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Research Article

PREPARATION AND EVALUATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS

Adimoolam Senthil*, Chauhan Pratik Navinchandra, Jismon Jose, Mahin MM, Siroya Yakinkumar Ravajibhai
Department of Pharmaceutics, Karavali College of Pharmacy, Mangalore-575028, Karnataka, India

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*Dr. A. Senthil, M.Pharm., Ph.D, Professor and HOD, Department of pharmaceutics, Karavali College of Pharmacy, Mangalore-575028, Karnataka, India.
E-mail: senthilac12@gmail.com

ABSTRACT
The present investigation was concerned with preparation and evaluation of mucoadhesive buccal tablets containing antihypertensive drug, Timolol maleate to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression method. Eight formulations were developed with varying concentrations of polymers like chitosan, hydroxyethylcellulose and hydroxypropylmethylcellulose. The formulated tablets were evaluated for weight variation, hardness, surface pH, drug content uniformity, swelling index, bioadhesive strength and in vitro drug dissolution study. FTIR studies showed no evidence on interactions between drug, polymers and excipients. The in vitro release of Timolol maleate was performed under sink conditions (Phosphate buffer pH 6.8, 37±0.5ºC, 50rpm) using USP-XXIV dissolution apparatus type II. The best in vitro drug release profile was achieved with the formulation F5 which contains the drug, chitosan and HPMC K4M in the ratio of 1:2.5:10. The surface pH, bioadhesive strength and swelling index of formulation F5 was found to be 6.34, 36.50g and 80%, respectively. The formulation F5, containing 10 mg of Timolol maleate exhibited 7 hrs sustained drug release i.e. 98.18% with desired therapeutic concentration. The in vitro release kinetics studies of optimized formulation reveal that follows zero order kinetics.
KEY WORDS: Timolol maleate, Mucoadhesive buccal tablet, Bioadhesive strength, Release kinetics.

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[1]. 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[2, 3]. 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 (c) strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery system promotes the residence time and act as controlled release dosage forms[4]. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site[5]. In addition, there is excellent acceptability and the drug can be applied, treatment period[6]. It is beneficial in the case of Timolol maleate to overcome the problem of frequent dosing due to its shorter half life (2.5 - 5 hrs). Prolonged release of the drug and increased bioavailability leads to the significant reduction in the dose and hence dose related side effects. Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for Timolol maleate using different mixtures of polymers in order to avoid extensive first pass metabolism, degradation in the stomach and prolonged effect.

MATERIALS AND METHODS

Materials

Timolol maleate was a gift sample from Sun Pharmaceuticals Industries Ltd, Silvassa, India. Bangalore. Hydroxyethylcellulose was gift sample from Glenmark Pvt. Ltd, Mumbai. Hydroxypropylmethylcellulose and Chitosan was gift sample from Colorcon Asia Pvt. Limited, Verna, India. All other reagents used were of analytical grade.

Methods

Formulation of Timolol maleate mucoadhesive buccal tablets

The drug, polymers and excipients were mixed homogeneously in a glass mortar for 15 min. The mixture (150 mg) was then compressed using an 8 mm, biconcave punch in a single-stroke using Cemach 12-station rotary machine. The formulation of Timolol maleate mucoadhesive buccal tablets were shown in Table 1.

EVALUATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS

Weight variation

Ten tablets from each formulation (F1 to F8) were weighed using an electronic balance and the average weight was calculated.

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were standard deviation values were calculated.

Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss was determined.

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper (Pico India). The average values were calculated.

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 10 mg of Timolol Maleate equivalent of mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 296 nm. This procedure was repeated thrice and this average was chosen.

Microenvironment pH

The microenvironment pH (surface pH) of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. 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 method adopted by Bottenberg et al[7] was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 5 ml of 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 tablets and allowing it to equilibrate for 1min.

Bioadhesion studies

In evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. In present study, sheep buccal mucosa was used as a model mucosal surface for bioadhesion testing[8]. Immediately after slaughter, the buccal mucosa was removed from the sheep and transported to laboratory in tyrode solution and kept at 40ºC.

Mucoadhesive strength

The Mucoadhesive forces of the tablets were determined by means of mucoadhesive measuring device. The sheep buccal mucosa was cut into strips/pieces and washed with tyrode solution. At time of testing a section of sheep buccal mucosa was secured keeping the mucosal side out, on the upper glass vial using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1cm. The vial with the sheep buccal mucosa was stored at 37°C for 10 min. Then one vial with section of sheep buccal mucosa and another vial were fixed on height adjustable pan. To a lower vial a tablet was placed with the help of bilayered adhesive tape, adhesive side facing downward. The height of the lower vial was adjusted so that a tablet could adhere to the sheep buccal mucosa on the upper vial. A constant force was applied on the upper vial for 2 min, after which it was removed and the upper vial waspan was slowly added in an increment of 0.5gm, till the two vials just separated from each other. The total weight (gm) required to detach two vials was taken as a measure of mucoadhesive strength. From this mucoadhesive strength, the force of adhesive was calculated.

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 hrs) 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 [9, 10]

$$\text{Percentage hydration} = [(W2-W1) / W1] \times 100$$

Were, W1 = Initial Weight, W2 = Final Weight

In vitro dissolution studies

The in vitro dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV Type II apparates[11]. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, at a rotation of speed of 50 rpm. 5 ml samples were withdrawn at predetermined time intervals (1 to 7hrs) and the volume was replaced with fresh medium. The samples were filtered through filter paper No.40 and analyzed after appropriate dilution by UV spectrophotometer at 296 nm. The % drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8.

Release kinetic studies

To find out the mechanism of drug release from hydrophilic matrices, the in vitro release data was treated with different kinetic models, namely zero order and first order.

Compatibility studies

The drug excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra red spectra of pure drug and mixture of drug and excipients were recorded. A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR.

RESULTS AND DISCUSSION

The present investigation was concerned with preparation and evaluation of Timolol maleate mucoadhesive buccal tablets by using three different mucoadhesive polymers HPMC K4M, HEC and Chitosan with varying concentrations by direct compression method. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The angle of repose between 30 and 32°, this indicates passable flowability, the percentage compressibility index and hausner's ratio were within the limits (< 15%). The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in Table 2. The drug content was found to be in the range of 98 to 100% (acceptable limits) and the hardness of the tablets was found to be 2.8 to 3.2 kg/cm^2 were tabulated in Table 2. Friability below 1% was indicating good mechanical resistance of tablets.

The weight variation test was conducted for each batch of all formulations F1 to F8 as per I.P and the results were shown in Table 2. All the formulations comply with the IP limit (± 10%). The adequate tablet hardness is necessary requisite for consumer acceptance and handling. The measured hardness of the tablets of each batch of all formulations i.e. F1 to F8 were ranged between 3.1 to 7.2 Kg/cm^2 and the results were shown in Table 2. The friability test for all the formulations were done as per the standard procedure I.P. The results of the friability test were tabulated in Table 2. The data indicates that the friability was less than 1% in all formulations ensuring that the tablets were mechanically stable. The thickness of the tablets was found to be almost uniform in all formulations F1 to F8. The thickness was found to be in the range of 2.4 to 2.9 mm. None of the formulations (F1 to F8) showed a deviation. Hence, it is concluded that all the formulations complied the thickness test and the results were shown in Table 2. The drug content of each batch of all the formulations (F1 to F8) was evaluated as per the standard protocol. The results indicate that the percentage of drug content was found to be 95 to 101%. Hence it is concluded that all the formulations are following acceptable limits as per Indian Pharmacopoeia i.e. ± 5%. Surface pH of all the

formulations F1 to F8 was found to be 5.8 to 6.38, which is well within the limit of acceptable salivary pH range of 5.69 to 6.34 (Table 2). Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface.

The in vitro bioadhesive strength study was performed and the results were shown in the Table 2. On the modified physical balance and measure the force (N) required detaching the tablet. The bioadhesion characteristics were affected by the concentration of the bioadhesive polymers. Increase in concentration of polymer increases bioadhesive strength of formulation. The formulations (F1, F2, F3 and F4) with chitosan and hydroxyethylcellulose showed the bioadhesive strengths of 34.5, 31.4, 29.5 and 27.6 gm respectively. The formulations (F5, F6, F7 and F8) with chitosan and HPMC K4M showed the bioadhesive strengths of 36.5, 34.1, 33.5 and 31.5 gm respectively. The swelling studies were conducted for all formulations i.e. F1 to F8 and the results were shown in Table 3 and Figure 1 and 2. All the formulations were hydrated generally by keeping the tablets in contact with water for 1 to 8 hrs. The highest hydration (swelling) i.e. 82.2% was observed with the formulation F1. This may be due to quick hydration of polymers (chitosan and HPMC K4M). The swelling rate of tablets increased in the case of formulation F1 containing chitosan and HPMC K4M.

In vitro drug release data of F1 to F8 were fitted to zero order; first order equations to ascertain the pattern of drug release were shown in Table 4. The R^2 values were found to be higher in zero-order followed by first order which indicates all the formulations followed zero-order release pattern. The formulations F1, F2, F3 and F4 containing drug, chitosan and HPMC K4M polymers in different ratios. The in vitro cumulative drug release profile of formulations F1, F2, F3 and F4 showed 97.36%, 96.90%, 93.36% and 94.64%, respectively. Among these four formulations, F1 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and no erodible over the period of 7 hrs. Formulations F5, F6, F7 and F8 containing chitosan and hydroxyethylcellulose with different ratios. The in vitro cumulative drug release profile showed 90%, 89%, 88% and 89%, respectively. Among these four formulations, F1 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and non-erodible over the period of 7 hrs. It was concluded that by increasing the concentration of chitosan in the formulation, the drug release rate from the tablets was found to be decreased. But when the concentration of secondary polymers (HEC and HPMC K4M) increased, the drug release rate was found to be increased. This may be due to increased hydration (or) swelling characteristics of polymers with increased concentrations. From the overall data it was found that the formulation F1 showed the maximum percentage of drug releases i.e. percentage at the end of 7 hrs. The incompatibility between the drug and excipients were studied by FTIR spectroscopy. The spectral data of pure drug and various drug excipient mixtures were presented in Figure 3, 4 and 5. The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation.

CONCLUSION

Timolol maleate mucoadhesive buccal tablets were prepared by using different mucoadhesive polymers chitosan, HPMC K4M and HEC with different ratios. Increasing the concentration of chitosan in the formulations, the drug release rate from the tablets was found to be decreased. But when the concentration of HPMC K4M increased, the drug release rate was found to be increased. The in vitro release kinetics studies reveal that all formulations fit well with zero order kinetics. Further, an elaborate in vivo study is to be carried out for the best formulation using a suitable animal model.

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Table 1: FORMULATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS

Ingredients (mg)*	F1	F2	F3	F4	F5	F6	F7	F8
Timolol maleate	10	10	10	10	10	10	10	10
HPMC K4M	95	85	75	65	-	-	-	-
HEC	-	-	-	-	95	85	75	65
Chitosan	30	40	50	60	30	40	50	60
Mannitol	10	10	10	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Average weight	150	150	150	150	150	150	150	150

*All the quantities expressed are in mg/tablet.

Table 2: EVALUATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLET

Formulation code	Average weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Surface pH	Bioadhesive strength (gm)
F1	148.99±0.02	5.0±0.11	0.31±0.04	2.9	98.03	5.91	29.5
F2	150.00±0.03	7.2±0.15	0.51±0.06	2.4	101.03	6.35	33.5
F3	149.67±0.06	5.5±0.25	0.55±0.02	2.7	99.12	6.23	34.2
F4	148.89±0.09	6.5±0.18	0.65±0.05	2.5	96.50	6.66	31.5
F5	151.59±0.02	4.5±0.19	0.75±0.03	2.8	94.60	5.78	31.4
F6	149.92±0.03	3.1±0.22	0.35±0.04	2.7	98.25	6.18	27.6
F7	149.53±0.05	5.0±0.17	0.45±0.5	2.9	97.87	6.02	29.5
F8	148.89±0.04	4.5±0.12	0.48±0.06	2.6	96.55	5.80	31.5

Table 3: PERCENTAGE HYDRATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS

Formulation Code	1hrs (%)	2hrs (%)	4hrs (%)	6hrs (%)	8hrs (%)
F1	48.8	63.7	72.3	77.3	82.2
F2	46.9	50.2	61.6	65.2	74.4
F3	47.2	48.6	53.3	59.5	66.0
F4	38.3	55.7	60.0	64.1	71.3
F5	44.8	56.2	61.2	65.8	68.9
F6	38.9	50.2	54.5	61.4	74.2
F7	40.9	50.5	58.3	69.4	71.1
F8	39.6	47.3	55.0	61.2	69.3

Table 4: IN VITRO DRUG RELEASE STUDIES OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
0	0	0	0	0	0	0	0	0
2	63.44	60.54	58.44	60.24	63.44	52.74	61.5	59.3
5	77.68	72.34	72.53	73.14	77.68	60.34	65.2	63.2
7	89.40	87.60	85.86	84.83	89.40	75.93	74.4	75.6
10	97.36	96.90	93.36	94.64	90.36	89.10	88.5	89.2
15	96.82	96.16	95.64	95.34	92.82	96.38	90.3	90.2
30	95.42	94.24	94.82	95.15	95.42	95.80	91.9	91.7
45	93.80	93.85	92.32	93.64	93.80	95.16	93.4	93.8

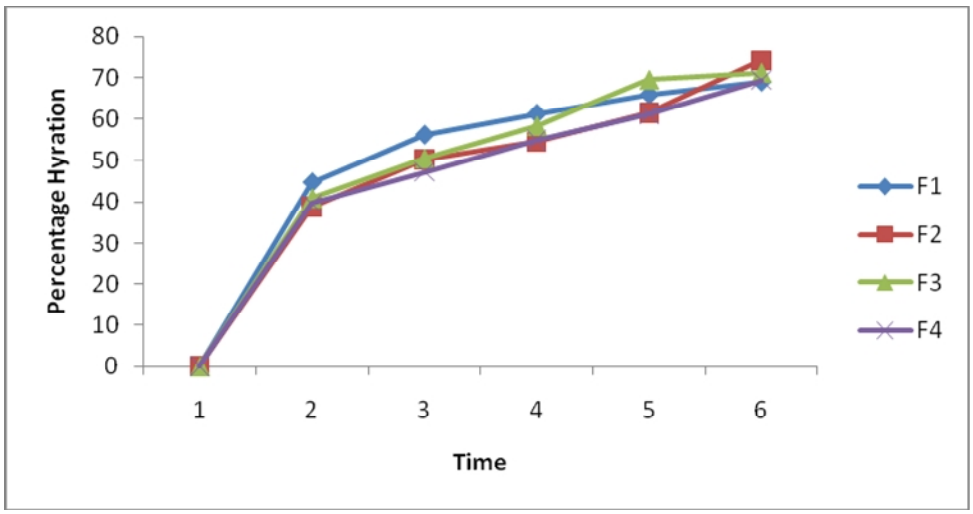

Figure 1: PERCENTAGE HYDRATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS (F1-F4)

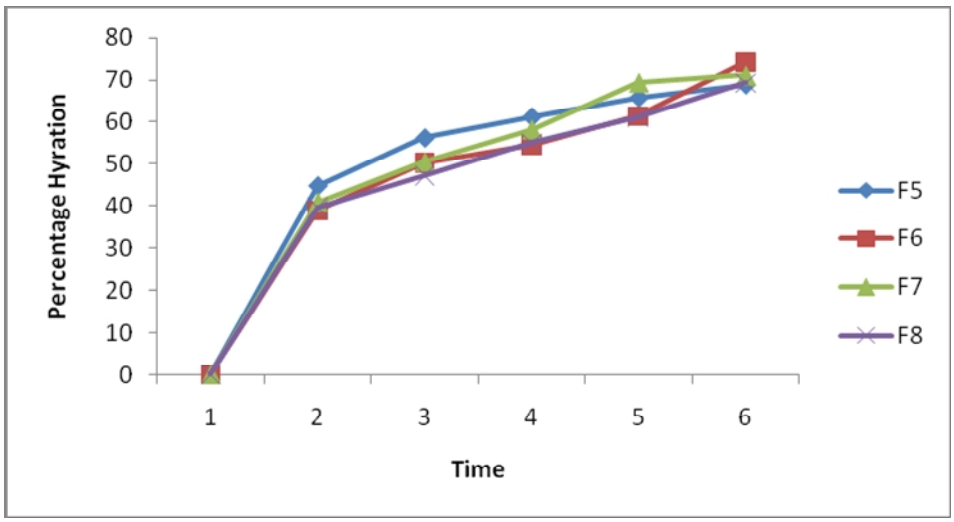

Figure 2: PERCENTAGE HYDRATION OF TIMOLOL MALEATE MUCOADHESIVE BUCCAL TABLETS (F5-F8)

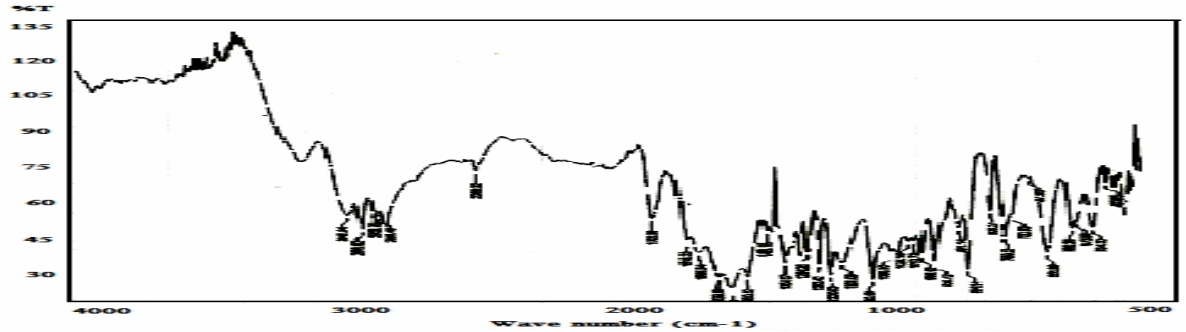

Figure 3: FTIR SPECTRA OF TIMOLOL MALEATE

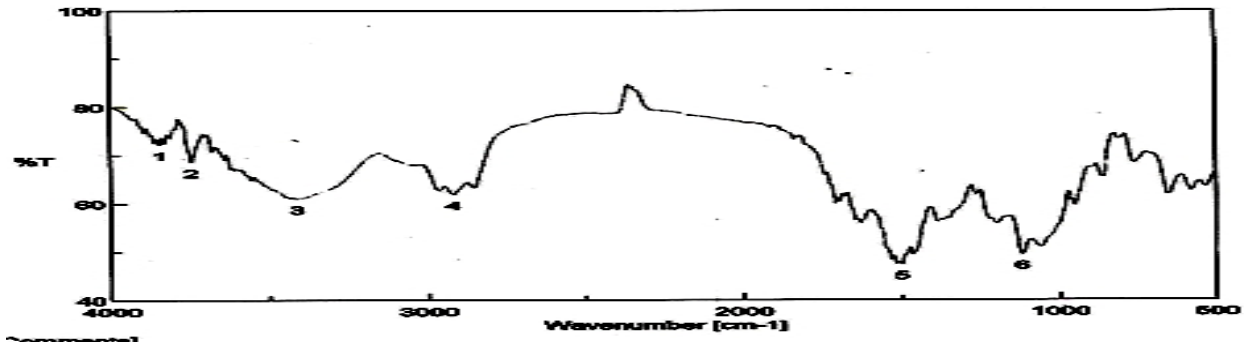

Figure 4: FTIR SPECTRA OF TIMOLOL MALEATE AND HYDROXYPROPYLMETHYLCELLULOSE

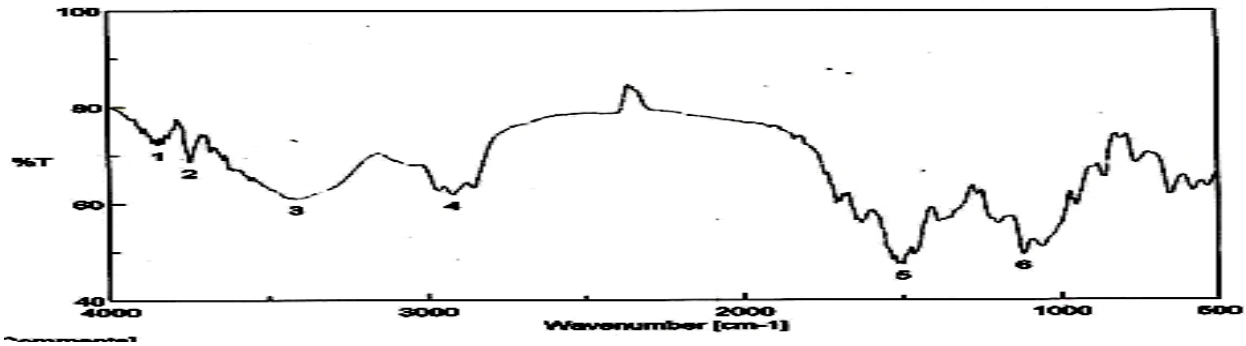

Figure 5: FTIR SPECTRA OF TIMOLOL MALEATE AND HYDROXYETHYLCELLULOSE

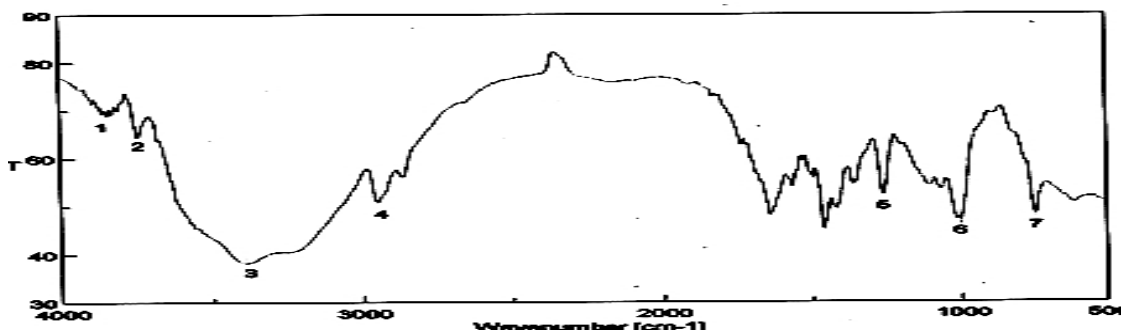

Figure 6: FTIR SPECTRA OF TIMOLOL MALEATE AND CHITOSAN

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