

FORMULATION OF MUCOADHESIVE TABLET BY USING *AEGLE MARMELLOS* GUM

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ABSTRACT: In the present work, the mucoadhesive tablet of diclofenac (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 $0.42 \pm 0.2 \text{ g/cm}^3$, tapped density $0.45 \pm 0.3 \text{ g/cm}^3$ and angle of repose $29^\circ \pm 0.15$. The six tablet formulation were prepared by using 0.25%, 0.50%, 0.75%, 1%, 1.25% and 1.50% w/w of *Aegle marmelos* gum by direct compression (F₁, F₂, F₃, F₄ and F₅ 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 is found to be optimized formulation. The *in-vitro* drug release of F₄ formulation exhibits complete release of Diclofenac Sodium with non fiction first order release kinetic. The formulation F₄ exhibited tensile strength 0.27 N with 10 hrs of mucoadhesion. From the study it can be conclude that the *Aegle marmelos* gum used as mucoadhesive sustained release matrix tablet.

Key words: *Aegle marmelos* gum, Mucoadhesive tablets

INTRODUCTION:^[2,10,11,12,17]

In recent years, researchers have become increasingly interested in the utilization of natural biopolymers due to their wide ranging advantages over synthetic polymers. Polysaccharide gums are the materials of choice because they are naturally abundant, biocompatible, biodegradable, and nonimmunogenic.

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. The pulp contains carbohydrates, proteins, vitamin C, vitamin A, angelenine, marmeline, dictamine, O-methyl fordinol and isopentyl halfordinol. The neutral oligosaccharides were characterized as 3-0-beta-D-galactopyranosyl-L-arabinose, 5-0-beta-D-galactopyranosyl-L-arabinose, and 3-0-beta-D-galactopyranosyl-D-galactose, and the acidic oligosaccharides.

In the present investigation mucoadhesive property of *A. marmelos* gum has been evaluated using diclofenac (as a model drug).

Mucoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. While the subject of 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. This is needed not only for targeting of drugs but also to better control of systemic drug delivery. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the blood stream and not be inactivated by enzymatic degradation in the gastrointestinal tract. Several polymeric bioadhesive drug delivery systems have been fabricated and studied in the past.

Tablets prepared in this study shows simple drug release behavior, on the surface, but the drug release pattern is a complex phenomenon, at the molecular level, it involves water penetration, polymer swelling, as well as drug dissolution, diffusion, swelling, and polymer erosion process. As shown by Matrix tablets, which can be used to control the release of both water soluble and water insoluble drugs.

Materials:

Diclofenac sodium was gifted by PANACEA Biotech, Punjab
 Microcrystalline Cellulose (FMC Biopolymer),
 Sodium Carboxyl Methyl Cellulose, Magnesium stearate (Samar Chemicals).
 All other reagents and chemicals used were of analytical reagent grade.

Method:**Purification and standardization of Gum:**^[3,4,10,11,17]

250g 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 at 60°C 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 °C under vacuum. The dried gum was powdered and stored in tightly closed container for further usages. The Gum was standardized for following properties.

Loss on drying:

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

Ash value:

1gm of gum was accurately weighed and evenly distributed it in the crucible. It was dried at 105 °C for one hour and ignited in muffle furnace at 60⁰ ± 25 °C. Percentage of ash content was found to be less than 7 % w/w.

The binder gum is natural and have P^H between 6.0 - 6.5. This gum was also tested for flow properties as per I.P. and shown in table 1.

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

Parameter	Value
Bulk density (g/cm ³)	0.42 ± 0.2
Tapped density (g/cm ³)	0.45 ± 0.3
Carr's index (%)	26.58 ± 0.2
Angle of repose(⁰)	29 ± 0.2
No. of experiments (n) = 3	

Swelling property of mucoadhesive materials^[6,7, 14,18]

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°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 (Table 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)
<i>A.Marmelos</i>	0.8	0.9	1.1	1.2	1.3	1.4	1.4

Shear stress method^[16,19,20]

Two smooth, polished plexi glass blocks were selected; one block was fixed with adhesive 'Araldide' on a glass plate, which fixed on leveled table. To the upper block a thread was tied and the thread was passed down through a pulley. At the end of the thread a beaker was fixed. The length of the thread from pulley to beaker was 7 cm.

The weight of the beaker was counteracted. 0.75% w/v solution of *A. marmelos* gum was prepared using purified water I.P. as solvent. A fixed volume (0.5 ml) of 0.75% w/v solution of *A. marmelos* gum were kept on the centre of the fixed block with a pipette, and then second block was placed on the first block and pressed by applying 100 g of weight, so that the drop of synthetic polymer and natural bioadhesive material solutions spreads as a uniform film in between the two blocks. After keeping it for a fixed time intervals of 5, 10, 15, and 20 min., purified water was added into the beaker gradually, the weight of purified water just sufficient to pull the upper block or to make it slide down from the base block was recorded. This weight was considered as the adhesion strength, i.e. shear stress required to measure the adhesion. Before every experiment, care was taken so that no air bubble form in between the two Blocks, which may give erratic results, and the distance from pulley to glass block shear stress was studied.

Drug-exipient interaction studies^[2,3,5]

Drug exipient interaction studies are very important for the successful formulation of any dosage form. 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. FT-IR studies were carried out with a Shimadzu FTIR 8400S facility using KBr pellet.

Preparation and evaluation of Tablet:^[1,6,15,17,18]

The formulation was developed with diclofenac IP as model drug by direct compression method. *A. marmelos* gum was used as a in the concentration 0.25, 0.50, 0.75, 1.00 and 1.25 w/w. Binder level was adjusted by lowering the level of MCC in the formula. All ingredients were dried, passed through 120 mesh sieve and mixed manually in mortar. The tablet formulation was developed for 250 mg tablet weight using 100 mg of Diclofenac (drug) and varying concentration of *A. marmelos* gum (as tablet binder)

The tablets were compressed by using single punch 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. The tablets were evaluated for uniformity of weight as per I.P. method. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester. Thickness was measured by vernier caliper.

In vitro drug release study^[8,9,16,18]

Release of Diclofenac from the tablets was studied in phosphate buffer of pH=6.8 (900 ml) as prescribed in the dissolution rate test of tablets in USP XXIV (method A) using USP Apparatus II by the rotation of the paddle at 50 rpm. The temperature was maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. 10 ml of the sample was withdrawn at different time intervals, filtered and diluted suitably and analyzed by UV spectrometer (PC-2401) at 274 nm. All the experimental units were analysed in triplicate (n=3). In order to study the exact mechanism of drug release data was analysed according to zero order, first order, Higuchi square root. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

Swelling studies^[5,6,7,16,19]

The extent of swelling was measured by taking different formulation of tablets and their initial weight was noted. Tablet from each batch was placed in Petri plate in pH 6.8 phosphate buffer. At time interval of 2, 4, 6, 8, 10, 12 hours tablets were removed from buffer medium and excess water on their surface was carefully absorbed with filter paper. The swollen tablets were weighed and swelling index was calculated.

$$\text{Swelling index} = (W_1 - W_2) / W_2 \times 100.$$

Mucoadhesive studies^[16,19,20,21]

The tablet was studied for Force of mucoadhesion as well as duration of mucoadhesion.

Force of mucoadhesion:

Bioadhesive strength of the tablet was determined by modified physical balance. The apparatus consist of a modified double beam physical balance in which right pan had been replaced by lighter pan and the left pan had been replaced by beaker. The left side of the balance was exactly 5 g heavier by right side. A teflon block was placed in a petri dish, which was placed below the left hand side of the balance.

Bovine Intestine was used for the study and phosphate buffer pH 6.8 was used as a moistening fluid. The mucosa was washed and spread on the Teflon block using thread. Peristaltic pump was used to pump the Phosphate buffer 6.8 at the flow rate 1ml/min. Tablet was fixed to the lower side of the lighter pan and the tablet was made to adhere to the membrane. Water was added slowly with an increment of 0.5 ml till tablet just separate from the membrane.

Duration of mucoadhesion

Tablets were thereby attached to freshly excise intestinal bovine mucosa, which has been spanned on a stainless steel cylinder. (Dissolution apparatus USP I basket). The cylinder was placed in the dissolution apparatus according to USP containing phosphate buffer pH 6.8 at 37°C. The fully immersed cylinder was agitated with 100 rpm. The detachment disintegration and erosion of the tablets were observed within a time period of 10 hrs.

Stability studies^[2,17]

The stability studies were carried out according to ICH and WHO guidelines to assess the drug and formulation stability QC1(13). Optimized formulation was sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 45°C and 75% RH for 3 months. At the end of the study period, samples were analyzed for drug content, dissolution studies and detachment stress.

RESULT AND DISCUSSION

The gum isolated from *A. marmelos* pulp and pH between 6-6.5 and evaluated for flow property as per I.P. result indicates the gum have good flow property^[17]. The swelling property show good swelling of gum in 35 min which reveals, it was suitable candidate for sustained release. The gum is also evaluated for shear stress property which showed better adhesiveness (17.8 g) after 20 min.^[7,19]

Sustained release tablets of Diclofenac sodium with *A. marmelos* gum were prepared by using different drug: gum ratios. All the formulation showed uniform thickness, hardness, weight and drug content and found to be within pharmacopoeial limit. The compositions of the tablets and the results of the physical characterization of tablets are summarized in Table 3 and 4. The friability value decreases with increases *A. marmelos* gum concentration and hardness of tablet increases with increases gum concentration.^[17]

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

Content of tablet	Formulation [Drug: Gum ratio]				
	1:0.25 F1	1:0.50 F2	1:75 F3	1:1 F4	1:1.25 F5
Diclofenac sodium(mg)	100	100	100	100	100
<i>A.Marmelos</i> gum(mg)	25	50	75	100	125
MCC 101(mg)	102.5	97.5	72.5	47.5	22.5
Mg. Stearate(mg)	2.5	2.5	2.5	2.5	2.5
Total wt of tablet (mg)	250	250	250	250	250

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

S. No	Formulation	Hardness (kg/cm ²)	Friability (%)	Drug content (%)	Thickness (mm)	Wt. variation
1	F1	6.20±1.25	0.70±0.02	100.2±4.45	5.1±0.21	249.45±0.45
2	F2	6.40±1.45	0.65±0.04	99.5±2.30	5.3±0.10	251.10±0.20
3	F3	6.50±1.35	0.65±0.02	99.7±2.50	5.0±0.35	250.35±0.15
4	F4	7.00±1.35	0.50±0.03	100.1±5.65	5.2±0.15	250.10±0.35
5	F5	7.50±1.40	0.45±0.05	99.50±3.40	5.2±0.30	249.25±0.30

Number of trials (n= 5)

For Wt. variation data no. of trials n=20

In vitro drug release study ^[6,8,9,10]

The results of in vitro drug release studies of different formulation are depicted in **Figure 1**.

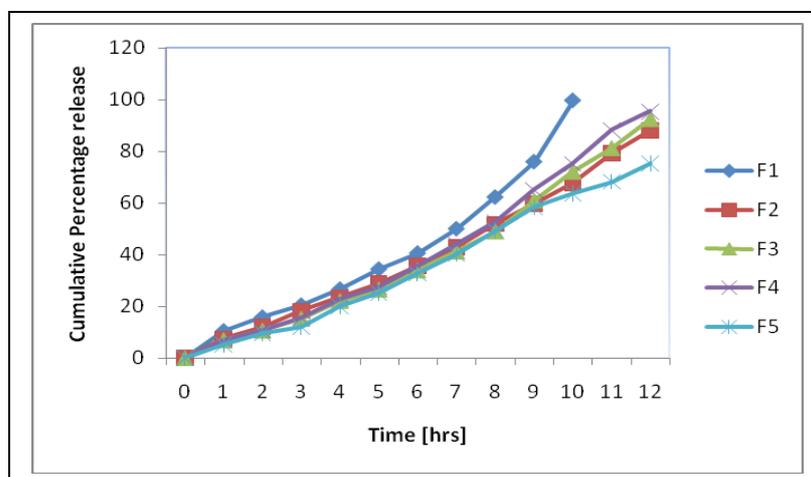


Figure 1: cumulative percentage release of drug

Formulation F1, F2, F3, F4 shows significant good release for 12 hrs with low burst effect. The formulation with 1:1 drug-gum ratio (formulation F4) exhibited the extended cumulative percentage of drug release value (95.5%) after 12 hr. the initial burst release decrease with increase in concentration of gum. Other formulation did not show the results of drug release upto that extend. The drug release follows the Higuchi release pattern i.e. diffusion followed by erosion and n value (n<0.05) indicates nonfician transport mechanisms. [table 5]

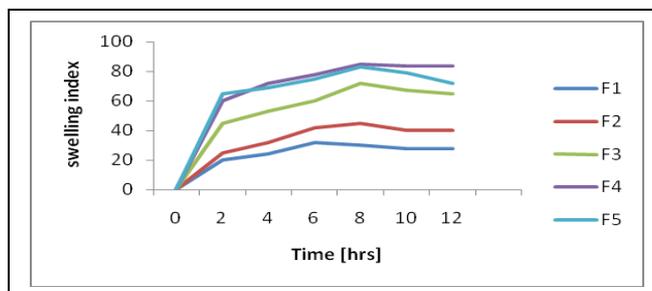
Table5 : Drug release kinetic studies of tablet formulation

Formulations	Zero order kinetics	First order kinetics	Higuchi square root equation	Regression co-efficient (r)
F1	0.9213	0.9131	0.9997	0.5210
F2	0.9326	0.8968	0.9988	0.5625
F3	0.9112	0.9200	0.9951	0.6212
F4	0.9231	0.9144	0.9990	0.5176
F5	0.9416	0.9106	0.9992	0.5426

Mucoadhesive study ^[16,19,20,21]

The swelling behavior is important for bioadhesion. Water sorption increases with increase in the concentration of hydrophilic polymers. The *A. marmelos* gum swells slowly and dissolves in presence of water. Hence SI increases with time up to 9 hours and then decreases. The reason behind this may be that as the time passes more the dissolution of outer gelled layer of tablets in dissolution medium. With no doubt, the hydrophilic content of the hydrogel will affect the intermolecular forces responsible for diffusion and swelling. As hydrophilicity of the hydrogel increases, the interaction between water and hydrogel will increase too; this facilitates water diffusion and leads to greater swelling. In formulation F1 to F-5 showed sharp increase in swelling (figure.2).

Figure 2: swelling index of formulated tablet



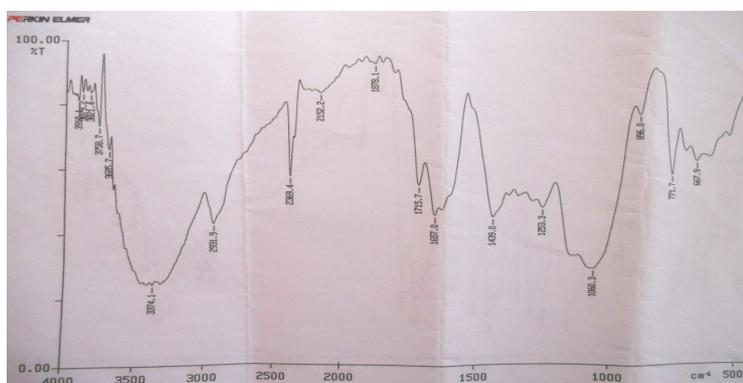
Mucoadhesion is determined by Mucoadhesive strength and duration of mucoadhesion. Formulation F1-F4 shows good mucoadhesive strength. As the viscosity gum increases swelling increases and mucoadhesion force depends on the swelling of the gum. This improves the consolidation step that increases the mobility of molecule and facilitates the interpretation with mucus layer, thus mucoadhesion increases. F4 shows maximum mucoadhesive strength i.e. 0.285 N But further F5 has least mucoadhesion strength; this is due to tremendous increase in viscosity, which leads to entangled structure of the polymer, which hinders the deep interpenetration between polymer and mucin molecules.

All the formulation except F5 passes the test of mucoadhesion . The order of mucoadhesion property among all the formulations was found as F4>F3>F2>F1 (Time = 10 hrs). The formulation F5 fails to retain due to the over hydration of the formulation .The targeting to the intestine can be achieved by the dynamic swelling behavior of crosslinked Natural polymers which depend on the polymer relaxation at different pH. In intestinal pH, networks swelled by a relaxation-controlled mechanism and leads to entanglement of natural polymers with mucin.

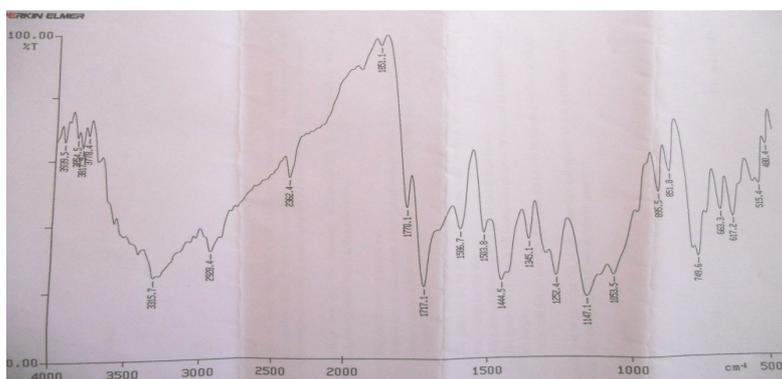
No interaction was observed in the IR spectra. All the principle peaks were observed in the tablet formulation spectrum (figure 3). Formulation was found to be stable for 3 months in accelerated condition.

Figure 3: FTIR study of formulation

3.1: FTIR of gum *A. marmelos*



3.2: FTIR of Formulation



Conclusion

The present study revealed that *A. marmelos* gum appears to be suitable for use as a release retardant in the manufacture of sustained release tablets because of its good swelling, good flow rate and suitability for mucoadhesion formulations. From the dissolution study, it was concluded that dried *A. marmelos* gum can be used as an excipient for making sustained release mucoadhesive tablets of diclofenac sodium.

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