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Research Article

DESIGN AND DEVELOPMENT OF BUCCAL MUCOADHESIVE TABLETS OF METOPROLOL TARTARATE BY USING NATURAL POLYMERS

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Abstract:

In the present work, the mucoadhesive tablets of Metoprolol tartarate were formulated by using natural polymers as a binder. Buccal mucosa targeted core-in-cup tablets were prepared in two steps. Core tablets were prepared by wet granulation technique and cup tablets were prepared by direct compression technique. In the present study, natural polymers such as Moringa oleifera gum and Almond gum were selected for the preparation of Metoprolol Tartrate buccal tablets. Tablets were subjected for evaluation of uniformity of weight, hardness, friability, drug content uniformity, swelling behavior, release rate study, mucoadhesive study, and tensile strength study. The release rate followed zero order release kinetics and log percentage of drug release versus log time curves shows linearity and proves that all the formulations followed Peppas mechanism. It was found that an increase in concentration of polymer increases the ex vivo Mucoadhesive residence time. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. The present study revealed that Moringa oleifera 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.

Key words: Metoprolol tartarate, Moringa oleifera gum, Almond gum, mucoadhesion

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INTRODUCTION:

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Other advantages such as low enzymatic activity, painless administration, easy drug withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions. Mucoadhesion is not new; there has been increased interest in recent years in using mucoadhesive polymers for drug delivery. Substantial effort has recently been focused on placing a drug or a formulation in a particular region of the body for extended periods of time¹.

Metoprolol Tartrate is a cardio selective β_1 blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmias and myocardial infarction. Metoprolol Tartrate is rapidly absorbed following an oral dose, undergoes extensive first pass metabolism, resulting in oral bioavailability of 50% only. The half life of Metoprolol Tartrate is approximately 3-4 hrs, major side effects are bronchoconstriction, fatigue and depression. Following oral administration, Metoprolol Tartrate is well absorbed and undergoes extensive first-pass metabolism. The systemic bioavailability of Metoprolol Tartrate is 50%. To reduce the frequency of administration and to improve patient compliance, a sustained release formulation of Metoprolol Tartrate is required². Buccal route offers several advantages such as rapid absorption and blood levels due to high vascularisation of the region. Ease of administration, rapid termination of therapy and administration of the drug to the buccal cavity for a prolonged period of time. It is beneficial in case of Metoprolol Tartrate to overcome the problem of frequent dosing due to its shorter half-life. Prolonged release of the drug and increased bioavailability leads to significant reduction in the dose and hence dose related side effects. Hence in the work to be undertaken, an attempt was made to formulate Mucoadhesive buccal tablets for Metoprolol Tartrate by employing natural polymers, in order to avoid extensive first pass metabolism and for prolonged effect³. In the present study, natural polymers such as Moringa oleifera gum and Almond gum were selected for the preparation of Metoprolol Tartrate buccal tablets.

Materials: Metoprolol tartarate (It is obtained as gratis sample from Hetero pharmaceuticals). Biodegradable-natural Gums were procured from Nutriroma Company at Hyderabad. Microcrystalline cellulose, Magnesium stearate, Talc (Analytical grades).

Method:

Preparation of Metoprolol tartarate core tablet: Buccal tablets were prepared by direct compression procedure involving two consecutive steps⁴. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 minutes. Microcrystalline 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 (Cadmach), 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.

Preparation of cup tablet: The cup formulations were formulated by direct compression technique. Ethyl cellulose, microcrystalline cellulose, talc and magnesium stearate were weighed and mixed uniformly according to the formula shown in Table-2. The powder mixture was compressed by 16 station rotary tablet compression machine by using special punch designed and fabricated, to prepare cup tablets. The newly designed upper 12 mm punch has protrusion and lower punch (12mm) remains flat faced⁵.

Evaluation of granules:

Flow properties of the prepared granules were evaluated using standard reported methods⁶.

Hardness: Hardness of tablet is determined by using the Monsanto hardness tester⁶. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. As the spring was compressed a pointer rides a long a gauge in the barrel to indicate the force. The hardness was measured in terms of Kg/cm².

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 percent

weight variation was calculated by using the following formula⁷.

$$\% \text{ Weight variation} = \frac{\text{Average weight} - \text{individual weight}}{\text{Average weight}} \times 100$$

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 formula⁸.

$$\% \text{ FRIABILITY} = \frac{\text{INITIALWEIGHT} - \text{FINALWEIGHT}}{\text{INITIALWEIGHT}} \times 100$$

Drug content: Twenty tablets were collected and powdered. The powder equivalent to 50mg of 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 271nm by using uv-spectrophotometer⁹.

In vitro drug release study

The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablets. The dissolution medium was 500ml, of phosphate buffer pH 6.8. of 50 rpm. The buccal tablets were allocated to the bottom of the dissolution vessel. 5ml sample were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were analysed after appropriate dilution by UV spectrophotometer at 224nm⁷.

Swelling studies

Three buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates and incubated at 37±1⁰c. After every 2h time interval until 6h the tablet was removed from the petridish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W2) and the swelling index were calculated by using the formula given in equation⁸

$$\text{Swelling index} = (W2-W1)/W1 \times 100.$$

Where,

W1 = initial weight of the tablet

W2 = final weight of the tablet

Surface pH study

The tablet was allowed to swell by keeping in contact with 1 ml, of distilled water for 2h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min⁹.

Ex-vivo Mucoadhesion time

The Ex-vivo mucoadhesion time was examined after application of the buccal tablet on freshly excised goat buccal mucosa which was obtained from 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 finger tips for 30 secs. 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±1⁰c. After 2min, stirring was applied by magnetic stirrer slowly to simulate the buccal cavity environment and the tablet adhesion was monitored for 10h. The time for the tablet to detach from the goat buccal mucosa was noted as the buccal mucoadhesion time¹⁰.

Ex-vivo Bioadhesive Strength

Ex-Vivo Bioadhesive strength of the buccal tablet was measured on the modified physical balance method. The fresh goat buccal mucosa obtained from slaughter house was cut in to pieces and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH6.8. The tablet was stuck to the lower side of second glass slide with glue. The both pans were balanced by adding an 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 required to detach the tablet from the mucosal surface it give the mucoadhesive strength¹¹.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength} \times 9.81}{1000}$$

RESULTS AND DISCUSSION:

Mucoadhesive buccal tablets of Metoprolol Tartrate with natural polymers were prepared by using different drug: gum ratios. The results of the physical characterization of tablets are summarized in Table 5. 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 increase in the concentration of hydrophilic polymers. Swelling index, Mucoadhesive strength and Ex-vivo residence time were shown in table 6.

The gums swells slowly and dissolves in 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 6.40 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 oral cavity.

Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulations shown 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. F₃ shown 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 F₃ showed maximum residence time of 11.28 Hrs. It was found that an increase in concentration of 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 5. Tablet formulations prepared by using drug and gum in ratios of 1:0.5, 1:0.75 and 1:1 shown drug release for a period of 10.5 hours, 11 hours and 12 hours respectively. The drug release decrease with increase in concentration of gum. To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) and dissolution kinetics values were shown in table 6. Amount of drug release versus time curves exhibited straight line for the formulations and confirmed that the release rate followed zero order release kinetics and mechanism of drug release followed Peppas mechanism.

The exponential coefficient(n) values were found to be in between 0.6752 to 0.8756 indicating non fickian diffusion mechanism. These results indicated that the release rate was found to be decrease with increase in concentration of polymer. The present study revealed that Moringa oleifera 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.

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Table 1: Metoprolol Tartrate Core formulations:

| Content of tablet | F ₁ (mg) | F ₂ (mg) | F ₃ (mg) | F ₄ (mg) | F ₅ (mg) | F ₆ (mg) |
|----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Metoprolol Tartrate | 50 | 50 | 50 | 50 | 50 | 50 |
| Moringa oleifera gum | 25 | 37.5 | 50 | 25 | 37.5 | 50 |
| Microcrystalline cellulose | 121 | 108.5 | 96 | 121 | 108.5 | 96 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 |
| Total weight (mg) | 200 | 200 | 200 | 200 | 200 | 200 |

Table 2: Cup formulations

| Ingredients | C ₁ | C ₂ | C ₃ | C ₄ | C ₅ | C ₆ |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Ethyl cellulose | 442 | 442 | 442 | 442 | 442 | 442 |
| Mg. stearate | 4 | 4 | 4 | 4 | 4 | 4 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 |
| Total | 450 | 450 | 450 | 450 | 450 | 450 |

Table 3: Metoprolol Tartrate Core in cup formulations

| S.No | Core in cup formulations | Combination of core and cup formulations |
|------|--------------------------|----------------------------------------------|
| 1 | MCC ₁ | F ₁ (core) + C ₁ (cup) |
| 2 | MCC ₂ | F ₁ (core) + C ₂ (cup) |
| 3 | MCC ₃ | F ₁ (core) + C ₃ (cup) |
| 4 | MCC ₄ | F ₁ (core) + C ₄ (cup) |
| 5 | MCC ₅ | F ₁ (core) + C ₅ (cup) |
| 6 | MCC ₆ | F ₁ (core) + C ₆ (cup) |

Table 4: Micromeritic properties of formulation blend of Metoprolol Tartratecore tablets

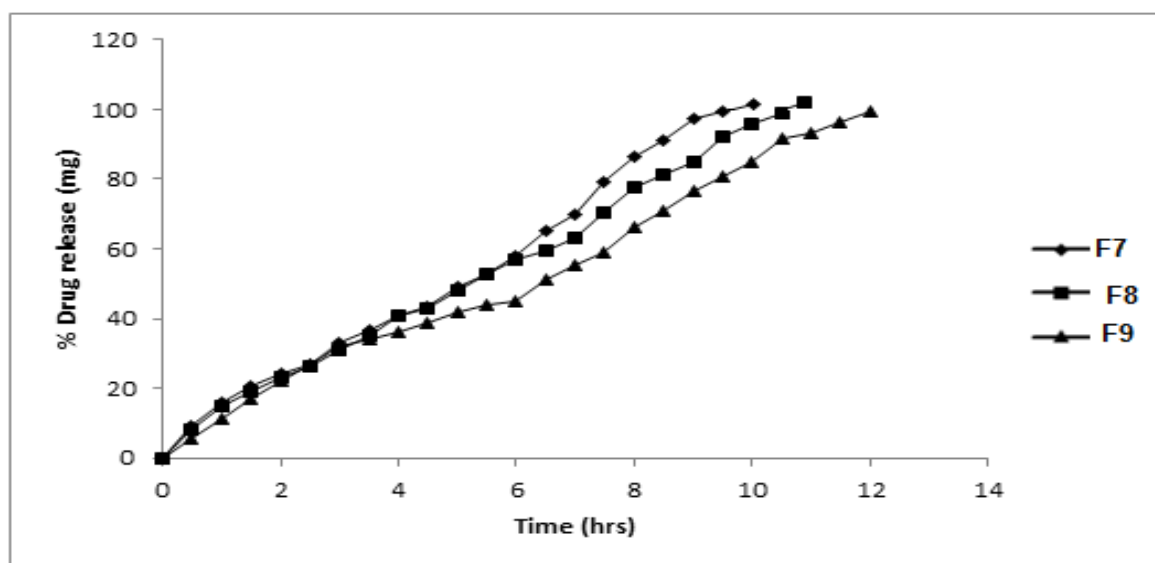
| Formulation | Evaluation parameters | | | | |
|----------------|-----------------------|-----------------------|---------------------------|-----------------|---------------------|
| | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hausner's Ratio | Angle of Repose (θ) |
| F ₁ | 0.426 ± 0.016 | 0.502 ± 0.021 | 15.13 ± 0.57 | 1.17 ± 0.010 | 23.12 ± 0.18 |
| F ₂ | 0.452 ± 0.019 | 0.543 ± 0.023 | 16.75 ± 0.53 | 1.20 ± 0.012 | 27.46 ± 0.15 |
| F ₃ | 0.469 ± 0.021 | 0.571 ± 0.022 | 17.86 ± 0.46 | 1.19 ± 0.013 | 28.12 ± 0.12 |
| F ₄ | 0.271 ± 0.024 | 0.316 ± 0.011 | 14.240 ± 0.019 | 1.166 ± 0.019 | 24.05 ± 0.16 |
| F ₅ | 0.314 ± 0.015 | 0.366 ± 0.019 | 14.207 ± 0.027 | 1.165 ± 0.011 | 25.32 ± 0.12 |
| F ₆ | 0.255 ± 0.025 | 0.291 ± 0.005 | 12.37 ± 0.024 | 1.142 ± 0.014 | 27.34 ± 0.13 |

Table 5: Physical properties of Metoprolol Tartrate buccal tablets formulated with different concentrations of natural gums

| Formulation | Parameters | | | |
|----------------|-----------------------|--------------------------------|----------------|------------------|
| | Weight variation (mg) | Hardness (kg/cm ²) | Friability (%) | Drug content (%) |
| F ₁ | 200 ± 2 | 4.2 ± 0.03 | 0.52 | 99.38 |
| F ₂ | 200 ± 1 | 4.1 ± 0.01 | 0.69 | 100.05 |
| F ₃ | 200 ± 3 | 4.4 ± 0.02 | 0.72 | 99.45 |
| F ₄ | 200 ± 1 | 4.0 ± 0.03 | 0.56 | 99.46 |
| F ₅ | 200 ± 3 | 4.2 ± 0.01 | 0.43 | 99.31 |
| F ₆ | 200 ± 2 | 4.2 ± 0.04 | 0.32 | 99.41 |

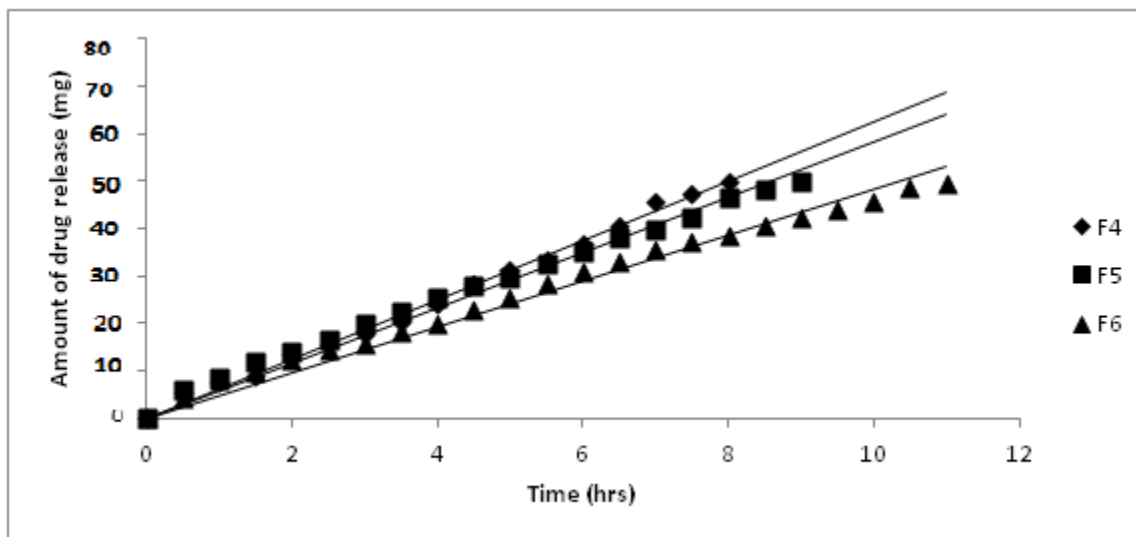
Table 6. Mucoadhesion strength, swelling index, retention time, and surface pH of buccal tablets prepared with different concentrations of natural gums

| Formulation | Swelling index | Ex-vivo Mucoadhesion time | Ex-vivo Bioadhesive strength | Surface pH |
|----------------|----------------|---------------------------|------------------------------|-------------|
| F ₁ | 3.29 ± 3.90 | 6 hours 56 minutes | 15.75 ± 0.51 | 6.30 ± 0.10 |
| F ₂ | 4.82 ± 3.05 | 8 hours 45 minutes | 16.34 ± 0.36 | 6.57 ± 0.12 |
| F ₃ | 5.30 ± 3.26 | 11 hours 28 minutes | 16.98 ± 0.12 | 6.62 ± 0.05 |
| F ₄ | 5.64 ± 3.32 | 4 hours 09 minutes | 15.54 ± 0.31 | 6.26 ± 0.33 |
| F ₅ | 6.52 ± 3.43 | 6 hours 41 minutes | 15.66 ± 0.13 | 6.35 ± 0.08 |
| F ₆ | 7.62 ± 2.12 | 9 hours 14 minutes | 16.22 ± 0.41 | 6.45 ± 0.08 |

Figure 1: Comparative *in vitro* drug release profile of Metoprolol Tartrate buccal tablets prepared with different concentrations of Moringa oleifera gum

- ◆ F₁ . Metoprolol Tartrate buccal tablets prepared with Moringa oleifera gum in 1:0.05 ratio
- F₂ . Metoprolol Tartrate buccal tablets prepared with Moringa oleifera gum in 1:0.75 ratio
- ▲ F₃ . Metoprolol Tartrate buccal tablets prepared with Moringa oleifera gum in 1:1 ratio

Figure 2: Comparative Zero order plots of Metoprolol Tartrate buccal tablets prepared with different concentrations of Almond gum



- ◆ F₄ . Metoprolol Tartrate buccal tablets prepared with Almond gum in 1:05 ratio
- F₅ . Metoprolol Tartrate buccal tablets prepared with Almond gum in 1:0.75 ratio
- ▲ F₆ . Metoprolol Tartrate buccal tablets prepared with Almond gum in 1:1 ratio

FTIR study of formulation

FTIR of *Aegle marmelos* gum

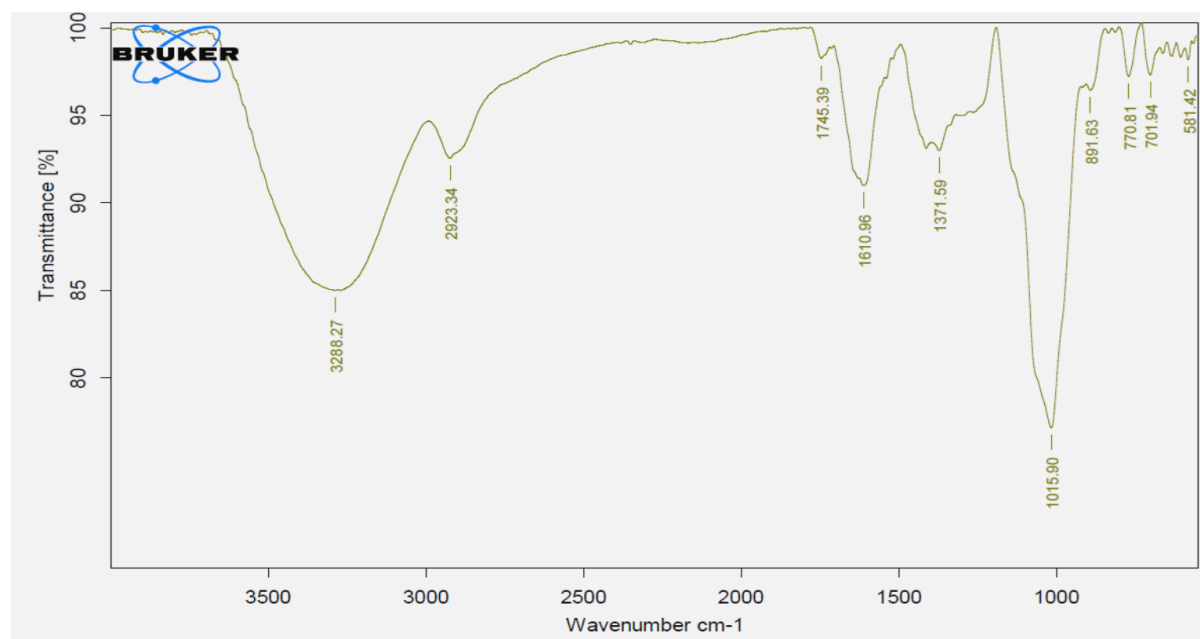


Table 1: Flow properties of dried *Aegle marmelos* gum

| Parameter | Value |
|-----------------------------------|------------|
| Bulk density (g/cm ³) | 0.45 ± 0.2 |

| | |
|-------------------------------------|-------------|
| Tapped density (g/cm ³) | 0.50 ± 0.2 |
| Carr's index (%) | 25.18 ± 0.2 |
| Angle of repose(°) | 29 ± 0.2 |

Table 2: Swelling property 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) |
|--------------------|------------------|-----------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Agele marmelos gum | 0.8 | 0.9 | 1.2 | 1.4 | 1.5 | 1.6 | 1.6 |

Table 3: Composition of tablets containing *Aegle marmelos* gum

| Content of tablet | 1:0.5 (F1) | 1:0.75 (F2) | 1:1 (F3) | 1:1.25 (F4) |
|----------------------------|------------|-------------|----------|-------------|
| Metoprolol succinate | 50 | 50 | 50 | 50 |
| Agele 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 4: Evaluation of tablets prepared from *Aegle marmelos* gum

| Formulation | Hardness(kg/cm ²) | Friability (%) | Drug content (%) | Weight variation |
|-------------|-------------------------------|----------------|------------------|------------------|
| F1 | 3.5 ± 0.2 | 0.41 | 96.62 | 248 ± 0.21 |
| F2 | 3.7 ± 0.3 | 0.48 | 97.75 | 249 ± 0.17 |
| F3 | 3.8 ± 0.5 | 0.56 | 98.37 | 250 ± 0.14 |
| F4 | 4.0 ± 0.3 | 0.73 | 99.75 | 251 ± 0.28 |

Table5: Drug release kinetic studies of tablet formulation

| Formulation | Zero order | First order | Higuchi | Peppas | T50 (hr) | T90 (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 |