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Formulation and Evaluation of Metoprolol Tartarate Buccal Adhesive Tablets Using Natural Edible Mucoadhesives

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Abstract

In the present work,the mucodhesive tablets of Metaprolol tartarate wre prepared by using different concentrations of Cashewnut tree gum,Aegle marmelos gum,Moringa Oleifera as a binder.The four tablet formulation was prepared by using drug and with polymer like cashew nut tree gum,Aegle marmelos gum,Moringa Oleifers gum ratio 1:0.5,1:0.75,1:1,1:1.25 by direct compression technique. Tablets were subjected to evaluation of uniformity of weight,hardness,friability,drug content uniformity,swelling studies,surface pH study, *Ex-vivo* mucoadhesive time, *Ex-vivo* Bioadhesive strength and *invivo* drug release study. Drug polymer interaction were evaluated by Fourier Transform Infrared Spectroscopy and Diffrential Scanning Colorimetry .All the formulations hardness,weight variation,friability and drug content values were found to be within pharmacopoeia limits. As the amount of polymer in the tablets increase,the drug release rate decreases,where as swelling index and mucoadhesive strength increases.The *in vitro* drug release of all formulations exhibits complete release of Metoprolol taratrate with zero order release kinetics and followed by Higuchi mechanism.From the study it can be concluded that cashew nut tree gum,Aegle marmelos gum,Moringa Oleifera gum used as a binding agent in mucoadhesive buccal tablet.

Keywords: *Metoprolol tartrate, buccal tablets, Formulation, Evaluation,Extraction of natural mucoadhesive polymers.*

Introduction

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted by the patients for the delivery of the therapeutically active drugs. But, after oral drug administration many drugs are subjected to pre systemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability [1-4]. Within the oral route, the oral cavity is an attractive site for drug delivery due to ease of administration and avoids first pass hepatic metabolism [5]. In the, oral cavity the delivery of drugs are classified into three categories: 1.Sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; 2. buccal delivery it is the drug administration through mucosal membranes lining the cheeks (buccal mucosa); and 3. Local delivery it is the drug delivery into the oral cavity [6, 7]. Among these routes, buccal delivery is suitable for administration of retentive dosage forms because of an excellent accessibility, an expanse of smooth muscle and immobile mucosa. So, buccal delivery of drugs is an attractive alternative to the oral route of drug administration [8-10]. Buccal delivery involves the administration of drug through buccal mucosal membrane (the lining of the oral cavity). Buccal drug delivery is the safest method of drug utilization because; drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity. The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability [11]. The other advantages of buccal drug delivery include: low enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or

irritate the mucosa, painless drug administration, easy drug withdrawal, possible to include the permeation enhancer or pH modifier in the formulation. A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a controlled to elicit the required therapeutic response [12-14]. Various buccal mucosal dosage forms for oral delivery which includes: buccal tablets, buccal patches and buccal gels [15, 16]. Metoprolol tartrate is a cardio selective β1 adrenergic antagonist and widely used in the treatment of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. It is rapidly absorbed from oral route, but undergoes first pass metabolism, which results in only 38% oral bioavailability. The half life of metoprolol tartrate is approximately 3-4 hours. Metoprolol tartrate was selected as model drug to avoid first pass hepatic metabolism and to improve the oral bioavailability and to control the release of the drug from the tablets by natural mucoahesive polymers, as the half life of drug is low [17-19].

In this study, muccoadhesive tablets of Metoprolol tartrate have been developed using natutal edible mucoadhesive polymers like Aegle marmelos, Cashew nut tree gum, Moringa oleifera and synthetic polymer like Ethyl cellulose each formulation had the combination. The main objective of this study is the effect of release in polymers combination and the effect of drug: polymer ratio on drug release and other bioadhesive properties.

Materials

Metoprolol tartrate was a gift sample from Hetero Pharma Pvt. Ltd, Hyderabad,India.Aegle marmelos gum, Cashew nut tree gum and Moringa Oliefera gum procured from Local Area. Microcrystalline cellulose and Ethyl Cellulose purchased from Qualigens fine chemicals, Mumbai. Sodium hydroxide, Sodium dihydrogen phosphate, Magnesium stearate and Talc purchased from SD fine chemicals, Mumbai. All other chemicals and reagents used were of analytical reagent grade and purchased from Himedia, Hyderabad.

Methods

Methods of preparation of Natural gums

A. Aegle marmelos gum: The fresh fruits of *Aegle marmelos* were soaked in double distilled water and boiled for 5 h in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight so that most of the undissolved portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm for 20 min. The supernatant was concentrated on a water bath until the volume reduced to one third of its original volume. The solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50^0C under vacuum. The dried gum was powdered and stored in tightly closed container for further usage[20].

B. Cashew nut tree gum: The collected crude *cashew nut tree gum* (100g) was crushed by using mortar and pestle. The crushed gum was dissolved in water (300ml). The solution was filtered through several folds of muslin cloth and the filtrate was collected. To the filtrate, alcohol (90% v/v) was added in 1:1 ratio and the precipitate were obtained. The precipitate was filtered and dried in a hot air oven at 45^0C. 100 g of powder obtained was dissolved in 100 ml water, filtered through several folds of muslin cloth. Then the filtrate was centrifuged at 3000 rpm for 10 minutes and the supernant layer was collected, evaporated and dried to obtain solid mass. This mass was passed through sieve no. 80 and stored in an airtight container for further studies[21].

C. Moringa oleifera tree gum: The gum was collected from incisions of trees. The gum was dried and crushed by using mortar and pestle. It is passed through sieve no.100. Dried gum was stirred in distilled water (300ml) for 4 – 5 hours at room temperature. The supernant layer was obtained by centrifugation. The residue was washed with water; this procedure was repeated for three times. Finally the supernant layer was made up to 500ml and treated with twice the volume of acetone by continuous stirring. The precipitate material was washed with water and dried at 50 – 60^0C under vacuum[22].

Evaluation Parameters powder blend:

Flow properties

A. Bulk density (g/ml): About 2 gm of powder was weighed and transferred to a measuring cylinder. The bulk volume was noted. The bulk density was calculated by using as following formula [23]:

Bulk Density= (Bulk Weight)/(Bulk Volume)

B. Angle of repose (θ): The friction forces in a loose powder can be measured by the angle of repose (θ). The powder mixture was allowed to flow through the funnel fixed to a stand at a definite height (h).The

angle of repose was calculated by measuring the height and radius of the heap of powder formed[23].

$\theta = \tan^{-1} h/r$
Where, r is the radius and h is the height.

C. Carr's index (%):2 gm of powder was weighed and transferred to a measuring cylinder and it was subjected to 100 tapings. The tapped density and poured density were noted. Carr's index was calculated by the following formula[23]:
Carr's Index= (Tapped Desity) - (Bulk Desity) /(Tapped Density)X100

D. Hausner's Ratio:2 gm of powder was weighed and transferred to a 25 ml measuring cylinder and subjected to 100 tapping's. The tapped density and poured density were noted. Hausner's ratio was calculated by the following formula[23]:

Hausner's Ratio=(Tapped Density)/(Bulk Desity)

E. Swelling property and viscosity
Natural Mucoadhesive gum was allowed to hydrate in 25ml of distilled water at 25^0C in a 25 ml graduated cylinder and volume measured at 5 minute intervals until there was no further hydration observed. The swelling property was determined at different time intervals. 1% w/v of gum solution viscosity was determined by using Broke – Field viscometer[24].

Preparation of Metoprolol tartarate buccal tablets
Buccal tablets were prepared by direct compression procedure involving two consecutive steps. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 Mins. Micro crystalline cellulose, Magnesium stearate and talc were added in the blended material and mixed. The blended powder was then lightly compressed on 9 mm flat punched using sixteen station tablet compression machine (Karnavati), the upper punch was then removed and backing material ethyl cellulose was added over it and finally compressed at a constant compression force. All ingredients were dried, passed through 100 mesh sieve and mixed manually in mortar. The tablets were compressed by using sixteen station tablet machine fitted with flat faced punches and ratios of drug and all ingredients were shown in tables1-3 [25].

Table.1.Composition of Metoprolol tartarate buccal tablets formulated with different concentrations of Aegle marmelos gum

Content of tablet	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)
Metoprolol tartarate	50	50	50	50
Aegle Marmelos	25	37.5	50	62.5
Microcrystalline cellulose	121	108.5	96	83.5
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Ethyl Cellulose	50	50	50	50
Total weight (mg)	250	250	250	250

Table.2.Composition of Metoprolol tartarate buccal tablets formulated with different concentrations of cashew nut tree gum

Content of tartarate	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)
Metoprolol succinate	50	50	50	50
Cashew nut tree gum	25	37.5	50	62.5
Microcrystalline cellulose	121	108.5	96	83.5
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Ethyl Cellulose	50	50	50	50
Total weight (mg)	250	250	250	250

Table.3.Composition of Metoprolol tartarate buccal tablets formulated with different concentrations of moringa oleifera gum

Content of tablet	F_9 (mg)	F_{10} (mg)	F_{11} (mg)	F_{12} (mg)
Metoprolol tartarate	50	50	50	50
Moringa oleifera gum	25	37.5	50	62.5
Microcrystalline cellulose	121	108.5	96	83.5
Magnesium stearate	2	2	2	2
Talc	2	2	2	2
Ethyl Cellulose	50	50	50	50
Total weight (mg)	250	250	250	250

Evaluation of tablets

A. Hardness: Hardness of tablet is determined by using the Monsanto hardness tester[26].

B.Weight variation: Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percentage of weight variation was calculated by using the following formula[26].

%Weight variation= (Average weight)-(Individual weight)/(Average weight) X100

C. Friability: The Roche friabilitor apparatus was used to determine the friability of the tablets. About 26 tablets were selected, dedusted and weighed. Then they were placed in a drum and rotated at 25 rpm for 4 minutes. Then tablets were dedusted to remove dust and reweighed. The percentage friability was calculated by the given formula[26].

%Friability=(Initial weight)-(Final weight)/(Initial weight)X100

D. Drug content: Twenty tablets were collected and powdered. The powder equivalent to 50mg of the drug was weighed accurately, dissolved in 100ml of phosphate buffer pH 6.8. The solution was filtered, suitably diluted and an aliquot was analyzed at 224nm by using uv-spectrophotometer[27].

E. *In-vitro* dissolution test: The release of Metoprolol tartarate from the tablet was studied using USP – Type II paddle apparatus. The drug release profile was carried out in 500 ml of 6.8 pH phosphate buffer maintained at 37 ± 0.5^{o}C temperature at 50 rpm. 5 ml of sample was withdrawn at regular time intervals. The samples were analyzed at 224 nm by UV spectrophotometer[28].

F. Surface pH study: The tablet was allowed to swell by keeping in contact with 1 ml of distilled water for 2hrs at room temperature. The pH measured was by bringing the electrode in contact with the surface of the tablet an allowing to equilibrate for 1 min[29].

G. Swelling study: Three buccal tablets were weighed individually (W_1) and placed separately in 2% agar gel plates at 37±1^{o}C. After every 2h time interval until 6h the tablet was removed from the Petri dish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W_2) and the swelling index (SI) were calculated using the formula given in equation[30].

Swelling index = $(W_2-W_1)/W_1$ X 100

Where, W_1 = initial weight of the tablet,W_2 = final weight of the table

H. Ex-vivo mucoadhesive time: The ex-vivo mucoadhesion time was examined after application of the buccal tablet on freshly excised goat buccal mucosa which was obtained from the slaughter house. The fresh goat buccal mucosa was tied on the glass slide and buccal tablet was pasted to the goat buccal mucosa by applying a light force with a fingertip for 30sec. The glass slide was then dipped down in the beaker, which was filled with 200ml of the phosphate buffer pH 6.8 maintained at 37±1^{o}C. After 2min, stirring was applied by a magnetic stirrer slowly to stimulate the buccal cavity environment and tablet adhesion was maintained for 10h. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time[31].

I. *Ex-vivo* Bioadhesive strength: Ex-vivo bioadhesive strength of the buccal tablets was measured by the modified physical balance method. The fresh goat buccal mucosa was obtained from the slaughter house was cut into pieces and washed with the phosphate buffer pH 6.8. The tablet was stick to the lower side of the second glass slide with glue. The both pans were balanced by adding an appropriate weight on the left-hand pan. The glass slide with mucosa was placed with appropriate

support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right hand pan and water equivalent to weight was added slowly to it until the tablet detach from the mucosal surface. The weight equipped to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and the average value was calculated[32].

Force of adhesion (N) = (Mucoadhesive strength) X (9.1)/(1000)

J. Infra-Red Spectral Analysis

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with gum, diluents and lubricants used in tablet formulations. In the present study 1:1 ratio was used for preparation of physical mixtures and analyzed for compatibility studies[33].

H. Differential Scanning Calorimetry Study: DSC Study: Differential Scanning Calorimetry of Metoprolol Tartarate and optimized formulations was recorded between 30.0°C to 300.0°C at the rate of 20.0°C per minute under the environment of nitrogen[34].

Results and Discussion

Preparation of Natural gums

Natural gums of plant origin have been used widely as demulcent because of their unique properties to bind to the mucus membrane. The selection of the materials for the current investigation was based on their edibility, blandness, availability and the economics.

Preparation of water-soluble components from the natural edible sources was carried out by cold/hot aqueous extraction process followed by the organic solvent precipitation. The selection of the process was based on previous literature giving utmost importance to preserve the components against thermal, enzymatic and hydrolytic degradation. The organic solvents used for precipitation can be recovered back by fractional distillation, making the process more economical. The processes used were found to be effective in the selective preparation of the interested constituents and the yielded components possessed good handling properties.

FT-IR spectrum and DSC Study

The FT-IR spectrum did not show the presence of any additional peaks for new functional groups, indicating no chemical interaction between drug and polymers. DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram results are shown in figure numbers 8-9. No interaction was found between drug and polymers. From the DSC results it was observed that the characteristic peak of drug is not observed in the drug and polymer mixer. Hence it indicates the physical nature of the drug is not changed in the formulation. Therefore, results showed that there is no significant change in the chemical integrity of the drug, indicating no interaction between the drug molecule and polymers results were shown in figures 1-7.

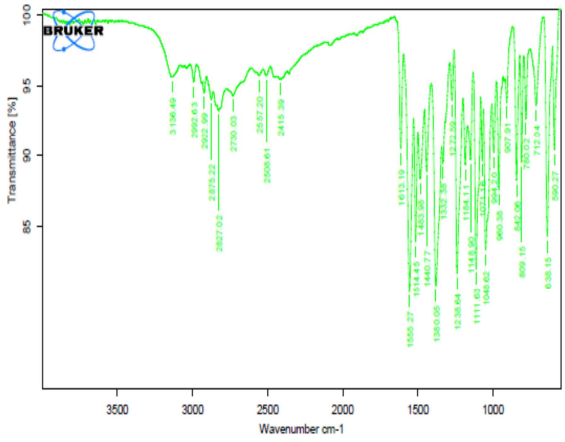


Fig.1. FTIR spectrum of Metoprolol tartarate

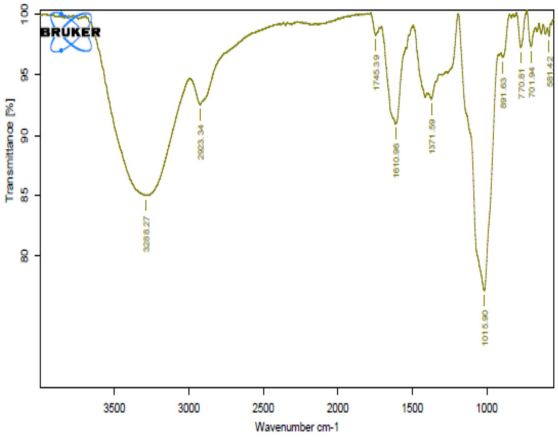


Fig.2.FTIR spectrum of Aegle marmelos gum

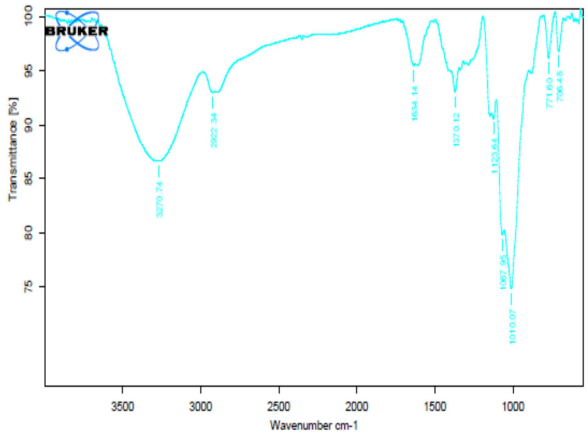


Fig.3. FTIR spectrum of Cashew nut tree gum

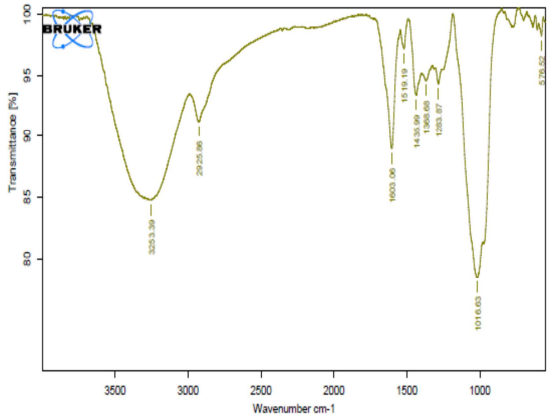
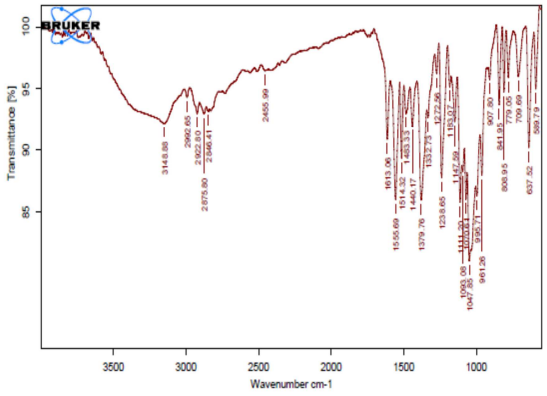


Fig.4.FTIR spectrum of Moringa oleifera gum



Fi.5.FTIR spectrum of Metoprolol tartarate buccal tablets prepared with Aegle marmelos gum

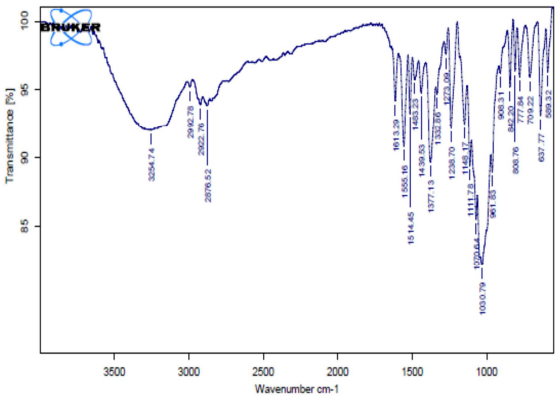


Figure 6 FTIR spectrum of Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum

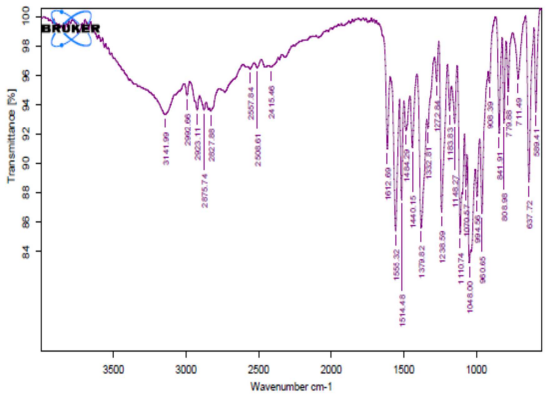


Figure 7 FTIR spectrum of Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum

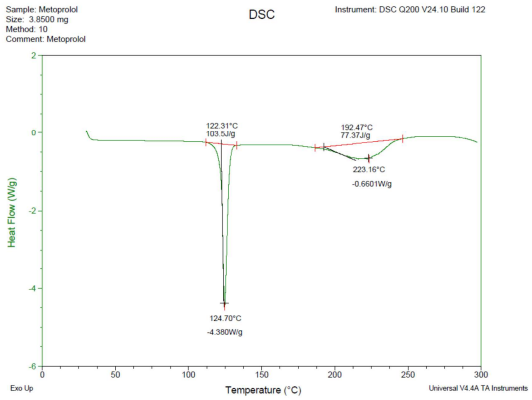


Fig.8DSC thermogram of Metoprolol tartrate

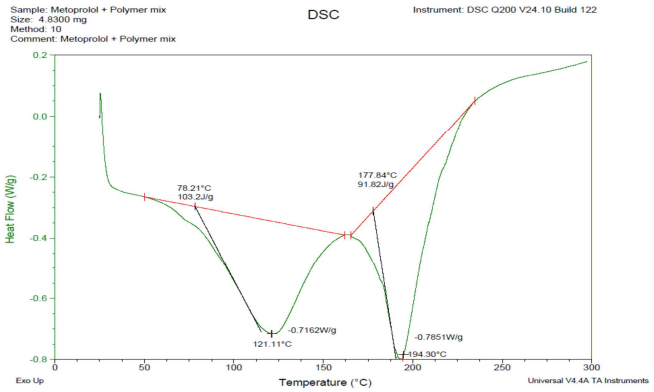


Fig.9 DSC thermogram of Metoprolol tartrate+ Polymer mixer

Evaluation Parameters

Table 4 represents the physical properties of the granules used for the preparation of tablets. The flow properties such as angle of repose, Hausner's ratio, Carr's index, Bulk density and Tapped density are considered as indirect measurements of powder flowability. Hausner's ratio is indicative of inter-particular friction; the Carr's index shows the propensity of a material to diminish in volume. As the values of these indices increase, the flow of the powder decreases. All parameter values are within the satisfactory limit compared with the standard values shown in tables 5-12.

Table. 4.Micromeritic properties of formulations blend of Metoprolol tartarate buccal tablets prepared with different concentrations of Aegle Marmelos gum

Formulation	Evaluation parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (θ)
F_1	0.419 ± 0.018	0.503 ± 0.20	14.16 ± 0.59	1.20 ± 0.012	28.04 ± 0.12
F_2	0.429 ± 0.021	0.507 ±0.025	14.93 ± 0.46	1.18 ± 0.019	28.96 ± 0.17
F_3	0.442 ± 0.023	0.511 ± 0.031	14.24 ± 0.51	1.18 ± 0.013	29.02 ± 0.18
F_4	0.477 ± 0.019	0.571 ± 0.021	14.67 ± 0.44	1.16 ± 0.012	29.31 ± 0.18

Table 5: Swelling property values of Aegle marmelos gum

Natural gum	After 5 min(ml)	After 10min(ml)	After 15 min(ml)	After 20 min(ml)	After 25 min(ml)	After 30 min(ml)	After 35 min(ml)
Aegle marmelos gum	0.8	0.9	1.2	1.4	1.5	1.6	1.6

Table 6: Viscosity of 1% W/V dispersion of Aegle marmelos gum

S.NO	POLYMER	VISCOCITY (cps)
1	1% w/v of aegle marmelos gum	2754.16

Table.7.Micromeritic properties of formulations blend of Metoprolol tartarate buccal tablets prepared with different concentrations of cashew nut tree gum

Formulation	Evaluation parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (θ)
F_5	0.439 ± 0.018	0.512 ± 0.026	14.24 ± 0.71	1.16 ± 0.011	24.02 ± 0.22
F_6	0.445 ± 0.011	0.522 ± 0.019	13.94 ± 0.52	1.17 ± 0.08	25.22 ± 0.16
F_7	0.478 ± 0.017	0.580 ± 0.023	17.58 ± 0.45	1.21 ± 0.010	27.36 ± 0.15
F_8	0.496 ± 0.015	0.594 ± 0.020	16.49 ± 0.56	1.19 ± 0.14	28.85 ± 0.18

Table.8.Swelling property of Cashew nut tree gum

Natural gum	After 5min (ml)	After10min (ml)	After 15min (ml)	After 20 min (ml)	After 25 min (ml)	After 30min (ml)	After 35min (ml)
Cashew nut tree gum	0.7	0.8	1.1	1.3	1.4	1.5	1.5

Table.9.Visocsity of 1% W/V dispersion of Cashew nut tree gum

S.NO	POLYMER	VISCOCITY (cps)
1	1% w/v of cashew nut tree gum	2186.29

Table.10.Micromeritic properties of Metoprolol tartarate buccal tablets formulated with different concentrations of Moringa oleifera gum

Formulation	Evaluation parameters				
	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's Ratio	Angle of Repose (θ)
F_9	0.426 ± 0.016	0.502 ±0.021	15.13 ±0.57	1.17 ±0.010	23.12 ± 0.18
F_{10}	0.452 ±0.019	0.543 ±0.023	16.75 ± 0.53	1.20 ±0.012	27.46 ± 0.15
F_{11}	0.469 ± 0.021	0.571± 0.022	17.86 ±0.46	1.19 ± 0.013	28.12 ± 0.0.12
F_{12}	0.478 ±0.023	0.580±0.018	17.58 ±0.49	1.21 ±0.09	29.30 ± 0.18

Table.11. Swelling property of Moringa oleifera gum

Natural gum	After 5 min(ml)	After 10 min(ml)	After 15 min(ml)	After 20 min(ml)	After 25 min(ml)	After 30 min(ml)	After 35 min(ml)
Moringa oleifera gum	0.6	0.7	0.9	1.0	1.2	1.3	1.3

Table.12. Visocsity of 1% W/V dispersion of Moringa oleifera gum

S.NO	POLYMER	VISCOCITY (cps)
1	1% w/v of Moringa oleifera gum	1546.95

Preparation and Evaluation of Metoprolol tartarate buccal tablets

Mucoadhesive buccal tablets of Metoprolol succinate with Aegle marmelos gum were prepared by using different drug: gum ratios. The results of the physical characterization of tablets are summarized in Table 13. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. The swelling behavior is important for bioadhesion. Water sorption increases with an increase in the concentration of hydrophilic polymers. Swelling index, Mucoadhesive strength and *Ex-vivo* residence time were shown in Table 14.

The *Aegle marmelos* gum swells slowly and dissolves in the presence of water. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH was bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.32 to 6.84 which were nearer to the salivary pH 6.8. Hence it was assumed that these formulations do not cause any irritation to the mucous layer of the oral cavity.

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulation F_1-F_4 shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F_4 shows maximum mucoadhesive strength this is due to the tremendous increase in viscosity.

Table.13. Physical properties of Metoprolol tartarate buccal tablets formulated with different concentrations of Aegle Marmelos gum

Formulation	Parameters			
	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F_1	250 ± 2	4.1 ± 0.01	0.22	99.12
F_2	250 ± 1	4.5 ±0.03	0.34	99.38
F_3	250 ± 2	4.2 ± 0.02	0.42	99.56
F_4	250 ± 3	4.4 ± 0.01	0.38	100.14

Table .14. Mucoadhesion strength, swelling index, retention time, and surface pH of buccal tablets prepared with different concentrations of Aegle marmelos gum

Formulation	Swelling index	Ex-vivo mucoadhesion time	Ex-vivo bioadhesive strength	Surface pH
F_1	8.13 ± 3.68	4 hours 45 minutes	16.09 ± 0.28	6.32 ± 0.07
F_2	8.95 ± 3.07	6 hours 20 minutes	16.78 ± 0.31	6.55 ± 0.05
F_3	10.17± 7.62	8 hours 15 minutes	17.12 ± 1.25	6.84 ± 0.09
F_4	11.75 ± 6.85	10 hours 50 minutes	18.19 ± 1.36	6.73 ± 0.06

The ex-vivo residence time was determined using USP disintegration apparatus. Among the four formulations subjected for this study F_4 showed maximum residence time of 10.5 Hrs. It was found that an increase in concentration of polymer increases the residence time. This was mainly due to the strong mucoadhesion nature which of the polymer used. The results of *in vitro* drug release studies of different formulation were shown in table 15 and Figure 10. Tablet formulations prepared by using drug and gum in ratios of 1:0.5, 1:0.75 1:1, and 1:1.25 shown drug release for a period of 7 hours, 8 hours, 10.5 hours and 12 hours respectively. The initial burst release decrease with increase in concentration of gum. To ascertain the mechanism of drug release, the dissolution data were analyzed by zero order, first order, Higuchi and Peppas equations. The correlation coefficient values (r) and dissolution kinetics values were shown in table 16. Amount of drug release versus time curves exhibited straight line for the formulations and confirmed that the release rate followed zero order release kinetics as shown in figure 11 percentages of drug release versus the square root of time curves shows linearity and proves that all the formulations followed Higuchi mechanism as shown in figure 12.

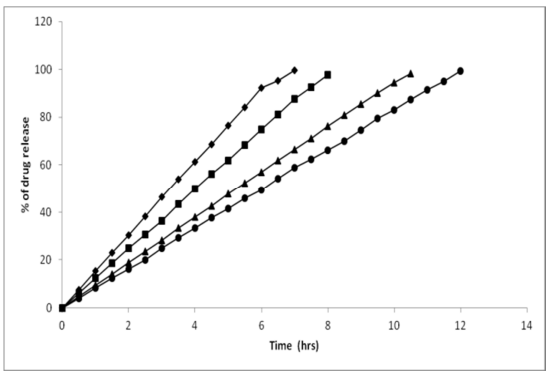


Fig.10.Comparative *in-vitro* drug release profile of Metoprolol Tartarate buccal tablets prepared with different concentrations of Aegle Marmelos gum

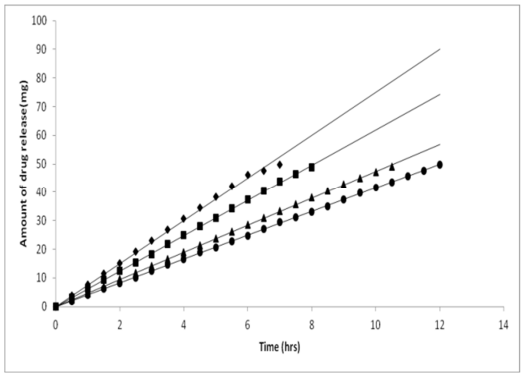


Fig.11.Comparative Zero order plots of Metoprolol tartarate buccal tablets prepared with different concentrations of Aegle Marmelos gum

♦ F_1 - Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:05 ratio
■ F_2 - Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:0.75 ratio
▲ F_3 - Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:1 ratio
● F_4 - Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:1.25

Table 15. *In vitro* release data of Metoprolol tartarate buccal tablets prepared with different concentrations of Aegle Marmelos gum

Time (hrs)	F_1(%Drug Release)	F_2(%Drug Release)	F_3(%Drug Release)	F_4(%Drug Release)
0	0	0	0	0
0.5	7.54 ± 0.05	6.10±0.07	4.75±0.10	4.03±0.09
1	15.48 ±0.07	12.49±0.09	9.32±0.07	8.28±0.06
1.5	23 ± 0.10	18.66±0.17	14.10±0.09	12.43±0.10
2	30.27±0.09	24.91±0.14	19±0.14	16.19±0.13
2.5	38.14±0.06	30.66±0.07	23.46±0.16	20.05±0.15
3	46.31±0.08	36.23±0.09	28.25±0.12	24.91±0.10
3.5	53.87±0.11	43.47±0.05	33.3±0.11	29.27±0.07
4	61.27±0.14	49.85±0.08	37.97±0.15	33.21±0.11
4.5	68.74±0.10	56.07±0.11	42.37±0.13	37.65±0.16
5	76.51±0.13	61.88±0.15	47.65±0.09	41.44±0.12
5.5	84.12±0.16	68.43±0.12	52.24±0.11	45.73±0.14
6	92.26±0.12	74.83±0.05	57.08±0.14	49.36±0.09
6.5	95.43±0.08	81.03±0.07	61.75±0.05	54.17±0.15
7	99.76±0.15	87.76±0.10	66.46±0.10	58.80±0.08
7.5	-	92.71±0.14	71.21±0.16	62.32±0.13
8	-	97.7±0.16	76.22±0.13	66.11±0.11
8.5	-	-	80.84±0.08	70.15±0.07
9	-	-	85.49±0.05	74.68±0.09
9.5	-	-	90.19±0.09	79.49±0.13
10	-	-	94.5±0.12	83.19±0.11
10.5	-	-	98.4±0.14	87.38±0.07
11	-	-	-	91.37±0.06
11.5	-	-	-	95.16±0.09
12	-	-	-	99.45±0.10

Table.16. *In vitro* drug release kinetic data of Metoprolol tartarate buccal tablets prepared with different concentrations of Aegle Marmelos gum

Formulation	Zero order	First order	Higuchi	Peppas	T_{50} (hr)	T_{90} (hr)
F1	0.992	0.954	0.994	0.940	3.0	5.4
F2	0.994	0.967	0.997	0.961	3.9	6.9
F3	0.997	0.974	0.993	0.972	4.9	8.8
F4	0.995	0.989	0.998	0.986	6.2	11.2

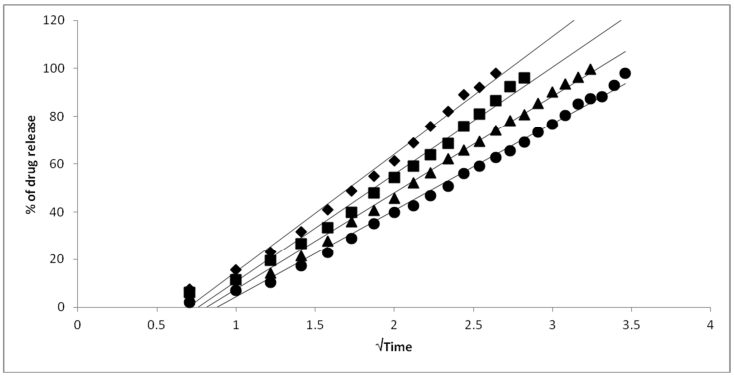


Fig.12.Comparative Higuchi plots of Metoprolol tartarate buccal tablets prepared with different concentrations of Aegle Marmelos gum

♦ F_1 . Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:05 ratio
■ F_2 . Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:0.75 ratio
▲ F_3 . Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:1 ratio
● F_4. Metoprolol tartarate buccal tablets prepared with Aegle Marmelos gum in 1:1.25 ratio

Mucoadhesive buccal tablets of Metoprolol tartarate with cashew nut tree gum were prepared by using different drug: gum ratios. The results of the physical characterization of tablets are summarized in Table 17. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. The swelling behavior is important for bioadhesion. Water sorption increases with an increase in the concentration of hydrophilic polymers. Swelling index, Mucoadhesive strength and *Ex-vivo* residence time were shown in table 18.

The cashew nut tree gum swells slowly and dissolves in the presence of water. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH was bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.27 to 6.79 which were nearer to the salivary pH 6.8 Hence it was assumed that these formulations do not cause any irritation to the mucous layer of the oral cavity.

Table.17.Physical properties of Metoprolol tartarate buccal tablets prepared with different concentrations of cashew nut tree gum

Formulation	Parameters			
	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F_5	250 ± 1	4.3 ± 0.02	0.31	99.56
F_6	250 ± 3	4.0 ± 0.01	0.48	99.34
F_7	250 ± 2	4.2 ± 0.03	0.54	99.47
F_8	250 ± 1	4.1 ± 0.01	0.67	100.02

Table .18.Mucoadhesion strength, swelling index, retention time, and surface pH of buccal tablets prepared with different concentrations of cashew nut tree gum

Formulation	Swelling index	Ex-vivo mucoadhesion time	Ex-vivo bioadhesive strength	Surface pH
F_5	7.62 ± 3.82	3 hours 10 minutes	15.52 ± 0.32	6.27 ± 0.36
F_6	8.56 ± 3.60	4 hours 46 minutes	15.86 ± 0.10	6.39 ± 0.07
F_7	9.61 ± 2.92	6 hours 12 minutes	16.20 ± 0.44	6.48 ± 0.09
F_8	9.95 ± 2.36	9 hours 35 minutes	17.61 ± 1.20	6.79 ± 0.12

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulation F_5-F_8 shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F_8 shows maximum mucoadhesive strength this is due to tremendous increase in viscosity.

The *ex-vivo* residence time was determined using USP disintegration apparatus. Among the four formulations subjected for this study F_8 showed maximum residence time of 9.35 Hrs. It was found that an increase in concentration of the polymer increases the residence time. This was mainly due to the strong mucoadhesion nature of the polymer used. The results of in vitro drug release studies of different formulation were shown in table 19 and Figure 13. Tablet formulations prepared by using drug and gum in ratios of 1:0.5, 1:0.75, 1:1, and 1:1.25 shown drug release for a period of 6.5 hours, 8.5 hours, 9.5 hours and 11 hours respectively. The initial burst release decrease with increase in concentration of gum. To ascertain the mechanism of drug release, the dissolution data were analyzed by zero order, first order, Higuchi and Peppas equations. The correlation coefficient values (r) and dissolution kinetics values were shown in table 20. Amount of drug release versus time curves exhibited straight line for the formulations and confirmed that the release rate followed zero order release kinetics (Fig.14) percentage of drug release versus the square root of time curves shows linearity and proves that all the formulations followed Higuchi mechanism (Fig.15).

Table 19.*In vitro* release data of Metoprolol tartarate buccal tablets Prepared with different concentrations of cashew nut tree gum

Time (hrs)	$F_{5(\%Drug\ Release)}$	$F_{6(\%Drug\ Release)}$	$F_{7(\%Drug\ Release)}$	$F_{8(\%Drug\ Release)}$
0	0	0	0	0
0.5	7.34±0.07	5.67±0.05	5.15±0.09	4.48±0.12
1	15.05±0.10	11.58±0.08	10.41±0.13	8.99±0.15
1.5	23.06±0.15	17.51±0.10	15.68±0.11	13.51±0.11
2	30.24±0.11	22.83±0.13	20.98±0.08	18.06±0.9
2.5	38.32±0.09	28.54±0.10	26.07±0.15	22.45±0.16
3	46.01±0.11	34.99±0.14	31.48±0.13	27.04±0.13
3.5	53.18±0.06	41.05±0.17	36.59±0.16	31.64±0.10
4	61.15±0.14	46.71±0.08	41.98±0.12	36.17±0.07
4.5	69.06±0.10	51.50±0.13	47.19±0.07	40.76±0.14
5	76.36±0.08	57.49±0.15	52.21±0.09	45.04±0.05
5.5	84.18±0.14	64.44±0.07	57.51±0.14	49.59±0.12
6	92.26±0.05	69.14±0.09	62.96±0.11	54.86±0.16
6.5	99.34±0.09	75.08±0.11	68.03±0.15	59.04±0.10
7		81.13±0.14	73.24±0.10	63.14±0.08
7.5		87.51±0.16	78.28±0.08	67.96±0.10
8		93.83±0.07	84.04±0.10	72.48±0.07
8.5		98.18±0.12	89.39±0.05	76.14±0.14
9			94.56±0.09	81.65±0.16
9.5			99.67±0.07	86.74±0.11
10				90.73±0.17
10.5				95.28±0.09
11				99.76±0.05

Table.20. *In vitro* drug release kinetic data of Metoprolol tartarate buccal tablets prepared with different concentrations of cashew nut tree gum

Formulation	Correlation coefficient				T_{50} (hr)	T_{90} (hr)
	Zero order	First order	Higuchi	Peppas		
F_5	0.9969	0.8604	0.9840	0.8408	3.1	5.5
F_6	0.9917	0.8664	0.9865	0.8886	4.3	7.8
F_7	0.9934	0.8673	0.9836	0.9054	4.8	8.6
F_8	0.9962	0.8761	0.9819	0.9139	5.5	9.7

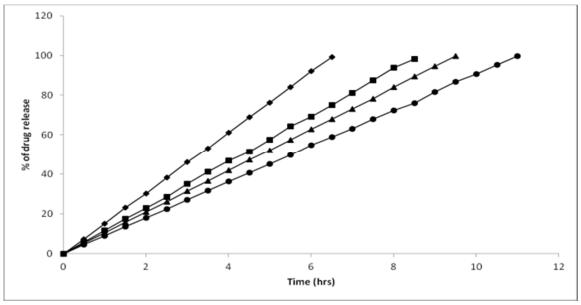


Fig.13. Comparative *in vitro* drug release profile of Metoprolol tartarate buccal tablets prepared with different concentrations of cashew nut tree gum

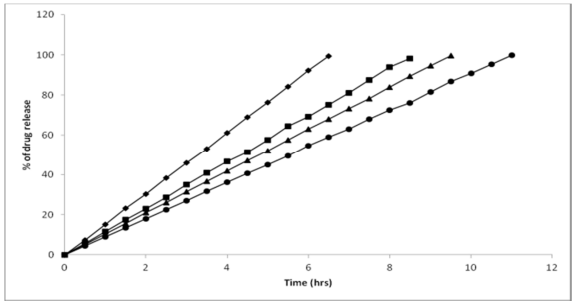


Fig.14. Comparative Zero order plots of Metoprolol tartarate buccal Tablets prepared with different concentrations of cashew nut tree gum

♦ F_5 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:05 ratio
■ F_6 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:0.75 ratio
▲ F_7 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:1 ratio
● F_8 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:1.25 ratio

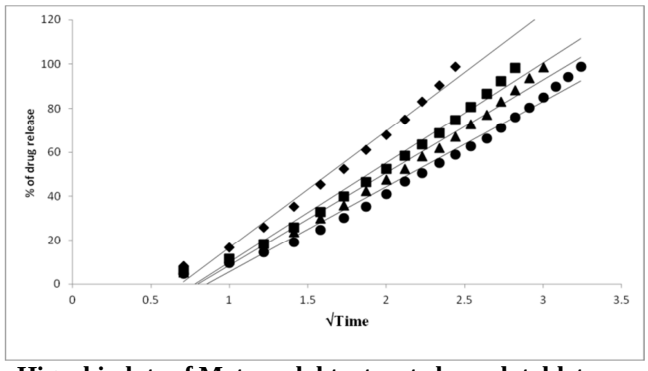


Fig.15. Comparative Higuchi plots of Metoprolol tartarate buccal tablets prepared with different concentrations of cashew nut tree gum

♦ F_5 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:05 ratio
■ F_6 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:0.75 ratio
▲ F_7 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:1 ratio
● F_8 - Metoprolol tartarate buccal tablets prepared with Cashew nut tree gum in 1:1.25 ratio

Mucoadhesive buccal tablets of Metoprolol tartarate with *Moringa oleifera* gum were prepared by using different drug: gum ratios. The results of the physical characterization of tablets are summarized in Table 21. All the formulations hardness, weight variation, friability and drug content values were found to be within pharmacopoeia limits. The swelling behavior is important for bioadhesion. Water sorption increases with an increase in the concentration of hydrophilic polymers. Swelling index, Mucoadhesive strength and Ex-vivo residence time were shown in table 22.

The *Moringa oleifera gum* swells slowly and dissolves in the presence of water. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH was bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 6.12 to 6.62 which were nearer to the salivary pH 6.8 Hence it was assumed that these formulations do not cause any irritation to the mucous layer of the oral cavity.

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulation F_9-F_{12} shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F_{12} shows maximum mucoadhesive strength this is due to tremendous increase in viscosity.

Table.21. Physical properties of Metoprolol tartarate buccal tablets formulated with different concentrations of Moringa oleifera gum

Formulation	Parameters			
	Weight variation (mg)	Hardness (kg/cm^2)	Friability(%)	Drug content (%)
F_9	250 ± 2	4.2 ± 0.03	0.52	99.38
F_{10}	250 ± 1	4.1 ± 0.01	0.69	100.05
F_{11}	250 ± 3	4.4 ± 0.02	0.72	99.45
F_{12}	250 ± 2	4.5 ± 0.01	0.81	99.16

Table.22. Mucoadhesion strength, swelling index, retention time, and surface pH of buccal tablets prepared with different concentrations of Moringa oleifera gum

Formulation	Swelling index	Ex-vivo mucoadhesion time	Ex-vivo bioadhesive strength	Surface pH
F_9	6.86 ± 4.02	3 hours 14 minutes	15.21 ± 0.45	6.12 ± 0.15
F_{10}	7.29 ± 3.90	5 hours 56 minutes	15.75 ± 0.51	6.30 ± 0.10
F_{11}	7.82 ± 3.05	6 hours 45 minutes	16.34 ± 0.36	6.57 ± 0.12
F_{12}	8.30 ± 3.26	8 hours 28 minutes	16.98 ± 0.12	6.62 ± 0.05

The *ex-vivo* residence time was determined using USP disintegration apparatus. Among the four formulations subjected for this study F_{12} showed maximum residence time of 8.28 Hrs. It was found that an increase in concentration of the polymer increases the residence time. This was mainly due to the strong mucoadhesion nature of the polymer used. The results of *in vitro* drug release studies of different formulation were shown in Table 23 and Figure 16. Tablet formulations prepared by using drug and gum in ratios of 1:0.5, 1:0.75 1:1, and 1:1.25 shown drug release for a period of 6 hours, 8 hours, 9 hours and 10.5 hours respectively. The initial burst release decrease with increase in concentration of gum. To ascertain the mechanism of drug release, the dissolution data were analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) and dissolution kinetics values were shown in table 24. Amount of drug release versus time curves exhibited straight line for the formulations and confirmed that the release rate followed zero order release kinetics (fig.17) percentage of drug release versus the square root of time curves shows linearity and proves that all the formulations followed Higuchi mechanism (Fig .18).

Table.23. *In vitro* release data of Metoprolol succinate buccal tablets Prepared with different concentrations of Moringa oleifera gum

Time (hrs)	$F_{9(\%Drug\ Release)}$	$F_{10(\%Drug\ Release)}$	$F_{11(\%Drug\ Release)}$	$F_{12(\%Drug\ Release)}$
0	0	0	0	0
0.5	8.23±0.08	6.13±0.05	5.32±0.09	4.69±0.11
1	16.59±0.12	12.45±0.09	11.03±0.11	9.45±0.15
1.5	24.79±0.06	18.23±0.14	16.31±0.07	14.41±0.17
2	33.26±0.13	24.91±0.06	21.78±0.16	18.92±0.08
2.5	41.37±0.09	30.87±0.13	26.91±0.11	23.65±0.10
3	49.54±0.17	35.89±0.08	32.86±0.08	28.21±0.15
3.5	58.03±0.14	43.42±0.15	37.52±0.05	33.29±0.07
4	64.54±0.11	49.56±0.09	43.63±0.16	37.96±0.012
4.5	74.99±0.06	55.29±0.11	49.54±0.11	42.67±0.05
5	83.03±0.08	62.46±0.16	54.13±0.08	47.42±0.13
5.5	91.37±0.05	67.86±0.07	60.82±0.13	52.16±0.08
6	99.78±0.09	74.67±0.15	66.20±0.07	57.06±0.10
6.5		80.64±0.06	71.86±0.12	61.71±0.15
7		86.57±0.11	77.11±0.15	66.41±0.11
7.5		93.46±0.09	83.09±0.11	71.15±0.17
8		99.33±0.015	88.21±0.09	76.10±0.13
8.5			93.83±0.14	80.52±0.07
9			98.82±0.07	85.15±0.05
9.5				89.28±0.12
10				95.13±0.06
10.5				99.73±0.14

Table.24. *In vitro* drug release kinetic data of Metoprolol tartarate Buccal tablets prepared with Moringa oleifera gum

Formulation	Correlation coefficient				T_{50} (hr)	T_{90} (hr)
	Zero order	First order	Higuchi	Peppas		
F_9	0.9945	0.8603	0.9887	0.8203	3.0	5.4
F_{10}	0.9929	0.8790	0.9818	0.8790	4.0	7.2
F_{11}	0.9919	0.8971	0.9834	0.8986	4.5	8.2
F_{12}	0.9962	0.9107	0.9855	0.9107	5.3	9.2

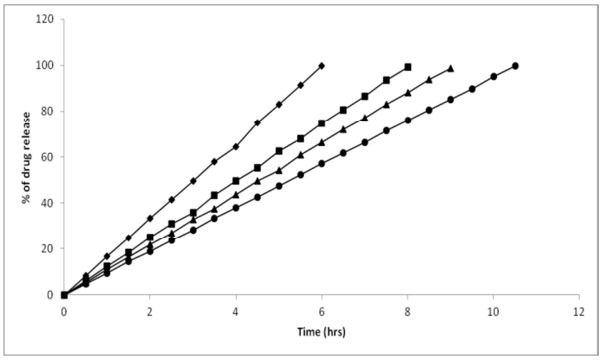


Fig.16. Comparative *in vitro* drug release profile of Metoprolol tartarate buccal tablets prepared with different concentrations of Moringa oleifera gum

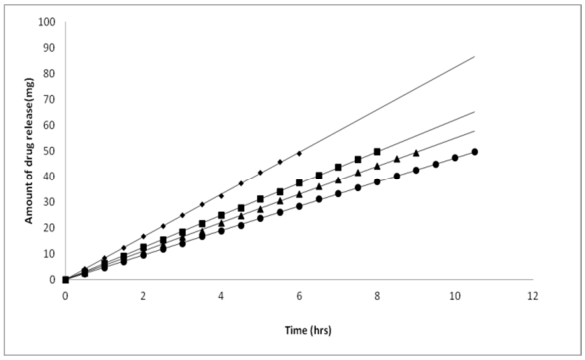


Fig.17. Comparative Zero order plots of Metoprolol tartarate buccal tablets prepared with different concentrations of Moringa oleifera gum

♦ F_9 - Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:05 ratio
■ F_{10} - Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:0.75 ratio
▲ F_{11}- Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:1 ratio
● F_{12}- Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:1.25 ratio

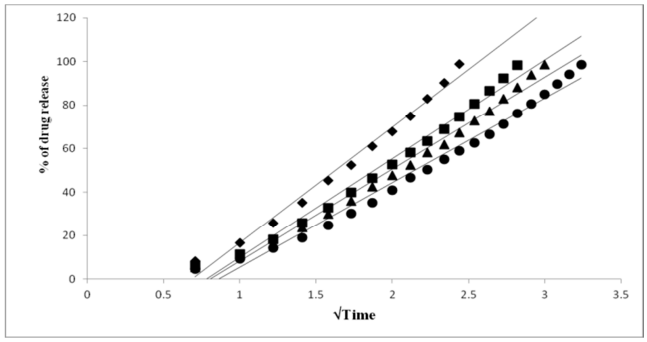


Fig.18.Comparative Higuchi plots of Metoprolol tartarate buccal tablets prepared with different concentrations of Moringa oleifera gum

♦ F_9 - Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:05 ratio
■ F_{10} - Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:0.75 ratio
▲ F_{11}- Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:1 ratio
● F_{12}- Metoprolol tartarate buccal tablets prepared with Moringa oleifera gum in 1:1.25 ratio

Conclusion

1. Metoprolol tartarate buccal tablets prepared with natural polymers such as *Aegle marmelos gum, Cashew nut tree* gum and *Moringa oleifera* gum has shown the prolonged release.
2. Among the three polymers, Aegle marmelos shows more prolonged release compared with other polymers (Aegle marmelos > Cashew nut tree gum > Moringa oleifera gum).
3.Metoprolol tartarate buccal tablets prepared with aegle marmelos gum in 1:3 ratios shows more prolonged drug release compared with the other polymers (1:3 > 1:2 > 1:1).
4.The prepared Metoprolol tartarate buccal tablets compiles with the Indian Pharmacopeia standards.
5. Surface pH of all formulations was found to be in the range of 6.12 - 6.82, which were nearer to the salivary pH 6.8. Hence it was assumed that these formulations do not cause any irritation to the mucous layer of the oral cavity.
6. It was found that an increase in concentration of the polymer increases the *ex vivo* Mucoadhesive residence time.
7. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum.
8. FTIR and DSC studies clearly indicate that there is no drug – polymer interaction.

9. All the formulations drug release followed zero order kinetics and the mechanism of the drug release was governed by Higuchi model.
By consideration of all above parameters, it that *Aegle marmelos* gum 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 dried Aegle marmelos gum can be used as an excipient for preparing Mucoadhesive buccal tablets.

"Cite this Article"

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