Asian J. Pharm. Res. Vol 5, Issue 3, 176-183, 2015.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

FORMULATION AND EVALUATION OF BUCCOADHESIVE BILAYER TABLETS OF TIMOLOL MALEATE

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ABSTRACT

An research has been made to formulate buccoadhesive bilayered tablets comprising of Timolol maleate containing bioadhesive layer and drug free backing layer to release the drug for extended period of time with reduction in dosing frequency. The buccoadhesive bilayer tablets of Timolol maleate, an non-selective beta-adrenergic receptor antagonist, class II antiarrhythmic drug used to treat high blood pressure were prepared by direct compression method by using various proportions of mucoadhesive polymers such as HPMC K100, SCMC, PVP K30 and Sodium alginate. Ethyl cellulose was used as an impermeable backing membrane. The prepared Timolol maleate buccal tablets were characterized based upon their physico-chemical characteristics like weight variation, thickness, hardness, friability, surface pH and drug content. The *in-vitro* swelling studies, *ex-vivo* buccoadhesive strength, *ex-vivo* permeation studies, *in-vitro* release studies and *in-vivo* release studies in rabbits were performed. The satisfactory results were obtained in all prepared formulation and based on the results TT5 [SCMC (25 mg) + Sodium alginate (12.5 mg) + PVP (12.5 mg)] was the best one when compared to other. Good correlation was observed between *in-vitro* and *in- vivo* profile with correlation coefficient value o.996, revealed the ability of the formulation to reproduce the *in-vitro* release pattern through the biological membrane. Stability studies of the best formulations were performed in natural human saliva and accelerated conditions showed no significant differences in physical appearance, swelling index, drug content, buccoadhsevive strength and in-vitro drug release profile. The *P*-value was statistically significant at <0.05. The correlation coefficient values (r) indicate that the kinetic of drug release was of zero order and the mechanism of drug release by Peppas model indicates the non-fickian evidenced with diffusion exponent values (n).

Key words: Buccoadhesive, Bilayer tablet, Timolol maleate, Buccoadhesive strength, Zero order, Non-fickian.

INTRODUCTION

Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such drugs. Various strategies have been implemented to promote the bioavailability of these drugs, including supplemental administration of enzyme inhibitors, use of absorption enhancers, novel formulation strategies, and reversible chemical modifications. Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa; hence the buccal region of oral cavity is an attractive target for the delivery of drug of choice [1]. Buccal mucosa is highly vascularized and more accessible for the administration and removal of a dosage form [2]. Apart from that buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration, avoiding acid hydrolysis in the GI tract and bypassing the first pass effect [3].

Timolol maleate is a Beta-blocker, Non-selective beta-adrenergic receptor antagonist, Class II antiarrhythmic drug. In its oral form it is used to treat high blood pressure and prevent heart attacks, and occasionally to prevent migraine headaches. In its opthalmic form it is used to treat open-angle and occasionally secondary glaucoma. The bioavailability of Timolol maleate following oral administration is 60% and has a shorter plasma half life (2.5 – 5h) due to first pass metabolism effect. After oral doses the peak plasma concentration attains 0.5-3h and the duration of therapeutic effect is less. Thus, the formulation of Buccoadhesive tablets with

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controlled release patterns could provide a single dosing and ensure good patient compliance. The buccal tablets of Timolol maleate were prepared by direct compression method by using various proportions of mucoadhesive polymers such as HPMC K100, SCMC, PVP K30 and Sodium alginate. Ethyl cellulose was used as an impermeable backing membrane.

MATERIALS AND METHODS

Timolol maleate was procured from Akin laboratories Ltd (Hyderabad, India) HPMC K100, SCMC, PVP K30, Sodium alginate and EC were procured from Drugs India (Hyderabad, India). All other chemicals and reagents employed were of analytical grade. The buccal tablets of Timolol maleate were prepared by direct compression method.

Drug-polymer interaction studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). In order to confirm that the entrapment of drug within the polymeric systems involve only the physical process and no interaction persists with drug and polymer combination. FTIR absorption spectra of pure drug, all the polymers used and the combination of drug and polymers were taken to confirm the identity of the drug and to detect the interaction of the drug with the excipients. The FTIR spectra are shown in Figures 1 and 2.

Preparation of buccoadhesive bilayered tablets of Timolol maleate

The Buccal tablets were prepared by the method of direct compression procedure involving two consecutive steps [4]. The drug and polymer mixture was prepared by homogeneously mixing the drug with HPMC, SCMC, PVP K-30 and Sodium alginate (mucoadhesive polymers), Mannitol and lactose (diluents) in a glass mortar for 15 minutes. Before direct compression, the powder were screened through a 60 µm sieve and thoroughly blended. The blend was lubricated with magnesium stearate for 3-5 min. The mixture (100 mg) was then compressed using an 8 mm diameter die in a 9-station rotary punching machine (Ahmadabad, India). The upper punch was raised and the backing layer of EC (50 mg) was placed on the above compact; the two layers were then compressed into a mucoadhesive bilayer buccal tablet. Each tablet weighed 150 mg. The compositions of buccoadhesive tablets were shown in table 1.

Powder characteristics

It is essential that drug and polymer should be characterized for their micromeritic properties [5]. This study gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the manufacture of a dosage form. The limits of powder flow characteristics were present in the table 2.

Physicochemical evaluation of buccoadhesive bilayered tablets

All the prepared formulation were evaluated for thickness, weight variation, friability, hardness, surface pH and drug content determined as per the procedure given for oral conventional tablets in accredited pharmacopoeia [6].

Surface pH

As an acidic or alkaline pH may cause irritation to the buccal mucosa, were necessary to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing 2%w/v (pH 6.8±0.01) agar medium for 2 h at room temperature [7]. The pH was measured by using pH meter. The mean of three reading was recorded.

Measurement of buccoadhesive strength

The *ex-vivo* buccoadhesive strength was determined by modified balance method [8, 9]. Fresh sheep buccal mucosa was obtained and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. The both sides of the balance were made equal prior to the experiment, by keeping a 5 g weight. The Sheep 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 firmly attached into a glass beaker containing phosphate buffer so that it just touched the mucosal surface. The buccal tablet was attached to the lower side of a rubber stopper with cyanoacrylate adhesive and adds weight on the right-hand pan. A weight of 5 g was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water was added slowly with an infusion set at a rate of 100 drops/min until equivalent weight. The weight was required to detachment from the mucosal surface was noted and this were referred as buccoadhesive strength in grams.

Force of adhesion (N) = (Bioadhesive strength (g) ×9.8)/1000

Bond strength (N m–2) = Force of adhesion / surface area

In-vitro swelling studies

The swelling studies of Timolol maleate buccal tablets were determined by gravimetric method [10, 11]. The swelling rate of the bioadhesive tablet was evaluated by using 1% agar gel plate. The average weight of the tablet was calculated (W1).The tablets were placed on gel surface in a petri dish placed in an incubator at 37.1^0C. Tablets was removed at different time intervals (1, 2, 3, 4, 5 and 6 h), wiped with filter paper and reweighed (W2). The swelling index was calculated by the formula.

Swelling Index (S.I) = [(W2-W1)/W1] x 100

Where, W1- initial weight of Tablet, W2- weight of disks at time t

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***In-vitro* drug release studies**

The release of drug was calculated using USP type II rotating paddle type [12-14]. The medium used is pH 6.8 phosphate buffer of 900 ml at 37±0.5^0 c with 50 rpm speed. Backing layer placed towards the glass slide with help of cyanoacrylate adhesive. Aliquots of 5 ml were withdrawn at regular intervals of time and fresh medium is replaced to maintain a sink condition. The samples were filtered and after dilution were analyzed spectrophotometrically at 225 nm.

***Ex-vivo* permeation study through sheep buccal mucosa**

An *ex-vivo* permeation study of Timolol maleate was carried out using a fresh sheep buccal mucosa using modified diffusion cell at 37±1°C [15]. Fresh sheep buccal mucosa was placed between the donor and receptor compartments. Sheep Buccal mucosa was tied to one end of an open ended cylinder, which acts as a donor compartment. The buccal tablet should be placed in such a way that it should be stuck on the mucous membrane. The receptor compartment was filled with isotonic phosphate buffer pH 6.8. The assembly was maintained at 37ºC and stirred magnetically. Samples were withdrawn at predetermined time intervals and analyzed using UV - Spectrophotometer at 225 nm.

***In-vivo* drug absorption studies on rabbits**

Six male New Zealand white rabbits (2-2.5 kg) were selected for the *in-vivo* study, which was already free from disease condition [16, 17]. The hind limbs were tied with the help of iron rod and kept rabbit in dorsal portion. The optimized formulation TT5 kept in the buccal region by the use of clip. A solution of dextrose is used for whole period of study. The blood samples of 1 ml are withdrawn with help of syringe in periodic intervals of time and add in to the test tube containing 1 ml of heparin to prevent blood clotting. These blood samples were subjected for centrifuging at 2,500 rpm for about 30 minutes. 1 ml of supernatant was taken, and after suitable dilution, analyzed at 225 nm using UV spectrophotometer.

Stability study in human saliva

The stability study of tablets was performed in natural human saliva [18]. Samples of human saliva were collected from 10 humans (ages 18-40 years) and filtered. The tablets were placed in petriplate containing 5 ml of human saliva and put in a temperature controlled oven at 37°C ± 0.2°C for 6 h. The tablets were examined for changes in morphology and physical stability at definite time intervals.

Stability studies as per ICH

The formulation TT5 was selected and the stability studies were carried out at accelerated condition of 40±2 ^{0}C, 75±5% RH conditions, stored in desiccators, the buccal tablets were packed in aluminium foil and kept in above said condition for period of three months [19, 20]. The tablets were analyzed periodically for their physical appearance, swelling index, drug content, buccoadhesive strength and *in-vitro* drug release. Results were analyzed by One-way ANOVA followed by Tukey's test. Differences were considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The buccal tablets of Timolol maleate were prepared by direct compression method by using various proportions of mucoadhesive polymers such as HPMC K100, SCMC, PVP K30 and Sodium alginate. Ethyl cellulose was used as an impermeable backing membrane to prevent release of drug into saliva of buccal cavity.

The micromeritic properties are very essential to know the flow ability of the powder materials were chosen for the formulations of buccoadhesive tablets. The derived and flow properties are within the limits and the results obtained were presented in the table 3. Drug release from the buccoadhesive tablets of Timolol maleate influenced by the physicochemical parameters such as thickness, weight variation, hardness, friability, drug content, surface pH. Hence evaluation of these parameters is very important to bring out the successful formulation. The physicochemical characteristics obtained for the formulation were presented in the table 3. The results are complying with the limits specified in the accredited pharmacopoeia and the surface pH of all the formulations closer to salivary pH 6.5 to 6.8.

The bioadhesive strength exhibited by Timolol maleate buccal tablets was satisfactory for maintaining them in oral cavity. The combination of SCMC and sodium alginate shows good adhesion. The SCMC content increases the bioadhesive strength will increase. Upon addition of PVP the bioadhesive strength increases which may be due to hydrogen bond formation and vanderwaals forces and the reaction between sodium ion and alginic acid. Hence the formulation TT5 shows maximum buccoadhesive strength when compared to all other formulation. The buccoadhesive properties of the formulated tablets were shown diagrammatically in the figure 3.

The swelling behavior of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to sudden drop in adhesive strength due to over hydration. The formulation TT5 shows maximum swelling index at the end of 6 h due to the highest percentage of SCMC with Sodium alginate. The results were graphically represented in figure 4.

Significant difference was observed in the release of Timolol maleate in all formulations. The *in-vitro* drug release and Higuchi's plot have shown that the drug release followed zero order kinetics, which was known from the

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regression value (r). Sodium alginate is present in an ionized state, and as a result, the polymeric network gets loosened comparatively, attributing for the higher drug release. The addition of PVP decreases the Timolol maleate release which may be due to enhancement in swelling of the polymer, which in turn increases the barrier effect and decreases the drug release, thereby controlling the drug release.

Data of *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of Timolol maleate from the buccal tablets. The kinetic models used were a zero order equation (Figure 5), Higuchi's model (Figure 6) and Peppa's models (Figure 7) [21, 22]. To find out the mechanism of drug release from hydrophilic matrices, the *in-vitro* dissolution data of each formulation were calculated with different kinetic drug release equations. The correlation coefficient values (r) indicate that the kinetic of drug release was of zero order. The mechanism of drug release by Peppas model indicates the non-fickian evidenced with diffusion exponent values (n). The diffusion characteristics data of all formulation were presented in the table 5 and normal values of diffusion exponent values are presented in the table 6.

The buccal mucosa represents a barrier to drug permeation and it is intermediate between skin epidermis and the gut in its permeability characteristics. The effectiveness of the buccal absorption could provide means for Timolol maleate administration can be determined through permeation sheep buccal mucosa. The *ex-vivo* permeation study of optimized formulation (TT5) through sheep buccal mucosa was shown in the figure 8.

The data obtained from the *in-vitro* drug release of formulation TT5 is correlated with *in-vivo* drug release in rabbit followed by diffusion of drug from TT5. The correlation of data was carried out by plotting graph in excel. The graph was plotted by taking *in-vitro* cumulative percentage of drug release on x-axis and *in-vivo* cumulative percentage of drug release on y-axis for the same period of time. The release was linear and follows zero order drug release by non-Fickian diffusion mechanism. The *In-vitro* and *In-vivo* correlation plot were shown in the figure 9. The correlation coefficient value was found to be 0.996.

The prepared formulation was placed in natural human saliva containing petridish and these were checked regularly for the appearance, color, shape and physical stability. The results were indicating there is no change in the tablet physical properties.The stability of the formulation at accelerated conditions shows satisfactory results in physical appearance, swelling index, drug content, buccoadhesive strength and *in-vitro* drug release. Differences were considered statistically significant at $p<0.05$ and the data were presented in table 7.

Table 1. Composition of buccal tablets of Timolol maleate

Ingredients (mg)		TT1	TT2	TT3	TT4	TT5	TT6	TT7	TT8	TT9	TT10	TT11	TT12
Core layer	Timolol maleate	10	10	10	10	10	10	10	10	10	10	10	10
	SCMC	25	-	12.5	12.5	25	6.25	25	6.25	37.5	-	-	-
	HPMC K100	12.5	25	-	25	-	6.25	6.25	25	-	37.5	-	12.5
	PVP K30	-	12.5	25	-	12.5	25	6.25	6.25	-	-	37.5	25
	Sodium alginate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
	Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Lactose	20	20	20	20	20	20	20	20	20	20	20	20
	Mannitol	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
	Soya bean powder	10	10	10	10	10	10	10	10	10	10	10	10
EC (Backing layer)		50	50	50	50	50	50	50	50	50	50	50	50
Total weight		150	150	150	150	150	150	150	150	150	150	150	150

Table 2. Limits for powder flow characteristics

Flow character	Hausner's ratio	Angle of repose (^{0})	Carr's index (%)
Excellent	1.00-1.11	25-30	≤10
Good	1.12-1.18	31-35	11-15
Fair	1.19-1.25	36-40	16-20
Passable	1.26-1.34	41-45	21-25
Poor	1.35-1.45	46-55	26-31
Very poor	1.46-1.59	56-65	32-37
Very, very poor	>1.60	>66	>38

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Table 3. Micromeritic properties of all formulations TT1-TT12

Formulation Code	Derived properties Mean± SD (n=3)		Flow properties Mean± SD (n=3)		
	Bulk density	Tapped density	Angle of repose (^{0})	Carr's index (%)	Hausner's ratio
TT1	0.437±0.010	0.493±0.015	26.45±0.30	11.44±1.97	1.129±0.02
TT2	0.447±0.015	0.503±0.020	27.21±0.39	11.22±1.96	1.126±0.03
TT3	0.493±0.015	0.560±0.010	24.97±0.68	11.86±3.97	1.135±0.05
TT4	0.476±0.015	0.526±0.015	23.21±0.96	10.48±1.81	1.105±0.02
TT5	0.433±0.020	0.496±0.030	25.94±0.73	9.48±1.12	1.101±0.03
TT6	0.420±0.010	0.463±0.006	24.25±0.36	13.32±3.16	1.103±0.04
TT7	0.453±0.025	0.536±0.025	28.21±0.29	15.54±1.19	1.184±0.02
TT8	0.450±0.010	0.510±0.017	23.87±0.40	11.69±3.61	1.126±0.05
TT9	0.410±0.010	0.457±0.025	25.17±0.34	10.87±2.84	1.113±0.04
TT10	0.443±0.015	0.517±0.032	26.78±0.63	14.21±1.11	1.165±0.01
TT11	0.406±0.020	0.470±0.010	23.93±0.46	13.47±2.48	1.156±0.03
TT12	0.413±0.020	0.477±0.015	28.21±0.27	14.23±3.22	1.154±0.02

Table 4. Physico-chemical evaluation of buccoadhesive tablets TT1-TT12

Formulation code	Thickness (mm)	Weight variation (%)	Friability (%)	Hardness (Kg/cm^2)	Surface pH	Drug content (mg)
TT1	2.17±0.02	148±1.55	0.43±0.025	4.1±0.13	6.51±0.048	9.07±0.41
TT2	2.24±0.03	149±0.94	0.54±0.030	4.3±0.15	6.72±0.033	9.35±0.19
TT3	2.16±0.04	149±0.81	0.60±0.042	4.2±0.34	6.72±0.024	8.82±0.48
TT4	2.19±0.06	149±0.72	0.48±0.036	4.0±0.13	6.76±0.043	9.76±0.41
TT5	2.23±0.02	148±0.19	0.48±0.010	4.1±0.26	6.56±0.043	9.95±0.15
TT6	2.24±0.04	150±0.84	0.51±0.020	4.3±0.16	6.57±0.064	8.69±0.01
TT7	2.18±0.06	150±0.38	0.61±0.038	4.3±0.27	6.52±0.069	9.71±0.03
TT8	2.19±0.06	149±0.52	0.54±0.025	4.6±0.28	6.57±0.068	9.65±0.65
TT9	2.18±0.05	147±0.76	0.44±0.010	4.4±0.36	6.54±0.047	9.24±0.31
TT10	2.20±0.04	149±0.41	0.44±0.026	4.3±0.39	6.58±0.044	8.93±0.15
TT11	2.26±0.05	150±0.82	0.48±0.030	4.5±0.37	6.58±0.052	9.53±0.44
TT12	2.18±0.04	148±0.48	0.69±0.025	4.3±0.27	6.74±0.075	9.85±0.61

Table 5. Diffusion characteristics of Formulations TT1-TT12

Formulation code	Correlation coefficient values (r)		Diffusion exponent value (n)
	Zero Order	Higuchi's Model	
TT1	0.997889	0.964041	0.930845
TT2	0.997147	0.975834	0.850836
TT3	0.994398	0.976983	0.893407
TT4	0.993929	0.978933	0.852143
TT5	0.998793	0.966999	0.860332
TT6	0.997477	0.973140	0.899473
TT7	0.995784	0.977618	0.842232
TT8	0.997341	0.962250	0.947175
TT9	0.996509	0.977730	0.835390
TT10	0.997588	0.963036	0.913481
TT11	0.996605	0.977255	0.835890
TT12	0.994456	0.978567	0.829208

Table 6. Diffusion exponent drug release mechanism

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.45	Fickian release
2	0.45 to 0.89	Non fickian release
3	0.89	Case II transport
4	> 0.89	Super case II transport

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Table 7. Stability studies of best formulation (TT5)

Parameters	1st month	2nd month	3rd month	p value
Physical appearance	No Change	No Change	No Change	-
Swelling index	78.59±0.412^{ns}	78.47±0.482^{ns}	78.35±0.293^{ns}	0.6432
Drug content	9.95±0.122^{ns}	9.93±0.116^{ns}	9.89±0.101^{ns}	0.4521
Buccoadhesive strength	34.88±1.09^{ns}	35.3±1.09^{ns}	36±0.34^{ns}	0.1539
In-vitro drug release	98.06±0.55^{ns}	98.13±0.32^{ns}	98.26±0.5^{ns}	0.8709

All values are expressed as Mean±S. ^{ns} = non significant

Fig 1. FTIR spectra of Timolol maleate

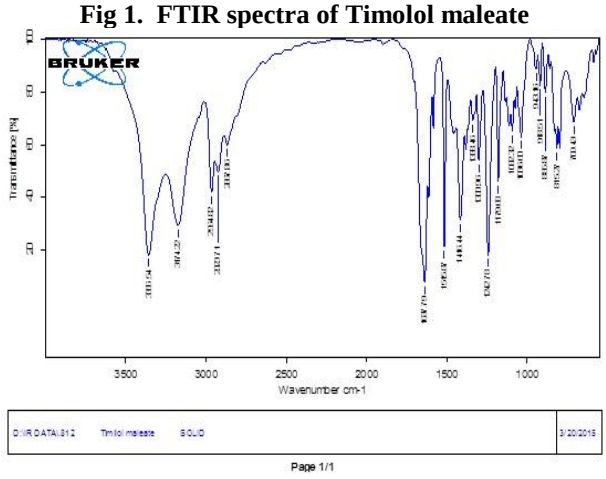

Fig 2. FTIR spectra of Timolol maleate with polymer mixtures

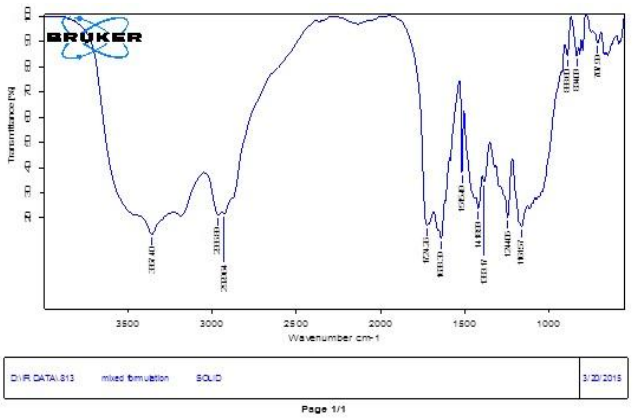

Fig 3. Buccoadhesive strength of formulations TT1-TT12

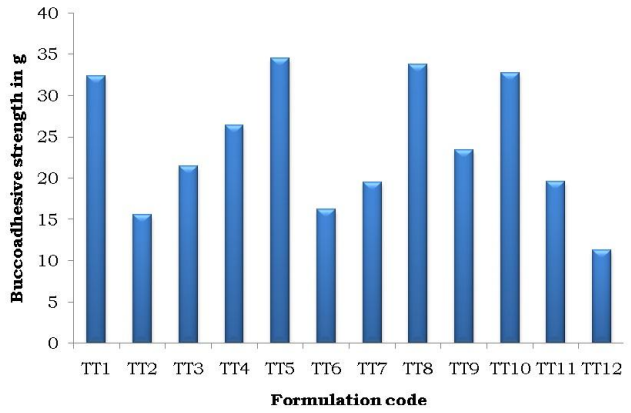

Fig 4. Swelling index of Formulations TT1-TT12

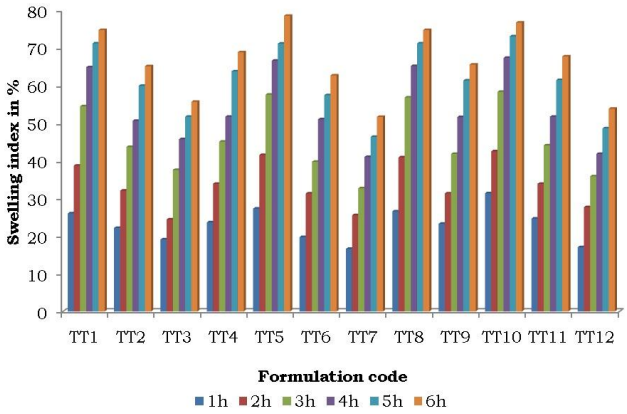

Fig 5. Cumulative % release of formulations TT1-TT12

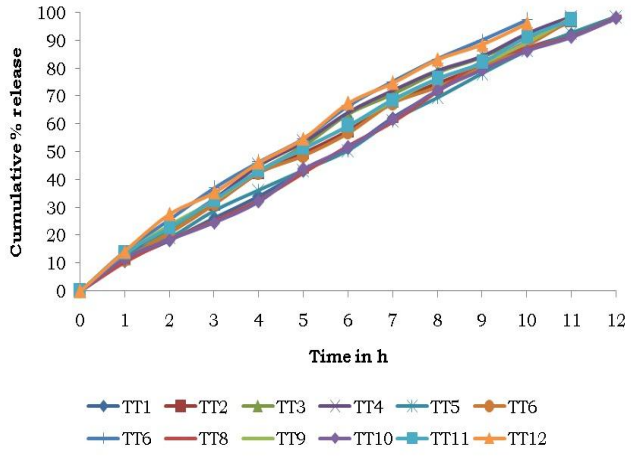

Fig 6. Higuchi's plot of TT1-TT12

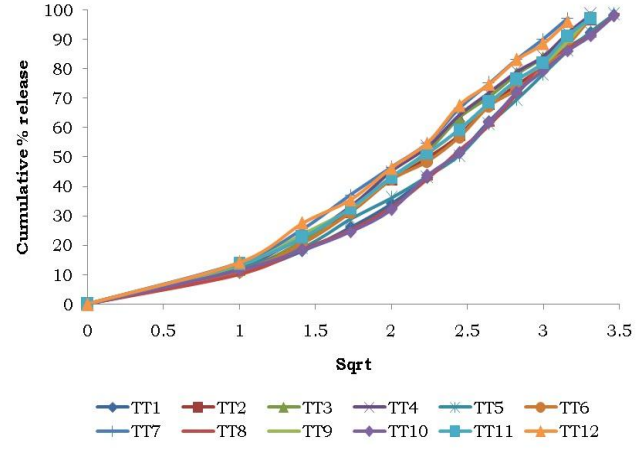

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Fig 7. Peppa's plot of TT1-TT12

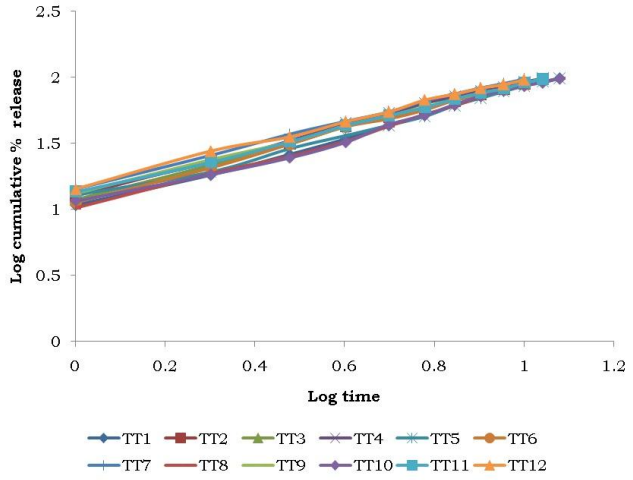


Fig 8. Ex-vivo permeation studies of best formulation TT5

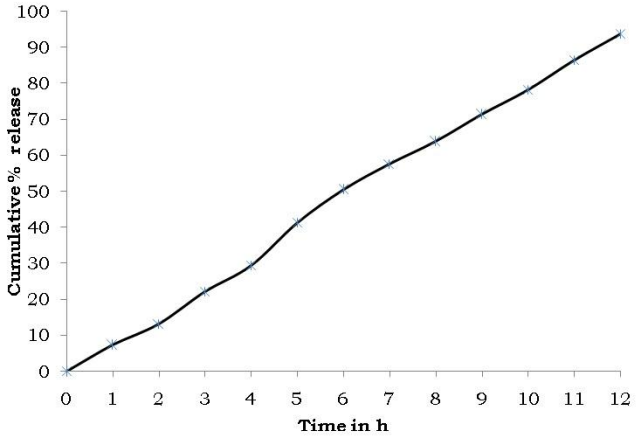
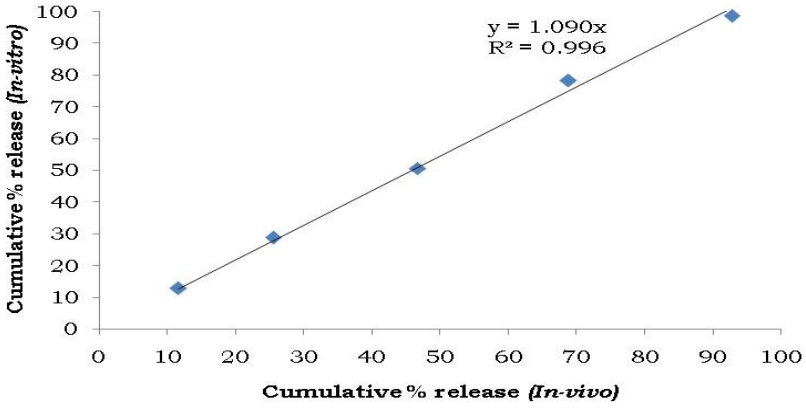


Fig 9. *In-vitro* and *In-vivo* correlation plot



CONCLUSION

The buccal tablets of Timolol maleate were prepared by direct compression method by using various proportions of mucoadhesive polymers such as HPMC K100, SCMC, PVP K30 and Sodium alginate. Ethyl cellulose was used as an impermeable backing membrane to prevent release of drug into saliva of buccal cavity. The prepared Timolol maleate buccal tablets were characterized based upon their physico-chemical characteristics like weight variation, thickness, hardness, friability, surface pH and drug content. The *in-vitro* swelling studies, *ex-vivo* buccoadhesive strength, *ex-vivo* permeation studies, *in-vitro* release studies and *in-vivo* release studies in rabbits were performed. The satisfactory results were obtained in all prepared formulation and based on the results TT5 [SCMC (25 mg) + Sodium alginate (12.5 mg) + PVP (12.5 mg)] was the best one when compared to other. Good correlation was observed between *in-vitro* and *in- vivo* profile, revealed the ability of the formulation to reproduce the *in-vitro* release pattern through the biological membrane. Hence Timolol maleate oral mucoadhesive buccal tablets which are used mainly in minimizing dose and mainly help to improve the patient compliance and Timolol maleate is a drug of choice for delivery through the control release via buccal tablets.

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