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FORMULATION DEVELOPMENT AND EVALUATION OF HERBAL EFFERVESCENT TABLET

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AIM

The main purpose of this research is to prepare the formulation of GRDDS acidity tablet frombael plant which has the medicinal property and is very helpful for stomach/gastric diseases.

OBJECTIVES

1. To perform literature review about different activities of Bael plant.
2. To collect fruit pulp from unripe fruit of Bael plant and drying along with powder preparation.
3. To perform phytochemical analysis of pulp powder.
4. To select excipients and prepare effervescent tablet from pulp powder.
5. To study powder flow properties.
6. To perform different physicochemical evaluation of compressed tablets.

ABSTRACT

Effervescent tablets were designed to produce solutions that release carbon dioxide simultaneously. Usually, these tablets are prepared by compressing the active ingredients. Themain advantages of effervescent tablets are quick production of solution. Thus, it is faster and better to absorb. Effervescent tablets are produced and controlled same as conventional tablets. These controls are included physicochemical properties such as hardness, weight variation, friability, solution time, pH and content uniformity.

KEYWORDS: Aegle marmelos, Beal, gastrointestinal, GRDDS, GIT, peptic ulcer, pylori, effervescent, herbalmedicine, fruit.

INTRODUCTION

•Peptic ulcer is a common disease caused by damage to the lining of the stomach. Causes of peptic ulcers are gastric acid, Pylori, blood flow to the mucosa, mucus, bicarbonate. A stomachulcer is also called a stomach ulcer. There are three types of stomach ulcers. Gastric or peptic ulcer: This type of ulcer occurs in the stomach Sore throat. This type of ulcer develops in thethroat Duodenal ulcers.

•This type of peptic ulcer grows in the upper intestine of the small intestine, called the duodenum. Symptoms of peptic ulcers changes in appetite, nausea, weight loss, vomiting and indigestion the drug Delivery System.

Advantages

1. Release of the active ingredient in the small intestine with a short absorption window.
2. In the treatment of the upper part of the small intestine, for example gastric ulcer, a longer residence time in the stomach may help with topical intervention.
3. Need a drug that is easily absorbed into the gastrointestinal tract after release, for example improved bioavailability B.Cyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.
4. Physician compliance with 1-day treatment.

Disadvantages

1. Drug delivery requires high levels of water to float in the stomach and work effectively to release the drug.
2. These forms of procedure are not suitable for GIT drug solubility and stability issues.
3. Product that cause gastric mucosa inflammation are not suitable candidate for GRDDS product.

Antidiabetic

Aegle marmelos has been used as a herbal medicine for the management of diabetes mellitus in Ayurvedic, Unani and Siddha systems of medicine in India. Bael extract, when administered at a dose of 250mg/kg of body weight, shows better result than glycenamide (antidiabetic drug). This antidiabetic effect may be due to the coumarins present in the fruit. Aqueous extract of bael seeds reduces blood glucose level in case of severe diabeticpatients.

Antioxidant

Bael fruit has proven to show antioxidant activity. On administration of Bael fruit extract of 250mg/kg of body weight, shows better results than glibenclamide (36µg/kg). The antioxidant activity may be due to presence of flavonoids, alkaloids, sterols, tannins, phlobatannins and flavonoid glycosides.

Antibacterial activity

➢ Beal is said to provide excellent protection against organisms responsible for a variety of diseases, including antibacterial, antitumor, antiviral, antiinflammatory, and antifungal.

➢ Malmerid extracted from Beal showed antibacterial activity when tested with Cox Sucky virusB1-B6 in the assay described by the 96-hour plaque inhibition assay.

➢ It has no toxic effects on host cells and the extract has been shown to have antiviral activity.

➢ Compared to the antibacterial drug ribavirin, Marmelid was found to have more potential activity.

➢ The viral killing activity of malmerid and extract follows inhibition at an early stage of thereplication cycle, such as adsorption and penetration.

Anti-ulcer activity

➢ The ulcer is nowadays a very common disease of the gastrointestinal tract. Reasons behind ulcer may be listed as oxidative stress, Helicobacter pylori bacteria when gastro protection is reduced or mucosal flow of blood get inhibited.

➢ Luvangetin, a pyranocoumarin present in bael seed shows protective activity against aspirin-induced and pylorus-ligated gastric ulcers experimented on rats.

➢ Another study reveals fruit pulp extract when used in treating albino rats there is a fall in mucosal thickness, catalase activity, and superoxide dismutase and also in glut- thione level.

Antifertility

Ethanolic extracts of leaves of A. marmelos had a considerable effect on the motility of sperm. It was also proposed that an increase in concentration of the extracts decreased the motility of sperms.

Toxicological

studies44 Total alcoholic, total aqueous, whole aqueous and methanolic extracts were collected from the leaves of A. marmelos but not reported any adverse effect up to a

maximum dose of 250mg/kg body weight.

Constipation

Ripe fruit has been considered as the best of all known laxatives. In case of constipation, administration of ripe fruits cleans and tones up the intestines. Its regular use for 2-3 months has been effective in removal of even old and accumulated fecal matter from bowels. For best results, the pulp of ripe fruit is crushed and made into a sherbet. Seeds are removed for reducing the bitterness and sugar and/or milk can be added to make it more palatable.

Gynecological disorders

The regular consumption of Bael helps to prevent gynecological related issues.

Digestive Disorders

It supports intestinal biological formulations and protects the digestive system from ulceration, reduces the frequency of Irritable Bowel Syndrome (IBS), intestinal spasm thus beneficial in treating of diarrhea, dysentery, and other infections of Elementary canal.

LITERATURE REVIEW

➢ Nature has provided a complete storehouse of remedies to cure ailment of mankind. About 80% of the world's population depends wholly or partially on traditional medicine for its primary health care needs.[1],[2] According to a survey (1993) of World Health Organization, the practitioners of traditional system of medicine treat about 80% of patients in India, 85% inBurma and 90% in Bangladesh.

➢ Balasubramanian et al. showed that A. marmelos extracts against white spot syndrome virusin shrimp at the concentration of 150 mg/kg of animal body weight.

➢ In 2004, Jagetia et al. showed that intraperitoneally used hydroalcoholic leaf extract of A. marmelos in mice increases its survival rate when the mice are exposed to lethal dose of 10 Gyof g-radiation.

➢ Abdulla Kasim et al.: The fruit is also reported to have potent free-radical scavenging and antioxidant effects. Recently, Abdullakasim et al. have observed that A. marmelos fruit drink had high quantities of total phenolic compounds and was a good antioxidant.

➢ Gupta et al. showed that A. marmelos fruit extracts have chemopreventive role against DMBA induced skin carcinogenesis in mice.

➢ Shukla et al. evaluated the antipyretic property of A. marmelos on Brewer's yeast induced pyrexia in albino rats. They reveal that the ethanolic extract, at dose of 200 mg/kg body

weight and 400 mg/kg body weight, produced significant reduction in elevated body temperature in adose dependent manner. This antipyretic effect of extracts was comparable to that of paracetamol (100 mg/kg body weight).

➢ Kaur et al.: Antigenotoxic activity of A. marmelos fruit extracts were tested by Kaur et al. using E. coli PQ37 (SOS chromotest) and the peripheral human blood lymphocytes (Comet assay).

Ecology and Distribution

The believed origin of bael is India. The species reached the nearby countries in prehistorical times and recently to the other faraway lands through human movements. The bael trees thrive well in dry, mixed deciduous, and dry dipterocarp forests and soils of India, Sri Lanka, Thailand, Pakistan, Bangladesh, Myanmar, Vietnam, the Philippines, Cambodia, Malaysia, Java, Egypt, Surinam, Trinidad, and Florida.

Bael occurs in India since 800 B.C. as a crop according to the historical reports. Bael is a subtropical species, although it can grow well in tropical environments. Bael can thrive well in high altitude as high as 1,200 m and withstand without any significant growth retardation at 50°C and −7°C. In the prolonged droughts, fruiting may cease, but the plant can survive with shallow soil moisture. Bael trees generally require well-drained soil (pH: 5–8), but many studies and grower-reports suggest that it can grow equally well in alkaline, stony, and shallow soils.

Bael grows well and produces bountiful harvests of fruits in the “oolitic-limestone” soils of southern Florida. In India and Sri Lanka, bael is famous as a fruit species, which can grow in verytough soils where other trees and other crops cannot grow.

Botanical Description

The comprehensive descriptions of the biological features of bael are available. The size and the architecture of the bael tree are highly variable depending on the soil and climatic factors; however, the essential botanical features remain constant regardless of the climatic factors. From an agricultural standpoint, growers must prune and manage the tree to a convenient size and maintain a suitable number of branches for maximum fruit production.

DRUG AND EXCIPIENT PROFILE

1. BAEL FRUIT PULP

Scientific Classification[25]

- Kingdom- Plantae.
- Order- Sapindales.
- Family- Rutaceae.
- Subfamily-Aurantioideae.
- Genus- Aegle.
- Species- Aegle Marmelos.
- Botanical name- Aegle marmelos.

PLAN OF WORK

1) Literature survey.
2) Selection of drug and excipient.
3) Procurement of drug and excipient.
4) Experimental work Phytochemical analysis of drug. Pre-compression study of drug and excipient.

a. Particle size analysis
b. Flow ability
c. Angle of repose
d. Tapped density
e. Bulk density
f. Hauser's ratio
g. Compressibility Index/ Car's Index

5) Evaluation Post-compression tests

a. Measurement of tablet hardness
b. Measurement of tablet thickness
c. Friability
d. Evaluation of weight variation
e. Measurement of effervescent time
f. Determination of effervescent solution pH

6) Data analysis
7) Result and conclusion.

Macroscopic Characters

A small to medium-sized aromatic tree, deciduous; stem and branches, light brown to green; strong auxiliary spines present on the branches; the average height of tree, 8.5 meters.

Leaves

are alternate, pale green, trifoliate; terminal leaflet, 5.7 cm long, 2.8 cm broad, having a long petiole; the two lateral leaflets, almost sessile, 4.1 cm long, 2.2 cm wide, ovate to lanceolate having reticulate pinnate venation; petiole, 3.2 cm long.

Leaflets

Are ovate or ovate-lanceolate, margins crenate, apex acuminate, glabrous and densely

minutely glandular-punctuate on both surfaces; lateral leaflets to 7 cm long and 4.2 cm wide, petiolules 0-3mm long.

Flowers

Greenish white, sweetly scented, bisexual, actinomorpbic, ebracteate. hypogynous, stalked; stalk, 8 mm long; diameter of a fully open flower,; flowers, borne in lateral panicles of about 10 flowers, arising from the leaf axil; calyx, gamosepalous, five-lobed, pubescent, light green, very small in comparison with petals; corolla polypetalous, with 5 petals, imbricate, leathery, pale yellow from above and green from beneath, length 4 mm; androecium, polyandrous, numerous, basifixed, 4 mm long, dehiscing longitudinally; gynoecium, light green, 7 mm long, having capitate stigma and terminal style.

Stamens

Numerous; another elongate, apiculate; filaments free or fascicled, inserted round an inconspicuous disk. Ovary ovoid, cells 10-20; style terminal, short, deciduous; stigma capitate; ovules numerous, 2-seriate.

Fruits

yellowish green, with small dots on the outer surface, oblong to globose, 5.3 cm to 7 2 cm in diameter; weight, 77.2 g; volume, 73.7 ml; pulp, yellow and mucilaginous, the pulp of dried fruits retains its yellow, and also remains intact; rind woody, 4 to 5 mm thick.

Seeds

numerous, embedded in the pulp, oblong, compressed, white, having cotton-like hairs on their outer surface. seeds numerous, oblong, compressed, embedded in sacs covered with thick, orange coloured sweet pulp root bark is 3 to 5 cm thick covered, with creamy yellowish surface. It has a firm leathery texture, a sweet taste and fracture is fibrous. Stream bark is extremely gray and internally cream in colour. The outer surface is rough warty due to a number of lenticels, ridges and furrows. It is 4-8 mm thick, film in texture and occurs as flat or channeled pieces6. The fracture is tough and gritty in outer region and fibrous in the inner.5The taste is sweet and there is no characteristic odour.

Minerals and Vitamins

Bael fruit is a rich source of a variety of nutrients that are useful for human health since it includes a number of vitamins and minerals. Because it is abundant in vitamins, including

vitamin A, vitamin B complex, and vitamin C, bael has been discovered to work as an antioxidant, thus preventing rancidity and color loss. The minerals reported from the part of bael include calcium, iron, phosphorus, potassium, and salts. Kumar et al.[26] reported that unripe fruit is more beneficial for medicinal purposes than ripe fruit. It includes mineral (1.9%), potassium (610 mg), phosphorus (52 mg), calcium (80 mg), fiber (2.9%), carotene (55 mg) and protein (1.6%), in fruit juice. In another study, it was found that bael fruit nutrients are extremely beneficial for human health, and this is already proved by various researchers by conducting various investigations on bael fruit. The main constitution of A. marmelos nutrients is fatty acids, vitamins, glucose, amino acids, and minerals. It can prevent color loss and rancidity because it contains a valuable amount of vitamin A (55 mg), vitamin C (8 mg), and vitamin B, which can act as a potential antioxidant agent. Fruit pulp of A. marmelos comprises of calcium (80 mg), mineral content (1.7%), phosphorous (52 mg), copper (0.21 mg), potassium (610 mg), and iron (0.60 mg/100 g). The calorific value of bael fruit (88 cal/100 g) is higher than that of mango (36 cal/100 g), apple (64 cal/100 g), and guava (59 cal/100 g).[38,40] In a separate study, it was found that it is also high in vitamins such as riboflavin (1190–1200 mg/100 g), vitamin B1 (0.13 mg), vitamin A (55 mg), vitamin B2 (1200 mg), ascorbic acid (8 mg/100 g), vitamin C (8 mg) and thiamine (0.13 mg) .In another study, bael fruit pulp was reported for numerous vitamin concentrations, including vitamin B1 (0.16 mg%), vitamin C (73.2 mg%), vitamin B2 (0.18 mg%), and vitamin B3 (0.87 mg%). According to vitamin analysis, the bael is recognized as a suitable source of ascorbic acid and several vitamins of the B group. Vitamin C concentration was found to be 73.2 mg/100 g, which was significantly higher than that found in Thai bael fruit (26.17 mg/100 g) and bael fruit growing under Indian conditions (40mg/100 g). Vitamin C levels in unripe bael fruit are relatively high (620 mg/100 g) Furthermore, vitamin C (8–60 mg), riboflavin (1.19 mg), vitamin A (55 mg), thiamine (0.13 mg), potassium (600 mg), calcium (85 mg), niacin (1.1 mg), and phosphorus (50 mg) are all known to be presentin bael fruit.

Diagnosis And Treatment

Polycystic kidney disease is diagnosed with certain blood tests and procedure which includes ultrasound, CT scan and MRI scan that can detect the size and number of cysts in the kidneys. Treatment of the disease depends on its type and level of severity. Treatment of dominant polycystic kidney disease includes painkillers, medication to regulate the blood pressure and kidney transplant in case of kidney failure. Children affected with recessive polycystic kidney disease need a kidney transplant in case of excess enlargement of kidneys. They are given

nutritional therapy to restore normal growth.

Physicochemical prameters of Aegle marmelos

Bael gets its medicinal values on basis of the various bioactive compound present in it like alkaloids, coumarins, polysaccharides, essential oils etc. The other nutritional constituents present in Bael fruits are water, sugar, protein, fiber, fat, calcium, phosphorus, potassium, Iron and vitamins (Vit A, Vit B, Vit C and Riboflavin). The major Alkaloids present in Bael are aegelin, aegelinine, fragine, o-methyl halforodinine, o-iso pentanyl halfordinol, ethyl cinnamide, ethyl cinnamide. It contains 9% tannin in the pulp of wild fruits and its percentage is less in cultivated type. Tannins are also present in leaves as skimmianine. The essential oil of the leaves contains d-limonene, 56% a-d-phellandrene, cineol, citronellal, citral; 17% pcyrnene, 5% cumin aldehyde. The gum enveloping the seeds is most abundantin wild fruits and especially when they are unripe. The coumarins present in Bael fruit include marmelosin, marmesin, imperatorin, marmin, alloimperatorin, methyl ether xanthotoxol, scoparone, scopoletin, umbeliferone, marmelide and marmenol. Marmelosin aresinous substance is most probably the therapeutically active principle of Bael fruits.

Ascorbic acid, sitosterol, crude fibers, α-amyrin, crude proteins are other minor constituent. The various polysaccharides present in Bael are Galactose, arabinose, uronic acid, L-rhamanose. Carotenoids are principle pigment responsible for imparting pale yellow colour to fruit.

Experimental work

Ingredients

Sr no.	Ingredient	Quantity	Role
1.	Bael fruit pulp powder	250 mg	API
2.	Sodium bicarbonate	44 mg	Alkali compound
3.	Citric acid	20 mg	Acid compound
4.	Talc	6 mg	Lubricant
5.	PEG 6000, Mannitol & water	30 mg	Binder
6.	Lemon essence	qasr.	Flavouring agent

Table.1 Ingredients, quantity and their role

Methods of preparation of effervescent tablet

1. Direct Compression:
2. Fusion method.

Fig.2 Tablet punching machine

Antimicrobial activity

The antibacterial activity of the Methanol, chloroform and aqueous extracts from the fruit of A. marmelos was studied using disc diffusion method against one gram positive bacteria (S. aureus) and two gram negative bacteria (P. aeruginosa and E. coli).

Preparation of Plant Extract

An extract is a mixture of phytochemicals from any plant which is obtained by extraction of specific parts of the plant. Aegle marmelos fruits were washed with distilled water and kept in incubator at 37°C for 3-4 days and grinded into fine powder. Now plant material was dissolved in 70% ethanol and 80% methanol, Hot water (1:10); 1 g sample should be dissolved in 10 ml of solvent. Mixtures were kept in the dark for 3 days at room temperature in sterilized beakers wrapped with aluminum foil to avoid evaporation and exposure to sunlight was avoided. After 3 days, mixtures were filtered through Whitman no.1 filter paper

and kept it in incubator at 37°C till all solvents had completely evaporated from mixtures. Now all mixtures were dissolvedin DMSO (Dimethyl sulfoxide).

Angel of report

Sr. no.	Angle of repose (θ)	Flowability
1.	<20	Excellent
2.	20-30	Good
3.	30-35	Passable
4.	>40	Very poor

Table.2 Angle of repose & flowability

Post compression Tests: 1.Measurement of Tablet Hardness: 2.Measurement of Tablet Thickness: 3.Friability: 4.Evaluation of Weight Variation: 5.Measurement of Effervescence Time: 6.Determination of Effervescent Solution pH.

Fig.Monsanto meter (tablet hardness tester)

Fig. Tablet friability tester

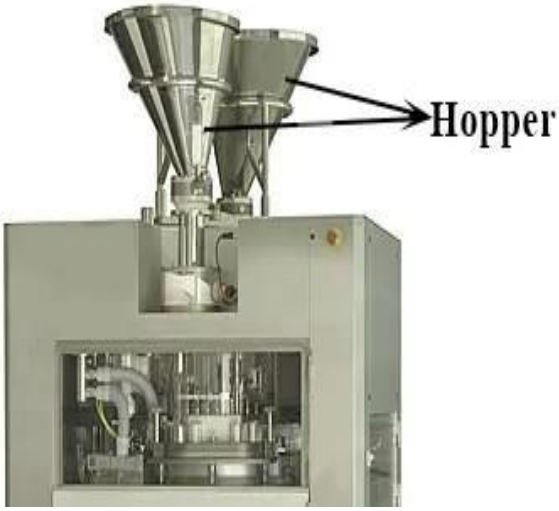
Applications of Tablet Compression Machine

The key application of the Tablet Compression Machine is used to compress the granules or mixture of API and excipients to uniform and predetermined size, shape, and weight of tabletsfor new tablet development and small batch production.

Compress the granules/ powder mix into tablets for pilot-scale and full-scale production.

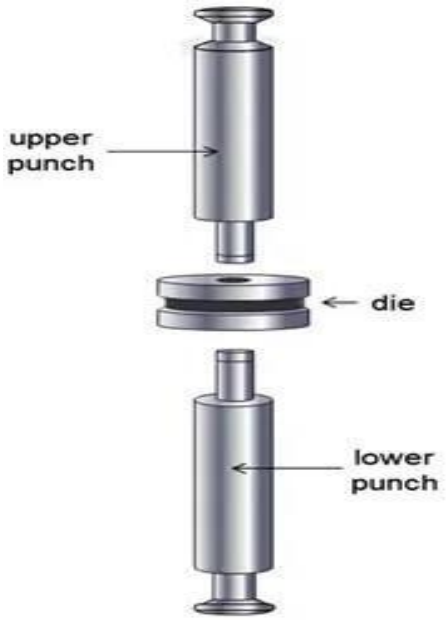
Hopper

The hopper holds and supplies the granules/powder mixture (API and excipient) to the feeder system. It is the input point of powder mix or granules to tablet press for compression of tablets. Granules or powder mix may feed manually or using automated systems.



Die

Die defines the size and shape of the tablet. Powder mix or granules are compressed into the desired size, diameter, and shape of tablets in die bore or die cavity.



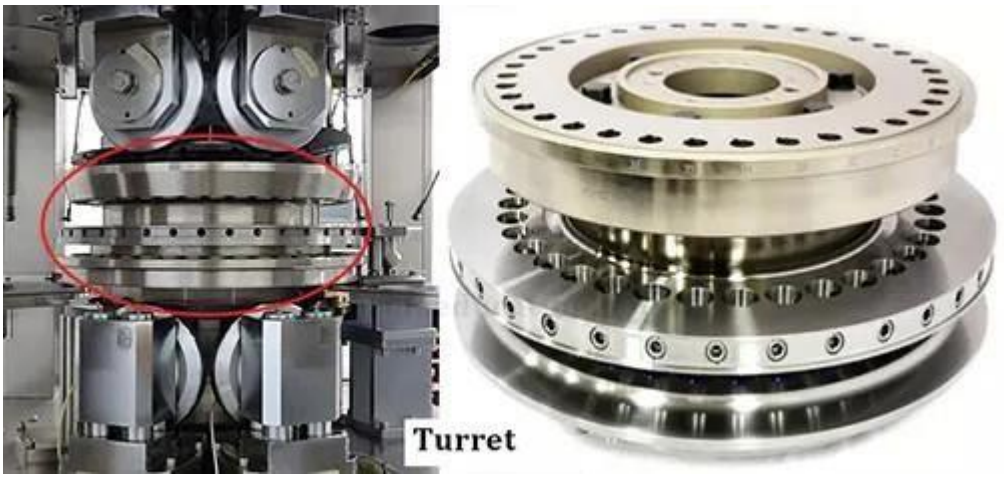
Punch

Two punches (upper and lower) compress the granules/powder mix in the die bore. The lower punch moves upward and the upper punch moves downward and compresses the tablet within the die cavity. Then the upper punch moves upward and the lower punch moves upward.

Turret

Turret hosts the die as well as upper and lower punches on its holes and ensures the position of the die bore and two punches (lower and upper) for the tablet compression process. The

turretis the heart-like part of the tablet press machine.



Compression Rollers

Tablet press machines have rollers that exert a predetermined and sufficient amount of force tocompress the granules into tablets with desired hardness. Most tablet press machines have twosets of compression rollers.

Pre-compression roller

They give the initial compression force. The aim of pre-compression is to eliminate air that could be in the die or granules/powder mix.

Tablet Weight Controller

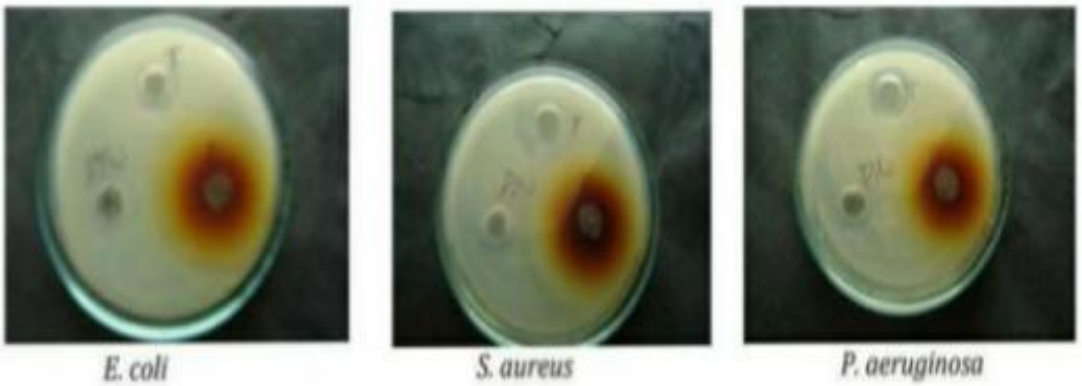
This is used to adjust the volume of the granules to be compressed and so determines the weight of the tablet with the help of different movements of the cam systems, material will flow into the die cavity depending on the position of the punches.

RESULT AND DISCUSSION

Sr. no.	Test	Observation
1	Reducing sugar test	Present
2	Test for saponin	Present
3	Test for tannins	Present
4	Test for flavonoid	Present
5	Test for phenol	Present

Cultures	Zone of inhibition by sample (mm)	Zone of inhibition by tetracycline (mm)
E.coli	14	18.5
P.aeruginosa	17	24.5
S.aureus	13	17

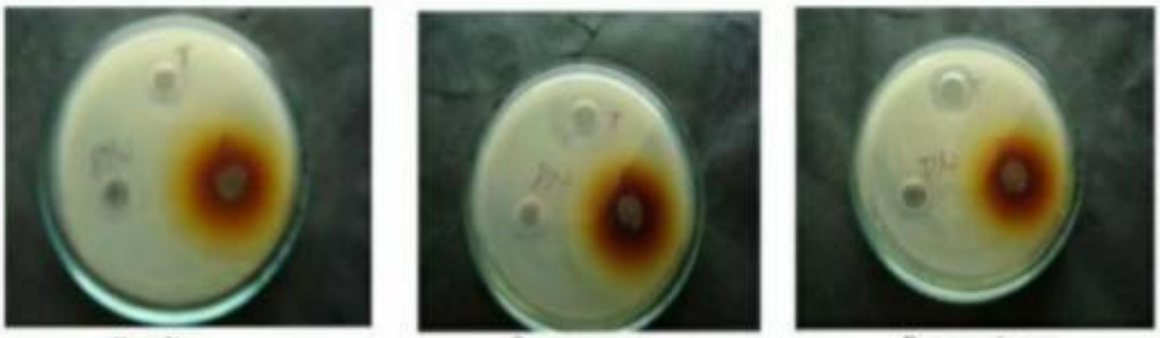
Table.4 Antibiogram of methanolic extract of Aegle marmelos fruits against different pathogens



Antibacterial activity of methanolic extract of fruits

Cultures	Zone of inhibition by sample (mm)	Zone of inhibition by tetracycline (mm)
E.coli	13	15.5
P.aeruginosa	13.5	23
S.aureus	19	16.5

Table.5 Antibiogram of ethanolic extract of Aegle marmelos fruits against different bacterial pathogens



E. coli *S. aureus* *P. aeruginosa*

Evaluation Test	Formulation
Hardness	10 N
Friability	0.94
Tablet thickness	4.13+_0.02
Weight variation	352.30 to 318.72
Effervescent time	4min 10sec
pH	4.8+_0.02

Table 8. Tablet characterization (post compression tests)

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