EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 10
200-204
Year: 2024

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF TIMOLOL MALEATE

***N. Umarani, Saniya K. Meghana, G. Vaishnavi, D. Swathi, K. Ajay Prakash and N. Rohith Reddy**

[1]Assistant Professor, Department of Pharmaceutics, Siddhartha Institute of Pharmacy, Korremula Rd, Narepally, Ghatkesar, Hyderabad, Telangana.
[2]Deparment of Pharmaceutics, Siddhartha Institute of Pharmacy, Korremula Rd, Narepally, Ghatkesar, Hyderabad, Telangana.

***Corresponding Author: N. Umarani**
Assistant Professor, Department of Pharmaceutics, Siddhartha Institute of Pharmacy, Korremula Rd, Narepally, Ghatkesar, Hyderabad, Telangana.

Article Received on 07/08/2024 **Article Revised on 01/09/2024** **Article Accepted on 22/09/2024**

ABSTRACT
Timolol maleate is a non-selective beta-adrenergic blocker, and having short biological half-life, approximate 4.1 h, and low oral bioavailability. Therefore, the present investigation is concerned with the development of the buccal mucoadhesive patches, which were designed to prolong the residence time and thus to improve the bioavailability of the drug and its half-life. Hydroxy propyl methyl cellulose (HPMC) is one the polymers which is having good mucoadhesive property so therefore various formulations were developed by using release rate controlling and gel forming polymers like HPMC K and Ethyl cellulose by solvent casting method. In addition to this glycerol and DMSO was used as plasticizer and permeation enhancer respectively. All the formulations had good physical appearance and physicochemical properties. From among all the developed formations, since formulation, F2 retarded the drug release in a controlled manner for a prolonged period of more than 6 h, gave satisfactory bio adhesion for a maximum duration of 6 h and drug diffused up to the 80%, so it was selected as the best formulation. Swelling studies indicated significant water uptake and contributed in drug release. The most satisfactory formulation had showed no significant change in physicochemical properties, drug content, bio adhesion properties, in vitro diffusion pattern after storage at 30 ± 2ºC (65% RH) and at 40 ± 2ºC (75% RH) during stability studies for 3months as per ICH guidelines. Thus, best formulation satisfied physicochemical parameters, in vitro bio adhesion strength, in vitro drug release and requirements for a buccal mucoadhesive drug delivery system.

KEYWORDS: Buccal delivery system, Timolol Maleate, polymers, solvent casting technique, Mucoadhesive patches, In-vitro release studies.

INTRODUCTION
The oral cavity has rich blood supply that drains directly into the jugular vein and bypassing the liver. Direct access to these systemic circulation through internal jugular vein (buccal mucosa) bypasses drugs from hepatic first pass metabolism, leading to high bioavailability. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. The buccal delivery thus implies the absorption of medication through the mucosal lining of the buccal cavity.[1] The buccal route also provides possible pathways for absorption of complex, high-molecular-weight polysaccharides, oligonucleotides, hydrophilic and unstable proteins, and the traditional small molecules of medicines. The oral cavity is being utilized for local and systemic intake of medicines.[2] the use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offers greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva.[3]

1. Oral route of drug delivery remains most popular route in drug
2. delivery. Most of the dosage forms are swallowed from oral cavity.
3. However, once swallowed enzymatic degradation and significant
4. first pass effect may limit the bioavailability
5. Oral route of drug delivery remains most popular route in drug
6. delivery. Most of the dosage forms are swallowed from oral cavity.

7. However, once swallowed enzymatic degradation and significant
8. first pass effect may limit the bioavailability

MATERIALS

Timolol maleate was obtained from Hetero labs, HYD. HPMC K 100M and Ethyl cellulose procured from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Drug- excipient compatibility study

The compatibility of drug and formulation components is important prerequisite for formulation development. It is therefore necessary to confirm that the drug does not interact with excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.[4]

Formulation Development

Table 1: Formulation Design of Timolol maleate buccal patches.

Ingredients	F1	F2	F3	F4
Drug	20	20	20	20
HPMCK100M	40	80	-	-
Ethyl cellulose	-	-	40	80
PEG	1	1	1	1
DMSO	0.1	0.1	0.1	0.1

Characterization of Buccal formulation

Physico- chemical evaluation

Physical appearance

All the formulated Timolol maleate patches were observed for color, clarity, flexibility, and smoothness.[5]

Folding endurance

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 patches for three times and the mean values plus standard deviation was calculated.[6]

Thickness of the patch

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.[7]

Weight uniformity

The formulated buccal patches are to be dried at 600C for 6 hours before trial. A identify the area of 4.52 cm2 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.[8]

Drug content

The formulated buccal patch were assayed for drug content in each case. 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 patches (4.52 cm2) 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 analysed spectrophotometrically. Similarly a blank was prepared from Buccal patches without drug.[9]

Moisture absorption studies

The buccal patches were weighed exactly and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the patches were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.[10]

Parentage moisture uptake = (Final weight- Initial weight)/(Initial weight) ×100

Moisture loss studies

Three patches were weighed separately and kept in a desiccator contains calcium chloride at 370C 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.[11]

Percentage moisture loss = (Initial weight-Final weight)/(Final weight) ×100

Swelling study

Three buccal patch were weighed individually (W1) and placed separately in 3% agar gel plates and incubated at 37 ± 1°C. After every 15min time interval until 1 h, the patches were removed from the Petri dish and excess surface water was removed carefully with blotting paper. The swollen patch was then reweighed (W2) and the swelling index (SI) were calculated using the formula given in equation.[12]

[Swelling Index = [(W2-W1) ÷ W1] × 100,

Where W1 = initial weight of the patchW2 = final weight of the patch.

Stability Studies

Optimized medicated buccal patches were subjected to short term stability testing. The Buccal patches were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 0C and 75 ± 5% RH for 3 months as per ICH guidelines.[13]

RESULTS AND DISCUSSION

Compatibility studies of drug and polymers

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

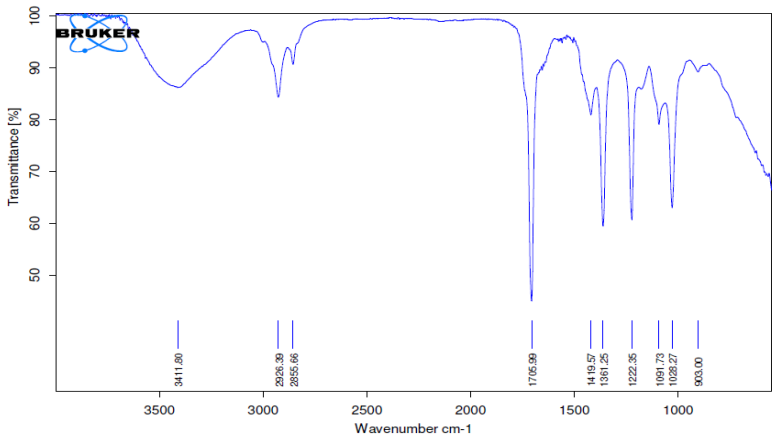

Fig-1: FTIR Studies of Timolol maleate.

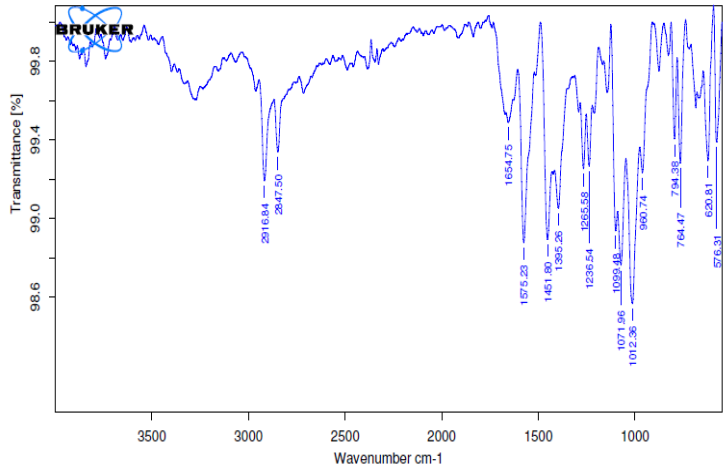

Fig-2: FTIR Studies of Physical mixture of drug and excipients.

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

Timolol maleate 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 Timolol maleate Buccal Patches.

F. code	F1	F2	F3	F4
Thickness (mm)	0.34	0.24	0.26	0.22
Weight variation (mg)	47.36	48.16	44.62	43.29
Drug content Uniformity	90.96	94.36	94.46	98.83
Folding endurance	76	79	82	88
% Moisture loss	8.16	8.82	8.92	8.57
% Moisture absorption	10.62	10.74	10.72	10.32
Swelling index	14.89	15.54	15.86	15.45

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	26.50	25.55	26.70	25.89
2	44.50	47.59	48.18	45.23
3	67.65	66.55	69.75	68.35
4	71.98	75.32	76.89	70.34
5	85.32	80.28	88.86	86.77
6	90.12	91.22	92.45	95.50

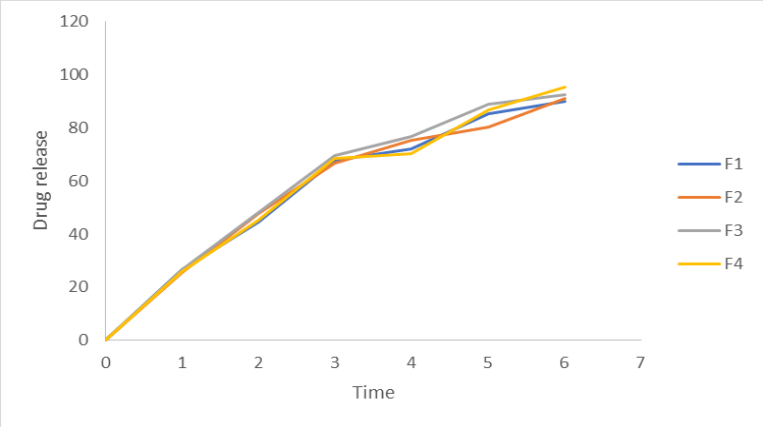

Fig-3: In vitro drug release of (F1- F4) formulation.

Stability Studies

Optimized formulations F4 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for colour, 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.

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F4	**25^0C/60%RH**	95.50	94.78	93.68	92.58	**Not less than**
F4	**30^0C/75% RH**	95.50	94.75	93.54	92.21	**Not less than**
F4	**40^0C/75% RH**	95.50	94.63	93.42	92.35	**Not less than**

CONCLUSION

FTIR studies revealed that there is no incompatibility or interaction between Timolol maleate and excipients. Formulated buccal films gives satisfactory film characteristics like physical appearance, surface texture, weight uniformity, thickness uniformity, folding endurance, surface pH, percentage swelling index, percentage moisture uptake, drug content uniformity, in-vitro drug release. The low values for standard deviation for average weight, thickness, surface pH, percentage swelling index, percentage moisture uptake, in vitro drug release and drug content indicated uniformity within the batches. Based on in vitro drug release, formulation F4 exhibited a drug release of 95.50% in 6 hours. The drug release could be retarded more than 6 hr with controlled release behaviour. The prepared buccal patches were

found to stable after performing stability testing for three month. Short term stability studies of optimized formulation as per ICH guidelines indicated that there is no significant change in physical appearance, drug content determination and in vitro drug release. So finally, it can be concluded that mucoadhesive buccal films of Timolol maleate could provide sustained buccal delivery for prolonged period. A further clinical investigation has to be conducted to establish the safety and efficacy of the developed formulation.

REFERENCES

1. Anuj Kumar, Vikas Phatarpekar, Naveen Pathak, Kumud Padhee, Minakshi Garg and Neeta Sharma. Development & Evaluation of Carvedilol Bioerodable Buccal Mucoadhesive patches. Pharmacie Globale, 2011; 3(7): 1-5.
2. Mitul P, Asif K, Pratik S, Mv R, Ashwini D. Buccal drug delivery system: the current interest. Res J Pharm, 2011; 2(12): 2011.
3. Nishan N. Bobade et. al, A Review on Buccal Drug Delivery System, International Journal of Pharmacy and Pharmaceutical Science Research, 2013; 3(1): 35-40.
4. Saisivam S, Muhammed Ashereff MH, Maria Gerald NS, Rajan, Jayaprakash S and Nagaranjan M. Design and evaluation of diltiazem hydrochloride buccal patches. Indian Journal of Pharmaceutical Sciences, 2000; 236-2.
5. S. Kishore, Formulation development and in vivo evaluation of zolmitriptan oral dissolving films, International Journal of Pharma and Bio Sciences, January 2013; 4(3): P638-P646.
6. 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.
7. Rossi Silvia, Sandri Giuseppina, Caramella Carla M., Buccal drug delivery: A challenge already won?, Drug Discovery Today: Technologies, 2005; 2(1).
8. 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.
9. Mohamed el-nabarawi, assessment of bioavailability of sumatriptan transdermal delivery systems in rabbits, International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5(2).
10. G. Sridhar, formulation development and evaluation of mucoadhesive buccal patches of zolmitriptan, International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(3).
11. Amit Khairnar, Parridhi J, Dheeraj B, Dinesh J. Development of mucoadhesive buccal patch containing aceclofenac: in vitro evaluations. Int J PharmTech Res, 2009; 1(4): 978-81.
12. Subhash VD, Madhuri A, channavar, Anil VC, Umesh MJ, Kailash RB. Chitosan based release mucoadhesive patches containing verapamil Hcl. Int J Pharm Pharmceut Sci, 2009 Nov-Dec; 1(1): 216-29.
13. Manish kumar, Garimagarg, Pushpendra kumar, Kulkarni GT, Arunkumar. Design and in vitro evaluation of mucoadhesive buccal films containing famotidine. Int J Pharm Pharmceut Sci, 2(3): 86-90.