Asian J. Pharm. Res. Vol 5, Issue 3, 167-175, 2015.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

FABRICATION DESIGN FOR BUCCAL FILMS OF SALBUTAMOL SULPHATE: AN *IN-VITRO* AND *EX-VIVO* EVALUATION

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ABSTRACT

The aim of this work was the design and evaluation of buccal patches consisting of Salbutamol sulphate. Buccal patches of about six formulations containing Salbutamol sulphate are designed by using film forming polymers such as HPMC, PVP, Sodium alginate. Glycerol 10% used as plasticizer and Solvent casting technique is adopted for the preparation of buccal patches, prepared patches were evaluated for Drug content, physical characteristics such as Folding Endurance, Surface P^H, Average weight ,Thickness, Swelling Studies and % cumulative Ex-vivo release. . Cumulative % Ex-vivo drug release of HPMC and sodium alginate (4:1) combination was found to be higher than all other formulations . Hence it is having higher bioavailability.

Key words: Salbutamol sulphate, Polymers, Buccal Patches, Ex-vivo release, Buccal delivery.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are among the most pre-valent diseases by which most of the population is affecting . Salbutamol sulphate (SS) is a short-acting Beta 2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and COPD. Salbutamol sulphate is readily absorbed from the GI tract and undergoes extensive first pass metabolism in the liver and also in the gut wall. The plasma half-life of this drug is 4 to 6 hours and thus it requires multiple dosing frequency. Buccal patches of SS which bypass the hepatic metabolism and release the drug at a desired rate may have distinct advantages over conventional dosage forms. The physicochemical and pharmacokinetic profiles of SS make it a suitable candidate for the preparation of a buccal drug delivery system. Therefore, the aim of the present study was to develop buccal patches of SS to ensure satisfactory drug release, and to prevent the first pass metabolism and improve bioavailability. Buccal drug delivery system has become an popular route of drug administration. The buccal cavity surface comprises of stratified squamous epithelium which was separated from the under lying tissue of lamina propria and submucosa by an undulating basement membrane [1]. An interesting thing to note that the permeability of buccalmucosa is higher than that of the skin, but less than that of the intestine [2–4]. It has been reported that the permeability of the buccal mucosa is approximately 4–4000 times greater than that of the skin [5].Hence the buccal delivery serves as an excellent basement for absorption of drug molecules that have poor dermal penetration. However, the primary barrier to permeability in the oral mucosa is due to intercellular material derived from the so-called ‘membrane coating granules’ present at the topmost 200 micron layer [6,7]. Negatively charged mucin have sulfhydryl groups and sialic acid residues that are responsible for the process of mucoadhesion [8].Saliva and salivary mucin attributes barrier properties to oral mucosa [9]. Major salivary glands consist of lobules of cells that secrete saliva, the minor salivary glands are located in the lips, buccal mucosa, and in linings of the mouth and throat [10]. Total turnover rate of the total saliva at normal physiological conditions having a flow rate of 1–2 ml/min [11]. Drug absorption through the buccal cavity can take place either by the transcellular

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route or paracellular pathway . The mucosa in sublingual region is more permeable leading to rapid absorption with improved bioavailability [12]. One of the reasons is that buccal mucosa is less permeable and is thus not able to produce a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. The primary disadvantage of buccal delivery route is the low flux that in turn results in low drug bioavailability. To overcome this drawback, various buccal penetration enhancers have been studied which improve the absorption of the molecules.The constant salivary secretion with in the buccal cavity makes it quite hard for dosage forms to be retained for long periods of time. It is documented that the maximum duration of buccal delivery is 4–6h [13].An ideal buccoadhesive system is the one that adhere to the site of attachment for a few hours, releases the drug in a controlled fashion, facilitates the rate and extent of drug absorption, does not produce any irritation to the patient.In spite of these challenges the buccal route is still the preferred route for delivery of active pharmaceutical ingredients (API) that are prone to high level of degradation in the gastrointestinal tract. Different buccal delivery products have been marketed or are proposed for certain diseases like trigeminal neuralgia,Meniere's disease, diabetes, addictionetc. [14–21]. Various bioadhesive mucosal dosage forms have been developed, which includes gels, adhesive tablets, ointments, patches and more recently the use of polymeric films for buccal delivery .[22].

MATERIALS AND METHODS

Materials

Salbutamol sulphate was obtained as gift sample from Hetero pharma Pvt Ltd, Hyderabad, Hydroxy propyl methyl cellulose, Sodium alginate and PVP was obtained as gift sample from Nicholas Piramal Pharmaceuticals Pvt Ltd, Glycerol and all other chemicals used in formulations are analytical grade.

Preparation of phosphate buffer p^H 6.6:

Phosphate buffer pH 6.6 is prepared by mixing 50 ml of 0.2M potassium Dihydrogen orthophosphate with the 17.80 ml 0.2M sodium hydroxide and the resulting solution is diluted to 200 ml with water.

Preparation of saline solution (0.9% w/v):

Weigh 0.9 gm of sodium chloride and take it in 100 ml volumetric flask, add few ml of distilled water for dissolution and finally make up the volume to 100 ml with distilled water, which gives 0.9% w/v saline solution.

Preparation of glycerol solution (10% v/v):

Measure 10 ml of glycerine with measuring cylinder, and transfer into 100 ml volumetric flask and dilute with distilled water and finally make up the volume to 100 ml with distilled water, which gives 10% v/v glycerine solution.

FTIR (Fourier Transform Infra-red Spectroscopy) Studies:

Infrared (IR) spectroscopy studies of Salbutamol sulphate and its formulations with polymers were recorded in a FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum for each sample showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived from 16 single average scans collected in the region of 400 - 4000 cm^{-1} at a spectral resolution of 2 cm^{-1}

Differential Scanning Calorimetry (DSC) Studies:

Salbutamol sulphate and its formulations with polymers were subjected to DSC studies. And were scanned at 5^0C/min. Thermal analysis of Ibuprofen and its formulations with β–cyclodextrin will be recorded on a DSC. The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 5^0/min was employed over a temperature range of 0^0 - 350^0 with nitrogen purging. Powder sample was weighed into an aluminium pan was used as reference.

Method of preparation of buccal films of Salbutamol sulphate:

Buccal films of Salbutamol sulphate were prepared by solvent casting technique using film formig polymers. Required amount of HPMC according to formulation table was weighed accurateiy and soaked in 10 ml of water. The beaker containing polymer and water was kept aside for 10 min for swelling of the polymer. Required amount of water was added to the above polymer solution and the dispersion was stirred. Simultaneously Salbutamol sulphate was accurately weighed and dissolved in 10 ml of distilled water in another beaker. Then the drug solution was added to the polymer solution and 5 ml of 10% w/v glycerol as plasticizer was mixed thoroughly with the help of a magnetic stirrer. The glass mould (petridish) having diameter 8.7 cm, whose surface was lubricated with liquid paraffin was placed over a flat surface and 10 ml of resulting solution with the help of measuring cylinder was transferred into petridish slowly drop by drop and spread it uniformly. Inverted funnel was placed over the petridish to have uniform evaporation. The petridish containing polymeric solution of drug was kept 12 hours at room temperature for drying. After drying the films were observed and checked for possible imperfections and upon their removal from moulds then they were cut into the required sizes they were covered with wax paper and preserved in dessicator till evaluation tests were performed. The films were examine in order to select the films having the best characteristics. Similarly formulations F2, F3, F4, F5 and F6 were prepared.

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Evaluation of buccal films

The films were evaluated for the following parameters.

Folding endurance: Folding endurance was determined by repeatedly folding a small strip of film at the same place 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: The thickness of the film is measured using screw gauge micrometer with a least count of 0.01 mm. The maximum probable size for buccal films is 15 cm^2 but usual range of comfortable size is 1 to 3 cm^2. The thickness of the films must be limited to a few mm. The shapes comfortable to be used by the patient are either ellipsoidal or circular.

Surface P^H: Surface pH of the buccal patches (without backing membrane) was determined by a modified method. Buccal patches were left to swell for 2 hours on the surface of an agar plate, prepared by dissolving 2%(m/V) agar in war isotonic phosphate buffer (pH 6.75) under stirring and then pouring the solution into a Petri dish till it gelled at room temperature. The surface pH was measured by bringing a combined glass electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The experiment was repeated thrice and the average was taken.

Film Weight:

six films from every formulation selected randomly and weighed individually on digital balance, than average weight was calculated

Swelling studies: 1cm^2 film of each formulation was accurately weighed ($w_1$gms) placed in a petridish containing 20ml of water. The weight of each film ($w_2$gms) was determined at 5 and 10 minutes by pressing the film with a tissue paper to remove the excess fluid. The swelling index was calculated by the formula

$$\text{Swelling index} = (w_2 - w_1)/ w_1$$

Where w_1 is initial weight of the film and w_2 is weight of the films after particular swelling time interval.

Tissue Preparation for Ex-vivo studies

From the local slaughter house the buccal mucosa was surgically removed from oral cavity and immediately transported to the laboratory in cold normal saline solution. The buccal mucosa with a part of submucosa was carefully separated from fat and muscles using surgical blade, then buccal epithelium was isolated from under lying tissue and was used with in 2hours.

Ex-vivo drug release studies of Salbutamol sulphate patches in phosphate buffer P^H (6.6):

A glass tube with two ends open was taken and a patch of 1.6 × 1.6 cm size was cut and attached. Then the buccal mucosa of same size was taken and then the setup was attached to glass tube containing the film. Then a250ml beaker was taken with 200ml of phosphate buffer PH 6.6 then with the help of a holder the test tube was dipped into the beaker such that the buccal mucosa touches the surface of the buffer. Then the buffer solution was circulated with help of magnetic bead in magnetic stirrer at speed of 50 rpm at regular intervals of time say 15,30,45,60,75,90,120,150,180,210 and 240 min . then 5ml of sample is withdrawn and same 5ml of buffer solution was replaced. Then finally the samples were analysed using U.V spectrometer at 276nm.

RESULTS AND DISCUSSION

Table 1. Formulation of buccal films of Salbutamol sulphate:

S.No	Formulation	F1	F2	F3	F4	F	F6
1	Salbutamol sulphate(mg)	50	50	50	50	50	50
2	HPMC(mg)	1000	2000	3000	4000	3000	4000
3	PVP(mg)	-	-	1000	1000	-	-
4	Sodium alginate(mg)	-	-	-	-	1000	1000
5	Glycerol (10%v/v) (ml)	5	5	5	5	5	5
6	Distilled water(ml)	30	30	40	40	40	40

Table 2. Standard plot of Salbutamol sulphate

S.No	Concentration (mcg/ml)	Absorbance
1	10	0.039
2	20	0.078
3	30	0.117
4	40	0.163
5	50	0.189

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Table 3. Reports of folding endurance of buccal films:

Formulation	Folding Endurance			
	Trial -1	Trial -2	Trial -3	Average
f1	285	291	289	288.3
f2	205	203	208	204.3
f3	214	217	215	215.3
f4	242	238	244	241.3
f5	14	16	16	15.3
f6	8	6	6	6.6

Table 4. Reports of surface P^H of buccal films:

Formulation	Surface P^H			
	Trial -1	Trial -2	Trial -3	Average
f1	6.20	6.22	6.24	6.22
f2	6.40	6.40	6.41	6.40
f3	6.69	6.71	6.72	6.70
f4	6.74	6.74	6.73	6.73
f5	6.66	6.67	6.66	6.66
f6	6.70	6.70	6.70	6.70

Table 5. Reports of film thickness of buccal films:

Formulation	Film Thickness(mm)			
	Trial -1	Trial -2	Trial -3	Average
f1	0.17	0.16	0.16	0.16
f2	0.28	0.38	0.29	0.38
f3	0.31	0.32	0.32	0.32
f4	0.34	0.34	0.33	0.34
f5	0.28	0.28	0.29	0.28
f6	0.32	0.34	0.34	0.33

Table 6. Reports of weight (mg) of buccal films:

Formulation	Weight (Mg)			
	Trial -1	Trial -2	Trial -3	Average
f1	58	57	56	57
f2	108	109	108	108.3
f3	78	79	78	78.3
f4	97	96	98	97
f5	88	88	88	88
f6	96	95	95	95.3

Table 7. Reports of Swelling index of buccal films:

Formulation	Swelling Index			
	Trial -1	Trial -2	Trial -3	Average
f1	49.1	52.6	49.1	50.2
f2	81.9	81.2	80.7	81.2
f3	25.9	24.8	25.3	25.3
f4	33	46	35	34.6
f5	40	43	42	41.6
f6	56.8	56.3	56.7	56.6

Table 8. In-Vitro drug release data for F1

S.No	Time (min)	Conc(mg/ml)	%drug release	Cumulative % drug release
1	15	0.56	7	7
2	30	0.24	3	10
3	45	0.28	3.5	13.5
4	60	0.32	4	17.5
5	75	0.36	5	22
6	90	0.44	5.5	27.5

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7	120	0.48	6	33.5
8	150	0.52	6.5	40
9	180	0.56	7	47
10	210	0.6	7.5	54.5
11	240	0.68	8.5	63

Table 9. In-Vitro drug release data for F2

S.No	Time (min)	Conc (Mg/200ml)	% Drug Release	Cumulative Drug Release
1	15	0.6	7.5	7.5
2	30	0.24	3	10.5
3	45	0.28	3.5	14
4	60	0.36	4.5	18.5
5	75	0.4	5	23.5
6	90	0.48	6	29.5
7	120	0.52	6.5	36
8	150	0.56	7	43
9	180	0.6	7.5	50.5
10	210	0.68	8.5	59
11	240	0.72	9	68

Table 10. In-Vitro drug release data for F3

S.No	Time (min)	Conc (Mg/200ml)	%Drug Release	Cumulative Drug Release
1	15	0.76	9.5	9.5
2	30	0.32	4	13.5
3	45	0.4	5	18.5
4	60	0.44	5.5	24
5	75	0.52	6.5	20.5
6	90	0.56	7	37.5
7	120	0.64	8	45.5
8	150	0.68	8.5	54
9	180	0.76	9.5	63.5
10	210	0.8	10	73.5
11	240	0.84	10.5	84

Table 11. In-Vitro drug release data for F4

S.No	Time (min)	**Conc** (Mg/200ml)	%Drug Release	Cumulative Drug Release
1	15	0.76	9.5	9.5
2	30	0.28	3.5	13
3	45	0.36	4.5	17.5
4	60	0.44	5.5	23
5	75	0.52	6.5	29.5
6	90	0.6	7.5	37
7	120	0.68	8.5	45.5
8	150	0.72	9	54.5
9	180	0.8	10	64.5
10	210	0.84	10.5	75
11	240	0.92	11.5	86.5

Table 12. In-Vitro drug release data for F5

S.No	Time (min)	Conc (Mg/200ml)	%Drug Release	Cumulative Drug Release
1	15	0.72	9	9
2	30	0.28	3.5	12.5
3	45	0.36	4.5	17
4	60	0.4	5	22

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5	75	0.44	5.5	27.5
6	90	0.48	6	23.5
7	120	0.56	7	40.5
8	150	0.6	7.5	48
9	180	0.64	8	56
10	210	0.68	8.5	64.5
11	240	0.72	9	73.5

Table 13. In-Vitro drug release data for F6

S.No	Time (min)	Conc (Mg/200ml)	%Drug Release	Cumulative Drug Release
1	15	0.64	8	8
2	30	0.24	3	11
3	45	0.32	4	15
4	60	0.4	5	20
5	75	0.48	6	26
6	90	0.56	7	33
7	120	0.64	8	41
8	150	0.68	8.5	49.5
9	180	0.72	9	58.5
10	210	0.76	9.5	68
11	240	0.8	10	78

Table 14. Comparision of cumulative % in-vitro drug release data for all formulations

S.No	Time(min)	Cumulative % drug release					
		F1	F2	F3	F4	F5	F6
1	15	7.5	7.5	9	8	9.5	9.5
2	30	10.5	10.5	12.5	11	13.5	13
3	45	13.5	14	17	15	18.5	17.5
4	60	17.5	18.5	22	20	24	23
5	75	22	23.5	27.5	26	30.5	29.5
6	90	27.5	29.5	33.5	33	37.5	37
7	120	33.5	36	40.5	41	45.5	45.5
8	150	40	43	48	49.5	54	54.5
9	180	47	50.5	56	58.5	63.5	64.5
10	210	54.5	59	64.5	68	73.5	75
11	240	63	68	73.5	78	84	86.5

Fig 1. Calibration curve of Salbutamol sulphate

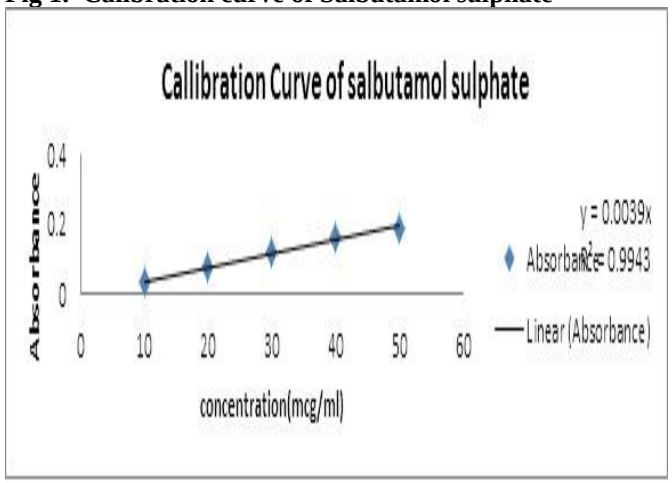

Fig 2. FT-IR Spectrum of Salbutamol sulphate

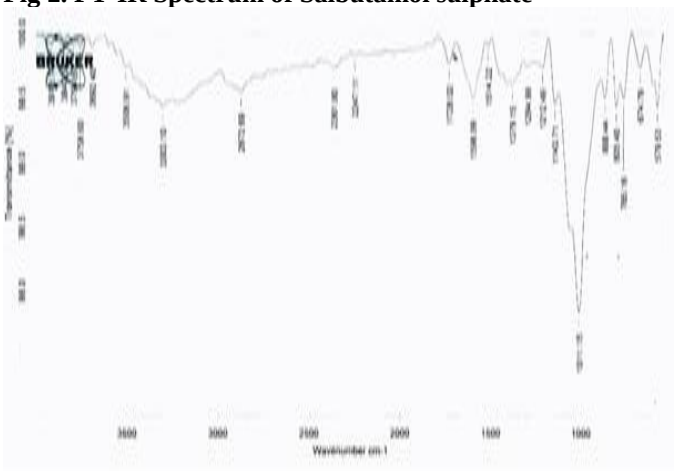

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Fig 3. FT-IR Spectrum of Salbutamol sulphate + PVP

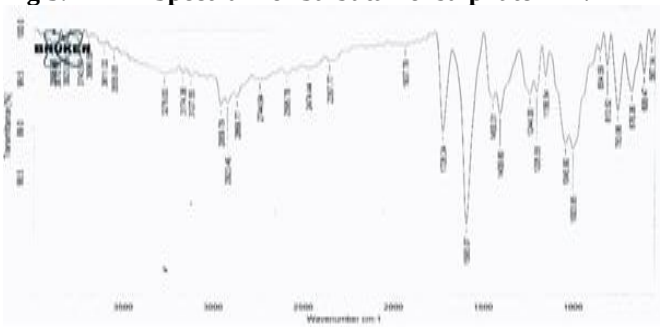

Fig 4. FT-IR Spectrum of Salbutamol sulphate + PVP+HPMC

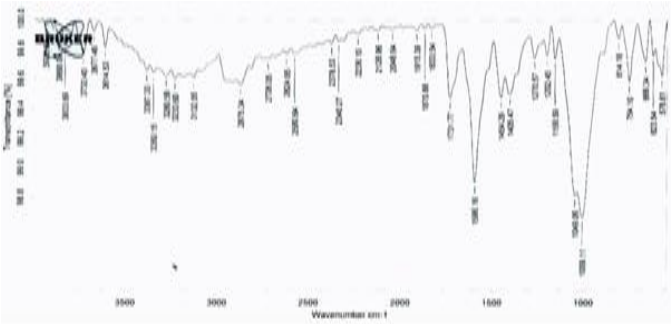

Fig 5. FT-IR Spectrum of HPMC

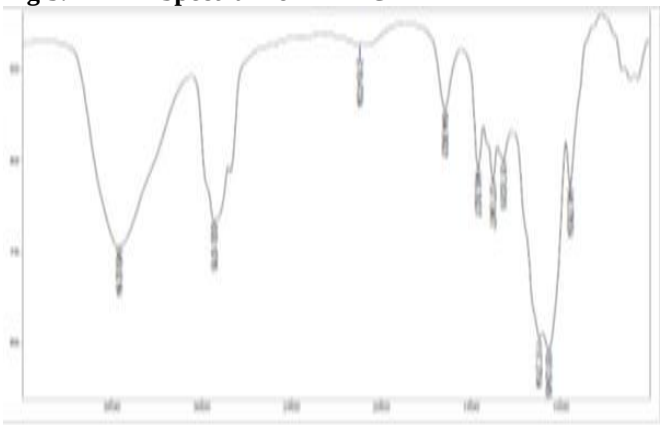

Fig 6. FT-IR Spectrum of HPMC with Salbutamol sulphate

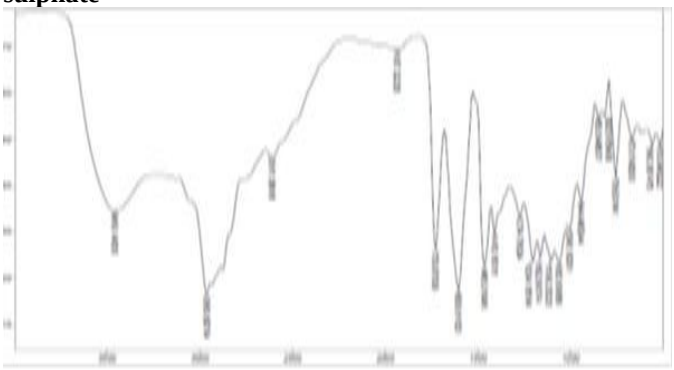

Fig 7. FTIR spectra of Sodium alginate

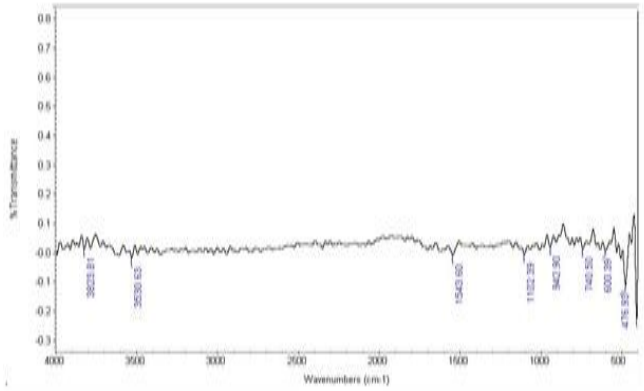

Fig 8. DSC thermogram of Sodium alginate

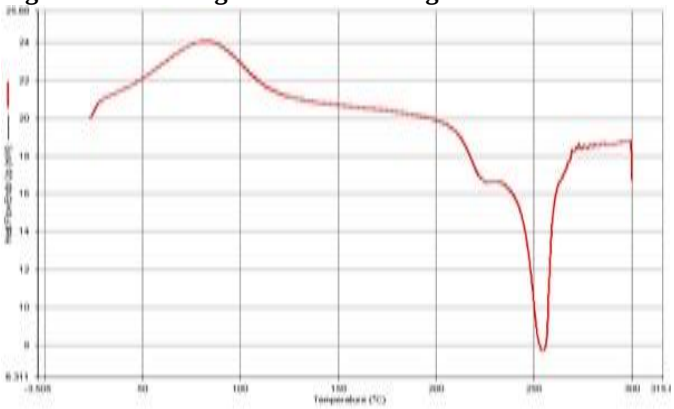

Fig 9. DSC of HPMC (50 cps)

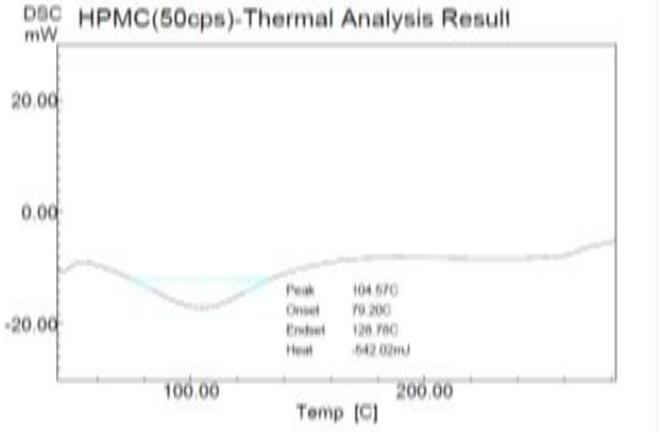

Fig 10. In-Vitro drug release plot for F1

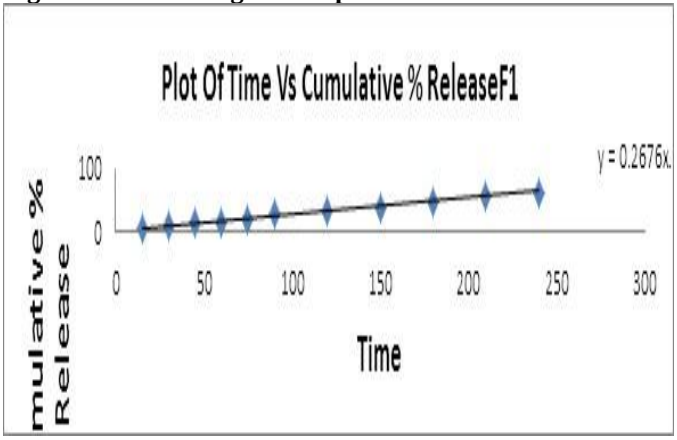

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Fig 11. In-Vitro drug release plot for F2

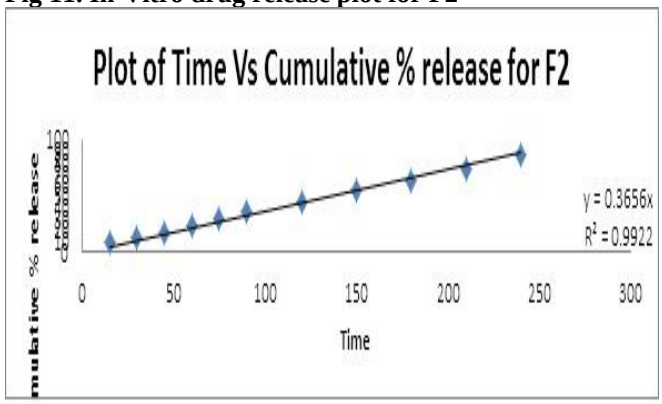


Fig 12. In-Vitro drug release plot for F3

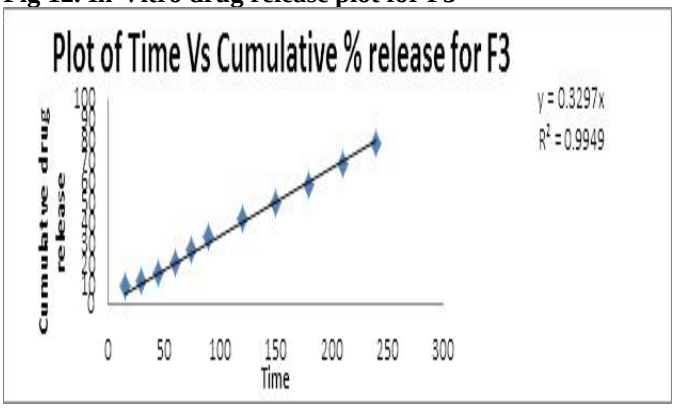


Fig 13. In-Vitro drug release plot for F4

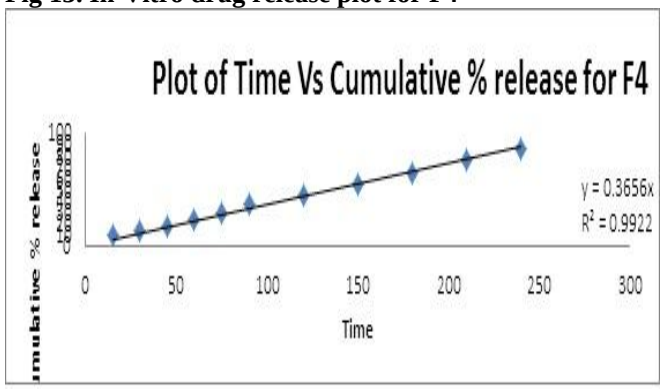


Fig 14. In-Vitro drug release plot for F6

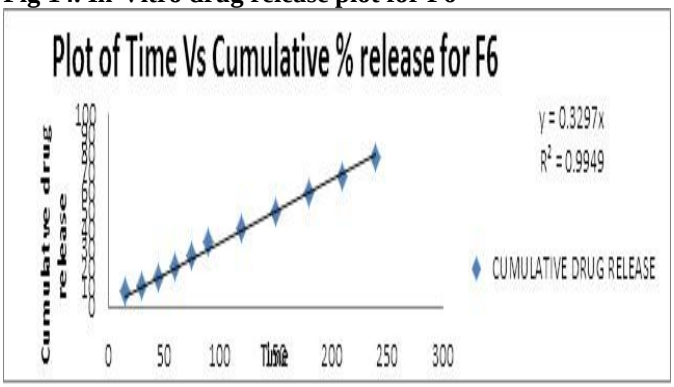
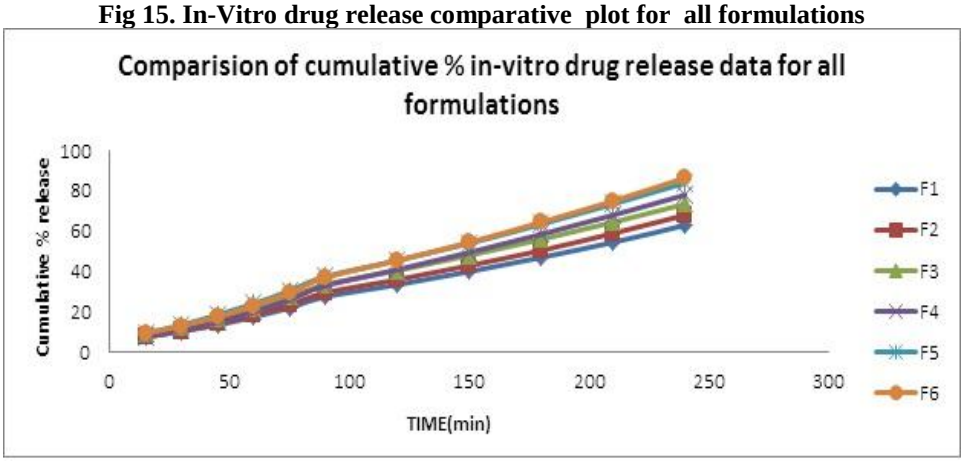


Fig 15. In-Vitro drug release comparative plot for all formulations



DISCUSSION

The prepared Salbutamol sulphate buccal films are characterized for FTIR, DSC, and various parameters have been evaluated.

The FTIR reports had concluded that the prepared Salbutamol sulphate buccal films showed no interactions between drug and the film forming polymers.

The DSC data revealed HPMC melting point and Salbutamol sulphate melting point which corresponds to melting point of pure forms of HPMC, Sodium alginate and Salbutamol sulphate.

Average folding endurance of Salbutamol sulphate buccal films was found in the range of 6.6 - 288.3 ,Average surface pH of Salbutamol sulphate buccal films was found in the range of 6.22-6.73,Average film thickness of Salbutamol sulphate buccal films was found in the range of 0.16-0.38mm.Average weight of Salbutamol sulphate buccal films was found in the range of 57-108.3mg .Average swelling index of Salbutamol sulphate buccal films was found in the range of 25.3-81.2.

Highest % drug release was found to be at time interval of 4 hours and lowest % drug release was found to be at time interval of 30 minutes for all formulations. However further studies like tensile strength , drug uniformity, mucoadhesive strength ,mucoadhesive time are required to confirm the results.

Asian J. Pharm. Res. Vol 5, Issue 3, 167-175, 2015.

CONCLUSION

Studies were carried out on the formulation and evaluation of Salbutamol sulphate buccal films with a view to determine % cumulative ex-vivo drug release , various types of films forming polymers used are HPMC, PVP, sodium alginate. Solvent casting technique was implemented for the preparation of buccal films. Cumulative % ex-vivo drug release of HPMC and sodium alginate (4:1) combination was found to be higher than all other formulations. Hence it is having higher bioavailability.

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