FORMULATION AND EVALUATION OF RANOLAZINE BUCCAL PATCHES BY USING NATURAL POLYMERS

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ABSTRACT: *The objective of present study was to develop matrix type buccal patch therapeutic systems of Ranolazine using natural polymers as matrix formers. Ranolazine buccal patches were developed by using solvent casting technique. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated. An **in vitro** drug release study was designed, and it was carried out using commercial semipermeable membrane. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction was observed. The in vitro release study revealed that F1 formulation showed maximum release in 8 hrs. The release of Ranolazine appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F1 formulation was concluded as optimized formulation.*

Key words: Buccal patch, Buccal delivery system, Ranolazine, natural polymers, solvent casting technique, Diffusion mechanism.

I.INTRODUCTION

Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo first-pass effect.[1] The buccal route appears to offer a number of advantages, like good accessibility, robustness of the epithelium, usage of the dosage form in accordance with need, and comparatively less susceptibility to enzymatic activity. Hence, adhesive mucosal dosage forms were prepared for oral delivery, in the form of adhesive tablets adhesive gels and adhesive patches. [2,3,4,5,6] Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre systemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for the drug absorption . Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. [7,8] The buccal cavity is easily accessible for self medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries.[9] Buccal patches are preferred over adhesive tablets in respect of its flexibility and patients comforts. Bioadhesive polymers are used to control the buccal drug delivery due to their ability to localize the dosage form in specific regions to enhance drug bioavailability. [10] Ranolazine is indicated for the treatment of chronic angina. Unlike other anti-anginal medications such as nitrates and beta blockers, ranolazine does not significantly alter either the heart rate or blood pressure. Hence, it is of particular use in individuals with angina that is nonresponsive to maximal tolerated doses of other anti-anginal medications. [11]

II.MATERIALS AND METHODS

2.1 MATERIALS
Ranolazine was collected as a gift sample from Hetero labs, Hyderabad. Natural polymers and various excipients poly ethylene glycol, dimethyl sulfoxide were purchased from AR chemicals, Hyderabad.

2.2 METHODOLOGY

Compatibility studies of drug and polymers:[12]

In the formulation of Ranolazine buccal patch formation , API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Ranolazine and the selected polymers. The pure drug and drug with excipients were scanned separately.

Formulation design:

Table-1: Formulation Design of Ranolazine buccal Patches

S. No	F.Code	Ingredients (mg)					
		Drug (mg)	Sodium alginate	Chitosan	Tragacanth	PEG	DMSO
1	F1	100	500	-	-	1ml	0.1ml
2	F2	100		500	-	1ml	0.1ml
3	F3	100	1000	-	500	1ml	0.1ml
4	F4	100	-	1000	-	1ml	0.1ml

Preparation method[13,14]

Solvent casting method:

Ranolazine buccal patches were formulated by the solvent casting evaporation technique. The drug Ranolazine was diffused in suitable solvent. Natural Polymers like sodium alginate, Tragacanth and Chitosan were taken in a boiling tube, to this add Ranolazine drug which was previously dissolved in methanol. Sufficient care was taken to prevent the creation of lumps. PEG was taken as a plasticizer and Dimethylsulfoxide as permeation enhancer and added to the mixture and mixed well. It was set aside for 1 hour to exclude any entrapped air and was then transferred into a previously cleaned Petri plate ($4cm^2$), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Fig-1: Ranolazine buccal patch

Characterization of Buccal formulation

Physico- chemical evaluation[15]

Physical appearance:

All the formulated Ranolazine films were observed for color, clarity, flexibility, and smoothness.

Folding endurance:[16]

Buccal patches folding endurance was estimated by frequently double over at the same place till it broke. The number of times the film could be folded at the same place without breaking is the folding endurance. This was restate on all the films for three times and the mean values plus standard deviation was calculated.

Thickness of the film:[17]

The thickness of each film was measured by using screw gauze. Buccal patches thickness was estimated at various sites on each patch and the average thickness of the Buccal patch was capture as the thickness of the patch.

Weight uniformity:[18]

The formulated Buccal patches are to be dried at 60^0C for 6 hours before trial. A identify the area of 4.52 cm^2 of film is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content :[19]

The formulated Buccal patch were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one patch from each was taken and assayed for content of drug.

The Buccal films (4.52 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4 contain 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analyzed spectrophotometrically for drug content at 230 nm. Similarly a blank was prepared from Buccal films without drug.

Moisture absorption studies:[20]

The buccal patches were weighed exactly and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies:[21]

Three patches were weighed separately and kept in a desiccator contains calcium chloride at 37^0C for 24 hours. Then the last weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Swelling ratio:[22]
Swelling ratio was studied by measuring the percentage water uptake by the buccal patch. Patches were accurately weighed and placed in 100 ml of 6.8 phosphate buffer. Ranolazine buccal film were removed from their respective swelling media after 8 h and weighed after drying the surface water using filter paper. The water uptake was calculated as the ratio of the increase in weight of beads after swelling to the dry weight.

$$\text{Swelling ratio} = \frac{\text{Swollen wt - Initial wt}}{\text{Initial wt}} \times 100$$

In vitro release study:[23]

The release rate of the drug was determined by using Franz diffusion cell apparatus temperature maintained at 37 ± 0.5 ^{0}C and stirred at a rate of 200 rpm. Sink conditions was maintained all over the study. The vessel containing 10ml of phosphate buffer pH 6.8 phosphate buffer solution. Aliquots of 1ml of samples were withdrawn at various time meanwhile and then analyzed using a UV Spectrophotometer at 230 nm against blank.

% release rate of drug was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug in the film

Da = The amount of drug released

Stability studies:[24]

Optimized medicated films were subjected to short term stability testing. The Buccal films were sealed in aluminium foils and kept in a humidity chamber maintained at $40 \pm 2\ ^0C$ and $75 \pm 5\%$ RH for 1 month as per ICH guidelines.

III. RESULTS AND DISCUSSION

Compatibility studies of drug and polymers:

All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Ranolazine and polymer. It also confirmed that the stability of drug during microencapsulation process.
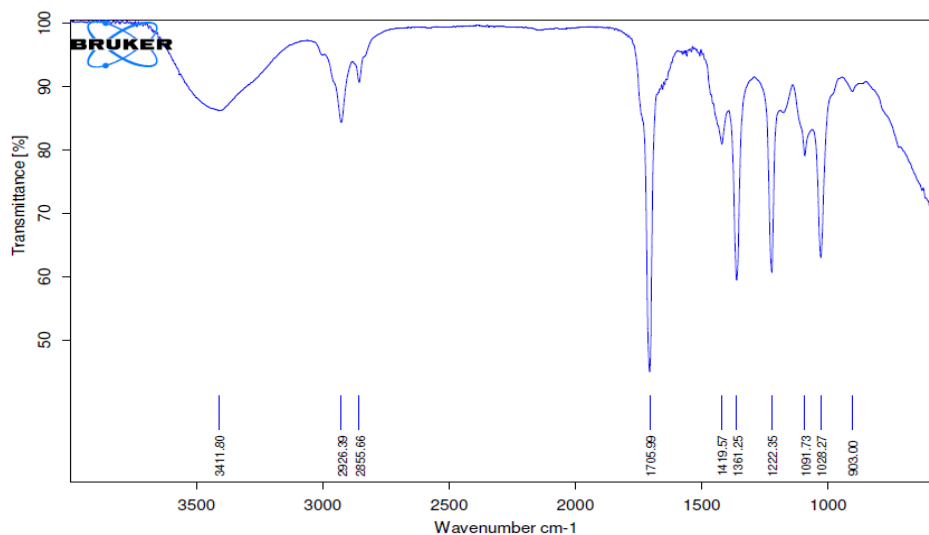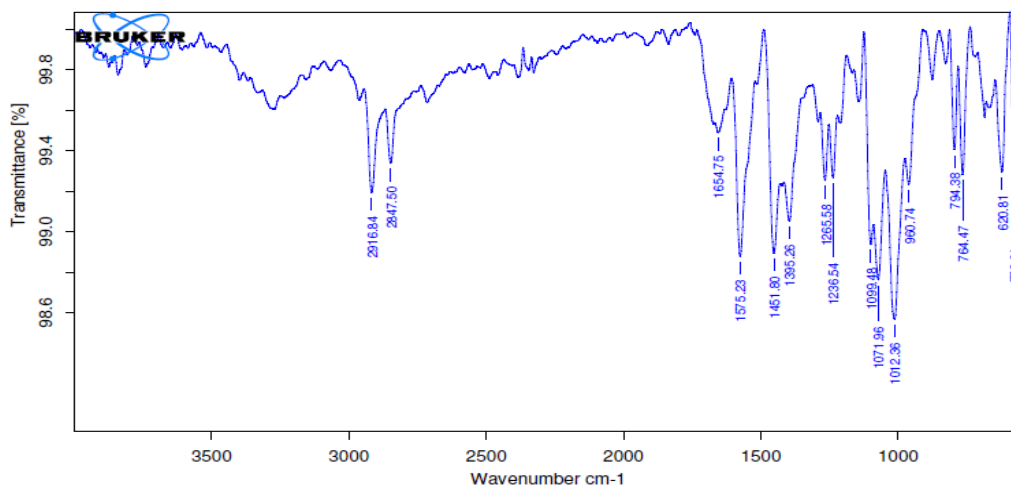

Fig-2: FTIR Studies of Ranolazine

Fig-3: FTIR Studies of optimized formulation

Physical appearance and surface texture of buccal patches:

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

Weight uniformity of buccal patches:

The weight of the patches was determined using digital balance and the average weight of all patches

Thickness of buccal patches:

The thickness of the patches was measured using screw gauge and the average thickness of all patches.

Folding endurance of buccal patches:

The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches.

Drug content uniformity of buccal patches:

Ranolazine buccal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated.

% moisture loss:
The moisture content in the buccal patches ranged from 8.75 to 8.96%. The moisture content in the formulations was found to be increased by increase in the concentration of polymers.

%moisture absorption:
The moisture absorption in the buccal patches ranged from 9.92 to 10.52%.

Swelling index:
The swelling index in the buccal patches ranged from 14.58 to 15.98 %.

Table -2: Physicochemical evaluation data of Ranolazine Buccal Patches

F. code	F1	F2	F3	F4
Thickness (mm)	0.28	0.26	0.30	0.27
Weight variation (mg)	49.93	48.93	52.14	50.10
Drug content Uniformity	96.41	92.26	90.84	88.82
Folding endurance	77	76	79	78
% moisture loss	8.96	8.78	8.90	8.75
%moisture absorption	10.26	10.52	9.92	10.23
Swelling index	15.98	15.85	14.58	15.25

Drug release studies

Table-3: *In vitro* release data of film F_1 to F_4

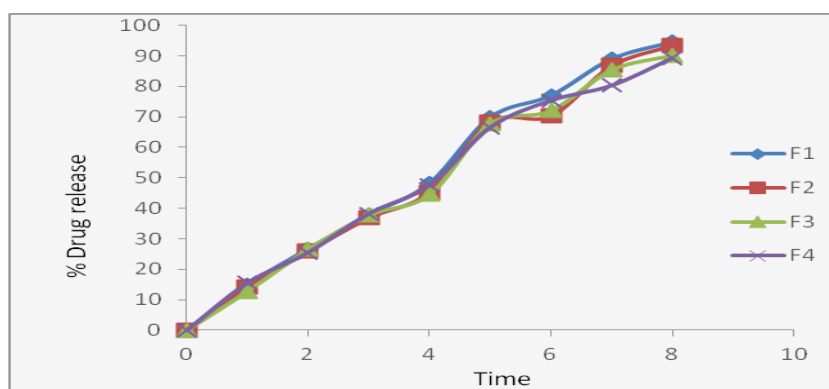| Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	14.90	14.15	12.80	15.56
2	26.70	25.89	26.50	25.55
3	37.89	36.87	37.70	38.25
4	48.18	45.23	44.50	47.59
5	69.75	68.35	67.65	66.55
6	76.89	70.34	71.98	75.32
7	88.86	86.77	85.32	80.28
8	94.45	93.50	90.12	89.22

Fig-4: In vitro drug release of all formulation

Stability studies:

Optimized formulations F1 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-4: Stability studies of optimized formulations

S.NO	Time in days	Physical changes	Mean % drug release		
			Ranolazine		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	94.45	94.45	94.45
2.	30	No Change	94.15	94.09	93.99

IV. CONCLUSION

From the present research work that is development and evaluation of Ranolazine buccal patches for buccal drug delivery, the following points can be concluded: The patches prepared were elegant in appearance and smooth surface. The weights of patches were uniform. The thicknesses of patches were uniform.The patches were completely dried. The patches had good flexibility. The patches shows uniform swelling index. The surface pH of the patches was uniform. There was no drug-excipients interaction between the drug and excipientsused in the formulation. The drug was distributed throughout the patch uniformly. More than 85 % of the drug was released from all the formulations at the end of 8 hrs. In short term stability studies indicate there were no significant changes in thedrug content and *in-vitro* drug release for the period of three month. From the result and conclusion of the research work we can summarize that Ranolazine can be delivered via buccal route.

REFERENCES

1. Gazzi Shanker, Chegonda K. Kumar, Chandra Sekhara Rao Gonugunta, B. Vijaya Kumar and Prabhakar Reddy Veerareddy. Formulation and Evaluation of Bioadhesive Buccal Drug Delivery of Tizanidine Hydrochloride Tablets. AAPS PharmSciTech, 10, 2009.
2. Davis SS, Daly PB, Kennerley JW, Frier M, Hardy JG, Wilson CG. Design and evaluation of sustained release formulations for oral and buccal administration. In: Bussmann WD, Dries RR, Wagner W, editors. Controlled release nitroglycerin in buccal and oral form. Basle: Karger; 1982, 17–25.
3. Schor JM, Davis SS, Nigalaye A, Bolton S. Susadrin transmucosal tablets. Drug Dev Ind Pharm, 9, 1983, 1359– 1377.
4. Ishida M, Nambu N, Nagai T. Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose. Chem Pharm Bull, 30, 1982, 980–984. 8. Bremecker KD, Strempel H, Klein G. Novel concept for a mucosal adhesive ointment. J Pharm Sci, 73, 1984, 548–52.
5. Anders R, Merkle HP. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int J Pharm, 49, 1989, 231– 240.
6. Gandhi The mucosa is relatively permeable, has a rich blood supply, is robust, and shows short recovery times after stress or damage A.H. Shojaei, Buccal mucosa as a route for systemic drug delivery: a review, J. Pharm. Pharmaceut. Sci., 1(1) (1998) 15-30.
7. Giradkar KP *et al*: Design development and in vitro evaluation of bioadhesive dosage form for buccal route. International journal of pharma research & development 2010: 2;1-24.
8. Amir H *et al*: Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology. 2001: 1-27.
9. Budavari S (ed). *The Merck Index*, 13th edn. Merck & Co. Inc. Whitehouse Station, NJ, 2001, p. 147.
10. Chen L.L.H., Chetty D.J., and Chien Y.W., A mechanistic analysis to characterize oramucosal permeation properties, Inter. J. Pharm., 1999, 184, 63-72.
11. Thomson. Physician Desk Reference. 61st ed. Montvale, New Jersey: Thomson PDR; 2007, p. 1035-37.
12. Yajaman S., Bandyopadhyay AK. Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs. J Controlled Release 2006;114:15–40.
13. Shimamoto T. Androl J 1987; 8 (1): S14-S16.
14. Amir H, Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology, 2001, 1-27.
15. Sudhakar Y, Knotsu K, Bandopadhyay AK. Bio adhesive drug delivery – A promising option for orally less efficient drugs. J Control Rel 2006;114:15-40.
16. Rajashree Mashru, Vijay Sutariya, Mayur Sankalia, Jolly Sankalia. Transbuccal delivery of lamotrigine across procine buccal mucosa in vitro determination of routes of buccal transport. J Pharm Pharmaceut Sci 2005;8:54-62.
17. Ceschel GC, Maffei P, Moretti MD, Demontis LS, Peana A. International Journal of Pharmaceutics 2000;195:45.
18. Haas J, Lehr CM. Developments in the area of bioadhesive drug delivery systems. Expert Opin Biol Ther 2002;2:287-298.
19. DeVries M.E, Ph.D. Thesis, University of Leiden, Leiden, The Netherlands, 1991.
20. Dixit R.P., Puthli S. P. , Oral strip technology: Overview and future potential, Journal of Controlled Release,2009, 139, 94–107.
21. Rossi Silvia, Sandri Giuseppina, Caramella Carla M., Buccal drug delivery: A challenge already won?, Drug Discovery Today: Technologies, 2005, 2(1).
22. Smart, J.D., The role of water movement and polymer hydration in mucoadhesion. In Bioadhesive drug delivery systems (Mathiowitz, E., Chickering, III D.E.,Lehr, C.M., eds), Marcel Dekker, 1999, PP11–23.
23. Nazilasalamat M, Montakarn C, Thomas J. The use of mucoadhesive polymers in buccal drug delivery. AdvDrug Del Rev 2005;57:1666-91.
24. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv Drug Del Rev 1994;13:43-74.