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DESIGN AND EVALUATION OF MUCOADHESIVE BUCCAL BILAYERED TABLETS OF METOPROLOL SUCCINATE

A. Anka Rao[1]*, Dr. C. H. Babu Rao[2] and Dr. N. Devanna[3]

[1]Department of Pharmaceutics, Hindu College of Pharmacy, Guntur.

[2]Department of Chemistry, Priyadarishini Institute of Pharmaceutical Science And Research, Guntur.

[3]Department of Chemistry J.N.T.U College of Engineering, Anantapur.

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***Corresponding Author**
A. Anka Rao
Department of Pharmaceutics, Hindu College of Pharmacy, Guntur.

ABSTRACT

The purpose of this research work was to establish mucoadhesive buccal tablets of Metoprolol succinate in the forms of bilayered tablets. The tablets were prepared using Hydroxy propyl methyl cellulose (HPMC $K_{100}M$) and Poloxamer 407 as a bio adhesive polymers to impart Mucoadhesion and ethyl cellulose (EC) to act as an impermeable backing layer. Buccal tablets were evaluated by different parameters such as weight variation, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, in vitro drug release, and in vivo studies. The mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0) for both the buccal tablets. The present study concludes that mucoadhesive buccal tablets of Metoprolol succinate can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Metoprolol succinate.

KEYWORDS: Bilayered buccal tablet, buccal delivery, Mucoadhesion, Metoprolol succinate.

1.0 INTRODUCTION

Metoprolol succinate, a widely used for Anti hypertensive agent. Although it is well absorbed in the gastrointestinal tract, its bioavailability is low (38-45%) as a result of extensive first-pass metabolism. Since the buccal route bypasses the hepatic first-pass effect, the dose of Metoprolol succinate can be reduced. The physicochemical properties of Metoprolol

succinate, its suitable half-life (3-6 hours) and its low molecular weight 294.81 make it a suitable candidate for administration by the buccal route.

In the present study, the objective was to prepare mucoadhesive buccal tablets of metoprolol succinate to prolong the residence time of the buccal tablets, which ensure satisfactory drug release in a unidirectional fashion to the mucosa and to avoid loss of drug resulting from wash out with saliva. The buccal tablets were evaluated by weight uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, In vitro drug release, and In vivo studies.

1.1 MATERIALS AND METHODS

MATERIALS

Metoprolol succinate (99.96% purity), were gift samples from Dr.Reddy's Labs Ltd, Hyderabad, India. Hydroxy propyl methyl cellulose (HPMC K4M), Poloxamer 407, ethyl cellulose and D-mannitol (S.D. Fine Chemicals, Mumbai, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

1.2 Preparation of Mucoadhesive Buccal Tablets[7]

Mucoadhesive buccal tablets containing metoprolol succinate were prepared by direct compression method. The ingredients of the core layer (Table : 1) were weighed accurately and mixed by trituration in a glass mortor & pestle. The mix was then compressed using 8mm die by a tablet press. In order to obtain constant tablet weight the manitol was added as filler excipient in the core layer. After compression of tablet the upper punch was removed carefully with out disturbing the set up and mixed ingredients of the backing layer (Table :1) were added over the tablet and compressed again.

Table 1: Composition of Mucoadhesive Buccal Tablets of Metoprolol Succinate.

Adhesive Layer						Backing Layer	
Formula code	**Drug (mg)**	**Poloxomer-407**	**HPMC K-100**	**PVP K 30**	**D-Mannitol**	**Ethyl cellulose**	**Total tablet weight(mg)**
F_1	50	45	45	6	4	50	200
F_2	50	40	50	6	4	50	200
F_3	50	38	52	6	4	50	200
F_4	50	35	55	6	4	50	200
F_5	50	33	57	6	4	50	200
F_6	50	30	60	6	4	50	200

Drug indicats metoprolol succinate;

poloxomer-407;

Hpmc k100-hydroxy propyl methyl cllulose k100; Pvp k 30-poly vinyl pyrrolidone k -30.

1.0 RESULTS OF MUCOADHESIVE BUCCAL TABLETS OF METOPROLOL SUCCINATE

1.1 STANDARD CALIBRATION CURVE

Table 2: Standard Curve Data For Metoprolol Succinate In P^h 6.8 Phosphate Buffer.

S.No	Concentration in µg/ml	Absorbance at 275nm
1	10	0.04
2	20	0.071
3	30	0.118
4	40	0.144
5	50	0.181
6	60	0.219

Slope = 0.00361
Regression = 0.9988

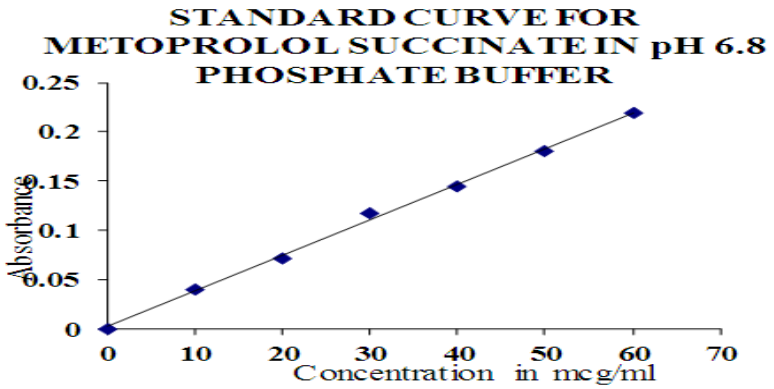

Fig 1: Standard curve of Metoprolol succinate.

1.2 Evaluation of Pre Compression Parameters of Buccal Tablets of Metoprolol Succinate.

Table 3: Results of pre compression parameters of Buccal Tablets of Metoprolol Succinate.

Formulation Code	Angle of repose(^{0})	Bulk density (gm/cc)	True density(gm/cc)	Carr's index(%)
F1	$32^0$59'	0.433	0.52	16.66
F2	$33^0$12'	0.371	0.43	14.28
F3	$33^0$27'	0.406	0.49	17.18
F4	$34^0$27'	0.433	0.50	13.33
F5	$33^0$35'	0.382	0.47	14.70
F6	$33^0$20'	0.317	0.43	14.28

1.3 Evaluation of Post Compression Parameters of Buccal Tablets of Metoprolol Succinate.

Table 4: Results of Post compression parameters of Buccal Tablets of Metoprolol Succinate.

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardnes (Kg/cm^3)	Friability (%)	%Drug Content Uniformity
F1	198	1.5	4.11	0.469	98
F2	195	1.5	4.76	0.412	99
F3	196	1.6	4.01	0.414	97
F4	194	1.5	3.96	0.353	98
F5	195	1.6	4.12	0.409	98
F6	198	1.5	4.05	0.353	99

1.4 *In vitro* Mucoadhesive Study of Buccal Tablets of Metoprolol Succunate.

Table 5: Results of *In vitro* Mucoadhesive study of Buccal Tablets of Metoprolol Succinate.

Formulation Code	Bioadhesion Strength	Force of Adhesion	Bond Strength (N/M^2)	Bioadhesion Time	Surface P^h
F1	9.0	0.0571	72.01	8	6.8
F2	9.6	0.0671	152.47	>12	5.9
F3	9.4	0.1209	133.93	>12	6.8
F4	10.4	0.1062	129.90	>12	6.9
F5	12.4	0.1030	119.43	>12	5.8
F6	14.0	0.0947	113.38	>12	6.2

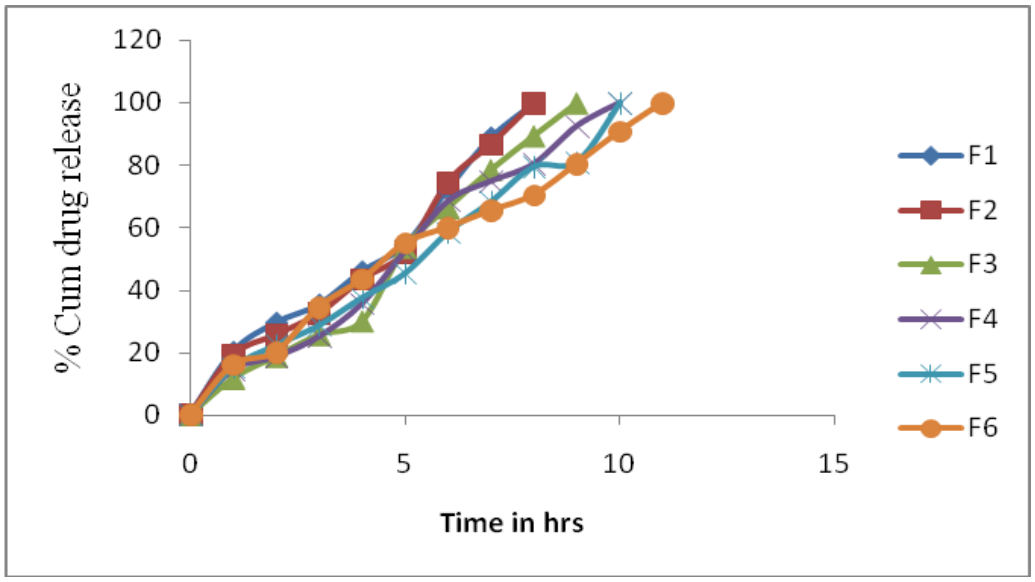

Fig 3: Cumulative Percent Drug Release Profile of Buccal tablets of Metoprolol succinate.

F1-F6 for Formulations.

1.5 RELEASE KINETICS

Table 6: Kinetic constants (k), Release exponent (n), and Determination Coefficients (r^2) Following Linear Regression of *in vitro* Drug Release of Buccal tablets of Metoprolol Succinate.

Formulation Code	Zero Order	First Order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.987	0.812	0.949	0.892	0.63
F2	0.988	0.858	0.934	0.970	0.69
F3	0.990	0.976	0.905	0.895	0.70
F4	0.998	0.912	0.914	0.879	0.75
F5	0.982	0.938	0.910	0.833	0.76
F6	0.984	0.831	0.952	0.833	0.78

1.6 Stability studies

Table 7: Accelerated Stability study of optimisied formulation (F9).

Condition	Period (months)	Thickness (mm)	Hardness (Kg/cm^2)	% Drug Content
Intial	Intial	1.5	4.93	98
40^0C+75%RH	1	1.6	4.95	99
40^0C+75%RH	2	1.5	4.92	98
40^0C+75%RH	3	1.5	4.94	97
25^0C+60%RH	3	1.6	4.92	99
25^0C+60%RH	6	1.5	4.93	98
25^0C+60%RH	3	1.6	4.95	98

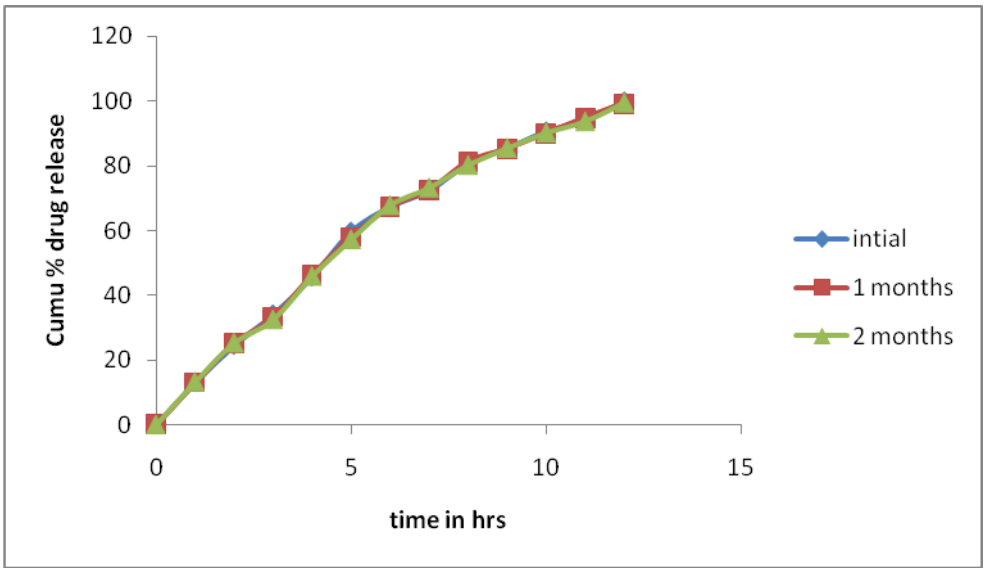

Fig 3: Comparative dissolution profiles of initial, 3 months and 6 months samples of F6 stored at 25^0C+60%RH.

1.3 *In vivo* Evaluation of Mucoadhesive Buccal Tablets of Metoprlol Succinate

In the present study *in vivo* clinical study of Metoprolol succinate buccal formulations was performed in healthy rabbits (New Zealand, White) of either sex weighing (2.5-3.5 kg) were divided into 3 groups viz. Group-I (control and received mucoadhesive buccal tablet free from drug), Reference group-II (Received aportion of buccal tablet containing 50 mg drug orally after grind and dissolved in distilled water) and test group-III (Received aportion of buccal tablet contaning 50 mg). Food was withdrawn from the rabbits 12 hr before drug administration and until 24 hr post dosing. All rabbits had free access to water throughout the study. The Institutional Animal Ethical Committee approved the protocol for this *in vivo* animal study of mtoprolol succinate.

Table 8: Comparative Pharmacokinetic Parameters of Metoprolol Succinate Oral and Buccal Administration in Rabbits.

Pharmacokinetic parameters	Orl route	Buccal route (F6)
T_{max}	7	8
C_{max}	265.5	289.2
AUC_{0-T}	1700.3	2791.3
$AUC_{0-\infty}$	1835.5	2971.5
K_{el}	0.10	0.17
$T_{1/2}$	5.4	6.27

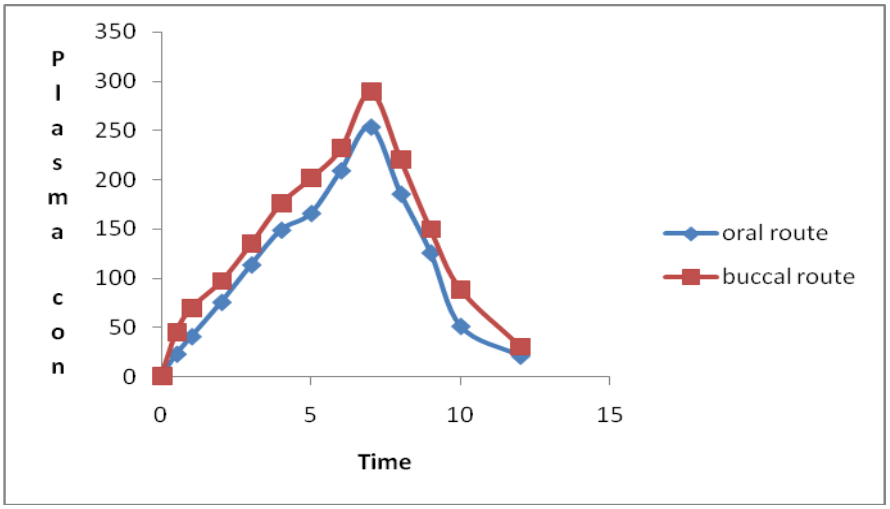

Fig 4: Plasma Concentration Time Profile of Metoprolol succinate after Oral and Buccal admimistration in rabbits.

1.4 DISCUSSION

In the present work efforts have been made to develop mucoadhesive buccal tablets of metoprolol succinate using direct compression technique involving mucoadhesive polymers like Poloxomer-407, various cellulose ethers having different degree of solubility and swellability, such as Hydroxy propyl methyl cellulose. Ethyl cellulose was selected as a backing material because this hydrophobic polymer has very low water permeability thus providing an impermeable backing layer that prevents drug loss.

All the prepared powdered blends were evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. are satisifactory, indicating all the values were within the limits as per IP.

The quality control tests such as uniformity of weight, hardness, friability and drug content for all the formulations prepared according to the formulae was carried out and the results were given in Table 4 and respectively was satisfactory.

In-vitro drug release studies for the prepared Metoprolol succinate buccal tablets (F1-F6) were conducted for a period of 12 hrs using the USP type II dissolution test apparatus. Dissolution study of all the formulations was carried out using phosphate buffer 6.8 for 12 hrs at 37 ± 0.5°C with 50 rpm. At every interval, 5ml of sample was withdrawn, after filtration appropriate dilution was done and the sample solutions were analyzed at 275 nm for Metoprolol succinate by UV-Visible Spectrophotometer.

The drug release rate appeared to increase amount of HPMC and decreasing amount of poloxomer 407 content. The results indicates that buccal tablets with a higher concentration of hpmc in the batches from F1 to F6 swell faster and consequently, give rise to more rapid release of drug. *In-vitro* drug release at for all the formulations was found to be 99.89 to 97.62% and was satisfactory. The optimized formulation (F6) of drug release was found to be is 99.98% over a period of 12 hrs.

By incorporating the release data in Higuchi and peppas models, the R^2 value of F1-F6 were greater for Higuchi model so it shows that drug release appears to fit the Higuchi model and suggests the release occurs by diffusion mechanism. To further confirm the exact mechanism of drug release, the data was incorporated into Korsmeyer- Peppas model and the mechanism of the drug release was indicated according the value of release exponent 'n'. The release

exponent values 'n' Buccal tablets of metoprolol succinate F1-F6 was found to be within the range of 0.63 to 0.97 which explained that drug released occurs by Non-fickian type of diffusion.

Overall results of kinetic modeling suggest that diffusion is dominant mechanism for drug release following Non-fickian type of diffusion.

NO visible physical changes were observed in both the formulations withdrawn from the humidity chambers. The hardness, moisture content and drug content in all the formulations were found to be satisfactory.

Decrease in elimination rate constant (K_{el}) from 0.10 hr^{-1} (R) to 0.17 hr^{-1} (T) indicates the slow release rate of the drug in the body. The plasma elimination half life ($t_{1/2}$) of the reference (R) and test (T) formulations were 5.4 hr and 6.2 hr respectively, which were significantly different. Thus the prolonged $t_{1/2}$ is another indication on the in vivo performance of the metoprolol succinate buccal tablets.

1.5 CONCLUSION

The Mucoadhesive buccal tablets of Metoprolol Succinate may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Metoprolol Succinate through buccal mucosa.

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