FORMULATION AND EVALUATION OF BILAYER TABLET OF ACEBROPHYLLINE AND N-ACETYLCYSTEINE

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SUBMITTED BY

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Under the guidance of

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This is to certify that the dissertation work entitled "**FORMULATION AND EVALUATION OF BILAYER TABLETS OF ACEBROPHYLLINE AND N-ACETYLCYSTEINE**" submitted to THE TAMILNADU Dr. M. G. R. MEDICAL UNIVERSITY, CHENNAI- 32 in partial fulfilment for the award of the degree of **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by GOKUL RAJ.M (Reg. No. 261910006) under my guidance and supervision was carried out at **Department of Pharmaceutics,** C. L. Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2019-2021.

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DECLARATION

M.GOKULRAJ (Reg. No. 261910006) hereby declare that the thesis entitled "**FORMULATION AND EVALUATION OF BILAYER TABLETS OF ACEBROPHYLLINE AND N-ACETYLCYSTEINE**" has been originally carried out by me, under the supervision and guidance of **Dr. KUMARAVEL RAJAN, M.Pharm., Ph.D.,** Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai-97 and **DR.VELMURUGAN. M.Pharm., Ph.D.,** FR&D Manager **Apex laboratories Pvt Ltd.** Irungattukottai, Chennai – 600032 during the academic year 2019-2021. This work has not been submitted in any other degree at any other university and that all the sources I have used or quoted have been indicated and acknowledged by complete reference.

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M.GOKUL RAJ

CONTENTS

CONTENTS OF TABLE

CONTENTS OF FIGURES

LIST OF ABBREVIATION

Abbreviation	Expansion
%	Percentage
^{O}C	Degree Celsius
BP	British pharmacopoeia
Ph.Eur.	European Pharmacopoeia
USPNF	United States Pharmacopoeia National Formulary
Cm	Centimetre
CS	Crospovidone
MCC	Microcrystalline cellulose
LM	Lactose monohydrate
BHT	Butylated Hydroxyl Toluene
PVP	Poly vinyl pyrrolidone
gm/mL	Gram per millilitre
Mins	Minutes
HCL	Hydrochloric acid
AB	Acebrophylline
A	Acetylcysteine
AR	Analytical Reagent
RPM	Rotation Per Minute
FBD	Fluidized Bed Dryer
ICH	International Conference on Harmonisation
API	Active pharmaceutical Ingredient
IPA	Iso Propyl Alcohol
HPLC	High performance liquid chromatography
FTIR	Fourier transformer infrared spectroscopy
RH	Relative Humidity
USP	United States Pharmacopoeia
IP	Indian Pharmacopoeia
CI	Compressibility Index
HR	Hausner Ratio
WHO	World Health Organisation
IR	Immediate Release
Mm	Micrometre
Ppm	Parts per million

1. INTRODUCTION

1.1 Oral dosage form: [1]

Oral dosage forms are taken orally for a local effect in the mouth, throat, or gastrointestinal tract or for a systemic effect in the body after absorption from the mouth or gastrointestinal tract.

Oral dosage forms can be divided into two main groups;

1. solid oral dosage forms (tablets, capsules, or powders)
2. Liquid oral dosage form (solutions, syrups, emulsions, and powders for suspensions).

1.2 *Tablets:* [2] [3]

Tablets are solid dosage forms containing one or more medicinal substances with or without added pharmaceutical ingredients. The pharmaceutical agents used are diluents, Disintegrants, colorants, binders, solubilizers, and coatings. Tablets may be coated for appearance, for stability, to mask the bitter taste of the medication. Tablets were prepared by either molding or compression methods. Although tablets are in discoid in shape, round, oval, oblong, cylindrical or triangular. It contains the amount of drug substance which may vary in size and weight and through the drug administration.

1.2.1 Properties of Tablets:

The attributes of an acceptable tablet are as follows:

1. The tablet must be sufficiently strong and resistance to shock and abrasion and to with stand handling, during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
2. Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
3. The drug content of the tablet must show good bioavailability. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels of the drug after its administration.
4. Tablets must be elegant in appearance and must have characteristic shape, color, and other markings necessary to identify the product.
5. Tablets must retain all these functional attributes, which include drug stability and efficacy.

1.2.2 Advantages of tablets:

1. They are easy to administer.
2. Their cost is lowest (oral dosage forms).
3. The Product identification is actually very cheap.
4. Lighter and compact.
5. Having greatest chemical and microbial stability over all oral dosage form.
6. Suitable for large scale production.
7. Easy to swallow with least tendency for hang-up.
8. Objectionable odour and bitter taste can be masked by coating technique.
9. Sustained release product is possible by enteric coating.

1.2.3 Disadvantages of tablets:

1. Difficult to swallow in case of children and unconscious patients.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.
5. Irritant effects on the GI mucosa by some solids (e.g., aspirin).
6. Possibility of bioavailability problems resulting from slow disintegration and dissolution.

1.3 Immediate release layer tablet: [4]

The term “immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Immediate release dosage forms are those for which >85% of the labeled amount dissolves within 30minutes. For immediate release tablets, the only barrier to drug release is

disintegration or erosion stage which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug for immediate release tablets, disintegration is one of the important process. Few super disintegrates are available commercially as croscarmellose sodium, Crospovidone and sodium starch glycolate.

Tablets for an immediate release often consist of filler, binder, lubricant and disintegrants. In many cases, the disintegration time of solid dosage form is too long to provide appropriate therapeutic effect. To improve the disintegration time, disintegrates are used. The most accepted mechanisms of their action are wicking, swelling, and deformation recovery and particle repulsion. Together, these phenomena create a disintegrating force within the matrix. In the past, non-modified disintegrates like alginates, starches, amberlite resins, cellulose materials, pectin and others were used to accelerate disintegration.

1.4 Immediate release layer tablet general components: [5]

A compressed tablet usually consists of active medicaments mixed with a number of inert substances known as “excipients or additives”. These additives are added to give the better quality to a tablet. Although these additives are termed as inert but they have a great influence on stability, bioavailability and the process by which the dosage forms are prepared.

Excipients are chosen in tablet formulation to perform a variety of functions like

- For providing essential manufacturing technology functions [binders, glidants, lubricants]
- For enhancing stability [antioxidant, UV absorbers]
- For optimizing or modifying drug release [disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers]
- For enhancing patient acceptance [flavors, Colourants]
- For providing aid in product identification [Colourants]

1.4.1 Diluents:

In order to facilitate tablet handling during manufacture and to achieve targeted content uniformity, the tablet size should be kept above 2-3 mm and weight of tablet above 50 mg. Many potent drugs have low dose (for e.g. Diazepam, Clonidine hydrochloride). In such cases diluents provide the required bulk of the tablet when the drug dosage itself is

inadequate to produce tablets of adequate weight and size. Usually the range of diluents may vary from 5-80%. Diluents are also synonymously known as “fillers”. Diluents are often added to tablet formulations for secondary reasons like to provide better tablet properties such as:

i) To provide improved cohesion
ii) To allow direct compression manufacturing
iii) To enhance flow
iv) To adjust weight of tablet as per die capacity Selection of diluents should be done after considering the properties of diluents such as: Compatibility, flow ability, solubility, disintegration qualities, hygroscopicity, lubricity and stability.

The ideal diluents should fulfill a series of requirements, such as:

- be chemically inert
- be non-hygroscopic
- be biocompatible
- possess good biopharmaceutical properties (e.g. water soluble or hydrophilic)
- possess good technical properties (such as compactability and dilution capacity)
- have an acceptable taste
- be cheap.

Some of the commonly used diluents are Lactose, Sucrose, Glucose, Mannitol, Sorbitol, Dicalcium phosphate dehydrate, Calcium carbonate, Cellulose.

1.4.2 Antioxidant: [6]

Antioxidants are currently used as efficient excipients that delay or inhibit the oxidation process of molecules. Excipients are often associated with adverse reactions. Stability studies can guide the search for solutions that minimize or delay the processes of degradation. The ability to predict oxidation reactions in different drugs is important

Example:

- Butylatedhydroxyanisole (BHA)
- butylatedhydroxytoluene (BHT)
- sodium metabisulfite (SMB)
- propyl gallate (PG)
- cysteine (CYS)

1.4.3 Disintegrants: [7, 8]

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a non-disintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.

Disintegrants an important excipient of the tablet formulation, is always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and the excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

Some of the commonly used disintegrants are starch (e.g., corn, maize, and potato starch), alginates (e.g. alginic acid and sodium alginate), and methyl cellulose (high-viscosity grades).

1.4.4 Mechanism of tablet Disintegrants:

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

- By capillary action
- By swelling
- Because of heat of wetting
- Due to disintegrating particle/particle repulsive forces
- Due to deformation
- Due to release of gases
- By enzymatic action

1.4.5 Superdisintegrants:

As days passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate Disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Some of the commonly used super disintegrants, which include croscarmellose sodium (also known as cross-linked sodium carboxymethylcellulose), Crospovidone(also known as cross-linked PVP), sodium starch glycolate (which is a modified form of starch), calcium silicate, and cross-linked alginic acid (also known as alginic acid National Formulary (NF)).

1.4.6 Binders:

A binder (also sometimes called an *adhesive*) is added to a drug–filler mixture to ensure that granules and tablets can be formed with the required mechanical strength. Binders can be added to a powder in different ways:

- As a dry powder which is mixed with the other ingredients before wet agglomeration. During the agglomeration procedure, the binder might thus dissolve partly or completely in the agglomeration liquid.
- As a solution which is used as an agglomeration liquid during wet agglomeration. The binder is often referred to here as a solution binder. Some of the commonly used solution binders are Gelatin, Polyvinylpyrrolidone, Cellulose derivative (e.g. hydroxypropyl methylcellulose), Polyethylene glycol, Sucrose, Starch.
- As a dry powder which is mixed with the other ingredients before compaction (slugging or tableting). The binder is often referred to here as a dry binder.Some of the commonly used dry binder is Cellulose, Methylcellulose, Polyvinylpyrrolidone, Polyethylene glycol.

1.4.7 Dissolution enhancer:

For drugs of low aqueous solubility, the dissolution rate of the drug may be the rate-limiting step in the overall drug release and absorption processes. Agents other than matrix formers may therefore sometimes be found in the composition of a tablet with the role to speed up the drug dissolution process by temporarily increasing the solubility of the drug during drug dissolution. An important example of a dissolution enhancer is the incorporation into the formulation of a substance that forms a salt with the drug during dissolution

Another example of a dissolution-enhancing agent is a surfactant. A surfactant may Facilitate wetting of hydrophobic drug particles and increase the surface area available for drug dissolution. A surfactant may also increase the rate of dissolution of poorly soluble drugs through a solubilization process.

1.4.8 Lubricants:

Lubricants are the agents that reduce friction by interposing an intermediate layer between the tablet constituents and the die wall during compression and ejection. Solid lubricants act by boundary mechanism which results from the adherence of the polar portions of molecules with long carbon chains to the metal surfaces to the die wall. Magnesium stearate is an example of boundary lubricant. Other process is hydrodynamic mechanism i.e. fluid lubrication where two moving surfaces are separated by a finite and continuous layer of fluid lubricant. Since adherence of solid lubricants on the die wall is more than that of fluid lubricants, solid lubricants are more effective and more frequently used.

1.4.9 Classification of lubricants:

Lubricants are classified according to their water solubility i.e. water insoluble and water soluble. Selection of lubricant depends partly on mode of administration, type of tablet, desired disintegration and dissolution properties, physicochemical properties of granules or powder and the cost.

I. Water insoluble lubricants:

Water insoluble lubricants are most effective and used at low concentration than water soluble lubricants. Since these lubricants function by coating, their effectiveness is

related with their surface area, extent of particle size reduction, time and procedure of addition and length of mixing. Some of the water insoluble lubricants are Magnesium stearate, Talc, waxes.

II. Water soluble lubricants:

Water soluble lubricants are used when a tablet is completely soluble or when unique disintegration and dissolution characteristics are required. Tablet containing soluble lubricant shows higher dissolution rate than tablet with insoluble lubricants. Physical mixture of this lubricant i.e. SLS or MLS with stearates can lead to the best compromise in terms of lubricity; tablet strength and disintegration. Some of the water soluble lubricants are Boric acid, Sodium benzoate, Sodium oleate, Sodium acetate, Sodium Lauryl Sulfate, Magnesium Lauryl Sulfate.

1.4.10 Glidants:

Guidant's are added to the formulation to improve the flow properties of the material which is to be fed into the die cavity and aid in particle rearrangement within the die during the early stages of compression. If the flow properties are extremely poor then glidants are ineffective and consideration of force free mechanisms may be necessary. Starch is a popular glidant because it has additional value of disintegrant. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material. Talc is a glidant which is superior to starch but its concentration should be limited because it has retardant effect on dissolution-disintegration profile. Silaceous material like colloidal silica i.e. syloid, pyrogenic silica (0.25%), hydrated sodium silioaluminate (0.75%) are also successfully used to induce flow.

Glidants act by interposing their particles between those of material and lower the overall interparticulate friction of the system by virtue of their reduced adhesive tendencies. Similar to lubricants, they are required at the surface of feed particles and they should be in fine state of division and appropriately incorporated in the mixture.

1.4.11 Antiadherent:

The function of an anti-adherent is to reduce adhesion between the powder and the punch faces and thus prevent particles sticking to the punches. Many powders are prone to adhere to the punches, a phenomenon (known in the pharmaceutical industry as

sticking or picking) which is affected by the moisture content of the powder. Such adherence is especially prone to happen if the tablet punches have markings or symbols. Adherence can lead to a build-up of a thin layer of powder on the punches, which in turn will lead to an uneven and matt tablet surface with unclear markings or symbols. Many lubricants, such as magnesium stearate, also have anti-adherent properties. However, other substances with limited ability to reduce friction can also act as anti-adherents, such as talc and starch.

1.4.12 Flavour:

Flavouring agents are incorporated into a formulation to give the tablet a more pleasant taste or to mask an unpleasant one. The latter can also be achieved by the coating of the tablet or the drug particles. Flavouring agents are often thermolabile and so cannot be added before an operation involving heat. They are often mixed with the granules as an alcohol solution.

1.4.13 Colourants:

Colourants are added to tablets to aid identification and patient adherence. Colouring is often accomplished during coating but a Colourants can also be included in the formulation before compaction. In the latter case, the Colourants can be added as an insoluble powder or dissolved in the granulation liquid.

1.5Antioxidant: [9]

Antioxidants are currently used as efficient excipients that delay or inhibit the oxidation process of molecules. Excipients are often associated with adverse reactions. Stability studies can guide the search for solutions that minimize or delay the processes of degradation. The ability to predict oxidation reactions in different drugs is important.

- Chemically they are reducing agents.
- They oxidize themselves and prevent oxidation of API.
- A substance that inhibits oxidation is called antioxidants.
- The effectiveness of antioxidant can depend on the concentration used and pH of solution.

Examples:

- Ascorbic acid,
- Butylated hydroxy anisole (BHA),
- Butylated hydroxyl toluene (BHT)

- Oxidation is a chemical reaction involving the loss of electrons or an increase in oxidation state.
    - Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions.
    - When the chain reaction occurs in a cell, it can cause damage or death to the cell.
    - Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions.

1.5.1 The following are some of the qualities of an ideal anti-oxidant:

- It should be readily soluble or dispersible in the medium.
- It should be effective in low concentration.
- It should be non-toxic.
- It should be non-irritant.
- It should be compatible with other ingredients of emulsion.
- It should be colorless, odorless and tasteless.

1.5.2 Classification of antioxidants:

- **On the basis of the source**

Antioxidants are 2 types. They are,

- Natural antioxidants:
    - Tocopherol (Vitamin E),
    - Sesamol,
    - Guaiac resin,
    - Mehionine.
- Synthetic antioxidant:
    - BHA,
    - BHT,
    - Tertiary butyl hydroquinone.

- **On the basis of solubility**

  Antioxidants are 2 types. They are,

  - Water soluble antioxidant:
    - Citric Acid,
    - Tartaric Acid,
    - Phosphoric Acid,
    - Ascorbic Acid,
    - Sodium Metabisulfite and
    - thiol derivatives.
  - Oil soluble antioxidant:
    - BHA
    - BHT

1.5.3 Brief detail of some antioxidant:

- **Butylated hydroxyl anisole (BHA)**
  - Description: White or slightly yellow. Waxy solid having a faint characteristic odor.
  - Solubility: Insoluble in water; 1 g in 4 mL alcohol, 2 mL chloroform or 1.2 mL ether.
  - Uses: An antioxidant in cosmetics and pharmaceuticals containing fat and oils.
- **Butylated hydroxyl Toluene (BHT)**
  - Description: White, tasteless crystal with a mild odor; stable in light or air; melts at 70'C.
  - Thermolabile substance and has low toxicity.
  - Solubility: Insoluble in water; 1 g in 4 mL alcohol, 1.1 mL chloroform or 1.1 mL ether.
  - Uses: An antioxidant employed to retard oxidative degradation of oils and fats in various cosmetics and pharmaceuticals.
- **Tocopherol:**
  - Natural antioxidant.
  - Present in vegetable oil in concentration range of 0.1% to 0.01%

- **Potassium metabisulfite**
  - Description: White crystals or crystalline powder with an odor of SO_2. Oxidizes in air to the sulfate. May ignite on powdering in a mortar if too much heat develops.
  - Solubility-Freely soluble in water; insoluble in "alcohol.
  - Uses: Antioxidant.

- **Sodium bisulfite:**
  - Description: White or yellowish white crystals or granular powder with the odor of sulfur dioxide; unstable in air.
  - Solubility: 1g in 4 mL water; slightly soluble in alcohol.
  - Uses-An antioxidant und stabilizing agent. Help to solubilize kidney stones.

- **Sodium Metabisulfite:**
  - Description: White crystals or white to yellowish crystalline powder with an odor of sulfur dioxide; on exposure to air and moisture, it is slowly oxidized to sulfate.
  - Solubility: 1 gm 2 mL water. lightly soluble in alcohol. freely. soluble in glycerin.
  - Uses: A reducing agent. It is used in easily oxidized pharmaceuticals. Such as epinephrine hydrochloride and phenylephrine hydrochloride injections, to retard oxidation.

1.6 Technique used in the preparation of immediate release *Tablets*: [10]

- Tablet molding technique
- Granulation technique
- Direct compression technique
- Mass extrusion technique Tablet Molding

1.6.1 Tablet molding technique*:*

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution.

Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

1.6.2 Mass extrusion technique tablet molding:

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking Immediate release solid dosage forms prepared by solid dispersions. When formulating such solid amorphous dispersions into immediate release solid dosage forms for oral administration to a use environment such as the GI tract of an animal such as a human, it is often desirable to maximize the amount of dispersion present in the dosage form. This minimizes the size of the solid dosage form required to achieve the desired dose. Depending on the drug dose, it is often desired that the solid amorphous dispersion comprise at least 30 wt. %, preferably at least wt. %, and more preferably at least 50 wt % or more of the solid dosage form. Such high drug loadings of dispersion in a solid dosage form minimize the dosage form's size, making it easier for the patient to swallow it and tending to improve patient compliance. The immediate release dosage forms containing a solid dispersion that enhances the solubility of a “low-solubility drug,” meaning that the drug may be either “substantially water-insoluble,” which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, “sparingly water soluble,” that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/ml. The drug dispersions used in fabricating the high loading immediate release dosage forms of the present invention comprise solid dispersions of a drug and at least one concentration enhancing polymer.

1.6.3 Direct compression method: [11]

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

Advantages:

- Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
- The most important advantage of direct compression is that it is an less economical process. Reduced processing time, reduced labor costs, fewer manufacturing step, and less number of equipments are required, less process validation, reduced consumption of power. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API.
- Particle size uniformity.
- In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.
- The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.
- Chemical stability problems for API and excipient would be avoided.
- Provides stability against the effect of aging which affects the dissolution rates.

Disadvantages:

- Problems in the uniform distribution of low dose drugs. High dose drugs having high bulk volume, poor compressibility and poor flow ability are not suitable

for direct compression for example, Aluminium Hydroxide, Magnesium Hydroxide.

- The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.
- Many active ingredients are not compressible either in crystalline or amorphous forms.
- Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
- Non-uniform distribution of color, especially in tablets of deep color

1.40 Granulation:

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates. The objective of granulation is to improve powder flow and handling, decrease dustiness, and prevent segregation of the constituents of the product. Granulation method can be broadly classified into two types:

1. Wet granulation
2. Dry granulation

Ideal characteristics of granules The ideal characteristics of granules include spherical shape, smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness. The effectiveness of granulation depends on the following properties:

- Particle size of the drug and excipients
- Type of binder (strong or weak)
- Volume of binder (less or more)
- Wet massing time (less or more)
- Amount of shear applied
- Drying rate (Hydrate formation and polymorphism)

1.6.4 Wet granulation:

Wet granulation is a commonly used unit operation in the pharmaceutical industry. Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables. Hence, additional process monitoring techniques would be valuable. Important steps involved in wet granulation.

- Mixing of drug(s) and excipients.
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve (6-12 screens).
- Drying of moist granules.
- Screening of dry granules through a suitable sieve (14-20 screen).
- Mixing of screened granules with disintegrant, glidant, and lubricant.

Advantages

- Rapid process.
- Ability to be operated continuously.
- Suitable for heat sensitive product.

Disadvantages

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- Loss of material during various stages of processing.
- Stability may be a major concern for moisture sensitive or thermo labile drugs.
- An inherent limitation of wet granulation is that any incompatibility between Formulation components is aggravated. It is a unique granulation technique that directly converts liquids into dry powder in a single step. This method removes Moisture instantly and converts pumpable liquids into a dry powder.

1.6.5 Dry granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre-compressed and the resulting tablets or slugs are milled to yield granules. The other method is to pre-compress the powder with pressure rolls using a machine such as chilsonator.

Advantages:

The main advantages of dry granulation or slugging are that it uses less equipment's and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

- For moisture sensitive material.
- For heat sensitive material.
- For improved disintegration since powder particles are not bonded together by a binder. Disadvantages:
- It requires a specialized heavy duty tablet press to form slug.
- It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
- The process tends to create more dust than wet granulation, increasing the potential contamination.
- **Steps in dry granulation**:

  1. Milling of drugs and excipients
  2. Mixing of milled powders Compression into large, hard tablets to make slug
  3. Screening of slugs
  4. Mixing with lubricant and disintegrating agent
  5. Tablet compression

1.6.6 Two main dry granulation processes:

a. Slugging process :

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The

accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b. Roller compaction:

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granule.

1.7 Immediate release layer tablet: [12]

Layer tablets are composed of two or three layers of granulation compressed together. As the edges of each layer are exposed they have the appearance of a sandwich. This dosage form has the advantage of separating two incompatible substances with an inert barrier between them. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added.

Multi-layer tablet dosage forms are designed for variety of reasons which are as follows:

- To control the delivery rate of either single or two different active pharmaceutical ingredients.
- To separate incompatible active pharmaceutical ingredients from each other to control the release of active pharmaceutical ingredient from one layer by utilizing the functional property of the other layer such as, different active pharmaceutical ingredients, to prolong the drug product life cycle.
- To modify the total surface area available for active pharmaceutical ingredients layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release.
- To fabricate novel drug delivery systems such as chewing device, buccal / mucoadhesive delivery systems and floating tablets for gastro-retentive drug delivery

1.8 Bilayer tablet: [13]

Bi-layer tablet is a unit compressed tablet dosage form intended for oral application. It contains two layers in which one layer having conventional or immediate release part of single or multiple active ingredients, another layer is sustained or controlled release part of single or multiple active ingredients.

Bi-layer tablets are novel drug delivery system where combination of two or more drugs in single unit having different release profiles improves the patient compliance, prolongs the drug action, resulting in effective therapy along with better control of plasma drug level.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer isimmediate release as initial dose and second layer is maintenance dose. Nowadays various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, diabetes and cardiovascular diseases. Combination preparation plays an important role in clinical treatment because of its better and wider curative synergism and weaker side effects. Combination therapy may be achieved by giving separate drugs or where available by giving combination drugs (monolithic or bilayer dosage form) which are dosage forms that contain more than one active ingredient.

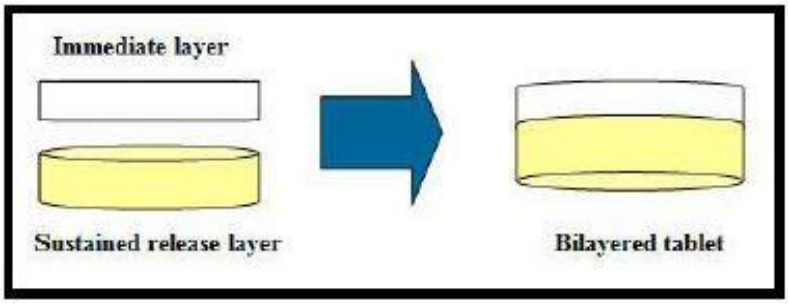


Fig.1: Bilayer Tablet

Advantages:

They are used as an extension of a conventional technology

- Ability to combine different release rate. IR and SR in the same tablet for chronic condition requiring repeated dosing.
- Promoting patient convenience and compliance because fewer daily doses arerequired compared to traditional delivery system.

- Two different drugs in same dosage form.
- Separation of incompatible components thus minimizes the physical and chemical incompatibilities.
- Solve degradation problem.
- Reduce pill burden to patient.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy.

1.8.1 Advantages of bi-layer tablets over conventional tablets:

Blood level of drug can be held at consistent therapeutic level for improved drug deliver, accuracy, safety and reduce side effects. Reduction of adverse side effects can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced. Patient convenience is improved by fewer daily doses are required compared to traditional system. Patient compliance is enhanced leading to improved drug regimen efficacy.

Bilayer tablets are readily lend themselves to repeat action products, where in one layer on layered tablet provides the initial dose, rapidly disintegration in the stomach, the layer are insoluble in gastric media but released in the intestinal environment. Separate physically and chemically incompatible ingredients.

Disadvantages:

- Inaccurate individual layer weight control.
- Cross contamination between the layers.
- Insufficient hardness.
- Reduced yield.
- Adds complexity and bi-layer rotary presses are expensive.

1.9 Challenges in Bilayer manufacturing: [14, 15, 16, 17]

Conceptually, Bilayer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

Delimitation:

Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.

Cross-contamination:

When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

Production Yields:

To prevent cross contamination, dust collection is required which leads to losses. Thus, Bilayer tablets have lower yields than single-layer tablets.

Cost:

Bilayer tableting is more expensive than single-layer tableting for several reasons:

- The tablet press costs more.
- The press generally runs more slowly in bilayer mode.
- Development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation

These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process.

1.9.2 Preparation of Bilayer tablets:

Bilayer tablets to produce adequate tablet formulation, certain requirements such as sufficient mechanical strength desired drug release profile must be met. At times, this may be difficult task for formulator to achieve these conditions especially in Bilayer tablet formulation where double compression technique is involved, because of poor flow and compatibility characteristic of the drug which will result in capping and/or lamination. The compaction of a material involves both the compressibility and consolidation.

Compression:

It is defined as reduction in bulk volume by eliminating voids and bringing particles into closer contacts.

Consolidation:

It is the property of the material in which there is increased mechanical strength due to inter-particulate interaction (bonding). The compression force on first layer was found to be major factor influencing tablet delimitation.

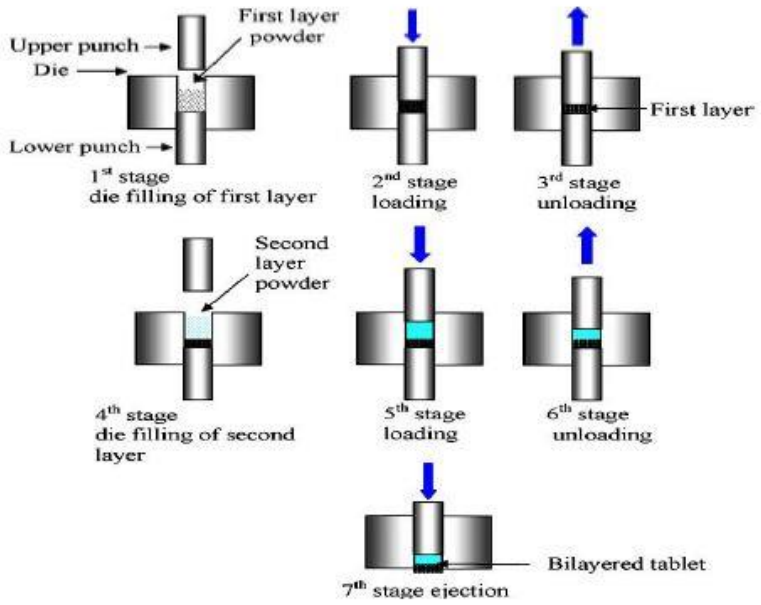


Fig.2: D-Tooling of Bilayer Tablets

1.9.3 Types of Bilayer tablet press:

1. Single sided tablet press
2. Double sided tablet press
3. Bi-layer tablet press with displacement monitoring

1.9.3.1 Single sided tablet press*:*

- The simplest design is a single sided press with both chambers of the doublet feeder separated from each other.
- Each chamber is gravity or force fed with different powers, thus producing the individual layers of the tablets.
- When the die passes under the feeder, it is at first loaded with the first layer powder followed by the second layer powder.
- Then the entire tablet is compressed in one or two steps.

Limitations:

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
- This may be corrected by reducing the turret-rotation speed (to extend the dwell time)but with the consequence of lower tablet output
- Very difficult first layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

1.9.3.2 Double sided tablet press:

- Most double sided tablet presses with automated production control use compression force to monitor and control tablet weight.
- The effective peak compression force exerted on each individual tablet or layer is measured by the control system at the main compression of the layer.
- This measured peak compression force is the signal used by the control system to reject out of tolerance tablets and correct the die fill depth when required.

1.10 Asthma: [18]

Asthma is defined as a chronic inflammatory disease of the airways. The chronic inflammation is associated with airway hyper responsiveness (an exaggerated airway-narrowing response to specific triggers such as viruses, allergens and exercise) that leads to recurrent episodes of wheezing, breathlessness, chest tightness and/or coughing that can vary over time and in intensity. Symptom episodes are generally associated with widespread, but variable, airflow obstruction within the lungs that is usually reversible either spontaneously or with appropriate asthma treatment such as a fast-acting bronchodilator.

Asthma is a long-term disease of the lungs. It causes your airways to get inflamed and narrow, and it makes it hard to breathe. Severe asthma can cause trouble talking or being active. You might hear your doctor call it a chronic respiratory disease. Some people refer to asthma as bronchial asthma.

Asthma is a serious disease that affects about 25 million Americans and causes nearly 1.6 million emergency room visits every year. With treatment, you can live well. Without it, you might have to go to the ER often or stay at the hospital, which can

affect your daily life. Asthma attack is the episode in which bands of muscle around the airways are triggered to tighten. This tightening is called bronchospasm. During the attack, the lining of the airways becomes swollen or inflamed, and the cells lining the airways make more and thicker mucus than normal.

All of these things –bronchospasm, inflammation, and mucus production - cause symptoms such as trouble breathing, wheezing, coughing, shortness of breath, and trouble with normal daily activities.

1.10.1 Three major signs of asthma:

1. Airway blockage.

When you breathe as usual, the bands of muscle around your airways are relaxed, and air moves freely. But when you have asthma, the muscles tighten. It's harder for air to pass through.

2. Inflammation.

Asthma causes red, swollen bronchial tubes in your lungs. This inflammation can damage your lungs. Treating this is key to managing asthma in the long run.

3. Airway irritability

People with asthma have sensitive airways that tend to overreact and narrow when they come into contact with even slight triggers.

1.10.2 Symptoms of asthma:

- Severe wheezing when breathing both in and out
- Very rapid breathing
- Tightened neck and chest muscles, called retractions
- Difficulty talking
- Feelings of anxiety or panic
- Pale, sweaty face
- Blue lips or fingernails
- Coughing, especially at night or in the morning
- Wheezing, a whistling sound when you breathe
- Shortness of breath
- Tightness, pain, or pressure in your chest
- Trouble sleeping because of breathing problems

1.10.3 Asthma causes and triggers:

- Infections like sinusitis, colds, and the flu
- Allergens such as pollens, mold, pet dander, and dust mites
- Irritants like strong odors from perfumes or cleaning solutions
- Air pollution
- Tobacco smoke
- Exercise
- Cold air or changes in the weather, such as temperature or humidity
- Gastro esophageal reflux disease (GERD)
- Strong emotions such as anxiety, laughter, sadness, or stress
- Medications such as aspirin
- Food preservatives called sulfites, found in things like shrimp, pickles, beer and wine, dried fruits, and bottled lemon and lime juices.

1.10.4 Asthma diagnosis& treatment: [19]

1. Inhaled corticosteroids.

- Beclomethasone (QVAR)
- Budesonide (Pulmicort)
- Fluticasone (ArnuityEllipta, ArmonairRespiclick, Flovent

a) Leukotriene modifiers.

- Montelukast (Singulair)
- Zafirlukast (Accolate)

b) **Long-acting beta-agonists.**

These medications relax the muscle bands that surround your airways. You might hear them called bronchodilators.

- Ciclesonide (Alvesco)
- Formoterol (Perforomist)
- Mometasone (Asmanex)
- Salmeterol (Serevent)

2. Xanthine Derivatives.

It opens your airways and eases tightness in your chest. You take this long-term medication by mouth, either by itself or with an inhaled corticosteroid.

- Aminophylline
- Ambroxalacefyllinate(Acebrophylline)
- Theophylline
- Doxophylline

3. Short-acting beta-agonists.

These are known as rescue medicines or rescue inhalers. They loosen the bands of muscle around your airways and ease symptoms. Examples include:

- Albuterol (Accuneb, ProAir FHA, Proventil FHA, Ventolin FHA)
- Levalbuterol (Xopenex HFA)

4. Xanthine Derivatives.

It opens your airways and eases tightness in your chest. You take this long-term medication by mouth, either by itself or with an inhaled corticosteroid.

- Aminophylline
- Ambroxalacefyllinate(Acebrophylline)
- Theophylline
- Doxophylline

1.11 Cough: [20]

A cough is your body's way of responding when something irritates your throat or airways. An irritant stimulates nerves that send a message to your brain. The brain then tells muscles in your chest and abdomen to push air out of your lungs to force out the irritant. An occasional cough is normal and healthy. A cough that persists for several weeks or one that brings up discolored or bloody mucus may indicate a condition that needs medical attention.

At times, coughing can be very forceful. Prolonged, vigorous coughing can irritate the lungs and cause even more coughing. It is also exhausting and can cause sleeplessness, dizziness or fainting, headaches, urinary incontinence, vomiting, and even broken ribs.

1.11.1 Symptoms of cough:

- Trouble breathing
- Chest pain
- Ongoing heartburn
- Coughing up blood

- Fever or night sweats
- Trouble sleeping

1.11.2 Causes cough

Acute cough

1. Common cold
2. Influenza (flu)
3. Inhaling an irritant (such as smoke, dust, chemicals or a foreign body)
4. Pneumonia
5. Whooping cough

Chronic cough

1. Allergies
2. Asthma (most common in children)
3. Bronchitis
4. Gastro esophageal reflux disease (GERD)
5. Postnasal drip

1.11.3 Cough Treatment: [21]

Mucolytics: mucolytics alter the structure of mucus to decrease its viscosity there by facilitating its removal by ciliary action or expectoration.

Acetylcysteine have thiol group, if this group is free as in Acetylcysteine, it may be substituted for di sulfide bonds in mucus and therefore break the mucus chain.

1.Acetylcysteine, Ambroxol, Bromhexine, Ethyl cysteinehydrochloride, Mecysteine

2. LITERATURE REVIEW

1. **Bhuvaneswari et al., (2016)** [22] has formulated Acebrophylline microballoons. They were prepared by emulsion solvent diffusion method using hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) as polymer. The micro balloons were evaluated with their Micromeritics properties, particle size, tapped density, compressibility index, angle of repose, percentage yield, *in vitro* buoyancy, entrapment efficiency; the results showed that the prepared floating micro balloons of Acebrophylline prove to be potential multiple-unit delivery devices adaptable for safe and effective sustained drug delivery.

2. **VermaRameshwar et al., (2014)** [23] reviewed Bilayer layer tablets. Bilayer tablet consist of two layers usually has slow release and immediate release layer. As well as improved beneficial technology to overcome the shortcoming of the single layer tablets. The preparations of bilayer tablet were needs due to separate incompatible active pharmaceuticalingredient(APIs) for each other. Various types of bilayer tablet press currently available in the market, various approaches used in bilayer tablet system, characterization as well as evaluation of the Bilayer tablet system. Now a day's Bilayer tablets are prepared such as Atorvastatin, Atenolol, Nifedipine, Aspirin, Losartan potassium and Trimetazidine hydrochloride, clopidogrelbisulphate.

3. **R.Charulatha et al., (2012)**[24]Formulated sustained release matrix tablets of Acebrophylline (200mg) prepared by wet granulation technique using hydrophilic polymers such as HPMC K 100M with Sodium CMC of various concentrations to examine their influence on tablet properties on drug release profile.The tablets were evaluated for physical characteristics like hardness, weight variation, friability and drug content. In-vitro release of drug was performed in 0.1 N HCl for 2 hours and remaining hours with PBS pH6.8. All the physical characters of the fabricated tablet were within acceptable limits. The stability studies showed that it followed zero order kinetics when fitted to kinetic models (Higuchi, Hixson and Peppas).It was clear from the dissolution profile of Acebrophylline from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent.

4. **Kang Jae Seon et al., (2014)** [25] studied to improve commercial twice-a-day Acebrophylline formulation to once-a-day new formulation to improve patient compliances. The double-layered tablet was composed of the fast release layer (Acebrophylline 50 mg) and sustained release layer (Acebrophylline 150 mg). To develop the double-layered tablet, the fast release and sustained release layers were prepared using polymer, wax, excipients and malic acid. The inclusion of malic acid in sustained release layer in double-layered tablet was showed to decrease release rates in pH 1.2 equal to dissolution rate of pH 6.8. This mean show that double-layered tablet using malic acid, Eudragit and carnauba wax is a promising approach for developing acebrophylline drug products.

5. VidaMokhtari et al., (2016) [26] reviewed on various applications of N-Acetylcysteine (NAC) in treatment of several diseases. N-Acetylcysteine (NAC), as a nutritional supplement, is a greatly applied antioxidant *in vivo* and *in vitro*. NAC is a precursor of L-cysteine that results in glutathione elevation biosynthesis. It acts directly as a scavenger of free radicals; especially oxygen radicals.NAC is a powerful antioxidant. It is also recommended as a potential treatment option for different disorders resulted from generation of free oxygen radicals. Additionally, it is protected and endured mucolytic drug that mellows tenacious mucous discharges. It has been used for treatment of various diseases in a direct action or in a combination with some other medications.

6. Tobias P. Dick et al., (2021) [27] reviewed N-Acetylcysteine (NAC). They were **i**nitially adopted as a mucolytic about 60 years ago, the cysteine prodrug N-Acetylcysteine (NAC) is the standard of care to treat paracetamol intoxication, and is included on the World Health Organization's list of essential medicines. Conventionally, it is assumed that NAC acts as (i) a reductant of disulfide bonds, (ii) a scavenger of reactive oxygen species and/or (iii) a precursor for glutathione biosynthesis. In this review, It was discussed that the validity of conventional assumptions and the scope of a newly discovered mechanism of action, namely the conversion of NAC into hydrogen sulfide and sulfane sulfur species.

7. **S. Dineshmohan et al., (2010)** [28] developed formulation of salbutamol sulphate fast dissolving tablet which can dissolve rapidly in the oral cavity. Asthma is an inflammatory disorder that results in the destruction of air pathways and causes difficulty in breathing. Thus, an attempt was made to improve the onset of action of bronchodilator used commonly in the treatment of asthma. The tablets were prepared by direct compression method using superdisintegrants such as Primojel, KollidonCL, L-Hydroxy propyl cellulose.The prepared tablets were evaluated for weight variation, thickness, friability, hardness, drug content, in vitro disintegration and in vitro drug release.

8.Niranjan panda et al., (2015)[29] developed Bilayer matrix tablet of doxofylline by providing a loading dose followed by the maintenance dose that suppose to enhance the therapeutic efficacy the drug for acute and sustainable asthma. Both immediate release layer and sustained release layer were prepared by wet granulation methods. Different Pre compression and post compression characterization of the tablet were carried out. In-vitro release studies were carried out in USP II paddle type dissolution apparatus for different formulations and release kinetic studies were carried out different kinetic model. Doxofylline bilayer matrix tablets were successfully developed and can be used as an alternative to the conventional dosage form because it can be therapeutically beneficial for management of asthma.

9. Swapna Ket al., (2014) [30] Developed and optimized sublingual tablets of montelukast sodium and levocetirizine dihydrochloride. The sublingual tablets of montelukast sodium and levocetirizine dihydrochloride were prepared by direct compression method using sodium starch glycolate, crospovidone (CP), and croscarmellose sodium (CCS) as superdisintegrants. An optimized tablet formulation F8 was found to have short wetting time of 18.36 seconds, water absorption ratio of 94.42 and *in-vitro* disintegration time of 45.42 seconds. The results indicated that the amount of super disintegrants such as CP and CCS significantly affected the dependent variables like wetting time, water absorption ratio and *in-vitro* disintegration time. The *in-vitro* drug release was found to be higher for formulation F8 with 94.59% for montelukast sodium and 95.48% for levocetirizine dihydrochloride within 60 minutes.

10. Balaji Maddiboyina et al., (2020) [31] developed bilayer floating tablet of Losartan and Hydrochlorothiazide as a fixed-dose combination for anti-hypertensive therapy. The bilayer tablets were primed through direct compression method. Losartan was formulated by means of a floating layer expending hydrophilic swellable polymer Hydroxy Propyl Methyl Cellulose K4M, ethyl cellulose (4cps) as a buoyancy enhancer, sodium bicarbonate as a gas spawning agent. The optimized formulation was imperilled to stability reading for three months at 40ºC/75% relative humidity. The stability revision exhibited no substantial alteration in the appearance of tablets, floating characteristics, drug content and in-vitrodrug dissolution. Consequently, a biphasic drug release design was effectively accomplished over the formulation of floating bilayer tablets.

11. **Remya PN et al., (2010)** [32]studied the formulation and evaluation of bilayer tablets of Ibuprofen and Methocarbamol. Wet granulation technique was employed for preparing granules using PVP K 30 as binder. The bilayer tablets were film coated using Advantiaprime clear film coat material. Nine batches of bilayer tablets were prepared. The *in vitro*release of the bilayer tablets were compared with the innovator and the release kinetics offormulation 8 were taken as optimized formulation due to its higher dissolution rate and complied all other parameters with the official specifications.

12. **Jadhav RT et al., (2011)**[33]formulated and evaluated bilayer tablets of Piracetam and Vinpocetine. Wet granulation technique was employed for formulation of both layers. PVP K 30 was used as binder for preparing Piracetam granules and maize starch was used as binder for preparing Vinpocetine granules. Sodium starch glycolate was used as superdisintegrant. Bilayer tablets were optimized based on the disintegration time and comparison of the dissolution profile with the innovator product.

13. **Hiremath JG et al., (2009)** [34]**S**tudied the preparation and physicochemical characterizationof Simvastatin loaded Mucoadhesive bilayer tablets. Tablets were prepared by directcompression technique by using mucoadhesive polymers such as Carbapol 934, HPMC and PVP in varying concentrations. Ethyl cellulose was used as backing membrane layer because of its water impermeable nature. The core layer was composed of drug andpolymer in varying concentrations. To the backing layer Carbapol 934 and PVP K 32 was added to avoid premature cracking. FTIR and DSC

were done to study the compatibility ofthe drug and excipients. F3 and F9 formulations were selected as optimized batch. F3 was selected for *in vitro* permeation studies based on its maximum drug release F9 formulation was selected based on the *in vitro* drug release, swelling index and good bioadhesive strength. The optimized batches were subjected to drug release kinetics.

14. AjitS Kulkarni et al., (2008) [35]prepared the floating bilayer tablets of Diltiazemhydrochloride and Lovastatin. Direct compression technique was employed for preparing bilayer tablets. Lovastatin was formulated as immediate release layer using sodium starch ,glycolate as super disintegrant and Diltiazem hydrochloride was formulated as sustained release layer comprising of HPMC K4M and Xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. All the formulations released the Lovastatin within 30 minutes. HPMC K4M and Xanthan gum sustained the release for 12 hours.

15. ZiyaurRahaman et al., (2006) [36] developed the Bilayer floating tablets of Captopril using direct compression technique. The floating layer was formulated with various HPMC grades (K4M, K15M and K100M) and effervescent mixture of citric acid and sodium bicarbonate. The sustained release layer comprised of Captopril and various polymers such as HPMC K15M, PVP K30 and Carbapol 934P alone or in varying combination with the drug. Final formulation released approximately 95% of drug in 24 hours, while the floating time was 10 min and the tablet remained floatable throughout the studies. Placebo formulation containing barium sulphate in the release layer administered to human volunteers for *in vivo* X-ray studies showed the BFT had significantly increased the gastric residence time.

16. Ankarao A et al.,(2010) [37]Prepared the buccoadhesive bilayer tablets of Metoprolol tartrate.Core tablet of Metoprolol tartrate was prepared by direct compression technique using HPMC K4M, SCMC and Carbapol 934 as bioadhesive polymers to impart mucoadhesion and ethyl cellulose to act as an impermeable backing layer. Six formulations containing the bioadhesive polymers were prepared. The formulation F2 and F5 were optimized and obeyed zero order release kinetics with Non-Ficki and diffusion.

17. Ankarao A et al., (2010) [38] studied the formulation and evaluation of Buccoadhesive Bilayertablets of Carvedilol. Direct compression was employed for preparing core tablets using HPMC K4M, SCMC, and Carbapol 934 as bio-adhesive polymer to impart mucoadhesion. Ethyl cellulose was used as impermeable backing membrane. The formulations containing HPMC and SCMC were optimized based on the buccoadhesive property and release characteristics.

18. Brijesh Patel et al., (2011) [39]designed and evaluated Mucoadhesive controlled release oral bilayer tablets of Indomethacin. Solid dispersion of Indomethacin was prepared using PEG6000 to improve the solubility of Indomethacin. Bilayer tablets were prepared using directcompression technique employing Ac-Di-Sol as superdisintegrant for immediate release layer and Carbapol 934 LR, HPC for sustained release layer. The polymers were used alone or in combinations. By varying the concentrations of polymers several batches were formulated. The batch containing the mixture of Carbapol 934 LR and HPC in the ratio of1:1 showed a better drug release than individual formulation containing Carbapol 934LR and HPC. The drug release kinetics was studied and it was found that the drug was released from the formulation by diffusion.

19. Nagaraju R et al., (2009) [40] Formulated and Evaluated bilayer sustained release tablets of Salbutamol and Theophylline. Wet granulation technique was employed for preparation of granules. PVP K30 in Isopropyl alcohol was used as a binder. Various polymers such as HPMC K4M, HPMC K100M, Xanthan gum, Ethyl cellulose and HPMC-P were studied. HPMC-P and HPMC K4M were found to be best in controlling the release.

20. **BhaveshShiyani et al., (2008)** [41] formulated and evaluated Bilayer tablets of Metoclopramidehydrochloride (MTH) and Ibuprofen (IB). MTH was formulated as immediate releaselayer by using various Disintegrants like Ac-Di-Sol, Polyplasdone XL, Explotab, Agar and Gellan Gum. The formulation containing Ac-Di-Sol was optimized for preparing Bilayer tablets. Sustained release layer of IB was formulated using hydrophilic matrix HPMCK4M, buffering agent, sodium bicarbonate and PVP K30. By increasing the concentrations of HPMC K4M and PVP K30 the release was reduced. By inclusion of buffering agent sodium bicarbonate the release was increased

as well as there is reduction in gastric irritation as IB is a weak acid. The drug release mechanism was found to be Quasi-Ficki and diffusion.

21. VinothkumarG et al., (2011) [42]formulated and evaluated bilayer tablets of Cefixime trihydrate and Dicloxacillin sodium. Wet granulation technique was used to formulate granules for both the layers. Cefiximetrihydrate was formulated as immediate release layer using Croscaramellose sodium as superdisintegrant. Sustained release layer of Dicloxacillin sodium was formulated by varying the concentrations of HPMC K4M and HPMC K100M. Nine batches of bilayer tablets were prepared. All the formulations were compared with the innovator product in respect to all tablet properties such as hardness, friability, disintegration time and dissolution. The percentage drug release of formulation F5 showed drug release comparable to the innovator product disintegration time and drug release and thus it was optimized and kept for further studies.

22. Naeem MA et al., (2010) [43] developed and evaluated controlled release bilayer tablets containing microencapsulated Tramadol and Acetaminophen. Microencapsulation based phase separation technique using medium viscosity ethyl cellulose was employed to formulate separate Micro particles for extending the release of both drugs. The Micro particles of both the drugs were prepared separately and were used for formulating the Bilayer tablets. The optimized batches were subjected for studying the release mechanism. The release kinetics was followed by Higuchi model with a good R2 value. The tablets were subjected to accelerated stability studies for 3 months.

23. Ashish A Pahade et al., (2010) [44] designed and developed Bilayer sustained release tablets of Isosorbidemononitrate. Wet granulation technique was employed for preparing granules using PVP K30 as binder. The immediate release granules were prepared using Croscaramellose Sodium as superdisintegrant. By varying the concentrations of HPMC K4M four formulations of bilayer tablets were prepared. The formulation containing HPMC K4M at a concentration of 19.33% w/w was selected as the optimized batch as it showed better *in vitro* release profile compared to other batches. The formulation containing 15% w/w showed better *in vitro* release profile and thus it was optimized for further studies.

24. Ramana G et al., (2010) [45] formulated and evaluated the sustained release Bilayer tablets of Ambroxol hydrochloride. The tablets were prepared by direct compression technique using sodium starch glycolate as super Disintegrants for fast release layer and CR grade polymers such as HPMC K4M, Ethyl cellulose independently and also in combinations. The formulation containing Drug: HPMC: EC at the ratio of 1:0.5:30% exhibited an initial burst effect followed by sustained release over a period of 12 hours. The dissolution data of various formulations were fitted into Higuchi and Peppas models, which are linear with Higuchi's plot and "n" values obtained from Peppas were within 0.45 to 0.89 indicate the mechanism of drug release diffusion coupled with erosion.

25. Gohel MC et al., (2010) [46] Fabricated and evaluated Bilayer tablets containing conventional Paracetamol and modified release Diclofenac sodium. A 2^3 full factorial design was adopted using the amount of polyethylene glycol, microcrystalline cellulose and Crospovidone as independent variables for fabricating Paracetamol tablets. Diclofenacsodium tablets were prepared using varying concentrations of HPMC K4M as matrixing agent. The results of analysis of variance showed that the friability of Paracetamol was distinctly influenced by the formulation variables. Diclofenac sodium layer was optimized by comparing the formulation with the innovator product. The optimized layers were finally compressed into bilayer tablets. The tablets were subjected for drug release mechanism. It was found out that the bilayer tablets followed Korsmeyer-Peppas model.

3. AIM OF THE WORK

More than 90% of the modern formulations are to be orally ingested. This shows the popularity of this formulation type over the world thus, a majority of the researchers prefer to focus on it. Bilayer tablets are the medicines which consist of two same or different drugs combined in a single dose for effective treatment of the disease. The aim of present research work was undertaken to formulate bilayer tablets of Acebrophylline (mucolytic and bronchodilator) and N-Acetylcysteine through its incorporation of an oral dosage form that is able to release immediately. Both of drugs compressed one after other in Bi-layer tablet machine rather mixed together to form single layer inorder to reduce incombatibility and formation of N, N-diacetylcystine (breakdown product) from N-acetylcysteine. While the layer of Acebrophylline unaffected, a computer-aided optimization technique using 2^3 (three-factor and two-level) factorial design was employed to investigate the effect of the amounts of three anti-oxidants of Butylated-hydroxy toluene 0.4 and 0.8 mg/tablet, Vitamin E (as concentrated) 0.1,0.4 mg/tablet, and Propyl gallate 0.4,0.8 mg/tablet, planned as three independent process variables (factors), and level of N, N-diacetylcystine used as dependent variable in the study. Therefore, eight trial formulation done with the independent variable and evaluated for micrometric properties and dissolution. The optimized batch also planned for evaluation of all parameter including kinetic and stability study.

4. PLAN OF WORK

The work was planned as mentioned below

Stage I

- Pre formulation study
- Drug – Excipent compatibility in IR
- To perform 2^3 factorial design to optimization of different type of antioxidant

Stage II

- Formulation of Immediate- release granules of Acebrophylline.
- Formulation of Immediate-release granules of Acetylcysteine.
- Evaluation of Immediate- release granules of Acebrophylline.
    - Bulk density
    - Tapped density
    - Carr's compressibility index
    - Hausner's ratio
- Evaluation of Immediate-release granules of Acetylcysteine.
- Compression of Bilayer tablets.
- Evaluation of compressed Bilayer tablets
    - Physical appearance
    - Thickness
    - Hardness
    - Weight variation
    - Friability
    - Assay

Stage III

Stability studies of the satisfactory formulation will be carried out as pre ICH – Guidelines

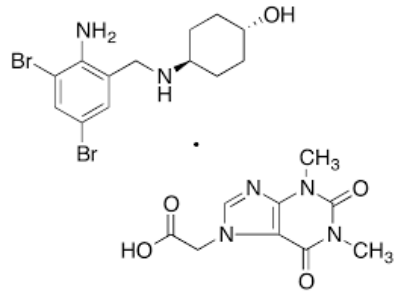
5. DRUG PROFILE

5.1 Acebrophylline: [47]

Category : Anti-Asthmatic

Class : Xanthines

Structure :



Chemical : 4-[(2-amino-3,5-dibromophenyl) methylamino] cyclohexan-1-ol;2-(1,3-dimethyl-2,6-dioxopurin-7-yl)acetic acid

Molecular formula : C22H28Br2N6O5

Molecular weight : 616.3 g/mol

Dose : Therapy usually is initiated with 100mg orally twice a day.

Description : Acebrophylline a white or off white powder.

Solubility : It is soluble slightly soluble in water and methanol and soluble in ethanol

5.2 Pharmacology:

Therapeutic category: Anti-asthmatic

5.3 Mechanism of action:

Theophylline-7-acetate ha bronchodilator effect due to inhibition of the intracellular phosphodiesterases, followed by increase in cyclic AMP level which promote the relaxation of bronchial muscles. Ambroxol act as a mucolytic agent by increases the mucociliary clearance by stimulating cilia motility. Acebrophylline inhibit the synthesis and release of leukotrienes and tumor necrosis factor and reduces inflammation.

5.4 Pharmacokinetics: [49]

Absorption	:	Absorbed after oral administration
Distribution	:	Widely distributed in the body
Metabolism	:	Metabolized in the liver
Excretion	:	Excreted through urine

Onset of Action for Acebrophylline: 1 to 2 hours

Half Life of Acebrophylline **:** 4 to 9 hours

5.5 Typical Dosage for Acebrophylline:

1. Adult : 100 mg twice daily
2. Children up to 2 years, it`s half a teaspoon, twice daily.
3. Age 2 to 5 is half a teaspoon, three times a day
4. Children age over 5 , it's a teaspoon 2 to 3 times a day.

5.6 Contra-indications of Acebrophylline:

1. Hypersensitivity to Ambroxol and xanthine derivative
2. Myocardial infraction
3. Hypotension
4. Renal disease
5. Liver disorder
6. Hemodynamic instability and arrhythmias

5.7 Side Effects of Acebrophylline:

1. Abdominal discomfort
2. Stomach/abdominal distension
3. Vomiting
4. Diarrhea
5. Constipation
6. Esophageal bleeding

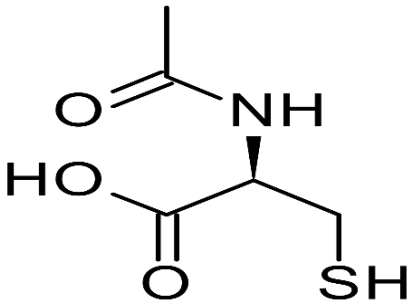
5.8 Therapeutic use:

Bronchodilator, Mucoregulator, Anti inflamatory drug salt of theophylline-7-acetic acid with ambroxol.

5.9 N- Acetylcysteine: [48]

Category : Mucolytic agent for bronchopulmonary disorders

Structure :



Chemical Name : (2*R*)-2-acetamido-3-sulfanylpropanoic acid

Molecular formula : C5H9NO3S

Molecular weight : 163.20 0g/mol

Dose : Therapy usually is initiated with 600mg orally once a day.

Description : N-Acetylcysteine is a white and white crystalline powder.

Odor : slightly acetic odour

Taste : characteristic sour taste

Melting point : 109-110

Solubility : 1 g in 5 ml water, 4 ml alcohol; practically insoluble in chloroform &Ether. Soluble in water, alcohol, hot isopropyl alcohol, methyl acetate, and ethyl acetate**.**

Stability : Stable in ordinary light; stable at temp up to 120 °C; non- hygroscopic (oxidizes in moist air)

5.10 Pharmacology:

Therapeutic category : Anti-asthmatic

Mechanism of action:

N-Acetylcysteine well-known mucolytic agents. In particular, when oral administered, acetylcysteine (and its metabolic by product cysteine) exerts its mucolytic action through its free sulfhydryl group, which reduces the disulfide bonds in the mucus matrix and lowers mucus viscosity. This action increases with increasing pH and is most significant at pH 7 to 9. The mucolytic action of Acetylcysteine is not affected by the presence of DNA.

5.11 Pharmacokinetics:

5.12 Absorption and Distribution:

Bioavailability is 6–10% following oral administration and less than 3% following topical administration.

Bioavailability	**:**	6-10%
Plasma protein binding	**:**	66-97%
Volume of distribution	**:**	0.47 L/kg
Biological half life	**:**	5.6 hours
Tmax	**:**	2 hours
Elimination	**:**	Acetylcysteine is 13-38% through urine

Drug interaction N-acetylcysteine:

Medication interaction	**:**	charcoal, ifosamide, insulin inhalation
Disease interaction	**:**	Hepatic encephalopathy, asthma, fluid overload gastric hemorrhage

5.13 Side Effects of N-Acetylcysteine: [50]

- Bronchospasm
- Disagreeable odor
- Drowsiness
- Fever
- Coughing up blood
- Increased volume of bronchial secretions
- Irritation of tracheal or bronchial tract
- Nausea
- Runny or stuffy nose
- Swelling and sores inside the mouth
- Vomiting
- Clamminess
- Wheezing
- Shortness of breath

5.14 Therapeutic use:

Acetylcysteine mainly used as a mucolytic agents and Paracetamol (acetaminophen) overdose.

6. EXCIPIENTS PROFILE

6.1 *Lactose, Monohydrate:* [51]

1. Synonyms:

CapsuLac; GranuLac; Lactochem; lactosum monohydricum;Monohydrate; Pharmatose;

2. Empirical Formula

C12H22O11_H2O

3. Molecular Weight:

360.31

4. Functional category:

Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

5. Description:

Lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate ,β-lactose anhydrous, and β-lactose anhydrous. The stable crystalline forms of lactose are α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous.

Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet.

6. Solubility:

It is practically insoluble in ethonal ,ether, chloroform. Soluble in water 1 in 5.4ml.

7. Applications:

Lactose is widely used as a filler and diluents in tablets and capsules and to a more limited extent in lyophilized products. Lactose is also used as diluents in dry-powder inhalation. Usually, fine grades of lactose are used in the preparation of tablets by the wet-granulation method or when milling during processing is carried out, since the fine size allows better mixing with other formulation ingredients and utilizes the binder more efficiently.

Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as granulated/agglomerated a-lactose monohydrate,

containing small amounts of anhydrous lactose. Direct-compression grades are often used to carry lower quantities of drug and this permits tablets to be made without granulation.

6.2 Microcrystalline Cellulose: [52]

1. Non proprietary Names:

BP: Microcrystalline Cellulose, JP: Microcrystalline Cellulose, PhEur: Cellulose, Microcrystalline, USP-NF: Microcrystalline Cellulose

2. Synonyms:

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum;

Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur

3. Chemical Name and CAS Registry Number:

Cellulose [9004-34-6]

4. Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)_n$~36 000

Where n~220.

5. Description:

Microcrystalline cellulose is a purified, partially de polymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available. In different particle sizes and moisture grades that have different properties and applications.

6. Solubility:

Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most organic solvents.

7. Functional Category:

Adsorbent, suspending agent, tablet and capsule diluents and tablet disintegrates.

8. Applications:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and Disintegrants properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

6.3 Povidone: [53]

1. Nonproprietary Names:

BP: Povidone, JP: Povidone, PhEur: Povidone, USP: Povidone

2. Synonyms:

polyvidone; polyvinyl pyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

3. Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

4. Empirical Formula and Molecular Weight:

(C6H9NO) n 2500–3000000

5. Description:

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidone with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidone are manufactured by drum drying and occur as plates.

6. Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

7. Functional Category:

Disintegrants; dissolution enhancer; suspending agent; tablet binder.

8. Applications

Povidone is used in a variety of pharmaceutical formulations; it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydro alcoholic solutions.

Povidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents or as binders when coating active pharmaceutical ingredients on a support such as sugar beads.

Povidone is additionally used as a suspending, stabilizing, or viscosity-increasing agent in a number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

6.4 Isopropyl Alcohol: [54]

1. Nonproprietary Names:

Isopropyl Alcohol (BP, JP, PhEur, USP)

2. Synonyms:

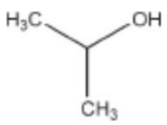
Alcohol isopropylicus, dimethyl carbinol, IPA, isopropanol, petrohol, 2propanol,sec-propyl

3. Chemical Name : Propan-2-ol

4. Empirical Formula : C_3H_8O

5. Molecular Weight : 60.1

6. Structural Formula :



7. Description:

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor and it has a slightly bitter taste.

8. Typical Properties:

Boiling point	:	82.4^0C
Flammability	:	Flammable.
Viscosity (dynamic)	:	2.43 mPas at 20^0C
Specific gravity	:	0.786

9. Solubility:

Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone.insolubl e in salt solutions.

10. Functional Category: Disinfectant, solvent.

11. Applications in Pharmaceutical Formulation or Technology

Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, where the isopropyl alcohol is subsequently removed by evaporation. It has also been shown to significantly increase the skin permeability of nimesulide. Isopropyl alcohol has some antimicrobial activity and a 70% v/v aqueous solution is used as a topical disinfectant. Therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

12. Storage Conditions:

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

13. Incompatibilities:

Incompatible with oxidizing agents such as hydrogen peroxide and nitricacid which cause decomposition.

14. Safety:

Isopropyl alcohol is most frequently used in topical pharmaceutical formulations where it may act as a local irritant. When applied to the eye it can cause corneal burns and eye damage.

6.5 Crospovidone: [55]

1. Non proprietary Names:

BP : Crospovidone, PhEur : Crospovidonum, USPNF : Crospovidone

2. Synonyms:

Crosspovidonum ; crospopharm ; croslinked povidone; polyplasdone XL ; Polyvinyl polypyrrolidine.

3. Chemical name:

1 – ethenyl – 2 - pyrrolidine homopolymer.

4. Empirical Formula and Molecular Weight:

(C6H9NO) n >1 000000

5. Description:

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

6. Moisture Content **:** Maximum moisture sorption is approximately 60%.

7. Solubility : Practically insoluble in water and most common organic solvents.

8. Functional Category: Tablet Disintegrants

9. Applications in Pharmaceutical Formulation:

Crospovidone is a water-insoluble tablet disintegrate and dissolution agent used at 2-5% concentration in tablets prepared by direct compression or wet and dry-granulation methods. It is rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

The drug is adsorbed on to Crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

10. Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, Crospovidone may form molecular adduct with some materials like sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital and tannin.

6.6 Colloidal Silicone Dioxide (Aerosil): [56]

1. Nonproprietary Names:

BP	:	Colloidal anhydrous silica
PhEur	:	Silica colloidal is anhydrica
USPNF	:	Colloidal silicon dioxide

2. **Synonyms:**
3. colloidal silica; fumed silica;fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silicacolloidalis anhydrica; silica sol; silicic anhydride; silicondioxidecolloidal; silicon dioxide fumed; synthetic amorphous silica;

3. Chemical Name and CAS Registry Number:

Silica [7631-86-9]

4. Empirical Formula and Molecular Weight:

SiO2 -60.08

5. Functional Category:

Adsorbent, anti-caking agent, emulsion stabilizer, glidant, suspending agent, tablet Disintegrants, thermal stabilizer, and viscosity-increasing agent.

6. Applications in Pharmaceutical Formulation or Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area gives desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting.

7. Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, and non-gritty amorphous powder.

8. Stability and Storage Conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0-7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity- increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

6.7 Talc: [57]

1. Nonproprietary Names:

BP: Purified Talc

JP: Talc

PhEur: Talc

USP: Talc

2. Synonyms:

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Imperial; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc;

Purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

3. Chemical Name and CAS Registry Number:

Talc [14807-96-6]

4. Empirical Formula and Molecular Weight:

Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg6 (Si2O5)4(OH) 4. It may contain small, variable amounts of aluminum silicate and iron.

5. Description:

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

6. Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents, and water

7. Functional Category:

Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

8. Applications in Pharmaceutical Formulation or Technology:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, although today it is less commonly used. However, it is widely used as a dissolution retardant in the development of controlled-release products.

6.8 Magnesium stearate: [58]

1. Nonproprietary Names:

BP: Magnesium Stearate

JP: Magnesium Stearate

PhEur: Magnesium Stearate

USP-NF: Magnesium Stearate

2. **Synonyms:**

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

3. Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt [557-04-0]

4. Empirical Formula and Molecular Weight:

$C_{36}H_{70}MgO_4$ 591.24

5. Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Crystalline Forms	:	High purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Flow ability	:	Poorly flowing, cohesive powder.
Melting range	:	117-150 ^{o}C (commercial samples) 126-130 ^{o}C (High purity magnesium stearate)
Solubility	:	Practically insoluble in ethanol, Ether and water; slightly soluble in warm benzene and warm ethanol (95 %)

6. Functional category:

Tablet and capsule, lubricant

7. Applications:

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and5.0 % w/w.

8. Safety:

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

6.9 Cyclodextrins: [59]

1. Nonproprietary Names:

BP: Alfadex Betadex

PhEur: Alfadex Betadex

USP-NF: Alfadex Betadex Gamma Cyclodextrin

2. Synonyms:

Cyclodextrin Cavitron; cyclic oligosaccharide; cycloamylose; cycloglucan; Encapsin; Schardinger dextrin.

α-Cyclodextrin alfadexum; alpha-cycloamylose; alpha-cyclodextrin; alpha-dextrin; Cavamax W6 Pharma; cyclohexaamylose;cyclomaltohexose.

β-Cyclodextrin beta-cycloamylose; beta-dextrin; betadexum;Cavamax W7 Pharma; cycloheptaamylose; cycloheptaglucan; cyclomaltoheptose; Kleptose.

γ-Cyclodextrin Cavamax W8 Pharma; cyclooctaamylose; cyclomaltooctaose.

3. Chemical Name and CAS Registry Number:

α -Cyclodextrin [10016-20-3]

β -Cyclodextrin [7585-39-9]

γ -Cyclodextrin [17465-86-0]

4. **Empirical Formula and Molecular Weight:**

α –Cyclodextrin- C36H60O30 972

β –Cyclodextrin- C42H70O35 1135

γ –Cyclodextrin- C48H80O40 1297

5. Description:

Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

6. Solubility:

α -cyclodextrin: soluble 1 in 7 parts of water at 20ºC, 1 in 3 at 50C.

β -cyclodextrin: soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20ºC, 1 in 20 at 50ºC; practically insoluble in acetone, ethanol (95%), and methylene chloride.

γ -cyclodextrin: soluble 1 in 4.4 parts of water at 20ºC, 1 in 2 at 45ºC.

7. Functional Category:

Solubilizing agent; stabilizing agent.

8. Applications in Pharmaceutical Formulation or Technology:

Cyclodextrins are crystalline, non-hygroscopic, cyclic oligosaccharides derived from starch. Among the most commonly used forms are α -, β -, and γ -cyclodextrin, which have respectively 6, 7, and 8 glucose units. Substituted cyclodextrin derivatives are also available Cyclodextrins are ‘bucketlike’ or ‘conelike’ toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type. The internal surface of the cavity is hydrophobic and the outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex. Cyclodextrin may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability.

Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material. β -Cyclodextrin

is the most commonly used cyclodextrin, although it is the least soluble. It is the least expensive cyclodextrin is commercially available from a number of sources; and is able to form inclusion complexes with a number of molecules of pharmaceutical interest. However, β -cyclodextrin is nephrotoxic and should not be used in parenteral formulations. β -Cyclodextrin is primarily used in tablet and capsule formulation.

α -Cyclodextrin is used mainly in parenteral formulations. However, as it has the smallest cavity of the cyclodextrins it can form inclusion complexes with only relatively few, small-sized molecules. In contrast, γ -cyclodextrin has the largest cavity and can be used to form inclusion complexes with large molecules; it has low toxicity and enhanced water solubility.

In oral tablet formulations, β -cyclodextrin may be used in both wet-granulation and direct compression processes. The physical properties of β -cyclodextrin vary depending on the manufacturer.

However, β -cyclodextrin tends to possess poor flow properties and requires a lubricant, such as 0.1% w/w magnesium stearate, when it is directly compressed. In parenteral formulations, cyclodextrins have been used to produce stable and soluble preparations of drugs that would otherwise have been formulated using a no aqueous solvent. In eye drop formulations, cyclodextrins form water-soluble complexes with lipophilic drugs such as corticosteroids. They have been shown to increase the water solubility of the drug; to enhance drug absorption into the eye; to improve aqueous stability; and to reduce local irritation.

9. Stability and Storage Conditions

β-Cyclodextrin and other cyclodextrins are stable in the solid state if protected from high humidity.

Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

6.10 Alpha Tocopherol: [60]

1. Nonproprietary Names:

BP: RRR-Alpha-Tocopherol

JP: Tocopherol

PhEur: RRR-α-Tocopherol

USP: Vitamin E

2. Synonyms:

Copherol F1300; (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol; E307; RRR-α-tocopherolum; synthetic alpha tocopherol; all-rac-α-tocopherol; dl-α-tocopherol;5,7,8-trimethyltocol.

3. Chemical Name:

(±)-(2RS,40RS,80RS)-2,5,7,8-Tetramethyl-2-(40,80,120-trimethyltridecyl)-6-chromanol

4. Empirical Formula and Molecular Weight:

C29H50O2 - 430.72

5. Description:

Alpha tocopherol is a natural product. The PhEur 6.0 describes alpha-tocopherol as a clear, colorless or yellowish-brown, viscous, oily liquid.

6. Solubility:

Practically insoluble in water; freely soluble in acetone, ethanol, ether, and vegetable oils.

7. Functional Category:

Antioxidant , therapeutic agent.

8. Applications in Pharmaceutical Formulation or Technology:

Alpha tocopherol is primarily recognized as a source of vitamin E, and the commercially available materials and specifications reflect this purpose. While alpha tocopherol also exhibits antioxidant properties, the beta, delta, and gamma tocopherols are considered to be more effective as antioxidants. Alpha-tocopherol is a highly lipophilic compound, and is an excellent solvent for many poorly soluble drugs. Of widespread regulatory acceptability, tocopherols are of value in oil- or fat-based pharmaceutical products and are normally used in the concentration range 0.001–0.05% v/v. There is frequently an optimum concentration; thus the autoxidation of linoleic acid and methyl linolenate is reduced at low concentrations of alpha tocopherol, and is accelerated by higher concentrations. Antioxidant effectiveness can be increased by the addition of oil-soluble synergists such as lecithin and ascorbyl palmitate. Alpha tocopherol may be used as an efficient plasticizer. It has been used in the development

of deformable liposomes as topical formulations. d-Alpha-tocopherol has also been used as a non-ionic surfactant in oral and injectable formulations.

6.11 Butylated Hydroxytoluene: [61]

1. Nonproprietary Names:

BP: Butylated Hydroxytoluene

PhEur: Butylhydroxytoluene

USP-NF: Butylated Hydroxytoluene

2. Synonyms:

Agidol; BHT; 2,6-bis(1,1-dimethylethyl)-4-methylphenol; butylhydroxytoluene;

butylhydroxytoluenum; Dalpac; dibutylated hydroxytoluene; 2,6-di-tert-butyl-p-cresol; 3,5-di-tert-butyl-4- hydroxytoluene; E321; Embanox BHT; Impruvol; Ionol CP;Nipanox BHT; OHS28890; Sustane; Tenox BHT; Topanol; Viano.

3. **Chemical Name and CAS Registry Number:**

2,6-Di-tert-butyl-4-methylphenol [128-37-0]

4. Empirical Formula and Molecular Weight:

C15H24O- 220.35

5. Description:

Butylated hydroxytoluene occurs as a white or pale yellow crystalline solid or powder with a faint characteristic phenolic odor.

6. Solubility:

Practically insoluble in water, glycerin, propylene glycol, solutions of alkali hydroxides, and dilute aqueous mineral acids. Freely soluble in acetone, benzene, ethanol (95%), ether, methanol, toluene, fixed oils, and mineral oil.More soluble than butylated hydroxyanisole in food oils and fats.

7. Functional Category:

Antioxidant**.**

8. Applications in Pharmaceutical Formulation or Technology:

Butylated hydroxyl toluene is used as an antioxidant in cosmetics, foods, and pharmaceuticals.(1–4) It is mainly used to delay or prevent the oxidative rancidity of fats and oils and to prevent loss of activity of oil-soluble vitamins.

Butylated hydroxytoluene is also used at 0.5–1.0% w/w concentration in natural or synthetic rubber to provide enhanced color stability.

Butylated hydroxytoluene has some antiviral activity and has been used therapeutically to treat herpes simplex labialis.

6.12 Propyl Gallate: [62]

1. Nonproprietary Names:

BP: Propyl Gallate

PhEur: Propyl Gallate

USP-NF: Propyl Gallate

2. Synonyms:

E310; gallic acid propyl ester; n-propyl gallate; Progallin P; propyl 3,4,5-trihydroxybenzoate; propylis gallas; Tenox PG.

3. **Chemical Name and CAS Registry Number:**

3,4,5-Trihydroxybenzoic acid propyl ester [121-79-9]

4. Empirical Formula and Molecular Weight:

C10H12O5 212.20

5. Description:

Propyl gallate is a white, odorless or almost odorless crystalline powder, with a bitter astringent taste that is not normally noticeable at the concentrations employed as an antioxidant.

6. Solubility:

Slightly soluble in water and practically insoluble in peanut oil. Ethanol(95%) and Ether soluble in 1 in 3 part of water at 20ºC.

7. Functional Category:

Antioxidant

8. Applications in Pharmaceutical Formulation or Technology:

Propyl gallate has become widely used as an antioxidant in cosmetics, perfumes, foods, and pharmaceuticals since its use in preventing antioxidation of oils was first described in 1943. It is primarily used, in concentrations up to 0.1% w/v, to prevent the rancidity of oils and fats; it may also be used at concentrations of 0.002% w/v to prevent peroxide formation in ether, and at 0.01%W/v to prevent the oxidation of paraldehyde. Synergistic effects with other antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene have been reported. Propyl gallate is also said to possess some antimicrobial properties. Studies have shown that, when added to powder blends containing ketorolac, propyl gallate significantly increases the drug stability in the preparation.Other alkyl gallates are also used as antioxidants and have approximately equivalent antioxidant properties when used in equimolar concentration; however, solubilities vary;Propyl gallate has also been investigated for its therapeutic properties, mainly in animal studies.

6.13 Quinoline yellow supra:

1. Synonyms:

Quinoline Yellow, Quinophthalone,Solvent yellow 33,Erio Chinoline Yellow 4G

2-quinolin-2-ylindene-1,3-dione,2-(2-Quinolyl)-1,3-indandione.

2. Chemical Name:

2-quinolin-2-ylindene-1, 3-dione

3. Empirical Formula and Molecular Weight:

C18H11NO2 273.3

4. Description:

D & c yellow 11 appears as bright greenish yellow solid or canary yellow powder.

Bright Greenish Yellow.

5. Solubility:

Soluble in acetone, benzene, toluene and xylene; slightly soluble in ethyl acetate, linseed oil, mineral oil, paraffin wax and stearic acid.

6. Functional Category:

Synthetic organic colorants

7. Applications in Pharmaceutical Formulation:

Quinoline yellow can be used to color cosmetics, drugs, and food, including dietary supplements

6.14 Ethyl Vanniline:

1. Synonyms:

3-Ethoxy-4-hydroxybenzaldehyde,Ethylvanillin

2. Chemical Name:

3-ethoxy-4-hydroxybenzaldehyde

3. Empirical Formula and Molecular Weight:

$C_9H_{10}O_3$ 273.3

4. Description:

Ethyl vanillin appears as White powder. More intense vanilla odor and taste than vanillin. Characteristic odour. Finer and more intense taste than vanillin.

5. Solubility:

Slightly soluble in water. Soluble in ethanol, ether, benzene, chloroform

6. Functional Category:

Flavoring agents

7. Applications in Pharmaceutical Formulation:

Vanillin is used in perfumes and fragrances in both cleaning products and candles, in the food industry to flavor chocolate, baked goods, and ice cream, and in medicines to mask unpleasant flavors.

6.15 Methylene Chloride:

1. Chemical Name:

Dichloromethane

2. Other Names:

Methylene chloride, methlene dichloride, narkotil, solaesthin.

3. Appearance **:** Colourless liquid

4. Melting point **:** 96.7˚C

5. Taste **:** Sweet aroma

6. Applications:

DCM's volatility and ability to dissolve a wide range of organic compounds makes it a useful solvent for many chemical processes. Concerns about its health effects have led to a search for alternatives in many of these applications.

- Paint stripping
- Pharmaceutical manufacturing
- Metal cleaning
- Paint remover

6.16 Mixed Fruits:

1. Description:

Appearance : white powder

Odour : Characteristic odour

Physical status: powder

2. Solubility:

Mixed fruits soluble in water

3. Functional Category:

Flavoring agents

4. Applications in Pharmaceutical Formulation:

Mixed fruits can be used to mask to unpleasant flavour.

7. MATERIALS

Table 1: Materials used in the study

S. no	Materials	Manufacturers/ suppliers
1	Acebrophylline	Kores India Ltd
2	Acetylcysteine	Wuhan Grand Hoyo,China
3	Microcrystalline Cellulose	DFE Pharmaltd,Cuddalore
4	Lactose Monohydrate	DFE Pharmaltd,Cuddalore
5	Povidone K30	JH Nanhang Life Science Ltd, China
6	Crospovidone 10	JH Nanhang Life Science Ltd,China
7	Quinoline yellow supra	Neelikon Food Dyes And Chemical Ltd , Mumbai
8	Colloidal silicon dioxide (Aerosil)	Cobatsanmer Ltd, Mettur Dam
9	Talc	Gangotria In Organic Ltd,Mumbai
10	Magnesium stearate	Accent Pvt Ltd, Ahmedabad
11	B-Cyclodextrin	Gangwal Chemical Ltd,Mumbai
12	Vitamin E concentrated pdt	Dsm Nutritional Pdtltd,Switzerland
13	ButylatedHydroxy Toluene	Finer Ltd,Mumbai
14	Propyl Gallate	Pan Reacapplichemltd,India
15	Banana Flavour	Kp Manish Growth Essential Ltd,Chennai
16	Powderome strawberry Flavour	Kp Manish Growth Essential Ltd,Chennai
17	Ethyl vanilline	Symega Food Ingredients Ltd,Kerala
18	Mixed fruits delight powder flavour	Symega Food Ingredients Ltd,Kerala
19	Isopropyl Alcohol	Deepak Fertiliser& Petrochemical Ltd,Mumbai
20	Methylene di chloride	Chemplast sanmar ltd,Chennai
21	Dr Coat Flv	Vikram Thermo Ltd, Ahmedabad

Table 2: Manufacturing Equipments used in the study

S. No	Equipments	Manufacturers/ Suppliers
1	Halogen Moisture Analyser	Radwag
2	Vibratory Sifter	Sams Techno Mechpvt.Ltd
3	Saizonar Mixer Granulator	Sainath Boiler & Pneumatics
4	Mechanical Stirrer	REMI Motors
5	Octagonal Blender	Sams Techno Mechpvt.Ltd
6	Tray Drier	Tapasaya Engineering Work PVT.Ltd
7	Compression (10 Station)	Karnavathi Engineering Ltd
8	Multi Mill	Sams Techno Mechpvt.Ltd
9	Vernier Caliper	Mitutoya Absolute
10	Coating Machine	Pharma R&D Coater,Ideal Cure Pvt.Ltd
11	Blister Packing Machine	Mech Tek
12	Photo Stability And Humidity Chamber	Newtronic

Table 3: List of Instruments used in the study

S. No	Instruments	Manufacturers/ Suppliers
1	Electronic Weighing Balance-220G	Mettler Toledo
2	Electronic Weighing Balance-3.2KG	Mettler Toledo
3	Tap Density Apparatus, ETD-1020	Electrolab
4	Hardness Tester	Thermonik- Campbell Electronics
5	Friability Test Apparatus, Et-2	Electrolab
6	Dissolution Apparatus, Tdt-08l,	Electrolab
7	Disintegration Apparatus	Electrolab
8	Ft-Ir Spectrophotometer 8300	Electrolab
9	HPLC With PDA&UV-Visible Detector	Shimadzu

Table 4: List of Reagents used in the study

S. No	Reagents/ chemicals	Manufacturers/suppliers
1	Acetonitrile HPLC	Rankam Laboratories
2	Methanol HPLC	Rankam Laboratories
3	Ortho Phosphoric Acid AR	Rankam Laboratories
4	Hydrochloric Acid AR	Rankam Laboratories
5	Potassium Hydroxide	Rankam Laboratories
6	Whatman Filter Paper	Rankam Laboratories
7	0.45 µ Filter Paper	Rankam Laboratories

8. METHODS

8.1 Preformulation studies:

8.1.2 Drug –excipients compatibility (FT-IR) study of Acebrophylline & Acetylcysteine:

Drug –excipient compatibility for Acebrophylline was done as per IP by the identification test carried out by the Fourier Transform Infrared spectrophotometer (FTIR) and the report was shown in figures 6-9.

Drug –excipient compatibility for for Acetylcysteine was done as per USP by the identification test carried out by the Fourier Transform Infrared spectrophotometer (FTIR) and the reports were shown in figures 6-9.

8.2 Manufacturing process of Acebrophylline and Acetylcysteine Bilayer Tablets:

8.2.1 Acebrophylline Part:

Sifting:

Acebrophylline was sifted individually by using #20mesh.Microcrystalline cellulose,lactose monohydrate was sifted by using #30mesh.

Binder solution:

Povidonek30 was dissolved in isopropyl alcohol added Quinoline yellow supra

Dry Mix and Granulation:

Transfer the sifted materials and Binder solution to Granulation area. Load the sifted material into the main bowl of Saizonar mixer granulator and slowly added to binder solution and mixed it for 15 minutes.

Initial Drying, Sifting and Milling:

Transfer wet granules in tray drier at 50°C. Initial air dry the wet granules for 20mins.after continue the drying at 50°C for 1hour 20mins.The Semi-Dried granules passed through mesh 16# and milled the retained granules through Multi-Mill fitted with 1.0 mm screen using knives forward medium speed.

Final drying and sifting:

Transfer the semidried sifted and milled granules into tray drier. Dry the semidried sifted granules .with infra-Red Moisture balance determine the moisture content at 105ºC If it is found more continue the drying until the desired moisture content is achieved(Limt:2-4%).Finally Passed the dried granules through #16 mesh.

Extra granular part:

Sifted the following materials cross povidone, colloidal silicon dioxide, talc sifted individually by using #40 mesh. Loaded the dried granular and sifted extra granular materials into Octagonal blender blended for 15minutes at 10 rpm.

Lubrication:

Magnesium stearate was dispensed and sifted by using # 60 mesh, To this above blend mixed for 5 minutes at 10 rpm.

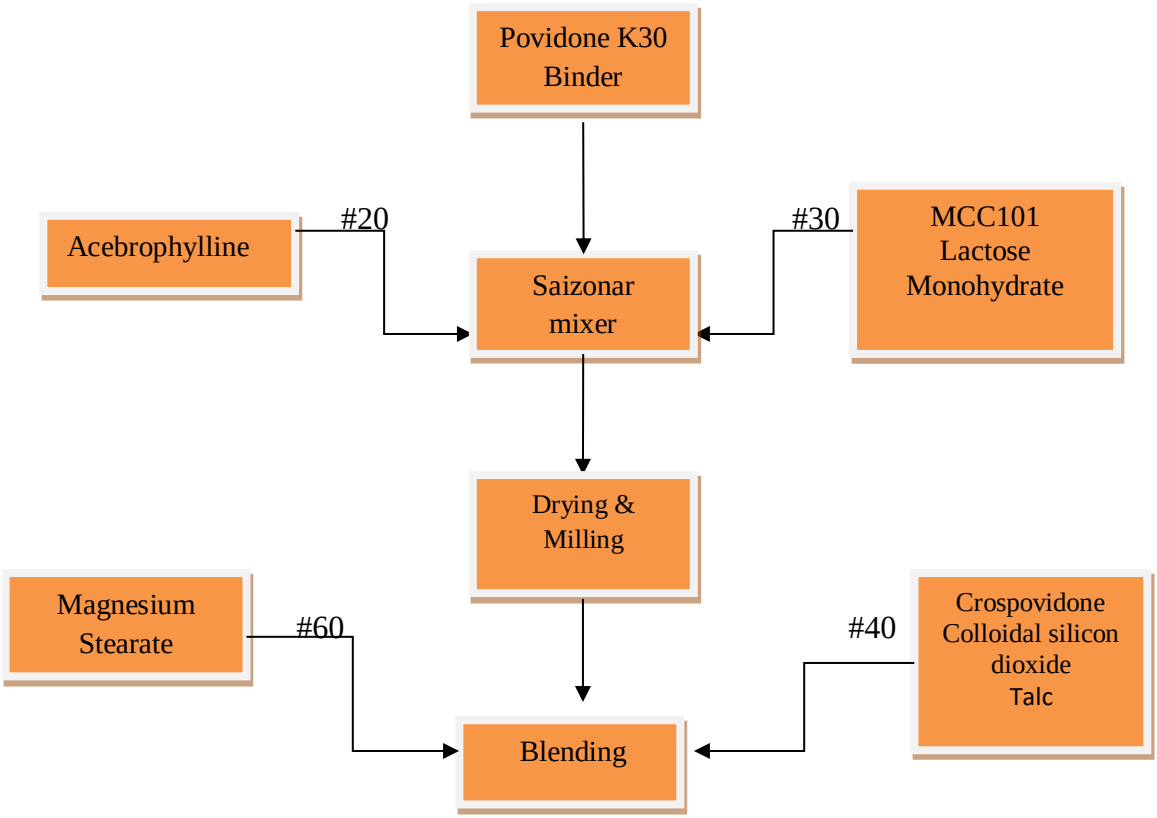


Fig. 3: Flow chart of Acebrophylline Granules preparation

8.2.2 Acetylcysteine Part:

Sifting:

Sift the weighed quantities of Acetylcysteine, β-cyclodextrin, colloidal silicon dioxide, Talc,butaylated hydroxyl Touene, propyl gallate,vitamine E concentrated powder pass through Mesh #30 .

Binder Solution:

Dissolve Povidone k30 in isopropyl alcohol and labeled as a binder .

Granulation:

Semi shifted material was loaded in into saizoner mixer granulator dry mixed for 15mins.binder solution was slowly added into saizonar mixer granulator.

Initial Drying, Sifting and Milling:

Transfer wet granules in tray drier at 50°C. Initial air dry the wet granules for 10mins.after continue the drying at 50°C for 1hour 30mins. The Semi-Dried granules passed through 16# mesh and retained granules milled through Multi-Mill fitted with 1.0 mm screen using knives forward medium speed.

Final drying and shifting:

Transfer the semidried sifted and milled granules into tray drier. Dry the semidried sifted granules .with infra-Red Moisture balance determine the moisture content at 50ºC If it is found more continue the drying until the desired moisture content is achieved(Limt:1-2%).Finally Passed the dried granules through #16 mesh.

Extra granular part:

Sift the following materials cross povidone, colloidal silicon dioxide, talc, Banana Flavor, powerome strawberry premium, Ethyl Vanilline, Mixed fruit Delight powder Flavour sifted by using #40 mesh. Loaded the intragranular dried and sifted Extra granular materials into Octagonal blender blended in15minutes at 10 rpm.

Lubrication:

Magnesium stearate sifted by using # 60 mesh. To this above blend mixed for 5 minutes at 10 rpm.

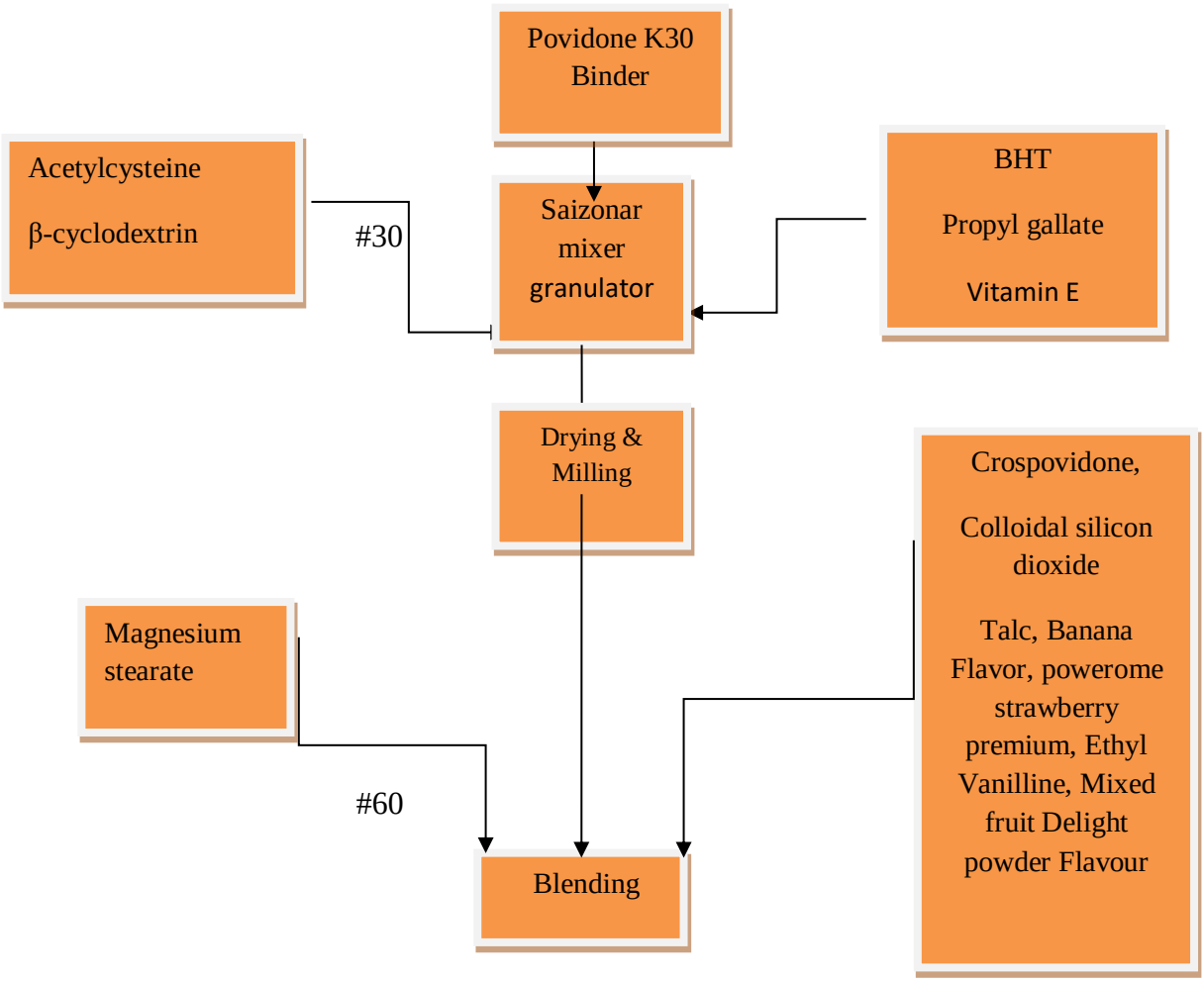


Fig.4: Flow chart of Acetylcysteine Granules Preparation: Wet Granulation Methods

8.2.3 Design of Experiment (DOE):

A three factor and two-level factorial design was used as the experimental design. The independent variables studied were amount of vitaminE (X1), amount of Butylated Hydroxyl Toluene (X2)& amount of Propyl Gallate(X3). Related substance (Y1) and were considered as dependent variable.

8.2.4 Experimental design:

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses.

Experimental runs were designed by Design Expert 11.0.1 [Stat Ease. Inc]Software

following full factorial method. 2^3 full factorial designs was applied for examining three variables (factors) at two levels with a minimum of 8 runs. Totally Eight Acetylcysteine layer formulations were prepared employing selected combinations of the three factors as per 2^3Factorial and evaluated to find out the significance of combined effects of the three factor to select the best combination required to achieve the desired immediate release Acetylcysteine layer tablet.

Table 5: Factors and Factor levels investigated in factorial experimental design

Factors: Formulation Variables	**Levels (mg/tablet)**	
	-1	1
Vitamin E concentrated Pdt	0.10	0.40
Butylated Hydroxyl Toluene	0.40	0.80
Propyl Gallate	0.40	0.80
Response	**Goal**	
N,N-Diacetyl-L-Cystine	Minimize	

8.2.5 Optimization:

To understand the influence of formulation variables on the quality of formulations with a minimal number of experimental trials and subsequent selection of formulation variables optimization was carried out using established statistical tools. Mathematical modeling, evaluation of the ability to fit to the model and response surface modeling were performed with employing Design-Expert® software (Version 11). In a full factorial design, all the factors are studied in all the possible combinations. Hence, 2^3factorial designs were chosen for the current formulation optimization study.

8.2.6 Compression of Bilayer tablets:

The quantity of granules for the immediate-release layer was compressed lightly using 10 station Compression (Karnavathi Engineering Ltd) using 19.5 × 9.5mm caplet shape punches having break line on one side plain on another side. Over this compressed layer, required quantity of the other immediate release layer was placed and compressed to obtain hardness in the range of 8-12 kg/cm² to form a bilayer tablet of immediate release of Acebrophylline and Immediate release of Acetylcysteine. Then the compressed Bilayer tablets were evaluated.

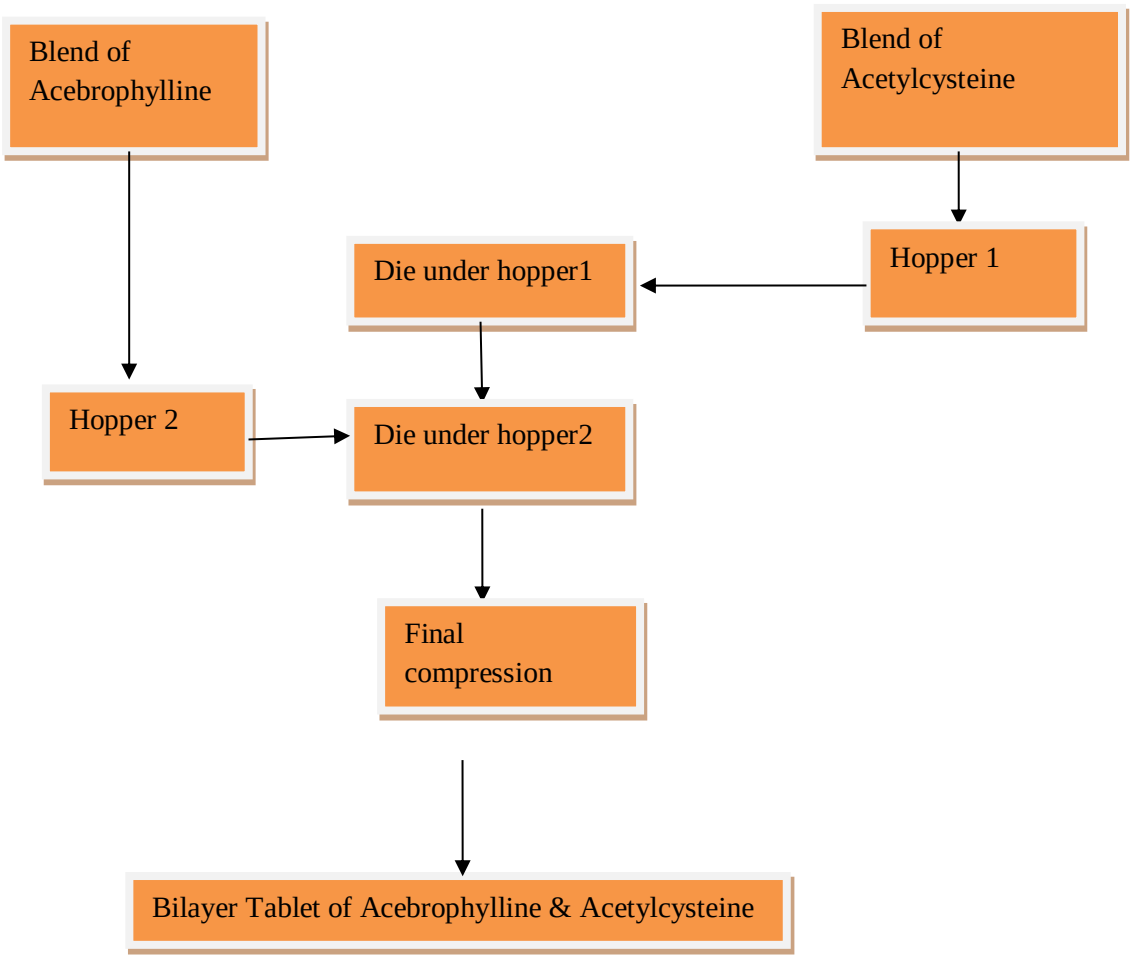


Fig.5: Flow chart of Bilayer Tablet of Acebrophylline & Acetylcysteine

8.3 Acebrophylline Layer Trials:

Table 6: Acebrophylline Layer Trials

Acebrophylline Part		F1	F2	F3	F4
S. No	**INGREDIENTS**	**Quantity/tablet/mg**	**Quantity/tablet/mg**	**Quantity/tablet/mg**	**Quantity/ tablet/mg**
Intra granular part:					
1	Acebrophylline	100.00	100.00	100.00	100.00
2	Lactose Monohydrate	138.50	135.00	131.50	124.00
3	Microcrystalline Cellulose 101	47.80	47.80	47.80	47.80
Binder Solution:					
4	povidone k30	3.00	4.50	6.00	9.00
5	Quinoline yellow supra	0.20	0.20	0.20	0.20
6	Methylene di chloride	50.00	50.00	50.00	50.00
7	Isopropyl Alcohol	40.00	40.00	40.00	40.00
Extra granular part:					
8	Crospovidone	3.00	4.50	6.00	9.00
9	Colloidal silicon dioxide	1.50	1.50	2.00	2.50
10	Talc	4.00	4.50	4.50	4.50
Lubrication:					
11	Magnesium Stearate	2.0	2.0	2.0	3.0
		300.0	**300.0**	**300.0**	**300.0**

8.4 N-Acetylcysteine layer trials:

Table 7: N-Acetylcysteine layer trials

Acetylcysteine Part		F1	F2	F3	F4	F5	F6	F7	F8
S.No	Ingredients	mg/Tab	mg/Tab	mg/Tab	mg/Tab	mg/Tab	mg/Tab	mg/Tab	mg/Tab
Intra Granular Part:									
1	N Acetylcysteine	600.0	600.0	600.0	600.0	600.0	600.0	600.0	600.0
2	β-cyclodextrin	52.90	52.20	52.70	41.80	49.10	48.80	49.10	48.80
3	colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
4	Talc	6.00	6.00	5.00	6.00	6.00	6.00	6.00	6.00
5	vitamin E concentrated Pdt	0.10	0.40	0.10	0.40	0.10	0.40	0.10	0.40
6	Butylated Hydroxyl Toluene	0.40	0.40	0.80	0.80	0.40	0.40	0.80	0.80
7	Propyl Gallate	0.40	0.40	0.40	0.40	0.80	0.80	0.80	0.80
Binder Solution:									
8	Povidone k30	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
9	MDC	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
10	Isopropyl alcohol	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00
Extra Granular part:									
11	Crospovidone	15.00	15.00	15.00	15.00	16.00	16.00	16.00	16.00
12	Collidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
13	Talc	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
14	Banana Flavor	25.00	10.00	-	-	-	-	-	-
15	Powerome strawberry premium	10.00	25.00	-	-	-	-	-	-
16	Ethyl Vanilline	-	-	20.00	30.00	50.00	50.00	50.00	50.00
17	Mixed fruit Delight powder Flavour	-	-	15.00	15.00	25.00	25.00	25.00	25.00
Lubrication:									
18	Magnesium Stearate	10.00	10.00	10.00	10.00	12.00	12.00	12.00	12.00
Theoretical Tablet Weight		**760.0**	**760.0**	**760.0**	**760.0**	**800.0**	**800.0**	**800.0**	**800.0**

Table 8: Formulation Trials of Bilayer tablets

Ingredients	F-1 (Mg/tab)	F-2 (Mg/tab)	F-3 (Mg/tab)	F-4 (Mg/tab)	F-5 (Mg/tab)	F-6 (Mg/tab)	F-7 (Mg/tab)	F-8 (Mg/tab)
Acebrophylline layer								
Acebrophy-lline	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Lactose Monohydrate	138.50	135.00	131.50	124.00	124.00	124.00	124.00	124.00
Microcrystalline Cellulose 101	47.80	47.80	47.80	47.80	47.80	47.80	47.80	47.80
povidone k30	3.00	4.50	6.00	9.00	9.00	9.00	9.00	9.00
Quinoline yellow supra	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Methylene di chloride	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Isopropyl Alcohol	40.00	40.00	40.00	40.00	40.00	40.00	40.00	40.00
Crospovidone	3.00	4.50	6.00	9.00	9.00	9.00	9.00	9.00
Colloidal silicon dioxide	1.50	1.50	2.00	2.50	2.50	2.50	2.50	2.50
Talc	4.00	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Magnesium Stearate	2.0	2.0	2.0	3.0	3.0	3.0	3.0	3.0
N-Acetylcysteine								
N Acetylcys-teine	600.00	600.00	600.00	600.00	600.00	600.00	600.00	600.00
β-cyclodextrin	52.90	52.20	52.70	41.80	49.10	48.80	49.10	48.80
colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Talc	6.00	6.00	5.00	6.00	6.00	6.00	6.00	6.00
vitamin E concentrated pdt	0.10	0.40	0.10	0.40	0.10	0.40	0.10	0.40
Butylated Hydroxyl Toluene	0.40	0.40	0.80	0.80	0.40	0.40	0.80	0.80
Propyl Gallate	0.40	0.40	0.40	0.40	0.80	0.80	0.80	0.80

Povidone k30	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
MDC	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Isopropyl alcohol	70.00	70.00	70.00	70.00	70.00	70.00	70.00	70.00
Crospovidone	15.00	15.00	15.00	15.00	16.00	16.00	16.00	16.00
Collidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Talc	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
Banana Flavor	25.00	10.00	-	-	-	-	-	-
Powerome strawberry premium	10.00	25.00	-	-	-	-	-	-
Ethyl Vanilline	-	-	20.00	30.00	50.00	50.00	50.00	50.00
Mixed fruit Delight powder Flavour	-	-	15.00	15.00	25.00	25.00	25.00	25.00
Magnesium Stearate	10.00	10.00	10.00	10.00	12.00	12.00	12.00	12.00
Total	1060	1060	1060	1060	1100	1100	1100	1100

8.5 Evaluation of Granules:

8.5.1 Bulk density [63]:

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. it is expressed in gm/ml. A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted.

Bulk density was calculated using the following equation;

$$\text{Bulk density} = \frac{\text{Mass of the powder Blend taken}}{\text{Volume occupied by the powder blend}}$$

8.5.2 Tapped density [63]:

A weighed quantity of powder blend previously shaken to break any agglomerates formed, was introduced in to a measuring cylinder and the volume was noted. The cylinder was placed in the tapped density apparatus and allowed to fall under its own

weight on to a hard surface (USP-II), that provides fixed a drop of 3mm(±10%) at a nominal rate of 250 drops per minute is used. Tapping was continued until no further change in volume was noted. Td was calculated using the following equation;

$$\text{Tapped density} = \frac{\text{Mass of the powder Blend taken}}{\text{Tapped Volume of the powder blend}}$$

8.5.3 Carr's Index [63]:

Carr's Index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. A material having values of less than 20 is defined as the free flowing material.[48] the formula for Carrs Index is as below:

Carrs Index is as below:

$$\text{Carrs Index (\%)} = 100 \frac{1 - Bd}{Td}$$

Table 9: Carr's index values and type of flow

Carr's index	Type of flow
5-15	Excellent
12-15	Good
18-21	Fair
23-30	Poor
33-38	Very poor
>40	Extremely poor

8.5.4 Hausner's ratio [63]:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausners ratio = (Tapped density)/ (Bulk density)

Table 10: Hausner's ratio and flow characters

Flow characters	**Hausner's**
Excellent	1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very Very poor	>1.60

8.6 EVALUATION OF TABLETS:

8.6.1 Evaluation of physical characteristics:

The formulated tablets were evaluated for the following physical parameters,

8.6.2 Thickness:

Thickness depends on die filling, physical properties of material to be compressed. There is possibility of small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter can be measured by vernier calipers.

8.6.3 Hardness:

Tablet must possess sufficient strength or hardness and can be measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and were evaluated for hardness and can be expressed in Kg/cm^2.

8.6.4 Friability:

Friability can be performed in Roche friabilator, Preweighed ten tablets were introduced in the friabilator. Then the machine was operated for 100 revolutions. Tablets were dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed. Loss of less than 1% in weight is considered to be within the specifications and acceptable.

$$F\ (\%) = \frac{\text{Initial wt} - \text{Final wt}}{\text{Initial wt}} \times 100$$

8.6.5 Weight variation test:[64]

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table and none deviate by more than twice the percentage.

Table 11: IP Specifications for weight variation

Average weight of tablet (mg)	Percentage difference allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

8.6.6Disintegration Time :[64]

The in-vitro disintegration time was determined by using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds.

8.7 DISSOLUTION BY HPLC:

8.7.1Dissolution Test Conditions

Apparatus	: Paddle
Rotation Speed	: 100 RPM
Medium	: 0.1M Hydrochloric acid
Media volume	: 1000 mL
Temperature	: 37°C ± 0.5°C
Sampling time	: 60 minutes

Preparation of Dissolution Medium: (*0.1M Hydrochloric acid****)***

Transfer 85 mL of Hydrochloric acid dissolved in 10000 mL of purified water.

Chemicals / Reagents

Water	:	Milli-Q/ HPLC water/Purified water
Hydrochloric acid	:	AR Grade
Orthophosphoric acid	:	AR Grade
Potassium hydroxide	:	AR Grade
Methanol	:	HPLC Grade
Acetonitrile	:	HPLC Grade

8.7.2 Chromatographic conditions:

Instrument	:	Shimadzu HPLC equipped with UV detector
Column	:	Agilent Eclipse XDB-C18 (150mm x 4.6mm, 5µ) Or equivalent.
Column Temperature	:	30°C
Flow rate	:	1.0 mL/minute
Wavelength	:	225 nm
Injection volume	:	10 µL
Run time	:	15 minutes.
Pump mode	:	Gradient

Gradient programme:

Table 12: Gradient programme of Dissolution

Time	Mobile phase'A' (%)	Mobile phase'B' (%)
0.01	100	0
3.5	100	0
5.0	65	35
11.5	65	35
14.0	100	0
15.0	100	0

8.7.3 Buffer preparation:

Take 1000 mL of purified water in a beaker and 2.0ml of ortho-phosphoric acid, mixed and filter through 0.45 µm nylon membrane filter.

Mobile phase 'A'

Mixed 950 ml of buffer and 50 ml of acetonitrile and adjust to pH 2.5 ± 0.05 with diluted potassium hydroxide solution. Filtered the mobile phase through 0.45 µm nylon membrane filter and degas.

Mobile phase 'B'

Mixed 500 ml of acetonitrile, 340 ml of methanol and 160ml of buffer and filtered the mobile phase through 0.45 µm nylon membrane filter and degas.

8.7.4 Preparation of standard solution:

Accurately weighed and transfer about 50.0 mg of **Acebrophylline** working standard in to a 50 mL volumetric flask. Added about 30 mL of the dissolution medium, sonicate to dissolved the content completely and dilute to volume with dissolution medium and mixed well (Solution A).

Accurately weighed and transfer about 30.0mg of **Acetylcysteine** working standard in to a 50mL volumetric flask. Added 5 mL of Solution A and 30ml of dissolution medium sonicate to dissolved the content and dilute to volume with dissolution medium and mixed well.

8.7.5 Preparation of Check standard solution:

Accurately weighed and transfer about 50.0 mg of **Acebrophylline** working standard in to a 50 mL volumetric flask. Added about 30 mL of the dissolution medium, sonicate to dissolve the content completely and dilute to volume with dissolution medium and mixed well (SolutionA).

Accurately weighed and transfer about 30.0mg of **Acetylcysteine** working standard in to a 50mL volumetric flask. Added 5 mL of Solution A and 30ml of dissolution medium sonicate to dissolved the content and dilute to volume with dissolution medium and mixed well.

Note: For storage, handling and potency of working standard to refer the respective label or COA.

8.7.6 Evaluation of System suitability:

a) The percentage RSD of peak area responses due to Acetylcysteine, Theophylline-7-acetate and Ambroxol from five replicate injections of standard solution should not be more than 2.0.
b) The tailing factor for the peak due to Acetylcysteine, Theophylline-7-acetate and Ambroxol in standard solution should not be more than 2.0
c) The theoretical plate count for peak due to Acetylcysteine and Theophylline-7-acetate in standard solution should not be less than 1500.

Calculation

Determine the amount of Acetylcysteine dissolved by using the following formula:

$$\text{Percentage of Drug Release} = \frac{A_{spl}}{A_{std}} \times \frac{W_{std}}{50} \times \frac{1000}{1\text{tablet}} \times \frac{P}{100} \times \frac{100}{L}$$

Where,

A_{spl} - Area due to Acetylcysteine in Sample solution.

A_{std} - Area due to Acetylcysteine in Standard solution.

W_{std} - Weight in mg of Acetylcysteine working standard taken

P - Percentage Purity of Acetylcysteine working standard on as is basis.

L - Label claim of Acetylcysteine

Determine the amount of Acebrophylline dissolved by using the following formula:

$$\text{Percentage of Drug Release} = \frac{A_{spl}}{A_{std}} \times \frac{W_{std}}{50} \times \frac{5}{50} \times \frac{1000}{1\text{tablet}} \times \frac{P}{100} \times \frac{100}{L}$$

Where,

A_{spl} - Area due to sum of Theophylline-7-acetate and Ambroxol HCl (Acebrophylline) in Sample solution.

A_{std} - Area due to Theophylline-7-acetate and Ambroxol HCl (Acebrophylline) in Standard solution.

W_{std} - Weight in mg of Acebrophylline working standard taken

P - Percentage Purity of Acebrophylline working standard on as is basis.

L - Label claim of Acebrophylline

8.8 ASSAY BY HPLC:

Note: For reagents, chromatographic conditions, preparation of Buffer, mobile phase refer Dissolution by HPLC.

8.8.1 Preparation of Diluent:

Mixed 650mL of methanol and 350 mL of purified water and mixed well.

8.8.2 Preparation of standard solution:

Accurately weighed and transfer about 50.0 mg of **Acebrophylline** working standard in to a 50 mL volumetric flask. Added about 30 mL of the diluent, sonicate to dissolved the content completely and dilute to volume with diluent and mixed well (Solution A).

Accurately weighed and transfer about 30.0mg of **Acetylcysteine** working standard in to a 50mL volumetric flask. Add 5 mL of Solution A and 30ml of diluent sonicate to dissolvedthe content and dilute to volume with diluent and mixed well.

8.8.3 Preparation of sample solution:

Weighed 20 tablets and calculate the average weight of a tablet. Transfer the tablets into a mortar crush the tablets into fine powder (Care should be taken that coating material is also reduced to fine powder). Accurately weighed and transfer 110.0mg of powdered tablet (equivalent to about 60mg of Acetylcysteine and 10mg of Acebrophylline) into a 100 mL volumetric flask. Added 70 mL of diluent, sonicate for 15 minutes, cool to room temperature and dilute to volume with diluent. Mixed well and filtered through 0.45 µm nylon membrane filter. Discard first 5 mL of the filtrate. (Conc. ≈ 600µg/ml of Acetylcytsteine and 100µg/ml of Acebrophylline)

8.8.4 Procedure

Separately inject each 10 µL of the blank (diluent), standard solution (5replicates), Checked standard solution (2 replicates) and sample solution (2replicates injections) into the chromatograph, record the chromatograms and measured the peak response due to Acetylcysteine, Theophylline-7-acetate and Ambroxol HCl (**Acebrophylline**). Discard peaks due to Ethyl vanillin at retention time of about 10 minutes in the sample chromatograms.

8.8.5 Evaluation of System suitability

1) The percentage RSD of peak area responses due to Acetylcysteine, Theophylline-7-acetate and Ambroxol from five replicate injections of standard solution should not be more than 2.0
2) The tailing factor for the peak due to Acetylcysteine, Theophylline-7-acetate and Ambroxol in standard solution should not be more than 2.0
3) The theoretical plate count for peak due to Acetylcysteine and Theophylline-7-acetate in standard solution should not be less than 1500.

Calculation:

a) Percentage label claim of Acetylcysteine determined by using the following formula:

$$\text{Percentage of Drug Release} = \frac{A_{Aspl}}{A_{std}} \times \frac{W_{Astd}}{50} \times \frac{100}{W_{spl}} \times \frac{P}{100} \times \frac{\text{Avg. wt}}{L} \times 100$$

b) Percentage label claim of Acebrophylline determined by using the following formula:

$$\text{Percentage of Drug Release} = \frac{A_{ABspl}}{B_{std}} \times \frac{W_{ABstd}}{50} \times \frac{5}{50} \times \frac{100}{W_{spl}} \times \frac{P}{100} \times \frac{\text{Avg. wt}}{L} \times 100$$

Where,

A_{std} = Average Peak area response due to Acetylcysteine in standard solution.

B_{std} = Sum of Average Peak area response due to Theophylline-7-acetate and Ambroxol in (Acebrophylline) standard solution.

A_A = Average Peak area response due to Acetylcysteine in sample solution.

A_{AB} = Sum of average Peak area response due to Theophylline-7-acetate and Ambroxol (Acebrophylline) in sample solution.

W_A = Weight in mg of Acetylcysteine working standard taken.

W_{AB} = Weight in mg of Acebrophylline working standard taken.

W_{spl} = Weight in mg of Sample taken.

LC = Label claim in mg/tablet

P = Percentage Purity of Working Standard on as is basis.

8.9 Related Substances by HPLC (% w/w)

<u>Note</u>: Prepare the solutions immediately before use.

8.9.1 Chemicals / Reagents:

Methanol	:	Gradient Grade
Acetonitrile	:	Gradient Grade
Ortho Phosporic acid	:	HPLC Grade
Potassium hydroxide	:	AR Grade
Purified water	:	HPLC Grade

8.9.2 Chromatographic Conditions:

Instrument	:	Shimadzu HPLC equipped with UV detector
Column	:	250 x 4.6mm, 5µ; Inertsil ODS-3V or equivalent.
Column Temperature	:	30°C
Flow rate	:	1.0 mL/minute

Wavelength	:	**225nm** for Acetylcysteine & **248nm** for Acebrophylline
Injection volume	:	20 µL
Run time	:	50 minutes.
Pump mode	:	Gradient

Gradient programme:

Table 13: Gradient programme of Related Substances

Time	Mobile phase'A' (%)	Mobile phase'B'(%)
0.01	100	0
15.0	100	0
22.0	90	10
32.0	75	25
40.0	75	25
45.0	100	0
50.0	100	0

8.9.3 Buffer preparation:

Taked 1000 mL of purified water in a beaker and 2.0ml of ortho-phosphoric acid and mixed well.

Mobile phase 'A'

Mixed 950 ml of Buffer and 50 ml of acetonitrile and adjust to pH 2.5±0.05 with diluted potassium hydroxide solution. Filtered the mobile phase through 0.45 µm nylon membrane filters and degas.

Mobile phase 'B'

Mixed 870 ml of acetonitrile and 130 ml of methanol and filtered the mobile phase through 0.45 µm nylon membrane filters and degas.

8.9.4 Preparation of Diluent:

Mixed 650ml of methanol and 350 ml of purified water and mixed well.

8.9.5 Theophylline standard stock solution:

Weighed accurately and transfer about 25.0 mg of Theophylline working standard to 100ml volumetric flask. Add 70ml of diluent and sonicate to dissolved the content and make up to mark with diluent and mixed well. (Conc. ≈ 250 µg/mL of Theophylline)

8.9.6 Standard solution:

Weigh accurately and transfer about 60.0 mg of Acetyl cysteine and 50.0mg Acebrophylline working standard into a 100 ml volumetric flask. Add 70 ml of diluent and sonicate to dissolve the content and make up to volume with diluent and mix well. Dilute 5ml of this solution and 1ml of theophylline standard stock solution to 50ml with diluent and mix.

(Conc. ≈ 60 µg/mL of Acetylcysteine50, µg/mL of Acebrophylline and 5 µg/mL of Theophylline)

8.9.7 Preparation of placebo solution:

Accurately weighed and transfer about 420.0mg of placebo into a 100 mL volumetric flask. Added 1ml of 1M hydrochloric acid and 70 mL of diluent, sonicate for 15 minutes, cool to room temperature and dilute to volume with diluent. Mixed well and filtered through 0.45 µm nylon membrane filter. Discard first 5 mL of the filtrate.

8.9.8 Preparation Sample solution:

Weighed 20 tablets and calculate the average weight of a tablet. Transfer the tablets into a mortar crush the tablets into fine powder (Care should be taken that coating material is also reduced to fine powder).Accurately weighed and transfer 1.13 g of powdered tablet (equivalent to 600.0 mg of Acetylcysteine and 100mg of Acebrophylline) into a 100 mL volumetric flask. Add 1ml of 1M hydrochloric acid and 70 mL of diluent and sonicate for 10 minutes (**Note:** To prevent heat from degrading the sample, do not extend the sonication time and also maintain the bath temperature at NMT 22°C by adding ice) and stir vigorously for 5 minutes. Allow to cool to room

temperature, dilute to volume with diluent. Mixed well and filtered through 0.45 µm nylon membrane filter, discard first 5 mL of the filtrate.

(Conc. ≈ 6000.0 µg/mL of Acetylcysteine and 1000 µg/mL of Acebrophylline)

8.9.9 Procedure:

Separately inject each 20 µL of Blank (duplicate injection), Placebo solution (single), standard solution (5 replicates) and each sample solution (single injection) in to the chromatograph, record the chromatograms, and measure the peak responses for all peaks. Disregard any peak corresponding to the blank and Placebo.

Note: After every six sample injections and end of the sequence, inject the Standard solution as Bracketing Standard.

8.9.10 Evaluation of System suitability:

a) The percentage RSD of peak area responses due to Acetylcysteine, Theophylline, Theophylline-7-acetate and Ambroxol from five replicate injections of standard solution should not be more than 2.0
b) The tailing factor for the peak due to Acetylcysteine, Theophylline, Theophylline-7-acetate and Ambroxol in standard solution should not be more than 2.5

Table 14: List of Related Substance

S.No.	Compound Name	Retention time (Mins.)	Acceptance criteria (%)
1	2-methyl-2-thiazoline-4-carboxylic acid	About 3.5	---
2	Acetyl cysteine	About 7.0	---
3	Theophylline	About 23.0	0.5
4	Theophylline -7- acetate	About 25.0	---
5	Ambroxol HCl	About 35.0	---
6	N,N Diacetyl-L-cystine	---	1.0
7	Individual impurity	---	1.0
8	Total impurities	---	1.5

Note: Disregard any peak due to the solvent, any peak appearing at retention time of about 3.0 minutes corresponding to 2-methyl-2-thiazoline-4-carboxylic acid and any

peak with an area less than 0.05% and also discard the peaks due to Ethyl vanillin at retention time of about 14,34 and 38 minutes in the sample chromatogram.

I.Calculation

I) Calculation of Acetylcysteine related substances:

a) Calculate the percentage of each unknown degradation impurity related to Acetylcysteine.

$$\% = \frac{AC_u}{AC_S} \times \frac{W_{AC}}{100} \times \frac{5}{50} \times \%P \times \frac{100}{W_U} \times \frac{ATW}{LC}$$

b) Calculate the percentage of total impurities related to Acetylcysteine.

$$\% = \frac{AC_T}{AC_S} \times \frac{W_{AC}}{100} \times \frac{5}{50} \times \%P \times \frac{100}{W_U} \times \frac{ATW}{LC}$$

Where,

AC_u = Peak area of each unknown degradation impurity at 225nm from the Test solution.

AC_T = Total peak area of unknown degradation impurities at 225 nm from the Test solution.

AC_S = Mean peak area of Acetylcysteine in standard solution

W_{AC} = Weight of Acetylcysteine working standard, in mg

W_u = Sample weight, in mg

% P = Purity of Acetylcysteine working standard, in percent.

LC = Label claim of Acetylcysteine, in mg

ATW = Average tablet weight, in mg

II.Calculation of Acebrophylline related substances:

a) Calculate the percentage of Theophylline impurity:

$$\% = \frac{T_u}{T_S} \times \frac{W_T}{100} \times \frac{1}{50} \times \%P \times \frac{100}{W_U} \times \frac{ATW}{LC}$$

Where,

T_u = Peak area of Theophylline at 248nm in the sample solution.

T_s = Mean peak area of Theophylline at 248nm in standard solution.

W_T = Weight of Theophylline impurity in mg

W_u = Sample weight, in mg

% P = Purity of Theophylline in percent

LC = Label claim, in mg

ATW = Average tablet weight, in mg

b) Calculate the percentage of each unknown degradation impurity related to Acebrophylline.

$$\% = \frac{AF_u}{AF_S} \times \frac{W_{AF}}{100} \times \frac{5}{50} \times \%P \times \frac{100}{W_U} \times \frac{ATW}{LC}$$

c) Calculate the percentage of total impurities related to Acebrophylline.

$$\% = \frac{AF_T}{AF_S} \times \frac{W_{AF}}{100} \times \frac{5}{50} \times \%P \times \frac{100}{W_U} \times \frac{ATW}{LC}$$

Where,

AF_u = Peak area of each unknown degradation impurity at 248nm from The sample solution.

AF_T = Total peak area of unknown degradation impurities at 248 nm from the Test solution.

AF_S = Mean peak area of Ambroxol HCl in standard solution

W_{AF} = Weight of Acebrofylline working standard, in mg

W_u = Sample weight, in mg

% P = Purity of Ambroxol HCl in Acebrofylline working standard, in percent.

LC = Label claim of Acebrofylline in mg

ATW = Average tablet weight, in mg

8.10 Coating of bilayered tablets:

Table 15: Coating solution composition

Ingredients	Mg/tab
DR coat FLV	33
Iso propyl alcohol	313.5
Methylene chloride	313.5

8.10.1 Film coating solution preparation:

Isopropyl alcohol was transferred into a clean stainless steel vessel. DR coat FLV was added to the part of isopropyl alcohol. To the part of isopropyl alcohol, Opadry white was added and was passed through the colloidal mill and mixed with the above solution. Finally methylene chloride was added to the above solution with continuous stirring. Care was taken that there were no lumps formation in the solution visually. The above solution was filtered through mesh 100# nylon cloth. The above solution was transferred into a SS vessel of pressure vessel fitted with stirrer.

Table 16: Coating process specifications:

S.No	Parameters	Limits
1.	Pan speed	4 to 5 rpm
2.	Temperature	
	Inlet	55º C
	Outlet	40º C ±2 ºC
3.	Gun operating pressure	NLT 4kg/cm2
4.	Atomizing air pressure	3.0 – 4.5 kg/cm2
5.	Spray rate	100-150ml/min
6.	Drying time	10 Minutes.

Table 17: Coating tablet specifications:

S.No	Parameters	Limits
1.	Description	Yellow colour, caplet shaped, plain surface film coating tablet
2.	Theoretical average weight	1100 mg ± 5%
3.	Uniformity of weight	± 3 %
4.	Thickness	5.70 – 6.10mm
5.	Disintegration time	NMT 30 minutes

8.11 Drug release kinetics:

8.11.1 Korsemeyer-peppas model

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released (vs) log time Table:

$$\mathbf{Mt / Md = Kt^n}$$

Where,

Mt / Md = Fraction of drug released at time t

t = Release time

K=Kinetics constant

N=Diffusional exponent indicature of mechanism of drug release

Table 18: Korsemeyer-peppas "n" value

Diffusion component (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anamolous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case – II transport

Table 19: Dissolution data modelling

Release mechanism	Y-axis	X-axis
Zero order kinetics	% cum drug release	Time in min
First order kinetics	Log % cum drug remaning	Time in min
Higuchi kinetics	% cum drug release	Square root at time
Korsemeyer-peppas equation	Log % cum drug release	Log time

8.12 Stability Studies: [65]

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized F8 formulation was sealed in alu-alu Blister packaging laminated with polyamide. Sample were kept at 40°C and 75% RH for 1, 2, 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. The values were showed in the **Table No.53.**

9. RESULTS

9.1 Raw material analysis:

Acebrophylline and Acetylcysteine were obtained from Kores India Pvt. Ltd (India) and Wuhan Grand Hoyo Pvt. Ltd (China) respectively was analysed for various physical and analytical characterizations and was found to comply with USP.

Table 20: Physio-chemical Characteristics of Acebrophylline and Acetylcysteine

S.No	Parameter	Inference	
		Acebrophylline	**Acetylcysteine**
1.	**Nature**	Powder	Crystalline Powder
2.	**Colour**	White Powder	White
3.	**Melting point**	216-220 ℃	108-110 ℃
4.	**Solubility** **- in Chloroform** **-in Ether** **- in Distilled water**	Insoluble In soluble slightly Soluble	Insoluble In soluble Soluble
5.	**Percentage Purity: (98.0~101.0%)**	100.5% (by HPLC Method)	99.8% (by HPLC Method)

9.2 Drug –excipients compatibility (FT-IR) study of Acebrophylline & Acetylcysteine:

The FT-IR analysis of the drug and polymer gave thermal profile characteristic of the substances are shown in **Fig 6 to Fig 7**. Principal peaks of Acebrophylline & Acetylcysteine are intact in the formulations**.**

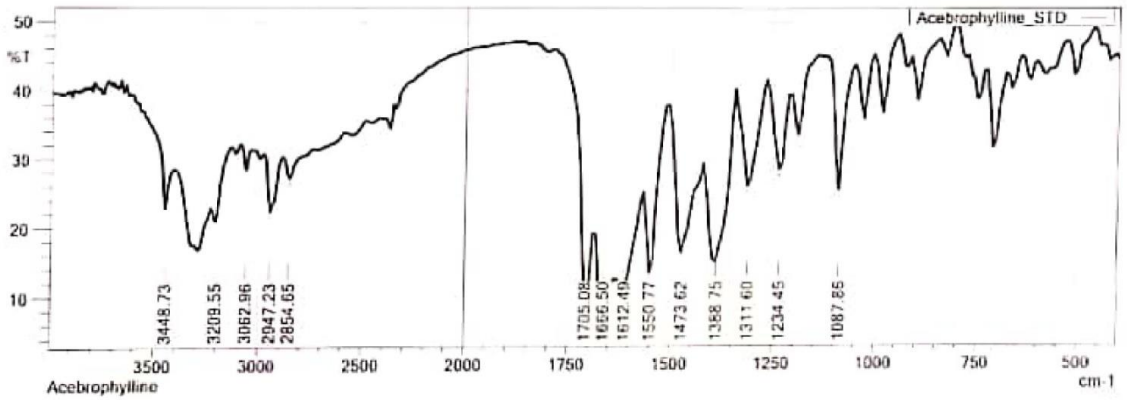


Fig.6: FTIR of Pure Acebrophylline

Table 21: FTIR of Pure Acebrophylline

S.no	Wave number cm^{-1}	Functional group
1	3448.7	O-H Stretching
2	2944.2	C-H Stretching
3	1666.5	COOH Stretching
4	1473.6	CH2 Bending
5	1311.6	O-H Bending C-O Stretching

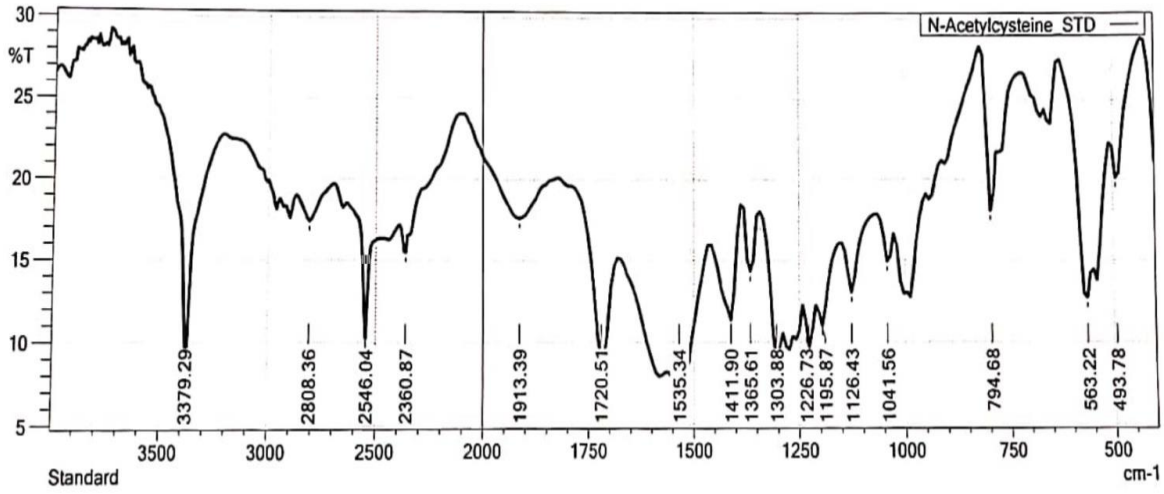


Fig. 7: FTIR of Pure Acetylcysteine

Table 22: FTIR of Pure Acetylcysteine

S.no	Wave number cm^{-1}	Functional group
1	2546.0	SH Stretching
2	3379.2	N-H Band
3	1535.3	C-N Stretching
4	1195.8	N-H Stretching

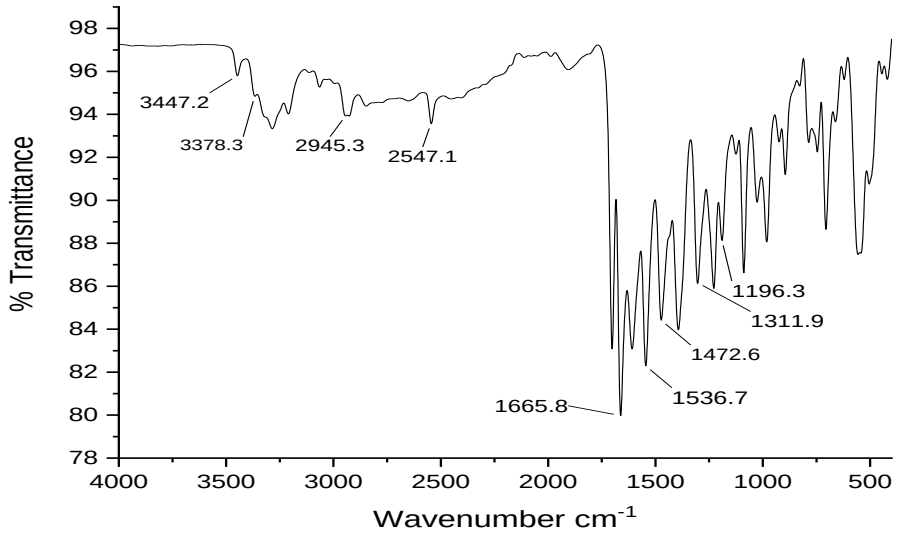


Fig. 8: FTIR of Pure Drug Acebrophylline & Acetylcysteine

Table 23: FTIR of Pure Drug Acebrophylline & Acetylcysteine

S.no	Wave number cm^{-1}	Functional group
1	3447.2	O-H Stretching
2	2945.3	C-H Stretching
3	1665.8	COOH Stretching
4	1472.6	CH2 Bending
5	1311.9	C-O Stretching
6	2547.1	SH Stretching
7	3378.3	N-H Band
8	1536.7	C-N Stretching
9	1196.3	N-H Stretching

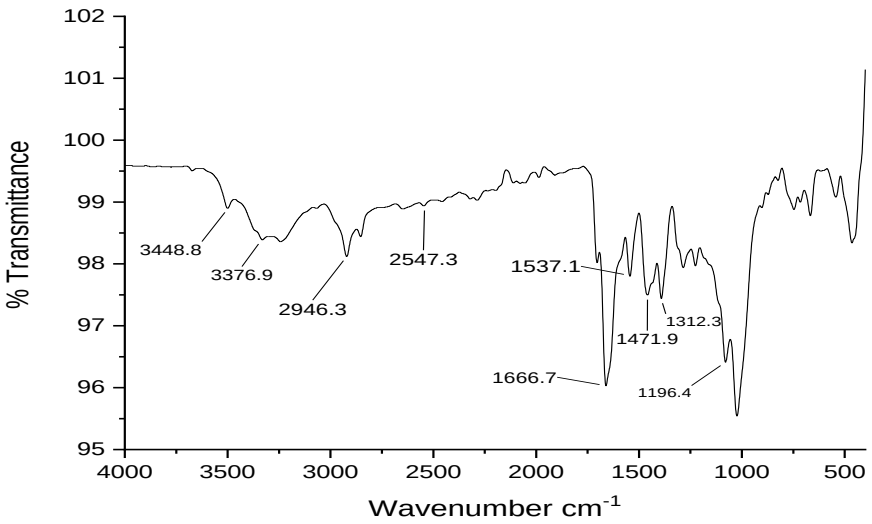


Fig. 9: FTIR of Bilayer tablet of Acebrophylline & Acetylcysteine

Table 24: FTIR of Bilayer tablet of Acebrophylline & Acetylcysteine

S.no	Wave number cm^{-1}	Functional group
1	3448.8	O-H Stretching
2	2946.3	C-H Stretching
3	1666.7	COOH Stretching
4	1471.9	CH2 Bending
5	1312.3	C-O Stretching
6	2547.3	SH Stretching
7	3376.9	N-H Band
8	1537.1	C-N Stretching
9	1196.4	N-H Stretching

9.1 PRE-COMPRESSION PARAMETERS:

Table 25: Pre-compression Parameters for Acebrophylline Layer Blend

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index (%)
F1	0.625	0.842	1.3472	25.771
F2	0.672	0.866	1.2887	22.402
F3	0.715	0.864	1.2083	17.245
F4	0.719	0.867	1.2058	17.070

Table 26: Precompression parameters for Acetylcysteine layer blend

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Index (%)
F1	0.681	0.848	1.2452	19.693
F2	0.685	0.851	1.2423	19.506
F3	0.689	0.852	1.2365	19.131
F4	0.691	0.859	1.2431	19.557
F5	0.722	0.891	1.2345	18.967
F6	0.724	0.893	1.2330	18.924
F7	0.729	0.897	1.2300	18.729
F8	0.735	0.902	1.227	18.514

9.2 Post Compression Parameters:

Table 27: Post compression parameters for core Bilayer tablets

Batch	Thickness (mm)	Hardness (kg/cm^2)	Friability %	Disintegration Time (minutes)
F-1	5.48-5.58	8.60-9.80	0.37	5Minutes 45Seconds
F-2	5.5-5.62	8.50-9.60	0.36	4 Minutes 23 Seconds
F-3	5.52-5.55	9.40-9.90	0.37	4 Minutes 03 Seconds
F-4	5.60-5.67	9.45-10.72	0.32	4 Minutes 41 Seconds
F-5	5.82-5.85	11.65-12.33	0.21	5 Minutes0 7 Seconds
F-6	5.83-5.85	11.20-12.01	0.22	5 Minutes 12 Seconds
F-7	5.83-5.88	11.00-11.32	0.24	5 Minutes 22 Seconds
F-8	5.85-5.92	11.17-11.36	0.25	5 Minutes 33 Seconds

Table 28: Weight Variation Test

Batch	F1	F2	F3	F4	F5	F6	F7	F8
Avg wt (20 tab)	1060	1060	1060	1060	1100	1100	1100	1100
% Max positive deviation	+1.03	+1.27	+2.00	+1.40	+2.40	+2.28	+2.08	+1.63
% Min Negative Deviation	-1.07	-1.48	-1.55	-1.11	-2.20	-1.69	-1.52	-1.60

Table 29: Post compression parameters for coated tablets

BATCH	THICKNESS (mm)	DISENTEGRATION TIME(Minutes)
F-1	6.19-6.20	6 Minutes 08 seconds
F-2	6.22-6.23	5Minutes17 seconds
F-3	6.25-6.28	5 Minutes 34 seconds
F-4	6.27-6.30	5 Minutes 52 seconds
F-5	6.45-6.49	6 Minutes 15 seconds
F-6	6.47-6.50	6 Minutes 27 seconds
F-7	6.52-6.56	6 Minutes 49 seconds
F-8	6.55-6.59	6 Minutes 52 seconds

6.3 DISSOLUTON:

6.3.1*In-vitro* dissolution studies:

Table 30: *In- vitro* dissolution profile of Bilayer tablet F-1

Immediate Release Layer of Acebrophylline			
S.NO.	**Time (mins)**	**Amount of drug release(mg)**	**% Drug Release**
1	5	63.88	63.88
2	10	67.24	67.24
3	20	71.79	71.79
4	30	79.36	79.36
5	45	85.05	85.05
6	60	98.31	98.31

Immediate Release Layer of Acetylcysteine			
S.NO.	**Time (mins)**	**Amount of drug release(mg)**	**% Drug Release**
1	5	394.86	65.81
2	10	414.96	69.16
3	20	446.82	74.47
4	30	469.74	78.29
5	45	523.14	87.19
6	60	558.36	93.06

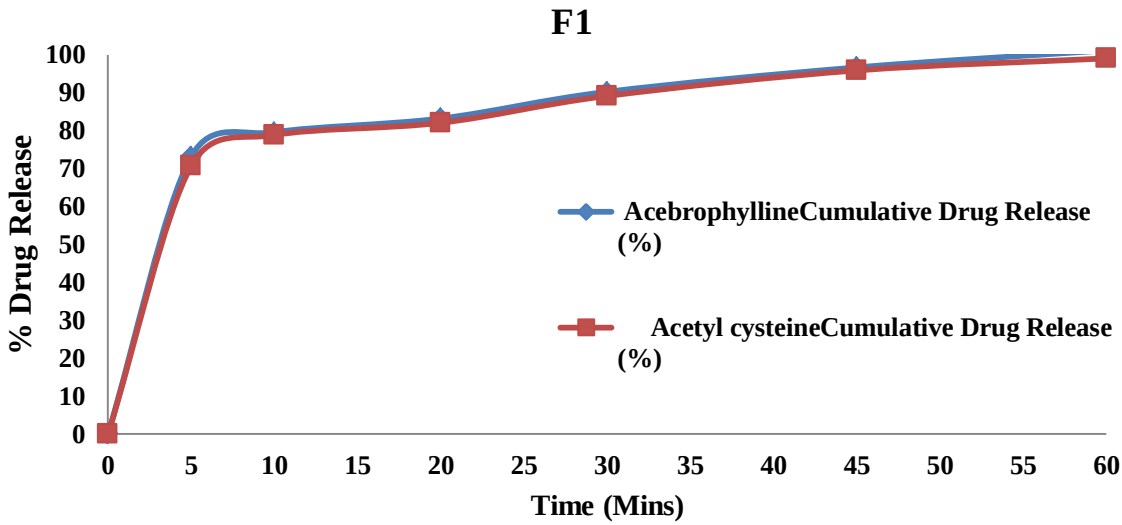


Fig.10: *In-vitro* dissolution profile of Bilayer tablet F-1

Table 31: In *-vitro dissolution profile of Bilayer tablet* F-2

Immediate Release Layer of Acebrophylline			
S.NO.	**Time (mins)**	**Amount of drug release(mg)**	**% Drug Release**
1	5	65.16	65.16
2	10	69.34	69.34
3	20	72.9	72.9
4	30	80.67	80.67
5	45	87.05	87.05
6	60	98.62	98.62
Immediate Release Layer of Acetylcysteine			
S.NO.	**Time (mins)**	**Amount of drug release(mg)**	**% Drug Release**
1	5	415.92	69.32
2	10	438.9	73.15
3	20	476.82	79.47
4	30	497.52	82.92
5	45	525.54	87.59
6	60	562.86	93.81

F2

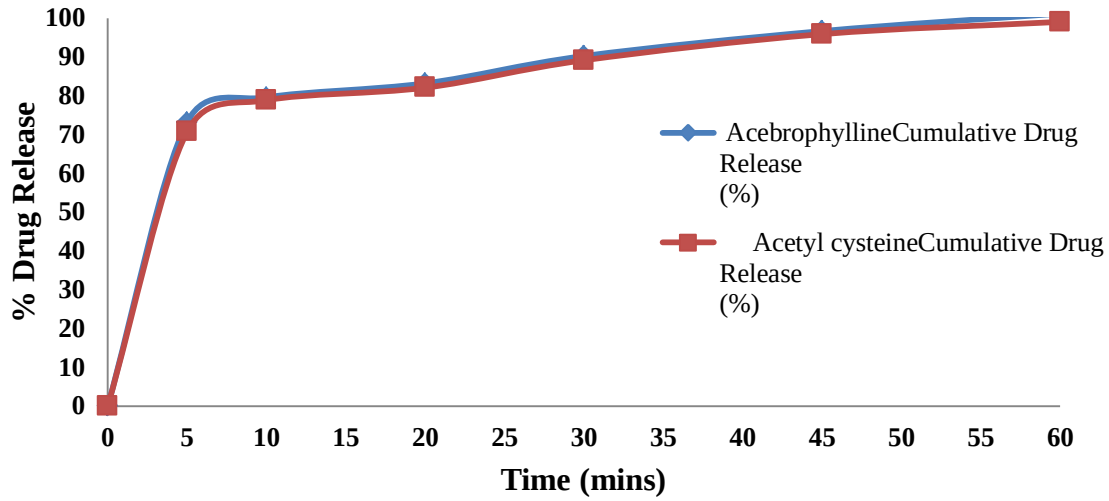


Fig. 11: *In -vitro* dissolution profile of Bilayer tablet F-2

Table 32: *In-vitro dissolution profile of Bilayer tablet* F-3

Immediate Release Layer of Acebrophylline			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	66.69	66.69
2.	10	70.72	70.72
3.	20	74.17	74.17
4.	30	81.96	81.96
5.	45	89.65	89.65
6.	60	99.12	99.12
Immediate Release Layer of Acetylcysteine			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	427.98	71.33
2.	10	465.06	77.51
3.	20	496.44	82.74
4.	30	517.74	86.29
5.	45	539.88	89.98
6.	60	566.58	94.43

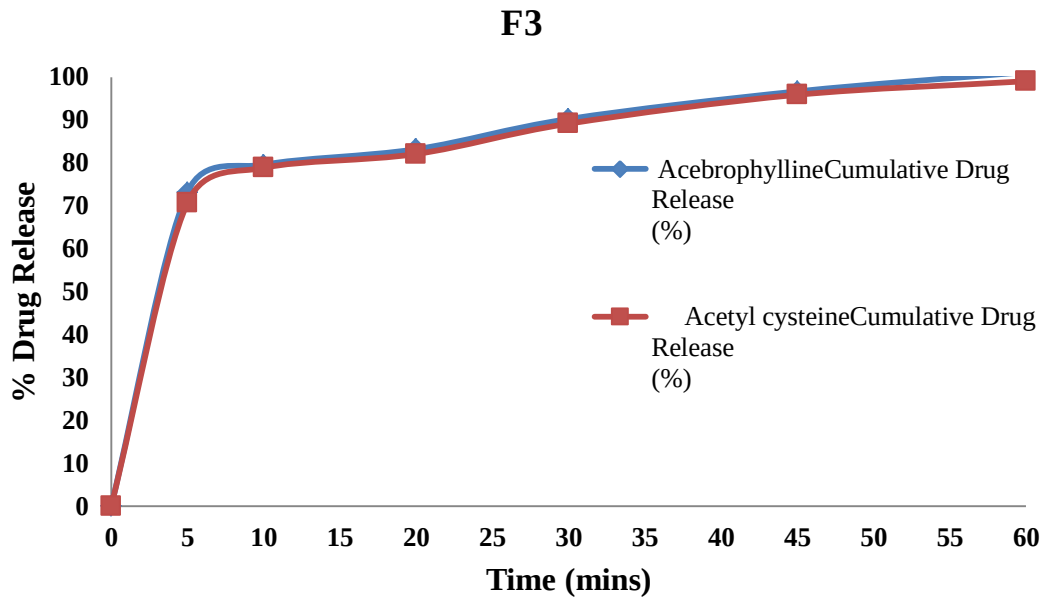


Fig.12: *In- vitro* dissolution profile of Bilayer tablet F-3

Table 33*: In- vitro dissolution profile of Bilayer tablet* F-4

Immediate Release Layer of Acebrophylline			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	68.59	68.59
2.	10	72.32	72.32
3.	20	75.77	75.77
4.	30	83.46	83.46
5.	45	90.37	90.37
6.	60	99.47	99.47
Immediate Release Layer of Acetylcysteine			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	423.36	70.56
2.	10	451.56	75.26
3.	20	490.74	81.79
4.	30	507.9	84.65
5.	45	556.29	92.71
6.	60	570.66	95.11

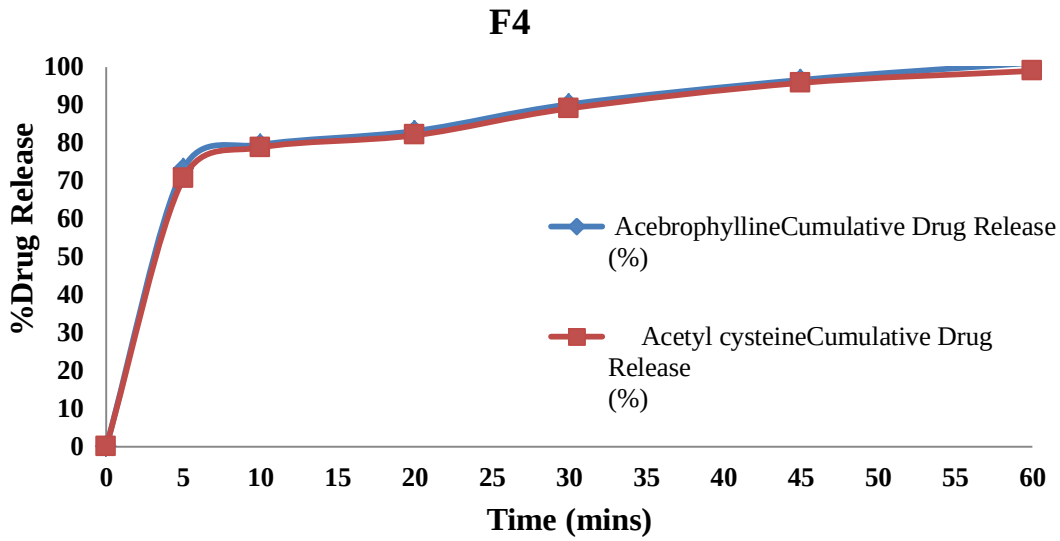


Fig.13: *In- vitro* dissolution profile of Bilayer tablet F-4

Table 34: ***In -vitro dissolution profile of Bilayer tablet*** **F-5**

Immediate Release Layer of Acebrophylline			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	69.92	69.92
2.	10	74.43	74.43
3.	20	79.85	79.85
4.	30	85.14	85.14
5.	45	92.73	92.73
6.	60	99.66	99.66
Immediate Release Layer of Acetylcysteine			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	431.58	71.93
2.	10	461.28	76.88
3.	20	502.20	83.71
4.	30	518.7	86.45
5.	45	546.54	91.09
6.	60	574.8	95.52

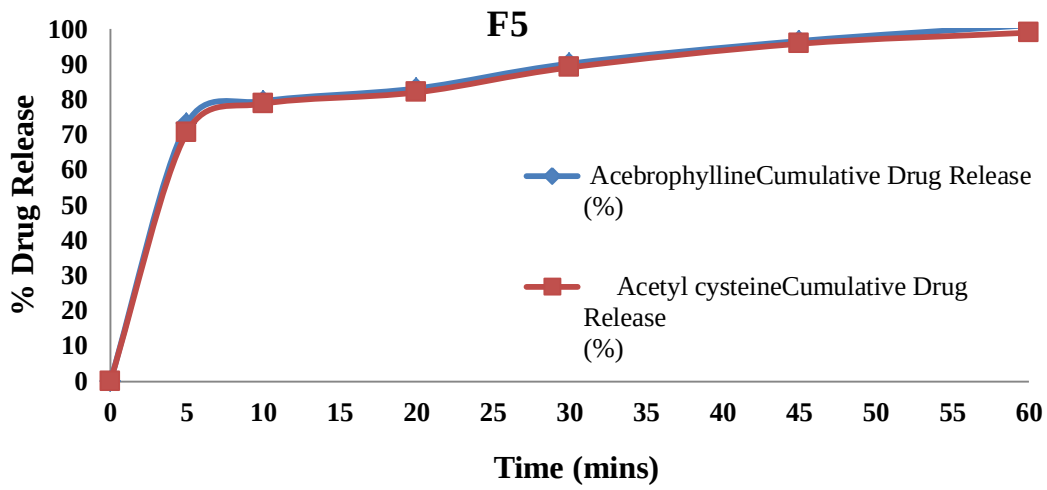


Fig.14: ***In- vitro*** **dissolution profile of Bilayer tablet F-5**

Table 35 : *In- vitro* dissolution profile of Bilayer Tablet F-6

Immediate Release Layer of Acebrophylline			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	71.62	71.62
2.	10	75.83	75.83
3.	20	80.45	80.45
4.	30	87.14	87.14
5.	45	93.27	93.27
6.	60	100.03	100.03
Immediate Release Layer of Acetylcysteine			
S.NO	**Time (mins)**	**Amount of drug release (mg)**	**Drug Release (%)**
1.	5	432.18	72.03
2.	10	464.52	77.42
3.	20	486.3	81.05
4.	30	511.32	85.22
5.	45	545.88	90.98
6.	60	576.6	96.20

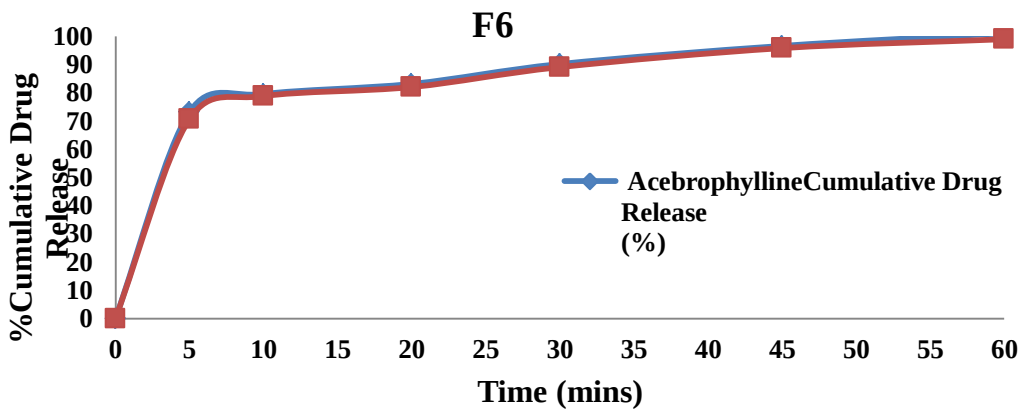


Fig.15: *In- vitro* dissolution profile of Bilayer tablet F-6

Table 36: *In-vitro dissolution profile of Bilayer tablet* F-7

Immediate Release Layer of Acebrophylline			
S.NO	Time (mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	72.72	72.72
2.	10	78.33	78.33
3.	20	82.83	82.83
4.	30	88.39	88.39
5.	45	95.46	95.46
6.	60	100.59	100.59
Immediate Release Layer of Acetylcysteine			
S.NO	Time (mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	442.02	73.67
2.	10	472.92	78.82
3.	20	498.3	83.05
4.	30	522.72	87.12
5.	45	551.1	91.85
6.	60	584.22	97.27

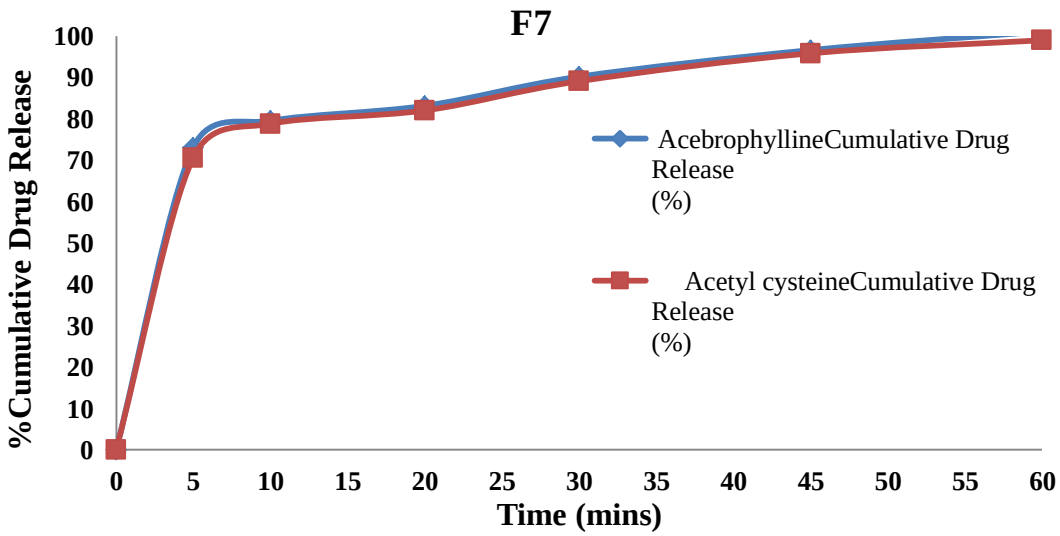


Fig.16: *In-vitro* dissolution profile of Bilayer tablet F-7

Table 37*: In-vitro dissolution profile of Bilayer tablet* F-8

Immediate Release Layer of Acebrophylline			
S.NO	Time (mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	73.12	73.12
2.	10	79.54	79.54
3.	20	83.17	83.17
4.	30	90.21	90.21
5.	45	96.64	96.64
6.	60	101.14	101.14
Immediate Release Layer of Acetylcysteine			
S.NO	Time (mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	424.02	70.67
2.	10	454.92	78.82
3.	20	492.3	82.05
4.	30	534.72	89.12
5.	45	575.1	95.85
6.	60	583.68	99.01

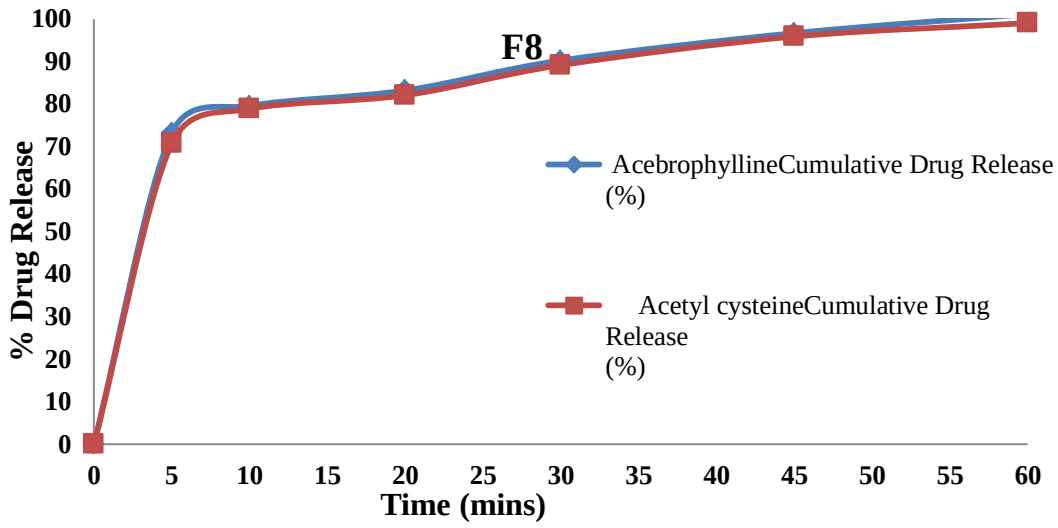


Fig. 17: *In- vitro* dissolution profile of Bilayer tablet F-8

9.4 ASSAY

Table 38: Assay of Acebrophylline & Acetylcysteine

Formulation	Assay of Acebrophylline %	Assay of Acetylcysteine %	Related substance for Acetylcysteine % (N,N Diacetyl-L-cystine)
F1	98.46	94.35	5.65
F2	98.88	95.69	4.31
F3	99.26	94.91	5.09
F4	99.67	95.73	4.27
F5	99.92	94.88	5.12
F6	100.33	96.44	3.56
F7	100.76	97.38	2.62
F8	101.55	99.24	0.76

9.4.1 Optimization by 2^3 Factorial Design: [66, 67, 68, 69]

On the basis of defined constraints for each independent variable, the Design Expert® Software version 11 automatically generated the optimized formulation. The experiments were performed and the responses were obtained.

Table 39: Results of independent variable and corresponding dependent variable according to 2^3 Factorial Design

Run	Factor 1	Factor 2	Factor 3	Response 1
	vitamin E mg/tablet	Butylated Hydroxyl Toluene mg/tablet	Propyl Gallate mg/tablet	Related substance (N, N Diacetyl-L-cystine) (%)
F1	0.10	0.40	0.40	5.65
F2	0.40	0.40	0.40	4.31
F3	0.10	0.80	0.40	5.09
F4	0.40	0.80	0.40	4.27
F5	0.10	0.40	0.80	5.12
F6	0.40	0.40	0.80	3.56
F7	0.10	0.80	0.80	2.62
F8	0.40	0.80	0.80	0.76

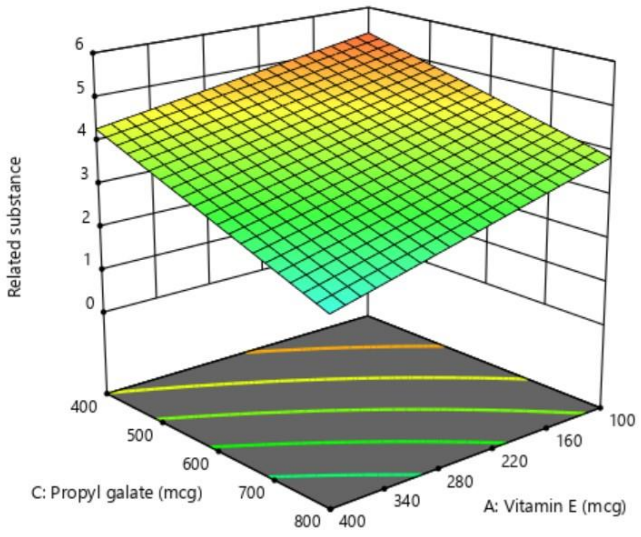
9.4.2 Response surface and contour:

A).This **3D surface graph** (**Fig -18**) illustrates that increasing the concentration of vitamin E& increases the concentration of propyl gallate and decrease related substance (**N,N Diacetyl-L-cystine)** .

Related substance
0.76 5.65

X1 = A: Vitamin E
X2 = C: Propyl galate

Actual Factor
B: BHT = 600

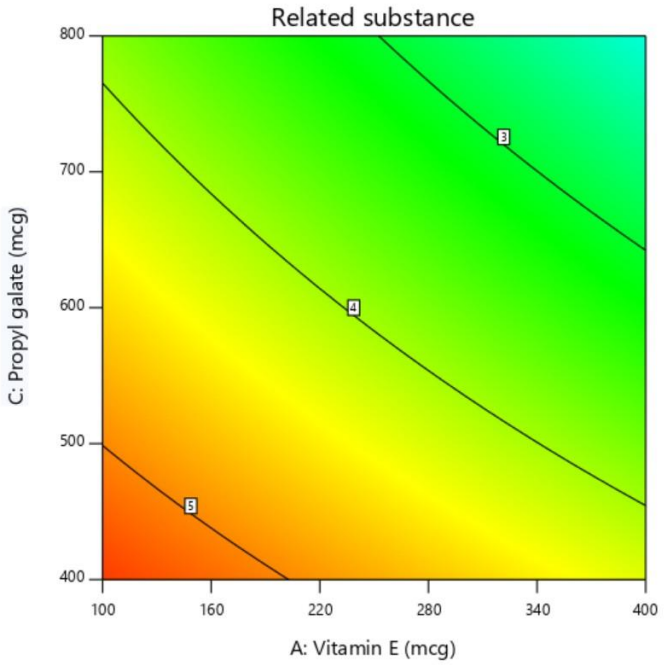


Design-Expert® Software
Factor Coding: Actual

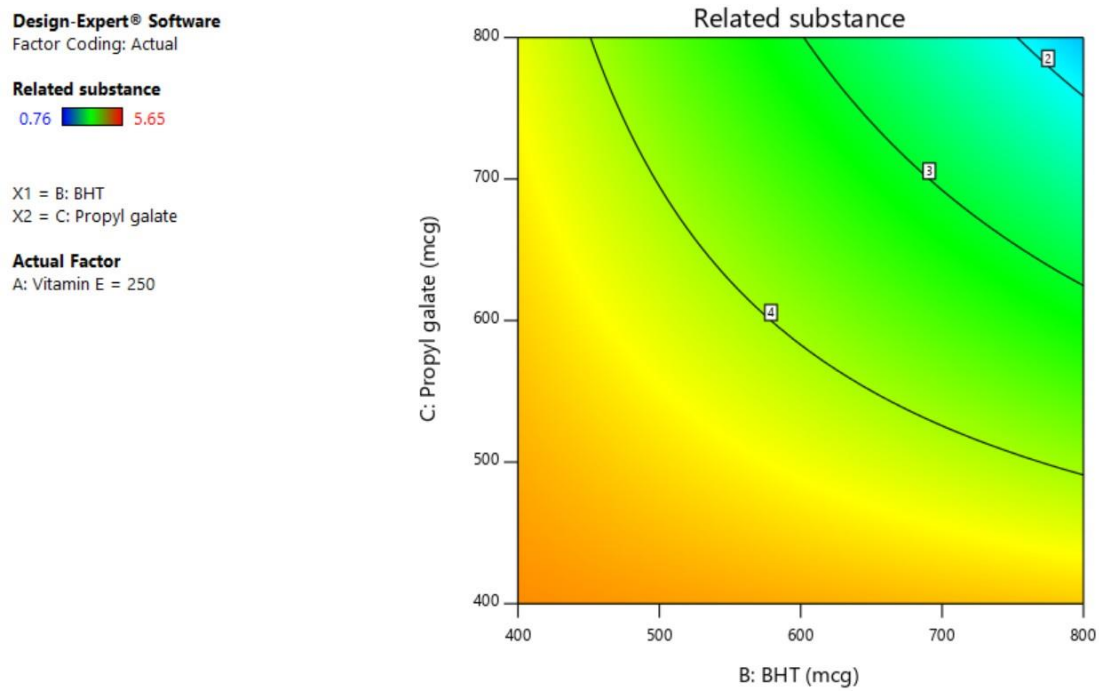
Related substance
0.76 5.65

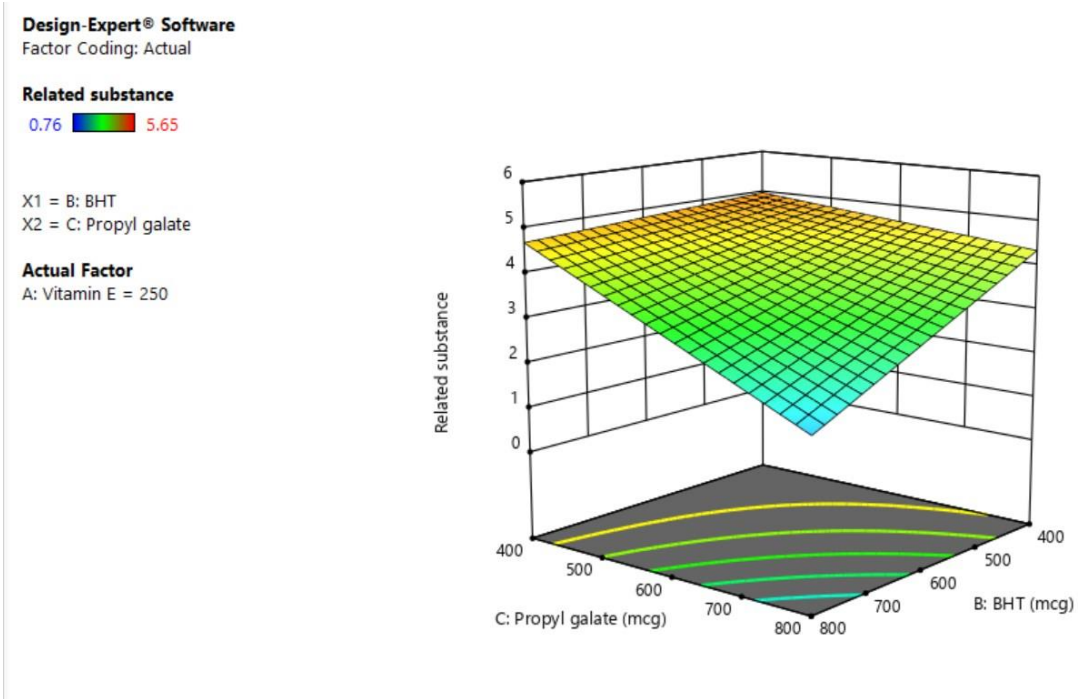
X1 = A: Vitamin E
X2 = C: Propyl galate

Actual Factor
B: BHT = 600



b).This 3D surface graph (**Fig -19**) illustrates that increasing the concentration of BHT & increases the concentration of propylgallate and decrease related substance**(N,N Diacetyl-L-cystine)**.





9.4.3ANOVA:

Table 40: **Response 1: Related substance (N, N Diacety-L-cystine)**

source	Sum squares	Df	Mean squares	F-value	P-value	
Model	17.79	5	3.56	78.99	0.0125	Significant
A-vitamin E	3.89	1	3.89	86.39	0.0114	
B-BHT	4.35	1	4.35	96.59	0.0102	
C-Propylgallate	6.59	1	6.59	146.25	0.0068	
AC	0.1984	1	0.1984	4.41	0.1707	
BC	2.76	1	2.76	61.29	0.0159	
Residual	0.0901	2	0.0451			
Cor Total	17.88	7				

Table 41: Response model and statistical parameters obtained from ANOVA for 2^3 Factorial Design

Responses	Adjusted R2	Predicted R2	Model P value	Adequate precision	%CV
Related substance	0.9824	0.9194	0.0125	25.4878	5.41

For optimization, the effects of independent variables upon the responses were modeled using the following first order polynomial equations involving independent variables and their interactions for various measured responses, studied in this investigation. For optimization, effects of various independent variables upon measured responses were modeled using following mathematical model equation involving independent variables and their interactions for various measured responses generated by 2^3 factorial design is as follows:

Y = + 3.94500 -0.001500 A + 0.005125 B + 0.005587 C -5.2500 AC-0.000015 BC

9.4.4 Point prediction:

Table42: **Optimum formulation derived by Factorial design**

Factor	Vitamin E	Propylgallate	BHT	Desirability
Optimum formulation	398.51	800	800	0.662

Table43: Point Prediction for Acetylcysteine

Point Prediction	N,N Diacety-L-cystine (%)
Predicted	0.84
Observed	0.78
%error	7.1

% error = (observed value-predicted value)/predicted value x 100

9.5 Post Compression Study of optimized Bilayer formulation:

Table 44: Post compression report of Optimized Bilayer Tablet

Trial	Weight variation	Thickness	Hardness	Friability	Assay	Disintegration
Optimized formulation	800±1.63	5.86-5.93	11.20-11.38	0.26	99.28	5minutes 35 seconds

Table 45: *In - Vitro* dissolution study of optimized formulation

Time(minutes)	Optimized Formulation
5	71.53
10	79.18
20	83.47
30	90.04
45	96.55
60	99.19

9.6 In-vitro dissolution of F-9(optimized formulation):

Table 46*: In-vitro* dissolution profile of Bilayer tablet F-9

Immediate Release Layer of Acebrophylline			
S.NO	Time (Mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	73.71	73.71
2.	10	79.60	79.60
3.	20	83.67	83.67
4.	30	90.88	90.88
5.	45	97.04	97.04
6.	60	101.52	101.52
Immediate Release Layer of Acetylcysteine			
S.NO	Time (Mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	424.02	70.53
2.	10	454.92	79.18
3.	20	492.3	83.47
4.	30	534.72	90.04
5.	45	575.1	96.55
6.	60	583.68	99.19

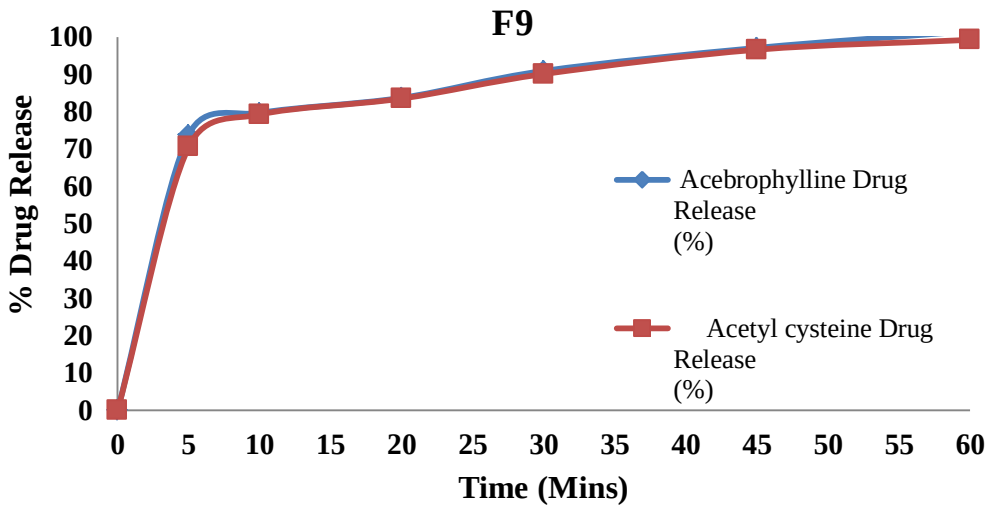


Fig.20: *In-vitro* dissolution profile of Bilayer tablets F9

9.7 In-vitro dissolution profile of Acebrophylline:

Table 47: *In-vitro* dissolution profile of Acebrophylline Formulation (F1-F9)

Acebrophylline									
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	63.88	65.16	66.69	68.59	69.92	71.62	72.72	73.12	73.71
10	67.24	69.34	70.72	72.32	74.43	75.83	78.33	79.54	79.60
20	71.79	72.9	74.17	75.77	79.85	80.45	82.83	83.17	83.67
30	79.36	80.67	81.96	83.46	85.14	87.14	88.39	90.21	90.88
45	85.05	87.05	89.65	90.37	92.73	93.27	95.46	96.64	97.04
60	98.31	98.62	99.12	99.47	99.66	100.03	100.59	101.14	101.52

Compartative Dissolution profile of Acebrophylline F1-F9

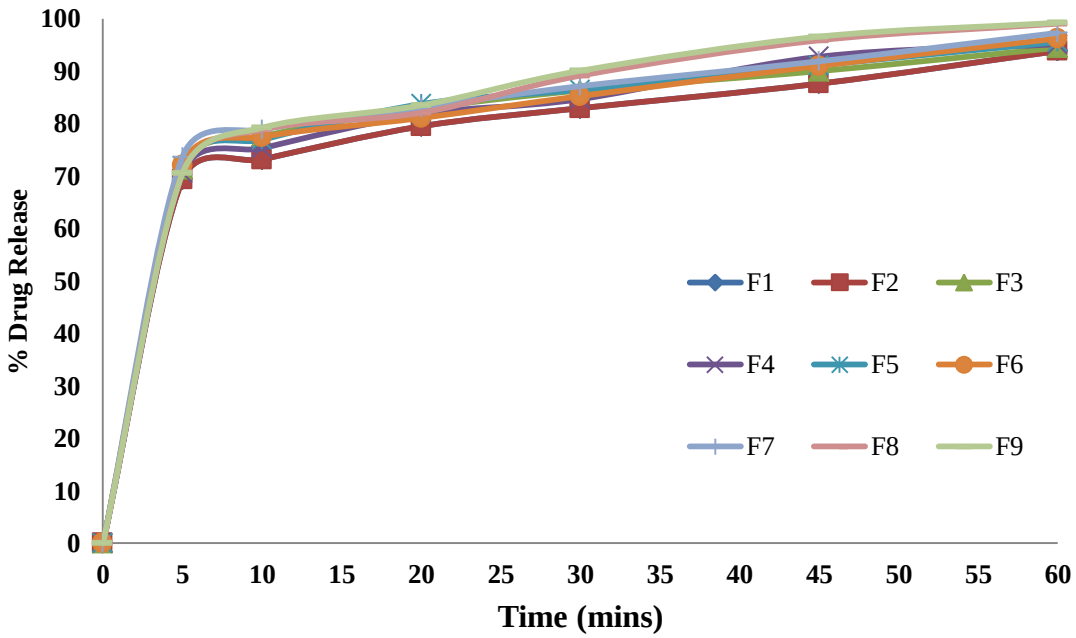


Fig. 21: Comparative Dissolution profile of Acebrophylline F1-F9

***In-vitro* Dissolution Profile of Acetylcysteine:**

Table 48*: In-vitro* dissolution profile of Acetylcysteine Formulation (F1-F9)

Acetylcysteine									
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	65.81	69.32	71.33	70.56	71.93	72.03	73.67	70.67	70.53
10	69.16	73.15	77.51	75.26	76.88	77.42	78.82	78.82	79.18
20	74.47	79.47	82.74	81.79	83.71	81.05	83.05	82.05	83.47
30	78.29	82.92	86.29	84.65	86.45	85.22	87.12	89.12	90.04
45	87.19	87.59	89.98	92.71	91.09	90.98	91.85	95.85	96.55
60	93.06	93.81	94.43	95.11	95.52	96.20	97.27	99.01	99.19

Compartative Dissolution profile of Acetylcysteine F1-F9

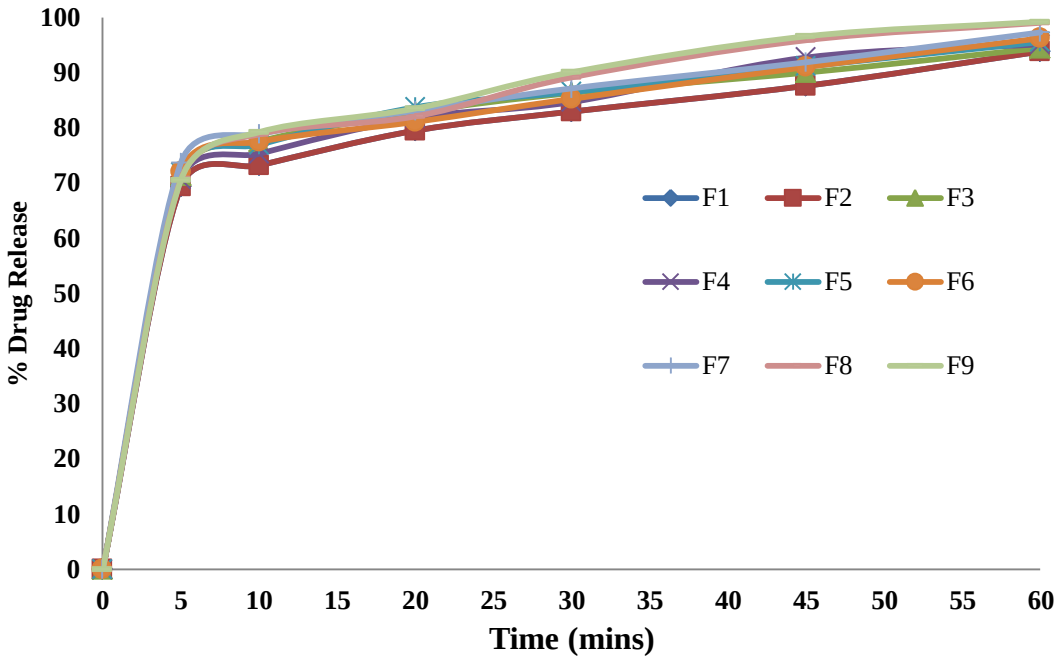


Fig. 22: Comparative Dissolution profile of Acetylcysteine F1-F9

Table 49: *In -vitro* dissolution profile of Market formulation

Immediate Release Layer of Acebrophylline			
S.NO	Time (Mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	74.31	74.31
2.	10	79.92	79.92
3.	20	84.46	84.46
4.	30	91.12	91.12
5.	45	97.54	97.54
6.	60	102.03	102.03
Immediate Release Layer of Acetylcysteine			
S.NO	Time (Mins)	Amount of drug release (mg)	Drug Release (%)
1.	5	430.56	71.76
2.	10	457.68	79.88
3.	20	501.0	83.50
4.	30	542.16	90.36
5.	45	576.9	96.15
6.	60	593.88	99.98

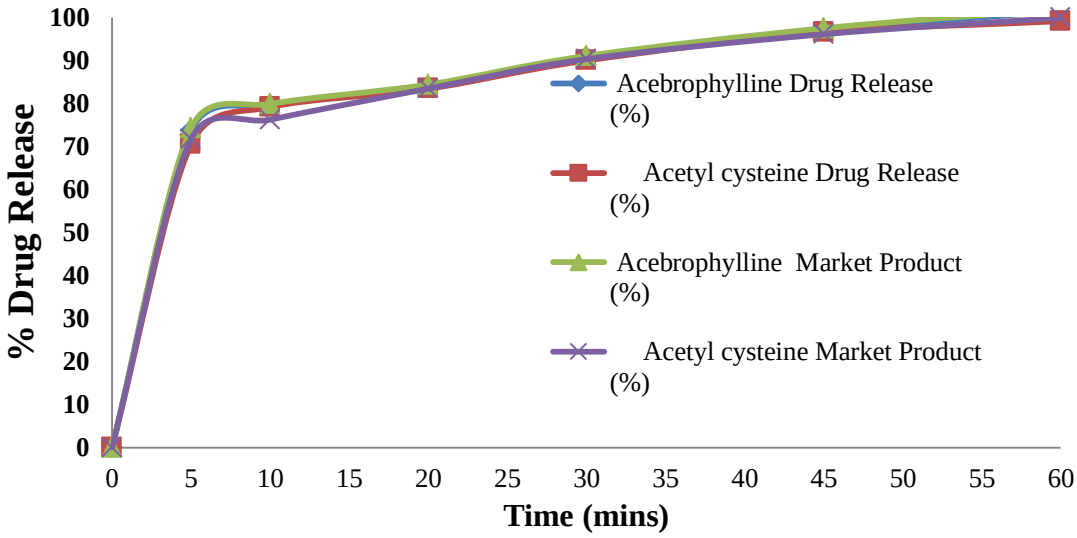


Fig.23: Comparison of Dissolution Profile of optimized Formulation F9 and Market product

9.8 Korsemeyer-peppas model

Table 50: Best fit values

Best fit values		
parameter	**No.1**	**Mean**
kKP	**57.587**	**57.587**
n	**0.132**	**0.132**

Table 51: Secondary parameter

Secondary parameter		
Parameter	**No.1**	**Mean**
T25	0.002	0.002
T50	0.344	0.344
T75	7.352	7.352
T80	11.968	11.968
T90	29.126	29.126

Table 52: Goodness of Fit

Goodness of Fit	
Parameter	**No.1**
N_observed	6
DF	4
R_obs-pre	0.9937
Rsqr	0.9874
Rsqr_adj	0.9843
MSE	1.7509
MSE_root	1.3232
Weighting	1
SS	7.0037
WSS	7.0037
AIC	15.6786
MSC	3.7101

9.5 Stability studies:

Table 53: Stability Studies of Optimized F9

S. No	Parameters	Conditions			
		Initial	**40°C& 75%RH**	**40°C& 75%RH**	**40°C& 75%RH**
		0 Day	**1 month**	**2 month**	**3 month**
1	Average weight	1100±5mg	1100±5mg	1100±5mg	1100±5mg
2	Thickness(mm)	6.55±0.014	6.56±0.014	6.55±0.014	6.55±0.014
3	Disintegration time	6min52sec	6min54sec	6min56 sec	6min58sec
4	Assay (%)	AB-101.39	AB-100.28	AB-100.25	AB-99.87
		A-99.28	A-99.14	A-98.84	A-98.72
5	Dissolution (60mins)	AB – 101.14	AB-101.08	AB-100.03	AB-99.82
		A-99.19	A-98.79	A-98.18	A-98.04

10. DISCUSSION

10.1 Formulation Development of Bilayer tablet:

Asthma **was found** to be a disease affects all aged people. Different FDC formulations were available for Asthma. Traditional tablet formulations developed using direct compression, wet granulation, or dry granulation technology, API **is weighed** and mixed with other excipients as a part of the manufacturing process. **In the Bilayer Tablet, both Acebrophylline and Acetylcysteine give as Bilayer in the form of immediate release dosage form.So the study moved to the development of both layer form to treat asthma.** Thus, traditional tablet formulation approaches were inadequate to **developed** a commercially viable tablet formulation for a worldwide distribution. This research describes a bilayer approach to stabilize the molecule and to develop a commercially viable tablet formulation.

10.2 Selection of Drug and Excipients:

Formulation development started from selection of API, the cost of efficiency, easy availability and challenging aspects of drug properties made to select the Acebrophylline and Acetylcysteine. Then the excipients were selected based on the compatibility.

10.3 Description and solubility:

The description of the Active Pharmaceutical Ingredient Acebrophylline and Acetylcysteine was found to be complies with USP. Solubility of the Acebrophylline and Acetylcysteine was found with the different solvents. The Results were shown in**Table20.**

10.4 Preformulation Study:

10.4.1Determination of Interaction:

A comprehensive understanding of physicochemical interactions in dosage forms is expected under quality design prototypes for drug development. The analytical methods into the initial steps of Preformulation studies have contributed significantly to early prediction, monitoring, and characterization of the API incompatibility to avoid costly

material wastage and considerably reduce the time required to arrive at an appropriate product formulation.

The drug and the excipients chosen for the formulation was screened for its interaction by physical methods. This study would suggest the excipients to be avoided and form a part of the preliminary assessment. The Drug – Excipients compatibility study was carried out by FTIR with their physical mixture of formulations.

10.4.2 Fourier Transformer Infrared spectroscopy (FT-IR) studies:

A complete understanding of the physicochemical interactions in dosage forms is expected under quality by design prototype of drug development. The analytical methods into the initial steps of preformulation studies have contributed significantly to early prediction, monitoring and characterization of the API incompatibility to avoid costly material wastage and considerably reduce the time required to arrive at an appropriate product formulation.

The drug and the excipients chosen for the formulation was screened for its interaction by physical methods. This study would indicate the excipients to be avoided and form a part ofthe preliminary assessment. The Drug – Excipients compatibility study was carried out by FTIRwith their physical mixture of formulations.

10.4.3 Fourier Transformer Infrared spectroscopy (FT-IR) studies:

The FTIR spectra of Acebrophylline are presented in (**Fig.6)**. The characteristic absorption of the Acebrophylline was the band at **3448.7 cm^{-1}**, which is assigned to the functional group O-H Stretching. Acebrophylline and **2944**.2 **cm^{-1}** assigned to the functional group C-H Stretching stretching. Another band at **1666.5cm^{-1}** is due to COOH Stretching. Another band **1473.6 cm^{-1}** is due to CH2 Bending.

The FTIR spectra of Acetylcysteine are presented in (**Fig.7)**. The characteristic absorption of the Acetylcysteine was the band at **2546.0cm^{-1}**, which is assigned to the SH Stretching vibration. the band at **3379.2 cm^{-1}** which is assigned to the N-H Band. the band **1535.3 cm^{-1}** which is assigned to the C-N Stretching. The characteristic absorption of the Acetylcysteine was the band at **1195.8cm^{-1}**, which is assigned to the N-H Stretching vibration.

The peaks **3448.7 cm^{-1}**, **2546.0cm^{-1},3379.2 ,cm^{-1} 1535.3,cm^{-1} 2944**.2**cm^{-1} ,1473.6cm^{-1},1195.8cm^{-1}**and **1666.5cm^{-1}** of Acebrophylline With Acetylcysteine **(Fig.8)** were similar to the spectrum Acebrophylline and Acetylcysteine. The peaks of various functional groups as described in the IR spectrum of Acebrophylline and Acetylcysteine were also present in the Acebrophylline with Acetylcysteine Tablet (**Fig.9)** without any shift or change. These observations revealed the intact nature of the Acebrophylline and Acetylcysteine present in the tablet. From these results, the absence of drug–drug interaction and the stability of the drug in the tablet were confirmed.

10.5 Evaluation of blend Property Studies:

The granules prepared for Bilayer tablets were physically evaluated with some parameters and was suggested to be suitable for compression into tablets. The flow properties of powder blend Acebrophylline and Acetylcysteine were checked by studying the bulk density, tapped density, compressibility Index, and Hausner's ratio. The powder blends were found to be free flowing with good flow properties as shown in **Table.25 and Table.26.**Bulk densities were found to be in the range of 0.625–0.735. (g/ml) and tapped density between 0.842 and 0.902 (g/ml) for all the formulations. The % compressibility index was calculated using the density data. The obtained values 17.04–19.6% that was found to be good flow and Hausner's ratio values were in the range of 1.205–1.245 for all powder blends.

10.6 Evaluation of Bilayer Tablet:

The results were shown in the **Table 27:** The hardness of tablets of each batch ranged between 8.5 to 12.01 kg/cm2, this fact ensures good handling characteristics of all batches. Thickness of all the formulation was found to be in the range 5.48mm to 5.92mm. Friability of all the formulations were found to be in the range 0.21% to 0.37%. Disintegration of all the formulation was found to be in the range 4- 6 minutes.

***10.7 In-vitro*Dissolutionstudy:**

The release profiles of Acebrophylline and Acetylcysteine from different batches of formulated Bilayer tablets were tabulated in **Table.30-38** and plotted in **Fig.10 -22.**

DissolutionprofileAcebrophylline:

The dissolution profile of Acebrophylline Bilayer tablet was studied in 0.1N HCL.It was found that the release profile of Acebrophylline Bilayer tablet (F1-F9) showed drug release Between 98.31-101.52.

DissolutionprofileAcetylcysteine:

The dissolution profile of Acetylcysteine Bilayer tablet was studied in 0.1N HCL.It was found that the release profile of Acetylcysteine Bilayer tablet (F1-F9) showed drug release Between 93.06-99.19.

10.7 Assay:

The results were shown in the **Table 38**: The drug content of formulations (F1-F9) of acebrophylline ranged between 98.46to101.55. The drug content of formulations F1 of Acetylcysteine 94.35% .the relative substance (N, N Diacetyl-L-cystine) was found to be 5.65%. The drug content of formulations F2 of Acetylcysteine 95.69% .the relative substance (N,N Diacetyl-L-cystine) was found to be 4.31%. drug content of formulations F3 of Acetylcysteine 94.91% .the relative substance(N,N Diacetyl-L-cystine) was found to be 5.09 %.drug content of formulations F4 of Acetylcysteine 95.73% .the relative substance(N,N Diacetyl-L-cystine) was found to be 4.27%.drug content of formulations F5 of Acetylcysteine 94.88 % .the relative substance(N,N Diacetyl-L-cystine) was found to be 5.12%. drug content of formulations F6 of Acetylcysteine 96.44% .the relative substance(N,N Diacetyl-L-cystine) was found to be 3.56%.drug content of formulations F7 of Acetylcysteine 97.38.the relative substance(N,N Diacetyl-L-cystine) was found to be 2.62%. drug content of formulations F8 of Acetylcysteine 99.24.the relative substance(N,N Diacetyl-L-cystine) was found to be 0.76.Thereby, increasing the concentration of antioxidants , relative substance was further reduced. His was carried by optimization.

10.8 Optimizationby2^3 Factorial Design:

The purpose of this study was to optimise the formulation of acetylcysteine with vitamin E, BHT, and valproic acid by a 2^3-factor design to achieve NMT 1% related substances **(N, N Diacetyl-L-cystine)**. For optimization of Acetylcysteine as per 2^3 factorial design the vitaminE, BHT and Propylgallate are considered as the three

factors. The two levels of the factor A (vitaminE) are 0.10mg and 0.40mg of Antioxidant; the two levels of the factor B (BHT) are 0.40mg and 0.80mg ratio of Antioxidants: the two levels of factor C (propylgallate) are 0.40mg and 0.80mg ratio of Antioxidant. Eight Acetylcysteine formulations employing selected combinations of the three factors i.e vitaminE, BHT and Propylgallate as per 2^3 factorial design were prepared. The tablets were prepared by wet granulation method as per the formulae given in Table 1 and were evaluated for drug content, hardness, friability, disintegration time and dissolution rate characteristics. The related substance rate values were analyzed as per ANOVA of 2^3 factorial designs to find out the significance of the individual and combined effects of the three factors involved on the dissolution rate of Acetylcysteine tablets formulated.

a).This 3D surface graph (**Fig -18**) illustrates that increasing the concentration of vitamin E& increasing the concentration of propyl gallate and decrease related substance .

b).This 3D surface graph (**Fig -19**) illustrates that increasing the concentration of BHT & increasing the concentration of propyl gallate and decrease related substance

10.9 ANOVA:

A total of 8 trial formulations of Acetylcysteine were proposed by the 23factorial design for three independent Variables. The The effects of these independent variables related substances were investigated as optimized response parameters in the current investigation. The results of the ANOVA indicated that these models were significant for all response parameters (**Table.40&41**). The Design- Expert 10.0.6.1 software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data.The model equation relating N,N Diacetyl-L-cystine as response become. ANOVA study was performed and the f inal equation of best yield was found to be.

Y = + 3.94500 -0.001500 A + 0.005125 B + 0.005587 C -5.2500 AC-0.000015 BC

Response surface methodology further elucidates the effect of the main influences (factors) on the investigated responses (in this case related substances). Response surface methodology is a widely proficient approach in the development and optimization of drug delivery devices. In order to evaluate the optimization capability

of these models generated according to the results of 23 factorial design, optimized Acetylcysteine layer tablets were prepared using one of the selected optimal process variable settings proposed by the experimental design. The selected optimal process variable settings used for the formulation of optimized Acetylcysteine were A = 398.51, B = 800, and C = 800 mcg.

Pointprediction:

The Acetylcysteine were formulated and responses were measured. The software generated the optimized formulation and predicts the response based on the constraint. Then batch was formulated based on the suggested formulation and responses were observed. The observed values of responses were compared to the predicted values of their response and %error was calculated to validate the method. The observed values of Y1 were in a close agreement to the predicted one. By this validity of optimization procedure was proven. The point prediction has been shown in **Table 42&43.**Desirability of optimum formulation was **0.662**.When desirability value is between and 1, the formulation quality is regarded to be acceptable and excellent. When this value is <0.63.Point prediction of predicted value was 0.84 and observed value of 0.78.

10.10 Post Compression Study of optimized Bilayer formulation:

The results were shown in the **Table.44&45:** The hardness of tablets of each batch ranged between 11.20-11.38 kg/cm2, this ensures good handling characteristics of all batches. Thickness of all the formulation was found to be in the range 5.86mm to 5.93mm. Friability of all the formulations was found to be in the range 0.26.Disintegration of all the formulation was found to be in the range 5 min 35 sec. The drug content of Acetylcysteine preparation F9 is between 99.28 the relative substance was found to be 0.78. The release profile of Acetylcysteine Bilayer tablet F9 – in-vitro drug release 99.19

10.11Drug release kinetics:

Dissolution data of the optimized formulation was fitted to various mathematical models (Koresmeyar - peppas) in order to describe the kinetics of drug release profile. the plot of cumulative percentage drug release as a function of time. **Table:50,51,52.** The Koresmeyar – peppas model,the drug release data further analyzed for curve fitting and results(n=0.132) confirmed that the formulation follows fickian diffusion kinetics.

10.12 StabilityStudy:

The colour and shape of the tablet **were found** to be unchanged even at the end of 3 Month stability study in all conditions. The results were shown in **Table 53**. In order to perform the stability study, the tablet was **placed** with Alu-Alu packing material and folded in to strips, then placed in to the stability chamber. At the end of the **month** one set of the tablet **was analysed** for shape average weight and drug content. There was no change in the colour and shape of the tablet. There was also no change in release behavior for up to three months compared to the optimized formulation.

11. SUMMARY

Chapter 1:

In this introduction chapter discussed about Formulation, Asthma, Immediate release layer tablet general components, General components, antioxidant, Technique used in the preparation of immediate release, Tablets Bilayer tablets: Advantages and Disadvantages, Immediate relase dosage Forms, Preparation of Bilayer tablets .

Chapter II:

In this Chapter the literature related to this work was surveyed and a brief discussion had been given on each literature.

Chapter III:

The objective of present investigation was to develop the fixed-dose combination Of bilayer tablets of Acebrophylline immediate-release (IR) layer on a Acetylcysteine immediate-release (IR) Bilayer tablet.

Chapter IV:

This Chapter gives an idea for the proposed plan of work that has to be carried out.

Chapter V & VI:

In this chapter information about the drug and the polymers used in the study was Given.

Chapter VII & VIII:

This chapter deals with the materials and methods used in the study. This chapter covers the details of experimental methods, Design of experiment, including evaluation of preformulation, *in-vitro* evaluation, and stability studies.

Chapter IX:

This chapter depicts the results for the all tests indicated in the **chapter VIII**. The results for all the parameter to be evaluated for the prepared film coated Bilayer tablet and the formulated **Acebrophylline and Acetylcysteine** forms were given in this chapter.The *In-vitro* evaluation of the optimized formulation were available.

Chapter VIII & X:

These chapters deal with the optimization of the formulation among the 8 batches of Acebrophylline and Acetylcysteine form. The best values of the different evaluation test were found and presented in it. Dissolution studies of different formulation are tabulated and stability study was given. The chapter discussion involves in discussion of the better fitvalues of the different evaluation test to optimize the best fit values.

A total of 8 trial formulations of Acebrophylline and Acetylcysteine were proposed by the 2^3factorial design for three independent Variables Ratio of antioxidant in drug and polymer in drug coat and spray rate with varied at two different levels (high and low). The effects of these independent variables related substance (N, N Diacetyl-L-cystine) were investigated as optimization response parameters in the current investigation. The results of the ANOVA indicated that these models were significant for all response parameters (**Table.40-41**). The Design- Expert software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data.

12. CONCLUSION

This study aimed to develop an immediate-release bilayer tablet of acetylcysteine. Combination of Acebrophylline and Acetylcysteine are indicated for the successful treatment and relief of Asthma. Prepared bilayer tablets were film coated in a conventional coating pan. Formulation properties such as content uniformity, hardness, and friability found to be satisfactory

In vitro dissolution studies of bilayer tablets were conducted for 60 minutes. Samples were analyzed by HPLC. The formulation (F1-F9) showed an acceptable range and complied with the internal specification for weight variation, thickness, hardness, friability, *in vitro* drug release. The drug content of Acebrophylline and Acetylcysteine in tablet were constant but major degradation of Acetylcysteine to form N,N Diacety-L-cysteine degradation was greatly reduced by the introduction of antioxidants of Propylgallate, Vitamin E, and Butylated Hydroxyl Toluene (BHT) as a variable in 2^3-factor design of experiments and optimized. Accordingly, A = 398.51 , B = 800, and C = 800 mcg used for optimized batch. The level of N,N Diacety-L-cystine reduced to 0.78.

Accelerated stability profile of bilayer tablets was found to be satisfactory. No sign of degradation was observed in HPLC analysis. Hence, it is finally concluded that, the Bilayer tablet technology can be successfully applied for Immediate-release layer of Acebrophylline and Acetylcysteine.

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