International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 3, Issue 3, 2011

Research Article

PREPARATION AND EVALUATION OF BUCCAL FORMULATION FOR TRIAMCINOLONE

AVINASH SINGH*, PINKESH PATEL, RAMA BUKKA, JIMMY PATEL

Department of Pharmaceutics, Nargund College of Pharmacy, Bangalore, Karnataka-560085 Email: avinash_394@yahoo.com

Received: 31 May 2011, Revised and Accepted: 21 June 2011

ABSTRACT

Buccal drug delivery system using muco-adhesive polymer has been recently interested due to avoidance of the first pass effect and high blood level.aim of the present study was to formulate the buccal films and selection of most satisfactory formulation by in vitro evaluation. Muco-adhesive films of Triamcinolone Acetonide composed of Carbopol 934 and Hydroxyl Propyl Methylcellulose (HPMC) were developed by solvent casting method. The films were evaluated for swelling study, surface pH, bio- adhesive strength, in vitro residence time, in vitro drug permeation study, and in vitro drug release study. In vitro drug permeation study showed that 3 % menthol gave 20% permeation than 6% menthol. In vitro studies revealed that F2 buccal patches gave low swelling index, longer muco-adhesion and intermediate muco-adhesive strength. In conclusion, this formulation is proposed as a good formula. It is suggested that in the development of buccal drug delivery system swelling behavior and duration if muco adhesion determined by in vitro study is critical factor in the selection of satisfactory formulation.

Keywords: Buccal Drug Delivery, Triamcinolone Acetonide, Carbopol 934, muco-adhesion.

INTRODUCTION

In recent years, significant interest has been expressed in development of controlled drug delivery to or via mucous membranes by the use of bioadhesive polymers. These dosage forms can be administered by different routes, ocular, nasal, rectal and vaginal, for local and systemic drug delivery[1-4]. The term bioadhesion is defined as the attachment of synthetic or biological micromolecules to a biological tissue[5]. Among the various routes of delivering mucoadhesive dosage forms, the buccal route appear to offer advantage of good accessibility, robust epithelium, easy removal of dosage forms in the need, good drug absorption, reduction of first pass metabolism and satisfactory patient compliance[2,3] . Buccal adhesive patches are a novel form of mucoahesive systems, which are thin and flexible and usually prepared by dissolving the bioadesive polymers along with plasticizer in a solvent, followed by solvent evaporation. Moreover, the buccal films are able to protect the wound surface, thus reduce pain and also could treat oral disease more effectively. Various synthetic and natural polymers have been investigated for their application in buccal delivery system as including poly (acrylic acid), hydro alkyl cellulose, polymethacrylate, chitosan, and collagen. Acrylic- based polymer devices exhibit very high adhesive bond strength.

Here carbopol having high swelling behavior so hydroxyl propyl methyl cellulose was added into it in order to reduce their swelling index. Triamcinolone acetonide having biological half life only 2-4 hours, and oral bioavailability only 23% so in order to increase their bioavailability this molecule was selected, having wide variety of application in asthama, inflammation, rhinitis, ulcers, chronic obstructive pulmonary disease. In this study, menthol was used as enhancer and selects the optimum concentration for TAA. Aim of The Study was to prepare buccal films of TAA and evaluate the most satisfactory buccal formulation based on in vitro evaluation test which having high mucoadhesive strength, low swelling index, long residence time and slow release.

METHODOLOGY

Determination of λ_{max}

11 mg of Triamcinolone acetonide equivalent to 10 mg of Triamcinolone was dissolved in 100 ml of ethanol giving 1mg/10ml solution. Suitable dilutions were made in phosphate buffer pH 7.4 and propylene glycol (6:4). And finally scanned for maximum absorbance using UV spectrophotometer in the range from 200 to 800 nm.

Construction of standard curve for Triamcinolone acetonide

110 mg of Triamcinolone acetonide equivalent to 100 mg of Triamcinolone was dissolved in 100 ml of ethanol and volume was made up to mark using ethanol, to make (1mg/ml) standard stock solution (I). Then 10 ml stock solution (I) was taken in another 100 ml volumetric flask and further dilute up to 100 ml with ethanol to give 100 µg/ml standard stock solution (II). Final concentrations were prepared 2, 4, 6, 8, 10, 20, 30, 40, 50µg/ml. The absorbance of standard solution was determined UV-VIS spectrophotometer at 241 nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least–square linear regression analysis.

Preparation of Triamcinolone acetonide buccal films

Preparation of polymeric solution: Buccal film of Triamcinolone acetonide was prepared by solvent casting method. Weigh the required quantity of Hydroxyl propyl methyl cellulose (HPMC) and Carbopol to make the 25 ml of the polymeric solution. Ethanol and dichloromethane solvent was added to HPMC polymer to make the polymeric solution. Calculated amount of glycerine was added and mixed properly. Finally Carbopol solution in water after neutralization was added to above polymeric solution and mixed well. The polymeric solution was left overnight at room temperature to obtain bubble- free solution.

Incorporation of drug: To the above solution, calculated amount of Triamcinolone acetonide (4mg/1.766cm^2) was added and mixed properly. Petri dish was kept on level surface which was adjusted by spirit level. The polymeric solution was casted onto Petri dish and covered with glass funnel for control evaporation of ethanol and allowed to dry at room temperature (25^{0}C) up to 30 hrs. The dried film (1.5cm diameter) was cut and packed in aluminium foil and stored in desiccators until use. Blank film was prepared following the same procedure without addition of drug.

Evaluation parameters

Pre-formulation studies of the drug: It is one of the important prerequisite in development of any drug delivery system. Pre-formulation studies were performed on the drug, which included melting point determination, solubility studies[30] and Infrared (IR) absorption spectroscopy.

Post-formulation studies: The buccal films were evaluated for their physical, mechanical and bio-adhesive properties such as Thickness uniformity, Weight uniformity, Folding endurance[6], Surface pH[7], Swelling study[8], Percentage moisture loss[9] (PML), Percentage moisture absorption[9] (PMA), *In vitro* residence time[10], Bio-adhesive strength.[9]

Table 1: Composition of films prepared using polymer and Triamcinolone acetonide drug

Ingredients	Formula							
	F1	F2	F3	F4	F5	F6	F7	F8
Triamcinolone acetonide	0.28%	0.28%	0.28%	0.28%	0.28%	0.28%	0.28%	0.28%
Carbopol	0.25%	0.25%	0.5%	0.15%	0.75%	0.75%	0.5%	0.5%
Hydroxypropyl methylcellulose	2%	10%	6%	6%	2%	10%	0.34%	11.5%
Water	8%	8%	12%	6%	14%	14%	12%	12%
Glycerine	1.03%	4.82%	3.05%	2.89%	1.29%	5.05%	0.39%	5.64%
Ethanol:DCM (1:1)	100%	100%	100%	100%	100%	100%	100%	100%

Drug content uniformity: Three film units (each 1.5cm diameter) of each formulation were taken in 100 ml conical flasks. 30 ml ethanol was added into flask and stirred continuously for 24 h. The solutions were filtered stock (1). From stock (1) solution, 2 ml was taken and diluted with 10 ml of ethanol stock (2). From this second stock solution 2 ml was taken and diluted up to 10ml with phosphate buffer pH 7.4 and propylene glycol (6:4). Blank film solution was prepared using the same procedure and considered as blank for spectrophotometric estimation at 241nm.

4.2.6.12 *In vitro* release study[8]: Dissolution apparatus USP type II rotating paddle method was used to study drug release from buccal patches. The dissolution medium consisted of 900 ml of phosphate buffer pH 7.4. The study was performed at 37^{0}C with 100 rpm. One side of each buccal patch (3 patches) (1.5cm diameter) was attached to glass slide with cyanoacrylate glue. The glass slide was put to bottom of the vessel so that patch remained on the upper side of the glass slide. Sample (5ml) was withdrawn at predetermined time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours and replaced with fresh medium. The samples were filtered through whatman filter paper and assayed by U.V spectrophotometer at 241 nm.

Short-term stability studies

All the patches (F1–F8) were cut in 1.5 cm diameter and seven patch of each formulation were wrapped individually in aluminium foil and placed in polybag. Then all the patches were charged in stability chamber at 40°C and 75 % RH for a period of one month. The patch from each formulation was analyzed for the drug content and dissolution study at the end of the month. Averages of triplicate readings were taken.

Table 2: Calibration Curve of Triamcinolone acetonide in phosphate buffer pH 7.4: Propylene glycol (4:6)

Sr. NO	Concentration (µg/ml)	Absorbance
1	2	0.052
2	4	0.164
3	6	0.258
4	8	0.296
5	10	0.398
6	20	0.808
7	30	1.236
8	40	1.649
9	50	2.051

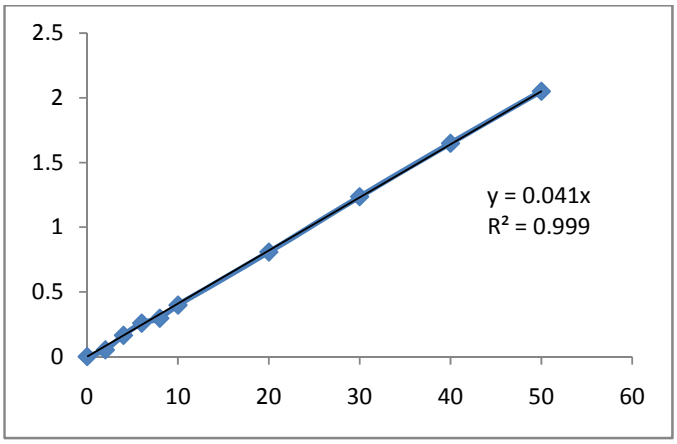

Fig. 1: Calibration curve of Triamcinolone acetonide Phosphate buffer pH 7.4 containing propylene glycol 60%

RESULTS

Melting point

Melting point of Triamcinolone acetonide was found to be 294^0**C**

Infrared (IR) absorption spectroscopy: Drug - Excipient Interaction Studies: Study is carried out using FTIR spectrophotometer (FTIR 1700S Spectrophotometer Shimadzu, Japan) by KBr pellet method, the spectra of drug with excipients and polymers confirms that drug is compatible with all excipients.

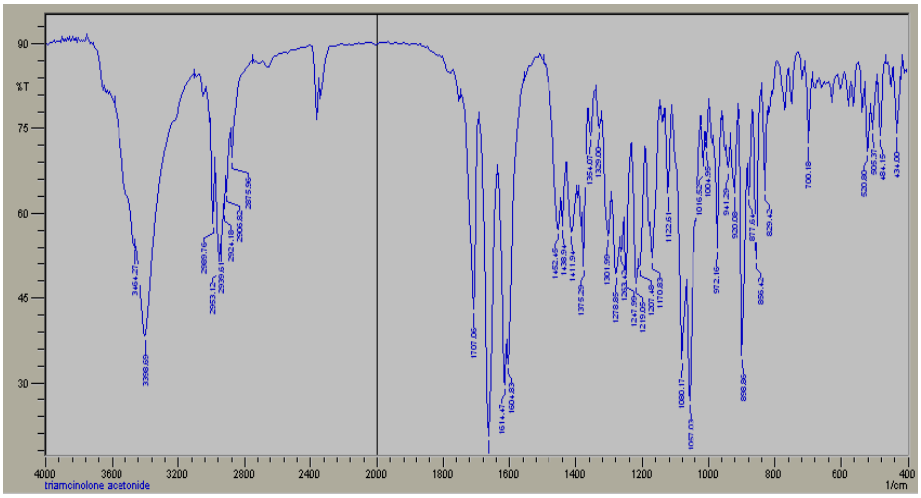

Fig. 2: IR Spectrum of Triamcinolone acetonide

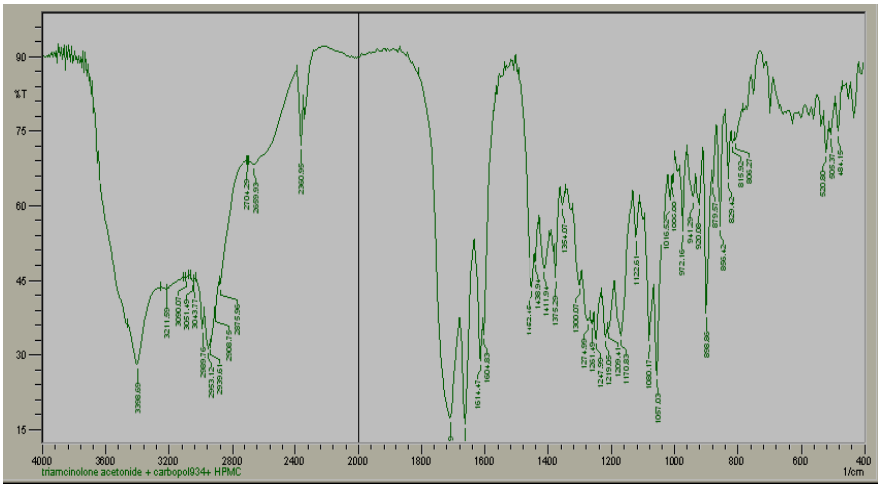

Fig. 3: Superimposed IR Spectrum of Triamcinolone acetonide & Carbopol, HPMC

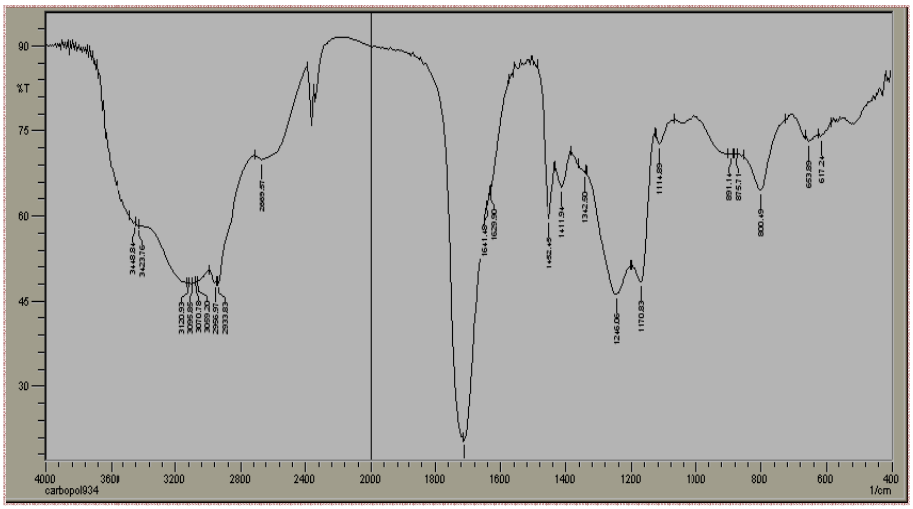

Fig. 4: IR spectrum of CARBOPOL 934

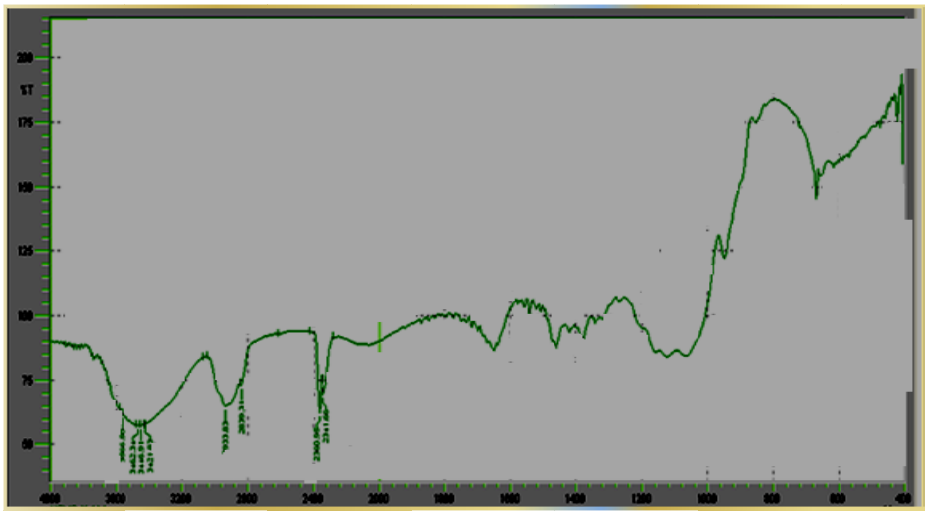

Fig. 5: IR Spectrum of HPMC

Physiochemical Evaluations of buccal Films of Triamcinolone acetonide:

Physical appearance and surface texture: All the patches were uniform, clear, flexible and continuous and can be easily removed from the Petridis after drying.

Folding endurance: Patches did not show any cracks even after folding for more than 250 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain patches and drug loaded patches..

Table 3: Thickness, Weight of film and Surface pH study:

Sr. No.	Formulation Code	Thickness (mm) ±S.D. (n = 10)	Weight of films in (mg) ± S.D. (n = 10)	Surface pH ± S.D. (n = 3)
1	F1	0.532 ± 0.013	53.64 ± 1.514	6.4 ± 0.141
2	F2	0.71 ± 0.015	1425.14 ± 2.285	6.5 ± 0.141
3	F3	0.606 ± 0.0151	79.02 ± 1.565	6.45 ± 0.07
4	F4	0.59 ± 0.0158	77.44 ± 1.757	6.55 ± 0.070
5	F5	0.558 ± 0.013	61.8 ± 1.742	6.2 ± 0.141
6	F6	0.752 ± 0.013	147.88 ± 2.244	6.0 ± 0.07
7	F7	0.772 ± 0.013	153.86 ± 3.227	6.1 ± 0.141
8	F8	0.688 ± 0.013	129.02 ± 1.50	6.45 ± 0.070

Table 4: Swelling Study:

Sr. No	Formulation Code	Percent Swelling (n=3)
1	F1	29.49 ± 0.06
2	F2	39.79 ± 0.48
3	F3	55.26 ± 0.23
4	F4	50.82 ± 0.83
5	F5	57.96 ± 0.81
6	F6	63.29 ± 0.33
7	F7	58.93 ± 0.43
8	F8	70.00 ± 0.64

Table 5: Percent Moisture Loss PML and Percent Moisture absorption PMA:

Sr. No.	Formulation Code	Percent Moisture Loss (w/w) ± S.D (n = 3)	Percent Moisture Absorption (w/w) ± S.D (n = 3)
1	F1	2.91± 0.01	2.29 ± 0.021
2	F2	4.1± 0.007	4.12 ± 0.028
3	F3	4.95 ± 0.021	6.09 ± 0.024
4	F4	1.7± 0.028	3.49 ± 0.042
5	F5	6.80± 0.007	4.21 ± 0.014
6	F6	7.5 ± 0.028	7.86 ± 0.021
7	F7	2.86± 0.035	3.23 ± 0.007
8	F8	5.51 ± 0.021	6.33 ± 0.028

Table 6: *In vitro* residence time:

Sr. No.	Formulation code	Time (min) ± S.D
1	F1	64 ± 1.41
2	F2	152.5 ± 3.53
3	F3	160
4	F4	147.5 ± 3.53
5	F5	121 ± 1.41
6	F6	181.5 ± 3.53
7	F7	98 ± 1.41
8	F8	142.5 ± 3.53

Table 7: *Ex vivo* mucoadhesive Strength:

Sr. No	Formulation Code	Bio-adhesive stren- -gth Mean ± S.D. (n = 3) (gm)	Force of adhesion ± S.D. (n = 3) (gm.)
1	F1	7.21 ± 0.021	0.070± 0.0002
2	F2	9.07 ± 0.098	0.088± 0.0009
3	F3	10.15 ± 0.056	0.099± 0.0005
4	F4	6.75 ± 0.070	0.066± 0.0006
5	F5	11.47 ± 0.035	0.112± 0.0003
6	F6	14.54 ± 0.028	0.142± 0.0002
7	F7	7.35 ± 0.22	0.072± 0.0022
8	F8	13.46 ± 0.014	0.132± 0.0001

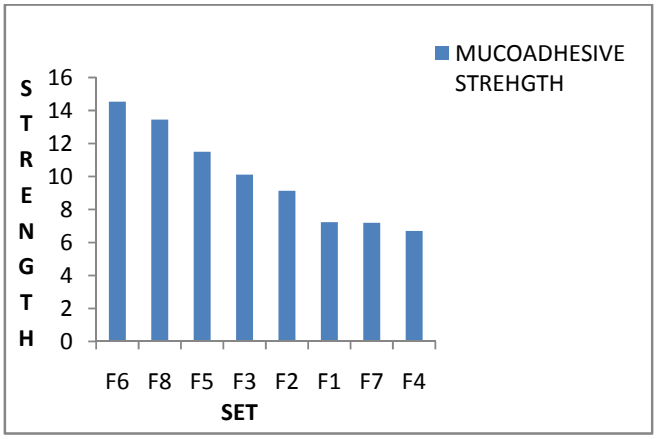

Fig. 6: Mucoadhesive Strength of Buccal Films

Table 8: Drug content uniformity (%)

Sr. No	Formulation Code	Percent of drug ± S.D. (n = 3)
1	F1	104.686± 1.578
2	F2	104.01± 1.262
3	F3	103.79± 0.578
4	F4	102.454± 0.31
5	F5	99.999± 0.631
6	F6	99.55± 1.262
7	F7	101.56 ± 0.31
8	F8	101.33 ± 1.262

Table 9: Cumulative percent release of Triamcinolone acetonide from F1 and F8 buccal Films

Time (hrs)	Cumulative percent release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	35.5	20.45	29.87	29.97	42.91	33.93	48.52	33.57
2	46.74	25.82	40.52	43.91	49.88	38.24	66.8	44.67
3	61.04	37.59	55.06	64.4	65.97	50.10	80.86	54.46
4	66.92	46.54	78.96	71.25	79.92	58.71	99.19	70.32
5	80.45	58.56	90.65	78	92.53	65.18	94.88	77.98
6	82.50	68.02	91	80.19	91.99	71.37	91.25	85.39
7	90.16	78.01	-	-	84.75	79.46	-	80.1
8	-	-	-	-	-	82.96	-	-
9	-	-	-	-	-	78.11	-	-

Table 10: *In vitro* release kinetic data of Triamcinolone acetonide from polymeric buccal films

Batch Code	Zero Order r^2	First Order r^2	Higuchi release r^2	Pappas release	
				r^2	N
F1	0.970	0.981	0.988	0.990	0.49
F2	0.995	0.962	0.965	0.968	0.717
F3	0.974	0.970	0.985	0.987	0.62
F4	0.913	0.969	0.961	0.972	0.579
F5	0.825	0.729	0.960	0.919	0.429
F6	0.934	0.934	0.985	0.964	0.445
F7	0.877	0.795	0.939	0.968	0.403
F8	0.933	0.933	0.997	0.986	0.457

Table 11: *In vitro* drug releases from F2 buccal film

Time (hr.)	Absorbance	Conc. (mg)	% CPR
1	0.041	0.899	22.49
2	0.050	1.108	27.71
3	0.073	1.602	40.05
4	0.504	1.98	49.66
5	0.115	2.53	63.38
6	0.132	2.89	72.43
7	0.155	3.40	85.05
8	0.149	3.27	81.76

Short-term stability studies

From one month stability data at 40º**C**/75 % RH, it was found that there were no significant differences in drug content as well as drug dissolution before and after stability. This indicates that the prepared buccal patches were stable.

CONCLUSION

Triamcinolone acetonide buccal patches (F1-F8) were prepared by the method of solvent casting technique. The prepared Triamcinolone acetonide buccal patches were evaluated.

The mean thickness and weight of buccal polymeric patches increased with an increase in the amount of polymer percent. The observed surface pH of all the formulations was found to be in between 6.00 to 6.55. This is in the range of salivary pH. So they may not produce any local irritation to the buccal mucosa. We have observed swelling study data on basis of weight. Swelling was found in order of F8>F6>F7>F5>F3>F4>F2>F1 which indicate that Carbopol having very high swelling capacity as compare to HPMC. Checking the physical stability of the patch at dry conditions and integrity of the patch at high humid conditions, the patches were evaluated for PML and PMA. The observed result indicates that as the percentage of Carbopol and HPMC increased, PML and PMA increased simultaneously. *In vitro* residence time of the patches were determined, which was found in the order of F6>F3>F2>F4>F8>F5>F7>F1. So we conclude that both Carbopol and HPMC imparts in *In vitro* residence time.

The *Ex vivo* muco-adhesive strength (bio-adhesive strength) of polymeric buccal patches was found to be in the following order F6>F8>F5>F3>F2>F7>F1>F4; which indicates that bio-adhesive strength increases with increasing the percentage of Carbopol. HPMC does not impart that much effect on muco-adhesive strength as Carbopol. *In vitro* drug release has been performed for all formulation up to 10 hrs which indicates that HPMC is extending the drug release at higher extent while Carbopol is having very less capacity extend the drug release as compare to HPMC. In most formulations, the release exponent values (n) for Korsmeyer-Peppas were found in the range 0.45 to 0.71 exhibited Anomalous (non-fickian) diffusion mechanism. Among all the formulations, F2 is optimized formula in terms of swelling study, bio-adhesive strength, *and in vitro* residence time and drug release behavior. Finally stability study was carried out for optimized formulation (F2).

So lastly we conclude that, Triamcinolone acetonide buccal patch of Carbopol and HPMC can meet the ideal requirement for sustained release buccal devices, which can be good way to by-pass the extensive hepatic first pass metabolism and increase bioavailability.

ACKNOWLEDGEMENT

The Authors are grateful to the Director, Dr. L.V.G. Nargund and the H.O.D. Dept. of Pharmaceutics Dr. C.S.R. Lakshmi, Nargund college of Pharmacy, Bangalore, for providing facilities necessary for the project undertaken and their constant encouragement.

REFERENCES

1. Gross l. hoffinman r.medical and biological adhesive. In skeist I. editor. Handbook of adhesives, 2nd ed. Newyourk:1977.
2. Peppas NA, Buri PA. surface interfacial and molecular aspect of bioadhesion on soft tissues. J Controllled rel 1985;2:257-75
3. Mortazavi SA, Smart JD. An in vitro method for assessing the duration of mucoadhesion. J Controllled rel. 1994;31:207-12
4. Ahuja A, Khar RK, Ali J. mucoadhesive drug delivery system drug dev. Ind pharm. 1997;23:489-515
5. Chen JL, Cyr GN. Compositions producing adhesion through hydration. Academic press, London pp 163-81
6. Khurana R, Ahuja A, Khar RK. Development and evaluation of mucoadhesive films of miconazole nitrate. Indian J Pharm Sci 2000; 62: 449-53.
7. Patel VM, Prajapati BG. Design and characterization of chitosan containing mucoadhesive buccal patches of propranolol hydrochloride. Acta pharm 2007; 57: 61-72.
8. Choi1 HK, Choi YJ, Cho CS. A Novel Mucoadhesive Polymer Film Composed of Carbopol, Poloxamer and Hydroxypropyl methylcellulose. Arch Pharm Res 2007; 30(3): 381-6.
9. Gupta A, Garg S, Khar RK. Measurement of bio-adhesive strength of muco-adhesive buccal tablets: design of an in-vitro assembly. Indian Drugs 1992; 30: 152-5.
10. Han RY, Fang JY, Sung KC, Hu OYP. Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. Int J Pharm 1999; 177: 201-9.
11. Şenel S, Atilla A. Drug permeation enhancement via buccal route: possibilities and limitations. Journal of controlled release 2001; 72:133-44.
12. Choudhary A, Tiwari G, Pandey M. Formulation and characterization of carvedilol buccal mucoadhesive patches. Int. J. Res. Pharm. Sci 2010; 1(4): 396-401
13. Mahmood AM, Ch'ng HS. Design of a dissolution apparatus suitable for in situ release study of Triamcinolone acetonide from bio-adhesive buccal tablets. International Journal of Pharmaceutics 1995 July; 121(2): 129-39.

14. Basu1 B, Garala1 K, Thimmasetty J. Formulation and Evaluation of Pimozide Buccal Mucoadhesive Patches, Int J Pharm Sci & Nanotech 2010 January-March; 2(4): 739-48

15. Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. Eur J Pharm Biopharm 2010 Dec;77(2):187-99.