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FORMULATION AND EVALUATION OF CONTROLLED RELEASE MUCOADHESIVE MATRIX TABLET OF NADOLOL

J.Gomathi[1], Palanisamy.P[1], Loganathan[1], B.Jaykar[2]

[1]Department of Pharmaceutics, Vinayaka Mission's College of Pharmacy, Salem-636008, Tamilnadu.

[2]Department of Pharmaceutical Chemistry,Vinayaka Mission's College of Pharmacy, Salem-636008, Tamilnadu.

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***Correspondence for Author**
J.Gomathi
Department of pharmaceutics, Vinayaka Mission's College of Pharmacy, Salem-636008 Tamilnadu.

ABSTRACT

In present study we have studied the feasibility of preparing mucoadhesive buccal delivery systems containing Nadolol to improve drug residence time on buccal mucosa and drug dissolution rate, to circumvent the first-pass metabolism and quick drug entry into the systemic circulation. Bilayer buccal tablets of nadolol were prepared by direct compression method using combination of polymers (such as HPMCK4M, and along with Carbopol934P). Eight formulations were developed with varying concentrations of polymers. The designed tablets were evaluated for various physical and biological parameters like hardness, weight variation, %friability, thickness, drug content uniformity, *in-vitro* drug release, stability studies, drug-excipients interaction (FTIR). Among the eight formulations, the formulation F2 containing Carbopol-934P and HPMC K4M in the ratio of (2 : 4) showed good mucoadhesive strength (36.8) was found to be promising. Cumulative drug release data revealed that nadolol formulation F2 was found to be 96.80% in 12 h. Stability studies on the promising formulation indicated that there are no significant changes in drug content and *in vitro* dissolution characteristics ($p < 0.05$). FTIR studies show no evidence on interaction between drug and excipients. The present study proves that mucoadhesive bilayer tablets of Nadolol with controlled drug release properties can be successfully prepared by direct compression method using HPMCK4M, and along with Carbopol934P. The prepared buccal tablets of Nadolol were able to stay in the buccal cavity for a longer period of time, which indicates a potential use of mucoadhesive tablets of Nadolol for treating blood pressure.

KEYWORDS: Mucoadhesive buccal tablet, Swelling index, Nadolol, Sodium CMC, HPMCK4M, Carbopol934P.

INTRODUCTION

Conventional routes of drug administration such as oral, intramuscular and intravenous have, in many cases, been supplanted by the advent of new, novel drug delivery systems. The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance.[1] Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectables and enterable methods.[2] Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route,[3-5] More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore mucoadhesive dosage forms were suggested for oral drug delivery which includes adhesive tablets,[6-8] adhesive gels,[9-10] and adhesive patches.[11-12]

Nadolol is a long acting, cardio selective beta blockers, currently licensed for the treatment of hypertension. Nadolol was selected as a model drug for investigation because of its suitable properties like half-life of 10 hours; molecular weight 44.1 g/mol make it suitable for administration by buccal route.[16] A suitable buccal delivery system should posse's good bioadhesive properties. So that it can retain in oral cavity for desired duration and localize the dosage form in a specific region and control the release rate of drug.

MATERIAL and METHODS

Nadolol was provided by Torrent pharmaceutical Ltd (Ahmedabad). Carbopol-934 was obtained as gift sample from Loba Chemie Pvt. Ltd. (Mumbai). Hydroxy propyl methyl cellulose K4M was gifted by Apex Pharmaceuticals (Chennai). All other chemicals employed

were of analytical grade.

Preparation of Mucoadhesive Tablets

Table 1 enlists the composition of different mucoadhesive formulations prepared using varying amount of polymers. Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.40 and 60, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 5 min. The mixture is compressed using 8 mm flat faced punch on 16 stages rotary tablet compress machine. Composition of the prepared bioadhesive buccal tablet .

Table 1: Formulation of Nadolol Mucoadhesive Tablet

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Nadolol	20	20	20	20	20	20	20	20
2	Carbopol934P	35	45	50	25	40	30	55	60
3	HPMCK4M	80	70	65	90	75	85	60	50
4	mannitol	10	10	10	10	10	10	10	10
5	Talc	2	2	2	2	2	2	2	2
6	Magnesium stearate	3	3	3	3	3	3	3	3

All quantities taken in mg

Total quantity of each formulation =150mg

Evaluation of Formulations

Physical Formulations

Ten tablets from each formulation were evaluated for uniformity in tablet weight and thickness. For each formulation the hardness of five tablets was determined using the monsanto hardness tester (cad mach), 10 tablets from each formulation were examined for friability using the Roche friabilator.

Drug Content Uniformity

Five tablets from each formulation were powdered individually and a quantity equivalent to 100mg of Nadolol was accurately weighed and extracted with a suitable volume of 0.1 N HCl. Each extract was suitably diluted and analysed spectrophotometrically at 254nm.

Swelling Studies

The tablets of each formulation were weighed individually (W1) and placed separately in Petri-dishes containing 15ml of phosphate buffer (pH 6.8). At regular intervals (1, 2, 4, and 8

hours) the tablets were removed from Petri dishes and excess water removed carefully using filter paper. The swollen tablets were re-weighed (W2); the swelling index of each formulation calculated by using this formula.

Swelling Index (S.I.) = W1-W2 / W1 (W1 = Initial Weight, W2 = Final Weight)

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any *in vivo* side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa. The method developed by Battenberg *et al* was used. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equiliberate for 1 min. The results are shown in Table 3.

***In vitro* mucoadhesive Study**

Mucoadhesive strength of the tablets was measured on a modified two-arm physical balance as described by Quadnich *et al*. The rabbit buccal mucosa was used as biological membrane for the studies. The rabbit mucosa was obtained from the local slaughter house and stored in krebs buffer at 4oC from the time of collection and used within 3 hrs of procurement. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37oC. The rabbit buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37o C ± 0.5oC), so that it just touches the mucosal surface. The buccal tablets were suck to lower side of a rubber stopper. The two side of the balance were made equal before the study, by keeping a 5 gms, was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in the position for 1 min contact time. Mucoadhesive strength was assessed in terms of weight (gms) required to detach the tablet from the membrane. Mucoadhesive strength which was measured as force of adhesion in Newton's by using following formula was used (Table 3), Force of adhesion (N) = Mucoadhesive strength / 100 X 9.81.

In-Vitro Release Studies

The drug release rate from buccal tablets was studied using the USP (II) dissolution test apparatus using paddle, fixing the tablet to the paddle. The assembly is kept in a jacketed

vessel of water maintained at $37^0C \pm 0.5^0C$. Buccal tablet was made to stick on bottom of the flask (so as to allow one sided release from the tablet). The beaker is filled with 900ml of pH 1.2 hydrochloric acid. The vessel maintained at 100rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus. At various intervals of time, samples were withdrawn and filtered through whatmann filter paper no.42. It is replaced immediately with equal amount of fresh buffer. The samples are then analyzed U.V. spectrophotometrically at 282nm.

Drug Release Kinetic Studies

To describe the kinetics of the drug release from the matrix base buccal patch of optimized batch F2, mathematical models such as zero-order, first order, Higuchi, Korsmeyer-Peppas models are where use. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Stability study

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product, which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Formulations were selected for stability on the basis of the In-vitro drug release profile. The formulations were subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines i.e. 250C/60% RH and 400C/75% RH in air tight high density ethylene bottles for 2 months in thermostated ovens. The samples were taken out at 0, 30, 40, 50 and 60 days. Tablets were evaluated for the different physicochemical parameters i.e. content uniformity, weight variation, bioadhesive strength, surface pH, swelling study, and percentage of drug release.

RESULT AND DISCUSSION

Physical Evaluation

The weights of all tablets were within ±5% of the average weight, thickness between 4.33 and 4.46mm, and hardness between 6.6 and 7.06kg/cm2. Friability ranged between 0.33and 0.41% thus all the physical parameters of the compressed tablets prepared were practically within the acceptable limits. The assayed content of drug in various formulations varied between 98% to 101%. The results showed no interference of the formulation excipients, i.e. HPMC K4M, sodiumCMC, and Carbopol-934p. The results are shown in (Table No.2).

Swelling Studies

The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The agar plate model used in this study simulates the secreting fluid around the buccal mucosa which is required for adhesion, swelling and release of the drug from tablets. The swelling index of mucoadhesive tablets for a period of 8 hours was studied. The value obtained is showed in (fig 1). Among all the formulations F2 swelling index was the highest, giving a value of 2.5.

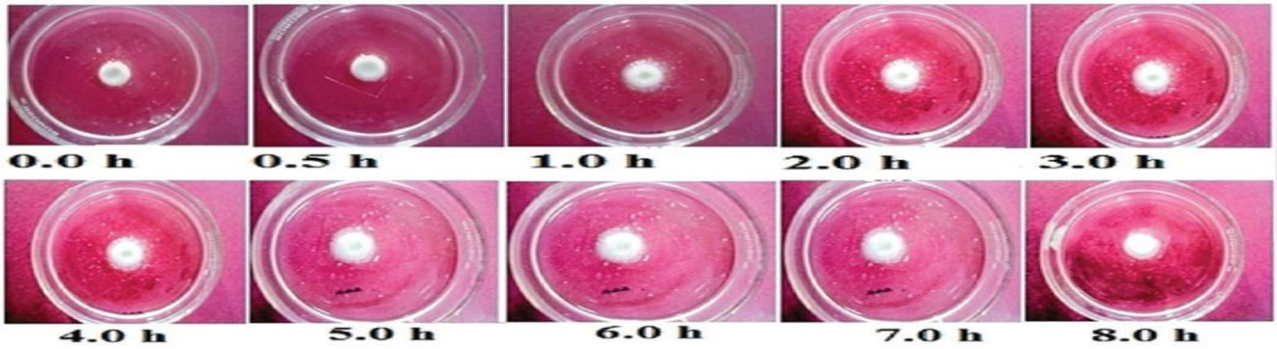

Fig no. 1: swelling index of mucoadhesive tablet formulation F2

Table no. 2: Physico-chemical parameters of formulations

Formulation code	Thickness (mm)	Harness (kg/cm^2)	Friability (%)	Averatge weight variation(n=10)	Drug content(%)
F1	4.36±0.074	7.06±.41	0.29±0.02	699±3.02	98.3
F2	4.41±0.046	6.8±0.40	0.40±0.12	700±1.95	100
F3	4.45±0.024	6.53±0.11	0.34±0.10	699±3.86	99
F4	4.46±0.061	6.93±0.61	0.39±0.05	701±0.60	99
F5	4.40±0.009	6.6±0.20	0.33±0.09	699±0.85	101
F6	4.33±0.169	6.8±0.34	0.41±0.13	695±1.20	101
F7	4.45±0.054	6.73±0.11	0.39±0.08	698±1.88	99
F8	4.44±0.077	6.86±0.30	0.40±0.18	701±1.60	98

Each value represents the mean ±SD (*n* =3)

Micro environment pH

The surface pH (microenvironment pH) of all the formulations (F1 to F6) was determined by using combined glass electrode and results are presented in Table no. 3. The maximum and minimum surface pH value from the formulations were found to be 6.50 and 5.93 respectively. The acceptable pH of saliva is in the range of 5 to 7. So these formulations may not produce any irritation to the buccal mucosa.

Bioadhesive strength

The bioadhesive strength of tablets were found to be function of the polymer concentration. The bioadhesive strength of tablets was found to be increased with increase in the concentration of mucoadhesive polymer (PEO). Formulation F6 showed the highest bioadhesive strength while F**1** showed lowest bioadhesive strength. The results are presented in Table 4

Table no 3: surface PH of Nadolol buccal tablet

Sintering temp	Sintering Time(HRS)	F1	F2	F3	F4	F5	F6
$60^{O}C$	1.5	5.43	6.27	6.35	6.32	6.42	6.12
	3	6.02	5.97	6.40	6.40	6.58	6.21
$70^{0}C$	1.5	6.34	6.40	6.50	6.50	6.20	6.32
	3	6.28	6.20	6.25	6.27	6.18	6.15

Table no 4: Bioadhesive strength of Nadolol buccal tablet

Sintering temp	Sintering Time(HRS)	F1	F2	F3	F4	F5	F6
$60^{O}C$	1.5	20.7	34.8	30.1	24.9	39.9	45.4
	3	20.5	34.8	30.0	24.5	39.8	45.2
$70^{0}C$	1.5	20.5	34.7	24.8	24.2	39.6	45.1
	3	20.3	34.5	24.2	24.3	39.7	44.2

In-Vitro Release Studies

Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative percent release of Nadolol (96.80±0.5%) from formulation F2 Further, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the drug. Moreover, the hydrophilic polymers would reach out and hence, create more pores and channels for the drug to diffuse out of the device .shown table no. 5

Table no 5: In-vitro percentage drug release profile of different formulations of Nadolol mucoadhesive tablets

S.no	Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	1	6.06	13.12	5.02	4.07	3.98	2.76	5.98	11.60
2	2	12.10	26.76	11.90	16.03	14.13	12.34	10.27	23.14
3	3	25.76	38.13	19.14	17.13	15.34	12.45	23.45	35.50
4	4	36.12	44.12	22.12	20.09	19.34	18.13	34.19	41.56
5	5	42.14	58.16	30.12	28.56	26.34	23.12	40.60	55.78
6	6	51.34	67.45	39.14	37.67	35.13	33.56	48.50	65.78
7	7	64.52	72.13	42.87	40.14	38.14	35.13	61.40	70.45

8	8	73.61	84.45	55.10	53.10	50.90	47.78	70.58	81.90
9	10	81.68	91.76	62.15	60.12	58.75	54.32	82.13	89.30
10	12	86.72	96.80	76.12	73.44	69.48	61.51	82.80	92.77

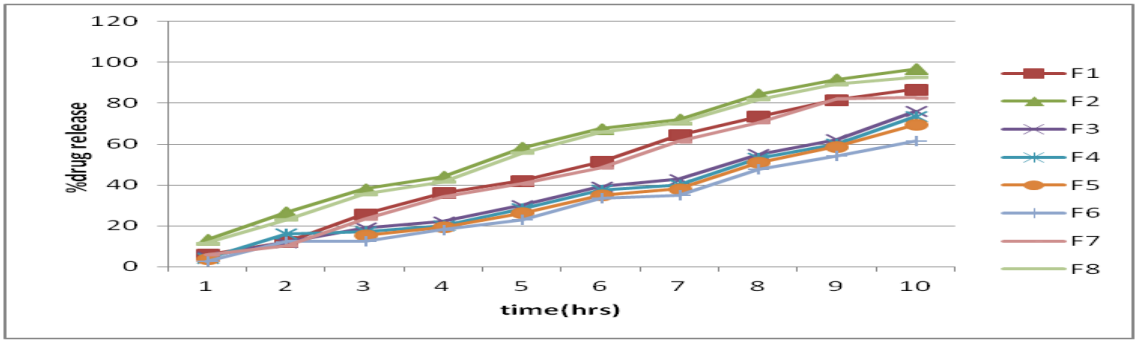

Fig 2 percentage drug release profile of different formulations of Nadolol mucoadhesive tablets [F1-F8]

Drug Release Kinetic Studies

The *in vitro* drug release data of all the buccal tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order equation, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table no.8. The values of regression co-relation coefficient (R2) were evaluated for all the formulations (F1 A to F6 D) whose values were close to 1. Among regression co-relation co-efficient (R2) values of Higuchi equation, Krosmeyer-peppas equation and Hixon-Crowell equation; R2 values of Higuchi equation were found to be higher. Similarly among zero-order equation and first-order equation; R2 values of first-order equation were found to be higher. Hence the drug release followed diffusive mechanism with first order release kinetics. Release mechanism and kinetics, optimized formulation (F2) was attempted to fit. The result are shown in (Table no.6)

Table no. 6: Release kinetics and mechanism of optimized formulation.

Formulation code	Mathematical models (Kinetics)			
	Zero order	First order	Higuchi	Korsmeyer-Peppas model
F2	r2	r2	r2	r2
	0.7756	0.9993	0.9871	0.9248

Stability studies

T h e stability studies were conducted on the selected formulation F2 (Sintered at 600 c for 1.5hr) as per the ICH guidelines. The stability studies were done at the intervals of 0,30,40,50

and 60days. The parameters studied were percentage drug content. surface pH, bioadhesive strength, swelling index and percentage of drug release. The results are shown in Table. No.7. From the results it was concluded that there were no significant changes in any values. Hence this formulation was considered to be highly stable.

Table no. 7 Stability study of Formulation F2.

	Times (days)				
Parameters	**0day**	**30 days**	**40 days**	**50 days**	**60 days**
	25 ± 20 C 60 ± 5% RH	**25 ± 20 C 60 ± 5% RH**	**40 ± 20 C 75 ± 5% RH**	**25 ± 20 C 60 ± 5% RH**	**40 ± 20 C 75 ± 5% RH**
Drug content (%)	99.87	99.28	94.50	94.30	98.50
Surface PH	6.25	6.20	5.76	6.05	5.98
Bioadhesive strength(gm)	34.6	35.4	35.2	35.6	34.3
Swelling index(after12 hrs)	178.54	180.2	180.6	181.6	179.04
% drug release	98	96	96	98	96

CONCLUSION

This study suggests that the polymers HPMC K4M (F2) can produce a controlled pattern of drug release in the prepared Nadolol tablets. The high mucoadhesive strength of this formulation is likely to increase its residence time in the gastrointestinal tract, which eventually improves the extent of bioavailability. However, an appropriate balance between various levels of the tow polymers is needed to acquire proper release and mucoadhesion. It can be concluded that by formulating mucoadhesive tablets of Nadolol , its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption can be solved by increasing the retention time of drug in GIT for a longer duration of time.

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