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TO STUDY THE FORMULATION ABILITY OF NEW POLYMER SOURCE OBTAINED FROM *AEGLE MARMELOS* FOR ITS FILM FORMING GEL USING AN ANTIFUNGAL AGENT-CLOTRIMAZOLE.

***[1]Prof. Saurabh Dilip Bhandare and [2]Dr. G. S. Deokar**

MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik-422003, Maharashtra, India. University: SPPU. Pune. Formerly Known as: University of Pune.

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***Corresponding Author**
Prof. Saurabh Dilip Bhandare
MET's Institute of Pharmacy, Bhujbal Knowledge City, Adgaon, Nashik-422003, Maharashtra, India. University: SPPU. Pune. Formerly Known as: University of Pune.

ABSTRACT

Investigating a new gum source physical, chemical, and functional performance of *Aegle marmelos* for food and drugs administration. Gums are a common type of naturally occurring polymer. They are a popular choice for usage in food and pharmaceuticals due to their availability and, economic. *Aegle marmelos'* physical, chemical, and functional performance for food and pharmaceuticals. Study of gum properties such as its compressibility index and other precompression studies were found with this study. The suitability of the gun in release modifying and thin film forming gel was evaluated for its formulation usage. Study of invitro drug release give large drug release data that was interpreted using graphs in studying the release of the drug though the formulation.

KEYWORDS: Polymer drug delivery systems, novel drug delivery system, modified drug delivery methods, polymer and drug release.

OBJECTIVE

The main objective of this study was characterisation and, evaluation of *Aegle marmelos* gum as a pharmaceutical adjuvants. Owing to the great medicinal value of *Aegle marmelos*, it becomes very important to explore the uses of this fruit.

Since polymers play important role in pharmaceutical industry as binder, viscosity enhancer, suspending agent; it becomes important to find out new and commercially important polymers.

The aim of the study was undertaken to isolate the gum, as a natural polymer; from the fruits of *Aegle marmelos and study its thin film forming ability to form thin film forming gel loaded with clotrimazole as an antifungal agent to cure the worst forming fungal infections. Example ringworms.*

1. INTRODUCTION

Aegle marmelos, commonly known as Bael also stone quince, golden apple, stone apple or wood apple, is a rare species of tree native to the Indian subcontinent and Southeast Asia.

BAEL-Latin: *Aegle marmelos:*

Aegle marmelos commonly known as 'Bael', is a species of tree native to India. Present through out southeast Asia, considered sacred by Hindus & is offered to Lord Shiva.

† Fruits used in traditional medicines and, as a food & beverage.[6]

Family- Rutaceae.

Sanskrit synonym- Shivdruum, Shandillya, Gandhgarbha, Maalur, Laxmiphal, Lakshxmiphal, Shayluysh.

Other synonym - Golden apple, stone apple, wood apple, stone Quince.

Local name: Falling hammer stone.

Appearance

Height= 8 – 10 m tall, 9 - 9.5m wide; thorny tree,

Leaves-alternate, compound, with two pairs of opposite stalked leaves with one large long petiole; terminal one.

Flower- white green in colour, aromatic.

Fruit- oval, hard woody shelled, yellowish green in colour, sweet scented.

Geographical region- India, Sri Lanka, Myanmar.

Figure 1: Aegle marmelos fruit and its tree.

1.1. Description

The *Aegle marmelos* fruit tree is slow-growing, of medium size, up to 40 or 50 ft (12-15 m) tall with short trunk, thick, soft, flaking bark, and spreading, sometimes spiny branches, the lower one's drooping. Young suckers bear many stiff, straight spines. A clear, gummy sap, resembling gum *Arabic*, exudes from wounded branches and hangs down in long strands, becoming gradually solid. It is sweet at first taste and then irritating to the throat. The deciduous, alternate leaves, borne singly or in 2's or 3's, are composed of 3 to 5 oval, pointed, shallowly toothed leaflets, 1 1/2 to 4 in (4-10 cm) long, 3/4 to 2 in (2-5 cm) wide, the terminal one with a long petiole. New foliage is glossy and pinkish-maroon. Mature leaves emit a disagreeable odour when bruised. Fragrant flowers, in clusters of 4 to 7 along the young branchlets, have 4 recurved, fleshy petals, green outside, yellowish inside, and 50 or more greenish-yellow stamens. The fruit, round, pyriform, oval, or oblong, 2 to 8 in (5-20 cm) in diameter, may have a thin, hard, woody shell or a more or less soft rind, gray-green until the fruit is fully ripe, when it turns yellowish. It is dotted with aromatic, minute oil glands. Inside, there is a hard central core and 8 to 20 faintly defined triangular segments,

with thin, dark-orange walls, filled with aromatic, pale-orange, pasty, sweet, resinous, more or less astringent, pulp. Embedded in the pulp are 10 to 15 seeds, flattened-oblong, about 3/8 in (1 cm) long, bearing woolly hairs and each enclosed in a sac of adhesive, transparent mucilage that solidifies on drying.

For medicinal use, the young fruits, while still tender, are commonly sliced horizontally and sun-dried and sold in local markets. They are much exported to Malaya and Europe. Because of the astringency, especially of the wild fruits, the unripe Bael is most prized as a means of halting diarrhoea and dysentery, which are prevalent in India in the summer months.

Bael fruit was resorted to by the Portuguese in the East Indies in the 1500's and by the British colonials in later times.[6]

Figure 2: Aegle marmelos fruit preparations.

1.2. Origin and distribution

The tree grows wild in dry forests on hills and plains of central and southern India, also in mixed deciduous and dry dipterocarp forests of former French Indochina.

Mention has been found in writings dating back to 800 B.C. It is cultivated throughout India, mainly in temple gardens, because of its status as a sacred tree; also, in Ceylon and northern Malaya, the drier areas of Java, and to a limited extent on northern Luzon in the Philippine Islands where it first fruited in 1914.

1.2. a.Propagation: Propagation includes propagating through seeds or from a sapling found to be grown under its tree during rainy season in the India.

1.3. Climate

The *Aegle marmelos* fruit tree is a subtropical species. In the Punjab, it grows up to an altitude of 4,000 ft (1,200 m) where the temperature rises to 120º F (48.89º C) in the shade in summer and descends to 20º F (-6.67º C) in the winter, and prolonged droughts occur. It will not fruit where there is no long, dry season, as in southern Malaya.[5]

1.4. Medicinal and pharmacological values

The leaves, bark, roots, fruits, and seeds are used in traditional medicine to treat various illnesses, although there is no clinical evidence that these methods are safe or effective.

All parts of the *Aegle marmelos* plant consist of immense medicinal properties. The herbal medicinal preparations of *Aegle marmelos* are used to treat chronic diarrhoea, dysentery,

peptic ulcers, laxative for astringency, and respiratory ailments. The medicinal properties of herbal preparations of *Aegle marmelos* are tested using animal models such as rats, rabbits, and mouse. Cancer is one of the significant causes of death worldwide, and novel drugs are required for efficient treatments. A total of reported 187 plant species from 102 genera and 61 families have proven antitumor properties. However, only 15 species from 10 genera from nine families are currently used in clinical studies. Bael has more considerable significance as it has many compounds with anticancerous properties. The anti-inflammatory activity was demonstrated by preparations of bael roots along with antidiabetic activity.[4]

1.5. Antidiabetic activity

Aegle marmelos extracts are shown to have significantly higher antidiabetic activities when tested using animal models. The fruit extracts of *Aegle marmelos* have demonstrated protective effects on pancreatic tissues of diabetic rats. Aqueous and alcoholic extracts of fruits administrated at a dose of 500 mg per kg of body weight produced hyperglycemia in rabbits. An elevation of vitamin C content was also accompanied by hyperglycemia when rats were administered with *Aegle marmelos* fruit extracts. Further observation of hyperglycemic activity and, antihypoglycemic activity of the *Aegle marmelos* aqueous extracts were made using rat models. These antidiabetic and hyperglycemic effects were further confirmed using aqueous extracts of *Aegle marmelos* seeds. *Aegle marmelos* leaves have also shown the hyperglycemic impact. *Aegle marmelos* leaf extracts can decrease Mi receptor gene expression and inhibit aldose reductase activity, anticataract activity, and free radical scavenging activity and, all of them are related to diabetics. The compound Aegeline-2 in *Aegle marmelos* leaves is the responsible compound for antihyperglycemic activity.

1.6. Other related medicinal usage

The bitter, pungent leaf juice, mixed with honey, is given to allay catarrh and fever. With black pepper added, it is taken to relieve jaundice and constipation accompanied by oedema. The leaf decoction is said to alleviate asthma. A hot poultice of the leaves is considered an effective treatment for ophthahnia and various inflammations, also febrile delirium and acute bronchitis.

A decoction of the flowers is used as eye lotion and given as an antiemetic. The bark contains tannin and the cournarin, aegelinol; also, the furocourmarin, marmesin; umbelliferone, a hydroxy coumarin; and the alkaloids, fagarine and skimmianine. The bark decoction is

administered in cases of malaria. Decoctions of the root are taken to relieve palpitations of the heart, indigestion, and bowel inflammations; also, to overcome vomiting.

The fruit, roots and leaves have antibiotic activity. The root, leaves and bark are used in treating snakebite. Chemical studies have revealed the following properties in the roots: psoralen, xanthotoxin, *O*-methylscopoletin, scopoletin, tembamide, and skimmin; also, decursinol, haplopine and aegelinol, in the root bark.[5]

Aegle leaves are useful in jaundice also they are beneficial in treatment of mild wounds.

1.7.Herb functions

† **Astringent:** Unripe Bael fruit has high tannin content, which makes it an effective for the treatment of dysentery and diarrhoea.

† **Laxative:** Ripe Bael fruit is an excellent laxative, which relieves constipation and is also helpful in eliminating intestinal worms.

† **Antimicrobial:** Bael exhibits antibacterial and antiviral activity against pathogens which cause intestinal infections such as infectious diarrhoea.

† **Antispasmodic and carminative:** Bael fruit relieves abdominal colic and flatulence because of its antispasmodic and carminative properties.

† **Anti-inflammatory:** Marmin, a coumarin isolated from the roots, possesses anti-inflammatory properties, which helps in the management of inflammatory intestinal disorders such as colitis.

1.8. Chemical composition

1.8.1. Chemical compounds

1.8.1.1. Alkaloids and other chemical substance with oils and, majour phyto-constituents

Aegelin, aegelenine, marmeline, dictamine, fragrine ($C_{13}H_{11}O_3N$), O- methylhalfordinine,O isopentenylhalfordinol, N-2-[4-(3',3'- dimethylallyloxy) phenyl]ethyl cinnamide, N-2-hydroxy-2-[4-(3',3'-dimethylallyloxy) phenyl]ethyl cinnamide, N-4 methoxystyryl cinnamide, N-2- hydroxy-2- (4-hydroxyphenyl) ethyl cinnamide O- (3,3-dimethylallyl) halofordinol, N-2- ethoxy-2-(4-methoxy phenyl) ethyl cinnamide, N-2-methoxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethylcinnamide, N-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamide.[6]

The Bael tree contains furocoumarins, including xanthotoxol and the methyl ester of alloimperatorin, as well as flavonoids, rutin and marmesin; a number of essential oils; and, among its alkaloids, á-fargarine(=allocryptopine), O-isopentenylhalfordinol, O-methylhafordinol. Aegeline (N-[2-hydroxy-2(4-methoxyphenyl) ethyl]-3-phenyl-2-propenamide) is a constituent that can be extracted from Bael leaves. Aeglemarmelosine, molecular formula C16H15NO2 [α] 27D+7.89° (c 0.20, CHCl3), has been isolated as an orange viscous oil.[3]

Figure 3. Pulp of fruit to analyse its chemical constituents apart from its rind.

The essential oil of the leaves contains *d*-limonene, 56% *a*-d-phellandrene, cineol, citronellal, citral; 17% p-cyrnene, 5% cumin aldehyde. The leaves contain the alkaloids *O*-(3,3-dimethylallyl)-halfordinol, *N*-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamide, *N*-2-methoxy-2-[4-(3',3'-dimethyalloxy) phenyll] ethylcinnamide, and *N*-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamamide. A bitter, light-yellow oil extracted from the seeds is given in 1.5 g doses as a purgative. It contains 15.6% palmitic acid, 8.3% stearic acid, 28.7% linoleic and 7.6% linolenic acid. The seed residue contains 70% protein.

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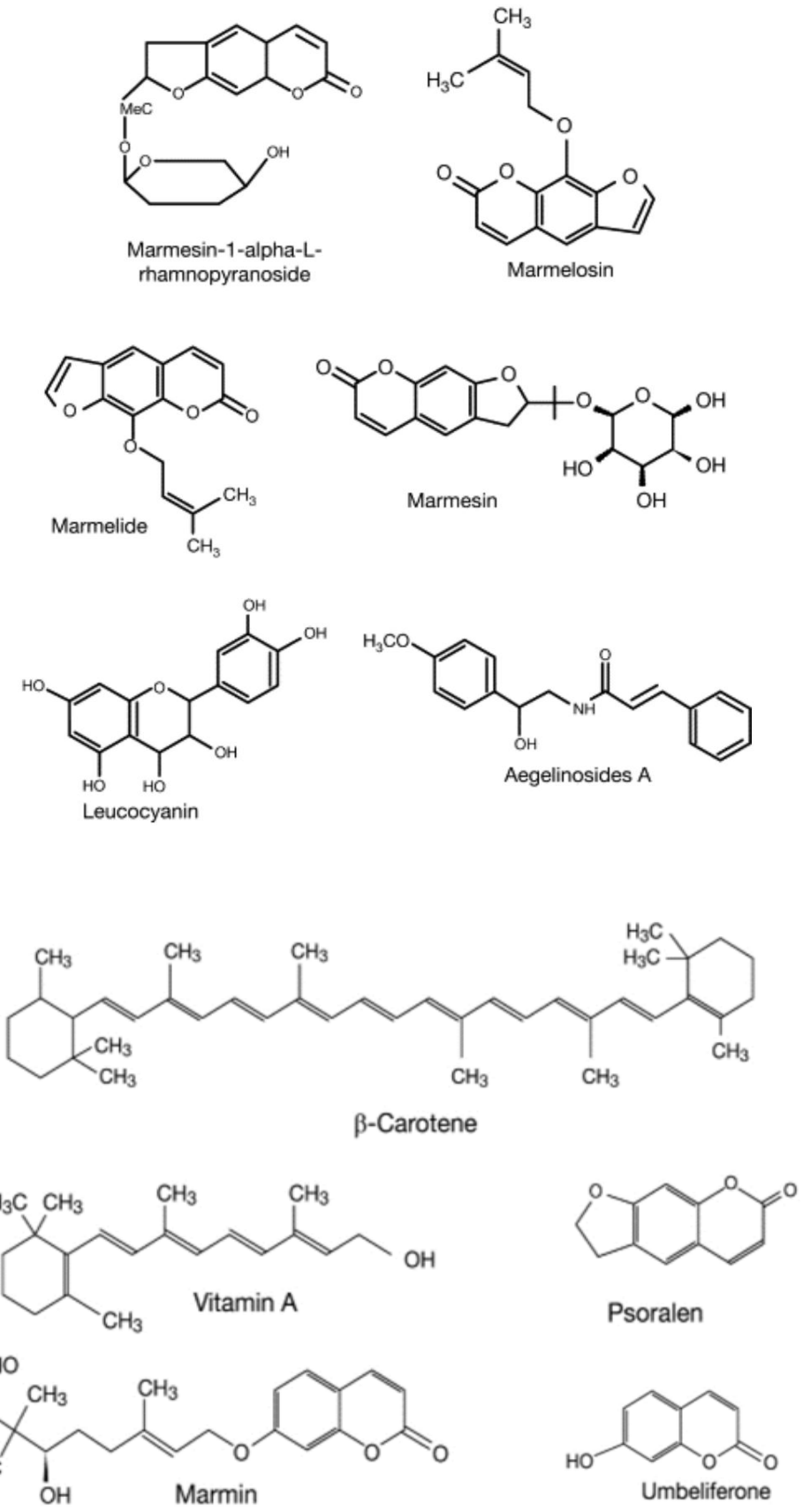

Figure 4: Structures of the chemical constituents found in *Aegle marmelos.*

Gums are a class of natural polymers capable of forming extremely viscous aqueous solutions or dispersions. Various gums have been studied for use in sustained release solid dosage forms, tablet binders, liquid dosage form stabilisers or suspending agents, and bioadhesive drug delivery systems, as well as in NDDS. They have the advantages of biocompatibility, low cost, and ubiquitous availability over their synthetic counterparts.

Previous research has demonstrated that a variety of commonly used gums can be utilised as an alternative or as a thickening ingredient in a variety of food products such as cake, cookies, soup, and, tempura.

1.8.1.2. Coumarins

Marmelosin, marmesin, imperatorin, marmin, alloimperatorin, methyl ether, xanthotoxol, scoparone, scopoletin, umbelliferone, psoralen and marmelide27. Marmenol, a 7-geranyloxycoumarin [7-(2, 6-dihydroxy- 7-methoxy-7-methyl-3-octaenyloxy) coumarin].

1.8.1.3. Polysaccharides

Galactose, arabinose, uronic acid and L-rhamanose are obtained on hydrolysis.

1.8.1.4. Seed oil

Composed of palmitic, stearic, oleic, linoleic and linolenic acid.

1.8.1.5. Tannins

The maximum tannin content in Bael fruit was recorded in the month of January. There is as much as 9% tannin in the pulp of wild fruits, less in cultivated type. Tannin is also present in leaves as skimmianine.

1.8.1.6. Carotenoids

Carotenoids are responsible for imparting pale colour to fruit. Marmelosin, skimmianine and umbelliferone are the therapeutically active principles of Bael plant. Minor constituents like ascorbic acid, sitosterol, crude fibres, tannins, α-amyrin, carotenoids, crude proteins are also present. Roots of the tree have also been found to contain psoralen, xanthotoxin scopoletin and tembamide.

Compounds such as praealtin D, trans-cinnamic acid, 4- methoxy benzoic acid, betulunic acid, and montanin have also been reported.[6]

1.9. Snippets

1.9.1. Snippet-1

Effect of sugars, galactose content and chainlength on freeze–thaw gelation of galactomannans: Cryogels of locust bean gum (LBG) were prepared by freezing and thawing 1.0 wt% solutions incorporating sucrose, glucose, fructose or sorbitol at concentrations of 40, 45, 50, 55 and 60 wt%, and were characterised by compression testing. Gel strength showed an initial increase and subsequent decrease with increasing concentration of sugar. Maximum strength was attained at 45 wt% fructose, 50 wt% sucrose or sorbitol, and 55 wt% glucose, but increased in the same order: fructose<sucrose≈sorbitol<glucose. The initial increase in gel strength is attributed to the reduction in water content with increasing concentration of sugar; the subsequent decrease is tentatively ascribed to inhibition of polymer–polymer association by binding of sugar molecules to the polymer chains, with differences in gel strength arising from differences in strength of binding.

Galactomannan samples with mannose: galactose (M/G) ratios spanning that of LBG were prepared by treatment of guar gum with α-galactosidase, and cryogels (1.0 wt%) were prepared at a fixed concentration (50 wt%) of sucrose. A sharp increase in gel strength was observed at M/G ratios around, and above, that of LBG, and is attributed to increasing content of unsubstituted sequences of mannan backbone long enough to form stable associations as junctions in the cryogel network. The samples of partially debranched guar gum had substantially lower molecular weights than LBG (attributed to some slight β-mannanase activity in the α-galactosidase used in their production), but the mechanical properties of the LBG cryogels fitted in reasonably well with the M/G-dependence observed for the other samples indicating that within the range studied (~10 to ~2000 kD.), chainlength has little effect. (Doyle et al., 2006).

1.9.2. Snippet–2

Bael (*Aegle marmelos* L. Corrêa) is an economically valuable tree species in South Asia. The ripen Bael fruits are popular among people because of the delicious fruit pulp, which is ideal for making jam, syrup, and pudding. Bael possesses many medicinal values and therefore used as an ingredient in ayurvedic herbal medical preparations. The fruits, bark, leaves, seeds, and roots of bael contain bioactive compounds such as coumarin, xanthotoxol, imperatorin, aegeline, and marmeline. These compounds can provide antidiabetic, anticancerous, antifertility, antimicrobial, immunogenic, and insecticidal activities. Bael is also essential as a

species for reforestation, especially in the unfertile marginal lands. Bael seeds possess a unique fatty acid (12-hydroxyoctadec-cis-9-enoic acid or ricinoleic acid), a convertible item into biodiesel. Bael is an underutilized fruit species in South Asian countries. However, numerous studies report the medically significant properties and industrially vital characteristics of Bael in India. The present review focused on summarizing and discussing the essential details and potentials of Bael for industrial applications towards economic development.

Guar gum, derived from the annual plant of *Cyamopsis tetragonolobus*, and locust bean gum, derived from the seed pods of *Ceratonia siliqua*, are the two galactomanans with the greatest practical significance as thickeners and stabilisers in industrial applications.

Guar gum, also called guaran, is a galactomannan polysaccharide extracted from guar beans that has thickening and stabilizing properties useful in food, feed, and industrial applications.[2]

1.10. Food uses

Aegle marmelos L. Corrêa fruits may be cut in half, or the soft types broken open, and the pulp, dressed with palm sugar, eaten for breakfast, as is a common practice in Indonesia. The pulp is often processed as nectar or "squash" (diluted nectar). A popular drink (called "sherbet" in India) is made by beating the seeded pulp together with milk and sugar. A beverage is also made by combining Bael fruit pulp with that of tamarind. These drinks are consumed perhaps less as food or refreshment than for their medicinal effects.

Mature but still unripe fruits are made into jam, with the addition of citric acid. The pulp is also converted into marmalade or sirup, likewise for both food and therapeutic use, the marmalade being eaten at breakfast by those convalescing from diarrhoea and dysentery. A firm jelly is made from the pulp alone, or, better still, combined with guava to modify the astringent lavour. The pulp is also pickled.

Aegle marmelos L. Corrêa pulp is steeped in water, strained, preserved with 350 ppm $S0_2$, blended with 30% sugar, then dehydrated for 15 hrs at 120º F (48.89º C) and pulverized. The powder is enriched with 66 mg per 100 g ascorbic acid and can be stored for 3 months for use in making cold drinks ("squashes"). A confection, *Aegle marmelos* L. Corrêa fruit toffee, is prepared by combining the pulp with sugar, glucose, skim milk powder and hydrogenated fat.

Indian food technologists view the prospects for expanded Bael fruit processing as highly promising.

The young leaves and shoots are eaten as a vegetable in Thailand and used to season food in Indonesia. They are said to reduce the appetite. An infusion of the flowers is a cooling drink.

The pulp also contains a balsam-like substance, and 2 furocoumarins-psoralen and marmelosin ($C_{13}H12O3$), highest in the pulp of the large, cultivated forms.

There is as much as 9% tannin in the pulp of wild fruits, less in the cultivated types. The rind contains up to 20%. Tannin is also present in the leaves, as skimmianine.

1.10.1. Food value per 100 g of edible portion*[5] Table-1.

Water	54.96-61.5 g
Protein	1.8-2.62 g
Fat	0.2-0.39 g
Carbohydrates	28.11-31.8 g
Ash	1.04-1.7 g
Carotene	55 mg
Thiamine	0.13 mg
Riboflavin	1.19 mg
Niacin	1.1 mg
Ascorbic Acid	8-60 mg
Tartaric Acid	2.11 mg

1.10.2. Toxicity

The leaves are said to cause abortion and sterility in women. The bark is used as a fish poison in the Celebes. Tannin, ingested frequently and in quantity over a long period of time, is antinutrient and carcinogenic.

2. METHODOLOGY

2.1. Materials and method

Aegle Marmelos fruit were collected from a house grown tree that is obtained from house garden space in Nashik. The gum; fruits were collected in the year 2012 and 2013 and sun dried. The fruit was collected from a old stable tree of age around 70-80 years.

Figure 5: *Aegle Marmelos* tree along with its fruit and branching.

The collection of gum was done carefully to obtain soil free sample or dust free gum. Therefore, the drying was done carefully in a glass container covered with a metal net.

2.2. Collected gum

The collected gum was clean dried and stored in an air tight container.

Figure 6: Isolated gum form *Aegle marmelos.*

2.3. Isolation of Bael Gum

† The fruit contains many seed cavity filled with numerous hairy seeds which are encapsulated in a slimy mucilage.

† This slimy mucilage was removed and then was dried in the shade.

† The isolated mucilage was put in distilled water dissolved and filtered to remove other adhering fruit material.

† The filtrate obtained was sundried and stored.

2.4. Purification of gum

† The well dried gum was powdered in mortar, passed through sieve no.80 and solubilised in distilled water.

† The concentrated solution was precipitated in acetone.

† The precipitate was separated and dried at 60ºC in the oven.

† The dried gum was powdered and stored in tightly closed container for further usages.

2.5. Standardization of Gum

The Gum was standardized for following properties.

2.5.1. Organoleptic properties

***Colour*:** The colour of the gum was observed and noted for its evaluation.

***Odour*:** The odour of the gum was evaluated and noted down.

***Appearance/ feel*:** The feel of the gum was evaluated and noted down.

***Fracture*:** The fracture of the gum was observed and noted down.

2.5.2. Loss on drying: The 5 gm gum was dried at 105 ± 5 ºC till the constant weight of gum was obtained.

2.5.3. Ash value: 1gm of gum was accurately weighed and evenly distributed it in the crucible. It was dried at 105 ºC for one hour and ignited in muffle furnace at 600 ± 25 ºC.

2.5.4. pH value

The pH value was measured using the laboratory pH meter. 1% solution was utilised to measure the pH of the *Aegle marmelos* gum.

2.5.5. Viscosity measurement

The viscosity of the gum was measured using the flow pattern by studying it under the viscometer. Ostwald viscometer.

The gum solution of 1 to 5 % in concentration was used to measure the viscosity.

2.5.6. Melting point

Melting point of pure extract of *Aegle marmelos* gum was measured using melting point apparatus.

2.6. General evaluation parameter for gums and polymers along with resins

2.6.1. Pre-compression parameters

2.6.1.1. 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.

2.6.1.2. 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.

2.6.1.3. 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

2.6.1.4. Hausner's ratio: It is calculated as Tapped density/bulk density. Hausner's ratio1.5 indicates poor flowability.

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

2.7. Formulation

Clotrimazole was utilised as a drug in the preparation of this drug loaded thin film forming gel to treat mild to severe skin fungal infection caused by:

2.7.1. Some common types of fungal infection include

- Athlete's foot, (transmitted with direct contact or touch).
- Jock itch, (sexually transmitted). (direct contact or touch).
- Ringworm, (transmitted with direct contact or touch).
- Yeast infection, (transmitted with direct contact or touch).
- Onychomycosis, or a fungal infection of the nail, (transmitted with direct contact or touch).
- Gradnerella vaginalis-bacterial vaginal infection occurring in both young and adult females/ bacterial vaginosis, vaginal yeast infection, vaginal candidiasis. (sexually transmitted). (STD).

2.7.2. Preparation of dermal gel: The polymeric solutions was obtained by dissolving gum, that were prepared in ethanol using dispersion method with 90;10 of ethanol and water respectively. The polymeric solution with 1% clotrimazole was prepared using the ethanol: water solution. The polymeric solutions were mixed properly with continuous stirring. Accurately weighed quantity (1%) of the clotrimazole was dissolved in 5 mL ethanol. The drug solution and polymeric dispersion were mixed properly with continuous stirring and volume was made up to the mark using ethanol and along with release modifier propylene glycol.

2.7.3. Composition of formulations as per 3^2 factorial designs. Table 2.

Formulation code.	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient									
1% Clotrimazole.	1%	1%	1%	1%	1%	1%	1%	1%	1%
Propylene glycol.	1ml	2ml	3ml	4ml	5ml	6ml	7ml	8ml	9ml
Ethanol:water.	90:10	90:10	90:10	90:10	90:10	90:10	90:10	90:10	90:10
Rose oil.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Preservatives.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Polymer	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

2.7.4. Evaluation of formulations: The formulations were tested for clarity, pH, and viscosity. Clarity was checked visually and pH of the formulations was checked using digital pH meter.

2.7.5. Drug content: To determine drug content 1 g of gel was taken in a 100 mL volumetric flask containing 10 mL phosphate buffer solution pH 7.4 and volume was made up to the mark with phosphate buffer solution pH 5.8 to get a concentration of 100µg/mL. An aliquot of 0.5 mL was transferred to a 10 mL volumetric flask and volume was made up with phosphate buffer solution pH 7.4. The absorbance of prepared solution was measured at λ max of 260 nm by using UV visible spectrophotometer.

2.7.6. Drying time: For the assessment of the drying time the formulation was applied to the inner sides of the forearm of a volunteer, who participated in the study on informed consent basis. After 2 minutes a glass slide was placed on the film without pressure. If no remains of liquid were visible on the glass slide after removal, the film was considered dry. If remains of liquid were visible on the glass slide the experiment was repeated until the film was found to be completely dry. To note drying time the drug content in the film or gel was eliminated and only base material was used to check the drying time.

2.7.7. Integrity of formulation on skin: The formulation was applied to the forearm of a volunteer as described for the assessment of the drying time. The dry film was then worn overnight by the test subject. After 24 hours the test area was examined visually for completeness of the film, appearance of cracks or flaking.

2.7.8. In-vitro drug release study (diffusion study): Laboratory-assembled apparatus resembling a Franz diffusion cell was used to determine the release profile of drug from film forming gel. The cell consisted of two chambers, the donor and the receptor compartment between which a diffusion membrane (egg membrane) was mounted. The donor compartment, with inner diameter 24 mm, was open i.e., exposed to the atmosphere at one end and the receptor compartment was such that it permitted sampling. The diffusion medium used was phosphate buffer solution pH 7.4 (PBS). 1 mL of the drug containing film forming gel was placed in the donor compartment over the drug release membrane and was separated from the receptor compartment by the egg membrane. The egg membrane was previously soaked for 24 hr. in PBS. The donor and receptor compartments were held together using a clamp. The position of the donor compartment was adjusted so that egg membrane just touches the diffusion medium. The whole assembly was fixed on a magnetic stirrer. The receptor compartment with 100 mL of PBS was placed on a thermostatically controlled magnetic stirrer. It was maintained at 37 ± 0.5 ^{o}C and stirred constantly at 50 rpm using a magnetic bead or stirring pins. Samples of 1 mL were collected at predetermined time intervals and analysed for drug content by UV Spectrophotometer at λ max against blank. The receptor cell was refilled with an equal volume of phosphate buffer at each time of sample withdrawal.

3. RESULT AND DISCUSSION

3.1. Standardization of gum

1. Colour: yellow resin, similar looking like gum *Arabica.*

2. Odour: none.

3. Appearance/ feel: thick sticky and, gummy.

4. Fracture: crystalline.

5. Loss on drying

The loss on drying was found to be less than 8 % w/w.

6. Ash value

Percentage of ash content was found to be less than 7 % w/w and 2 to 8 % w/w of gum.

7. pH of gum solution

Solutions have pH 6.0 to 6.5.

8. Viscosity measurement

The increased concentration of gum showed good viscosity and thickness in the solution thus, can be used as a viscosity enhancer in the formulations.

Due to its highly viscous nature, it can be used as a suspending agent in formulation of Suspension.

It can also be used as binding agent to formulate sustain release tablets.

The gum solution is also used in the paste form to make thin film forming gels for topical application.

9. Melting point

Melting point of pure extract of *Aegle marmelos* gum was observed to be 91.0°C to 93.0°C.

3.2. General evaluation parameter for gums and polymers along with resins

3.2.1. Pre-compression parameters

3.2.1.1. Bulk density

Bulk density was calculated to be 0.36 - 0.43 gm/ cm^3 indicating good flow properties.

3.2.1.2. Tapped density

Tapped density was calculated to be 0.43 - 0.67 gm/cm3 indicating good flow properties.

3.2.1.3. Carr's index (compressibility index)

Carr's index was observed to be in the range of 15.6- 25.21 % indicating the powder blend have the required flow property for compression which is suitable for content uniformity and less weight variation in final tablets.

3.2.1.4. Hausner's ratio

Hausner's ratio was calculated to be 1.30-1.35 indicating good flowability.

3.2.1.5. Angle of repose

The values calculated for angle of repose were found to be in the range of 25.600 to 36.550 indicating good flow properties.

3.2.1.6. Evaluation of formulations

The formulations were tested for clarity and was found to be clear homogeneous gel, pH was found to be 7.2 pH, and viscosity was found to be quite consistent. Clarity was checked visually and pH of the formulations was checked using digital pH meter.

3.2.1.7. Drug content: The Drug content of formulations is shown in table 3 below. The percentage drug content of all prepared dermal formulations was found to be in the range of 98-100 %. Therefore, uniformity of content was maintained in all formulations.

3.2.1.8. Table 3: Per cent drug content of antifungal dermal gel.

Sr. no.	Formulation code	Drug content (%) (±S.D.)
1.	F1	98.00±0.1
2.	F2	98.10±0.12
3.	F3	98.17±0.15
4.	F4	98.14±0.17
5.	F5	98.19±0.19
6.	F6	100.12±0.16
7.	F7	98.19±0.19
8.	F8	98.17±0.15
9.	F9	100.00±0.20

3.2.1.9. Drying time: The drying time or film formation time for formulations F1 to F9 has been tabulated in table 4.

Sr. no.	Formulation code	Drying time in minutes.
1.	F1	5 min 15 sec ±5 sec
2.	F2	5 min 30 sec ±5 sec
3.	F3	5 min 25 sec ±5 sec
4.	F4	7 min 17 sec ±5 sec
5.	F5	7 min 50 sec ±5 sec
6.	F6	8 min 40 sec ±5 sec
7.	F7	8 min 54 sec ±5 sec
8.	F8	12 min 30 sec ±5 sec
9.	F9	20 min 35 sec ±5 sec

3.2.1.10. Integrity of formulation on skin: The integrity of the formulations on the skin in the form of a thin, almost invisible film was evaluated for formulations F1 to F9. The results of the test have been tabulated below.

3.2.1.11. Table 5: Results for integrity of film after 24 hours.

Sr. no.	Formulation code	Integrity of film after drying.
1.	F1	Scaly and Scabrous.
2.	F2	Scaly and Scabrous.
3.	F3	Scaly and Scabrous.
4.	F4	Scaly and Scabrous.
5.	F5	Scaly and Scabrous.
6.	F6	Good.
7.	F7	Good.
8.	F8	Excellent.
9.	F9	Excellent.

3.3. In-vitro drug release study (diffusion study)

3.3.1. The In-vitro drug release study of formulations in table 6.

Cumulative Drug Release (%) (±S.D.)									
Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.25	9.01	11.65	23.96	25.87	27.88	22.7	24.37	36.50	25.76
	±0.02	±0.01	±0.02	±0.01	±0.04	±0.03	±0.05	±0.04	±0.01
0.5	10.8	17.37	24.53	31.88	30.29	28.30	31.62	44.53	31.57
	±0.02	±0.02	±0.02	±0.42	±0.03	±0.07	±0.02	±0.03	±0.01
1	18.16	30.63	35.43	37.50	40.59	36.23	40.82	47.18	38.56
	±0.07	±0.05	±0.01	±0.05	±0.08	±0.01	±0.03	±0.02	±0.01
2	24.37	40.03	41.59	45.95	50.03	42.10	43.52	54.43	47.30
	±0.01	±0.01	±0.02	±0.02	±0.03	±0.02	±0.04	±0.04	±0.03
3	36.10	46.88	43.35	53.22	56.29	46.13	48.20	59.39	51.34
	±0.02	±0.03	±0.03	±0.05	±0.06	±0.03	±0.04	±0.02	±0.04
4	42.84	56.26	46.35	58.51	63.03	55.15	51.87	62.64	57.42
	±0.06	±0.04	±0.04	±0.03	±0.04	±0.09	±0.06	±0.03	±0.03
5	50.15	59.05	51.78	62.52	72.14	62.41	55.50	63.67	62.56
	±0.02	±0.07	±0.05	±0.06	±0.02	±0.25	±0.02	±0.05	±0.03
6	61.14	68.83	60.89	72.36	83.04	66.14	62.98	74.75	65.55
	±0.02	±0.05	±0.05	±0.05	±0.05	±0.03	±0.04	±0.02	±0.05

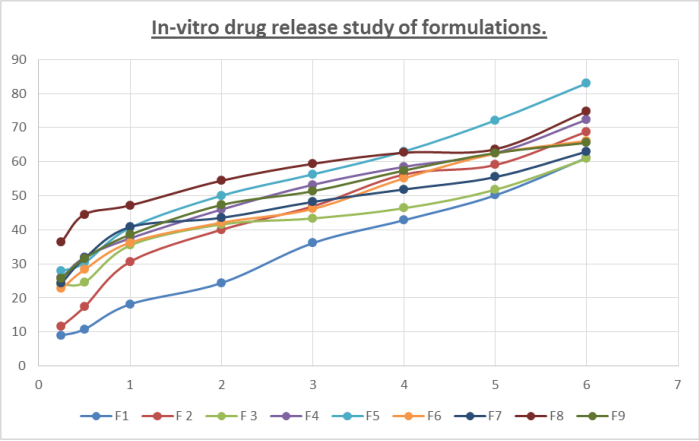

Figure 7: In-vitro drug release study of formulations.

Time.	F1	F 2	F 3	F4	F5	F6	F7	F8	F9
0.25	9.01	11.65	23.96	25.87	27.88	22.7	24.37	36.5	25.76
0.5	10.8	17.37	24.53	31.88	30.29	28.3	31.62	44.53	31.57
1	18.16	30.63	35.43	37.5	40.59	36.23	40.82	47.18	38.56
2	24.37	40.03	41.59	45.95	50.03	42.1	43.52	54.43	47.3
3	36.1	46.88	43.35	53.22	56.29	46.13	48.2	59.39	51.34
4	42.84	56.26	46.35	58.51	63.03	55.15	51.87	62.64	57.42
5	50.15	59.05	51.78	62.52	72.14	62.41	55.5	63.67	62.56
6	61.14	68.83	60.89	72.36	83.04	66.14	62.98	74.75	65.55

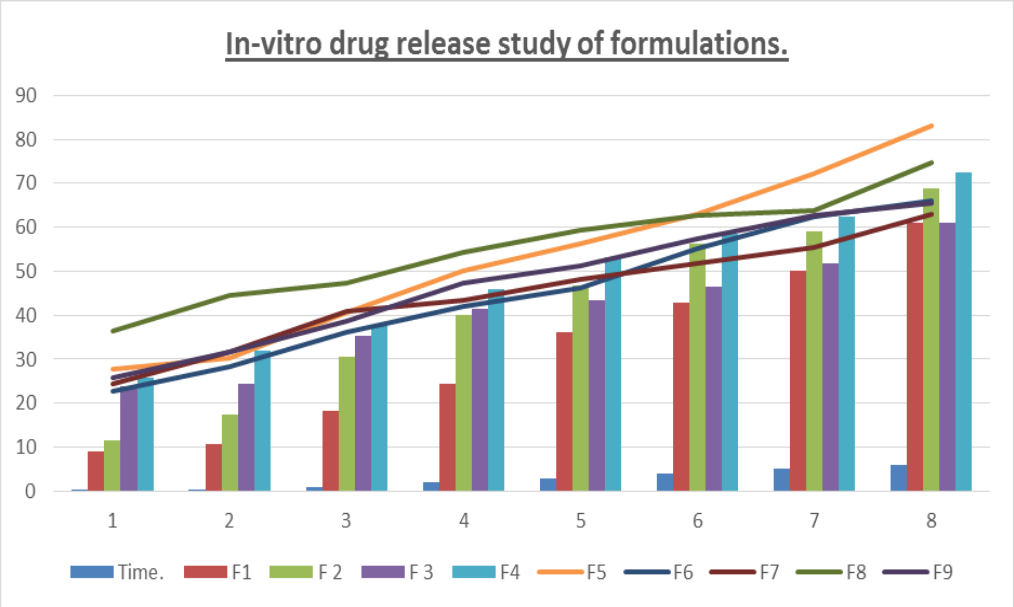

Figure 8: Graph of in-vitro drug release study of formulations.

4. CONCLUSIONS

The present investigation revealed high super potential of *Aegle marmelos* gum to form thin film forming gel. The isolation process was easy and the formulation stability is suitable to form a good quality antifungal product to cure the fungal disease using 1% clotrimazole. The release pattern of the formulation was studied in-vitro and was found to be suitable to use it as a sustain release type of medication preparation.

The cause of adhering the formulation or wearing the formulation of skin for longer period of time is very important to cure topical skin infections. Therefore, this type of formulations is very suitable to give 100% benefit in cause of therapeutics; formulation therapeutics. Also, the gum supports the development of fast drying new topical drug delivery method and suits an excellent formulation polymeric base that can carry drug delivery at the targeted site of action.

In comparison to the gum *Arabica*; *Agele* gum had good drying time with much ability to form thin films and be adherent to then surface without forming scales and flake out from the skin or the surface.

Another advantage of choosing *Agele* gum was its low content of sugars than that of gum *Arabica* that help the medication to sustain over the infection and be an adjuvant in treatment of it. Also, gum had poor drying time and also decomposes on long duration of storage.

5. Other notable usage: The hard shell of the fruit or its rind is also capable in treatment of fungal infection of derma. Thus, antifungal in nature and, is used as a tincture in treatment of topical mild fungal infections or wash the fungal infected part or have swab of it along 1% aspirin solution in fungal treatment or as a mild face wash in case of acene and topical fungal infection along with other natural herbs.

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7. Conflict of interest

None. The researcher declares that there is no conflict of interest in the publication of this research paper and, that all the individual permissions had been granted to publish this research work either individually or with publishing partners. The research was carried out during the year 2013-2015, before publishing this research work, it was under study and investigation for analysing and obtaining significant scientific information on the ability and stability of polymer as a source of drug delivery in critical and acute cases of fungal infections in both humans and animals. The entire research study was carried out to meet the requirement of minor research work that was a part of curriculum and, required to be produced to fulfil the grades in: SEM-1 and, SEM-2, examination.

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