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# DESIGN AND DEVELOPMENT OF BUCCAL MUCOADHESIVE TABLETS OF *LOSARTAN POTASSIUM* BY AGELE MARMELOS GUM

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**Abstract:**

*In the present work, the mucoadhesive tablet of Losartan Potassium(as a model drug) by using Aegle marmelos fruit gum as a binder was formulated. The preliminary evaluation of Aegle marmelos gum showed that bulk density 0.45 ± 0.2 g/cm3, tapped density 0.50 ± 0.3 g/cm3 and angle of repose $30^0$ ± 0.2. The four tablet formulation were prepared by using of Aegle marmelos gum and drug ratios 1:0.5, 1:0.75 1:1, 1:1.25 by direct compression technique (F1,F2,F3, andF4 respectively). 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. Formulation was studied for drug additive interaction (FTIR). F4 was found to be optimized formulation. The in-vitro drug release of F4 formulation exhibits complete release of Losartan Potassiumwith zero order release kinetics and followed by Higuchi mechanism. From the study it can be conclude that the Aegle marmelos gum used as mucoadhesive sustained release matrix tablet.*

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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 pHmodifier 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 time [1].

Gum is obtained from fruits of *Aegle marmelos* belonging to family Rutaceae is indigenous to India. The ripen fruit pulp is red in colour with mucilaginous and astringent taste [2]. The pulp contains carbohydrates, proteins, vitamin C, vitamin A. In the present investigation mucoadhesive property *of A. marmelos* gum has been evaluated using Losartan Potassium(as model drug) used in the treatment of anti-hypertension and cardiovascular diseases and it is known to have low oral bioavailability (50%) due to an extensive high first-pass effect. Hence, it is suitable for buccal drug delivery. The aim of the present study was to design and develop mucoadhesive buccal tablets of Losartan Potassiumthat could be applied to the buccal mucosa to release the drug unidirectionally in buccal cavity in order to decrease gastric irritation and avoid first pass effect for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance.

**Materials:** Losartan Potassium (It is obtained as gratis sample from Hetero pharmaceuticals). Microcrystalline cellulose Magnesium sterate, Talc (Analytical grades)

**Method:**

**Purification and standardization of Gum:**

200g edible fruits of *A. 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. 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 $50^0$C under vacuum. The dried gum was powdered and stored in tightly closed container for further usages. The Gum was standardized for following properties [3].

**Loss on drying**:

The 5 gm gum was dried at 105 ± 5 ºC till the constant weight of gum was obtained [4]. The loss on drying was found to be less than 8 % w/w.

**Swelling property of mucoadhesive materials**

Natural mucoadhesive material obtained from the fruits of *A. marmelos* is nontoxic. 250 mg of *A. marmelos* gum was allowed to hydrate in 25ml of distilled water at $25^0$C in a 25 ml graduated cylinder and volume measured at 5 min. intervals until there was no further hydration observed. The swelling property was determined at different time intervals [5].

**Drug-excipient interaction studies**

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 A.marmelos 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 [6].

**Preparation and evaluation of Tablet:**

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. Magnesium stearate was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 9mmflat 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. The tablets composition was shown in the table 3.All ingredients were dried, passed through 100 mesh sieve and mixed manually in mortar. The tablet formulation was developed for 250 mg tablet weight using 50 mg of Losartan Potassium(drug) and varying concentration of *A.marmelos* gum. The tablets were compressed by using sixteen station tablet machine fitted with flat faced punches. The batch size prepared was 50 tablets. The prepared tablets were stored in closed container for 30 days. No evidence of chemical change was observed.

**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 224nm [7].

**Swelling studies**

Three buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates and incubated at 37±1$^0$c. 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 equation[8]

Swelling index = (W2-W1)/W1 X 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 min[9].

**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±1$^0$c. 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 time [10].

**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 strength[11].

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

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**Figure 1: FTIR spectra of A*gele marmelos gum***

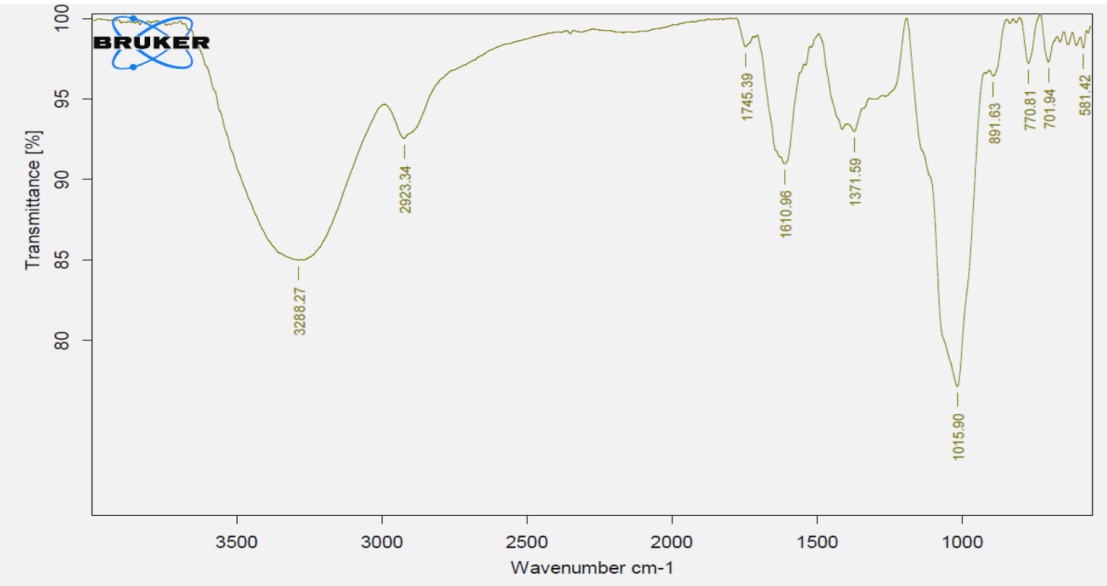



**Table 1: Flow properties of dried *Aegle marmelos* gum**

| Parameter | Value |
|---|---|
| Bulk density (g/cm3) | 0.45 ± 0.2 |
| Tapped density (g/cm3) | 0.50 ± 0.2 |
| Carr's index (%) | 25.18 ± 0.2 |
| Angle of repose(0) | 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) |
|---|---|---|---|---|
| Losartan Potassium | 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 |

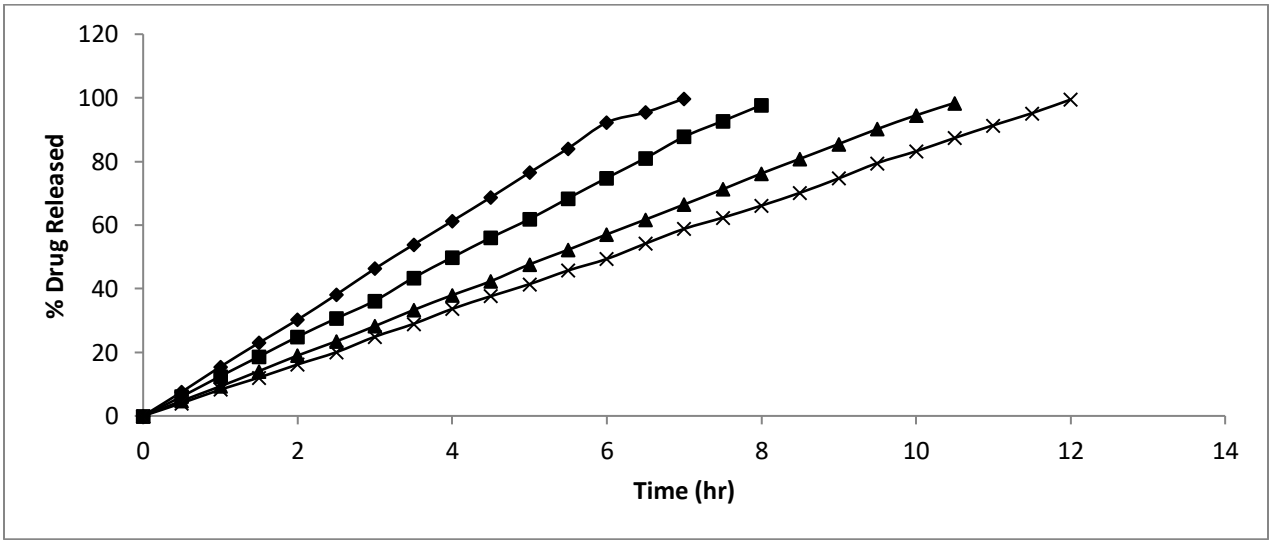
**Table 4: Evaluation of tablets prepared from *Aegle marmelos* gum**

| Formulation | Hardness(kg/cm$^2$) | Friability (%) | Drug content (%) | Weight variation |
|---|---|---|---|---|
| F1 | 3.5 ± 0.3 | 0.42 | 96.63 | 248 ± 0.21 |
| F2 | 3.7 ± 0.5 | 0.47 | 97.76 | 249 ± 0.17 |
| F3 | 3.8 ± 0.4 | 0.55 | 98.38 | 250 ± 0.14 |
| F4 | 4.0 ± 0.3 | 0.71 | 99.78 | 251 ± 0.28 |

**Table 5: Drug release kinetic studies of tablet formulation**

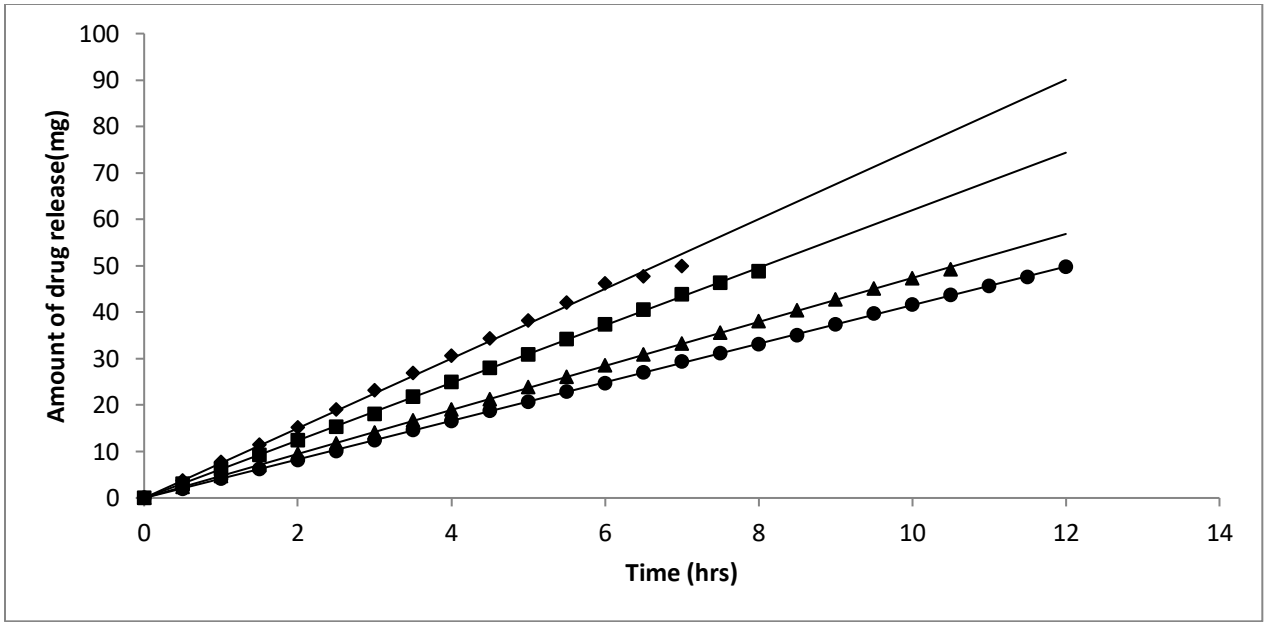
| Formulation | Zero order | First order | Higuchi | Peppas | T50 (hr) | T90 (hr) |
|---|---|---|---|---|---|---|
| F1 | 0.992 | 0.954 | 0.994 | 0.940 | 3.0 | 5.4 |
| F2 | 0.994 | 0.967 | 0.997 | 0.961 | 3.9 | 6.9 |
| F3 | 0.997 | 0.974 | 0.993 | 0.972 | 4.9 | 8.8 |
| F4 | 0.995 | 0.989 | 0.998 | 0.986 | 6.2 | 11.2 |

**Figure 2: Comparative *in-vitro* drug release profile of Losartan Potassium buccal tablets prepared with different concentrations of Aegle marmelos gum**



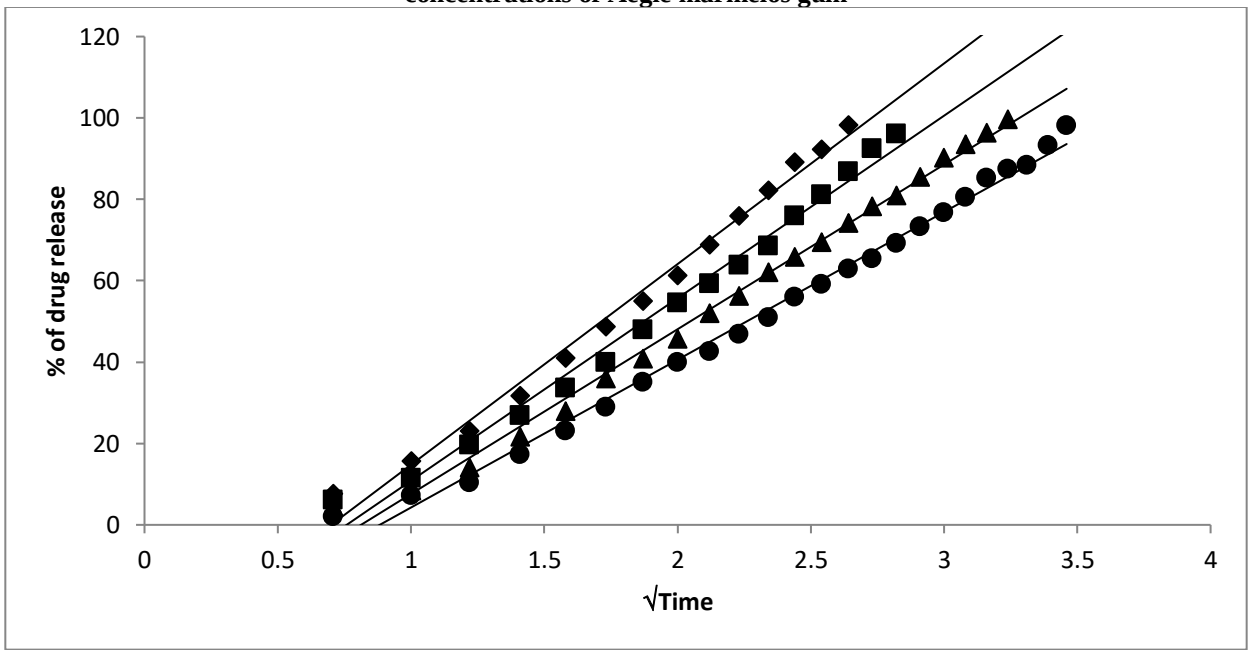

♦ $F_1$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:05 ratio
■ $F_2$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:0.75 ratio
▲ $F_3$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:1 ratio
● $F_4$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:1.25

**Figure 3: Comparative Zero order plots of Losartan Potassium buccal tablets prepared with different concentrations of** Aegle marmelos **gum**




♦ $F_1$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:05 ratio
■ $F_2$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:0.75 ratio
▲ $F_3$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:1 ratio
● $F_4$ - Losartan Potassium buccal tablets prepared with Aegle marmelos gum in 1:1.25

**Figure 4: Comparative Higuchi plots of Losartan Potassium buccal tablets prepared with different concentrations of Aegle marmelos gum**

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