FORMULATION AND EVALUATION OF ACETAMINOPHEN AND DIPHENHYDRAMINE HYDROCHLORIDETABLETS

Dissertation

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF ACETAMINOPHEN AND DIPHENHYDRAMINE HYDROCHLORIDE TABLETS**" submitted by **Miss. M. RAJANI KUMARI**to TamilNadu Dr. M. G. R. Medical University, Chennai, in partial fulfillmentfor the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by her under my guidance and supervision during the academicyear2011-2012.

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(M. Rajani kumari)

Dedicated to

Almighty

&

My Family

LIST OF ABBREVIATIONS

BP	:	British pharmacopoeia
Conc	:	Concentration
CDDS	:	Controlled drug delivery system
CR	:	Controlled release
MCC	:	Microcrystalline cellulose
CCS	:	Croscarmellose sodium
APAP	:	Acetaminophen
DP	:	Diphenhydramine hydrochloride
FTIR	:	Fouriertransform Infrared
IR	:	Infrared
ICH	:	International Conference on Harmoniation
RH	:	Relative humidity
SR	:	Sustained release
UV	:	Ultraviolet
USP	:	United States Pharmacopoeia
µg	:	Microgram
µm	:	Micrometer

CONTENTS

1. INTRODUCTION

Drugs can be administered through different routes. However, of all the routes of administration, oral route of administration is the most convenient for administering drugs for systemic effect because of ease of administration, manufacturing and dosage adjustments. Parentral route is not routinely used because of difficulty in self administration and hence hospitalization may be required. Topical route is recently developed and is employed for only few drugs like Nitroglycerine, Scopolamine for systemic effect. Topical route has limitations in its ability to allow effective drug absorption for systemic drug action. Parentral administration is employed in the case of emergency and in which the subject is comatose or cannot swallow. Nevertheless it is possible that at least 90% of all drugs used to produce systemic effect are administered by oral route.

Oral route of drug administration has wide acceptance and of the drugs administered orally in solid dosage forms represents the preferred class of products. The reasons are, Tablets and capsules represent unit dosage form in which one usual dose of drug has been accurately placed.

By comparison liquid oral dosage forms such as syrups, suspensions, emulsions, solutions, and elixirs are usually designed to contain one dose medication in 5-30ml. Such dosage measurements are typically error by a factor ranging from 20-50% when the drug is self administered by patient. Liquid oral dosage forms have other disadvantages and limitations[1].

1.1. TABLETS:

Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in water before being administered and some are retained in the mouth, where the active ingredients are liberated. Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach

and intestine and then absorbed into systemic circulation by which it reaches its site of action.

1.2. ADVANTAGES OF TABLETS[2]:

1. They are unit dosage forms and have dose precision and least content variability.
2. Their cost is less.
3. Product identification is potentially the simplest and cheapest and greatest ease of Swallowing.
4. They have the best combined properties of chemical, mechanical and micro biological stability of all the oral dosage forms.

1.3. PROPERITES OF TABLETS:

A Tablet

1. Should be an elegant product, free of defects such as chips, cracks and discoloration.
2. Should have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.
3. Should have physical and chemical stability.
4. Must be able to release the medicinal agent in the body in a predictable and reproducible manner.

1.4. TABLET DESIGN AND FORMULATION[3]:

Compressed tablets may be made by three basic methods.

1.4.1 Wet granulation

1.4.2 Direct compression

1.4.3 Slugging (Dry granulation)

1.4.1. Wet granulation

Wet granulation is a process of using a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed and over wetting will cause the granules to be too hard and under wetting will cause the granules to be too soft

and friable. Aqueous solutions have the advantage of being safer to deal with than other solvents.

Procedure of Wet Granulation

Step 1: Weighing and Blending - the active ingredient, filler, disintegration agents are weighed and mixed.

Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, CMC, gelatin, and povidone. Ingredients are placed within a granulator which helps ensure correct density of the composition.

Step 3: Screening the damp mass into pellets or granules.

Step 4: Drying the granules.

Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity.

Step 6: Lubrication- A dry lubricant, antiadherent and glidant are added to the granules either by dusting over the spread-out granules or by blending with the granules. It reduces the friction between the tablet and the walls of the die cavity. Antiadherents reduce sticking of the tablet to the die and punch.

Step 7: Tableting: Last step in which the tablet is fed into the die cavity and then compressed between a lower and an upper punch.

Water may be used as the liquid binder, but sometimes many actives are not compatible with water. Water mixed into the powder can form bonds between powder particles that are strong enough to lock them in together. However, once the water dries, the powders may fall apart and therefore might not be strong enough to create and hold a bond. Povidone also known as polyvinyl pyrrolidone (PVP) is one of the most commonly used pharmaceutical binders. PVP and a solvent are mixed with the powders to form a bond during the process, and the solvent evaporates. Once the solvent evaporates and powders have formed a densely held mass, then the granulation is milled which results in formation of granules.

Advantages of wet granulation:

1. The cohesiveness and compressibility of powders is improved due to the added binder that coats the individual powder particles causing them to adhere to each other so they can be formed into agglomerates called granules. Drugs having a high dosage and poor flow must be granulated by the wet granulation method to obtain suitable flow and cohesion for compression.
2. Good distribution and uniform content for the soluble low dosage drugs and color additives are obtained if these are dissolved in binder solution.
3. Wet granulation prevents segregation of components of a homogenous powder mixture during processing, transferring, and handling.
4. The dissolution rate of an insoluble drug may be improved by wet granulation.
5. Controlled release dosage forms can be accomplished by the selection of suitable solvents.

Limitations of wet granulation

1. This method is very costly because of space, time and equipment involved.
2. The process is labour intensive because of large number of processing steps, number of pieces of extensive equipment.
3. It is time consuming, especially the wetting and drying steps.
4. Material loss during processing due to transfer of material from, one unit operation to another.

1.4.2. Dry granulation

This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification. However, the process may require repeated compaction steps to attain the proper granule end point.

Process times are often reduced and equipment requirements are streamlined; therefore the cost is reduced. However, dry granulation often produces a higher

percentage of fines or non compacted products, which could compromise the quality or create yield problems for the tablet. It requires drugs or excipients with cohesive properties.

1. Some granular chemicals are suitable for direct compression (free flowing) e.g. potassium chloride.
2. Tablet excipients with good flow characteristics and compressibility allow for direct compression of a variety of drugs.

1.4.3. Slugging:

In this method, after weighing and mixing the ingredients, the powder mixture is "slugged" or compressed into large flat tablets or pellets of about 1 inch in diameter. The slugs then are broken up by a mill and passed through a screen of desired mesh for sizing. Lubricant is added in the usual manner, and tablets are prepared by compression. Aspirin, which is hydrolyzed on exposure to moisture, may be prepared into tablets after slugging.

1.5. FORMULATION TECHNIQUES[4]

Generally dispersible tablets are formulated by conventional techniques like direct compression technology, wet granulation and slugging process.

1.5.1. Factors to be considered in formulation development

The Success of formulations by direct compression depends on careful consideration of excipient properties and optimization of the compressibility, fluidity and lubricating ability of power blends.

1.6. COMPRESSIBILITY

Formulation should be direct at optimizing tablet hardness without applying excessive compression force while at the same time assuring rapid tablet disintegration and drug dissolution. In those cases where the drug makes up the greater part of final tablet weight, the functional properties of active ingredient, type and concentration of excipient dominate the problem.

In regard to the active ingredients it is important to determine the effect of particle size on compressibility as well as the effect of crystalline form on compressibility and density.

The most effective dry binder is microcrystalline cellulose. It can add significant hardness of 3-5% it is considered in tablet formulation when the hardness or friability is a problem. Almost all disintegrating agents retard compressibility as well as fluidity due to particle size for optimal disintegration, particle size of disintegrating agent is small.

Generally direct compression formulation is less compressible than wet granulation.

1.7. FLUIDITY:

The fluidity of tablet blends is important not only from the direct effect on uniformity of die fill and thus uniformity of tablet weight, but also from the role it plays in blending and power homogeneity.

Fluidity of active ingredients becomes a factor when the drug has been micronized to improve dissolution rate.

In order to design tablet machine with high output more sophisticated feeders with adequate contact of feeder with die cavity to allow uniform filling. There are two basic approaches to increasing die-feeding efficiency.

a. To force material into die cavity.
b. To improve flow properties of material directly above the die cavity.

1.8. CONTENT UNIFORMITY:

Highly fluid powder blends facilitate unblending. The narrower the particle size range of all components and the more alike the particles densities, the less chance for unblending or segregation.

Major problem with segregation can occur in spherically shaped fillers, if the particle is large and spherical, such as in the case with compressible dextrose.

It is theorized that blending of all materials at once would have interfered with the surface attraction of drug particles to filler and resulted in decreased homogeneity.

1.9. LUBRICATION:

The problem associated with lubricating direct compression blends are

1. Type and amount needed to produce adequate lubrication.
2. The softening effect of lubrication.

The small particle size of lubricants in granulation is of great importance in direct compression. Even when all surfaces of granules are covered by a layer of lubricant, clean surfaces are formed during compression. Standard blending times will results in complete coverage of these surfaces.

The lengths of blending become much more critical in direct compression than in lubrication of tablet granulation.

Ejection force, hardness, disintegration and dissolution of all directly compressed tablets of lactose and microcrystalline cellulose where all significantly affected by blending times.

1.10. STUDY OF PHYSICOCHEMICAL TABLETING PROPERTIES OF DRUG:

The formulation of tablets is governed by a number of factors like particle size, size frequency, bulk density, compressibility, flow ability, porosity, moisture content, solubility and melting point. Influences of particle size on dissolution rate, study of compacts of the drug in order to compress the tablet directly are important.

1.10.1. Powder characteristics:

A number of empirical studies exist in the pharmaceutical literature with the aim of mapping factors that affects the structure of tablet and its mechanical strength, i.e. tensile strength, resistance towards attrition and capping tendencies. These factors can be classified into three groups.

1) Material and formulation factors
2) Processing factors

3) Environmental factors

Of special importance from a formulation perspective are the physical and mechanical properties of the particles used in the formulation and how these particles are combined in granulation and mixing steps.

1.10.2. Flow properties[5]:

The flow properties of a powder result from many forces. Solid particles when they are in contact are predominantly surface forces. Many types of forces act between solid particles they are

a) Frictional force
b) Surface tension forces
c) Mechanical forces caused by interlocking of particles of irregular shape.
d) Electrostatic forces.
e) Cohesive or vanderwaal's force.

All these forces can affect flow properties of a solid. They can also effect granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy and surface area.

The test to determine flow rate are two types

1. Direct methods
    a) Hopper flow method
    b) Recording flow meter method
2. Indirect methods
    a. Determination of angle of repose
    b. Measurement of bulk density and compressibility index, carr's index and Hausner's ratio
    c. Shear cell determination
    d. Critical orifice diameter determination

1.10.3. Angle of repose:

Angle of repose has been used as an indirect method of quantifying powder flow ability, because of their relationship with interparticle cohesion. A static heap of powder will begin to slide when the angle of inclination is large enough to overcome frictional forces. This sliding will stop when the angle of inclination is below to that of the required to overcome adhesion/cohesion, i.e. sliding occurs until the gravitational forces balance the inter-particle forces. This balance of forces causes the powder poured from a container onto a horizontal surface to form conical mount or heap. The sides of the heap formed in this way make an angle with the horizontal which is called the angle of repose represented by φ

It is given by

$$\theta = \mathrm{Tan}^{-1}(h/r)$$

Where θ = Angle of repose

h = height of heap

r =horizontal surface radius of heap.

Three are different methods of determining angle of repose such as

1. Fixed height cone method
2. Fixed base cone method
3. Tilting table method
4. Rotating cylinder method

1.10.4. Bulk density:

Bulk density is a property of powders, granules and other divided solids. It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume. Bulk density is not an intrinsic property of a material; it can change depending on how the material is handled. For example, a powder poured in to a cylinder will have a particular bulk density; if the cylinder is disturbed, the powder particles will move and usually settle closer together, resulting in a higher bulk density. For this reason, the bulk density of powders is usually reported both as "freely settled" and "tapped" density (where the tapped density refers to the bulk

density of the powder after a specified compaction process, usually involving vibration of the container.)

Bulk density= fractional solid content × true density

1.10.5. Melting point:

It is defined as the temperature at which the pure liquid and solid exist in equilibrium. If the melting point is more, solubility of drug decreases and vice versa.

Porosity:

The porosity of voids of the powder is defined as the ratio of the void volume to bulk volume of the packing.

Porosity is frequency expressed in present, Ex 100 the release of solid drug from a tablet involves the simultaneous penetration of the surrounding liquid, dissolution of drug and leaching out of the drug through interstitial channels or pores. For penetration of surrounding liquid in large amount, numerous pores must be present which enables faster release of drug. Thus, an increase in porosity increases the dissolution rate of the drug.

1.11. CONVENTIONAL TABLETS:

A novel, fast-dissolving delivery system that releases active ingredients in seconds is one of the fastest-growing segments of the supplements marketplace. Advances in technology continue to break the barriers of conventional encapsulation methods. Today, active ingredients can be delivered with a level of convenience, performance and bioavailability never before seen in the marketplace. And, as our scientific understanding of the prevention and management of diseases continues to grow, companies find themselves in ever-greater competition—investing millions of dollars to develop novel ways of delivering nutrients orally to patients. Fast-dissolving tablets or rapid-melt tablets are one such innovation.

This novel type of delivery system offers convenience for treatment-resistant populations who have difficulty in swallowing oral dosage forms. The demand for these formulations has gone up significantly for children and older populations. They

are particularly convenient for pediatric and geriatric segments of the population because they rapidly disintegrate in the mouth without the need for chewing or drinking water. Fast-melting formulations even offer advantages for drug-compliant patients who take other orally administered pills, such as chewable, suspensions and effervescent tablets. When placed in the mouth, these tablets disintegrate in a few seconds, resulting in quick absorption of the actives through the buccal and oesophageal mucous, thus offering faster bioavailability of active ingredients with minimal side effects. Fast-melting tablets can also serve as carriers for a wide range of nutritional and dietary supplements including calcium, caffeine, antioxidants and folic acid.

1.12. CLASSIFICATION OF TABLETS[7]:

1.12.1. Disintegrating tablets:

The most common type of tablet is intended to be swallowed and to release the drug in a relatively short time by disintegration and dissolution i.e, the goal of the formulation is fast and complete drug release In-vivo, such tablets are called conventional or plain tablets. A disintegrant tablets includes the following type of excipients: filler (if the dose of the drug is low), disintegrant, binder, glidant, lubricant and anti adherent. The type of lubricant and filler can also be of significant importance for tablet disintegration. Tablet disintegration may also be affected by the production conditions during manufacture. Important samples are the design of granulation procedures(will affect the physical properties of the granules), mixing conditions during the addition of lubricants and antiadherents and the applied punch force during tabletting and the punch force during tabletting and the punch force-relationship.

1.12.2. Effervescent tablets

Effervescent tablets are dropped into a glass of water before administration, during which carbon dioxide is liberated. This facilitates tablet disintegration and drug dissolution; the dissolution of the tablet should be completed within minutes as mentioned above the Effervescent carbon dioxide is created by a reaction in water between a carbonate and bicarbonate and a weak acid such as citric or tartaric. Effervescent tablets are used to obtain rapid drug action, for example analgesic drugs,

or to facilitate the intake of drug, for example for vitamins. The amount of sodium bicarbonate in an effervescent tablet is quite often high (about 1gm). After dissolution of such a tablet, a buffered water solution will be obtained which normally temporarily increase the pH of the stomach. The result is rapid emptying of the stomach and the residence time of the drug in the stomach will thus be short, which increases the absorption of the drug in the intestine.

1.12.3. Dispensing tablets

Dispensing tablets are intended to be added to a given volume of water by the pharmacist or the consumer, to produce a solution of a given drug concentration. Materials that have been commonly incorporated in dispensing tablets include mild silver proteinate, bichloride of mercury, merbromin, and quarternary ammonium compounds. The dispensing tablet comprises of the excipients which are soluble in water. The main difficulty with this formulation is the above mentioned excipients are highly toxic and extremely hazardous.

1.12.4. Hypodermic tablets

Hypodermic tablets comprises of one or more drugs with other readily water soluble ingredients and are intended to be added to sterile water or water for injection. Hypodermic tablets are less used today in this country because their use increases the likely hood of administering a non sterile solution.

1.12.5. Tablet triturates

Tablet triturates are small, usually cylindrical, molded, or compressed tablets. The drugs employed in such products were usually quite potent and were mixed with lactose and possibly a binder such as powdered acacia, after which the mixture was moistened to produce a moldable, compactable mass. This mass was forced into the holes of a mould board fabricated from wood or plastic, after which the tablets are ejected using a peg board, whose pegs matched the holes in the mould. The tablets were allowed to dry and ready for dispensing.

1.12.6. Lozenges

Lozenges are the tablets that dissolve slowly in the mouth and so release the drug dissolved in the saliva. Lozenges are used for local medication in the mouth or

throat, e.g. with local anesthesia, antiseptic and antibiotic drugs. They can thus be described as slow release tablets for local drug treatment. In addition, lozenges are often colored and include a flavor. The choice of filler and binder is of particular importance in the formulation of lozenges, as these excipients should contribute to a pleasant taste or feeling during tablet dissolution .Examples of fillers are glucose, sorbital and mannitol. Most common binder is gelatin. Lozenges are prepared by compaction at high pressures in order to obtain tablet of high mechanical strength and low porosity which can dissolve slowly in the mouth over a period of perhaps 30 minutes or less.

1.12.7. Sublingual and buccal tablets

Sublingual and buccal tablets are used for drug release in the mouth followed by systemic uptake of the drug. A rapid systemic drug effect can thus be obtained without first pass liver metabolism. Sublingual tablets are placed below the tongue and buccal tablets are placed in side of the cheek. Sublingual tablets and buccal tablets are often small and porous, latter facilitating fast disintegration and drug release. Buccal and sublingual tablets should be formulated with bland excipients, which do not stimulate salivation. These tablets should be designed such that they do not disintegrate but rather dissolve slowly, typically over a period of 15 to 30 minutes.

1.12.8. Chewable tablets

Chewable tablets are chewed and thus mechanically disintegrated in the mouth. The drug is, however, normally dissolved in the mouth but swallowed and dissolves in the stomach or intestine. Thus, chewable tablets are used primarily to accomplish a quick and complete disintegration of the tablet and hence obtain a rapid drug effect or to facilitate the intake of the tablet. A common example of the former is antacids tablets. In the latter case, the elderly and children in particular have difficulty in swallowing tablets, and so chewable tablets are attractive forms of medication. Important examples are vitamin tablets. Flavouring and coloring agents are common. Sorbital and mannitol are the common examples for fillers.

1.12.9. Dental cones

Dental cones are relatively minor tablet forms that are designed to be placed in the empty socket remaining following a tooth extraction. Their usual purpose is to prevent the growth and multiplication of bacteria in the socket such extraction by employing a slow releasing antibacterial compound, or to reduce bleeding by containing an astringent or coagulant. The usual vehicles of these tablets are sodium bicarbonate, sodium chloride, or an amino acid.

1.12.10. Implantation tablets

Implantation tablets or depot tablets are designed for subcutaneous implantation in animals or man. Their purpose is to provide prolonged drug effects, ranging from one month to one year. The tablets are usually small, cylindrical or rosette shaped forms, and are typically not more than 8mm in length. The safety problems include surgical technique to discontinue therapy, and tissue toxicity in the area of implantation site. These forms are mostly replaced by the diffusion controlled silicone tubes filled with drug or bio degradable polymers that contain entrapped drug in a variety of forms.

1.12.11. Vaginal tablets

Vaginal tablets or inserts are designed to undergo slow dissolution and drug release in the vaginal cavity. The tablets are pear shaped or ovoid to facilitate retention in vagina. This tablet form is used to release anti bacterial agents , antiseptics or astringents to treat vaginal infections, or possibly to release steroids for systemic absorption. The tablets are often buffered to promote a pH favorable to the action of a given antiseptic agent. The tablets should be designed to be compatible with some type of plastic tube inserter, which is usually employed to place the tablet in the upper region of vaginal tract.

1.12.12. Enteric coated tablets

All enteric coated tablets are a type of delayed release tablets. In human drug application, a product may be designed to pass through the stomach intact and then release gradually for several hours or longer in intestines. The compendial specifications for an enteric coated tablet are that all of the six tablets placed in

separate tubes of USP disintegration apparatus remain intact after 30 minutes of exposure in simulated gastric fluid at 37 ± 2^0C and then disintegrate within the time specified for the products monograph, plus 30 min. if one or two tablets fail to disintegrate completely in the intestinal fluid. The test is repeated on 12 additional tablets; not less than 16 of the total 18 tablets tested must disintegrate completely.

1.12.13. Sugar or chocolate coated

Sugar coated tablet role was to produce an elegant, glossy, easy to swallow tablet dosage form. The process developed was time consuming. Earlier sugar coating doubled the tablet weight. Today water soluble polymers are incorporated in the sugar solution, automated spray coating equipment is employed, and high drying efficiency side vented coating pans are used and the process can be completed in a day or less.

1.12.14. Film coated tablets:

Film coated tablets were developed as an alternative procedure to the preparation of coated tablets in which the drug was not required in the coating. The initial film coating compositions employed one or more polymers, which usually included a plasticizer for the polymer and possibly a surfactant to facilitate spreading. The film coating process was an attractive tablet coating method since it permitted the coating of the tablet in a period of one or two hours. Polymers such as hydroxypropyl cellulose and hydroxypropyl methylcellulose, which are dissolved in water with an appropriate plasticizer, are now widely used to prepare immediate release film coating tablets.

1.13. INACTIVE INGREDIENTS[7]:

The selection and testing of non active ingredients or excipients in tablet formulas present to the formulator the challenge of predictive foresight.

Two major classifications of additives by function include those which affect the compressional characteristics of the tablet,

- Diluents
- Binders and adhesives
- Lubricants, anti adherents, and glidants.

And those which affect the biopharmaceutics, chemical and physical stability and marketing considerations of the tablet,

- Disintegrants
- Colors
- Flavors and sweeteners
- Miscellaneous components (e.g., buffers and adsorbents)

1.13.1. Diluents:

Although diluents are normally thought of as inert ingredients, they can significantly affect the biopharmaceutics, chemical and physical properties of the final formulation. The classic example of calcium salts interfering with the absorption of tetracycline from the gastrointestinal tract was presented by Bolger and Gavin. The interaction of amine bases or salts with lactose in the presence of alkaline lubricants, and subsequent discoloration, emphasized that excipient inertness may often not exist in the design of drug dosage forms.

Usually tablets are designed so that the smallest tablet size which can be conveniently compressed is formed. Thus, where small dosage level drugs are involved, a high level of diluent or filler is necessary. If however, the dosage level is large, little or no diluent will be required, and the addition of other excipients may need to be kept to be kept to a minimum to avoid producing a tablet that is larger than acceptable. In such large drug dosage situations, nevertheless, excipient materials must often be added to produce a granulation or direct-compression mixture which may be compressed into acceptable tablets.

Eg: Sucrose, Mannitol, Sorbitol, Microcrystalline cellulose, Dextrose, Amylose etc[8].

1.13.2. Binders and adhesives:

Binders or adhesives are added to tablet formulation to add cohesiveness to powders, thereby providing the necessary bonding to form granules, which under compaction form a cohesive mass or compact referred to as a tablet. The primary criterion when choosing a binder is its compatibility with the other tablet components.

Secondarily, it must impart sufficient cohesion to the powders to allow for normal processing (sizing, lubrication, compression, and packaging), yet allow the tablet to disintegrate and the drug to dissolve upon injection, releasing the active ingredients for absorption.

Eg: Acacia, Tragacanth, Sucrose, Gelatin, Poly vinyl pyrolidine, Polymethacrylate etc,.

1.13.3. Disintegrants:

The purpose of the disintegrants is to facilitate the breakup of the tablet by swelling after administration. Disintegrating agents may be added prior to granulation or during lubrication step prior to compression or at both processing steps. Six basic categories of disintegrants have been described: starches, clays, cellulose, algins, and gums and miscellaneous. Intra granular and extra granular disintegrating agents were reviewed by shot- ton and leonard. The extra granulation formulations disintegrated more rapidly than the intra granular ones, but the later resulted in a much finer dispersion of particles.

Eg: Sodium starch glycolate, Celluloses, Alginates, Resins etc,.

1.13.5. Lubricants, Antiadherants, and Glidants:

The primary function of the tablet lubricants is to reduce the friction arising at the interface of the tablet and the die wall during compression and ejection.

- **Lubricants :** Reduce friction between the granulation and die wall during compression and Ejection.
  Eg: Boric acid, Sodium chloride, Stearic acid etc,.
- **Antiadherents:** Prevent sticking to the punch and, to a lesser extent, the die wall.
  Eg: Talc, Magnesium stearate, Colloidal silica etc,.
- **Glidants :** Improve the flow characteristics of the granules.
  Eg: Corn starch, Aerosil etc,.

1.13.6. Colors, Flavors and Sweeteners:

The use of the colors and dyes in tablet making has served three purposes; disguising of off color drugs, product identification and production of a more elegant product. With the continual decertification of many synthetic dyes, pharmaceutical manufacturers are becoming quite concerned as to how future tablet formulations will be colored. Two forms of colors have typically been used in tablet preparation. These are the FD&C and D&C dyes – which are applied solutions, typically in the granulating agent- and the salt forms of these dyes. Lakes and dyes that have been absorbed on a hydrous oxide and usually are employed as dry powders for coloring. When using water soluble dyes, pastel shades usually show the least mottling from uneven distribution in the final tablet. When wet granulation is employed, care should be taken to prevent color migration during drying.

Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. Flavor oils that are added to the tablet during granulation in solvents, or dispersed on clays and other absorbents or emulsified in aqueous granulating agents. Usually, the maximum amount of oil that can be added to the granulation without influencing its tablet characteristics is 0.5 to 0.75%.

The use of sweeteners is primarily limited to chewable tablets to exclude or limit the use of sugars in tablets. Mannitol is 72% as sweet as sucrose. Until recently, saccharin was the only artificial sweetener available. This material is about 500 times sweeter than sucrose. Its major disadvantage is it has bitter after taste and has been reported to be carcinogenic. Aspartame is the sweetener which replaced saccharin very much in the formulation now a days. But the primary disadvantage with aspartame is its unstable nature in the presence of moisture.

1.14 PROCESSING PROBLEMS[9]:

In the normal process of developing formulations, and in the routine manufacture of tablets, various problems occur. Sometimes the source of the problem is formulation, the compression equipment, or a combination of two.

TABLE – 1

PROCESSING PROBLEMS OF TABLETS

PROBLEMS	CAUSES	REMEDY
CAPPING AND LAMINATION	• Granulation too dry • Compression too hard • Damaged upper punches • Machine RPM too fast • Excessive lubrication • Less binder in granules • Entrapped air in granules	• Increase moisture content • Reduce compression • pressure • Replace the tools which are damaged • Reduce machine speed • Reduce or change the • lubricant • Increase binder concentration • Improve granulation by using tapered dies
CHIPPING	• Damaged punches or dies • Compression too fast • Faulty machine testing • Less binder • Compression too soft	• Replace the damaged punches or dyes • Reduce compression speed • Reduce the speed • Increase binder • Increase the compression pressure
STICKING, PICKING, FILMING	• Compression too soft • Uneven granulation • High moisture content • High relative humidity • Improper lubrication • Damage of upper punch	• Increase compression pressure • Improve granulation • Reduce moisture content in granulation • Use dehumidifier • Improve lubrication • Polish the punches • Buffering the punches with lubricants

NON UNIFORM WEIGHT	• Machine RPM too fast • Non uniform granules • Restricted free flow of granules • Granules sticking to lower punches • Feed frame/ hopper flow Restricted	• Reduce machine speed • Provide uniform granules • Add glidant to improve the flow properties • Improve lubricant • Adjust the hopper to get free flow
BINDING	• Rough edges • Vertical score marks on the edges	• Increase lubricants • Decrease the size of the granules and use tapped dyes.
DISSOLUTION	• Large Granules • Tablets Too Hard • Excess lubricants	• Reduce granules size • Reduce tablet hardness • Reduce compression hard ness
COLLAR FORMATION	• Too Much Fines	• Reduce fines
BLACK MARKS ON TABLETS	• Improper feed frame setting • Excessive moisture • Over sized granules • Granules having black particles prior to compression • Lubricants, grease or oil may be contaminating the powder	• Improve feed frame setting • Avoid excesive moisture • Reduce granules size • Avoid contamination with oil or grease
DELAYED DISINTEGRATION	• Compression Too Hard • Over granulation • Excess blending times with lubricants or glidants	• Reduce the compression pressure • Improve the granulation • Reduce the blending time of lubricants

1.15 TABLET COATING[10]:

Tablet coating is the application of coating composition to moving bed of tablets & concurrent use of heated air to facilitate evaporation of solvent.

1.15.1 FILM COATING:

Film coating is deposition of thin film of polymer surrounding the tablet core. Conventional pan equipments may be used but now-a-days more sophisticated equipments are employed to have a high degree of automation and quality coating. The polymer is solubilised or suspended in solvent & other additives like plasticizers and pigments are added. Resulting solution is sprayed onto a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition of coating material around each tablet[11].

Factors to be considered during coating process:

- Check and ensure that the coating pan and other equipments are cleaned as per specification.
- Check and ensure that the speed of the coating pan, gun to bed distance, inlet and exhaust air temperature, spray rate, spray type, number of guns, temperature of the coating solution is as per specification.
- After coating is completed, samples are collected for dissolution testing and weight variation.

Coating parameters to be considered*:*

- Spray gun model
- Pan load (kg)
- Pan speed (rpm)
- Spray procedure
- Spray rate (g/min or ml/min)
- No. of spray guns
- Distance between spray guns (cm)
- Distance between spray gun & tablet bed
- Main inlet pressure (kg/cm²)

- Atomization pressure (kg/cm²)
- Inlet air temperature (ºC)
- Tablet bed temperature (ºC)
- Position of dampers – inlet, Outlet
- Quantity of coating suspension in the liquid vessel (kg/lit)
- Average weight of preheated core tablets (mg)

1.15.2 PROCESS VARIABLES DURING FILM COATING:

The variables to be controlled during pan spray film coating processes are:

1. Pan variables:
    - Pan design/baffling
    - Speed
    - Pan load

2. Process- Air
    - Air quality
    - Temperature
    - Airflow rate/volume/balance

3. Spray variables
    - Spray rate
    - Degree of atomization
    - Spray pattern
    - Nozzle to bed distance

1.15.4 COATING PROBLEMS[12]:

Picking and sticking:

This is when the coating removes a piece of the tablet from the core. It is caused by over-wetting the tablets, by under-drying or by poor tablet quality

Bridging:

This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet

embossing, high coating viscosity, high percentage of solids in the solution or improper atomization pressure.

Capping:

This is when the tablet separates in laminar fashion. The problem stems from improper tablet compression, but it may not reveal itself until the coating is started.

Erosion:

This can be the result of soft tablets, an over-wetted tablet surface, inadequate drying, or lack of tablet surface strength.

Twinning:

This is the term for two tablets that stick together, and it's a common problem with capsule shaped tablets. Assuming you don't wish to change the tablet shape, you can solve this problem by balancing the pan speed and spray rate. Try reducing the spray rate or increasing the pan speed. In some cases, it is necessary to modify the design of the tooling by very slightly changing the radius. The change is almost impossible to see, but it prevents the twinning problem.

Peeling and frosting:

This is a defect where the coating peels away from the tablet surface in a sheet. Peeling indicates that the coating solution did not lock into the tablet surface. This could be due to a defect in the coating solution, over-wetting, or high moisture content in the tablet core.

Chipping:

This is the result of high pan speed, a friable tablet core, or a coating solution that lacks a good plasticizer.

Mottled color:

This can happen when the coating solution is improperly prepared, the actual spray rate differs from the target rate, the tablet cores are cold, or the drying rate is out of specification.

Orange peel:

This refers to a coating texture that resembles the surface of an orange. It is usually the result of high atomization pressure in combination with spray rates that are too high.

1.2.5 COATED TABLET EVALUATION[13]:

A number of test methods are employed:

1) Adhesion tests with tensile strength testers have been used to measure the force required to peel the film from the tablet surface.
2) Diametric crushing strength of coated tablets can be determined with a tablet hardness tester.
3) Coated tablet disintegration and / or dissolution must also be assessed. The coating should have a minimal effect on tablet disintegration or dissolution.
4) Stability studies must be conducted on coated tablets to determine whether the temperature and humidity changes will cause film defects.
5) Attempts have been made to quantify film surface roughness, hardness and colour uniformity through instrumental means, but in general visual inspection is sufficient to define relative coated tablet quality[14].

2. LITERATURE REVIEW

- **B.Jayakar[15] et al., (2010)** Prepared rapid release gelcaps of Diphenhydramine HCl, for treatment of allergic symptoms and irritant cough. By Direct compression method using Pregelatinised maize starch and croscarmellose sodium in various concentrations. The granules showed satisfactory flow properties and compressibility Diphenhydramine HCl successful formulation was found.

- **Biljana Govedarica[16] et al., (2011),** Formulation and evaluation of immediate release tablets with different types of Paracetamol powders prepared by direct compression.The mechanical strength of tablets several kind of " paracetamol for direct compression " as present in the combination with both investigated super disntegrate such as vivasol and polyplasdone x-10 showed faster dissolution time and dissolution rate in compression.

- **Nielsen and Bjerring[17] et al., (1991),** summarized that the analgesic efficacy of single doses of immediate release Paracetamol 500 mg and 1000 mg, sustained release paracetamol 2000 mg, and placebo was evaluated over a 12 hrs period in 10 healthy volunteers. The efficacy was related to the concurrent plasma concentrations of paracetamol. Experimental pain was induced by brief cutaneous application of argon laser pulses, and the analgesic effect was assessed as change in pricking pain threshold.

- **Wayne M. Camarco[18] et al., (2009),** studied the incorporation of low dose co-active into acetaminophen (APAP) based solid dosage formulations is normally achieved by wet-granulation techniques. Direct compression methods could offer a simplified and more economical alternative, as long as content uniformity criteria can be fulfilled.

- **Surendra C. Mehta[19] et al., (1994),** an evaluated acrylic polymer-wax matrix system for oral sustained-release tablets of diphenhydramine HCl incorporating Eudragit L in a carnauba wax matrix. In this polymer-wax system, carnauba wax maintained the integrity of the matrix, whereas Eudragit L slowly eroded in the

matrix as the drug was released. Thus, the area-to-volume ratio of the tablet remained constant over the duration of the drug release. In vitro drug release studies were conducted at physiological pH that exist in the gastrointestinal tract. Drug release rates decreased as the polymer: drug ratio increased from 1:2 to 2:1. The drug release rate was faster in pH 7.5 phosphate buffer than in 0.1 N HCl solution.

- **Takeshi Kawaguchi[20] et al., (2002),** evaluated the use of a rotating fluidized-bed granulator to produce acetaminophen granules with sufficient binding force between particles and good plasticity. Ascorbic acid was used to compare the relationship between the granules and sample wetness.

- **Aniruddha[21] et al., (2011)** indicated that moist granulation technique (MGT) appears to be applicable in developing controlled release formulation of Acetaminophen tablets. A small amount of granulating fluid was added to powder bland to activate a dry binder at 2% and facilitate agglomeration then moisture absorbing material was added to absorb any excesses moisture by adding MCC in this way a drying step is not nessecery.

- **Joshua E. Lane[22] et al., (2002)**proved that both acute and chronic overdoses of Acetaminophen can be fatal. Patient ingested approximately 5.0 to 6.5 g of acetaminophen daily for 6 to 8 weeks via multiple medications. The inclusion of acetaminophen in numerous medications combined with the frequency of use of acetaminophen necessitates an increased concern for not only acute but also chronic acetaminophen toxicity.

- **Marieke Nauta[23] et al., (2009),** proved that the oral acetaminophen/ codeine can be used for postpartum pain. Codeine has opioid-related adverse effects and may not be safe during breastfeeding in the postpartum period for all neonates. Nonsteroidal anti-inflammatory drugs (NSAIDs) are devoid of opioid-related adverse effects and could be a possible alternative for analgesia in postpartum pain. They compared the analgesic effect and safety profile of Acetaminophen/ codeine with NSAIDs in the management of pain after laparotomy.

- **Elke Leinisch[24] et al., (2005)** The efficacy of intravenous acetaminophen (1000 mg) in the treatment of acute migraine attacks as an alternative to parenteral application of lysine acetylsalicylate or triptans was investigated, using a multi-center, randomized, double-blind, placebo controlled study design.

- **Terrence[25] et al., (2007)** proved that the acetaminophen or diphenhydramine premedication before more than 50% of blood component transfusions prevents the Febrile nonhemolytic and allergic reactions which are the most common transfusion reactions.

- **MA Naeem [26]et al.,** developed and characterized bilayer tablet formulations of tramadol HCl (TmH) and acetaminophen (AAP) microparticles. Coacervation via temperature change was the encapsulated method used for the preparation of the microparticles, with ethyl cellulose (EC) of medium viscosity as the polymer for extending drug release. The microparticles of the two drugs were prepared separately and then compressed into bilayer tablets.

- **Nourudin W.Ali[27].et al., (2011)** stability indicating methods for simultaneous determination of paracetamol and diphenhyramine HCl in their binary mixture and in presence of P-aminophenol, and also determine potential impurity and degradation product of Paracetamol were developed. Analysis of Paracetamol and Diphenhydramine in their paranaceutical formulation without interference of other dosage forms additive and the result were statistically compared and official method.

- **P.V.Swamy[28] et al., (**2009), designed Orodispersible tablets of pheniramine maleate by effervescent method. The tablet containing mixture of sodium bicarbonate, tartaric acid with super disintegrants. Evaluation of the formulation showed an invitro dispersion time of approximately 40seconds, which facilitates the fast dispersion in mouth.

- **D.M.Patel[29] et al.,** (2004), studied that formulations of orodispersible tablets of Rofecoxib using sodium starch glycolate, crospovidone and croscarmellose sodium along with mannitol as diluent and the tablets were evaluated.

- **S. A. Sreenivas[30] et al.,** (2005), studied on an orodispersible tablets new fangled drug delivery system to solve the problem of Dysphagia and to improve patient compliance. Orodispersible tablets have emerged as an alternative to conventional and dosage forms. These tablets are very useful in the condition where water is not available and in case of motions sickness (kinetosis), sudden episodes of coughing during common cold, allergic conditions and bronchitis.

- **Nagendrakumar[31] et al., (**2009), prepared and evaluate fast dissolving tablet of Fexofenadine Hcl by Effervescent method using crospovidone, croscarmellose sodium and sodium starch glycollate as super disintegrants. The formulation showed the in vitro dispersion time of 290 seconds when compared to commercial tablet.

- **Sarasija Suresh[32] et al., (**2008), designed and evaluate Fast dissolving tablet of Clonazepam by direct compression method using super disintegrants viz. croscaramellose sodium, sodium starch glycollate along with Mannitol to enhance mouth feel. Time taken for the in vitro dispersion time of the formulation was found to be approximately 13seconds.

- **T.V.Rao[33] et al**., **(**2008),worked on the formulation and evaluation of cefadroxil dispersible tablets by direct compression technique using superdisintegrants such as crospovidone, croscarmellose sodium, sodium starch glycolate. The tablets were evaluated for hardness, weight variation, friability, and wetting time, D.T and in vitro dissolution studies. It was concluded the dispersible tablets of cefadroxil with cros- carmellose sodium showing rapid release rate/enhance dissolution hence better patient compliance and effective therapy.

- **Mallikarjuna shetty[34] et al., (**2008), studied the fast dispersible Aceclofenac tablets and effects of functionality of superdisintegrants. Aceclofenac fast dispersible tablets have been prepared by direct compression method. Effect of superdisintegrants such as croscarmellose sodium, sodium starch glycolate and crospovidone on wetting time, disintegration time, drug content, in-vitro release and stability parameters has been studied. It is concluded that the dissolution

parameters and disintegration times increased with increase in the level of croscarmellose sodium and sodium starch glycolate in tablets and were sensitive to high humidity conditions.

- **T.V.Rao[35] et al.,** (2008) developed a fast dissolving of Simvastatin by direct compression with moisture activation technique i.e., exposed in humidity chamber 75% RH at 30°c for 1hr, which offers a new range of product having desired characteristics and intended benefits. Fast dissolving tablets of Simvastatin were prepared by using effervescent mixture i.e., sodium bicarbonate and citric acid, mannitol, spray dried lactose. All the formulations were evaluated for hardness, friability, weight variation, absorption ratio, in vitro dispersion time and in vitro drug release studies. All effective pleasant tasting and stable formulation F_4 containing sodium bicarbonate and citric acid was found to have hardness 3.8kg/cm^2 in vitro dispersion time was 10 second, maximum amount of drug released with in 5 min than other prepared and marketed formulati .

- **Shishu[36] et al**., **(**2007), prepared taste masked granules of rapidly disintegrating tablets of Chlorpheniramine maleate. The taste masked granules were prepared to using eudragit (E-100) by the extrusion method, sodium starch glycolate as a superdisintegrant. The prepared tablets containing the taste masked granules having sufficient strength of 3.5Kg/cm^2 were evaluated for taste by both spectrophotometric methods and through panel testing. Panel testing data collected from 20 healthy volunteers indicate successful formulation of oral fast disintegrating tablets.

- **Sheetal Make[37] et al.,** (2007), designed formulation and evaluation of oxcarbazepine FDT. FDT of oxacarbazepine were prepared containing Avicel pH102 as a diluent and Ac-Di-Sol as a superdisintegrant by wet granulation process. All the formulation were evaluated for characteristics such as hardness, friability, weight variation, wetting ability, disintegration time and dissolution rate and found drug release of not less than 90% within 30min. Since the drug is poorly water soluble drug release was tested in various media and the effect of

surfactant on drug release was studied.

- **Aithal.k.[38] et al., (**2006), developed once daily fast dissolving tablets of Granisetron Hcl by direct compression method using superdisintegrants. Formulations containing crospovidone and croscarmellose sodium shows shortest disintegration time.
- **Sajal Kumar Jha[39] et al.,** (2008), developed and evaluates the melt in mouth tablets of Halopridol by direct compression method using superdisintegrants as croscarmellose sodium, sodium starch glycolate and crospovidone. formulation containing higher concentration of crospovidone decrease the disintegration time and optimize the drug release.

- **G. Abdelbary[40] et al., (**2004), evaluated the disintegration profile of RDT and correlation with oral disintegration. RDT was manufactured by main commercialized technologies. The excellent disintegration time and correlation was found.Qualitative mouth feel was achieved by comparing the thickness of the tablet.

- **Mohanad Naji Sahib[41] et al., (**2009), designed Prednisolone tablets as a potential colon delivery system by using wet granulation & coating. The tablet contains the Acetone, Dibutyl phthalate, Ethanol 99%, Eudragit L 100, S100, Glucose, Mannitol, Starch, Lactose, Hydrochloric acid, Ethyl cellulose, Methanol, Microcrystalline cellulose-Avicel -PH 101, PH 102, PH 302, Polyvinylpyrrolidone (PVP K 30), Potassium dihydrogen phosphate, Sodium hydroxide, Zinc stearate, and Prednisolone. Eudragit S 100 coating is not allowing the drug to release in pH less than 7.

- **Rabia Bushra[42] et al., (**2010), formulated enteric coated ibuprofen tablets in order to avoid gastric mucosal irritation, diffusion of drug across mucosal lining and to let active ingredient be absorbed easily in small intestine. The formulation was developed and manufactured through the direct compression process, the simplest, easiest and most economical method of manufacturing. Enteric coating was done using an Opadry white subcoating and an aqueous coating dispersion of Acryl-Eze.

- **K. L. Senthil Kumar[43] et al., (**2010), developed enteric coated tablets of Didanosine to get resistance from Gastric juice when it presents in stomach, because Didanosine is incompatible with gastric juice. The tablets were prepared by using wet granulation technique using polymer Ethyl Cellulose std 100 FP, Ethyl Cellulose Med 70 P, Ethyl Cellulose Med 50 P and other excipients are Povidone Micro crystalline Cellulose in different ratios. These polymers and excipients are used for sustained the drug release. And 20% solution of Eudragit L 100 with isopropyl alcohol used for enteric coat. And diethyl phthalate added as polishing agent in enteric coat solution.

- **Vaishali[44]et al., (2010)** prepared immediate-release enteric-coated pellets of aceclofenac, a poorly soluble nonsteroidal anti-inflammatory drug that has a gastrointestinal intolerance as its serious side effect. Formulation of enteric-coated pellets with improved solubility of aceclofenac could address both of these problems. The goals, pellets were prepared by extrusion–spheronization method using pelletizing agents that can contribute to the faster disintegration and thereby improve the solubility of the drug. Different disintegrants like β-cyclodextrin, kollidon CL, Ac-Di-Sol, and sodium starch glycolate were tried in order to further improve disintegration time.

- **Bhaunia biswajit[45] et al., (2006)** described orodispersible tablet or uncoated tablets intended to be placed in the mouth where they disperse before being swallowed. Orodispersable tablets disintegrate with in 3 min tablets and capsules. Orodispersible tablets in which cross povidone, crosscormellose sodium these are the super disintegrates are used rapidly release of the Amlodepine by using and maintain the release profile. **Syed azeem hyder[46] et al., (2011).** Prepared and evaluated the immediate release tablets of Rupatadine Fumarate by using different disintegrating agents by using manitol, MCC, cross-povidone , alginic acid as super disintegrates in different concentrations. All formulations evaluated for precompression and post compression. The result showd the cross-povidone shows the short disintegration time.

- **Rai V.K[47].et al., (2009),** carried out an optimization of immediate release tablet

of Raloxifene hydrochloride by wet granulation method. Different filters, binders, disintegrants and lubricant were taken as variables.

- **Vasanth kumar Sekar[48] et al., (2008)** prepared immediate release tablet of Telmisartan anti hypertensive drug by using cross povidone at intra granular, extra granular and partial intra and extra granular level of addition and increases the rate of release of drug from dosage form.

- **Pani Nihar Ranjan[49]et al., (2011),** carried out an optimization and formulation of immediate release tablet of Nateglinide by using 3^2 factorial design and compatability of nateglinide with selected excipients in the developent of immediate release tablet of Nateglinide by thermal and also thermal stress testing techniques.

- **Rizvanulla[50] et al., (2011),** prepared and evaluated the Oxcarbazepine fast dissolving tablets by using various super disintegrates. Batch is prepared without disintegrants designated as four differentgroups of formulation chemical incompatability studies confirm that there is no interaction between drug and excipients used in the formulation by direct compression method.

- **Honey goel[51] et al., (2008)** described orally disintegrating system have amongst the orally drug delivery systems due to highest component of compliance the gastric and pediatrics. Drug satisfactory absorption from the oral mucosa immediate pharmacological action can be formulated. A variety of dosage forms like tablets, films, wafers, chewing gums, micro particles, nano-particles.

- **Jensc.Nielsen[52] et al., (1991)** studied the hypoalgesic effect of paracetamol in flow release and pain tablets on laser- induced pain a double-blind three way, cross over study received plain paracetamol slow tablets 100mg ever 6 hrs. Paracetamol 2000 mg every 12^{th} hr and placebo. Hypoalgesia, measured by experimentally laser-induced pain. Slow release formulation was given once at the start of the session.

- **Karl G. Wagner[53] et al.,** Developed disintegrating multiple-unit tablets on a

highspeed rotary tablet press .Enteric coated bisacodyl pellets were compressed into divisible disintegrating tablets on a high speed rotary tablet press and investigated for pellet damages.

- **Shlyankevich, L. Liu[54] et al.,** made a comparison between USP Apparatus 2 and 3 in Dissolution Testing of Immediate Release/Controlled Release Bilayer Tablets. *In vitro* release of bilayer tablets was studied using USP apparatus 2 (paddles) and 3 (reciprocating cylinders) in water. In case of apparatus 2 it was noted that if the tablet landed on its CR layer it tended to adhere to the vessel and stayed in this position for the rest of the run.

- **Chinam Niranjan Patra[55] et al.,** developed a bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as Ethyl cellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer.

- **N. Damodharan[56] et al.,** (2010), formulate and evaluated the delayed release Doxycycline tablets. The tablets were prepared by wet granulation method. Doxycycline hydrochloride, dicalcium phosphate, microcrystalline cellulose, starch, lactose, PVP-K-30, sodium starch glycolate, eudragit-L100, HPMC pthalate-55, isopropyl alcohol, methylene chloride, titanium dioxide, talc, magnesium stearate, methyl paraben, propyl paraben were used in the formulation. Polymers like Eudragit L 100 and HPMC Phthalate are selected where dissolution is above pH 6 and pH 6.4 respectively.

- **Mohanad Naji Sahib[57] et al.,** (2009), designed Prednisolone tablets as a potential colon delivery system by using wet granulation & coating. The tablet contains the Acetone, Dibutyl phthalate, Ethanol 99%, Eudragit L 100, S100, Glucose, Mannitol, Starch, Lactose, Hydrochloric acid, Ethyl cellulose, Methanol, Microcrystalline cellulose-Avicel -PH 101, PH 102, PH 302, Polyvinylpyrrolidone (PVP K 30), Potassium dihydrogen phosphate, Sodium hydroxide, Zinc stearate, and Prednisolone. Eudragit S 100 coating is not allowing the drug to release in pH less than 7.

- **F. Siepmann[58], et al.,** (2010), prepare and characterized polymeric film coatings with pH-dependent properties for oral administration; and (ii) to better understand the underlying mass transport mechanisms upon exposure to simulated gastric and intestinal fluids. Propylene glycol alginate (containing free carboxylic groups) was chosen as a pH-sensitive film former, which was blended with different amounts of ethylcellulose.

- **Chakraborty S. et al.,[59]** (2008), formulate and evaluated pantaprazole enteric coated tablets. Pantaprazole 5-(difluoromethoxy)- 2-[(3,4-dimethoxypyridin-2-yl) methylsulfinyl]- 3H-benzoimidazole is a proton pump inhibitor belongs to group of benzimidazole. This compound inhabits gastric acid formation and there it is very efficient for treatment of gastric acid duodenum ulcers. In aqueous media more acidic than pH 4 it suffers a practically complete decomposition within a period shorter than 10 minutes.

3.1 AIM OF THE WORK

Now a day's patients are suffering with fever and cold so that we want quick recovery. For this we are using two different drugs (Analgesics& anti histamines). Acetaminophen and Diphenhydramine combination gives very quick recovery from fever and cold. It is available in various type of formulations. When compared with these formulations the present study formulation is pharmacological responds and minute difficulties in formulation. The aim of the present study is to develop a pharmaceutically stable and robust formulation of Acetaminophen 500mg and Diphenhydramine Hydrochloride 25mg tablets comparable with innovator.

This goal various types of superdisintegrant and excipient with different concentrations are used in various prototype trials are taken & evaluated with respect to various quality parameters like weight variation, friability, hardness, thickness and also perform various stability studies in these formulation. The formulation shall be finalized by comparing the in -vitro dissolution profile with that of the innovator in various pH media by using HPLC method and produce a desirable and stable tablet.

3.2 PLAN OF THE WORK

- Pre formulation studies.
- Preparation of granules.
- Evaluation of granules.
- Formulation of different batch of coated tablets.
- Characterization of uncoated tablets
- Physical and chemical evaluation during and after stability studies.
    - Physical parameters like weight variation, friability and hardness.
    - Drug content uniformity
    - In-vitro drug release studies
- Characterization of coated tablets.
    - Physical parameters like weight variation , friability and hardness
    - Drug content uniformity
    - Invitro drug release studies
- Stability studies.

4. MATERIALS AND METHODS

4.1 MATERIALS USED:

The following were the list of excipients selected for the formulation but the finalized list of excipients was based on the innovator product.

TABLE -2

S.N	INGREDIENTS USED	CATEGORY	SUPPLIED BY
1	Acetaminophen	Active	Granules India, Hyderabad
2	Diphenhydraminehydrochloride	Active	Wanbury pharmaceuticals, Hyderabad.
3	Pre gelatinized starch	Diluent	SA Pharma,Hyderabad.
4	Micro crystalline cellulose	Adsorbent	Mingtai pharmaceuticals,Hyderabad.
5	Povidone k-30	Binder/diluents	Roquette frères, UK
6	Croscarmellose sodium	Disintegrant	Roquette frères, UK
7	Colloidal silicon dioxide	Glident	Evonik Degussa, SA
8	Stearic acid	Lubricant	Tauras chemicals Ltd, Hyderabad, India
9	Opadry 13B 80923 Blue	Coating material	Colorcon, Hyderabad.

4.2 INSTRUMENTS USED

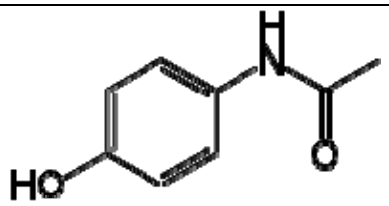
TABLE - 3

S.NO.	NAME OF INSTRUMENT	MANUFACTURING COMPANY
1	Automatic tablet dissolution apparatus USP I	Pharma Test Hyderabad
2	Electronic thickness measurement apparatus	Mitutoyos Hyderabad
3	Friability tester USP 23	Electro Lab Hyderabad
4	Tablet hardness tester	Pharma Test, Hyderabad
5	Electronic LOD measurement apparatus (Halogen Moisture Analyzer)	Mettler Toledo, Mumbai
6	Tap Density Apparatus USP	Electro lab, Hyderabad
7	Electronic weighing balance, 150 Kg,6kg,30gms	Mettler Toledo, Mumbai
8	Lab stirrer 8 Liters	Eltech, Hyderabad
9	Single Deck Sifter	SWECO, Hyderabad
10	Octagonal Blender 10 Liters	Saan, Hyderabad
11	Tablet compression machine 12 station	RIMEK, Pune
12	Fluid Bed Processor (FBP) FBE – 5	P+am Glatt, Hyderabad
13	Tablet Coating Machine (Neocota – 5 kg)	Neomachines, Ahmedabad
14	Moisture Content (KF Titrino)	Metrohm, Hyderabad
15	UV – Spectrometer	Shimadzu, Hyderabad
16	HPLC	Watersalliance, Mumbai
17	Disintegration Test Apparatus	Electro lab, Hyderabad
18	Rapid Mixer Granulator	Sainath Boilers & Pneumatics, pune
19	Electronic Sieve shaker	SWECO, Hyderabad
20	pH meter	Polmon, Mumbai.

4.3 DRUG PROFILE

PHYSICO- CHEMICAL PROPERTIES OF ACETAMINOPHEN[60,61]:

TABLE -4

S.NO	CONTENTS	ACETAMINOPHEN
1	Description	White crystalline powder having a slight bitter taste
2	Synonym	Acetaminophen
3	Odour	Odour less
4	Chemical name	N-(4-hydroxy phenyl)acetamide
5	Structure	
6	Molecular formula	$C_8 H_9 NO_2$
7	Molecular weight	151.17g/mol
8	Solubility	Very slightly soluble in cold water, considerably more in hot water. Soluble in methanol, acetone.
9	Melting point	169^0c
10	Pk_a	9.51 at 25^0c
11	Stability	Stable under ordinary conditions of use & storage
12	Half life	1-4hrs
13	pH	4-7 PH Stable
14	Log-P	0.4
15	Wavelength	240-310nm
16	Elimination half life	2-4hrs
17	C_{max}	0.5-3hrs
18	T_{max}	1-4hrs
19	Volume of distribution	0.95L/kg

DESCRIPTION:

Acetaminophen is the active metabolite of phenacetin. Acetaminophen possesses analgesic and antipyretic activity however, some clinicians consider Acetaminophen a poor analgesic. Since Acetaminophen has no peripheral anti-inflammatory activity, its efficacy as an analgesic may indeed be less than aspirin's in situations in which this action is desirable. Acetaminophen is preferred over aspirin as an analgesic/antipyretic for patients in whom aspirin is contraindicated, such as those who have a history of gastric ulcer or a coagulation disorder. Also, Acetaminophen does not interfere with the actions of uricosuric agents as aspirin can. Acetaminophen was first used in clinical medicine in 1893, but widespread use began after its FDA approval in 1950. It is available without a prescription as an individual agent in several dosage forms, and in combination with a variety of other drugs, although there is little evidence to show that therapeutic agents are more effective when combined with Acetaminophen. Recently, Acetaminophen has been implicated as a cause of renal disease. Sustained-release product, "Feverall Extended Release", was submitted for FDA approval 12/30/97.

PHARMACOLOGY[62]:

Acetaminophen is a popular analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. It is a major ingredient in numerous cold and flu medications and many prescription analgesics. It is extremely safe in standard doses, but because of its wide availability, deliberate or accidental overdoses are not uncommon. Acetaminophen unlike other common analgesics such as aspirin and ibuprofen has no anti inflammatory properties or effects on platelet function, and so it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs. In normal doses Acetaminophen does not irritate the lining of the stomach nor affect blood coagulation, the kidneys, or the fetal ductus arteriosus (as NSAIDs can). Like NSAIDs and unlike opioid analgesics, Acetaminophen does not cause euphoria or alter mood in any way. Acetaminophen and NSAIDs have the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal. Acetaminophen is used on its own or in

combination with pseudo ephedrine, dextromethorphan chlorpheniramine, Diphenhydramine, doxylamine, codeine, caffeine, hydrocodone, or oxycodone.

Pharmacokinetics:

Following oral administration, Acetaminophen is rapidly and almost completely absorbed from the GI tract. Peak plasma concentrations are attained within 30-60 minutes, although serum concentrations and analgesia are not necessarily correlated. Binding to serum protein is about 25% after normal therapeutic dosages.

Between 90-95% of the Acetaminophen dose is metabolized in the liver via glucuronidation and sulfate conjugation. At normal therapeutic doses, 94% of Acetaminophen is excreted in the urine as glutathione conjugates and only 2% as metabolites. After an acute overdose, conjugation of the hepatotoxic metabolite with glutathione is overwhelmed and hepatotoxicity occurs. At all doses, metabolites, but not unchanged drug, can accumulate in renal impairment. Plasma half-life is between 1-2.5 hours in normal, healthy patients. After about 8 hours, only traces of the drug are detectable. Half-life can be prolonged in patients with hepatic disease, and, conversely, a prolonged half-life during an acute overdose can predict the subsequent development of hepatic necrosis.

Dosage:

- All dosage forms: Administer with a full glass of water.
- Oral solution: Administer using a calibrated measuring device.
- Oral suspension: Shake well before administration. Administer using a calibrated measuring device.
- Chewable tablets: May be swallowed whole or chewed.
- Oral granules: Mix with a small amount of soft food (i.e., applesauce, ice cream, or jam) prior to administration.
- Oral powders: Do not administer the capsules containing the powder whole. Open capsule and sprinkle over a small amount of water (<5 ml) or mix with a small amount of soft food (i.e., applesauce, ice cream, or jam) prior to administration[63].

Mechanism of Action:

Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1 and COX-2, enzymes involved in prostaglandin (PG) synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclo-oxygenase in peripheral tissues and thus, has no peripheral anti inflammatory effects. While aspirin acts as an irreversible inhibitor of COX and directly blocks the enzyme's active site, studies have found that acetaminophen indirectly blocks COX, and that this blockade is ineffective in the presence of peroxides. This might explain why acetaminophen is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides. Studies also report data suggesting that acetaminophen selectively blocks a variant of the COX enzyme that is different from the known variants COX-1 and COX-2. This enzyme is now referred to as COX-3. Its exact mechanism of action is still poorly understood, but future research may provide further insight into how it works.

Contraindications:

- Alcoholism
- Anemia
- Aspirin hypersensitivity
- Hepatic disease
- Hepatitis
- Infection
- Phenylketonuria
- Renal impairment

Drug Interactions with:

- Antacids
- Cimetidine
- Ethanol
- Phenobarbital
- Phenothiazines

- Sulfinpyrazone
- Warfarin

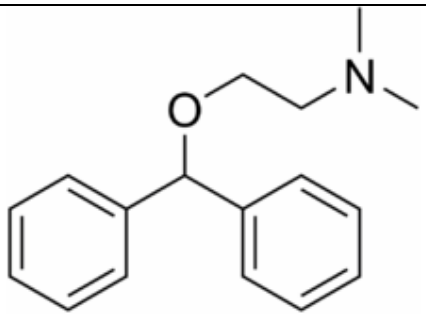
Adverse Reactions:

- Abdominal pain
- Anemia
- Elevated hepatic enzymes
- Hemolysis
- Hemolytic anemia
- Hepatic necrosis

DIPHENHYDRAMINE HYDROCHLORIDE:

PHYSICO-CHEMICAL PROPERTIES OF DIPHENHYDRAMINE HCl[64]:

TABLE - 5

S.NO	CONTENTS	DIPHEN HYDRAMINE
1	Description	White crystalline powder
2	Synonym	Diphenhydramine hydrochloride HCL
3	Odour less	Odour less
4	Chemical name	2-benzhydrolox –N,N-dimethyl-1-ethanamine
5	Structure	
6	Molecular formula	C_{17} H_{21} NO. Hcl
7	Molecular weight	291.82g/mol
8	Solubility	Freely soluble in acetone alcohol, ether
9	Melting point	166-170^{0}c
10	PK_a	8.98
11	Stability	Stable under ordinary conditions of use and storage
12	Storage	Preserve in tight, light resistant containers.
13	Therapeutic Category	Anti histamine
14	CAS NO	58-73-1
15	Ph	Acidic range 4-6
16	Log-p	3.27
17	Wave length	215-258nm

Pharmacology[65]

Diphenhydramine is an antihistamine of the ethanolamine class. Ethanolamine antihistamines have significant antimuscarinic activity and produce marked sedation in most patients. In addition to the usual allergic symptoms, the drug also treats irritant cough and nausea, vomiting, and vertigo associated with motion sickness. It also is used commonly to treat drug-induced extrapyramidal symptoms as well as to treat mild cases of Parkinson's disease. Rather than preventing the release of histamine, as do cromolyn and nedocromil, Diphenhydramine competes with free histamine for binding at HA-receptor sites. Diphenhydramine competitively antagonizes the effects of histamine on HA-receptors in the GI tract, uterus, large blood vessels, and bronchial muscle. Ethanolamine derivatives have greater anticholinergic activity than do other antihistamines, which probably accounts for the antidyskinetic action of Diphenhydramine. This anticholinergic action appears to be due to a central antimuscarinic effect, which also may be responsible for its antiemetic effects, although the exact mechanism is unknown. For the treatment of symptoms associated with Vertigo/Meniere's disease, nausea and vomiting, motion sickness and insect bite.

Mechanism of action

Diphenhydramine competes with free histamine for binding at HA-receptor sites. This antagonizes the effects of histamine on HA-receptors, leading to a reduction of the negative symptoms brought on by histamine HA-receptor binding.

Pharmacokinetics:

In Humans DiphenhydramineHCL is well absorbed after oral administration, but because of a relatively high first pass effect, only about 40-60% reaches the systemic circulation. Diphenhydramine is metabolized in the liver and the majority of the drug is excreted as metabolites in to urine. The terminal elimination half life in adult humans ranges from 2.4-9.3 hours.

Drug Interaction:

- Histamine H1 Antagonists
- Anti-allergic Agents
- Hypnotics and Sedatives
- Antitussives
- Antipruritics
- Antiparkinson Agents
- Antiemetics
- Anasthetics

Contraindications:

- nausea
- vomiting
- motion sickness
- insect bite

4.4 EXCIPIENTS PROFILE[66]

TABLE - 6

Pre gelatinized starch:

Synonyms	Compressible Starch, Lycatab C, Lycatab PGS, Mrigel, Starch 1500 G, Pharma Gel.
Chemical Name	Pregelatinized Starch
Empirical Formula	$C_6H_{10}O_5$
Molecular Weight	300-1000
Functional Category	Tablet and capsule diluent; tablet and disintegrant; tablet binder.
Uses	Use concentration (%) Diluent(hard gelatin capsule) 5-75 Tablet binder (direct compression) 5-20 Tablet binder (wet granulation) 5-10 Tablet disintegrant 5-10
Description	Pregelatinized Starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.Examination of Pregelatinized Starch as slurry in cold water, under a polarizing microscopic, reveals no significant ungelatinized granules, no "maltese crosses" characteristic of the starch birefringence pattern.
Moisture Content	Pregelatinized Starch is hygroscopic.
Solubility	Practically insoluble in organic solvents. Slightly soluble in cold water, depending upon the degree of pregelatinization. Pastes can be prepared by sifting the Pregelatinized Starch into stirred, cold water. Cold water-soluble matter for partially Pregelatinized Starch is 10-20%.
Safety	Pregelatinized Starch and starch are widely used in oral solid dosage formulations. Pregelatinized Starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of massive amounts of Pregelatinized Starch may be harmful.
Stability and Storage Conditions	Pregelatinized Starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

TABLE – 7

Microcrystalline Cellulose:

Synonyms	Celex, Avicel pH, crystalline cellulose
Chemical Name	Cellulose
Empirical Formula	$(C_6H_{10}O_5)n$
Functional Category	Adsorbent, diluent, disintegrant
Description	It is purified, partially depolarized cellulose that occurs as white, odorless, crystalline powder composed of porous particles.
Uses of MCC	Use — concentration (%) Adsorbent — 20-90 Antiadherent — 5-20 Capsule binder/diluent — 20-90 Tablet disintegrant — 5-15 Tablet binder/diluent — 20-90
Melting Point	$260\text{-}270^0$ C
Moisture Content	less than 5%
Solubility	Slightly soluble in 5% w/v hydroxide solution; practically soluble in water, dilute acids, and most organic solvents.
stability and storage	It is a stable through hygroscopic material. Bulk material should be stored in a well – closed container in a cool, dry place.
Incompatibilities	Incompatible with strong oxidizing agents
Safety	Non toxic and non irritant material
Precautions	It may be irritant to the eyes. So gloves, eye protection, and dust mask are recommended.
Regulatory status	GRAS listed.

TABLE – 8

Povidone K-3:

Synonyms	Kollidone, pvp, plasdone
Chemical Name	1-Ethyl-2-pyrrolidinone homopolymer
Empirical Formula	$(C_6H_9NO)n$
Functional Category	Disintegrant, dissolution aid, suspending agent, tablet binder.
Uses of Povidone	Use — concentration (%) Carrier for drugs — 10-25 Dispersing agent — up to 5 Eye drops — 2-10 Suspending agent — upto5 Tablet binder, tablet diluent, or coating agent — 0.5-5
Description	It occurs as a fine, white to creamy – white colored, odorless or almost odorless, hygroscopic powder.
Melting Point	Softens at 150°C
Moisture Content	It is very hygroscopic
Solubility	Freely Soluble In Acids, Chloroform, Ethanol, ketone and Water; practically insoluble in ether, hydrocarbons, and mineral oil.
Stability and storage conditions	Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130°C,steam sterilization of an aqueous solution does not alter its properties.
Incompatibilities	Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. Thimersol, may be adversely affected by the formation of complexes with povidone.
Safety	It is nontoxic, nonirritant and it is not absorbed from the GI or mucous membranes.

TABLE – 9

Stearic acid:

Synonyms	Crodacid, Hystreme, Pristerene
Chemical Name	Octadecanoic acid
Empirical Formula	$C_{18}H_{36}O_2$
Molecular weight	284.47g/mol
Functional Category	Emulsifying agent, solublizing agent, tablet & capsule lubricant.
Concentration Used	Ointment &creams-1-20% Tablet lubricant-1-3%
Description	It is a hard, white or yellow colored, somewhat glossy, crystalline solid or a white or yellowish white powder. It has a slight odor & taste suggesting tallow.
Melting Point	$\geq 54^{o}C$
Solubility	Freely soluble in benzene, carbon tetrachloride, chloroform & ether; soluble in ethanol, PEG & hexane, practically insoluble in water.
Incompatibilities	It is incompatible with most metal hydroxides & may be incompatible with oxidizing agents.
Safety	Nontoxic
Related substances	Calcium stearate, Magnesium stearate, zinc stearate
Stability and Storage Conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Stability And Storage Conditions	It is a stable material, an antioxidant may be added.
Regulatory status	Including in the FDA Ingredients Guide (oral capsules and tablets).

TABLE - 10

Colloidal Silicon dioxide:

Synonyms	Aerosol, Cab-o-sil, colloidal silica.
Chemical Name	Silica
Empirical Formula	SiO_2
Functional Category	Glidant, Adsorbent, Anticaking agent
Description	It is a light, loose, bluise-white collored, odorless, tasteless, nongritty amorphous powder.
Uses of colloidal silicon dioxide	Use — concentration (%) Aerosols — 0.5-2.0 Emulsion stabilizer — 1.0-5.0 Glidant — 0.1-0.5 Suspending and thickening agent — 2.0-10.0
Solubility	Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide.
stability and storage	It should be stored in a well closed container
Incompatibilities	Incompatible with diethylstilboestrol preparations.
Safety	Non toxic and non irritant material.
Precautions	It may be irritant to the eyes. So gloves, eye protection, and dust mask are recommended.
Regulatory status	GRAS listed.

TABLE -11

Croscarmellose sodium:

Synonyms	Exploeel, Nymcelzsx, Pharmacel xl, Vivasol, Solutab.
Functional Category	Tablet and capsule disintegrate.
Description	Odorless, grayish white powder.
Uses of croscarmellose sodium	Used as oral pharmaceutical formulation, disintegrate for capsule, tablet and granules. ➢ For capsules 10-25 concentration ➢ For tablet 0.5-5.0
Solubility	Insoluble in water, partially insoluble in acetone, ethanol and toluene.
stability and storage	It is hygroscopic material, stored in well closed container in cool and dry place.
Acidity	PH= 5.0-7.0 in aqueous dispersion.

4.5 CONSTRUCTION OF STANDARD CURVE

Standard preparation of acetaminophen:

Accurately weighed and quantitatively transferred 500mg of Acetaminophen to a 100 ml volumetric flask and it is dissolved in 10 ml of methanol. 5ml of Diphenhydramine HCl stock standard is pipetted to the volumetric flask, and 20 ml Mobile phase A is added, diluted to volume with Diluent, mixed well. The solution is stable for 48 hrs when stored at ambient conditions.[67]

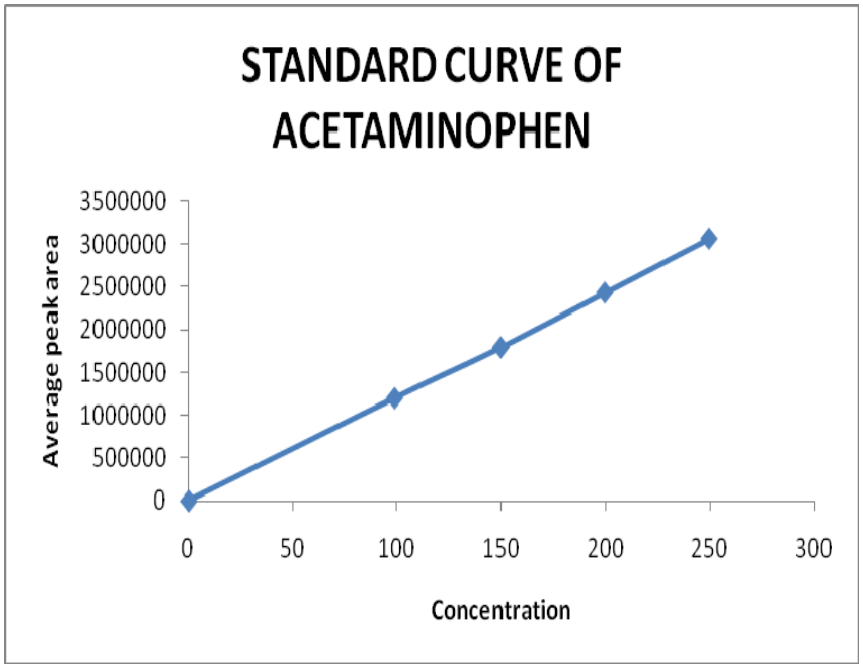
TABLE - 12

Standard curve of Acetaminophen:

S.NO	Concentration	Average peak area
1	99.83	1202025
2	149.74	1795911
3	199.66	2436852
4	249.57	3071035
5	299.49	3626465

FIGURE – 1

STANDARD CURVE OF ACETAMINOPHEN



STANDARD CURVE OF DIPHENHYDRAMINE

Diphenhydramine HCl stock standard:

500mg Diphenhydramine hydrochloride is accurately weighed and quantitatively transferred to a 100 ml volumetric flask. 70 ml of diluent was added and sonicated for 15 min and volume is made.[68]

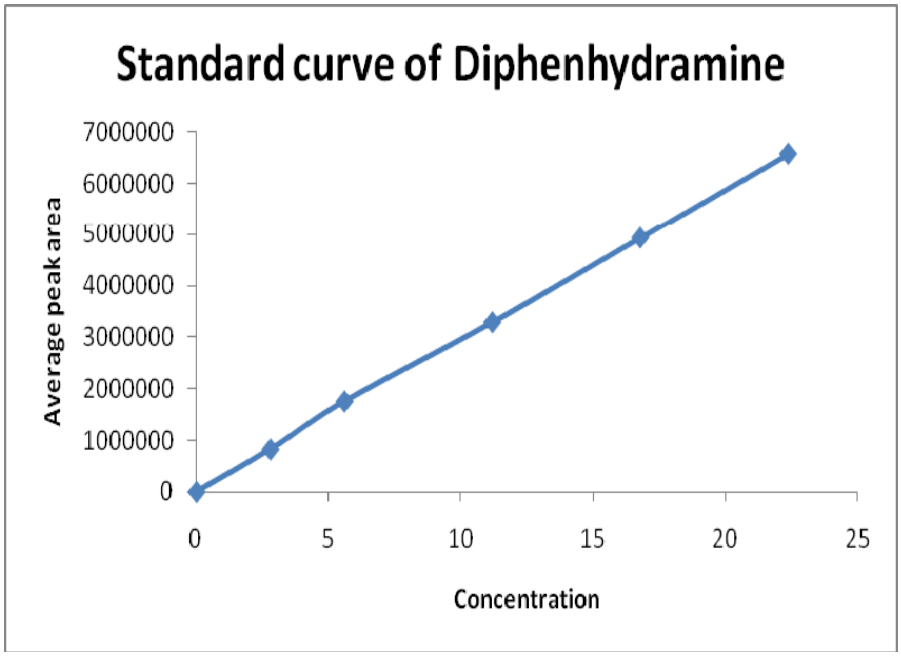
TABLE – 13

Standard curve of Diphenhydramine HCl:

S.N	Concentration	Average peak area
1	2.8	0820830
2	5.6	1748992
3	11.2	3283345
4	16.8	4925730
5	22.4	6566988

FIGURE – 2

Standard curve of Diphenhydramine HCl:



4.6 PRE FORMULATION STUDIES[5]

Pre-formulation testing is an investigation of physical and chemical properties of a drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Description and solubility:

Acetaminophen is white, odourless, crystalline powder. It is soluble in boiling water, 1N NaOH, freely soluble in alcohol.

Diphenhydramine Hydrochloride is white, odourless, crystalline powder. It is freely soluble in water, alcohol, chloroform and slightly soluble in benzene and ether.

Determination of bulk density and tapped density:

The bulk density is ratio of the weight of the powder and volume it occupies. It is expressed as g/ml; bulk density is imparted in determining the size of the container needed for handling and processing.

Procedure:

An accurately weighed quantity of the Acetaminophen powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the following formulas:

$$\text{Bulk density} = W / V_o$$

$$\text{Tapped density} = W / V_f$$

Where,

W = weight of the powder

V_O = initial volume

V_F = final volume

Compressibility Index:

The compressibility index is indirectly related to relative flow rate, cohesiveness and particle size of the powder. The compressibility index of material can be estimated from the tapped and bulk density of power.

Hausners ratio	**Type of flow**
Less than 1.25	Good flow
1.25-1.5	Moderate flow
More than 1.5	Poor flow

%Compressibility index = [(T.D – B.D) / T.D] 10

Where T.D and B.D are bulk density and tap density respectively.

TABLE – 14

Carrs Index:

COMPRESSIBILITY	**FLOW DESCRIPTION**
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Poor
28-35	Poor
35-38	Very poor
>40	extremely poor

Hausners ratio:

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Housner's Ratio	**Type of Flow**
Less than 1.25	Good Flow
1.25-1.5	Moderate Flow
More than 1.5	Poor Flow

Sieve analysis:

The main aim of sieve analysis is to determine the size of drug particles present. A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size (larger sieve number towards the bottom).

Procedure:

A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) i.e. sieve number 20, 40, 60, 80, 100, 120, 200, 325# and pan. 100 grams of drug was weighed accurately and transferred to sieve 20 which were kept on top. The sieves were shaken for about 5-10 minutes. Then the drug retained on each sieve was taken, weighed separately and amount retained was expressed in terms of cumulative percentage retained[69].

4.7DRUG EXCIPIENT COMPATIBILITY STUDIES

Compatibility studies are carried out to study the possible interactions between Acetaminophen and Diphenhydramin Hydrochloride and other excipients.

Procedure[7]:

The compatibility studies were carried out by taking a mixture of drug and excipients at the ratio in which they are expected to be present in the innovator product. A part of mixture can be exposed to different storage conditions like $40^{o}C/75\%$ RH and control samples were to be kept at $2\text{-}8^{o}C$. They were tested with respect to their physical and chemical aspects.

TABLE - 15

Conditions for compatibility studies:

S. NO	CONDITIONS	SAMPLES PACKED IN	SAMPLES OBTAINED AT
1	Accelerated $40^{o}C/75\%$ RH	3 Double polythene bags	First week to 4^{th} week.
2	Refrigeration $2\text{-}8^{o}C$	1 Double polythene bag + 1 glass vessel	First week to 4^{th} week.

4.8MANUFACTURING PROCEDURE

Granulation:

Dry Mixing:

Acetaminophen had loaded into rapid mixing granulator along with microcrystalline cellulose mixed for 5 min at slow mixer speed.

Preparation of Binder Solution:

The binder was dissolved in hot Purified water. Then Stirred with stainless steel paddle until complete Povidone and Diphenhydramine Hydrochloride has transferred into solution.

Wet Granulation:

The binder was added into rapid mixing granulator while it mixed at slow mixer speed. Then extra water was added and until required consistency of mass was obtained.

Drying:

The FBP was started in manual mode & the process parameters are arranged. Wet granules were dried untill LOD of 0.3%w/w – 0.8 %w/w was achieved. (Actual limit established during the trials) The granules are then unloaded. All the parameters of fluid bed processor from the process record sheet were recorded.

Sifting:

The granules were sifted and dried through # 16 mesh.

Blending and Lubrication:

Blending:

The sifted granules were loaded into Octagonal blender and blended with Croscarmellose- sodium, Stearic acid & aerosil for 5 min at 6 rpm.

Lubrication:

Sifted Stearic acid was weighed and added into blender and lubricated for 10 minutes at 8 rpm.

Compression:

The blend was compressed into tablets using 19.2 X 6.00 mm punches and suitable dies with a tablet weight of 525mg.

Coating:

The tablets were coated to get 2.0 % buildup by using 15% coating solution. The following parameters were maintained during coating:

Inlet temp	-	60-70 °C
Exhaust temp	-	40-50 °C
Spray rate	-	6g/min.
Spray pump rpm	-	6
Atomization air pressure	-	2.5Kg/cm^2
Gun to bed distance	-	11.5cm

4.9COMPARATIVE DATA OF VARIOUS FORMULATIONS

TABLE – 16

Formulation details in percentage:

Trial Ingredient	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**
DRYMIX											
Acetaminophen	80.0	80.0	80.0	80.0	80.0	80.00	80.00	80.00	80.00	80.00	80.0
Microcrystalline cellulose	8.50	7.50	7.50	7.50	7.00	7.00	2.00	2.00	2.00	2.00	2.00
BINDER											
PVP K-30	3.50	4.0	2.00	2.50	3.0	1.60	0.80	1.0	1.0	0.80	0.80
Pregelatinised starch	-	-	-	-	-	2.0	10.20	10.20	10.20	10.20	10.20
Diphenhydramine Hydrochloride	4.0	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
LUBRICATION											
Croscarmellose sodium	2.0	2.00	3.5	3.0	3.0	3.0	1.0	1.0	1.0	1.0	1.0
Polycrinilic potassium	-	-	-	1.0	1.50	1.0	-	-	-	-	-
Stearic acid	-	-	-	1.40	1.50	1.0	1.50	1.50	1.50	1.50	1.50
Colloidal silicon dioxide	-	-	2.0	0.60	0.40	0.40	0.50	0.50	0.50	0.50	0.50
Corn starch	1.0	1.00	-	-	-	-	-	-	-	-	-
Magnesium stearate	1.0	1.50	1.0	-	-	-	-	-	-	-	-

4.10 EVALUATION OF GRANULES

The granules were evaluated for tap density, Hausner ratio and Carr's index as per standard procedures.

4.11 EVALUATION OF TABLETS

1. Description:

About 20 tablets of sample were taken on a white porcelain plate and the description is observed.

2. Identification by HPLC:

The retention time of Acetaminophen and Diphenhydramine HCl peaks in the sample chromatogram of the assay preparation corresponds those in the chromatogram of the standard preparation as obtained in the assay.

3. Average weight (mg) (In house method):

20 tablets were randomly taken and weigh accurately. Then average weight is calculated.

Average weight =weight of 20 tablets/ 20.

4. Weight variation:

20 tablets were weighed accurately and average weight was calculated. Then again the 20 tablets were individually weighed. The tablet which has highest weight and the tablet which has lowest weight was found out. Then the maximum and minimum deviations were calculated as follows. The number of tablets that are deviated from the specification are noted. As per IP not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that percentage.

5. Hardness (kp):

The tablet was placed in between the jaws of hardness tester and the test was continued with a already arranged program for hardness determination and note down

the result and continued the test for 10 such tablets. The valve displayed in kp for hardness is recorded.

6. Disintegration time:

One tablet each was placed in 6 tubes of the basket. This assembly was Suspend in water and maintained at temperature of $37^0C \pm 2^0C$ and the apparatus is operated. The tablets were Observed, until last tablet gets disintegrated. The tablets pass the test, as all tablets have disintegrated in the specified time of the specification. The test is repeated as the failure of one or two tablets disintegrate completely. Not less than 16 of the total of 18 tablets tested should disintegrate completely.

7. Dissolution by HPLC[71]:

Solution A: 0.2 monobasic potassium phosphate(KH_2PO_4):

About 27.22 gm of monobasic potassium phosphate was weighed and 1000 ml purified water is added and dissolved.

Sodium solution B: 0.2 M hydroxide solution:

About 0.8 gm of sodium hydroxide pellets are weighed in 100 ml volumetric flask and 60 ml of water was added and dissolved. The volume was made with purified water.

Dissolution medium preparation (USP Phosphate buffer pH-5.8):

250 ml of solution (A) was taken and added to 18 ml of solution (B),made up to the volume of 1000 ml with purified water . The p^H was adjusted to 5.8± 0.05 with 0.2 M sodium hydroxide solution if necessary.

Dissolution parameters:

Medium	:	900ml phosphate Buffer pH 5.8
Apparatus	:	USP – type 2 (paddle)
RPM	:	50
Time	:	45 min
Temperature	:	37 ± 0.5^0C

Chromatographic conditions:

Column	:	L10, 250×4.6 mm, 5µ (Inertsil-CN,250×4.6mm
Wavelength	:	UV -220 nm
Flow rate	:	2.0 ml per min
Injection volume	:	10µ L
Run time	:	15 min

Preparation of Buffer solution:

About 6.8 gms of mono basic potassium phosphate was weighed in 1000 ml of milli-Q water , 2 ml of Triethylamine was added and pH was adjusted to 4.0± 0.05 with ortho phosphoric acid and filtered through 0.45 µm PVDF filter paper.

Mobile phase Preparation:

940 ml of buffer solution was mixed with 60 ml of acetonitrile and filtered through 0.45µ m PVDF filter and degased.

Diphenhydramine hydrochloride standard solution preparation:

About 28 mg of diphenhydramine hydrochloride is accurately weighed and transferred into 100 ml volumetric flask, sufficient amount of dissolution medium is added and sonicated to dissolve and make up to volume with dissolution medium.

Standard preparation

About 55 mg of acetaminophen is accurately weighed and transferred into 100ml volumetric flask, and added to 50 ml dissolution medium, sonicated to dissolve, to it 10 ml of diphenhydramine hydrochloride is added .Standard solution was stocked , mixed well and made up to volume with dissolution medium. (0.55 mg/ml of acetaminophen and 0.028 mg/ml of diphenhydramine hydrochloride respectively).The solution is stable for 24 hrs when stored at ambient conditions.

Sample preparation:

One tablet was placed in each of the 6 vessels containing 900 ml of the dissolution medium that has been equilibrated to 37^0C±0.5 ^{0}C. Care is taken to

exclude air bubbles from the surface of the tablet, apparatus is immediately operated with prescribed instrumental conditions for 45 minutes.

10 ml of the sample solution is withdrawn after completion of the dissolution from a zone midway between the surface of the dissolution medium and the top of the rotating paddle, not less than 1cm from the vessel wall and filter through Millex-HV 0.45 μm PVDF filter .The solution is stable for 24 hrs when stored at ambient conditions.

Procedure:

10 ml of the blank (dissolution media) is separately injected, standard preparation (5 replicate injections) and sample preparations into the chromatograph, chromatograms are recorded, and responses for the major peaks are measured. The % release of Acetaminophen and Diphenhydramine HCl are calculated.

TABLE – 17

Solutions into the HPLC system are injected following sequence:

<table>
<tr><th>Injection Name</th><th>Run time</th><th>Number of injections</th></tr>
<tr><td>Blank (dissolution media)</td><td rowspan="4">15 minutes</td><td>Minimum of 1 injection or until the base line stabilizes.</td></tr>
<tr><td>Dissolution standard</td><td>5 Injections</td></tr>
<tr><td>Dissolution sample</td><td>1 Injection per sample</td></tr>
<tr><td>Bracketing standard</td><td>Inject after every 6 samples injections or as per Bracketing standard SOP.</td></tr>
</table>

System suitability:

Chromatograph the standard preparation and record the peak responses as directed.

1. The % RSD of areas for five replicate injections of standard preparation shall not be more than 2.0%.
2. Tailing factor of Acetaminophen and Diphenhydramine HCl peaks shall not be more than 2.0.
3. The column efficiencies determined from the Acetaminophen and DiphenhydramineHCl peak shall not be less than 2000 theoretical plates.

Calculations:

% of Acetaminophen:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{900}{L.A} \times P$$

% of Diphenhydramine HCl:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{10}{100} \times \frac{900}{L.A} \times P$$

Where,

SA = Area/ response due to Acetaminophen in standard preparation.

TA = Area /response due to Acetaminophen in sample preparation

SW = Weight of Acetaminophen working standard in mg

P = Potency of Acetaminophen working standard.

L.A = Labeled amount of Acetaminophen in mg.

Assay by HPLC:

Mobile phase A:

Weighed and dissolved about 6.8 gm monobasic potassium phosphate 1000mL of milli-Q water, and it is adjusted to pH to 4.5 ± 0.05 with orthophosphoric acid or sodium hydroxide. Filtered through 0.45-µm PVDF filter paper.

Mobile phase B:

Acetonitrile.

Diluent:

Milli-Qwater.

Chromatographic conditions:

Column **:** Phenomenex Columbus C8, 150mm x 4.6 mm, 5mm x 4.6 mm, 5µ, EO or phenomenex Luna C8(2),150MM X 4.6MM, 5µ.

Guard column: Phenomenex security guard with a 4.0 mm L x 3.0mm ID C8 catridge.

Wavelength : 300 nm switching to 225 nm at 4 min or run dual wavelength

Flow rate : 1.5ml/minute

Injection volume: 5µL

Run time: 8 minutes

Column temperature: 35^{o}C.

TABLE – 18

TIME(min)	Flow rate (Ml/min)	Mobile phase A	Mobile phase B	Curve
0.00	1.5	85.0	15.0	--
5.00	1.5	45.0	55.0	6
5.10	1.5	85.0	15.0	6
8.00	1.5	85.0	15.0	6

Standard preparation of acetaminophen:

Accurately weighed and quantitatively transferred 500mg of Acetaminophen WS to a 100 ml volumetric flask and it is dissolved in 10 ml of Methanol. 5ml of Diphenhydramine HCl stock standard is pipetted to the volumetric flask, 20 ml Mobile phase A is added and diluted to volume with Diluent, mixed well. The solution is stable for 48 hrs when stored at ambient conditions.

Diphenhydramine HCl stock standard:

Accurately weighed and quantitatively transferred 500 mg Diphenhydramine HCl to a 100 ml volumetric flask. 70 ml of Diluent is added and sonicated for 15 min or until dissolved. Diluted to volume with diluent and mixed well.

Sample preparation:

Accurately weighed and tablets are added in to 1000 ml volumetric flask. 100 ml of water, 100 ml of methanol and 200 ml of mobile phase A is added. Sonicated for 30 minutes. 2 ml of concentrated phosphoric acid is added, swirl and to return to room temperature. The flask is diluted to volume with diluents. Mixed thoroughly. This preparation is filtered through a 0.45µm pore size membrane filter, discarding atleast the first 2 ml of the filterate. The solution is stable for 48hrs when stored at ambient conditions.

Procedure:

5µl of the blank (mobile phase A)is separately injected until the suitable base line is established.Working standard(5 replicate injections) and working sample is injected into the chromatograph, chromatograms are recorded, and responses for the major peaks are measured. The percentage of Acetaminophen and Diphenhydramine hydrochloride are calculated.

TABLE - 19

INJECTION NAME	RUN TIME	NUMBER OF INJECTIONS
Blank (mobile phase A)	8 minutes	Minimum of 1 injection or until the line stabilizes.
Standard		5 injections
Sample		➢ 1 injection per sample for uniformity of dosage form. ➢ 2 injections per sample for Assay
Bracketing standard		As per bracketing standard SOP

System suitability:

1. The 5% of area for 5 replicate injections of both Acetaminophen and Diphenhydramine from standard preparation shall not be more than 2.0.
2. Tailing factor of Acetaminophen and Diphenhydramine HCl peaks shall not be more than 2.0.
3. The column efficiencies determined from the Acetaminophen and Diphenhydramine HCl peak shall not be less than 2000 theoretical plates.

Calculation:

% of Acetaminophen:

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{1000}{TW} \times \text{Ave. wt.} \times \frac{P}{100} \times \frac{100}{L.A}$$

% of Diphenhydramine HCl(% of LA):

$$\frac{TA}{SA} \times \frac{SW}{100} \times \frac{5}{100} \times \frac{1000}{TW} \times \text{Ave. wt.} \times \frac{P}{100} \times \frac{100}{L.A}$$

Where,

SA = Area/ response due to Acetaminophen in standard preparation.

TA = Area /response due to Acetaminophen in sample preparation

SW = Weight of Acetaminophen working standard in mg

P = Potency of Acetaminophen working standard.

L.A = Labeled amount of Acetaminophen in mg.

T.W= Weight of sample taken in mg

Ave.wt = Average weight of the tablet in mg

4.12 DISSOLUTION PROFILE COMPARISON USING f1 f2 FACTORS

f1=Dissimilarity factor

f2=Similarity factor

A dissolution profile can characterize the product more precisely than a single point dissolution test. It helps to assure similarity in product performance and signals bioequivalence. The factor f1 is proportional to the average indifference between two profiles, where as factor f2 inversely proportional to the average squared indifference between two profiles. The factor f2 measures the closeness between two profiles, FDA has set a public standard of f2 value between 50-100 to indicate similarity between two profiles.

$$f1 = \Sigma D(1/\Sigma t)\ 100$$

$$f2 = 50 \times \ln\{1/\surd 1+\Sigma\ (Rt-Tt)^2\}$$

Procedure:

Mean dissolution values of the two profiles (test and innovator) are taken and they are made under same test conditions and same time points. The time points taken as 2, 4, 6, 10, 15,20, 30,35 and 45 minutes. The following mathematical approach is made to compare the dissolution profiles of Acetaminophen and Diphenhydramine HCl tablets using two factors f1 and f2.

4.13 STABILITY STUDIES

Stability studies are an integral part of the drug development program & are one of the most important areas in the registration of pharmaceutical products. The purpose of stability testing is to provide evidence on how the quality of a drug substances or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity & light and enables recommended storage conditions, re-test periods and shelf half lifes to be established. Stability assessment starts with studies on the substances to determine degradation products degradation pathway. In these type of studies the product is analyzed at intervals for various parameters which may include assay of active ingredient, measurement of known degradation products, hardness, disintegration time, dissolution time, appearance, etc., Acetaminophen 500mg and Diphenhydramine Hydrochloride 25mg tablets were evaluated for their stability by means of accelerated stability studies at 40ºC/75% RH, 25ºC/60% RH conditions[72].

Storage conditions: 40ºC/75%RH, 25ºc/60% RH

Packs: Unit pack & bulk pack

Period: 1, 2, and 3 months.

5. RESULTS AND DISCUSSION

5.1 Preformulation parameters:

The various preformulation factors are evaluated and found to be satisfactory within the limits prescribed.

The results are tabulated in below.

TABLE - 20

Blend properties

Formula	Bulk density g/mL(untapped)	Tap density(g/mL)	Angle of repose(ɵ)	Compressibility or Carr's index	Hausner's ratio
1	0.575±0.065	0.757±0.053	36.34±0.9	24.04±0.31	1.31±0.02
2	0.328±0.076	0.403±0.059	24.93±0.93	18.61±0.36	1.22±0.04
3	0.324±0.079	0.403±0.061	30.35±0.95	19.60±0.39	1.24±0.06
4	0.327±0.082	0.401±0.065	32.53±0.98	18.45±0.43	1.22±0.081
5	0.336±0.085	0.397±0.069	29.56±0.1	15.36±0.48	1.18±0.09
6	0.341±0.089	0.402±0.073	29.85±0.13	15.17±0.54	1.17±0.13
7	0.343±0.093	0.399±0.078	28.86±0.14	14.03±0.58	1.14±0.15
8	0.347±0.096	0.412±0.082	29.02±0.16	15.77±0.67	1.18±0.17
9	0.340±0.115	0.401±0.086	28.46±0.17	15.21±0.74	1.17±0.19
10	0.337±0.120	0.398±0.091	29.91±0.18	15.32±0.78	1.18±0.20

Sieve analysis:

PARTICLE SIZE	% CUM. RETENTION
20#	0.1
40#	2.9
60#	11.4
80#	26.0
100#	32.9
200#	9.5
325#	71.0
Pan	19.5

5.2 FORMULATION DEVELOPMENT

TRIAL 1

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE – 21

Formula for Trial 1

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY (mg)
1	Acetaminophen	80.0	420.00
2	Microcrystalline cellulose	8.50	44.625
3	Povidone K-30	3.50	18.375
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Water	q.s	q.s
6	Croscarmellose sodium	2.00	10.50
7	Magnesium stearate	1.00	5.25
8	Corn starch	1.00	5.25

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Conclusion**: Big lumps were formed during granulation, Poor flow of granules was observed.

VI. **Further Plan of action:**Next batch is planned with increased binder and glidant concentrations. Microcrystalline cellulose concentration is decreased.

TRIAL 2

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg Tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE – 22

Formula for Trial 2

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420.00
2	Microcrystalline cellulose	7.50	39.375
3	Povidone k-30	4.00	21.0
4	Diphenhydramine Hydrochloride	4.00	21.0
5	Water	q.s	q.s
6	Croscarmellose sodium	2.00	10.5
7	Magnesium stearate	1.00	8.4
8	Corn starch	1.50	7.35

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Conclusion**: Small lumps are formed, Poor flow of granules, more disintegration time than intended.

VI. **Further Plan of action**: Next batch with increased disintegrant concentration and change of glidant.

TRIAL 3

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE - 23

Formula for Trial 3

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.0	420.00
2	Microcrystalline cellulose	7.50	39.375
3	Povidone k-30	2.00	10.50
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Water	q.s	q.s
6	Croscarmellose sodium	3.50	18.375
7	Magnesium stearate	1.00	5.25
8	Colloidal silicon dioxide	2.00	10.50

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Conclusion:** Better disintegration time but flow is not good and sticking was observed.

VI. **Further Plan of action**: Next batch is planned with another disintegrant along with croscarmellose sodium and stearicacid instead of magnesium stearate.

TRIAL 4

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE – 24

Formula for Trial 4

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420.00
2	Microcrystalline cellulose	7.50	39.375
3	Povidone k-30	2.50	13.125
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Water	q.s	q.s
6	Croscarmellose sodium	3.00	15.75
7	Polycrinilic potassium	1.00	5.25
8	Stearic acid	1.40	7.35
9	Colloidal silicon dioxide	0.60	3.15

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Conclusion**: Disintegration time increased.

VI. **Further plan of action:** Next batch is planned by changing the proportions of disintegrants.

TRIAL 5

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE -25

Formula for Trial 5

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420.00
2	Microcrystalline cellulose	7.00	36.75
4	Povidone k-30	3.00	15.75
5	Diphenhydramine Hydrochloride	4.00	21.00
6	Water	q.s	q.s
7	Croscarmellose sodium	3.00	15.75
8	Polycrinilic potassium	1.00	5.25
9	Stearic acid	1.40	7.35
10	Colloidal silicon dioxide	0.60	3.15

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Inference**: Disintegration is good but Rat holing of blend in the hopper.

VI. **Further plan of action**: Next batch with Pregelatinized maize starch in binder is planned.

TRIAL 6

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE – 26

Formula for Trial 6

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420
2	Microcrystalline cellulose	7.00	36.75
3	Povidone k-30	1.60	8.4
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Pregelatinized starch	2.00	10.50
6	Water	q.s	q.s
7	Croscarmellose sodium	3.00	15.75
8	Polycrinilic potassium	1.00	5.25
9	Stearic acid	1.00	5.25
10	Colloidal silicon dioxide	0.40	2.1

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Inference**: Coarser granules are obtained but disintegration is beyond the required range.

VI. **Further plan of action:** Next batch is planned by removing the Polycrinilic potassium, reducing the microcrystalline cellulose concentration and increases concentration of Pregelatinized starch.

TRIAL 7

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE -27

Formula for Trial 7

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420.00
2	Microcrystalline cellulose	2.00	10.50
3	Povidone k-30	0.80	4.2
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Pregelatinized starch	9.20	48.3
6	Water	q.s	q.s
7	Croscarmellose sodium	1.00	5.25
8	Pregelatinized starch	1.00	5.25
9	Stearic acid	1.50	7.875
10	Colloidal silicon dioxide	0.50	2.625

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Inference**: All the compression parameters are good.

VI. **Further plan of action**: Next batch with the same formula is planned for film coating.

TRIAL 8

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg Tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE – 28

Formula for Trial 8

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420
2	Microcrystalline cellulose	2.00	10.50
3	Povidone k-30	0.80	4.2
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Pregelatinized starch	9.20	48.3
6	Water	q.s	q.s
7	Croscarmellose sodium	1.00	5.25
8	Pregelatinized starch	1.00	5.25
9	Stearic acid	1.50	7.875
10	Colloidal silicon dioxide	0.50	2.625
11	Opadry 13B88093 Blue	2.00	10.50

IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Inference**: Orange peel effect was observed.

VI. **Further plan of action:** Next batch is planned with same coating material and procedure with increase in drying temperature.

TRIAL 9

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE -29

Formula for Trial 9

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420.00
2	Microcrystalline cellulose	2.00	10.50
3	Povidone k-30	0.80	4.2
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Pregelatinized starch	9.20	48.30
6	Water	q.s	q.s
7	Croscarmellose sodium	1.00	5.25
8	Pregelatinized starch	1.00	5.25
9	Stearic acid	1.50	7.875
10	Colloidal silicon dioxide	0.50	2.625
11	Opadry 13B88093 Blue	2.00	10.50

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IV. **Procedure:** Wet granulation procedure was followed.

V. **Observation/Inference**: Coating parameters are found to be good.

VI. **Further plan of action**: Two batches are planned with same formula for reproducibility of results and for checking dissolution profile.

TRIAL 10 & 11

I. **Objective:** To manufacture Acetaminophen 500mg and Diphenhydramine hydrochloride 25 mg tablets.

II. **Batch size:** 2.0 kg.

III. **Formula**

TABLE – 30

Formula for Trial 10 & 11

S.No	INGREDIENTS	QUANTITY (%)	QUANTITY(mg)
1	Acetaminophen	80.00	420.00
2	Microcrystalline cellulose	2.00	10.50
3	Povidone k-30	0.80	4.2
4	Diphenhydramine Hydrochloride	4.00	21.00
5	Pregelatinized starch	9.20	48.3
6	Water	q.s	q.s
7	Croscarmellose sodium	1.00	5.25
8	Pregelatinized starch	1.00	5.25
9	Stearic acid	1.50	7.875
10	Colloidal silicon dioxide	0.50	2.625
11	Opadry 13B88093 Blue	2.00	10.50

IV. **Procedure:** wet granulation procedure was followed.

V. **Observation/Inference**: Desired compression and coating tablet parameters are observed.

VI. **Further plan of action**: The two batches are planned for stability studies.

5.3COMPRESSION PARAMETERS

Compress the blend into tablets by using 19.5 X 6.03mm punches and suitable dies.

TABLE - 31

Compression parameters

TEST	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11
Tablet weight	570	570	570	570	610	620	620	620	640	640
Hardness (Kp)	10.0± 0.12	10.5± 0.35	10.9± 0.21	10.9± 0.17	10.9± 0.15	11.2± 0.24	11.4± 0.25	11.0± 0.09	11.2± 0.08	11.7± 0.13
Thickness-mm	5.08± 0.008	5.09± 0.007	5.07± 0.005	5.20± 0.010	5.18± 0.009	5.19± 0.009	5.21± 0.010	5.50± 0.025	5.50± 0.025	5.50± 0.025
Disintegration time –min	1.28	1.00	0.48	0.34	1.26	0.47	0.46	2.24	2.44	2.37
Friability - %w/w	0.60± 0.023	0.17± 0.013	0.17± 0.013	0.17± 0.013	0.16± 0.012	0.16± 0.012	0.12± 0.006	0.11± 0.006	0.21± 0.010	0.16± 0.012
Weight variation-mg	570± 2.64	565± 2.62	566± 2.63	565± 2.63	585± 2.72	607± 2.82	601± 2.80	592± 2.76	608± 2.81	608± 2.81

COATED TABLET PARAMETERS:

Coated tablet parameters

TEST	T09	T10	T11
Hardness-kp	11.0±0.09	11.2±0.08	11.7±0.13
Thickness-mm	5.50±0.025	5.50±0.025	5.50±0.025
Disintegration time –min	2.24	2.44	2.37
Weight variation-mg	592±2.76	608±2.81	608±2.81

5.4COMPATABILITY STUDIES

TABLE – 32

FTIR OF ACETAMINOPHEN

S.NO	PEAK AREA(cm^{-1})	MODE OF VIBRATION
1	3326	O-H Stretching
2	3161	N-H Stretching
3	1610-1563	Aromatic Stretching
4	1226-1171	C-0 Stretching
5	796	Aromatic C-H out plain bending

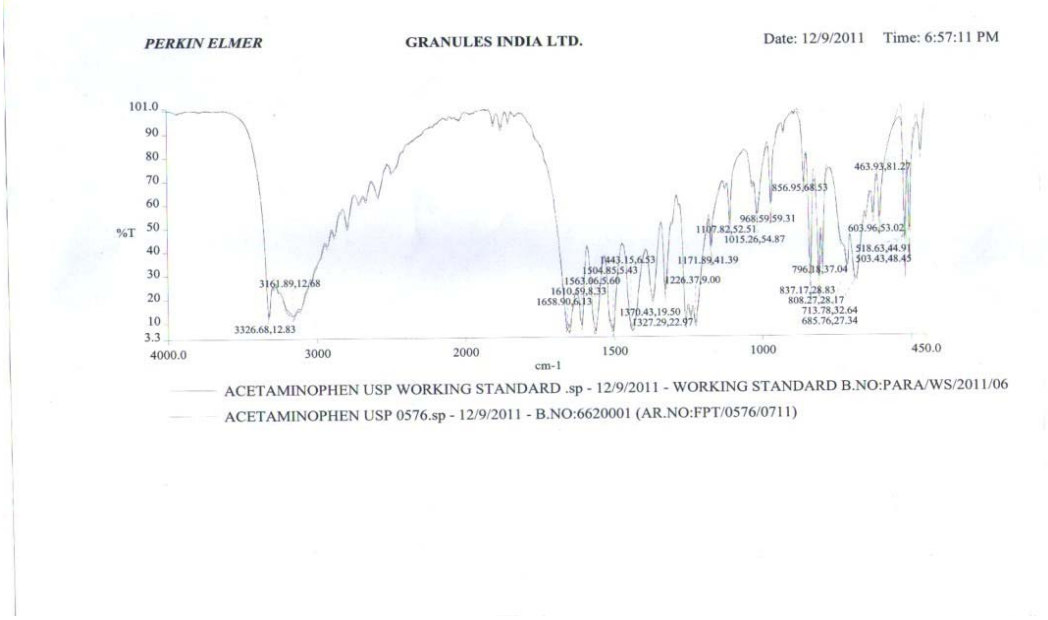


FIGURE - 3

TABLE - 33

FTIR of DiphenhyDamine Hydrochloride:

S.NO	PEAK AREA(cm^{-1})	MODE OF VIBRATION
1	3032	Aromatic C-H Stretching
2	2896	Aliphatic C-H Stretching
3	1108-1019	C-H Bending
4	882	Aromatic C-H out of plain bending.

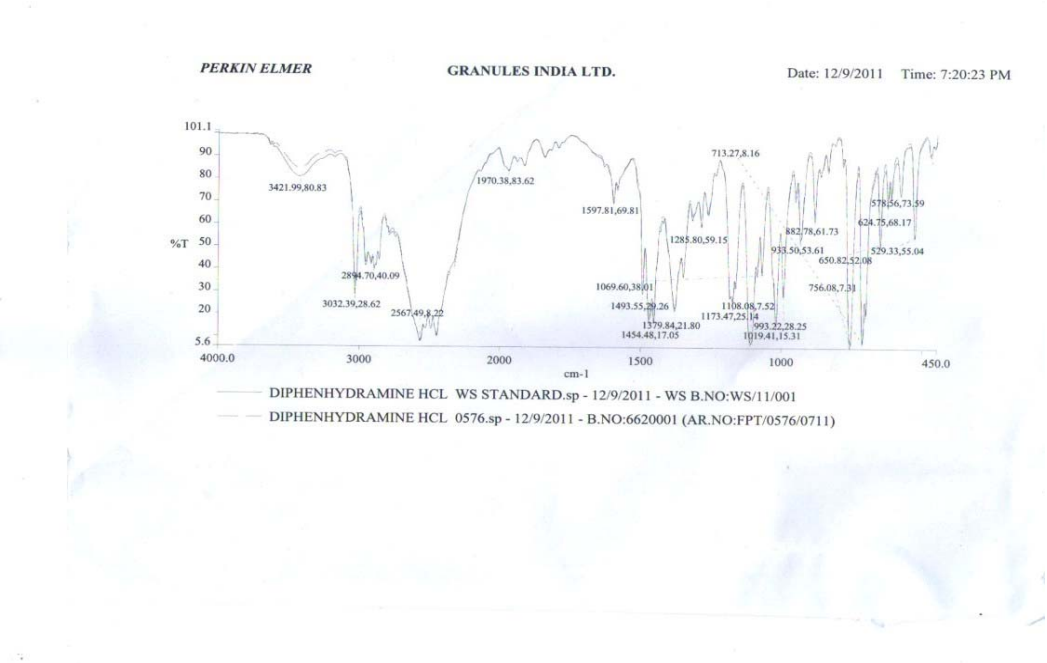
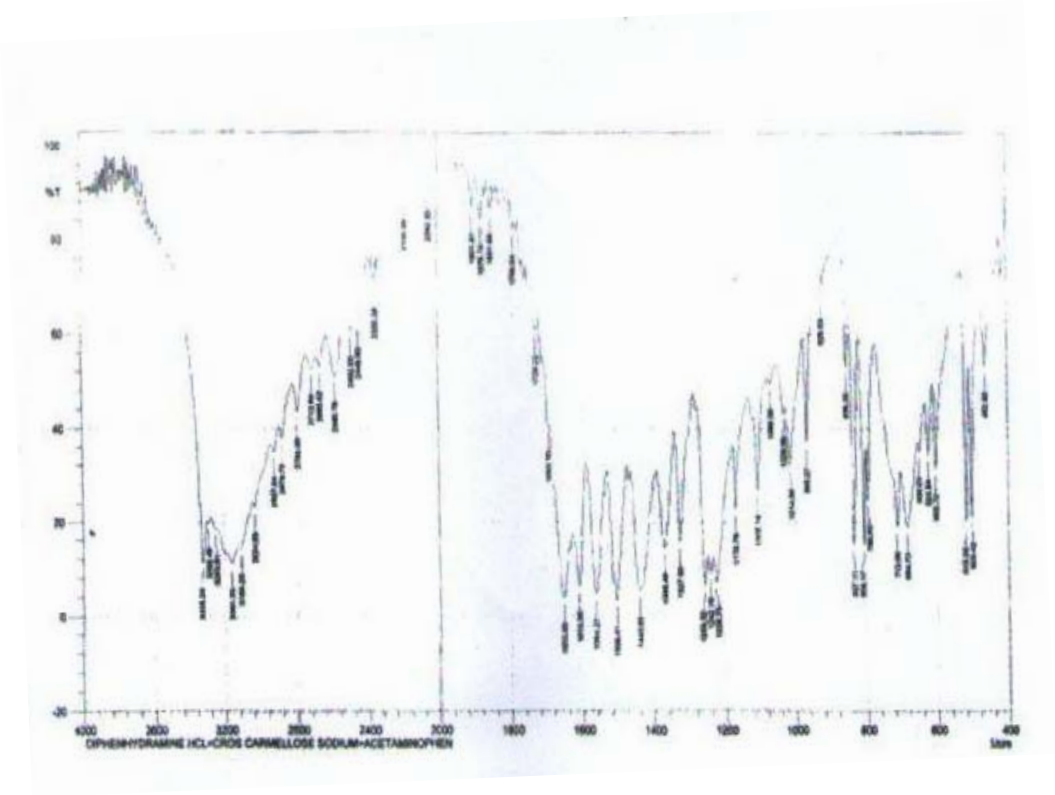


FIGURE - 4

FTIR OF ACETAMINOPHEN + DIPHENHYDRAMINE + CCS

FIGURE - 5



REPORT:

These results indicated that there is no chemical interaction between drug and excipients when formed as tablet**.**

TABLE – 34

S NO	NAME OF THE EXCIPIENT	CATEGORY	COMPATIBILITY STATUS
1	Microcrystalline cellulose MCC)	Diluent	Compatible
2	Pregelatinised Starch (PGMS)	Diluent/Binder	Compatible
3	Povidone K-30	Binder	Compatible
4	Croscarmellose sodium	Disintegrant	Compatible
5	Colloidal silicon dioxide	Glident	Compatible
6	Stearic acid	Lubricant	Compatible
7	Purified Water	Vehicle	Compatible
8	Opadry 13B80923 Blue	Coating material	Compatible

Report:

These result indicated that there is no chemical interaction between drug and excipients when formed as tablets.

5.5 IN-VITRO RELEASE STUDIES

Innovator

Dissolution medium : Purified water

Volume of medium : 900ml

Apparatus : USP-II (Paddle Type) apparatus.

Speed (RPM) : 50

Temperature : 37^{o}C ±0.5^{o}C

Sampling points : 5, 10, 15, 20, 25, 30, 30, 35,40and 45.

Result:

TABLE – 35

Innovator dissolution profile.

S.NO	TIME (min)	CUMULATIVE % ACETAMINOPHEN	CUMULATIVE % OF DIPHENHYDRAMINE
1	5	31.9	19.3
2	10	67.3	57.8
3	15	78.5	72.4
4	20	82	79.3
5	25	88.2	84.5
6	30	89.4	89.1
7	35	92.5	92.7
8	40	94.0	95.0
9	45	95.5	96.8

Graph:

FIGURE – 6

INNOVATOR DISSOLUTION PROFILE.

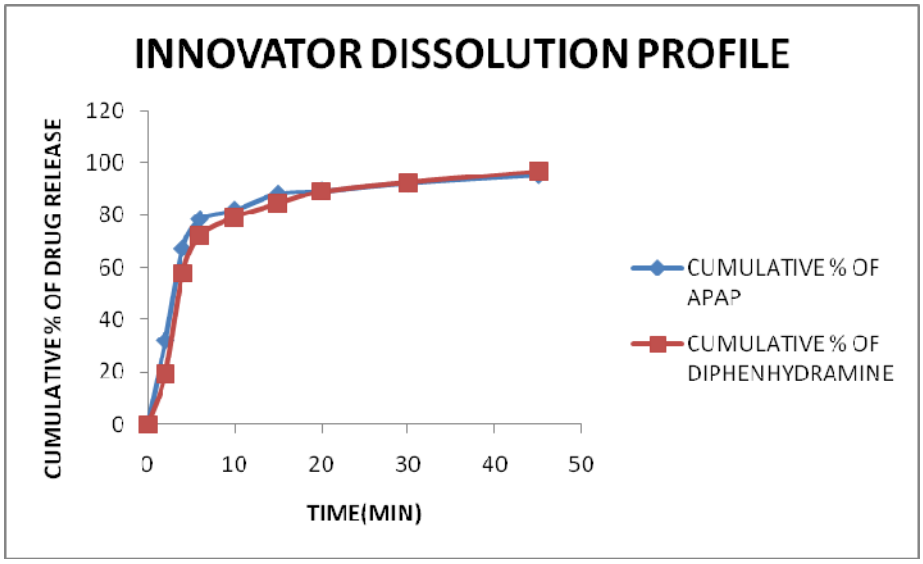


TABLE – 36

In vitro drug release profile of Acetaminophen and Diphenhydramine.HCl tablet formulation:

Formulation 9:

S.NO	TIME (min)	CUMULATIVE % ACETAMINOPHEN	CUMULATIVE % OF DIPHENHYDRAMINE
1	5	34.9	28.7
2	10	76.4	79.8
3	15	85.9	88
4	20	92.4	91.1
5	25	93.6	93.2
6	30	94	94.8
7	35	94.7	96.3
8	40	96.2	97.0
9	45	97.2	97.9

FIGURE – 7

IN VITRO DRUG RELEASE PROFILE OF ACETAMINOPHEN AND DIPHENHYDRAMINE

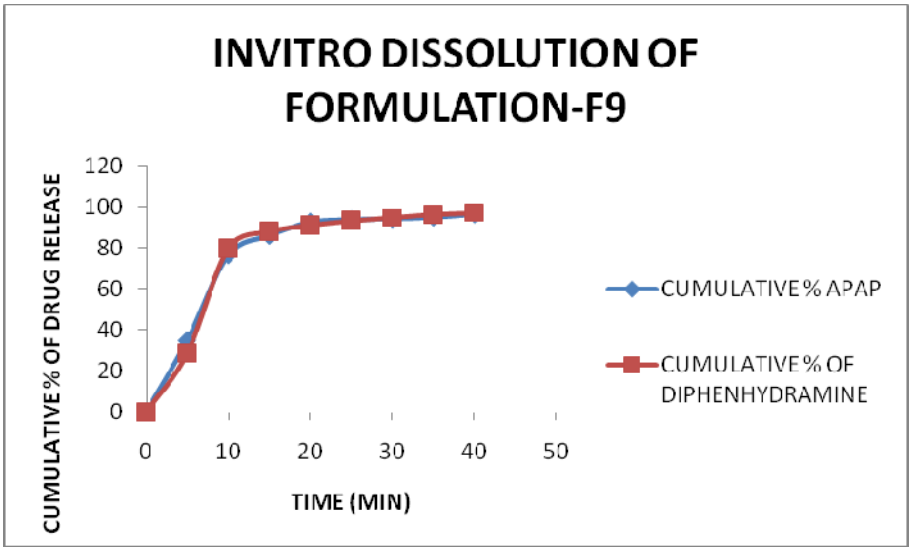


TABLE – 37

In vitro drug release profile of Acetaminophen and Diphenhydramine hydrochloride tablets formulation:

Formulation 10:

S.NO	TIME (min)	CUMULATIVE % ACETAMINOPHEN	CUMULATIVE % OF DIPHENHYDRAMINE
1	5	34.2	22.8
2	10	69.7	59.1
3	15	80.1	73.6
4	20	84.3	81.4
5	25	89.8	86.3
6	30	92.6	90.4
7	35	92.8	93.8
8	40	96.0	94.0
9	45	98.6	98.1

FIGURE - 8

IN VITRO DRUG RELEASE PROFILE OF ACETAMINOPHEN AND DIPHENHYDRAMINE HYDROCHLORIDE

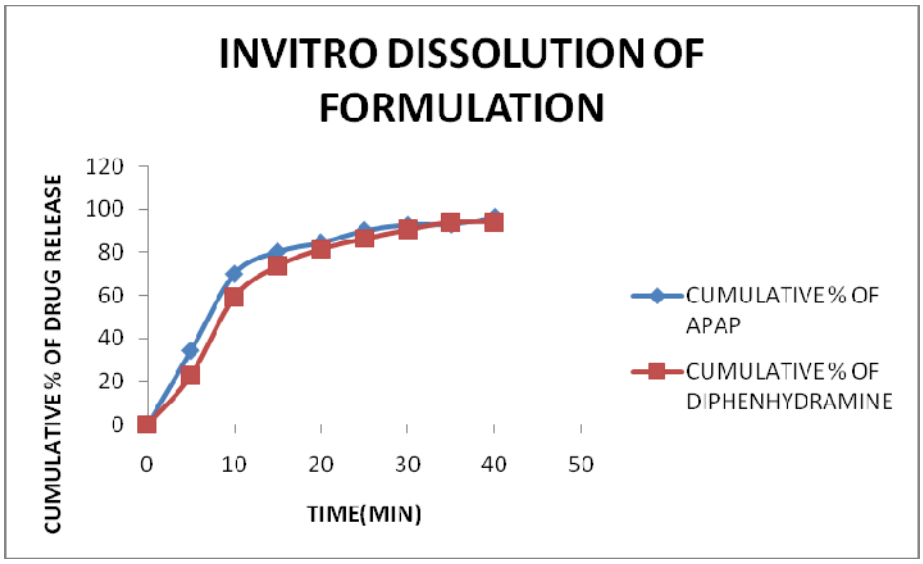


TABLE – 38

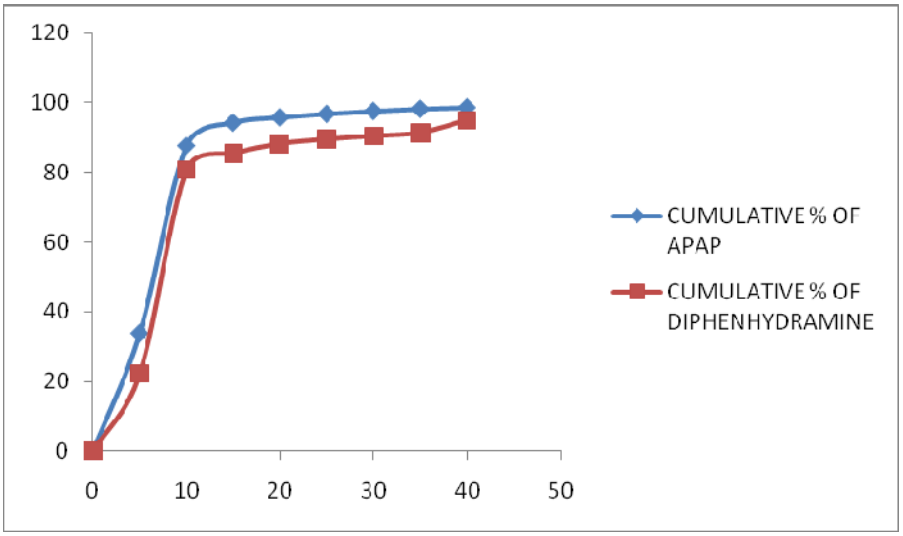
In vitro drug release profile of Acetaminophen and Diphenhydramine hydrochloride tablet formulation:

Formulation 11:

S.NO	TIME (min)	CUMULATIVE % ACETAMINOPHEN	CUMULATIVE % OF DIPHENHYDRAMINE
1	5	33.9	22.3
2	10	87.6	80.7
3	15	94.2	85.4
4	20	95.7	88.2
5	25	96.7	89.5
6	30	97.5	90.4
7	35	98.1	91.4
8	40	98.5	95.0
9	45	99.7	98.5

FIGURE – 9

IN VITRO DRUG RELEASE PROFILE OF ACETAMINOPHEN AND DIPHENHYDRAMINE HYDROCHLORIDE



COMPARATIVE DISSOLUTION STUDIES:

Dissolution was carried out at following conditions

Dissolution medium: Purified water

Volume of medium : 900ml

Apparatus : USP-II (Paddle Type) apparatus.

Speed (RPM) : 50

Temperature : 37^{o}C ±0.5^{o}C

Sampling points : 5, 10, 15, 20, 25, 30, 35,40 and 45 minutes.

TABLE - 39

Comparative dissolution profile:

Time (min)	Innovator %Drugrelease		Trail 9		Trail 10		Trail 11	
	APAP	DPHCl	APAP	DPHCl	APAP	DPHCl	APAP	DPHCl
5	31.9	19.3	34.9	28.7	34.2	22.8	33.9	22.3
10	67.3	57.8	76.4	79.8	69.7	59.1	87.6	80.7
15	78.5	72.4	85.9	88.0	80.1	73.6	94.2	85.4
20	82.0	79.3	92.4	91.1	84.3	81.4	95.7	88.2
25	88.2	84.5	93.6	93.2	89.8	86.3	96.7	89.5
30	89.4	89.1	94.0	94.8	92.6	90.4	97.5	90.4
35	92.5	92.7	94.7	96.3	92.8	93.8	98.1	91.4
40	94.00	95.00	96.2	97.00	96.0	94.00	98.5	95.00
45	95.5	96.8	97.2	97.9	98.6	98.1	99.7	98.5

Graphs:

FIGURE – 10

COMPARATIVE DISSOLUTION PROFILE OF ACETAMINOPHEN

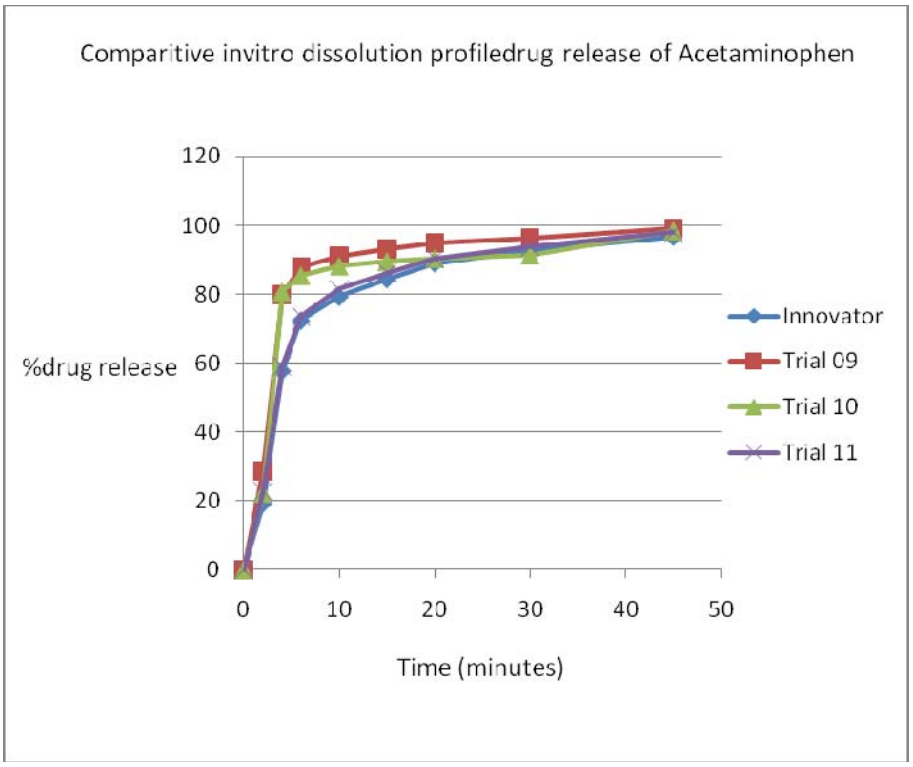
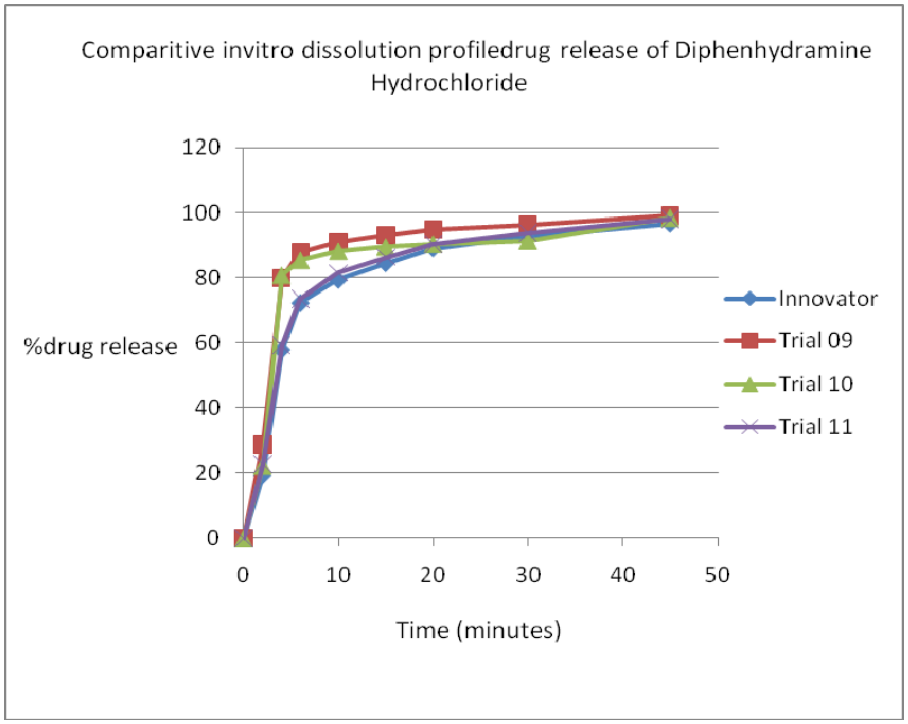


FIGURE - 11

COMPARATIVE DISSOLUTION PROFILE OF DIPHENHYDRAMINE HYDROCHLORIDE



Discussion:

FORMULATION F9:

The Invitro dissolution was low in Acetaminophen i.e., 97.2% and Diphenhydramine hydrochloride was 97.9% respectively at the end of 45 minutes. Hence another formulation is done.

FORMULATION F10:

The Invitro dissolution of Acetaminophen was 98.6% and Diphenhydramine hydrochloride was 98.1% respectively at the end of 45 minutes. The drug release in the 10^{th} formulation was good but to know the further drug release another formulation was done.

FORMULATION F11:

The Invitro drug release profile of optimized formula of Acetaminophen was 99.7% and diphenhydramine hydrochloride was 98.5%. The formula was compared with innovator product and it was found that the drug release was more in the formulation F11 so it was selected as best formulation.

TABLE – 40

Dissolution by HPLC: Acetaminophen:

S.N	Name	Vial	Injection	Retention time	Area(µV sec)	% Area	Height (µV)	% Height	Sample ID
1	Acetaminophen	2	1	3.058	5196656	94.97	643310	98.34	Std
2	Acetaminophen	2	1	3.055	5119333	94.88	640328	98.32	Std
3	Acetaminophen	2	2	3.058	5173326	95.00	641917	98.35	Std
4	Acetaminophen	2	3	3.063	5200779	95.06	640827	98.35	Std
5	Acetaminophen	2	4	3.062	5192686	94.95	639005	98.34	Std
6	Acetaminophen	2	5	3.064	5180926	95.02	637093	98.35	Std
Mean				3.060	5177284				
Std.Dev				0.00	30172.0				
% RSD				0.11	0.58				

TABLE - 41

Diphenhydramine Hcl:

S.N	Name	Vial	Injection	Retention time	Area(µV sec)	% Area	Height (µV)	% Height	Sample ID
1	D.P HCl	2	1	9.455	275180	5.03	10888	1.66	Std
2	D.P HCl	2	1	9.429	276288	5.12	10930	1.68	Std
3	D.P HCl	2	2	9.467	272513	5.00	10778	1.65	Std
4	D.P HCl	2	3	9.477	270424	4.94	10740	1.65	Std
5	D.P HCl	2	4	9.480	276460	5.05	10790	1.66	Std
6	D.P HCl	2	5	9.485	271317	4.98	10692	1.65	Std
Mean				9.465	273697				
Std.Dev				0.02	2620.0				
% RSD				0.22	0.96				

TABLE – 42

Dissolution by HPLC: Acetaminophen Sample:

S.N	Name	Vial	Injection	Retention time	Area(µV sec)	% Area	Height (µV)	% Height	Sample ID
1	Acetaminophen	33	1	3.050	5120650	94.97	641149	98.35	sample
2	Acetaminophen	34	1	3.050	5097151	94.88	637560	98.36	sample
3	Acetaminophen	35	1	3.049	5114663	95.00	640683	98.36	sample
4	Acetaminophen	36	1	3.049	5102620	95.06	639074	98.36	sample
5	Acetaminophen	37	1	3.051	5108731	94.95	640646	98.37	sample
6	Acetaminophen	38	1	3.053	5099698	95.02	639000	98.36	Sample
Mean				3.060	5107252				
Std.Dev				0.00	9134.4				
% RSD				0.05	0.58				

TABLE – 43

Dissolution by HPLC: Diphenhydramine HCl Sample:

S.N	Name	Vial	Injection	Retention time	Area(µV sec)	% Area	Height (µV)	% Height	Sample ID
1	D.P HCl	33	1	9.396	269306	5.00	10724	1.65	sample
2	D.P HCl	34	1	9.397	267184	4.98	10635	1.64	sample
3	D.P HCl	35	1	9.400	268283	4.98	10688	1.64	sample
4	D.P HCl	36	1	9.396	268132	4.99	10680	1.64	sample
5	D.P HCl	37	1	9.406	267041	4.97	10633	1.63	sample
6	D.P HCl	38	1	9.420	267937	4.99	10633	1.64	Sample
Mean				9.403	267981				
Std.Dev				0.01	823.4				
% RSD				0.10	0.31				

TABLE - 44

Calculation Acetaminophen:

No. of standard replicates:

INJECTION	Area
Injection 1	5196656.60000
Injection 2	5778322.60000
Injection 3	5200779.60000
Injection 4	5192086.60000
Injection 5n	5192081.60000
Average	5188874.60000
Standard Deviation	11420.7147
Relative standard deviation	0.2201

TABLE – 45

Dissolution of Acetaminophen:

SAMPLE NO	AREA	mg OF DRUG DISSOLVED	% OF DRUG DISSOLVED
1		490.037	98.00
2		487.788	97.55
3		481.464	97.89
4		488.311	97.66
5		488.896	97.77
6		488.032	97.60
	Average	488.75	97.75
	Minimum	487.79	97.55
	Maximum	490.04	98.00
	Standard deviation	0.87	0.17
	Relative standard deviation	0.18	0.17

TABLE – 46

Calculation of Diphenhydramine. HCl:

No. of standard replicates:

INJECTION	Area
Injection 1	215180.8000
Injection 2	279951.8000
Injection 3	267024.8000
Injection 4	267012.8000
Injection 5n	247081.8000
Average	273178.80000
Standard Deviation	2562.6933
Related standard deviation	0.9381

TABLE - 47

Dissolution of Diphenhydramine HCl:

Sample NO	Area	mg of drug Dissolved	% of Drug Dissolved
1		25.430	101.72
2		25.230	100.91
3		25.333	101.33
4		25.319	101.27
5		25.216	100.86
6		25.301	101.20
	Average	25.30	101.202
	Minimum	25.22	100.86
	Maximum	25.43	101.72
	Standard deviation	0.08	0.31
	Relative standard deviation	0.32	0.31

DISSOLUTION PROFILE COMPARISON USING f1 f2 Factors:

TABLE-48

Acetaminophen

f1,f2 calculation of Acetaminophen

Time(min)	Rt	Tt	D = |Rt-Tt|	$(Rt-Tt)^2$
2	31.9	34.2	2.3	5.29
4	67.3	69.7	2.4	5.76
6	78.5	80.1	1.6	2.56
10	82.0	84.3	2.3	5.29
15	88.2	89.8	1.6	2.56
20	89.4	92.6	3.2	10.24
30	92.5	92.8	0.3	0.09
45	95.5	98.6	3.1	9.61
Total	$\sum$ Rt = 625.3	$\sum$ Tt = 642.1	$\sum$ D = 16.8	$\sum (Rt-Tt)^2 = 41.4$

Result of Acetaminophen:

Factors	Standards	Obtained
f1	0-15	2.61
f2	50-100	93.6

TABLE:49

Diphenhydramine Hydrochloride:

f1,f2 calculation of Diphenhydramine Hydrochloride:

Time(min)	Rt	Tt	D = |Rt-Tt|	$(Rt-Tt)^2$
2	19.3	22.8	3.5	12.25
4	57.8	59.1	1.3	1.69
6	72.4	73.6	1.2	1.44
10	79.3	81.4	2.1	4.41
15	84.5	86.3	1.8	3.24
20	89.1	90.4	1.3	1.69
30	92.7	93.8	1.1	1.21
45	96.8	98.1	1.3	1.69
Total	∑ Rt = 591.9	∑ Tt = 605.5	∑ D = 13.6	∑ $(Rt-Tt)^2$ = 27.62

Results of Diphenhydramine Hydrochloride:

Factors	Standards	Obtained
f1	0-15	2.24
f2	50-100	83.85

Where:

f1=Dissimilarity factor, f2=Similarity factor

Rt and Tt are Test and Innovator cumulative percentage dissolution respectively at selected time points.

N= Number of time points

- The assay of Acetaminophen 500mg And Diphenhydramine Hydrochloride 25mg tablets was within the limit and complies with the specifications
- The film coating process was also found to be smooth with no processing problems.
- There is not much variation in the release of drug from the core and coated tablet. Indicating that the coating of tablets to obtain a 2.0% weight gain is found to be sufficient to coat the tablets.

TABLE – 50

5.6 STABILITY DETAILS OF FORMULATION 11:

Result→ ↓	Stability Specifi-cation	40^0C/75 %RH				25^0C/60%RH		
		Initial	30days	60bays	90days	30days	60days	90days
Description	Blue colored, caplet shaped, film coated tablets with 'L751' engraving on one side & plain on other side.	Complies	Complies	Complies	Complies	Complies	complies	Complies
Moisture content % w/w	NMT 3.0%	0.98	1.02	1.03	1.17	1.00	1.01	1.02
%Drug release 1.APAP 2.Diphenhydramine.HCl	NLT 85% of label claim in 30 min. NLT 85% of label claim in 30 min.	101.8% 94.1%	99.7% 93.0%	99.5% 93.5%	99.1% 93.5%	99.5% 96.2%	99.6 % 96.4 %	99.8 % 96.5 %
Assay % w/w 1.APAP 2.Diphen-hydramine	Between 95%-105% of label claim.	101.% 94.1%	99.7% 93.0%	99.55 93.5%	95.1% 93.7%	96.4% 98.0%	96.8 % 98.4 %	97.1 % 98.7 %

Following results were observed after 3 months stability studies of Acetaminophen 500mg and Diphenhydramine Hydrochloride 25mg Tablets.

1. **Description:** The manufactured Acetaminophen 500mg and Diphenhydramine Hydrochloride 25mg tablets are meeting the specification.

2. **Identification:** No change observed after 3 months storage.

3. **Moisture content:** Slight increase in moisture content of Acetaminophen 500mg and Diphenhydramine Hydrochloride 25mg tablets were observed during 3 months storage at 40ºC/75% RH.

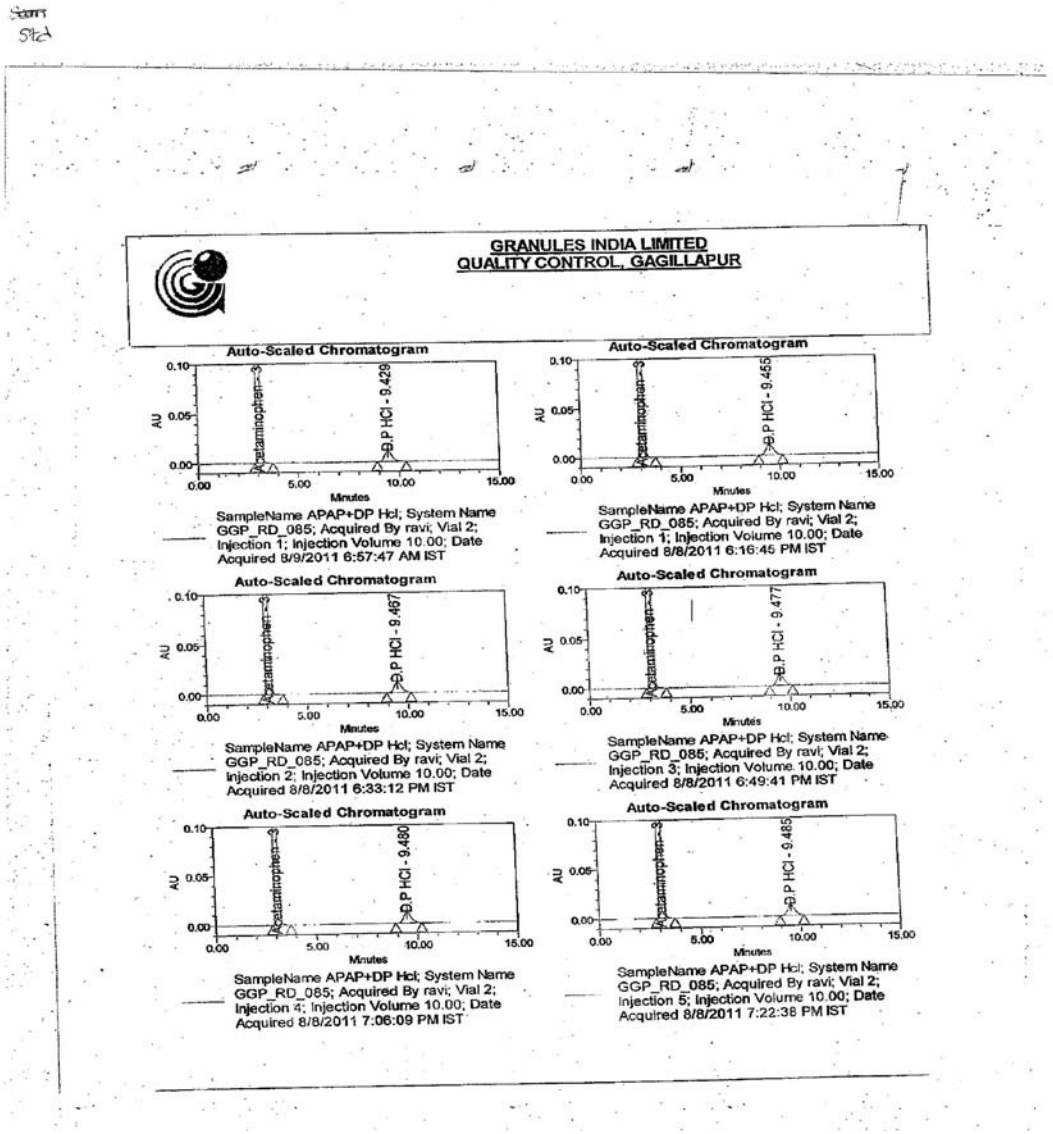
4. **Dissolution:** The tablets meet the specification criteria.

5. **Related substance:** The impurities or RS are well in the limits of the specification.

6. **Assay:** No significant change in assay of Acetaminophen 500mg and Diphenhydramine Hydrochloride 25mg tablets was observed during 3 months storage at 40ºc/75% RH and 25ºc/60% RH.

FIGURE – 12

STANDARD



Sample -

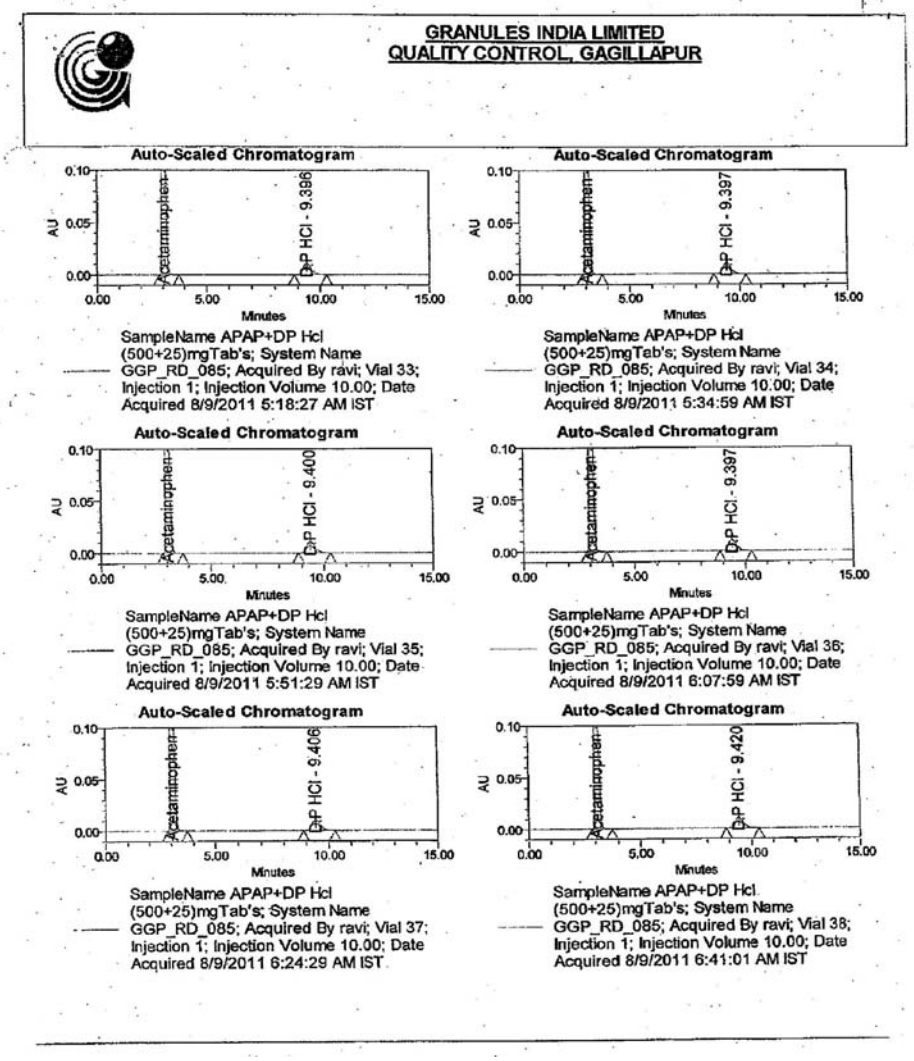


FIGURE - 13

6. CONCLUSIONS

- The main objective of this study was to develop and evaluate the formulation of Acetaminophen 500mg and Diphenhydramine Hydrochloride 25 mg tablets.
- Several trials have been taken to optimize and develop a robust formulation.
- Various processing problems were encountered during the formulation development and these were overcome with proper optimization of composition of formulation ingredients and processing conditions.
- The reproducibility batch (T11) was taken for the finalized batch ie. T11 was charged for stability studies at accelerated and real time conditions.
- The stability study for 3 months shows that the formulation is stable enough at 40^0C/75%RH.
- The formulation is a robust one and the performance is less likely to be affected by the various factors studied. The stability data is found to be satisfactory and so the scale up, Exhibit as well as validation batches can be planned for further progress.
- So it can be concluded that the Acetaminophen 500mg and Diphenhydramine-hydrochloride 25mg tablets formulation T11 is robust and stable.

BIBLIOGRAPHY

1. Chien, Y.W., Novel drug delivery system, Marcel decker Inc;2nded, Newyork, 1992;139-140.
2. Lawrence H. Block, Andrew, Pharmaceutical principles and drug dosage forms, 61-63.
3. Herbert A, Lieberman Leon Lachman, Granulation technology & tablet characterization, Pharmaceutical dosage forms, Marcel Dekker Inc, 2nded, 1990,254-252.
4. Ansel's, Dosage form design, Biopharmaceutical & pharmacokinetics considerations, Pharmaceutical dosage forms and drug delivery systems, Lippincott Williams &wilkins, 7th ed,2007;165-171.
5. Martin, Micrometrics, Physical pharmacy, Lea &febiger Philadelphia, 1963, 491-493.
6. Ansel's, Tablets, Pharmaceutical dosage forms & drug delivery system, Lippincott Williams &wilkins, 7thed, 228-257.
7. HamedM.Abdou, Factors effecting rate of dissolution of solid dosage forms, Dissolution bioavailability and bioequivalence, Mack publishing company, 1989, 73-92.
8. Bentley's, Tablets & capsules, Text book of pharmaceutics, The English language book society &bailieretindall, 8thed, 1982, 271-279.
9. Leon lachman, Herbert a.liberman, the industrial pharmacy, the tablets and capsules, special Indian edition, cbs publishers, 2009,347-344,359-376.
10. Michael E.Aulton, Coating of tablets & multi particulates, Pharmaceutics the science of dosage form design, Churchill livingstone, 2ndedi,1988, 441-448.
11. Donald L.wise, An overview of controlled release system, Hand book of pharmaceutical controlled release technology,2000,444.
12. http://en.wikipedia.org/wiki/Film_coating.
13. basak SC, Kumar PS,Manavalan R, Narendranath, preparation and evaluation of film coated tablets, Ind J Pharm Sci 2002;64;260-64.

14. Turkoglu M, Varol H, Celikok M, Tableting and stability evaluation of film coating tablets. Eur J Pharma and Biopharma 2004;56:270-85.
15. B.Jayakar, A.Pasupathi, C.Saravanan., Formulation and evaluation of Diphenhydramine HCl Rapid release Gelcaps 25 mg, journal of pharmacy research, 2010, (3) 8, 2015-2019.
16. BiljanaGovedarica, RadeInjac ,RokDreu and StaneSrcic, formulation and evaluation of immediate release tablets with different type of paracetamol powders prepared by direct compression, African journal of pharmacy and pharmacology,2011.11.
17. Jens C. Nielsen, Peter, Lars, A comparison of the hypoalgesic effect of paracetamol in slow release and plain tablets on laser induced pain, Br. J. Clin. Pharmac. 1991, 31, 267-270.
18. Wayne M. Camarco, Ajay H. Upadhyay, Acetaminophen / Low Dose Co-active Tableting By Direct Compression Using A Novel High Surface Area Apap Granulation (dc-90 Uf).
19. Surendra C. Mehta*et.al*, mechanism of drug release from an acrylic polymer wax matrix tablet, Journal of pharmaceutical sciences, 1994, 795-797.
20. Takeshi Kawaguchi , HisakazuSunada*et al*, Granulation of Acetaminophen by a RotatingFluidized-Bed Granulator, Pharmaceutical Development and Technology,2000, 5(2), 141–151.
21. Aniruddha M. Railkar and Joseph B. Schwartz *et.al*,Use of a Moist Granulation Technique(MGT) to Develop Controlled-ReleaseDosage Forms of Acetaminophen, Drug Development and Industrial Pharmacy, 2001, 27(4), 337–343.
22. Joshua E. Lane MD, Martin G Journal of emergency medicine, 2002.
23. MariekeNauta, MariekeL.A.The American journal of surgery, 2009.
24. ElkeLeinisch, Stefan Evers, Pain, 2005, 117.
25. Terrence L. Geiger and Scott C. Howard, Transfusion medicine reviews, 2007**.**
26. MA Naeem, A Mahmood, SA Khan and Z Shahiq., Development and Evaluation of Controlled-Release Bilayer Tablets Containing Microencapsulated Tramadol and Acetaminophen, *Tropical Journal of Pharmaceutical Research*, 2010,9(4), 347-354.

27. Nourudin W.Ali[1],HalaE.zaaa zaa[2],M .Abdelkawy[2].a.Mangdy[1],simultaneous determination of paracetamol and diphenhydramine HCL in presence of paracetamol degradation product,2011,2-8.
28. PV Swamy, SP Divate, SB Shirsand, P. Rajendra, Preparation and evaluation of orodispersible tablets of Pheniraminemaleate by effervescent method. Indian Journal of Pharmaceutical Sciences, 2009, 71 (2), 151 – 154.
29. D.M. Patel and N.M. Patel, R.R. Shah, P.D. Joganiad A.J. Balapatel, Studies in formulation of orodispersible tablets of Rofecoxib, Indian Journal of Pharmaceutical Sciences, 2004, 66 (5), 621 – 625.
30. S.A. Srenivas, P.M. Dandagi, A.P. Gadad, A.M. Godbole, S.P. Hiremth, Orodispersible tablets: New – fangled Drug delivery System – A Review, Indian Journal Pharmaceutical Education, Research, 2005, 39(4), 177 – 180.
31. D. Nagendrakumar, S.A. Raju, S.B. Shirsand, M.S. Para and M.V. Rampure, Fast dissolving tablets of Fexofendrine HCL by effervescent method, Indian Journal of Pharmaceutical Sciences, 2009, 71 (2), 116.
32. S.B. Shisand, Sarasija Suresh, P.V. Swamy, D. Nagndra Kumar and M.V. Rampure Design and evaluation of fast dissolving tablets of Clonazepam, Indian Journal of Pharmaceutical Sciences, 2008, 70 (6), 791.
33. T.V. Rao, R. Ramakrishna, R.E.G.K. Murthy, S. Vidyadhara, Formulation and evaluation of Cefadroxil dispersible tablets; Direct compresssion technique, The Pharma Review, 2008,135 – 136.
34. C. Mallikarjunasetty, D.V.K. Prasad, V.R.M. Gupta and B.SA, Development of fast dispersible Aceclofenac tablets: Effect of functionality of superdisintegrants, Indian Journal of Pharmaceutical Sciences, 2008, 70 (2), 180 - 182.
35. T.V. Rao and S. Vidyadhara, Formulation and evaluationof mouth dispersible tablets of Simvastatin by direct compression technique, The Pharma Review, 2008, 6 (34), 137 - 139.

36. Shisu, AshimaBhatti and Tejbir Singh, Preparation of tablets rapidly disintegrating in saliva containing bitter taste-masked granules by compression method, Indian Journal of Pharmaceutical Sciences, 2007, 69 (1), 80 – 84.
37. SheetalMalke, SupriyaShidhaye and V.J. kadam, Formulation and evaluation of Oxcarbazepine fast dissolve tablets, Indian Journal of Pharmaceutical Sciences, 2007, 69 (2), 211 - 214.
38. K. Aithal, N.M. Rathnanand, A. Shirwaikar and m. Dutta, Once daily fast dissolving tablets of Granisetron Hydrochloride – formulation and in vitro evaluation, Indian Drugs, 2006, 43 (7), 576- 581.
39. SajalkumarJha, P. Vijayalakshmi, RoopaKarki, DivakarGoli, Formulation and evaluation of melt-in-mouth tablets of Haloperidol, Asian Journal of Pharmaceutics, 2008, 2 (4), 255 – 260.
40. Abdelbary, C. Eounai, P. Prinderre, J. Joachim, JP. Reynier, Ph. Piccerelle, Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration, International Journal of Pharmaceutics, 2005, 29 – 41.
41. Mohanad N. S., Design and in vitro evaluation of Prednisolone tablets as a potential colon delivery system, Asian Journal of Pharmaceutical and Clinical Research, October-December 2009, Vol.2 Issue 4, 84-93.
42. RabiaBushra, Muhammad Harris Shoaib, NousheenAslam, ZafarAlamMehmood, DurriyaHashmat, Enteric coating of ibuprofen tablets (200 mg) using an aqueous dispersion system, Brazilian Journal of Pharmaceutical Sciences, Jan./Mar., 2010, vol. 46 (1), 99-108.
43. L. Senthil Kumar*, S. Ashokkumar, R. P. Ezhilmuthu, Formulation and evaluation of Didanosine enteric coated sustained release tablet, J Biomed Sci and Res., 2010, Vol 2 (3), 126-13.
44. Vaishali A. Kilor, Nidhi P. Sapkal, Jasmine G. Awari and Bharti D. Shewale., development and characterization of Enteric coated immediate release pellets of

aceclofenac by extrusion/ spheronization technique using carrageenan as a pelletizing agent, AAPS PharmsciTech, 2010,252.

45. Bhauniabiswajit, varunjoshi, Formulation and evaluation of orodisprsable tablets of Amlodepinebesilatee, international journal of pharmacy & technology, vol-3, Issue-4, 3745-3766.
46. Syed azeemhyder, shawetaSharma., design and evolution of immediate release tablet of rupatadineFumarate, International journal of Pharma professional research, 2011.
47. Rai V.K. , Pathak N., bhaskar R, Nandi B.C. Dey S. and Tyagi L.K., optimization of immediate release tablet of Raloxifene hydrochloride by wet granulation method, International journal of pharmaceutical sciences and drug research 2009; 1 (1) 51-54.
48. VasanthkumarSekar, VijayaRagavanChellan., Immediate release tablets of Telmisartan using super disintegrant formulation, evaluation and stability studies, chem. Pharm Bull.2008, 56 (4), 575-577.
49. NiharRajanPani, lilaKantaNath, SujathaAcharya, Compatibility studies of Nateglinide with excipients in immediate release tablets, Acta pharm., 2011,61, 237-247.
50. Rizvanulla, A, Madhubabu, B. Jainendrakumar, preparation and evaluation of Oxcarbazepine fast dissolving tablets, International journal of Pharma professional's research, 2011.
51. Honey goel, parshuramrai, vikasrana and ashoktiwary, 2008,259.
52. Jensc and nielsen volume issue 1991.
53. Karl G. Wagnera, Markus Krummeb, Thomas E. Beckertc, Peter C. Schmidt., Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press, *European Journal of Pharmaceutics and Biopharmaceutics*,2000,50, 285-291.
54. Shlyankevich, L. Liu, P. Lynch, M. Awad, T. McCall., Comparison of USP apparatuses 2 and 3 in Dissolution Testing of Immediate Release/Controlled Release Bilayer Tablets, Penwest company.

55. ChinamNiranjanPatra, ArethiBharani Kumar, Hemant Kumar Pandit, SatyaPrakashSingh,MeduriVimala Devi.,Design and evaluation of sustained release bilayer tablets of Propranolol hydrochloride,*Acta Pharm.* ,2007,57, 479–489.
56. N. Damodharan*, V.Manimaran, B. Sravanthi, Formulation development and evaluation of delayed release Doxycycline tablets, International Journal of Pharmacy and Pharmaceutical Sciences, 2010, Vol 2 (1), 116-119.
57. Mohanad N. S., Design and in vitro evaluation of Prednisolone tablets as a potential colon delivery system, Asian Journal of Pharmaceutical and Clinical Research, October-December 2009, Vol.2 Issue 4, 84-93.
58. Sipemann F., Whale C., Leclercq B., Carlin B., Siepmann J., pH-sensitive film coatings: Towards a better understanding and facilitated optimization, European Journal of Pharmaceutics and Biopharmaceutics, 2010, 68, 2-10.
59. Chakraborty S., Sarkar S., Debnath S. K., Formulation development and evaluation of pantaprazole enteric coated tablets, International Journal of ChemTech Research, 2009, 1 (3), 663-666.
60. Indian pharmacopoeia, the controller of publications, volume-3, 2010, 1861-1862.
61. Remington, analgesic, antipyritics, anti inflimatory, the science and practices of pharmacy, volume-2, 1445-1447.
62. Good man and gilman's, analgesic-antipyretic agents,pharmacotherapy of gout,the pharmacological basis of therapeutics,L.parker,11th edi,693-694,634-640,197.
63. R.S satoskar, S.D Bhandarkar, NSAIDS,Pharmacology and pharmacotherapeutics,popular prakashan,20th edi,2007,169-170,319.55. K.D Tripathi, NSAIDS, 5th edi,2003, 167-184.
64. Indian pharmacopoeia, the Indian pharmacopoeia commission, volume -2, 1232-1234.
65. Lippincott's, anxiolytics & hypnotic drugs pharmacology, 3rdedi, Lippincott Williams &wilkins, 112-114.
66. Ainley wade and paul J weller, Hand book of excipients, the American pharmaceutical association,2nded, 1994,84,392,491,424,494,143.

67. The united states pharmacopeia,official monographs for usp xx, USP NF,1980,11-13.
68. USP, General notice and requirements, 2002, 16-19.
69. Cooper and gun's, tutorial pharmacy, size separation, cbs publishers,6thedi, 2005, 194-196.
70. Moji christiananadeyeye harry G.brittain, Introduction and overview of pre formulation development of solid dosage forms,informa health care, 2008,1-15.
71. USP NF,Acetaminophen and Diphenhydramine HCl, Asian the national formulatory, 2005, 42-44.
72. Jens T.carstensen,c.tRhodes,solid state stabilitydrugstability,marceldekker, vol 107, 3rd edi,2000,145-200.