Product development and standardization of immune enhancing tablets made from crude powder of *Emblica officinalis, Tinospora cordifolia and Terminalia chebula* (Jeewya)

By

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Thesis submitted to the University of Sri Jayawardenepura for the award of the Masters Degree in Food Science and Technology on 2015
DECLARATION

The work described in this project was carried out by me at the Institute of Indigenous Medicine, University of Colombo, under the supervisions of Dr. P.K Perera, Head, Department of Ayurveda Pharmacology and Pharmaceutics, Institute of Indigenous Medicine, University of Colombo and Prof. K.K.D.S. Ranaweera, Department of Food Science and Technology University of Sri Jayewardenepura/Director at Bandaranaike Memorial Ayurveda Research Institute. This thesis has not been submitted to any University for another degree.

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ACKNOWLEDGEMENT

First and foremost I wish to express my gratitude to my supervisors, Professor K.K.D.S. Ranaweera, Professor of Department of Food Science and Technology, University of Sri Jayewardenepura and Director at Bandaranaike Memorial Ayurveda Research Institute and Dr. Pathirage Kamal Perera, Head, Department of Ayurveda Pharmacology and Pharmaceutics, Institute of Indigenous Medicine, University of Colombo for the advices, guidance and suggestions given by them throughout the project. I am grateful to them for providing me with the opportunity to undertake my project work at the Institute of Indigenous Medicine, University of Colombo and for the facilities made available to me to carry out my studies successfully.

I wish to express my sincere gratitude to 4everskin natural PVT Ltd who granted the funds for research works and for giving me their valuable help for successful completion of this task and the staff for their utmost help.

I last but not least deeply appreciate and thank my Mother and my Husband, for the encouragement given by them to me to continue my education.
ABSTRACT

Product development and standardization of immune enhancing tablets made from crude powder of *Emblica officinalis*, *Tinospora cordifolia* and *Terminalia chebula* (Jeewya)

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Combination of dried fruit powder of *Emblica officinalis* (Local name, *Nelli*), dried stem powder of *Tinospora cordifolia*, (Local name, *Rasakida*) and dried fruit powder of *Terminalia chebula* (Local name, *Aralu*) has been used in Sri Lankan Ayurveda for immune enhancing properties in many years form of decoction and ingredients of other formulations. The aim of this study was to formulate ready to use tablets by direct compression method using acacia as a binder. The tablets were evaluated using the necessary official tests viz moisture content, total ash, TLC finger print, weight variation, crushing strength, friability, thickness and disintegration time. Formulated tablet moisture content and total ash values were respectively 8.6% w/w and 5.0%w/w. TLC finger printing showed that similar pattern of Rf values and spots in tablet mixture compare with their raw materials. The formulated tablets complied with British Pharmacopoeia specification for weight uniformity, hardness (≥5 kgf) and tablet friability (<1%). For disintegration test, tablets formulated with acacia at concentrations of 1% w/w also complied with Pharmacopoeia specification. The average tablet weight was 450±0.45 mg. Tablet had a crushing strength and friability of 4.5 kgf and 0.21%, respectively. From the results of disintegration, tablets formulated with acacia at concentrations 1% w/w complied with BP 2009 specification for normal release tablets. When considering all the quality parameters of Jeewya tablets, tablets are in standard quality for human consumption.

Key words: *Emblica officinalis*, *Tinospora cordifolia*, *Terminalia chebula*, tablets
CHAPTER I

INTRODUCTION

Ayurvedic medicine is one of the world’s oldest medical systems. It originated in India more than 3,000 years ago and remains one of the country’s traditional health care systems. Its concepts about health and disease promote the use of herbal compounds, special diets, and other unique health practices.

For the process of rejuvenation, Ayurveda has described a unique therapy viz. Rasayana therapy. Rasayana Stands as an answer to solve the problem of healthful longevity including mental development and resistance against disease. That is why; Rasayanatherapy has been included as one of the eight major divisions of Ashtanga Ayurveda. Rasayana Chikitsa or rejuvenation therapy helps to promote and preserve health and longevity in the healthy, and to cure disease in sick. Drugs described under Rasayana, act on Agni, Dhatu and Srotas level and help in formation of prashasta dhatus maintaining a perfect equilibrium of all the Doshas and Dhatus.

Amalaki (Sinhalese name, Nelli) (*Emblica officinalis*), Guduchi (Sinhalese name, Rasakida) (*Tinospora cordifolia*) and Haritaki (Sinhalese name, Aralu) (*Terminalia chebula*) are the best of plants for the Rasayana described by Charaka and Sushruta where Bala i.e Ojus is involved. Guduchi, Amalaki, and Haritaki are well known rasayana herbs were selected to evaluate their role in boosting the immunity. Amalaki, Guduchi share common properties. Amalaki is best among Vayasthpaka (anti-ageing) herbs. Amalaki, is fortified with Vit-C which is a natural, abundantly available powerful antioxidant, anti inflammatory and free radical scavenger of the metabolism. Guduchi include in almost among all Rasayana remedies in Ayurveda. They possess Tridosha hara, Sheeta Virya, Dahaprashamana, Chakshushya, Keshya, Vayasthapaka, Hridhya, Rasayana, Vrishya, Pramehaghna, Yakriduttejak properties. Guduchi a bitter active principle has anti-inflammatory and hepato-protective properties. It acts on liver, the chief site of metabolism of food and...
drugs, normalizing the elevated transaminases and repletes the hepatocyte glutathione
sod dismutases responsible for scavenging of free radicals.

*T. cordifolia*, an herbaceous vine of the family Menispermaceae. It is
indigenous to the tropical areas of India, Myanmar and Sri Lanka. The plant is a
glabrous climbing shrub found throughout Sri Lanka, typically growing in deciduous
and dry forests. The whole plant is used in traditional medicine for various ailments. *T.
cordifolia* shows anti-inflammatory, analgesic, hepatoprotective and antipyretic actions.
These activities have also been confirmed with animal studies. Ethanolic extract of the
stem exhibits protective effect in carbon tetrachloride induced hepatotoxicity. Aqueous
extract of stem and root of the plant has been used therapeutically because of
immunomodulation property as well as antimalarial and antileprotic activities. The
alcoholic extract of the plant is prescribed in Ayurveda and Allopathy as an immune
promoter. The active principles of *T. cordifolia*, a traditional Indian medicinal plant
were found to possess immune modulatory activities.

*T. cordifolia* is generally prescribed in general debility, diabetes, fever, jaundice,
skin diseases, rheumatism, urinary diseases, dyspepsia, gout, gonorrhoea and
leucorrhoea. The plant is used in Ayurvedic, "Rasayanas" to improve the immune
system and the body resistance against infections. A decoction of the stems, leaves and
roots is used to treat fever, cholera, diabetes, and snake-bites; an infusion of the stem is
drunk as a vermifuge and also to treat sore eyes and syphilitic sores. The stem is
registered in the Thailand Pharmacopoeia, and commonly use in hospital to treat
diabetes. Traditionally an infusion is used to treat fever due to malaria and also in cases
of jaundice and for use against intestinal worms. The leaves are given for the cure of
gonorrhoea. It is also used externally as a cooling and soothing application in prurigo,
eczema and impetigo.

Dried fruits of *E. officinalis* are found both in the wild and cultivated state all
over Sri Lanka.*E. officinalis* fruits are very rich in Vitamin C. Studies indicate that it
does not lose its Vitamin C content on storage. Vitamin C is highly important in the
body mainly due its ability to remove free radicals which are harmful to body mainly
due to its ability to remove free radicals. Emblica being a natural source of vitamin C
serves great purpose. *E. officinalis* is effective in the treatment of Amlapitta (Gastritis)
and in dyspepsia. The fruit exhibit hypolipidaemic and antiatherosclerotic effects in
experimental studies. The fruit extract has antimutagenic activity on certain directly acting mutagens in some strains of *Salmonella typhimurium*.

In Ayurveda, *Haritaki (Terminalia Chebula)* is praised as the best salutary drug which can be used in almost all stages and ages of human life. *T. chebula* (family-Combretaceae) is native to southern Asia. In traditional medicine, mostly the peel of the fruit is used. Researchers have isolated a number of glycosides from Haritaki, including Chebulic acid, Ellagic acid, Chebulinic acid, Gallic acid, Ethyl gallate, and Tannic acid.

Haritaki is one of the most versatile plants having a wide spectrum of pharmacological and medicinal activities. It shows rejuvenative, laxative (unripe), astringent (ripe), anthelmintic, expectorant, tonic, carminative, and appetite stimulant actions. It is used in people who have leprosy (including skin disorders), anaemia, narcosis, piles, chronic or intermittent fever, heart disease, diarrhoea, anorexia, cough and excessive secretion of mucus, and a range of other complaints and symptoms.

These three plant combination widely used in Sri Lankan traditional medicine as form of decoction or herbal tea for various disease conditions. The difficulty of the administration as decoction is the bitter taste. Therefore our research aim was to develop a user friendly dosage forms viz. tablets form using this combination and standardization of this product for human consumption.

The main objective of the research was to develop a solid dosage form (Tablet) using the crude powde of *Emblica officinalis* (Gaertn.) *Tinospora cordifolia* (Thunb., Miers) and *(Terminalia chebula* Retz.) by direct compression method and standardized the product.

Specific objectives was,

1. Drug development and standardization
2. Developing a user friendly patent drug with market feasibility report.

In direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. Direct compression is both efficient and economical, well suited to the production of high quality tablets, which exhibit
hardness, low friability and excellent dissolution rates. As an added benefit, direct compression can improve the physical and chemical stability of tablets as compared to wet granulation.

The presented novel tablet thought to be of better quality and will give answers to many of health problems related to human beings.
CHAPTER II

LITERATURE SURVEY

2.1 ARALU - *Terminalia chebula* (Yellow Myrobalan or Chebulic Myrobalan)

2.1.1 Botanical description

Kingdom: Plantae

Order: Myrtales

Family: Combretaceae

Genus: Terminalia

Species: Chebula

Binomial name: *Terminalia chebula*

Part used: Fruit

Figure 2.1: *Terminalia chebula* Fruit
It is a deciduous tree growing to 30-metre (98 ft) tall, with a trunk up to 1-metre (3 ft 3 in) in diameter. The leaves are alternate to sub opposite in arrangement, oval, 7–8-centimetre (2.8–3.1 in) long and 4.5–10-centimetre (1.8–3.9 in) broad with a 1–3-centimetre (0.39–1.18 in) petiole. Flowers monoecious, dull white to yellow, strong unpleasant odour, borne in terminal spikes or short panicles. The fruit is drupe-like, 2–4.5-centimetre (0.79–1.77 in) long and 1.2–2.5-centimetre (0.47–0.98 in) broad, blackish, with five longitudinal ridges, glabrous, ellipsoid to ovoid drupes, yellow to orange brown in colour, single angled stone. Found in deciduous forests of Indian subcontinent, dry slopes up to 900 meters in elevation.

There are many varieties such as:

- *Terminalia chebula* var. *chebula*.
  
  Leaves and shoots hairless or only hairy when very young.

- *Terminalia chebula* var. *tomentella*
  
  Leaves and shoots silvery to orange hairy.

Seven types are recognized (i.e. vijaya, rohini, putana, amrta, abhaya, jivanti and chetaki), based on the region the fruit is harvested, as well as the colour and shape of the fruit. Generally speaking, the vijaya variety is preferred, which is traditionally grown in the Vindhya mountain range of central India, and has a roundish as opposed to a more angular shape. Aralu fruit is one among the three that constitute Triphala. It is a very famous rejuvenating herb.

**Seven types of Aralu**

Although Bhavaprakasha has explained seven types of Aralu, all are the same *Terminalia chebula*, available in different places.

The seven types explained are –

1. Vijaya – used in all diseases
2. Rohini – fruit is circular in shape – Useful in wound healing.
3. Putana – Having small fruits with big seed – used for external application.
4. Amruta – Having thick fruit pulp, useful for Panchakarma (detoxification)
5. Abhaya – Having five creases in fruit skin, useful in eye disorders
6. Jivanti – Yellow coloured fruit – useful in all diseases
7. Chetaki – Having three creases in fruit skin, useful for purgation

Of these seven types, Vijaya variety is considered as best.

2.1.2 Major chemical constituents

T. chebula contains 32% of tannin. T. chebula are of pyrogallol (hydrolysable) type, they contain 14 components of hydrolysable tannins (gallic acid, chebulic acid, punicalagin, chebulanin, corilagin, neochebulinic, ellagic acid, chebulegic acid, chebulinic acid, 1,2,3,4,6-penta-Ogalloyl-B-D-glucose, 1,6-di-O-galloyl-D-glucose, casuarinin, 3,4,6-tri-O-galloyl-D-glucose and terchebulin). The tannin content varies with the geological variation. Flavonol glycosides, triterpenoids, coumarin conjugated with gallic acid called chebulin, as well as phenolic compounds were also isolated. In addition, ethyl gallate and luteolin were isolated from the fruit of T. chebula. It also consists of nutrients such as vitamin C, protein, amino acids and minerals.

2.1.3 Qualities of T. chebula according to Ayurveda

Rasa – Five tastes except salt
Guna – Laghu – lightness, Rooksha – dryness
Vipaka – Madhura – Undergoes sweet taste conversion after digestion.
Veerya – Ushna – Hot potency

Chewing the T. chebula fruit causes increase in digestion power.
If it is made into a paste and eaten, it clears and cleanses bowels.
If it is steamed or boiled, it becomes absorbent, useful in malabsorption syndrome.
If it is fried and used, it is useful in Tridosha imbalance conditions.
If T. chebula is taken after food, it helps to eliminate all the toxic effects due to food poisoning.
If it is taken along with salt, it balances Kapha.
If taken with sugar, it balances Pitta and if taken with ghee, it balances Vata disorders.

2.1.4 Qualities of different parts of Terminalia chebula fruit

T. chebula seed kernel is sweet, the fiber part is sour, fruit rind is bitter, skin is pungent and seed is astringent in nature.

- **Vranya** - it helps to improve skin complexion
- **Ushna** - hot in nature
- **Sara** - promotes bowel movement
- **Medhya** - improves intelligence.
- **Doshagha** - natural detoxifying
- **Shothanut** - relieves inflammation
- **Kushtanut** - useful in skin diseases
- **Deepana** - improves digestion strength
- **Chakshushya** - good for eyes, improves vision power
- **Rasayana** - anti aging, rejuvenative
- **Ayushya** - improves life expectancy
- **Bruhmani** - nourishing, improves body weight
- **Anulomani** - helps in normalising bowel movements
- **Shwasahara** - useful in Asthma, COPD< wheezing, breathing difficulty
- **Kasahara** - relieves cold and cough
- **Pramehahara** - Useful in diabetes and urinary tract disorders
- **Arshahara** - useful in piles
2.1.5 Medicinal uses of Terminalia chebula

Kushta – skin diseases
Gulma – Abdominal tumor, bloating
Udavarta – bloating of abdomen
Shotha – inflammation
Pandu – Anemia, initial stages of liver diseases
Mada – delirium
Arsha – haemorrhoids
Shiroroga – diseases pertaining to head, headache
Atisara – diarrhoea, dysentery
Arochaka – anorexia
Kasa – cough, cold
Prameha – diabetes, urinary tract disorders
Anaha – bloating
Pleeha – splenomegaly
nava Udara – early stages of ascites
Kaphapraseka – increased salivation due to Kapha dosha
Vaisvarya – hoarseness of voice
kaamala – jaundice
Krimi – worm infestation, infection
Shvayathu – oedema, inflammation
Tamaka – asthma
Chardi – vomiting
Klaibya – impotency
Angavasada – bodyache
Srotovibandha – obstruction to body channels, constipation
Pralepa, Hrudayoraso – stiffness of chest, heaviness of chest
Pramoa – delusion and lack of memory and intelligence
Kushtahara – Useful in skin diseases
Shothahara – relieves inflammation
Udarahara – useful in ascites
Krimihara – useful in worm infestation

- **Use of** T. chebula in **hemorrhoids** – A special quality of T. chebula

Aralu helps to ease bowel movement, one of the complications in hemorrhoids. It helps in reducing the pile mass and reducing / stopping the bleeding.

- **Effect on Tridosha**

Because of sweet, bitter and astringent tastes, it balances Pitta
Because of its pungent, bitter and astringent tastes, it balances Kapha
Because of its sour taste, *Terminalia chebula* balances Vata.

- **Ritu Haritaki**

For the purpose of Rasayana (rejuvenation, anti aging),
T. chebula is taken along with different ingredients in different seasons. This regimen is called as Ritu Haritaki. Ritu means seasons.

Varsha Ritu – In rainy season, given along with Saindhava – Rock Salt.
Sharat Ritu – In Autumn, it is given along with Sharkara – sugar
Hemanta Ritu – In early winter, it is given along with shunti – ginger
Shishira Ritu – In winter, it is given along with Pippali – Long pepper – *Piper longum*
Vasanta Ritu – In Spring, it is given along with Madhu (honey)
Greeshma Ritu – in summer, it is given along with Guda (jaggery)
Antioxidant activity

Antioxidant activity of T. chebula High performance liquid chromatography (HPLC) analysis confirmed that the fruit of Terminalia extract contains phenolic compounds. Since these compounds are good scavengers of free radicals, the aptitude of the extract to deactivate the free radicals

Gallic acid has been found to be a pharmacologically active compound which possesses antioxidative, antimitogenic, anticarcinogenic, anti-inflammatory, and hepatoprotective activities.

4-OMethylgallic acid has been reported to be the major metabolite of gallic acid.

Other minor metabolites such as 3-O-methylgallic acid, 3, 4-O- dimethylgallic acid and pyrogallol (both the conjugated and unconjugated forms) have been reported as well.

Prevention of Inflammation

Glucocorticoids are the most effective drugs for preventing and repressing inflammation caused by mechanical, chemical, infectious and immunological stimuli. One major mechanism for glucocorticoids to exert their activity is through binding to the glucocorticoids receptor resulting in either activation or repression of a large set of glucocorticoids responsive genes. Gallic acid and its metabolites is also a glucocorticoids receptor agonist, which on binding with these receptors shows potent anti-inflammatory activity.

Cosmetic uses

Melanin inhibition depigmenting agent like kojic acid has been found to have carcinogenic effect. So, safe agents like plant extract of T. chebula should be developed as a depigmenting ingredient in cosmetic industry. Extract of T. chebula have great potential as safe effective depigmenting agent. The methanolic extract of T. chebula showed a melanin inhibitory effect higher than 90% at 100 ppm.
Anti-inflammatory activity

Gallic acid (3, 4, 5-trihydroxybenzoic acid) is one of the main endogenous phenolic acids found in T. chebula plant, which possess the anti-inflammatory activity.

Cellular aging

The ethanol extract from the fruit of T. chebula exhibited significant inhibitory effect on cellular aging.

Astringent

In allopathy, T. chebula extract is used as an astringent

Miscellaneous uses

In Unani medical system, it is used as a blood purifier. The pulp of the fruit is given in piles, chronic diarrhea, dysentery, costiveness, flatulence, asthma, urinary disorder, vomiting, hiccup, intestinal worms, ascites and enlarged spleen and liver. The rapid increase in utilization of herbal remedies worldwide has been inspired by several factors, including the concept that all herbal products are safe and effective and so investigation on medicinal plants is increasing day by day. T. chebula is known as the mother of medicine as it has a biodiversity of both nutritional as well as medicinal components.

2.1.6 Terminalia chebula side effects and contra indications

Though Chebulic myrobalan has immense health benefits, due to its astringent and hot nature, it is contra indicated in a few cases.
*Terminalia chebula* is best avoided in

- **Adhva Ati Khinna** – people who have walked for very long and who are tired,
- **Balavarjita** – Who have depleted immunity and strength
- **Rooksha (dry)** – Who are feeling dry and are emaciated
- **Krusha** – having lean body
- **Langhanakarshita** – who have fasted for long
- **Pittadhika** – In people with increased Pitta (burning sensation)
- **Garbhavati** – in pregnant woman
- **Vimuktarakta** – After blood letting treatment, during and soon after menstruation
- **Kshut, Trishna, Ushnarta** – who are having severe thirst, hunger and have got exposed to Sun for long.
- **Ajeerna** – in patients suffering from indigestion
- **Stri madya karshita** – those who are emaciated due to increased sexual activity and alcohol
- **Mukhashosha** – in people having dry mouth
- **Hanusthambha** – in people with neck stiffness
- **Galagraha** – in people with dry throat
- **Navajvara** – in early stages of fever

Though there are a few nutritive health benefits, *Terminalia chebula* is more of cleansing, moisture absorbing, weight reducing in nature. Hence it is advised to avoid during pregnancy.

In most of the contra indications explained above – all have dryness, lack of water supply – kind of symptoms. *Terminalia chebula*, already being astringent, is not advisable because it may further contribute to dryness.
Aralu, is best avoided in infants, up to 5 years of age. It should be given under medical supervision in children.

Single herb usage of *Terminalia chebula* is contra indicated in lactating mother. It may decrease breast milk production.

### 2.1.7 Terminalia chebula Dosage

1 – 6 grams of fruit powder along with required co-drink or ingredient, based on disease, once or twice a day, in single or divided dose, as per discretion of Ayurvedic doctor.

So far no clearly recognized drug interactions about *Terminalia chebula* fruit were reported. And generally it is believed with no toxicity when taken in the recommended doses. Overdose may cause a variety of adverse reactions, such as extreme leanness, serious weakening, loss of energy, and depletion of bodily fluids.
2.2 RASAKINDA - *Tinospora cordifolia*

(English name:-Heart leaved mouseed)

2.2.1 Botanical description

Kingdom: Plantae
Order: Ranunculales
Family: Menispermaceae
Genus: Tinospora
Species: cordifolia

Binomial name: *Tinospora cordifolia*

Part used: Stem

Figure 2.2: *Tinospora cordifolia* Stem
Tinospora cordifolia, which is known by the common names Guduchi and rasakinda, is an herbaceous vine of the family Menispermaceae. It is indigenous to the tropical areas of India, Myanmar and Sri Lanka.

The plant is a glabrous climbing shrub found throughout India, typically growing in deciduous and dry forests. The leaves are heart shaped. The succulent bark is creamy white to grey in color, with deep clefts spotted with lenticels. It puts out long, slender aerial roots, and is often grown on mango or neem tree. Flowers are yellow, growing in lax racemes from nodes on old wood. Fruits are drupes, turning red when ripe.

The bark is gray or creamy white, deeply cleft spirally and longitudinally, with large rosette-like lenticels. The wood is white, soft, and porous, and when freshly cut, quickly assumes a yellow tint. The branches bear smooth, heart-shaped leaves, unisexual greenish flowers in summer, and red berries in winter. Long thread-like aerial roots arise from the branches. The viscous sap is light yellow, with an odor and a nauseating bitter taste.

2.2.2 Qualities of Tinospora cordifolia according to Ayurveda

<table>
<thead>
<tr>
<th>Rasa</th>
<th>Tikta-Bitter, Kasaya-Astringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guna</td>
<td>Laghu-Light, Guru-heavy, Snigdha-Unctuous</td>
</tr>
<tr>
<td>Vipaka</td>
<td>Madhura – Undergoes sweet taste conversion after digestion.</td>
</tr>
<tr>
<td>Veerya</td>
<td>Ushna – Hot potency</td>
</tr>
</tbody>
</table>

2.2.3 Major chemical compounds

A large number of compounds have been isolated from the aerial parts, roots, and whole plant of T. cordifolia. Major constituents include the alkaloids berberine, tinospporin, palmitine, tembetarine, choline, isocolumbin, and tetrahydropalmatine.
The steroids sitosterol, octacosanol, heptacosanol, nonacosan-15-one, hydroxyecdysone, makisterone, giloinsterol, diterpenoid lactones, furanolactones, tinosporon, and columbin; and the glycosides, nonderodane glycoside, furanoid diterpene glycosides, tinocordifoloside, tinocordiside, cordiside, cordifoliside, plamatosides, and syringin.

The active adaptogenic constituents are diterpene compounds, polyphenols, and polysaccharides, including arabinogalactanpolysaccharide.

According to the 1918 United States Dispensatory, the plant has a long history of use in India as a medicine and in the preparation of a starch known as Giloe-ka-sat or as Palo. In Ayurveda, Guduchi is considered one of the most divine herbs.

### 2.2.4 Medicinal uses of *Tinospora cordifolia*

*Tinospora cordifolia* is used for diabetes, high cholesterol, allergic rhinitis (hay fever), upset stomach, gout, lymphoma and other cancers, Rheumatoid arthritis (RA), hepatitis, peptic ulcer disease (PUD), fever, gonorrhea, syphilis, and to boost the immune system.

*Tinospora cordifolia* contains many different chemicals that might affect the body. Some of these chemicals have antioxidant effects. Others might increase the activity of the body's immune system. Some chemicals might have activity against cancer cells in test animals. Most research has been done in test tubes or in animals.

### Major biological properties of *Tinospora cordifolia*

**Immunomodulatory property**

The immuno modulatory property of *Tinospora cordifolia* is well documented. Active compounds 11-hydroxymustakone, N methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside and syringing has been reported to have
potential immunomodulatory and cytotoxic effects. They have been reported to function by boosting the phagocytic activity of macrophages, production of reactive oxygen species (ROS) in human neutrophil cells, enhancement in nitric oxide (NO) production by stimulation of splenocytes and macrophages indicative of anti-tumor effects. Aqueous *Tinospora* extracts has been also reported to influence the cytokine production, mitogenicity, stimulation and activation of immune effector cells. In mice, *Tinospora cordifolia* extracts has been shown to result in up-regulation of IL-6 cytokine, resulting in acute reactions to injury, inflammation, activation of cytotoxic T cells, and B cell differentiation. Active compounds in aqueous extracts like alkaloids, di-terpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds or polysaccharides in experimental rat model have been reported for their cytotoxic action. Dry stem crude extracts of *Tinospora cordifolia* with a polyclonal B cell mitogen, G1-4A on binding to macrophages have been reported to enhance immune response in mice by inducing secretion of IL-1, together with activation of macrophages. Reports on *Tinospora cordifolia* in prevention of oxidative damage also exist. The (1,4)-alpha-d-glucan (alpha-d-glucan), derived *Tinospora cordifolia* have been shown to activate human lymphocytes with downstream synthesis of the pro- and anti-inflammatory cytokines. Synergistic effects of compounds in the immune modulatory activity of *Tinospora cordifolia* are reported\(^\text{16}\).

**Anti-diabetes property**

The stem of *Tinospora cordifolia* is widely used in the therapy of diabetes by regulating the blood glucose. It has been reported to mediate its anti-diabetic potential through mitigating oxidative stress (OS), promoting insulin secretion and also by inhibiting gluconeogenesis and glycogenolysis, thereby regulating blood glucose. Alkaloids, tannins, cardiac glycosides, flavonoids, saponins, and steroids as the major phytoconstituents of *Tinospora cordifolia* have been reported to play an anti-diabetic role.

The isoquinoline alkaloid rich fraction from stem, including, palmatine, jatrorrhizine, and magnoflorine have been reported for insulin-mimicking and insulin-releasing effect both *in vitro* and *in vivo*. Oral treatments of root extracts have been reported to regulate blood glucose levels, enhance insulin secretion and suppress OS markers. Initiation and
restoration of cellular defense anti-oxidant markers including superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione (GSH), inhibition of glucose 6-phosphatase and fructose 1, 6-diphosphatase, restoration of glycogen content in liver was reported in in vitro studies. The crude stem ethyl acetate, dichloromethane (DCM), chloroforms and hexane extracts of Tinospora cordifolia inhibited the enzyme's salivary and pancreatic amylase and glucosidase, thus increasing the post-prandial glucose level and finds potential application in treatment of diabetes mellitus.

**Anti-toxic effects**

* Tinospora cordifolia extracts have been reported to scavenge free radicals generated during aflatoxicosis. It exhibited protective effects by lowering thiobarbituric acid reactive substances (TBARS) levels and enhancing the GSH, ascorbic acid, protein, and the activities of anti-oxidant enzymes viz., SOD, CAT, GPx, Glutathione S-transferase (GST) and glutathione reductase (GR) in kidney. Alkaloids such as a choline, tinosporin, isocolumbin, palmatine, tetrahydropalmatine, and magnoflorine from Tinospora cordifolia showed protection against aflatoxin-induced nephrotoxicity. *Tinospora cordifolia* stem and leaves extract has shown hepatoprotective effect in Swiss albino male mice against lead nitrate induced toxicity. Oral administration of plant extracts prevented the occurrence of lead nitrate induced liver damage.

**Anti-arthritic, anti-osteoporotic effects**

Single or synergistic formulations of *Tinospora cordifolia* with *Zingiber officinale* has been used in rheumatoid arthritis treatment in traditional medicine. *Tinospora cordifolia* have been reported to affect the proliferation, differentiation and mineralization of bone like matrix on osteoblast model systems in vitro and hence finds potential application as an anti-osteoporotic agent. Alcoholic extract of *Tinospora cordifolia* have been shown to stimulate the growth of osteoblasts, increasing the differentiation of cells into osteoblastic lineage and also increasing the mineralization of bone like matrix. Ecdysteroids isolated from the plant have been reported of protein anabolic and anti-osteoporotic effects in mammals. Beta-Ecdysone (Ecd) from *Tinospora cordifolia* extracts have been reported to induce a significant increase in
the thickness of joint cartilage, induce the osteogenic differentiation in mouse mesenchymal stem cells and to relieve osteoporosis in osteoporotic animal models.

**Anti-HIV effects**

TCE has been shown to demonstrate a decrease in the recurrent resistance of HIV virus thus improving the therapeutic outcome. Anti-HIV effects of TCE was revealed by reduction in eosinophil count, stimulation of B lymphocytes, macrophages and polymorphonuclear leucocytes and hemoglobin percentage thus, revealing its promising role of application in management of the disease.

**Anti-cancer effects**

The anti-cancer effects of *Tinospora cordifolia* are mostly studied in animal models. TCE have been shown to have a radioprotective role by significantly increase in body weight, tissue weight, testes-body weight ratio and tubular diameter and inhibit the harmful effects of sub-lethal gamma radiation on testes in male Swiss albino mice. In pre-irradiating mice, TCE significantly affected radiation induced rise in lipid peroxidation and resulted in the decline of GSH concentration in testes. Pre-treatment of HeLa cells by TCE have been shown to decrease the cell viability, increase LDH and decrease in GSH S-transferase activity. Dihydrotestosterone (DHT) in TCE has been reported to stimulate the growth and proliferation of Human LNCaP cells (which are androgen-sensitive human prostate adenocarcinoma cells).

**Anti-microbial activity**

The methanol extracts of *Tinospora cordifolia* have been reported to have potential against microbial infections. The anti-bacterial activity of *Tinospora cordifolia* extracts has been assayed against *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Proteus vulgaris, Salmonella typhi, Shigella flexneri, Salmonella paratyphi, Salmonella typhimurium, Pseudomonas aeruginosa, Enterobacter aerogene, and Serratia marcesenses* (Gram-positive bacteria).
Anti-oxidant activity

The anti-oxidant capacity of *Tinospora cordifolia* stem methanol extracts administered orally increased the erythrocytes membrane lipid peroxide and catalase activity. It also decreased the activities of SOD, GPx in alloxan-induced diabetic rats. *Tinospora cordifolia* Willd. (Menispermaceae) extracts possess possible inhibitors of aldose reductase and anti-oxidant agents[86] thereby reducing chemotoxicity induced by free radicals.

2.2.5 *Tinospora* cordifolia Dosage

300 mg of a standardized aqueous tinospora stem extract taken 3 times daily for up to 6 months.

2.2.6 Contraindications of *Tinospora cordifolia*

Contraindications have not been determined. An in vitro study found an increase in prostate cancer cells; therefore, tinospora probably should not be consumed in this condition until further studies are conducted.

2.2.7 Adverse Reactions of *Tinospora cordifolia*

GI symptoms (anorexia, nausea, vomiting) have been reported. No toxicity has been observed at Ayurvedic therapeutic doses.
2.3 NELLI - *Emlica Officinalis* or *Phyllanthus emblica*

(English Name: Indian Gooseberry)

2.3.1 Botanical description

Kingdom: Plantae

Order: Malpighiales

Family: Phyllanthaceae

Genus: Phyllanthus

Species: emblica

Binomial name: *Phyllanthus emblica*

Part used: Fruit

Figure 2.3: *Phyllanthus emblica* Fruit
Phyllanthus emblica, also known as emblic, emblic myrobalan, myrobalan, Indian gooseberry, is a deciduous tree of the family Phyllanthaceae. It is known for its edible fruit of the same name.

The tree is small to medium in size, reaching 8 to 18 m in height, with a crooked trunk and spreading branches. The branchlets are glabrous or finely pubescent, 10–20 cm long, usually deciduous; the leaves are simple, subsessile and closely set along branchlets, light green, resembling pinnate leaves. The flowers are greenish-yellow. The fruit is nearly spherical, light greenish yellow, quite smooth and hard on appearance, with six vertical stripes or furrows.

Ripening in autumn, the berries are harvested by hand after climbing to upper branches bearing the fruits. The taste of Indian gooseberry is sour, bitter and astringent, and it is quite fibrous.

2.3.2 Qualities of Phyllanthus emblica according to Ayurveda

Rasa – sour (amla), astringent (kashaya), sweet (madhura), bitter (tikta) and pungent (katu) secondary tastes (anurasas)

Guna – light (laghu) and dry (ruksha)

Vipaka – Madhura – Undergoes sweet taste conversion after digestion.

Veerya – cooling (shita)

According to Ayurveda, amla balances all three doshas. While amla is unusual in that it contains five out of the six tastes recognized by Ayurveda, it is most important to recognize the effects of the "virya", or potency, and "vipaka", or post-digestive effect. Considered in this light, amla is particularly helpful in reducing pitta due to its cooling energy. It also balances both Pitta and vata by virtue of its sweet taste. The kapha is balanced primarily due to its drying action. It may be used as a rasayana (rejuvenative) to promote longevity, and traditionally to enhance digestion (dipanapachana), treat constipation (anuloma), reduce fever (jvaraghna), purify the blood.
(raktaprasadana), reduce cough (kasahara), alleviate asthma (svasahara), strengthen the heart (hrdaya), benefit the eyes (chakshushya), stimulate hair growth (romasanjana), enliven the body (jivaniya), and enhance intellect (medhya).

In Ayurvedic polyherbal formulations, Indian gooseberry is a common constituent, and most notably is the primary ingredient in an ancient herbal rasayana called Chyawanprashawaleha. This formula, which contains 43 herbal ingredients as well as clarified butter, sesame oil, sugar cane juice, and honey, was first mentioned in the Charaka Samhita as a premier rejuvenative compound.

2.3.3 Major chemical compounds of Phyllanthus emblica

Experimental studies have shown that amla and some of its phytochemicals such as gallic acid, ellagic acid, pyrogallol, some norsesquiterpenoids, corilagin, geraniin, elaeocarpusin, and prodelphinidins B1 and B2 also possess antineoplastic effects. Amla is also reported to possess radiomodulatory, chemomodulatory, chemopreventive effects, free radical scavenging, antioxidant, anti-inflammatory, antimutagenic and immunomodulatory activities, properties that are efficacious in the treatment and prevention of cancer.

2.3.4 Nutritional value of Phyllanthus emblica

Amla is highly nutritious and is an important dietary source of Vitamin C, minerals and amino acids. The edible fruit tissue contains protein concentration 3-fold and ascorbic acid concentration 160-fold compared to that of the apple. The fruit also contains considerably higher concentration of most minerals and amino acids than apples. Glutamic acid, proline, aspartic acid, alanine, and lysine are 29.6%, 14.6%, 8.1%, 5.4% and 5.3% respectively of the total amino acids. The pulpy portion of fruit, dried and freed from the nuts contains: gallic acid 1.32%, tannin, gum 13.75%; albumin 13.08%; crude cellulose 17.08%; mineral matter 4.12% and moisture 3.83%. Amla fruit ash contains chromium, 2.5 ppm; zinc 4 ppm; and copper, 3 ppm.
2.3.5 Medicinal use of *Phyllanthus emblica*

Dried and fresh fruits of the plant are used. All parts of the plant are used in various Ayurvedic/Unani medicine herbal preparations, including the fruit, seed, leaves, root, bark and flowers.

The fruit is used either alone or in combination with other plants to treat many ailments such as common cold and fever; as a diuretic, laxative, liver tonic, refrigerant, stomachic, restorative, alterative, antipyretic, anti-inflammatory, hair tonic; to prevent peptic ulcer and dyspepsia, and as a digestive. Preclinical studies have shown that amla possesses antipyretic, analgesic, antitussive, antiatherogenic, adaptogenic, cardioprotective, gastroprotective, anemia, antihypercholesterolemia, wound healing, antidiarrheal, antiatherosclerotic, hepatoprotective, nephroprotective, and neuroprotective properties.  

*Phyllanthus emblica* protects cells against free radical damage and provides antioxidant protection

- Amla is used to treat skin disorders, respiratory infections, and premature aging
- Amla is useful in hemorrhage, diarrhea, dysentery, and has therapeutic value in treating diabetes
- Amla has anti-bacterial and astringent properties that help prevent infection and help in the healing of ulcers
- Amla is sometimes used as a laxative to relieve constipation in piles

**Immunity booster:**

One reason for Amla's reputation as a general energy-promoting, disease-preventing
tonic may be its effect on the immune system. Multiple studies have shown significant increases in white blood cell counts and other measures of strengthened immunity in rodents given Amla.

**Respiratory disorders:**

Indian gooseberry is beneficial in the treatment of respiratory disorders. It is especially valuable in tuberculosis of the lungs asthma and bronchitis.

**Diabetes:**

This herb, due to its high vitamin C content, is effective in controlling diabetes. A tablespoon of its juice mixed with a cup of bitter gourd juice, taken daily for two months will stimulates the pancreas and enable is to secrete insulin, thus reducing the blood sugar in the diabetes. Diet restrictions should be strictly observed while taking this medicine. It will also prevent eye complication in diabetes.

**Heart Disorder:**

Indian gooseberry is considered an effective remedy for heart disease. It tones up the functions of all the organs of the body and builds up health by destroying the heterogeneous or harmful and disease causes elements. It also renews energy.

**Eye disorder:**

The juice of Indian Gooseberry with honey is useful in preserving eyesight. It is beneficial in the treatment of conjunctivitis and glaucoma. It reduces intraocular tension in a remarkable manner. Juice mixed with honey can be taken twice daily for this condition.

**Scurvy:**

As an extremely rich source of vitamin C, Indian gooseberry is one of the best remedy
for scurvy. Powder of the dry herb, mixed with an equal quantity of sugar, can be taken in doses of 1 teaspoon, thrice daily with milk.

Ageing:

Indian gooseberry has revitalizing effects, as it contains an element which is very valuable in preventing ageing and in maintaining strength in old age. It improves body resistance and protect the body against infection. It strengthens the heart, hair and different gland in the body.

2.3.6 Phyllanthus emblica Dosage

1 to 3 g of powdered, dried fruit daily

2.3.7 Contraindications of Phyllanthus emblica

Contraindications have not been identified.
2.4 THIN LAYER CHROMATOGRAPHY (TLC)

Reproducible TLC separations can be guaranteed only if standardized adsorption layers are used. Commercially available TLC plates are therefore used. (E.g.: Silica gel 60 F_{254} pre coated TLC plates; Merck, Germany)

Silica gel is an efficient absorbent for the TLC separation of most of the drug extracts. In specific cases Aluminium oxide or cellulose pre coated plates are used.

Special chromatographic rooms are not always needed; most separations can be performed at room temperature. Generally a distance of 15cm is used for the development of a chromatography.

Chromatography solvents

In choosing suitable solvent systems, performance are given to those which are not too complicated in their composition, which process minimal temperature sensitivity and which give exact and sufficient separations of constituents, enough for a significant characterization of drug.

Concentration of substances for TLC

In order to obtain sharply resolved zones, the quantity of material applied to the chromatogram should be as small as possible. Rather large sample of volumes are, however, often necessary for the detection (by colour reactions) of substances that are, present in low concentration: this inevitably results on broadening and over lapping of zones.
Detection methods

For the detection of the main, characteristic compounds of a drug, methods should choose that give the most striking colours. These spots of bands have different Rf values. By calculating Rf value can be identify active ingredients.

Method of calculating Rf value

\[
Rf = \frac{\text{Distance traveled by the spot}}{\text{Distance traveled by the solvent front}}
\]
2.5 AYURVEDIC LITERATURE ON PREPARATION OF TABLETS – VATI KALPANA

2.5.1 Introduction

- Vati kalpana is the outcome of Kalka kalpana.
- Vati usually prepared with the combination of Kastoushadi dravya curna, bhasma, suddha, rasa, uparasa, sadaranarasa, guda, sarkara, guggulu, jala swarasas, mutra etc.\(^25\).

**Basic preparation methods**

- Cooking powder of drugs with jaggery, sugar or guggulu
- Without cooking, by maceration the powder with any liquid like honey and guggulu then rolling in to pills, but varies in size.

**Synonyms of vati**

Gutika
Vati
Modaka
Vatika
Pindi
Guda
Varti

- These names are given according to shape, dose, and root of administration
1. Gutika-
Small circular shape masses

2. Vati-
Flat circular mass (similar to tablet)

3. Guda-
Kashtaoshadi curna is mixed with gudapaka

4. Guggulu-
Kashtaoshadi curna and bhasma etc. are mixed with guggulu

5. Varti-
Long oval shaped solid form
Ex: Guda, Yoni, Sisna, Netra varti

6. Vataka-
Big circular mass

7. Modaka-
Big circular mass (weight around 20g-100g)

Sweetening agents and additives

- Sugar - 4 times to the quantity of powder
- Salt (sahindhavalavana), Ksara (alkalies), guggulu, honey - equal quantity of the powder

This can be changed according to necessity of preparation.
2.5.2 Production flow diagram of Vati/Gutika

- Powdering the raw materials- herbs and minerals separately
- Add sweetening agents and additives
- Cooking or without cooking- Macerate with liquid —up to matrapaka
- Roll in to pills (One Karsha)
- Drying
- Packaging

Figure 2.4: Production flow diagram of Vati/Gutika
Drying of vati can be done by

- Drying in sunlight
- Drying in shade (Chayasuska) - Photosensitive drugs
- After drying it should preserved in glass containers

Final appearance of Vati

- Depends fineness of powder
  
  Coarse powder: vati will be rough and cracked
  
  Fine powder: vati smooth and shine
  
  To make vati round, smooth and shiny they are allowed for rolling over a deep plate smeared with ghee or decoction

Preservation and characteristics of vati

- Vegetable origin pills:
  
  Kept in air tight containers – shelf life 2 years

- Mineral pills: indefinite period
  
  Pills should kept away from moisture

TRADITIONAL WAY OF MAKING PILLS - GUGGULU (A variety of vati kalpana)

General Description:

- Guggulu is an exudate (Niryasa) obtained from the plant Commiphora mukul. Preparations having the exudates as main effective ingredient are known as Guggulu.

- There are five different varieties of Guggulu described in the Ayurvedic text, viz, MahiSāksa and Kanaka Guggulu are usually preferred for medicinal
preparations. MahiSāksa Guggulu is dark greenish brown and Kanaka Guggulu is yellowish brown in color.

- Before using, Guggulu is cleaned in the following manner:
  1. Sand, stone, plant debris, glass etc. are first removed.
  2. It is then broken into small pieces.
  3. It is thereafter bundled in a piece of cloth and boiled in *Dola Yantra* containing any one of the following fluids.
     a. Gomūtra,
     b. Triphalā kaSāya,
     c. Nirgundhi patra Svarasa with Haridrā Cūrna,
     d. Vāsāpatra Kasāya,
     e. Vāsāpatra Svarasa and
     f. Dugdha.

**Process of Guggulu Shodana**

- The boiling of Guggulu in Dolā Yantra is carried on until all the Guggulu passes into the fluid through the cloth. By pressing with fingers, much of the fluid that can pass through is taken out. The residue in the bundle is discarded. The fluid is filtered and again boiled till it forms a mass. This mass is dried and then pounded with a pestle in a stone mortar, adding ghee in small quantities till it becomes waxy.

- Guggulu cleaned as above, is soft, waxy and brown in color. Characteristics of preparations of guggulu vary depending on the other ingredients added to the preparations.

- Guggulu is kept in glass or porcelain jars free from moisture and stored in a cool place. The potency is maintained for two years when prepared with ingredients of plant origin and indefinitely when prepared with metals and minerals.
2.5.3. Basic Machineries used in preparation of vati

Figure 2.5: vati making process (I)
Figure 2.6: vati making process (II)
2.5.4 Methods of tablet formulation

Optional feeders for more ingredients (i.e. lubricant)

API Feeder → Excipient Feeder

Comill (optional)

Blender

Granulator

Dryer

Roller Compactor

Mill

Tablet Press → Coater (optional) → Dissolution

Dry Granulation
Wet granulation
Direct Compaction
Common processing steps

Figure 2.7: Methods of tablet formulation
2.6 STANDARDIZATION (QUALITY CONTROL /QC) OF VATI (TABLETS)

- Quality control refers to a procedure or a set of steps taken during the manufacturing of a product to ensure that it meets requirements and that the product is reproducible.

- It is a small part of QA and it is concerned with sampling, testing and documentation during manufacturing and also after completion of manufacturing.

- Quality control is the monitoring process through which manufacturer measures actual quality performance, compares it with standards and find out the causes of deviation from standard to ensure quality product not once but every time.

2.6.1 Quality control tests for tablets

1. General Appearance:
   - Size, shape, and thickness:
     This is important to facilitate packaging and to decide which tablet compressing machine to use.
   - Organoleptic properties:
     Include color and odor of the tablets.

2. Weight uniformity and content uniformity:
   The tablet should include the correct dose of the drug

   - Dissolution test: Drug should be released from tablet in a controlled and reproducible way.

   - Weight variation, thickness & diameter: The appearance of tablet should be elegant & its weight, size & appearance should be consistent.
• Hardness & friability: The tablet should show sufficient mechanical strength to withstand fracture & erosion during manufacture & handling.

Weight variation

• UNIFORMITY OF ACTIVE INGREDIENTS: It measured to ensure a constant dose of drug between individual tablets. Traditionally, dose variation between tablets is tested in two separate tests.

A) Weigh 20 tablet selected at random, each one individually X1, X2, X3... Xz.

Determine the average weight. \( \bar{X} = \frac{(X_1+X_2+X_3+...+X_z)}{20} \) Not more than 2 of the individual weights deviate from the average weight (\( \bar{X} \)) by more than the % deviation given below & none deviates by more than twice that %.

Limits

Weight of tablet 80 mg or less, then % deviation = ±10%

Weight of tablet >80-<250 mg, then % deviation = ±7.5

Weight of tablet 250 mg or more, then % deviation = ±5%

B) Content uniformity test

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content.

If these conditions are not met, remaining 20 tablet assayed individually and none may fall outside of the 85 to 115% range.
2.6.2 Official standards as per B.P/ I.P. / U.S.P.

- OFFICIAL STANDARDS AS PER B.P. /I.P. / U.S.P. comparison of different pharmacopoeia quality control tests:
  
  BRITISH PHARMACOPOEIA: FOR ALL TABLETS: Content of active ingredients Disintegration Uniformity of content Labeling

2.6.3 Hardness (crushing strength)

- It measures crushing strength property defined as compression force applied diametrically to a tablet which just fractures it.

- This is done to determine the need for pressure adjustments on the tableting machine. Hardness can affect the disintegration. So if the tablet is too hard, it may not disintegrate in the required period of time. And if the tablet is too soft, it will not withstand the handling during subsequent processing such as coating or packaging.

In general, if the tablet hardness is too high, we first check its disintegration before rejecting the patch. And if the disintegration is within limit, we accept the patch.

Procedure

The apparatus consists of 2 jaws facing each other, one of which move towards the other. Measurements are carried out on 10 tablets, taking care to remove all the fragments of the broken tablets before each determination and then take the average hardness.
Normal tablet hardness ranges from 4 – 6 Kg (1 Kg = 10 Newton), however, certain tablets as lozenges and buccal tablets that are intended to dissolve slowly show deliberate higher hardness values.

- **Factors Affecting the Hardness:**
  
  - Compression of the tablet and compressive force.
  
  - Amount of binder (More binder à more hardness).
  
  - Method of granulation in preparing the tablet (wet method gives more hardness than direct method; Slugging method gives the best hardness).

    - Monsanto tester, Pifzer tester, Stong cobb hardness tester are manually used & Heberlien schleuniger, Eweca, Casburt hardness tester are motor driven testers.

Figure 2.8: Tablet Hardness Tester
2.6.4 Friability

The tablet will be subjected to a tumbling motion.

For e.g.: Coating, packaging, transport, which is not severe enough to break the tablet, but may abrade the small particle from tablet surface. To examine this, tablets are subjected to a uniform tumbling motion for specified time and weight loss is measured.

- Friability is a property that is related to the hardness of the tablet & and also add weight variation, content uniformity problems.
- An instrument called Friabilator is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping.

Procedure

1. Weigh 20 tab altogether = W1
2. Put these tablets in the friabilator and adjust the instrument at 100 rpm (i.e. = 25 rpm for 4 min)
3. Weigh the 20 tablets (only the intact ones) = W2
4. Friability (% loss) = It must be less than or equal to1% but if more we do not reject the tablets as this test is non-official.

Perform this test using 20 tablets that were used first in the weight variation test.
2.6.5 Disintegration

- It is the time required for the tablet to break into particles, the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles.

- Liquids used in disintegration: Water, simulated gastric fluid (PH = 1.2 HCl), or Simulated intestinal fluid (PH = 7.5, KH2PO4 (phosphate buffer) pancreatic enzyme +NaOH)

Procedure

U.S.P. METHODS

- FOR UNCOATED TABLETS: Start the disintegration test on 6 tablets. If one or two tablets from the 6 tablets fail disintegrate completely within 30min repeat the same test on another 12 tablet. (i.e. the whole test will consume 18 tablets).

- Not less than 16 tablets disintegrate completely within the time if more than two tablets (from the 18) fail to disintegrate, the batch must be rejected.

- FOR COATED TABLETS: To remove or dissolve the coat, immerse the tablet in distilled water for 5min. Put the tablet in the apparatus in water or HCL for 30min at 37° C (according to the U.S.P). If not disintegrated, put in intestinal fluid. If one or two tablets fail to disintegrate, repeat on 12 tablets. So 16 tablets
from the 18 must completely disintegrate within the time >>if two or more not
disintegrated the batch is rejected.

• FOR ENTERIC COATED TABLETS: Put in distilled water for five minutes to
dissolve the coat. Then put in simulated gastric fluid (0.1M HCL) for one hour.
Then put in simulated intestinal fluid for two hours. If one or two tablets fail to
disintegrate, repeat this test on another 12 tablets. So 16 tablets from 18 should
completely disintegrate. If more than two fail to disintegrate the patch must be
rejected.

• B.P. METHOD FOR ENTERIC COATED TABLETS: Put in distilled water for
five minutes to dissolve the coat. Put in simulated gastric fluid for two hours
(emptying time). Put in phosphate buffer (PH 6.8) for one hour. If one or two
tablets fail to disintegrate repeat on 12 tablets. So 16 tablets should disintegrate.
If more than two tables fail to disintegrate reject the batch.

2.6.6 Dissolution test

The release of drug from the tablet into solution per unit time under standardize
condition is called dissolution test. Media used in dissolution testing may be purified
water, simulated gastric fluid, simulated intestinal fluid or others. Organic solvents are
not recommended. Seven official dissolution test apparatuses are present in the USP;
however, the most commonly used are USP apparatus I (basket) and USP apparatus II
(paddle).
Procedure

APPARATUS-1 (BASKET TYPE): A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 1000 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37±0.5°C by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions.

APPARATUS-2 (PADDLE TYPE): It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, and time limit of the test and assay procedure for. The test tolerance is expressed as a % of the labeled amount of drug dissolved in the time limit.
CHAPTER III

EXPERIMENTAL METHODS

Experiments were performed three times independently, and the results were expressed as the mean ± S.D. Statistically significant values were compared using ANOVA and T post hoc test, and P values of less than 0.05 were considered statistically significant.

3.1 Methods

3.1.1 Preparation of tablet crude powder

Materials and equipments

Aralu
Rasakinda bark
Dried Nelli fruits
Acasia
Grinder
Blender
Direct compressing tablet machine

Method

Aralu, Rasakinda bark and Nelli fruits were kindly provided by 4Ever Skin Naturals (Pvt) Ltd., Pallekele, Sri Lanka. The method of preparation is described in figure 1.
Figure 3.1: Crude powder of Rasakinda bark

Figure 3.2: Crude powder of Nelli fruit

Figure 3.3: Crude powder of Aralu fruit
Aralu Fruit, Rasakinda bark and Dried Nelli fruits

- Washing
- Drying
- Cutting
- Grinding (powdering)
- Blending (all together with Gum acacia 1% (W/W)) (Statistically determined)
- Making tablet by direct compression method

Figure 3.4: Flow diagram for the preparation of Jeewya tablet
Aralu Fruit, Rasakinda bark and Dried Nelli fruits were washed by using distilled water for three times separately and were dried in direct sun light. Cutting was done with cleaned stainless steel knives. They were ground separately by using a grinder. Grinding was done until getting a crude powder of each of them.

500g of each of three powders were weighed separately. All three powders and 15g of gum acacia were blended by using a blender. Powder was put in to the Single Punch Tablet Press Pill Making Machine and the tablet was obtained.

Figure 3.5: Single Punch Tablet Press Pill Making Machine
Figure 3.6: Jeewya tablets
3.2 CHEMICAL ANALYSIS

3.2.1 Determination of Moisture (oven drying method)

Materials

Moisture dish - made out of Stainless Steel - 03

Oven - maintained at 105 °C.

Weighing balance

Mortar and pestle

Method

- 5g of grounded sample was weighed in to a previously dried and weighed moisture dish to the nearest milligram.
- Uncovered dish was dried along with the lid for 3 hours at 105 °C.
- Dish was covered and transferred immediately to desiccators and allowed to cool.
- This drying and weighing procedure was repeated for several times until the weight difference between two successive readings are smaller than one milligram (1mg).
- Above procedure was repeated for 3 samples.

Calculation

Moisture percentage = \( \frac{\text{Weight loss}}{\text{Weight of the sample}} \) x 100

Moisture percentage = \( \frac{m_2 - m_3}{m_2 - m_1} \) x 100

Where,

52
m₁ = Weight of the empty dish
m₂ = Weight of the dish + sample before drying
m₃ = Weight of the dish + Sample after drying

3.2.2 Determination of Total Ash

Materials

Muffle furnace
Silica dishes - 03
Weighing balance
Deciccator
Tongs
Glows (Thermal)

Method

- 2 g of sample was weighed into a pre weight silica dish.
- Sample was ignited slowly over a Bunsen flame until no more fumes are evolved.
- Dish was transferred in to a muffle furnace set at 550 °C and incinerate until free from black particles.
- Dish was removed carefully and allowed to cool in a desiccators. Weight was taken after cooling. This process of ashing and cooling repeated until no further loss in weight is indicated.
- Dish was cooled and weighted.
Calculation

Ash % m/m = \[ \frac{\text{Weight of Ash}}{\text{Weight of the sample}} \times 100 \]

\[ = \frac{(m_2 - m_0) \times 100}{(m_1 - m_0) \times 100} \times 100 \]

\[ = \frac{(m_2 - m_0)}{(m_1 - m_0)} \times 100 \times (100 - \% \text{ moisture}) \]

\[ m_0 = \text{Weight of empty dish} \]

\[ m_1 = \text{Weight of empty dish + sample before ashing} \]

\[ m_2 = \text{Weight of empty dish + Ash} \]
3.2.3 Analysis of active ingredients using the crude powder of Nelli, Aralu and Rasakinda and the Jeewya tablet

A) Thin Layer Chromatography of crude powder of Nelli, Aralu and Rasakinda (Raw material)

Materials
Crude powder of Nelli, Aralu and Rasakinda
Graduated micro pipettes
TLC chamber
Reagent sprayer
An ultra violet light (range 254nm – 366nm)
TLC Plate – Silica Gel GF 254

Reagent
Dichloromethane 100%

TLC parameters
TLC Plate – Silica Gel GF 254
Solvent system - Dichloromethane 100%
Direct evaluation – under ultra violet light (range 254nm – 366nm)
Spray reagent – Vanilline Sulphuric Acid heated at 105 °C for 5 minutes

Method
The samples of raw materials of Nelli, Aralu and Rasakinda were extracted into Dichloromethane, concentrated and spotted on a pre-coated TLC Plate. Then results were analyzed by using their Rf values with direct evaluation under UV light at 254 nm and 366nm; before and after spraying Vanilline Sulphuric Acid heated at 105 °C for 5 minutes.
B) Thin Layer Chromatography of tablet

Materials

Tablet-01
Graduated micropipettes
TLC chamber
Reagent sprayer
An ultra violet light (range 254nm – 366nm)
TLC Plate – Silica Gel GF 254

Reagent
Dichloromethane 100%

TLC parameters
TLC Plate – Silica Gel GF 254
Solvent system - Dichloromethane 100%
Direct evaluation – under ultra violet light (range 254nm – 366nm)
Spray reagent – Vanilline Sulphuric Acid heated at 105°C for 5 minutes

Method
The sample of tablet was powdered by using mortar and pestle and extracted into Dichloromethane and concentrated and spotted on a pre-coated TLC Plate. Then results were analyzed by using their Rf values with direct evaluation under UV light at 254 nm and 366nm; before and after spraying Vanilline Sulphuric Acid heated at 105°C for 5 minutes.
3.3 QUALITY CONTROL METHODS

3.3.1 General Appearance

Ten tablets were selected randomly and measured the diameter and the thickness by using the Vernier Caliper.

3.3.2 Weight uniformity testing method

20 tablet selected at random was weighed by using the Electronic Analytical Balance and the average weight was calculated.

3.3.3 Hardness (crushing strength) testing method

- Monsanto Tester was used.
- Measurements were carried out on 10 tablets.
- Each tablet was put into the apparatus separately, while taking care to remove all the fragments of the broken tablets before each determination and the average hardness was measured.

3.3.4 Friability testing method

- 20 tablets that were used first in the weight variation test was used to test friability.
- 20 tablets were weighed altogether.
- All tablets were put into the instrument and the instrument was adjusted at 100 rpm. (25 rpm for 4 min).
- All 20 tablets were weighed again.
- Friability was calculated.

3.3.5 Disintegration testing method

- Distilled water was used as the liquid
- 6 tablets were put into the disintegrator and the instrument was operated for 15 minutes.
CHAPTER IV
RESULTS AND DISCUSSION

4.1 CHEMICAL ANALYSIS

4.1.1 Determination of moisture content

Table 4.1: Results of moisture determination

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Weight of the empty dish ($m_1$) (g)</th>
<th>Weight of the sample (g)</th>
<th>Weight of the sample + dish before drying ($m_2$) (g)</th>
<th>Weight of the sample + dish after drying ($m_3$) (g)</th>
<th>Moisture content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62.0030</td>
<td>5.0000</td>
<td>67.0030</td>
<td>66.5700</td>
<td>8.6000</td>
</tr>
<tr>
<td>2</td>
<td>12.0001</td>
<td>5.0000</td>
<td>17.0001</td>
<td>16.5750</td>
<td>8.5000</td>
</tr>
<tr>
<td>3</td>
<td>45.0012</td>
<td>5.0000</td>
<td>50.0012</td>
<td>49.5650</td>
<td>8.7000</td>
</tr>
</tbody>
</table>

Average Moisture content = \(\frac{(8.6000 + 8.5000 + 8.7000)}{3}\)

\[= 8.6\%\]

Average moisture content for the prepared sample was 8.6%. This represents the amount of moisture that was in the raw materials and the absorbed moisture from the environment while making the tablet.

4.1.2 Dry matter content

Results

Moisture percentage = 8.6 %

Dry matter percentage = 100 - moisture %

\[= 100 - 8.6\]

\[= 91.4\%\]

Tablet has a high percentage of dry matter.
4.1.3 Determination of total ash

Table 4.2: Results of total ash content determination

<table>
<thead>
<tr>
<th>Sample number</th>
<th>Weight of Empty crucible ($m_0$) (g)</th>
<th>Sample weight (g)</th>
<th>Weight of empty crucible + sample ($m_1$) (g)</th>
<th>Weight of the Ash + Crucible ($m_2$) (g)</th>
<th>Ash content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.0020</td>
<td>2.0000</td>
<td>16.0020</td>
<td>14.1020</td>
<td>5.1</td>
</tr>
<tr>
<td>2</td>
<td>16.0001</td>
<td>2.0000</td>
<td>18.0001</td>
<td>16.1000</td>
<td>5.0</td>
</tr>
<tr>
<td>3</td>
<td>13.0023</td>
<td>2.0000</td>
<td>15.0023</td>
<td>13.1010</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Average total ash content = \(\frac{(5.1 + 5.0 + 5.1)}{3}\)

= 5.0 %

The average percentage of ash is 5.0 %. This figure is an indicator of the mineral content of the sample. The tablet contain significant amount of minerals.
4.1.4 Analysis of active ingredients using the crude powder of Nelli, Aralu and Rasakinda and Jeewya tablet

A) Table 4.3: Results of Thin Layer Chromatography of crude powder of Nelli, Aralu and Rasakinda (Raw material)

Direct evaluation – Under UV light at 254nm and 366nm

<table>
<thead>
<tr>
<th>Before spraying Vanilline Sulphuric Acid</th>
<th>After spraying Vanilline Sulphuric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>0.20 (Light Brown)</td>
</tr>
<tr>
<td>0.13</td>
<td>0.28 (Light Pink)</td>
</tr>
<tr>
<td>0.33</td>
<td>0.44 (Light Purple)</td>
</tr>
<tr>
<td>0.46</td>
<td>0.53 (Dark Purple)</td>
</tr>
<tr>
<td>0.57</td>
<td>0.77 (Purple)</td>
</tr>
<tr>
<td>0.73</td>
<td>0.86 (Light Pink)</td>
</tr>
<tr>
<td>0.93</td>
<td>0.95 (Dark Purple)</td>
</tr>
</tbody>
</table>

TLC analysis indicates the presence of active ingredients in raw material of the tablet.
B) Table 4.4: Results of Thin Layer Chromatography of Tablet

Direct evaluation – Under UV light at 254nm and 366nm

<table>
<thead>
<tr>
<th>Before spraying Vanilline Sulphuric Acid</th>
<th>After spraying Vanilline Sulphuric Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>0.20 (Light Brown)</td>
</tr>
<tr>
<td>0.13</td>
<td>0.28 (Light Pink)</td>
</tr>
<tr>
<td>0.33</td>
<td>0.44 (Light Purple)</td>
</tr>
<tr>
<td>0.46</td>
<td>0.53 (Dark Purple)</td>
</tr>
<tr>
<td>0.57</td>
<td>0.66 (Blue)</td>
</tr>
<tr>
<td>0.73</td>
<td>0.77 (Purple)</td>
</tr>
<tr>
<td>0.93</td>
<td>0.86 (Light Pink)</td>
</tr>
<tr>
<td></td>
<td>0.95 (Dark Purple)</td>
</tr>
</tbody>
</table>

TLC analysis indicates the presence of active ingredients in the tablet. TLC fingerprint profile of the tablet is similar in terms of Rf values and colours to the TLC fingerprint profile of raw material of the tablet. The additional Blue colour Rf value 0.66 which had obtained after spraying may be due to the binder Acacia which was used in tablet manufacturing.
4.2 TABLET QUALITY CONTROL

4.2.1 General Appearance

Colour: Pale Yellow

Odour: Smell of dried herbs

Diameter: 11±0.03mm

Thickness: 6±0.41mm

Table 4.5: Diameter

<table>
<thead>
<tr>
<th>TABLET</th>
<th>DIAMETER (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>1</td>
<td>10.98</td>
</tr>
<tr>
<td>2</td>
<td>11.02</td>
</tr>
<tr>
<td>3</td>
<td>10.99</td>
</tr>
<tr>
<td>4</td>
<td>11.02</td>
</tr>
<tr>
<td>5</td>
<td>11.03</td>
</tr>
<tr>
<td>6</td>
<td>10.98</td>
</tr>
<tr>
<td>7</td>
<td>11.02</td>
</tr>
<tr>
<td>8</td>
<td>11.01</td>
</tr>
<tr>
<td>9</td>
<td>10.98</td>
</tr>
<tr>
<td>10</td>
<td>11.02</td>
</tr>
<tr>
<td>Total</td>
<td>110.05</td>
</tr>
<tr>
<td>Diameter</td>
<td>110.05/10</td>
</tr>
</tbody>
</table>

Average Diameter of a tablet = (11.005+10.999+11.009)/3

=11.00 mm
Table 4.6: Thickness

<table>
<thead>
<tr>
<th>TABLET</th>
<th>THICKNESS (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>1</td>
<td>5.63</td>
</tr>
<tr>
<td>2</td>
<td>6.32</td>
</tr>
<tr>
<td>3</td>
<td>5.78</td>
</tr>
<tr>
<td>4</td>
<td>6.22</td>
</tr>
<tr>
<td>5</td>
<td>6.39</td>
</tr>
<tr>
<td>6</td>
<td>5.88</td>
</tr>
<tr>
<td>7</td>
<td>6.00</td>
</tr>
<tr>
<td>8</td>
<td>5.84</td>
</tr>
<tr>
<td>9</td>
<td>6.25</td>
</tr>
<tr>
<td>10</td>
<td>5.97</td>
</tr>
<tr>
<td>Total</td>
<td>60.28</td>
</tr>
</tbody>
</table>

Thickness

\[
\frac{60.28}{10} = 6.028
\]

\[
\frac{60.32}{10} = 6.032
\]

\[
\frac{60.36}{10} = 6.036
\]

Average Thickness of a tablet = \(\frac{(6.028+6.032+6.036)}{3}\)

= 6.032 mm
4.2.2 Weight uniformity

Table 4.7: Weight of tablets

<table>
<thead>
<tr>
<th>TABLET</th>
<th>WEIGHT (mg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group C</td>
</tr>
<tr>
<td>1</td>
<td>449.55</td>
<td>450.24</td>
<td>449.54</td>
</tr>
<tr>
<td>2</td>
<td>449.65</td>
<td>450.33</td>
<td>450.32</td>
</tr>
<tr>
<td>3</td>
<td>450.25</td>
<td>449.88</td>
<td>450.21</td>
</tr>
<tr>
<td>4</td>
<td>450.21</td>
<td>449.98</td>
<td>449.98</td>
</tr>
<tr>
<td>5</td>
<td>449.98</td>
<td>450.40</td>
<td>449.65</td>
</tr>
<tr>
<td>6</td>
<td>449.68</td>
<td>450.11</td>
<td>450.25</td>
</tr>
<tr>
<td>7</td>
<td>450.11</td>
<td>449.85</td>
<td>450.26</td>
</tr>
<tr>
<td>8</td>
<td>450.22</td>
<td>449.75</td>
<td>450.33</td>
</tr>
<tr>
<td>9</td>
<td>449.78</td>
<td>450.12</td>
<td>450.89</td>
</tr>
<tr>
<td>10</td>
<td>449.77</td>
<td>450.23</td>
<td>449.98</td>
</tr>
<tr>
<td>Total</td>
<td>4499.20</td>
<td>4500.89</td>
<td>4501.41</td>
</tr>
<tr>
<td>Weight</td>
<td>4499.20/10</td>
<td>4500.89/10</td>
<td>4501.41/10</td>
</tr>
</tbody>
</table>
<pre><code>     | =449.920    | =450.089 | =450.141 |
</code></pre>

Average weight of a tablet = (449.920+450.089+450.141)/3

=450.05 mg

Weight of tablet 250 mg or more, then % deviation must be = ±5% (BP)

The average tablet weight is 450±0.45 mg

Sample of tablets has a uniform weight.
4.2.3 Hardness (crushing strength)

Table 4.8: Hardness of tablets

<table>
<thead>
<tr>
<th>TABLET</th>
<th>HARDNESS (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
</tr>
<tr>
<td>1</td>
<td>3.97</td>
</tr>
<tr>
<td>2</td>
<td>4.84</td>
</tr>
<tr>
<td>3</td>
<td>4.56</td>
</tr>
<tr>
<td>4</td>
<td>4.92</td>
</tr>
<tr>
<td>5</td>
<td>4.75</td>
</tr>
<tr>
<td>6</td>
<td>4.87</td>
</tr>
<tr>
<td>7</td>
<td>4.55</td>
</tr>
<tr>
<td>8</td>
<td>4.90</td>
</tr>
<tr>
<td>9</td>
<td>3.87</td>
</tr>
<tr>
<td>10</td>
<td>3.99</td>
</tr>
<tr>
<td>Total</td>
<td>45.22</td>
</tr>
</tbody>
</table>

Hardness

<table>
<thead>
<tr>
<th></th>
<th>45.22/10</th>
<th>44.98/10</th>
<th>45.28/10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>=4.522</td>
<td>=4.498</td>
<td>=4.528</td>
</tr>
</tbody>
</table>

Average hardness of a tablet = (4.522+4.498+4.528)/3

= 4.516 kg

Normal tablet hardness ranges from 4 – 6 Kg (1 Kg = 10 Newton)

Tablet is within the range.
4.2.4 Friability

Initial weight of 20 tablets = 9001.00 mg
Weight of the tablets after putting into instrument = 18.9021 mg
Amount of weight loss = (9001.00 – 8982.0979) = 18.9021 mg
Loss % = \[
\frac{18.9021 \times 100}{9001.00}
\] = 0.21 %

Friability of tablet is 0.21 %.

Friability must be less than or equal to 1%. Tablet is within the range.

4.2.5 Disintegration

6 tablets which were put into the disintegrator were disintegrated completely within 15 minutes.

According to British Pharmacopoeia the complete disintegrate time of all the tablets must not exceed 15 minutes. The tablet has the correct disintegrate time.
4.3 CONCLUSION

Amalaki (Sinhalese name, Nelli) (*Emblica officinalis*), Guduchi (Sinhalese name, Rasakida) (*Tinospora cordifolia*) and Haritaki (Sinhalese name, Aralu) (*Terminalia chebula*), three plant combination is widely used in Sri Lankan traditional medicine as form of decoction or herbal tea for various disease conditions. The difficulty of the administration as a decoction is, 'the bitter taste'. Therefore our research aim was to develop a user friendly dosage forms viz. tablets form using this combination and standardization of this product for human consumption.

The tablets were evaluated using the necessary official tests viz moisture content, total ash, TLC finger print, weight variation, crushing strength; friability, thickness and disintegration time. Formulated tablet moisture content and total ash values were respectively 8.6% w/w and 5.0% w/w. The average tablet weight was 450±0.45 mg. The formulated tablets complied with British Pharmacopoeial specification for weight uniformity, hardness (≥5 kgf) and tablet friability (<1%). As the hardness and tablet friability was 4.5 kgf and 0.21% respectively. For disintegration test, tablets formulated with acacia at concentrations of 1% w/w also complied with Pharmacopoeial specification.

TLC finger printing showed that similar pattern of Rf values and spots in tablet mixture compare with their raw materials. Tablet had a crushing strength and friability of 4.5 kgf and 0.21%, respectively. From the results of disintegration, tablets formulated with acacia at concentrations 1% w/w complied with BP 2009 specification for normal release tablets. When considering all the quality parameters, Jeewya tablets are in standard quality for human consumption. Therefore Jeewya tablet is a ready to use product which can be easily commercialized.

**Future plans**

01. Clinical trial and product registration

02. Product commercialization
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