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CALCIUM SALT OF CARBOXYMETHYLED *AEGLE MARMELOS* (BAEL FRUIT) GUM: A NOVEL SUPERDISINTEGRANT FOR FAST DISINTEGRATING TABLETS.

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ABSTRACT

The present study was carried out for the preparation of modified *Aegle marmelos* gum as natural superdisintegrant and assessed it on various parameters for preparing fast dissolving dosage form. The extracted gum from *Aegle marmelos* fruit is chemically modified by carrying out its carboxymethylation and further complexed with Calcium chloride. Therefore, the natural Superdisintegrant prepared from *Aegle marmelos* gum followed swelling and wetting mechanism for disintegration of the dosage form. The change in the functional groups of the extracted gum, carboxymethyled gum and the calcium complexed gum was studied by FT-IR spectrophotometer and DSC studies. Pre-compression parameters of the tablet such as Swelling index, bulk density, tapped density, carr's index, angle of repose and hausner's ratio were determined. Dummy tablets containing calcium complexed *Aegle marmelos* gum were formulated to check the disintegrating efficiency of the tablets. The disintegrating properties of calcium complexed *Aegle marmelos* gum as superdisintegrant was compared with the marketed Superdisintegrant Sodium starch glycolate. The comparison between both the formulations containing different superdisintegrants in various batches was done to check the disintegrating efficiency of the modified *Aegle marmelos* gum as superdisintegrant. The disintegrating time for calcium complexed *Aegle marmelos* gum was observed to be 1min±2sec to 1min±5sec showing good disintegrating properties.The present study may serve as a prototype approach for formulation and development of novel superdisintegrant from various natural gums.

Key words: *Aegle marmelos* gum, Sodium Starch glycolate, modified gum, Superdisintegrant.

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INTRODUCTION

Some of the major ingredients are encapsulated into the tablet formulation which helps to break up the tablet or capsule into smaller fragments called as 'slugs' and thus are named as 'Superdisintegrants' [(1)]. They works in the presence of aqueous environment. This helps in the fast release of the drug from the tablet or capsule. Superdisintegrants enhances the penetration of moisture and further the tablet matrix disperses. The mechanism behinds the disintegration is just the swelling of the superdisintegrant when it comes in contact with water and further it hydrates, and produces disruption in tablet[(2)]. This helps in rapid release of drug from the tablet. For the disintegration, this is necessary for the disintegrant, to interact completely with water [(3)].Therefore, the present study deals with a novel idea of preparing superdisintegrant from *Aegle marmelos* (Bael fruit) gum. *Aegle marmelos* (Indian Bael) fruit contains a gummy material containing highly branched nature of Terminal units of Galactose, Arabinose, Rhamnose and Galactutronic acid [(4)]. The carboxylic nature of the gum is responsible for the disintegrating activity. *Aegle marmelos* is used as antifertility agent, to cure diabetes and cholesterol levels. It has anti-inflammatory, analgesic and antimicrobial properties.Carbohydrates are the main chemical constituent present in *Aegle marmelos*

gum which is modified under chemical reactions, providing it disintegrating properties. The *Aegle marmelos* gum is carboxymethyled and further complexed with calcium chloride that helps to change its properties for disintegration and finally be called as a "Natural Superdisintegrant". This novel idea of using the natural superdisintegrant is helpful in increasing rate of disintegration by rapid drug release. Moreover, rate of drug absorption as well as bioavailability also enhances. Some of the known natural superdisintegrants contains *Isapghula Husk Mucilage* (Plantago ovata) *Aloe Vera*, Guar gum, *Lepidiumsativum mucilage*, *Hibiscus Rosa sinensis* and *Fenugreek fruit mucilage* whereas synthetic superdisintegrants consists of Cross povidone, Modified cellulose, Resin, Cross linked cellulose, Cross linked starch, Crosslinked polyvinylpyrrolidone, Cross linked alginic acid and Cross carmellose sodium[5,6]

Materials and Method:

Aegle Marmelos fruit as a gift sample from Shivalik college of Pharmacy, Nangal. Monochloroacetic acid, Sodium chloride and Calcium chloride were obtained from Thermo Fischer Scientific India, Pvt. Ltd., Mumbai. Alcohol and isopropanol were obtained from Avantor Performance Materials India Ltd., Gujrat. Eriochrome black-T and EDTA were obtained from Himedia Laboratories Pvt. Ltd., Mumbai.

PREPARATION OF SUPERDISINTEGRANT FROM *AEGLE MARMELOS* GUM

Extraction of *Aegle marmelos* gum

Extraction of the gum from the fruit of *A. marmelos* was done by crushing the fruit of *A. Marmelos* in mortar pestle. The crushed material was then transferred to the 1000 ml beaker and boiled in 500ml of distilled water for 5-6 hrs. After complete boiling of the crude material, filtered using a muslin cloth. The filtrate was the concentrated by boiling for 2-3 hrs using water bath. The concentrate was then cooled and alcohol was added till the formation of precipitates takes place. The precipitates were separated out using vacuum filtration apparatus. The precipitates were then dried under the sunlight. The resulted precipitates is the resultant *Aegle. marmelos* gum.

Preparation of Carboxymethyled *Aegle marmelos* gum (CMAM)[7]

CMAM was synthesized from *Aegle marmelos* gum. Briefly, an aqueous dispersion of *Aegle Marmelos* gum (1.25%, w/v) in ice cold sodium hydroxide (45%, w/w) was prepared by stirring for 30 min. To this 25 mL of aqueous solution of monochloroacetic acid (45%, w/v) was added with constant stirring. The reaction mixture was then heated to 70 ◦C under constant stirring for 30 min, cooled and suspended into (80%, v/v) methanol. Precipitates of CMAM so formed were filtered and neutralized with glacial acetic acid, followed by washing with 3 × 60 mL portions of methanol (80%, v/v), filtration and drying in an oven at 40 ◦C.

Calcium complexation of the Carboxymethyled *Aegle marmelos* gum (CMAM) [8]

The calcium cross linked gum derivatives were prepared by reacting the respective derivative with calcium chloride. 2.5 g of Carboxymethyled gum was dissolved in 50 ml of water. Calcium chloride (5%, w/v, 50 ml) solution in water was added drop wise to the gum solution (5%, w/v, 50 ml) with constant stirring. IPA (50 ml) was added drop wise to thegum–calcium chloride solution mixture with stirring to obtainthick, uniform and gelatinous precipitates. These precipitates were repeatedly washed with distilled water to remove unreacted calciumand/or gum. The washing was stopped when the filtrate didnot yield red color from blue color after adding it to standardmagnesium–EDTA complex solution containing Eriochrome blackT indicator solution. These washed precipitates were freeze driedand then passed through #80 sieve.

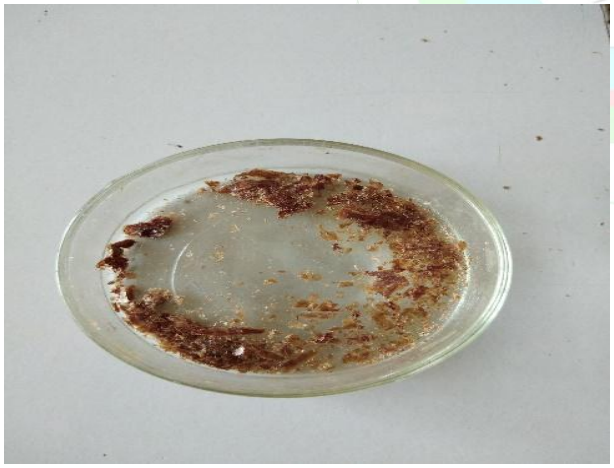

Fig. 1: Carboxymethyled *Aegle marmelos* gum

Fig. 2: Calcium complexed *Aegle marmelos* gum

CHARACTERIZATION OF *AEGLE MARMELOS* GUM

The simple extracted gum and modified gum was characterized for following parameters:

Melting point: Melting point of pure extract of *Aegle marmelos* gum was observed to be 91^0C to 93^0C.

Swelling index: Swelling index is defined as the amount of water absorbed by the gum when placed in water for a predetermined time. It gives the percent of weight gain

by the gum after absorbing water[9,10]. Swelling index is calculated from following equation:

$$\text{Swelling index} = \frac{\text{Final weight of the gum-Initial weight of the gum}}{\text{Initial weight of the gum}} \times 100$$

Swelling index of the *Aegle marmelos* gum was found to be **92.85%**. It reveals *Aegle marmelos* gum has good swelling properties.

FT-IR Studies

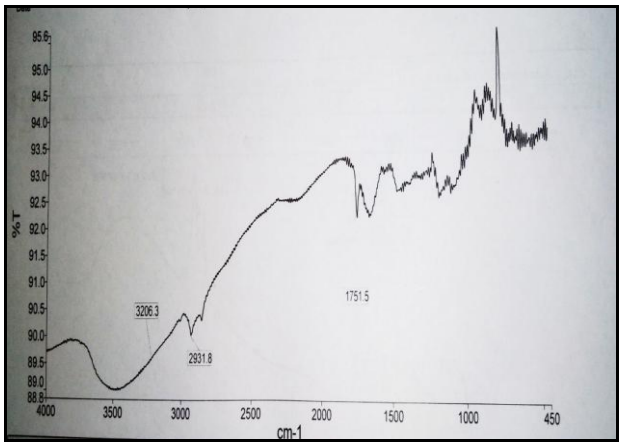

Fig. 3: FT-IR spectra for pure extracted gum from *Aegle Marmelos*.

FT-IR studies reveals characteristic bands for pure *Aegle marmelos* gum. The main chemical constituent of gummy material in *Aegle marmelos* fruit is carbohydrates and which is required for the modification of the gum. Modification enhances the property of the gum which is required for the disintegration purpose. Infrared spectra gives peak for carboxylic acid at 3600-2500 cm^{-1}. Thus, the FT-IR spectra for pure *Aegle marmelos* gum shows carboxylic acid peak at 2931cm^{-1} which implies presence of carbohydrates in the gum.

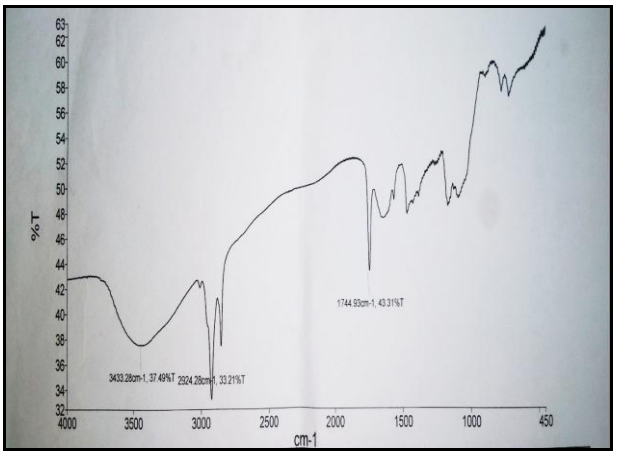

Fig. 4: FT-IR spectra for Carboxymethyled *Aegle marmelos* gum

Upon carboxymethylation of the gum, the property of the gum was modified by adding a methyl group. The carboxymethylation using monochloroacetic acid and NaOH helps to change the functional groups present in the gum. These modifications add up a methyl group to the carbohydrate group (COO^-) that changes the property of the gum. As the methyl group ($-CH_3$) was introduced in the gum, the property of the gum becomes completely hydrophilic in nature and thus it becomes COO^-CH-. After modifying the carbohydrate group to carboxymethyled group, the peak shifts to 2924.28cm^{-1} showing presence of methyl group. This hydrophilic nature of the gum helps in the rapid dissolution of the formulation inside the gastric fluid. This modification becomes an effective way for *Aegle marmelos* gum to acts as aSuperdisintegrant.The carboxymethylation reaction is followed by the following mechanism:

COOH + CH_3 = COO^-CH-

(Carboxylic acid) (Methyl group) (Carboxymethyled product)

After adding a methyl group to the extracted gum and enhancing its hydrophilic property, it was further complexed with Ca^{2+} ion so as to increasing its swelling property. To enhance this property of the carboxymethyled gum (COO^-CH-), it was reacted with Calcium chloride. In this way the –CH- group was replaced by Ca^{2+} to form COO^-Ca^{2+}. This results in shift in the IR peak towards carbonyl group i.e, C-OH group at 1078.24 cm^{-1} along with the presence of carboxylic peak at 3448.01cm^{-1}.The precipitates obtained after complexing with calcium chloride were observed to be somewhat porous in structure. The presence of the pores helps in enhancing the swelling property of the gum that acts as superdisintegrant. Therefore, the formulation absorbs the fluid, swells and disintegrates rapidly.Calcium complexation of the gum follows the following mechanism:

Ca^2 + COO^-CH_3 = COO^-Ca^{2+}

(Calcium ion) (Carboxymethyled product) (Calcium complexed product)

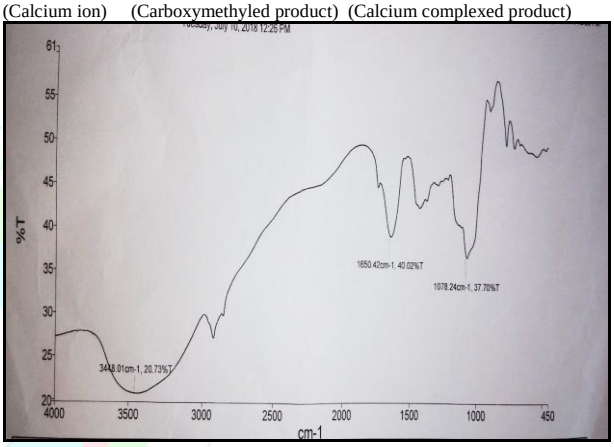

Fig. 5: FT-IR spectra for calcium complexed modified *Aegle marmelos* gum

DSC studies:

DSC studies reveals melting point for pure *Aegle marmelos* gum. The endothermic peak is observed to be at 92.59^{0}C. After modifications of the *Aegle marmelos* gum under certain chemical reactions, the peaks get shift.

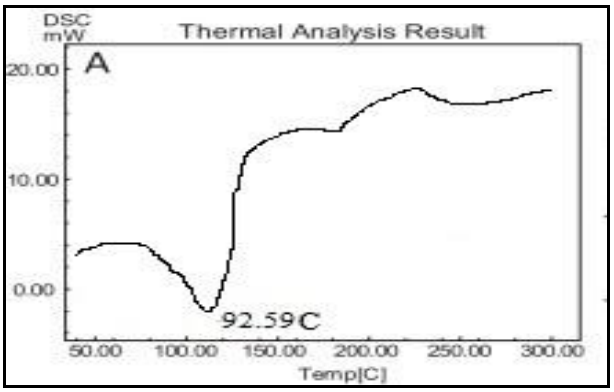

Fig. 6: DSC thermogram of Pure *Aegle Marmelos* gum

Figure 6 showed that upon carboxymethylation of the *Aegle marmelos* gum, a sharp endothermic peak at 85.81^{0}C was observed along with a small exothermic peak was also observed at 173.58^{0}C. The shift in the endothermic peak and variation in the heat flow provided more proof on the insertion of carboxymethyl group which provides hydrophilic properties to the gum.

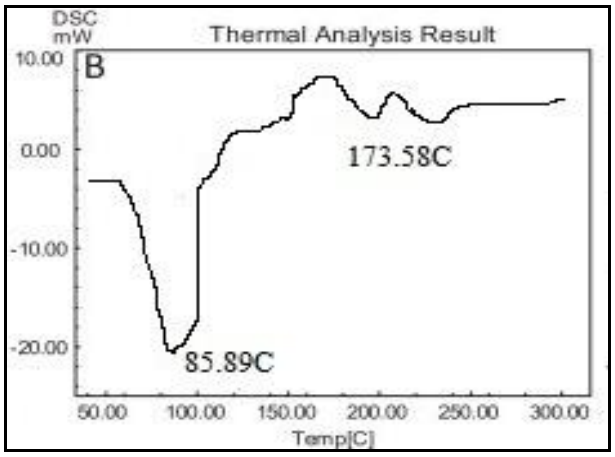

Fig. 7: DSC thermogram of Carboxymethyled *Aegle marmelos* gum

Figure 7 showed Calcium complexation of the carboxymethyled ***Aegle Marmelos*** gum shifts the endothermic peak towards 80.12^{0}C alongwith the exothermic peak towards 285.89^{0}C which reveal the alteration in the internal arrangement. From the above results of DSC, shift in the peaks reveals insertion of carbonyl group giving swelling properties to the gum so that it can easily disintegrate the formulation.[11,12]

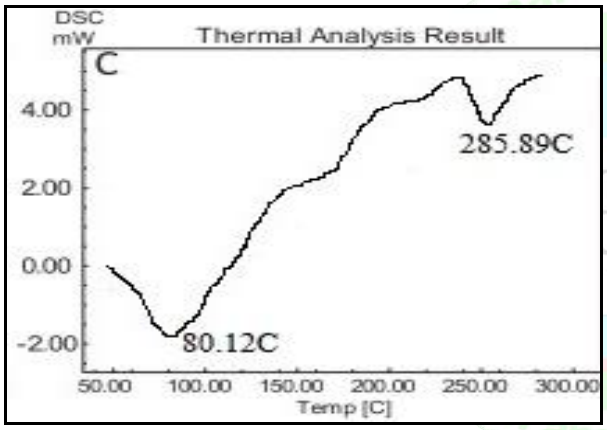

Fig. 8: DSC thermogram of Calcium complex Modified *Aegle marmelos* gum

Formulation of Dummy tablet Containing *Aegle Marmelos* Gum as Natural Superdiintegrant:

Pre-compression parameters:

Bulk density: Bulk density is defined as the total mass of the powder to the total bulk of the powder. It is indicative of the packing of particles and as such is greatly influenced by the size of granules. Loose bulk density of Tablets was determined by pouring gently 2g of the powder blend from each formula through a glass funnel into 10ml measuring cylinder. The volume occupied by the samples were noted. Loose bulk density was expressed in (g/ml) and calculated by using following formula.

Bulk density = mass/bulk volume

Bulk density was calculated to be **0.35 - 0.45 gm/ cm^3** indicating good flow properties.

Tapped density:

Tapped density is defined as the total mass of the powder to the tapped volume of the powder. It was determined by pouring gently 2 g of the powder blend from each formula through a glass funnel into 10 ml measuring cylinder. The cylinder was tapped gently on to a hard surface from the height of 2 inches at second interval until a constant volume was obtained. Volume occupied by the sample after tapping was noted. Tapped density was expressed in (g/ml) and calculated by using following formula. Tapped density was calculated to be **0.45 - 0.65 gm/cm^3**indicating good flow properties [13]

Carr's index (compressibility index): Carr's index is defined as the ratio of bulk density to tapped density.

[(Tapped density – Bulk Density) / Tapped Density] × 100

Carr's index was observed to be in the range of **15.8-25.40 %** indicating the powder blend have the required flow property for compression which is suitable for content uniformity and less weight variation in final tablets.

Hausner's ratio: It is calculated as Tapped density/bulk density. Hausner's ratio<1.25 indicates good flow properties whereas >1.5 indicates poor flowability. Hausner's ratio was calculated to be **1.20-1.40** indicating good flowability.

Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane; it was measured by pouring the weighed powder mixture into the funnel which was fixed to stand at a definite height (h).

$\theta = \tan^{-1} h/r$

The values calculated for angle of repose were found to be in the range of **25.74^0 to 38.82^0** indicating good flow properties.[14]

Table 1: Various pre compression parameters for superdisintegrant

S.No.	Bulk density	Tapped density	Carr's index	Angle of repose	Hausner's ratio
1.	0.41	0.46	22.12	25.74	1.30
2.	0.38	0.53	25.66	29.36	1.10
3.	0.40	0.60	18.43	35.12	1.20
4.	0.35	0.55	23.56	38.17	1.40
5.	0.45	0.65	15.67	33.65	1.10

FORMULATION OF FAST DISINTEGRATING TABLETS

Dummy FDT's were formulated containing calcium complexed *Aegle Marmelos* gum as natural superdisintegrant and were compared to the synthetic superdisintegrant starch glycolate containing tablet for disintegration time in F1 to F5 formulations[15]. The concentration of the gum was varied in each batch such as 2.5mg, 5mg, 7.5mg 10mg and 12.5mg. The effect of the increasing amount of the superdisintegrant was evaluated by comparing the disintegration time of the tablet.

Table 2: Formulation of dummy Fast disintegrating tablets using modified gum as superdisintegrant

Formulation code	MCC (mg)	Lactose (mg)	Calcium complexed *Aegle Marmelos* gum (mg)	Magnesium stearate	Talc (mg)
F1	100	43.5	2.5	2	2
F2	100	41	5	2	2
F3	100	38.5	7.5	2	2
F4	100	36	10	2	2
F5	100	33.5	12.5	2	2

Table 3: Formulation of dummy tablet using Sodium starch glycolate as superdisintegrant

Formulation code	MCC(mg)	Lactose (mg)	Sodium starch glycolate (mg)	Magnesium stearate (mg)	Talc (mg)
F1	100	43.5	2.5	2	2
F2	100	41	5	2	2
F3	100	38.5	7.5	2	2
F4	100	36	10	2	2
F5	100	33.5	12.5	2	2

Table 4: Evaluation of the Tablets Containing Different Superdisintegrant for Their Disintegration Time

Formulation No.	Calcium complexed Aegle Marmelos gum	Sodium starch glycolate
F1	45±3s	47±2s
F2	44±5s	45±4s
F3	39±2s	42±6s
F4	41±3s	44±3s
F5	36±2s	39±3s

CONCLUSION

The present investigation revealed high super disintegrating potential of modified *Aegle Marmelos* gum. The fast disintegrating tablets prepared from calcium complexed *Aegle marmelos* gum (12.5%) in F5 formulation showed faster disintegration of the tablet as compared to the synthetic superdisintegrant(sodium starch glycolate). The mechanism behind the rapid disintegration of tablet by calcium complexed *Aegle marmelos* gum is the modification of the gum by the chemical reactions so as to enhance the disintegration properties of the gum. The carboxymethylation of the *Aegle marmelos* gum provides hydrophilicity to the gum so that it can easily disintegrate in the environmental fluid. Further, the carboxymethyled gum was complexed with Ca^{2+} that forms intra or inter cross linked bridges in calcium complexed gum for water transporting system even when aqueous channels in the fast disintegrating tablets were blocked. Overall, the findings pointed calcium complexed *Aegle marmelos* gum could be a better superdisintegrant that provides FDT's with good mechanical strength and lowest disintegration time. Thus, this superdisintegrant could be considered useful in near future for the formulation development of fast disintegrating tablets.

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