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Research

Formulation And Evaluation Of Mucoadhesive Buccal Tablets Of Timolol Maleate

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Abstract

In the present work, the mucoadhesive tablets of Timolol Maleate were prepared by using different concentrations of Chitosan and Carbopol as a binder. The formulation was prepared by wet granulation method. The compatibility studies of drug and excipient were performed by FT- IR spectroscopy. After examining the flow properties of the powder blends the results were found to be within prescribed limits and indicated good flowing property, hence it was subjected to compression. The tablets were evaluated for post-compression parameters like weight variation, hardness, thickness, friability, drug content uniformity, surface pH, *in-vitro* studies like swelling, mucoadhesive strength and drug release. In dissolution studies TM6 formulation was considered as optimised formulation. The *in vitro* drug release of all formulations exhibits complete release of Timolol Maleate with followed by Higuchi mechanism. All the evaluation parameters given the positive result and comply with the standards. The results indicated that the mucoadhesive buccal tablets of Timolol Maleate may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in bioavailability of Timolol Maleate through buccal mucosa.

Keywords: Timolol Maleate, Chitosan, Carbopol and Buccal tablets.

INTRODUCTION

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 dosing .Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) A vehicle the release the drug at an appropriate rate under the conditions

prevailing in the mouth and (c) Strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promote the residence time and act as controlled release dosage forms.

The use of many hydrophilic macromolecular drugs as potential therapeutic agents is their in adequate and erratic oral absorption. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. Based on our current understanding, it can be said that many drugs can not be delivered effectively through the conventional oral route.

The main reasons for the poor bio-availability of many drugs through conventional oral route are:

- ✓ Pre-systemic clearance of drugs.
- ✓ The sensitivity of drugs to the gastric acidic environment which leads to gastric irritation. Limitations associated with gastro intestinal tract like variable absorption characteristics.

Buccal mucosa composed of several layers of different cells. The Epithelium is similar to stratified squamous epithelia found in rest of the at least one of which is biological nature are held together by means of interfacial forces.

Buccal drug delivery is a type of bioadhesive drug delivery especially it is a mucoadhesive drug delivery system is adhered to buccal mucosa.

- ➢ The term bioadhesion is commonly defined as an adhesion between two materials where at least one of the materials is of biological origin. In the case of bioadhesive drug delivery systems, bioadhesion often refers to the adhesion between the excipients of the formulation (i.e. the inactive media) and the biological tissue.
- ➢ The term mucoadhesion can be considered to refer to a sub group of bioadhesion and, more specifically, to the case when the formulation interacts with the mucous layer that covers a mucosal tissue.

The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye.

Overview of the Oral Mucosa Structure The oral mucosa is composed of an outermost layer of stratified squamous epithelium. The epithelium of the buccal mucosa is about 40- 50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days, and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm. The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, nonkeratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

MATERIALS AND METHODS

Terbutaline sulfate Procured From Themis Laboratories PVT LTD, Mumbai (India). Provided by SURA LABS, Dilsukhnagar, Hyderabad. Chitosan fromPanchi Chemicals Pvt Ltd, Mumbai, Carbopol from Alkem Labs Pvt, Ltd, Mumbai, Lactose from Sd fine Chem.Ltd. Mumbai, Magnesium stearate from SD Fine chemicals, Mumbai, Talc from Qualigens fine chemicals, Mumbai, Aspartame from SD Fine chemicals, Mumbai.

Preformulation studies

Analytical method used in the determination of Timolol Maleate

Preparation of pH 6.8 phosphate buffer

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed. Dissolved 6.805 g of potassium dihydrogen orthophosphate in to 800mL of Purified water and mixed. Added 112mL of 0.2M NaOH solution in to this solution, diluted to volume with purified water. Then adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

Preparation of pH 7.4 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 195.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of standard graph in phosphate buffer pH 6.8: 100 mg of Pure drug was dissolved in small amount of Methanol (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 6.8. From this secondary stock 1, 2, 3, 4, 5 ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 10, 20, 30, 40, 50 µg/ml respectively. The absorbance was measured at 290 nm using a UV spectrophotometer.

Preparation of standard graph in phosphate buffer pH 7.4: 100 mg of drug was dissolved in small amount of phosphate buffer and make the volume up to 100ml with phosphate buffer pH 7.4, from this primary stock(1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 7.4. From this secondary stock 1, 2, 3, 4, 5 ml were taken separately and made up to 10 ml with phosphate buffer pH 7.4, to produce 10, 20, 30, 40, 50 µg/ml respectively.

Solubility Studies

The solubility of Timolol Maleate in phosphate buffer solution pH 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 ml of phosphate buffers (pH 6.8). Vials were closed with rubber caps and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whattman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 290 nm using a UV spectrophotometer.

The standard curves for Timolol Maleate were established in phosphate buffers (pH 6.8) and from the slope of the straight line the solubility of Timolol Maleate was calculated. The studies were repeated in triplicate (n = 3), and mean was calculated.

Preparation of Tablets

1. The ingredients were weighed.
2. All the ingredients except Magnesium stearate, Chitosan, Carbopol, PVP K90 and IPA were sieved and hand mixed together.
3. Then PVP K 90 was dissolved in sufficient quantity of IPA was added slowly in small quantities to the previous blend and it was hand mixed thoroughly.
4. The wet mass was air dried to remove the IPA.
5. The dried mass was then passed through sieve no. 30 to obtain granules.
6. The granular mixture was then compacted using a 10 station punching machine using 7mm punch tooling with an average weight of 150mg per tablet.

Table 1: Formulation Chart

INGREDIENTS (MG)	FORMULATION CODES							
	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8
Timolol Maleate	5	5	5	5	5	5	5	5
Chitosan	5	10	15	20	-	-	-	-
Carbopol	-	-	-		5	10	15	20
Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	6	6	6	6	6	6	6	6
Aspartame	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100

Drug-excipient compatibility studies

Fourier Transform Infrared spectroscopic studies

A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 cm^{-1}. Pure drug of Timolol Maleate with physical mixture (excipients) compatibility studies were performed.

RESULT AND DISCUSSION

Solubility Studies

Table 2: Solubility studies

S.No	Medium	Amount present (µg/mL)
1	Phosphate pH6.8 buffer	98.18
2	Phosphate pH 7.4 buffer	96.71

Standard graph in phosphate buffer pH 6.8 (λ_{max} 293 nm)

Standard graph of Timolol Maleate was plotted as per the procedure in experimental method and its linearity.The standard graph of Timolol Maleate showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Table 3: Standard graph values of Timolol Maleate in pH 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
10	0.201
20	0.371
30	0.528
40	0.694
50	0.862

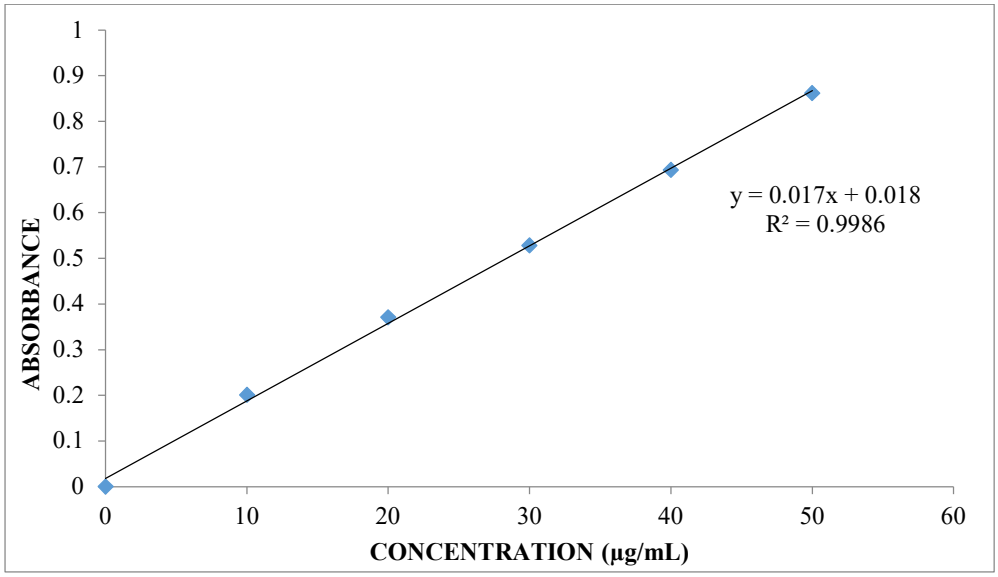

Fig 1: Standard graph of Timolol Maleate in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ_{max} 290 nm)

Standard graph of Timolol Maleate was plotted as per the procedure in experimental method and its linearity. The standard graph of Timolol Maleate showed good linearity with R^2 of 0.999, which indicates that it, obeys "Beer- Lamberts" law.

Table 4: Standard graph values of Timolol Maleate in pH 7.4 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
10	0.133
20	0.249

30	0.365
40	0.472
50	0.592

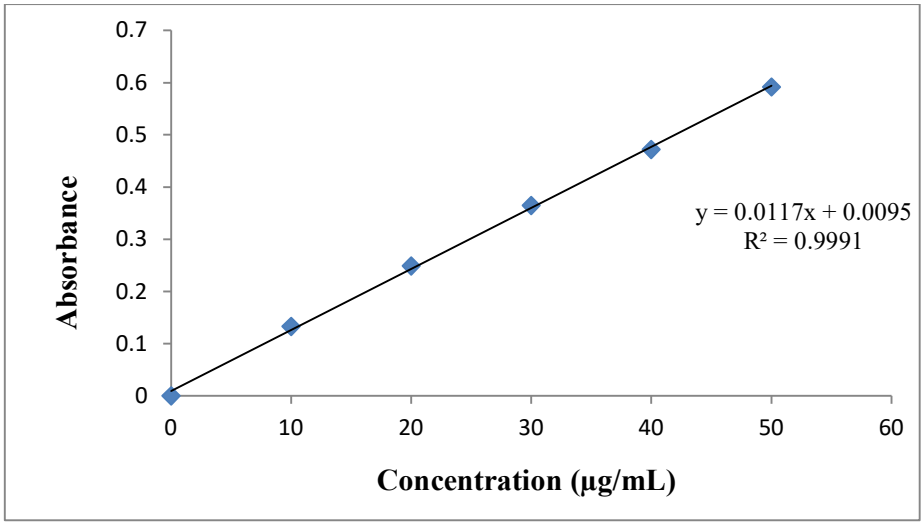

Fig 2: Standard graph of Timolol Maleate in pH 7.4 phosphate buffer

Evaluation

Characterization of pre-compression blend

The pre-compression blend of Timolol Maleate buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 23.45º, Carr's index values were less than 14.7 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.24 for all the batches indicating good flow properties.

Table 5: Physical properties of pre-compression blend

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
TM1	18.8	0.38	0.43	11.6	1.13
TM2	19.6	0.39	0.44	11.3	1.12
TM3	19.4	0.42	0.47	10.6	1.11
TM4	21.9	0.40	0.45	11.1	1.12
TM5	17.5	0.41	0.46	10.8	1.12
TM6	19.2	0.37	0.43	13.9	1.16
TM7	19.5	0.38	0.46	17.3	1.21
TM8	21.3	0.39	0.45	13.3	1.15

Evaluation of buccal tablets

Physical evaluation of Timolol Maleate buccal tablets

The results of the weight variation, hardness, thickness, friability and drug content of the tablets are given in Table 9.5. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.01 to 4.99 kg/cm^2 and the friability values were less than 0.77 % indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 3.21 – 3.81 mm. All the formulations satisfied the content of the drug as they contained 97.01-100.24 % of Timolol Maleate. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table 6: Physical evaluation of Timolol Maleate buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity(%)
TM1	100.4	3.24	4.16	0.27	98.15
TM2	98.96	3.66	4.97	0.61	99.15
TM3	99.39	3.81	4.12	0.44	97.01
TM4	100.24	3.21	4.99	0.86	100.01
TM5	97.35	3.47	4.22	0.54	98.72
TM6	99.12	3.72	4.98	0.35	100.24
TM7	98.24	3.31	4.01	0.52	99.48
TM8	96.92	3.67	4.29	0.71	98.31

Table 7: Swelling Index and Mucoadhesive strength (G)

S.NO.	Formulations	Swelling Index (%)	Mucoadhesive strength (G)
1	TM1	0.82	11.72±0.82
2	TM2	1.19	13.38±0.85
3	TM3	2.26	12.24±0.92
4	TM4	2.96	15.62±0.79
5	TM5	1.25	14.30±1.44
6	TM6	2.31	18.93±1.11
7	TM7	3.10	19.13±1.09
8	TM8	4.21	15.34±1.75

Swelling index is an important parameter in judging the mucoadhesion property, at least in the initial stages, since water uptake is important for the polymers to uncoiland interacts with the mucin. The swelling indices of the Timolol Maleate buccal tablets reveals that while the buccal tablet formulations are all made of different materials, the extent of swelling differs based on the individual tablet composition. The Swelling indices of the first three formulations are quite low because of the fact that theystarted to disintegrate and lose mass soon after placing them upon the Petri-dish. Theformulations containing higher levels of the polymers Carbopol displayed the highest swelling index.

***In vitro* release studies**

*In vitro*drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Timolol Maleate from different formulations varies with characteristics and composition of matrix forming polymers.

Table 8: *In vitro* dissolution data for formulations F1 – F9

TIME (H)	CUMULATIVE PERCENTE OF DRUG RELEASE							
	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8
0	0	0	0	0	0	0	0	0
0.5	38.89	28.74	30.62	25.15	50.32	32.61	28.46	21.58
1	47.74	35.92	38.44	31.83	56.23	49.52	33.59	28.31
2	58.62	43.53	46.31	43.52	62.19	54.64	41.85	33.72
3	62.21	59.29	51.346	50.23	70.25	60.87	45.63	49.47
4	70.77	65.85	61.43	57.33	76.941	64.66	57.92	53.49
5	76.13	69.63	65.92	63.82	82.29	79.76	63.84	67.51
6	83.49	76.16	72.44	70.12	98.33	85.84	65.63	71.34
7	90.46	85.24	86.31	76.23		93.93	78.44	84.69
8	95.26	92.68	90.24	86.16		99.59	92.84	89.36

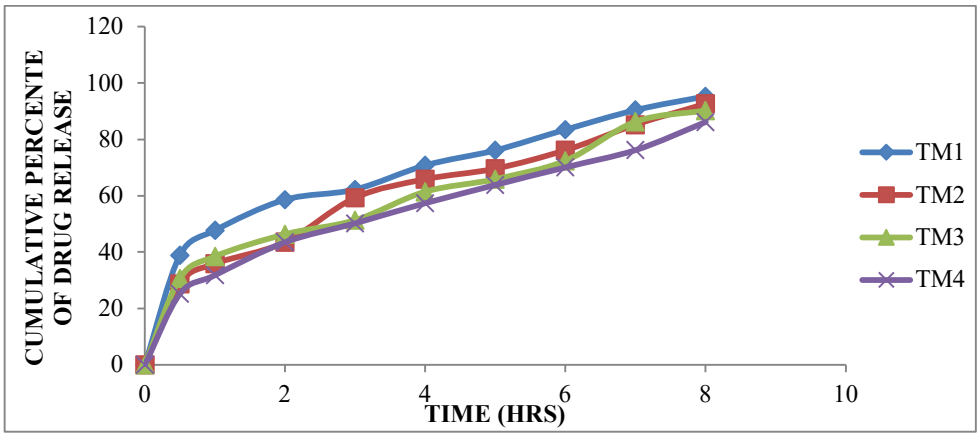

Fig 3: *In vitro* dissolution data for formulations F1 – F4 by using Chitosan polymer

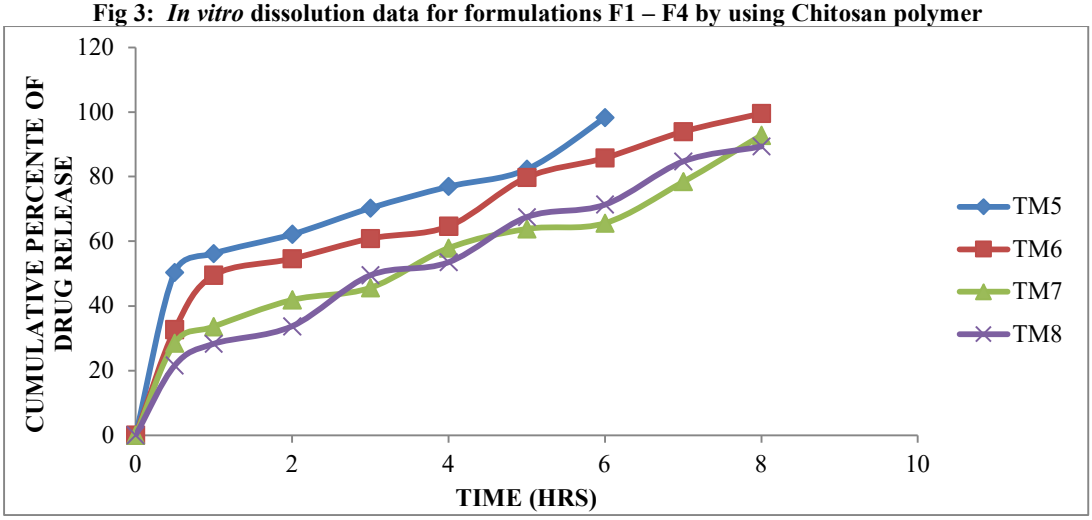

Fig 4: *In vitro* dissolution data for formulations F5–F8 by using Carbopol polymer

From the dissolution studies observed Total Eight Formulation are prepared. The formulations prepared with Chitosan in different concentrations. The formulation TM2 was maximum drug released 92.68 % in 8 h. Concentration of polymer increased the drug release was decreased. The formulation was prepared with Carbopol the drug release was observed, the formulation TM6 was showed 99.59 % maximum drug release in 8 hours. Among all formulations TS6 was showed maximum drug r release in 8 hrs. So Formulation TM6 was selected as optimised formulation.

Table 9: Moisture absorption, surface pH of selected formulations

Formulation Code	Moisture absorption	Surface pH
TM2	92	6.19
TM6	98	6.01

The moisture absorption studies give important information of the relative moisture absorption capacities of polymers and it also give information regarding whether the formulations maintain the integrity or not. Among the selected formulations TM6 formulation shown good moisture absorption.

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The surface pH of the selected formulations was found to be 6.01 to 6.19 and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations were not irritant to the buccal mucosa.

Release kinetics

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Timolol Maleate release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics;higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 10: Release kinetics and correlation coefficients (R^2)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
32.62	0.5	0.707	1.513	0.301	1.829	65.240	0.0307	-0.487	67.38	4.642	4.069	0.572
49.54	1	1.000	1.695	0.000	1.703	49.540	0.0202	-0.305	50.46	4.642	3.695	0.946
54.63	2	1.414	1.737	0.301	1.657	27.315	0.0183	-0.263	45.37	4.642	3.567	1.075
60.86	3	1.732	1.784	0.477	1.593	20.287	0.0164	-0.216	39.14	4.642	3.395	1.246
64.64	4	2.000	1.811	0.602	1.549	16.160	0.0155	-0.189	35.36	4.642	3.282	1.359
79.73	5	2.236	1.902	0.699	1.307	15.946	0.0125	-0.098	20.27	4.642	2.727	1.915
85.89	6	2.449	1.934	0.778	1.150	14.315	0.0116	-0.066	14.11	4.642	2.416	2.225
93.92	7	2.646	1.973	0.845	0.784	13.417	0.0106	-0.027	6.08	4.642	1.825	2.816
99.58	8	2.828	1.998	0.903	-0.377	12.448	0.0100	-0.002	0.42	4.642	0.749	3.893

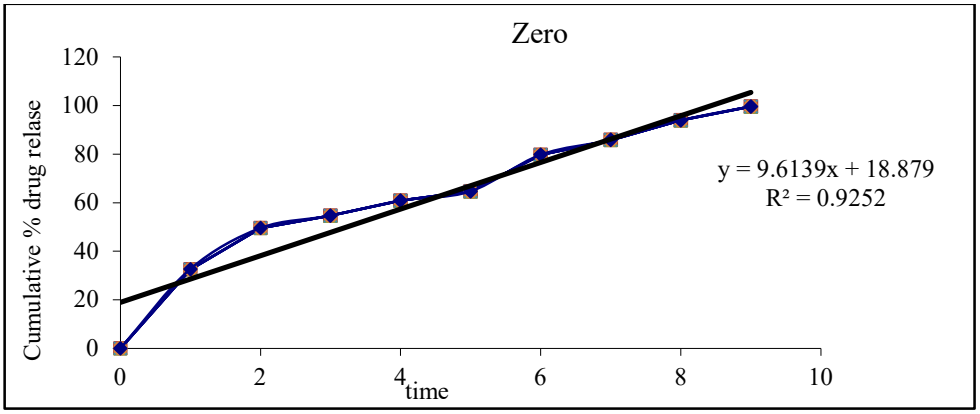

Fig 5: Zero order plot of optimized formulation

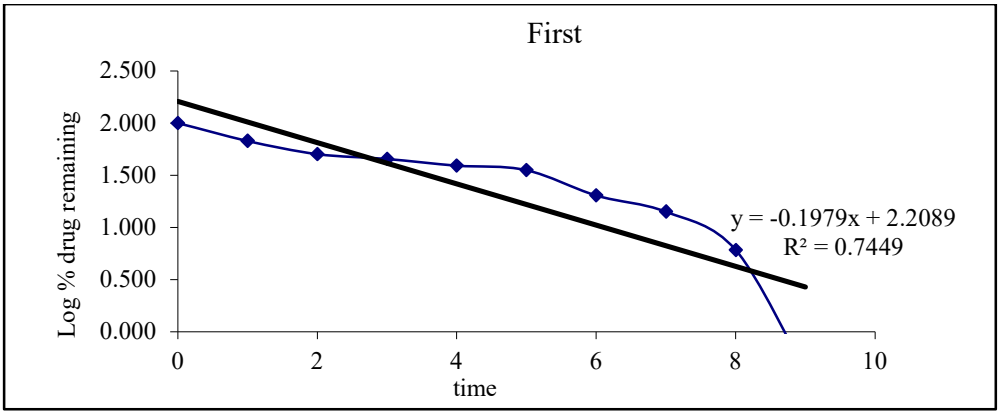

Fig 6: First order plot of optimized formulation

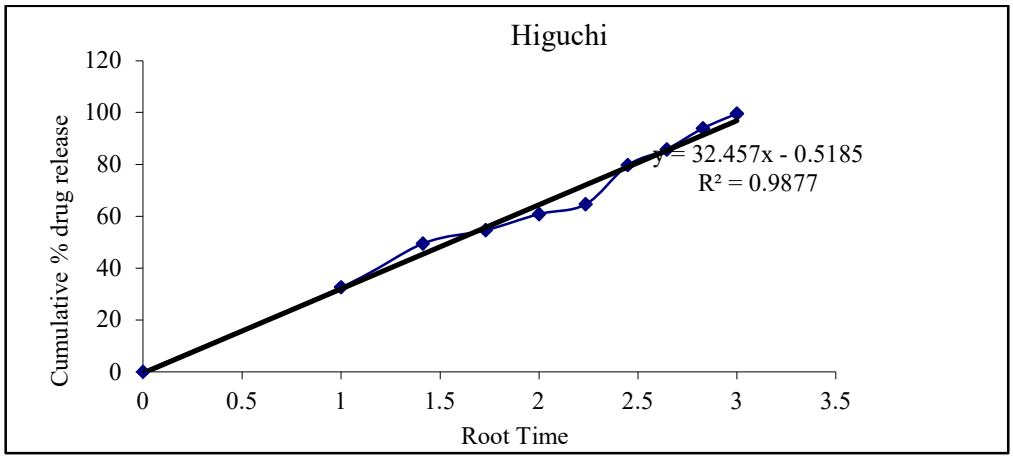

Fig 7: Higuchi plot of optimized formulation

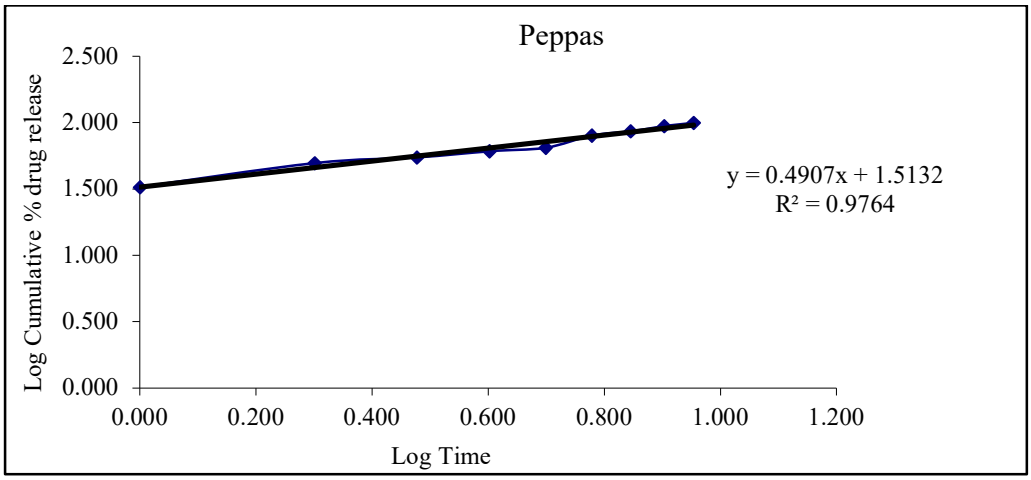

Fig 8: Koresmeyer-peppas plot of optimized formulation.

This formulation was following Higuchi release mechanism with regression value of 0.987.

Drug – excipient compatibility studies by physical observation:

Timolol Maleate was mixed with various proportions of excipients showed no color change at the end of two months, proving no drug-excipient interactions.

FTIR

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Timolol Maleate drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Timolol Maleate are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug. There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

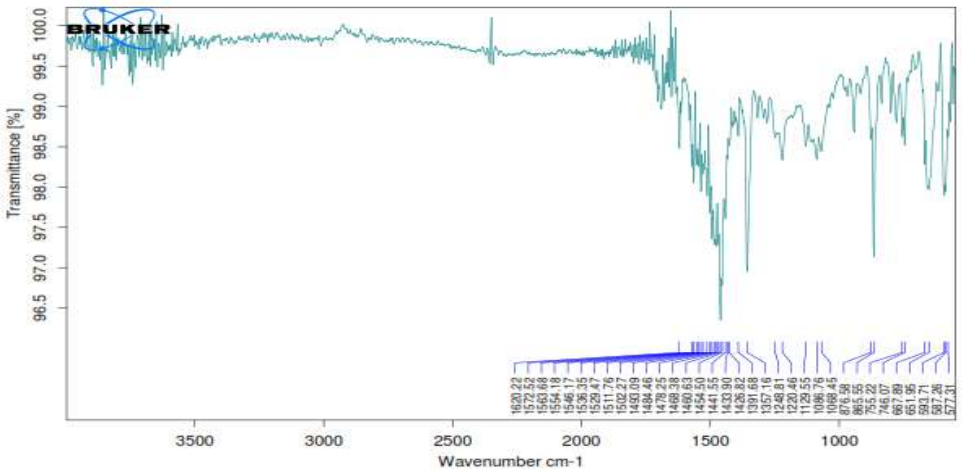

Fig 9: FTIR Peak of pure drug Timolol Maleate

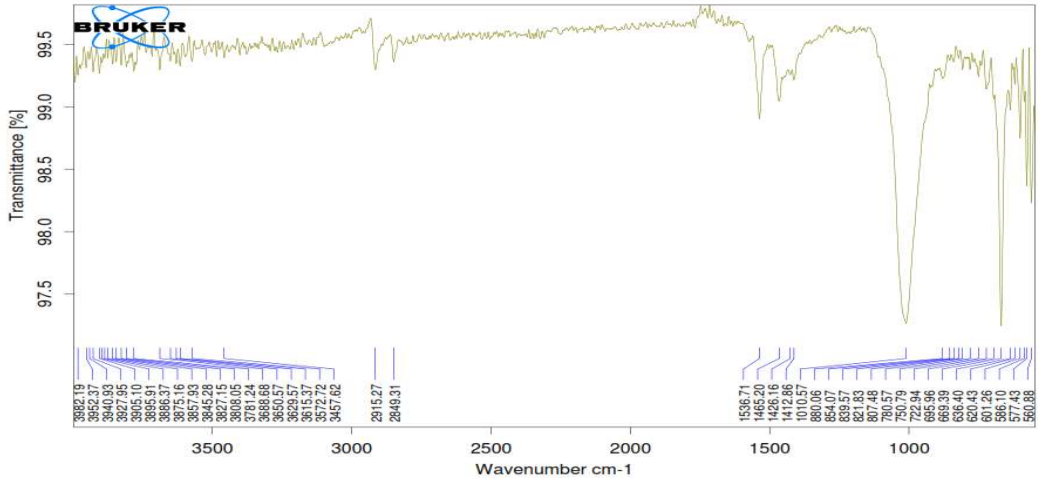

Fig 10: FTIR Peak of Optimised formulation

CONCLUSION

The outcomes of this study indicate that Mucoadhesive tablets of Timolol Maleate with controlled drug release can be successfully prepared by wet granulation method using Chitosan and Carbopol as mucoadhesive polymers. The prepared mucoadhesive buccal tablets subjected to infrared spectrum study suggested that there was no drug -polymer interaction. All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification. The surface pH of prepared buccal tablets was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation. The buccal tablets showed good swelling property maintaining the integrity of formulation which is required for bioadhesion. The *in-vitro* release of Timolol Maleate was extended for 8 h. Formulations TM6 batch shows good *in- vitro* drug release 99.58%. All the tablets showed good mucoadhesive strength. By consideration of all above parameters, it that Carbopol appears to be suitable for use as a release retardant in the manufacture of buccal tablets because of its good swelling, good flow rate and suitability for mucoadhesion formulations. From the dissolution study, it was concluded that Carbopol can be used as an excipient for preparing Mucoadhesive buccal tablets.

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