

FORMULATION AND EVALUATION OF ANTI-HYPERLIPIDEMIC TABLET

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ABSTRACT

Hyperlipidemia is one of the leading causes of mortality in developed as well as in developing countries like India. It attributes to the high risk of coronary heart disease and atherosclerosis which is referred as a silent killer. Herbal treatment for hyperlipidemia is inexpensive, readily available locally, and has no negative side effects. Medicinal plants are the "backbone" of traditional medicine so considered as good source of life for all people due to its wealthy therapeutic properties and being 100% natural. Several drugs in Siddha have been found to be beneficial in lowering lipid levels without any major adverse effects. Numerous plants like arjuna, ashwagandha, garlic, guggul, etc. have been reported to have lipid-lowering effects. The goal of the review paper is to examine the potential anti-hyperlipidemic effects of herbal plants using a variety of models. The anti-hyperlipidemic activity of the most well-known medicinal herbs is the focus of this review.

KEYWORDS: Hyperlipidemia, Antihyperlipidemic Agents, Hypolipidemic medicinal plants.

INTRODUCTION

Tablet- Tablet is defined as solid pharmaceutical dosage form containing drug substance generally with suitable diluents and prepared by either compression or molding methods. Tablets remain popular as a dosage form because of the advantages afforded, both to the manufacturer (e.g. simplicity and economy of the preparation, stability, and convenience in packing, shipping and dispensing) and the patient.^[1]

Types of tablets

1. Compressed Tablets
2. Molded tablets or tablet triturates
3. Dispensing Tablets
4. Hypodermic Tablets

Advantages of the tablets

1. Their cost is lowest of all the dosage forms.
2. They are in general the easiest and cheapest to package and ship of all oral dosage forms.

3. They lend themselves to certain special release profile products, such as enteric or delayed release products.
4. They are better suited to large-scale production than the other unit oral forms.
5. They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.

Disadvantages of the tablets

1. Some drugs resist compression in to dense particles, owing to their amorphous nature or flocculent, low-density character.
2. Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features are very challenging for the formulators.

Method of preparation

1. Direct compression
2. Wet granulation
3. Dry granulation

Additives used in Tablets

1. Binders

Starch-Acts as a binding agent.

Povidone (Polyvinylpyrrolidone - PVP)- Provides cohesive strength.

Hydroxypropyl cellulose (HPC) or Hydroxypropyl methylcellulose (HPMC)-Enhances tablet binding.

2. Diluents/Fillers

Lactose-Commonly used filler.

Microcrystalline cellulose (MCC)-Provides bulk and aids in tablet formation.

Dicalcium phosphate-Used as a filler and a source of calcium.

3. Disintegrates

Croscarmellose sodium-Facilitates tablet disintegration.

Sodium starch glycolate-Another disintegrating agent.

4. Lubricants

Magnesium stearate- Reduces friction during tablet compression.

Stearic acid-Also used for lubrication.

5. Glidants

Colloidal silicon dioxide (Aerosil)- Improves powder flow, aiding in tablet uniformity.

6. Flavoring and Coloring Agents

Artificial flavors-To improve taste.

Colorants-For aesthetic purposes, ensuring brand recognition.

7. Coating Agents (for coated tablets)

Hydroxypropyl methylcellulose (HPMC)- Used in film-coating. Polyethylene glycol (PEG)-Enhances the coating process.

8. Preservatives (if required)

Methylparaben, Propylparaben- Prevent microbial growth.

9. Sweeteners (for chewable tablets)

Mannitol, Sorbitol- Provide sweetness and aid in the chewable formulation.

10. Anti-oxidants

Butylated hydroxytoluene (BHT)-Protects against oxidation.^[2]

Hyperlipidemia

Hyperlipidemia is also termed acquired hyperlipoproteinemia; high blood triglycerides; high blood cholesterol; high cholesterol; high triglycerides; hyperlipidemia etc. It is an elevation of one or more of the plasma lipids, including triglycerides, cholesterol, cholesterol esters phospholipids etc. It is also described by elevation of serum total cholesterol and low-density and very low- density lipoprotein cholesterol and decreased high- density lipoprotein levels Number of clinical trials have verified that increase in plasma total cholesterol (TC) and triglycerides (TG) levels are implicated in the development of atherosclerosis.^[3]

Symptoms

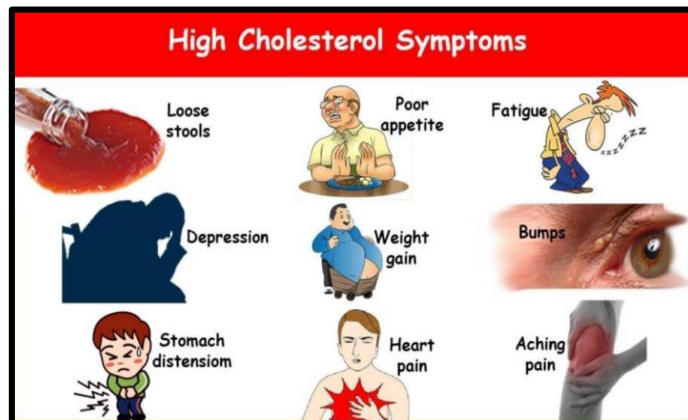


Fig. no. 01: Signs and symptoms of hyperlipidemia.

The signs and symptoms of hyperlipidemia may be no noticeable and the patient discovers this disorder by routine blood tests. In general, patients may suffer chest pain, abdominal pain, hepatic enlargement, spleen hypertrophy, heart diseases, and athermanous plaques in blood vessels.^[4] Other symptoms are illustrated in the above fig. no. 01.

Plasma lipoproteins

Water insoluble plasma lipids are transported in the following classes of lipoproteins.

1. Chylomicrons
2. Chylomicron remnants
3. Very low-density lipoproteins (VLDL)

4. Intermediate density lipoproteins (IDL)
5. Low density lipoproteins (LDL)
6. High density lipoproteins (HDL)
7. Lipoproteins(a)^[5]

Table No. 01.

Lipid	Desirable level (Low risk)	Abnormal level (High-risk)
Total cholesterol	<200	>240
LDL cholesterol	<130	>160
HDL cholesterol	>60	<40
Triglycerides	<200	>400

Classification of hyperlipidemia

1. On the idea of lipid type

- a. Hypercholesterolemia-In this the level of cholesterol is elevated.
- b. Hypertriglyceridemia-It is outlined as level of triglycerides elevated.

2. On the idea of causing factor

1) Primary (Familial: hyperlipidemia)

It is also called familial due to a genetic defect; it may be monogenic: a single gene defect or polygenic: multiple gene defects. Primary hyperlipidemia can usually be resolved into one of the abnormal lipoprotein patterns summarized.

- 1) Type I–Raised cholesterol with high triglyceride levels.
- 2) Type II–High cholesterol with normal triglyceride levels.
- 3) Type III–Raised cholesterol and triglycerides.
- 4) Type IV–Raised triglycerides, atheroma and uric acid.
- 5) Type V–Raised triglycerides.

2) Secondary (Acquired hyperlipidemia)

It is acquired because it is caused by other disorders like diabetes, glomerular syndrome, chronic alcohol intake, hypothyroidism, and with use of drugs like corticosteroids, beta blockers and oral contraceptives.

Secondary hyperlipidemia combined with significant hyper-triglyceridemia can cause pancreatitis.^[6]

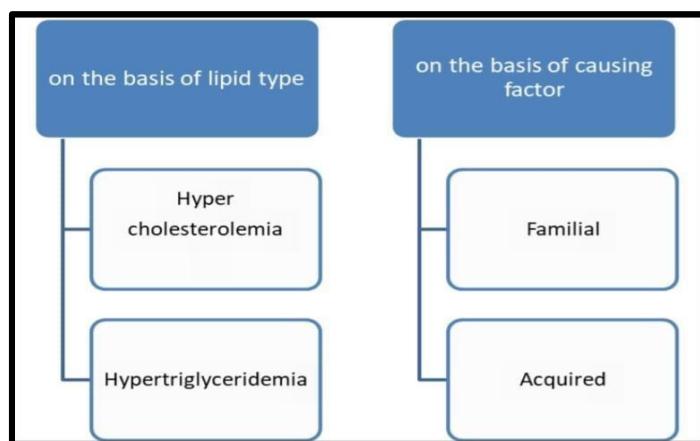


Fig no.02: Classification of hyperlipidemia.

Causes

Sterol, fatty acids, trans fat in the following food may increase the lipid level in blood.

- a) Dairy products
- b) Ice cream pastries
- c) Fried and junk foods
- d) Meat
- e) Excessive use of alcohol also increases the risk of hyperlipidemia
- f) Certain drugs steroids and β -blockers may cause hyperlipidemia.^[7,8]

Several other causes of hyperlipidemia

- a. Obesity
- b. Genetic or inheritance
- c. Smoking
- d. corticosteroids, estrogen, beta-blockers may risk for hypertriglyceridemia
- e. Alcohol, steroids, hypothyroidism, kidney failure
- f. Low exercise^[8]
- g. Age and Number-It has been shown that cholesterol levels rise as the person gets older.^[9,10] Heredity has also been a modifying factor for the progression of hyperlipidemia as it has been noted that the genes partly determine the amount of cholesterol.^[9,10]

Anti-Hyperlipidemic Drugs**1] Arjuna**

Synonym- *Dhananjaya, Kaakubha, Kakubha, Aartagala, Indravriksha, Paartha, Virataru, Viravriksha.*

Biological Source- Arjun consists of dried stem bark of the plant known as Terminalia arjuna Rob.

Family- *Combretaceae.*

Chemical constituents- Arjun contains about 15 percentage of tannins (hydrolysable). It also contains triterpenoid saponin, arjunolic acid, arjunic acid, arjungenin. In addition, it contains beta sitosterol, ellagic acid and arjunic acid.^[11]

Mechanism of Action- In Arjuna (*Terminalia arjuna*), the main active constituents that are believed to contribute to its potential effects on hyperlipidemia include triterpenoid saponins like arjunic acid and arjunolic acid, flavonoids, tannins, and glycosides.

These compounds possess antioxidant and cardioprotective properties that might aid in managing lipid levels. Studies suggest that Arjuna extracts may help in reducing total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol. These effects could be attributed to their ability to influence lipid metabolism enzymes, exhibit antioxidant actions, and potentially modulate cholesterol synthesis.^[12,14]

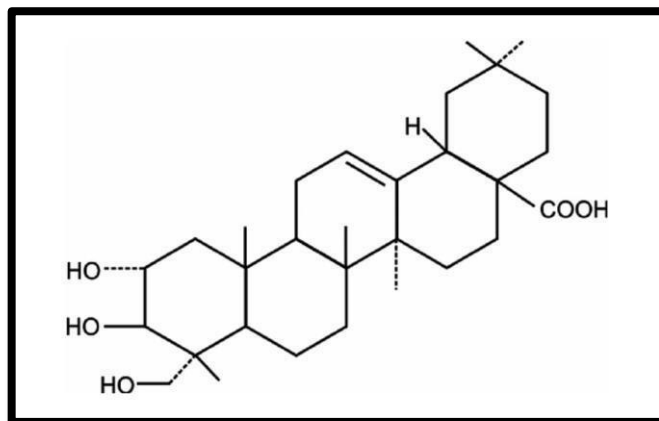


Fig. No. 03: Chemical structure of Arjunolic Acid.

Uses and Effectiveness

- 1. Arjuna for Angina (heart-related chest pain)-** Arjuna is beneficial in the management of chest pain (angina). Studies suggest that the bark of Arjuna shows a significant reduction in chest pain by lowering the level of cortisol i.e. the stress hormone. Arjuna also increases exercise tolerance, improves HDL levels and reduces blood pressure in people with stable angina.
- 2. Arjuna for Heart disease-** Arjuna might be beneficial in managing heart diseases as it acts as a cardiogenic and strengthens the heart muscles. Certain constituents such as Tannins and glycosides present in Arjuna bark have an antioxidant property that protects the heart muscles and blood vessels against damage caused by free radicals. Arjuna also helps in the dilation of the blood vessels and dissolves the plaque to improve blood flow. Thus, it is effective in managing cardiac problems such as high blood pressure, palpitations and rapid heartbeat.
- 3. Arjuna for Diarrhea-**Arjuna might be beneficial in managing diarrhea. Certain constituents present in Arjuna has antimicrobial and astringent properties. It also has an antibacterial property that controls the intestinal infection caused by microorganisms. It regulates the gut motility and prevents excessive loss of water and electrolytes from the body.^[13]
- 4. Arjuna for Inflammation of the airways (bronchitis)-**Arjuna is useful to manage lung problems like infection, cough, asthma and bronchitis According to Ayurveda lung problems like bronchitis is known as Karonga and is caused by poor digestion. Poor diet and incomplete elimination of wastes leads to the formation of Ama (toxic remains in the body due to improper digestion). This Ama accumulates in the form of mucous in the lungs and leads to bronchitis. Taking Arjuna helps to reduce Ama and remove mucous due to its Kapha balancing property.
- 5. Arjuna for Urinary tract infections (UTIs)-** Arjuna has antibacterial property and helps in the management of urinary tract infection. Arjuna also manages symptoms like increased urine frequency.^[15]

Side Effects

When taken by mouth: Terminalia arjuna is possibly safe when used for up to 3 months.

But don't use Terminalia arjuna without medical supervision. It might affect your heart.

Dosing

Terminalia arjuna has most often been used by adults in doses of 500 mg by mouth three times daily for up to 3 months. Terminalia chebulia has most often been used by adults in doses of 200 mg by mouth 2-3 times daily for up to

3 months. There isn't enough reliable information to know what an appropriate dose of Terminalia Billerica might be. Keep in mind that terminalia can affect the heart.

Contraindication

Medications that slow blood clotting (Anticoagulant / Antiplatelet drugs) interacts with TERMINALIA ARJUNA. Terminalia arjuna might slow blood clotting. Taking Terminalia arjuna along with medications that also slow blood clotting might increase the risk of bruising and bleeding.

Interactions

- Medications that slow blood clotting (Anticoagulant / Antiplatelet drugs) interacts with TERMINALIA ARJUNA.
- Medications changed by the liver (Cytochrome P450 2C9 (CYP2C9) substrates) interacts with TERMINALIA ARJUNA.
- Medications changed by the liver (Cytochrome P450 2D6 (CYP2D6) substrates) interacts with TERMINALIA ARJUNA.
- Medications changed by the liver (Cytochrome P450 3A4 (CYP3A4) substrates) interacts with TERMINALIA ARJUNA.^[15]

2] Cinnamon

Synonym- *Cinnamon bark, Kalmi – Dalchini, Ceylon cinnamon.*

Biological Source- The biological source of cinnamon is the dried inner bark of the shoots of compiled trees of *Cinnamomum zeylanicum* Nees (*Cinnamomum verum* J.S. Presl).

Family- *Lauraceae.*

Chemical Constituents- It contains Calcium oxalate, Mucilage, 1.2% of Tannins, 0.5-1.0% of volatile oil (active constituent, light yellow in fresh, changes to red on storage.), Starch and Mannitol. The Cinnamon oil contains 5-10% eugenol, benzaldehyde, cuminaldehyde, 60-70% of Cinnamaldehyde and other Terpenes such as pinene, Cyrene, Caryophyllene

Mechanism of Action - In the context of hyperlipidemia, cinnamon's main active components believed to have potential lipid-lowering effects are cinnamaldehyde, cinnamic acid, and various polyphenols like procyanidins and catechins. These compounds possess antioxidant and anti-inflammatory properties that may contribute to managing lipid levels. Specifically, cinnamaldehyde has been studied for its potential to impact lipid metabolism, insulin sensitivity, and cholesterol synthesis.^[16,17,18]

Structure

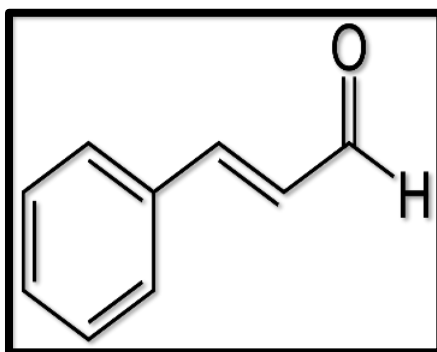


Fig. No. 04: Chemical structure of Cinnamaldehyde.

Uses & Effectiveness- It is mainly used as an aromatic spices and flavoring agent in a broad variety of cooking, sweet and savory dishes, breakfast, snacks foods, tea and traditional foods. It is commonly known as Cinnamon bark, Kalmi-Dalchini, Ceylon cinnamon. Although to be useful as a medicinal herb Ayurveda.

Side Effects- When taken by mouth: Ceylon cinnamon is commonly consumed in foods. It is possibly safe when used as a medicine. It has been safely used in doses of 0.5-3 grams daily for up to 6 months.

Dosing- Ceylon cinnamon has most often been used by adults in doses of 3 grams by mouth daily. It's also been used in nasal sprays and mouthwashes.

Contraindication- Cinnamon is safe to eat in small to moderate amounts with most medications. However, taking too much may be an issue if you're taking medication for diabetes, heart disease, or liver disease.

Interaction

a. Medications for diabetes (Anti diabetes drugs) interacts with ceylon cinnamon- Ceylon cinnamon might lower blood sugar levels. Taking ceylon cinnamon along with diabetes medications might cause blood sugar to drop too low. Monitor your blood sugar closely.

b. Medications for high blood pressure (Antihypertensive drugs) interacts with ceylon cinnamon- Ceylon cinnamon might lower blood pressure. Taking ceylon cinnamon along with medications that lower blood pressure might cause blood pressure to go too low. Monitor your blood pressure closely.^[19]

Storage- It's essential to store medications containing cinnamon in a cool, dry place away from direct sunlight. Follow the specific instructions on the medication's packaging for optimal storage conditions.

3] Garlic

Synonyms- *Allium sativum*, *Ail*, *Ail Cultive*, *Alho*, *Allium*, *Allium sativum*, *Angio D'India*, *Black Garlic*.

Biological constituent- This consists of bulbs of the plant known as *Allium sativum* Linn.

Family- *Alliaceae*.

Chemical constituent- Allicin (yellowish liquid), alillin, mucilage, albumin, alpha-glutamyl peptides, volatile oils, amino-acids as: methionine, lucine, cysteine, vitamin C. Garlic powder is 73% carbohydrates (including 9% dietary fiber), 17% protein, 1% fat, and 6% water.

Mechanism of Action- Garlic contains various sulfur-containing compounds, with allicin being one of the primary active components. Allicin is believed to have potential effects on hyperlipidemia by reducing cholesterol levels and inhibiting lipid synthesis. Other compounds in garlic, such as diallyl disulfide, diallyl trisulfide, and S-allyl cysteine, also contribute to its potential lipid-lowering properties by influencing lipid metabolism and reducing cholesterol synthesis in the liver. However, while studies suggest these constituents may have beneficial effects on lipid levels, more research is needed to fully understand their mechanisms and effectiveness in managing hyperlipidemia.^[20,21,22]

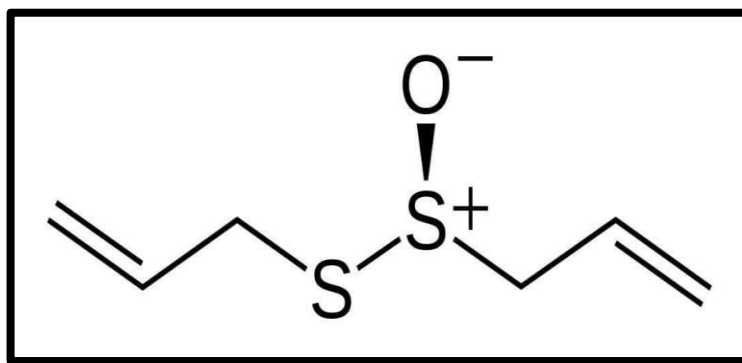
Structure

Fig. No. 06: Chemical structure of Allicin.

Uses & Effectiveness

- a. A painful uterine disorder (endometriosis)-** Taking garlic powder tablets by mouth daily for 3 months seems to improve pain in people with this condition. Hardening of the arteries (atherosclerosis). Taking garlic powder by mouth, alone or with other ingredients, seems to help slow hardening of the arteries.
- b. Diabetes-** Taking garlic powder by mouth seems to reduce pre-meal blood sugar levels by a small amount in people with or without diabetes. It seems to work best if it is taken for at least 3 months. It's unclear if garlic reduces post-meal blood sugar levels or HbA1c levels.
- c. High levels of cholesterol or other fats (lipids) in the blood (hyperlipidemia)-** Taking garlic by mouth daily for at least 8 weeks might reduce total cholesterol and low-density lipoprotein (LDL, "bad" cholesterol) in people with high cholesterol levels. But any benefit is probably small. And taking garlic doesn't help increase high-density lipoprotein (HDL, "good" cholesterol) or lower levels of other blood fats called triglycerides.
- d. High blood pressure-** Taking garlic by mouth seems to reduce systolic blood pressure (the top number) by about 7-9 mmHg and diastolic blood pressure (the bottom number) by about 4-6 mmHg in people with high blood pressure.
- e. Buildup of fat in the liver in people who drink little or no alcohol (nonalcoholic fatty liver disease or NAFLD)-** Taking garlic powder by mouth seems to help to improve liver health in people with NAFLD. People who eat more garlic also seem to be less likely to be diagnosed with NAFLD.
- f. A serious gum infection (periodontitis)-** Taking aged garlic extract by mouth twice daily for 18 months can help improve gum health in people who have mild or moderate periodontitis.

Side Effects

- a. When taken by mouth:** Garlic is likely safe for most people. Garlic has been used safely for up to 7 years. It can cause side effects such as bad breath, heartburn, gas, and diarrhea. These side effects are often worse with raw garlic. Garlic might also increase the risk of bleeding and cause allergic reactions in some people.
- b. When applied to the skin:** Garlic products are possibly safe. Gels, pastes, and mouthwashes containing garlic have been used for up to 3 months. But garlic might cause skin damage that is similar to a burn. raw garlic is possibly unsafe when applied to the skin. It might cause severe skin irritation.^[23]

Dosing- Garlic has most often been used by adults in doses of 2400 mg by mouth daily for 12 months.

MATERIALS AND METHODS**Materials**

API- Arjuna, Cinnamon and Garlic.

Excipients- Lactose, Sodium Saccharin, Talc, Magnesium stearate.

Methods- Preparation of Anti-hyperlipidemic Tablets.

Wet granulation

This is the most widely used method of tablet preparation. In this method the powders are bound by suitable binder by "adhesion". The binder is added by diluting with suitable solvent prior to addition to the blended powders to form wet granules which in turn are dried suitably to expel the solvent forming dried granules. The surface tension forces and capillary pressure are primarily responsible for initial granules formation. The main advantage being it meets all the requirements for tablet formation though it is multistage, time consuming.^[23]

- a) Weigh all the excipients along with API as shown in table.
- b) Passed through sieve no.20. Sieve 20 used in tablet formulation to ensure uniformity and smoothness of the granules or powder blend used in the tablet. It helps in removing any larger particles, ensuring a consistent particle size distribution. This is crucial for tablet compression, as uniformity in particle size contributes to the tablets' overall quality, dissolution, and content uniformity.
- c) Mix all ingredients following geometric mixing excluding glidant and lubricant thoroughly for 15 min.
- d) Mix the powder blend was thoroughly with talc and magnesium stearate.
- e) Compress 300 mg tablet using single rotary punching machine.

Formulation Table**Table No. 02: Formulation Table.**

Sr. no.	Ingredients	Quantity (Mg)	Uses
1	Arjuna	120	Anti-Hyperlipidemic
2	Cinnamon	80	Anti-Hyperlipidemic
3	Garlic	60	Anti-Hyperlipidemic
4	Lactose	30	Diluent
5	Sodium Saccharin	2	Sweetening Agent
6	Talc	4	Anti-adherent
7	Magnesium stearate	4	Lubricant

Evaluation test of tablet

1) Tablet thickness and size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier Callipers.

2) Hardness

Hardness exhibits tensile strength of tablet. The force needed to fracture the tablet by diametric compression is referred as crushing strength of tablet. Hardness is a deformation property of solid. The hardness of the six tablets from each formulation batch was determined using Monsanto hardness tester.

3) Friability

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Formula for friability: % loss = $\frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$

4) Uniformity of weight

Twenty tablets were taken and their weight was determined individually and collectively using single pan electronic balance. The average weight of the tablets was determined from collective weight. From the individual tablet weight, the range and percentage deviation were calculated. Not more than 2 tablets should deviate from the average weight of tablet and maximum percentage of deviation allowed.

Table no. 03: Standard values for uniformity of weight.

Average weight of Tablet (mg)/ IP/BP	Maximum percentage of deviation allowed (%)
80 or less	10
80-250	7.5
More than 250	5

5) Disintegration study

In the disintegration time study, six tablets were tested. Each tablet was put into 900 ml HCL solution (0.1N) at $37 \pm 2^{\circ}\text{C}$. Time required for complete dispersion of a tablet was measured with the help of disintegration test device.

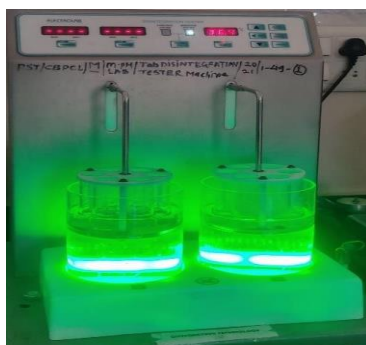


Fig. No. 07: Disintegration Apparatus.

6) Dissolution Study

All the tablet dissolution studies were carried out for three tablets (triplicate) per formulation.

USP Type II dissolution apparatus was used for drug release studies.^[24,25]

Table No. 04: Parameters were used in release study.

Sr. No.	Speed of paddle	100 rpm
1.	Temperature	$37 \pm 0.5^{\circ}\text{C}$
2.	Sampling time	3 hrs
3.	Volume drawn	10 ml
4.	Dilution factor	10
5.	Volume of dissolution medium	900 ml
7.	Spectrophotometric analysis	UV-Visible at 280 nm



Fig. No. 08: Dissolution Test Apparatus.

RESULT AND CONCLUSION

Table No. 05: Results.

Sr. No.	Parameters	Observation
1.	Shape	Oval
2.	Colour	Brownish
3.	Strength (mg)	300
4.	Odour	Pungent
5.	Thickness(mm)	6.025
6.	Hardness(kg/cm ²)	2.7
7.	Friability (%)	0.69
8.	Weight Variation (mg)	0.282
9.	Disintegration (min)	07.16

CONCLUSION

Hyperlipidemia is a condition characterized by elevated levels of lipids in the blood, which can increase the risk of cardiovascular diseases. Treatment is often recommended for people with hyperlipidemia due to the associated risks. Terminalia arjuna, cinnamon, and garlic are herbs that have been studied for their potential benefits in managing heart-related conditions, such as angina, heart disease, and high blood pressure. However, more research is needed to fully support these uses. The main point of the given text is that garlic is commonly used in Arjuna, Cinnamon, Garlic doses of 120,80,60 mg respectively daily for 12 months, and it is important to look for coated supplements to ensure they dissolve in the intestine. Additionally, the text provides information on the method of preparation and evaluation tests for tablets.

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