform. The average weight of the patch found was about 33.18 mg.

Surface pH

The surface pH was in the range of 6.08-6.45.As the pH was in the range of saliva ,no irritation occurs to patient.

Mucoadhesive strength (gm) & force of adhesion (N)

The peak detachment force and bioadhesive strength for formulation H5 were 0.0654 N and 5.21 gm respectively. These values for bioadhesion and peak detachment force were within the range for suitable bioadhesion as reported for various buccal patches.

Swelling index was shown in Figure – 1

In vitro release study

In vitro release study shows the following trend. An increase in the polymer content was associated with a corresponding decrease in the drug-release rate. The formulation F9 having both HPMC and carbopol 934P in varying proportion shows good release compared to others. Hence F9 was considered to be the compromising formulation.

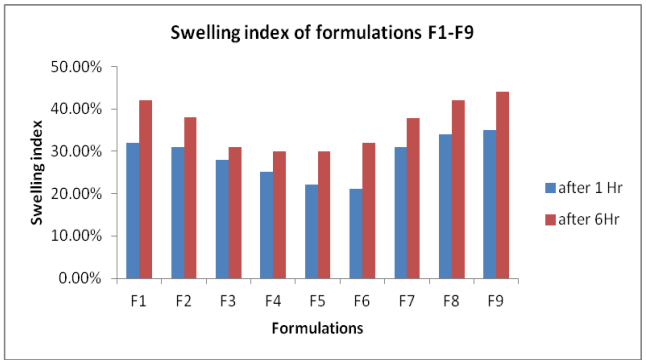

Figure 1: swelling index of formulations F1-F9.

Table 2: Showing mucoadhesive strength, force of adhesion, Ex vivo mucoadhesion time and bond strength.

Formulations	mucoadhesive strength (gm)	force of adhesion (N)	Ex vivo mucoadhesion time (Hr)	bond strength
F1	4.55	0.057	1.8	0.0689
F2	5.56	0.054	2.1	0.0789
F3	4.23	0.0498	1.9	0.0645
F4	5.24	0.0521	2	0.0548
F5	4.56	0.0512	2.2	0.0698
F6	5.23	0.0544	2.3	0.0635
F7	5.78	0.0515	2.6	0.0621
F8	5.37	0.0612	2.1	0.0698
F9	5.21	0.0654	2.9	0.0611

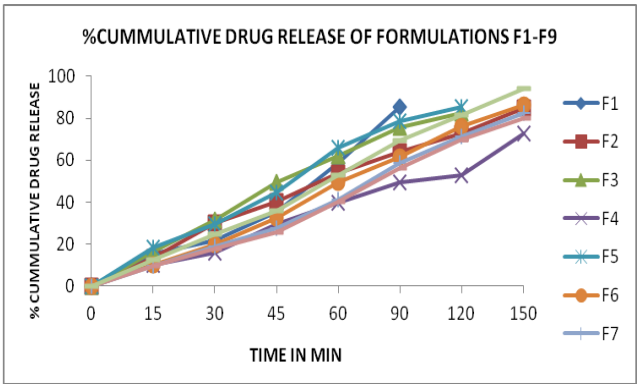

Figure 2: Showing % cumulative drug release of formulations F1-F9.

Table: 3 showing Vapor transmission test (VTR) for optimized batch F9.

Vapor transmission rate, g cm^{-2} h^{-1}

Day 1	Day 2	Day 7
0.00351	0.00298	0.00312

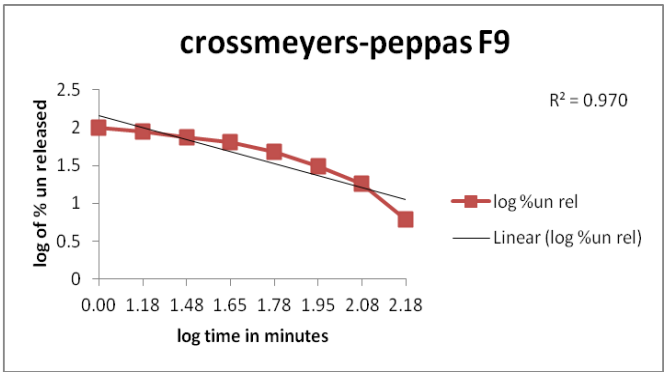

Figure 3 : Showing crossmeyers-peppas plot of formulation F9.

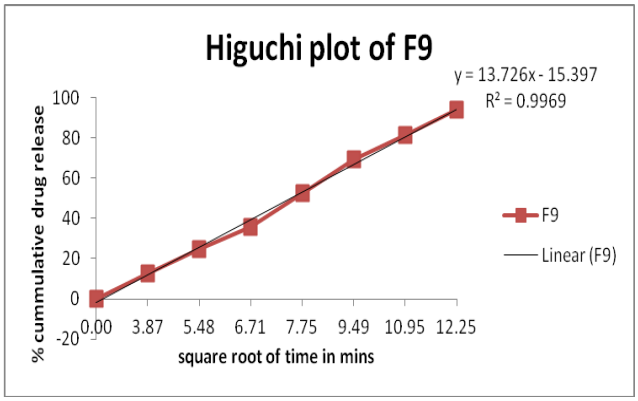

Figure 4: Showing Higuchi plot of formulation F9

Figure 5 : Showing Zero order plot of formulation F9.

REFERENCES

1. J Thimmasetty, GS Pandey and PR Sathesh babu "Design and in vivo evaluation of Carvedilol buccal mucoadhesive patches", Pak. J. Pharm. Sci., Vol.21, (2008) 241-248.
2. Nazila Salamat-Miller, Montakarn Chittchang1, Thomas P. Johnston, "The use of mucoadhesive polymers in buccal drug delivery", Advanced Drug Delivery Review 57, (2005) 1666–169.
3. John D. Smart, Drug delivery using buccal-adhesive systems, Advanced Drug Delivery Reviews, II, (1993) 253 270.
4. Kelly, H.W., Murphy, S., 1992. Beta-adrenergic agonists for acute severe asthma. Ann. Pharmacother. 26, 81–91.
5. Ahrens, R.C., Smith, G.D., 1984. Albuterol: an adrenergic agent for use in the treatment of asthma pharmacology, pharmacokinetics and clinical use. Pharmacotherapy 4, 105–121.
6. Swarbrick, J., Boylon, J.C., 2002. Encyclopedia of Pharmaceutical Technology, second ed. Marcel Dekker Inc., New York, USA.
7. Chowdary, K.P.R., Srinivasa Rao, Y., 2003. Preparation and evaluation of mucoadhesive microcapsules of indomethacin. Saudi Pharm. J. 11, 97–103.
8. S. Burgalassi, L. Panichi, M.F. Saettone, J. Jacobsen, M.R. Rassing. Development and in vitro/in vivo testing of mucoadhesive buccal patches releasing benzydamine and lidocaine. International Journal of Pharmaceutics 133, (1996) 1-7.
9. C. Li; P. P. Bhatt; T. P. Johnston. Evaluation of a Mucoadhesive Buccal Patch for Delivery of Peptides: In Vitro Screening of Bioadhesion. Drug Development and Industrial Pharmacy, Volume 24, (1998) pp. 919–926.
10. Noha A. Nafee Nabila A. Boraie Fatma A. Ismail, Lobna Mohamed Mortada, Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, International Journal of Pharmaceutics, 264, (2003) 1–14.
11. Y. Vamshi Vishnu, K. Chandrasekhar, G. Ramesh and Y. Madhusudan Rao. Development of Mucoadhesive Patches for Buccal Administration of Carvedilol. Current Drug Delivery, 4, (2007)page 27-39.
12. Vishnu M. Patel Bhupendra G. Prajapati Madhabhai M. Patel Design and characterization of chitosan containing Mucoadhesive buccal patches of propranolol hydrochloride";Acta Pharm. 57, (2007) page 61–72.
13. B. Parodi, E. Russo, G. Caviglioli, S. Cafaggi and G. Bignardi, Development and characterization of a buccoadhesive dosage form of oxycodone hydrochloride, Drug Dev. Ind. Pharm. 22 (1996) page 445–450.
14. Luana Periol Valeria Ambrogi, Fausta Angelici, Maurizio Ricci, Stefano Giovagnoli Marinella, Capuccela Carlo Rossi, Development of mucoadhesive patches for buccal administration of ibuprofen; Journal of Controlled Release 99, (2004) page 73– 82.
15. Supriya S. Shidhaye, Nilesh S. Saindane, Sagar Sutar, Vilasrao Kadam. Mucoadhesive Bilayered Patches for Administration of Sumatriptan Succinate. AAPS PharmSciTech, Vol. 9, Issue No. 3, (2008) page 909-916.
16. Subhash V. Deshmane, Madhuri A. Channawar, Anil V. Chandewar, Unmesh M. Joshi, Kailash R. Biyani. Chitosan based sustained release mucoadhesive buccal patchescontaining verapamil Hcl International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 1, Suppl. 1, (2009) page 216-229.
17. Amit Khairnar, Parridhi Jain1, Dheeraj Baviskar and Dinesh Jain1, Developmement of mucoadhesive buccal patch containing aceclofenac: in vitro evaluations. International Journal of PharmTech Research, Vol.1, Issue No.4, (2009) page 978- 981.
18. Chandra Sekhar Kolli, Ramesh Gannu, Vamshi Vishnu Yamsani, Kishan V and Madhsudan Rao Yamsani, Development of Mucoadhesive Patches for Buccal Administration of Prochlorperazine: Evaluation of In Vitro Release and Mechanical Properties. International Journal of Pharmaceutical Sciences and Nanotechnology Volume 1 (2008). page 64-70.