FORMULATION AND EVALUATION OF DELAYED RELEASE TABLETS OF RABEPRAZOLE SODIUM

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Submitted by

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During the period of project He was sincere and dedicative in his project related works. We wish him success in his future career.

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Dedicated
To My
Loveable
Parents.

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ABBREVIATIONS

E/C	Enteric Coated
GIT	Gastro Intestinal Tract
U/C	Uncoated
U.S.P	United State Pharmacopoeia
I.P	Indian Pharmacopoeia
F.D.A	Food & Drug Administration
HPLC	High Performance Liquid Chromatography
UV	Ultra Violet
FT-IR	Fourier Transform Infra-Red Spectrophotometer
API	Active Pharmaceutical Ingredient
ICH	International Council for Harmonization
ACN	Acetonitrile
CI	Compressibility Index
CP	Crospovidone
MDC	Methyline di chloride
HCl	Hydrochloric Acid
PVP	Poly Vinyl Pyrrolidone
Conc.	Concentration
NLT	Not Less Than
NMT	Not More Than
RT	Retention Time
TD	Tapped Density
BD	Bulk Density
MG	Milligram

RPM	Rotations Per Minute
MM	MilliMetre
µG	Microgram
ML	MilliLitre
NM	Nanometer
GM	Gram
W/V	Weight by Volume

CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1.ORAL DRUG DELIVERY[1,2]

Oral route is the most acceptable route of drug administration among all routes that have been explored for the systemic delivery of drug via various pharmaceutical products of different dosage form. Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets. These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug. The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large scale economic manufacture, have led to a steady decline in the prescribing of powders and pills. Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world.

1.2.TABLETS[3]

Tablets are solid dosage forms usually obtained by single or multiple compression of powders or granules. In certain cases tablets may be obtained by moulding or extrusion techniques. They are uncoated or coated. Tablets are normally right circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may have lines or break-marks (scoring), symbols or other markings. Tablets containing active ingredients having a narrow therapeutic window should generally not be presented with break-marks for subdivision. Non-functional break-marks should be avoided. Tablets contain one or more active ingredients.

Advantages of Tablets[4,5]

Some of the potential advantages of tablets are as follows.

1. The unit dosage form having greatest capabilities amongst all the oral dosage form for the dose precision and least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.

5. Easy to swallowing with least tendency for hang- up.
6. Sustained release product is possible by enteric coating.
7. Objectionable odour and bitter taste can be masked by coating technique.
8. Suitable for large scale production.
9. Greatest chemical and microbial stability over all oral dosage form.

Disadvantages of tablets

1. When the dose of drug is large, tablets might be to big for children or even adults to swallow.
2. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3. Drugs with poor wetting, slow dissolution properties, optium absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter tasting drug with an objectable odour or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

1.2.1. ADDITIVES USED IN TABLETS[6]

Excipients are pharmacologically inactive substances included in the formulation which is used as a carrier of active ingredient. In a conventional tablet the excipients used in the tablet formulation including,

1. Diluents/fillers
2. Binders
3. Disintegrants
4. Lubricants
5. Glidants
6. Miscellaneous

Diluents

Diluents are used to increase the bulk content of the dosage form this is done in a situation where the active constituent to be incorporated in the formulation is of less quantity. For example if the active ingredient is just 5 mg, is such a case a tablet of just 5 mg is very difficult to manufacture and handle too, thus the bulk content is increased by addition of inactive excipients. Round tablets of weight 120mg to 700mg and for oval tablets 800mg are easy to handle. E.g. Lactose, lactose anhydrous, lactose spray dried, directly compressible starch, hydrolyzed starch, MCC, other cellulose derivatives, dibasic calcium phosphate dihydrate, mannitol, sorbitol, sucrose, calcium sulphate dehydrate, dextrose.

Binders

These are the dry powders or liquid which are added during wet granulation to promote granules or to promote cohesive compact during direct compression. It provides mechanical strength to the tablet. Binders can be in powder form and liquid form. Examples of the binders are

1. Powder binders: cellulose, methyl cellulose, polyvinyl pyrolidine, PEG.
2. Solution binders: Gelatin, PVP, HPMC, PEG, sucrose, starch.

Disintegrants

Disintegrants are added to the formulation as it breaks the dosage form into smaller particles when it comes in contact with the liquid, these smaller fragments have greater surface area which will increase the dissolution of the drug. Various mechanisms of disintegrations are proposed by breaking into fragments. When the tablet comes in contact with the liquid, the liquid penetrates into the pores of the tablets and breaks it into fragments. To improve the water uptake into the pores certain hydrophilic polymers are added to the formulation by swelling when the tablet comes in contact with the water it swells and ruptures the tablet into small particles. e.g. starch, starch derivatives, clay, cellulose, alginates, polyvinyl pyrolidone, cross linked sodium carboxy methyl cellulose.

Lubricants

Lubricants are used to reduce the friction between the tablets and die cavity when the tablet die cavity is getting ejected from the die. Lack of lubricant can lead to problems like capping, scratch on the sides of the tablet, fragmentation of the tablet, shape out etc. Thus to avoid this lubricants are to be used. For a lubricant the time of addition, concentration in

which it is to be added and the combination are the important parameters. e.g. stearic acid, stearic acid salt, stearic acid derivatives, talc, PEG, surfactants, waxes, calcium stearate and magnesium stearate (0.25-0.50%w/w) are the most commonly used lubricants followed by talc.

Glidants

Glidants are used to improve the flow property of the formulation. It reduces the friction between the particles and between the hopper and particles and die cavity and particles. Actually glidant, lubricant and anti adherent have a close relation to each other. They have some functions in common. Most of the glidants used are hydrophobic thus they are to be carefully added i.e. concentration regulated. E.g. talc, colloidal silicone dioxide, corn starch.

Miscellaneous

Above from the above mentioned principal ingredients following excipients also improve the dosage form characters they are adsorbents, flavoring agents and colouring agents.

- **Adsorbent**

Adsorbents are used when there is an need to add a liquid or semisolid ingredient in the formulation, adsorbents are capable of sorbing the liquid component on to the dry powder. Thus oil or liquid component can be in corporate into the powder. E.g.Magnesium oxide, kaolin/bentonite.

- **Flavouring agents**

These are incorporated into the formulation to improve the flavor or give a pleasant taste to the formulation. Flavoring agents are mostly restricted to the formulations in which are intended to be released in the mouth or chewable tablets. They are usually added in along with the granules.

- **Colourants**

Colouranats are added to the formulation in order to increase the patent compliance or for identification of the formulation. Usually the colurants are added in the form of insoluble powder or in the form as liquid in the granulation liquid. e.g. FD&C and D&C dyes and lakes.

1.2.2. TYPES OF TABLETS[7]

1. Tablet ingested orally
    - **a.** Compressed tablets
    - **b.** Multiple compressed tablets
        - **i.** Layered tablet
        - **ii.** Compression coated tablet
    - **c.** Repeat action tablet
    - **d.** Delayed action and enteric coated tablet
    - **e.** Sugar and chocolate coated tablet
    - **f.** Film coated tablet
    - **g.** Chewable tablet
2. Tablet used in the oral cavity
    - **a.** Buccal tablet
    - **b.** Sublingual tablet
    - **c.** Troches and lozenge
    - **d.** Dental cones
3. Tablet administrated by other routes
    - **a.** Implantable tablet
    - **b.** Vaginal tablet
4. Tablet use to prepare solution
    - **a.** Effervescent tablet
    - **b.** Dispensing tablet
    - **c.** Hypodermic tablet
    - **d.** Tablet triturate

1.2.3. MANUFACTURING PROCESS OF TABLET[8]

1. Dispensing (weighing and measuring)

Dispensing is the first step in any pharmaceutical manufacturing process. Dispensing is one of the most critical steps in pharmaceutical manufacturing; as during this step, the weight of each ingredient in the mixture is determined according to dose. Dispensing may be done by purely manual by hand scooping from primary containers and weighing each ingredient by hand on a weigh scale, manual weighing with material lifting assistance like Vacuum transfer and Bag lifters, manual or assisted transfer with automated weighing on weigh table, manual or assisted filling of loss-in weight dispensing system, automated dispensaries with mechanical devices such as vacuum loading system and screw feed system. Issues like weighing accuracy, dust control laminar air flow booths, glove boxes), during manual handling, lot control of each ingredient, material movement into and out of dispensary should be considered during dispensing.

2. Sizing

The sizing (size reduction, milling, crushing, grinding, pulverization) is an impotent step (unit operation) involved in the tablet manufacturing. In manufacturing of compressed tablet, the mixing or blending of several solid ingredients of pharmaceuticals is easier and more uniform if the ingredients are approximately of same size. This provides a greater uniformity of dose. A fine particle size is essential in case of lubricant mixing with granules for its proper function. Advantages associated with size reduction in tablet manufacture are as follows:

- ✓ It increases surface area, which may enhance an active ingredient's dissolution rate and hence bioavailability.
- ✓ Improved the tablet-to-tablet content uniformity by virtue of the increased number of particles per unit weight.
- ✓ Improved flow properties of raw materials.
- ✓ Improved colour and/or active ingredient dispersion in tablet excipients.
- ✓ Uniformly sized wet granulation to promote uniform drying.

There are also certain disadvantages associated with this unit operation if not controlled properly. They are as follows:

- ✓ A possible change in polymorphic form of the active ingredient, rendering it less or totally inactive, or unstable.
- ✓ A decrease in bulk density of active compound and/or excipients, which may cause flow problem and segregation in the mix.
- ✓ An increase in surface area from size reduction may promote the adsorption of air, which may inhibit wettability of the drug to the extent that it becomes the limiting factor in dissolution rate.

3. Powder blending

The successful mixing of powder is acknowledged to be more difficult unit operation because, unlike the situation with liquid, perfect homogeneity is practically unattainable. In practice, problems also arise because of the inherent cohesiveness and resistance to movement between the individual particles. The process is further complicated in many system, by the presence of substantial segregation influencing the powder mix. They arise because of difference in size, shape, and density of the component particles. The powder/granules blending are involved at stage of pre granulation and/or post granulation stage of tablet manufacturing. Each process of mixing has optimum mixing time and so prolonged mixing may result in an undesired product. So, the optimum mixing time and mixing speed are to be evaluated. Blending step prior to compression is normally achieved in a simple tumble blender. The Blender may be a fixed blender into which the powders are charged, blended and discharged. It is now common to use a bin blender which blends. In special cases of mixing a lubricant, over mixing should be particularly monitered. The various blenders used include “V” blender, Oblicone blender, Container blender, Tumbling blender, Agitated powder blender, etc. But now a day to optimize the manufacturing process particularly in wet granulation the various improved equipments which combines several of processing steps (mixing, granulation and/or drying) are used. They are “Mixer granulator” or “High shear mixing machine”.

4. Granulation

Following particle size reduction and blending, the formulation may be granulated, which provides homogeneity of drug distribution in blend.

5. Drying

Drying is a most important step in the formulation and development of pharmaceutical product. It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties. The commonly used dryer includes Fluidized bed dryer, Vacuum tray dryer, Microwave dryer, Spray dryer, Freeze dryer, Turbo tray dryer, Pan dryer, etc.

6. Tablet compression

After the preparation of granules (in case of wet granulation) or sized slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to get final product. The compression is done either by single punch machine (stamping press) or by multi station machine (rotary press). The tablet press is a high-speed mechanical device. It 'squeezes' the ingredients into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval. Also, it can press the name of the manufacturer or the product into the top of the tablet. Each tablet is made by pressing the granules inside a die, made up of hardened steel. The die is a disc shape with a hole cut through its centre. The powder is compressed in the centre of the die by two hardened steel punches that fit into the top and bottom of the die. The punches and dies are fixed to a turret that spins round.

As it spins, the punches are driven together by two fixed cams - an upper cam and lower cam. The top of the upper punch (the punch head) sits on the upper cam edge .The bottom of the lower punch sits on the lower cam edge. The shapes of the two cams determine the sequence of movements of the two punches. This sequence is repeated over and over because the turret is spinning round. The force exerted on the ingredients in the dies is very carefully controlled. This ensures that each tablet is perfectly formed. Because of the high speeds, they need very sophisticated lubrication systems. The lubricating oil is recycled and filtered to ensure a continuous supply.Various types of machines are used as follows:

1. Single punching machines.
2. Multi punching machines.
3. Rotary tablet machines.
4. High speed rotary tablet machines.
5. Multilayer rotary tablet machines.

Common Stages Occurring During Compression

Stage1: Top punch is withdrawn from the die by the upper cam, Bottom punch is lowered in the die so powder falls in through the hole and fills the die.

Stage2: Bottom punch moves up to adjust the powder weight-it raises and expels some powder

Stage 3: Top punch is driven into the die by upper cam, Bottom punch is raised by lower cam Both punch heads pass between heavy rollers to compress the powder.

Stage 4: Top punch is withdraw by the upper cam, Lower punch is pushed up and expels the tablet. Tablet is removed from the die surface by surface plate.

Stage 5: Returned to stage 1.

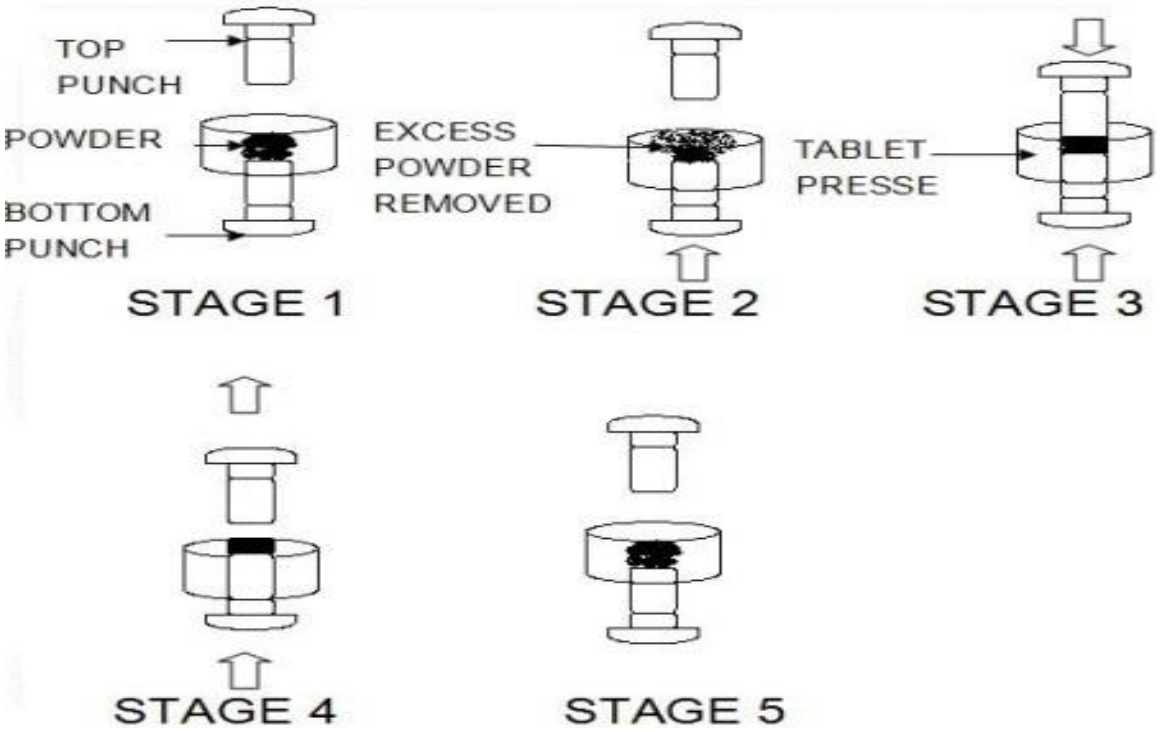


Figure 1: Stages Occurring During Compression

7. Packaging

Pharmaceutical manufacturers have to pack their medicines before they can be sent out for distribution. The type of packaging will depend on the formulation of the medicine. 'Blister packs' are a common form of packaging used for a wide variety of products. They are safe and easy to use and they allow the consumer to see the contents without opening the pack. Many pharmaceutical companies use a standard size of blister pack. This saves the cost of different tools and to change the production machinery between products. Sometimes the pack may be perforated so that individual tablets can be detached. This means that the expiry date and the name of the product have to be printed on each part of the package. The blister pack itself must remain absolutely flat as it travels through the packaging processes, especially when it is inserted into a carton. This poses interesting problems for the designers. Extra ribs are added to the blister pack to improve its stiffness.

1.3.TABLET COATING[9]

Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it. Coating may be applied to a wide range of oral solid dosage form, including tablets, capsules, multi particulates and drug crystals. When coating composition is applied to a batch of tablets in a coating pan, the tablet surfaces become covered with a tacky polymeric film. Before the tablet surface dries, the applied coating changes from a sticky liquid to tacky semisolid, and eventually to a non-sticky dry Surface pans. The entire coating process is conducted in a series of mechanically operated acorn-shaped coating pans of galvanized iron stainless steel or copper. The smaller pans are used for experimental, developmental and pilot plant operations, the larger pans for industrial production.

Basic Principles involved in Tablet Coating[10,11]

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

1. Solution in which influences the release pattern as little as possible and does not markedly change the appearance.

2. Modified release with specific requirement and release mechanism adapted to body function in the digestive tract.
3. Colour coating which provides insulation.
4. To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.

1.3.1. COATING PROCESS DESIGN & CONTROL

In most coating methods, when the tablets are being agitated in a pan, fluid bed, etc. at that time spraying on tablets by coating solution takes place. As the solution is being sprayed, a thin film is formed that adheres directly to each tablet. The coating may either be formed by a single application or may be built up in layers through the use of multiple spraying cycles[7]. Firstly, uncoated tablets are placed in the pan, which is typically tilted at an angle from the horizontal, and then the liquid coating solution is introduced into the pan while the tablets are tumbling.

By passing air over the surface of the tumbling tablets, the liquid portion of the coating solution is then evaporated. In comparison, a fluid bed coater operates by passing air through a bed of tablets at a velocity sufficient to support and separate the tablets as individual units. Once separation takes place, then the tablets are sprayed with the coating composition[12,13,14].

The coating process is usually a batch operating task consisting of the following phases:

- Identification of batch and Recipe selection (film or sugar coating)
- Loading/Dispensing (accurate dosing of all required raw materials)
- Warming
- Spraying (Both application and rolling are carried out simultaneously)
- Drying
- Cooling
- Unloading

Coating Equipment

A modern tablet coating system combines several components

- A coating pan
- A spraying system

- An air handling unit
- A dust collector

Advantages of Tablet Coating[15,16]

1. Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets.
2. Coatings can also facilitate printing on tablets, if required. Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow.

Disadvantages of Tablet Coating

1. Disadvantages of coating such as relatively high cost, long coating time and high bulk have led to the use of other coating materials.
2. This process is tedious and time-consuming and it requires the expertise of highly skilled technician.

1.4. ENTERIC COATING[16-18]

A tablet that has a special outer covering designed to dissolve in the small intestine. Once the enteric-coating is dissolved the tablet disintegrates and the active ingredient can be absorbed by the patient. An enteric coating is a barrier that controls the location of oral medication in the digestive system where it is absorbed. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. The enteric coated polymers remain unionize at low pH, and therefore remain insoluble. But as the pH increases in the GIT, the acidic functional groups are capable of ionization and the polymer swells or becomes soluble in the intestinal fluid. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers.

There are four reasons for putting such a coating on a tablet or capsule ingredient: Protection of active pharmaceutical ingredients, from the acidic environment of the stomach (e.g. enzymes and certain antibiotics).

- To prevent gastric distress or nausea from a drug due to irritation (e.g. sodium salicylate).

- For the delivery of drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed-release component for repeat action.
- Required for minimizing first pass metabolism of drugs.

The choice of the polymer and the thickness of the coated layer are critical to control the pH solubility profile of the enteric coated dosage form.

1.4.1. PROPERTIES OF ENTERIC COATING MATERIAL

1. Resistance and susceptibility
2. Stability and compatibility
3. Low cost and non-toxicity
4. Ease of application without specialized equipment.
5. Ability to be readily printed or to allow film to be applied to debossed tablet.
6. Formation of continuous (uninterrupted) film.

1.4.2. COMPOSITION OF ENTERIC COATED TABLET

The Enteric coated formulation usually contains the following component

a) Polymer.
b) Plasticizer.
c) Solvent.
d) Colourant.

a). Polymers

Polymers are substance containing a large number of structural units joined by the same type of linkage. These substances often form into a chain-like structure starch, cellulose, and rubber all possess, polymeric properties.

With an acid-resistant property, enteric coating polymers generally possess free carboxylic acid groups on the polymer backbone. They are insoluble in acidic media but become deprotonated and dissolved in basic media at pH nearly neutral values (pH>5).

b). Plasticizer

Success of enteric coating efficiency mostly relies on the addition of plasticizers. Plasticizers are a group of auxiliary components that improve elasticity of the polymeric film.

A wide range of plasticizers are available to the formulator such as phthalate esters, phosphate esters, other esters like citrates, stearates, sebacate, oleate, adipate etc. oils, glycerol, glycols etc.

The type of plasticizer should be selected carefully as it influences the film brittleness, compatibility with the coating substrates and product stability. Hydrophilic plasticizer, triethyl citrate, is reported to improve the property of Eudragit L 30 D-55 film in the soft gelatin capsule formulations regardless of the type of filled liquid whereas hydrophobic plasticizer, tributyl citrate, gives satisfactory enteric protection only with hydrophobic filled liquid. The latter plasticizer could migrate to the hydrophobic filled liquid upon storage, resulting in the reduction of the enteric protection.

c). Solvent

Solvents are used to dissolve or disperse the polymers and other additives and convey them to substrate surface.

1. Water.
2. Alcohols.
3. Ketones.
4. Esters.
5. Chlorinated Hydrocarbons.

d). Additives

The properties and composition of other components of the film coating formulation also need to be considered and optimized to get the most desired effects without affecting the quality of the film. Various other components which could be used in coating formulation are:

- **Pigments/Colorant**

The commonly used colorants in coating are water soluble dyes. However, the overall colour effect of these dyes depend on the dye concentration at a particular point, thickness of film at that point and the residual moisture content in the film at that point. As these parameters can differ from tablet to tablet, the colour difference among various tablets within the same batch may become very visible.

- **Opacifier**

The opacity of the film depends on the difference between the refractive index of the polymer and other components of the coating formulation. The lake colours used in enteric coating has refractive index similar to that of various polymers, thus the opacity of lake colours is very poor.eg Titanium Oxide.

- **Anti-tacking agent**

The most commonly used anti- tacking agent is Talc, which if used in higher concentration tends to settle down from the coating suspension, thus affecting the composition of suspension during the coating process.

1.4.3. DEFECTS OCCOUR IN COATED TABLETS [19-22]

Here is a list of common defects associated with coated tablets and some likely causes and the remedies.

1) Picking and sticking

This is when the coating removes a piece of the tablet from the core. Over wetting or excessive film tackiness causes tablets to stick to each other or to the coating pan. On drying, at the point of contact, a piece of the film may remain adhered to the pan or to another tablet, giving a "picked" appearance to the tablet surface and resulting in a small exposed area of the core. It is caused by over-wetting the tablets, by under-drying or by poor tablet quality.

Remedy

A reduction in the liquid application rate or increase in the drying air temperature and air volume usually solves this problem. Excessive tackiness may be an indication of a poor formulation.

2) Twinning

This is the term for two tablets that stick together and it is a common problem with capsule shaped tablets.

Remedy

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.

3) Colour Variation

This problem can be caused by processing conditions or the formulation. Improper mixing, uneven spray pattern and insufficient coating may result in colour variation. The migration of soluble dyes, plasticizers and other additives during drying may give the coating a mottled or spotted appearance.

Remedy

The use of lake dyes eliminates dye migration. A preformulation with different plasticizers and additives is the best way to solve film instabilities caused by the ingredients.

4) Orange Peel

This refers to a coating texture that resembles the surface of an orange. Inadequate spreading of the coating solution before drying causes a bumpy or "orange-peel" effect on the coating. It is usually the result of high atomization pressure in combination with spray rates that are too high. This also indicates that spreading is impeded by too rapid drying or by high solution viscosity.

Remedy

Thinning the solution with additional solvent may correct this problem.

5) Mottling

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.

Remedy

Use smaller sized granules and appropriate binding agent and change the solvent system and decrease the drying temperature.

6) Capping and Lamination

This is when the tablet separates in laminar fashion. Capping is partial or complete separation of top or bottom crowns of tablet main body. Lamination is separation of a tablet into two or more distinct layers. Friability test can be used to reveal these problems.

The problem stems from improper tablet compression, but it may not reveal itself until you start coating.

Remedy

Be careful not to over-dry the tablets in the preheating stage. That can make the tablets brittle and promote capping.

7) Roughness

A rough or gritty surface is a defect often observed when coating is applied by a spray. Some of the droplets may dry too rapidly before reaching the tablet bed, resulting in the deposits on the tablet surface of "spray dried" particles instead of finely divided droplets of coating solution. Surface roughness also increases with pigment concentration and polymer concentration in the coating solution.

Remedy

Moving the nozzle closer to the tablet bed and reducing the degree of atomization can decrease the roughness due to spray drying.

1.4.4. EVALUATION PARAMETERS[23,24]

Tablets when formulated may undergo physical and chemical changes, which may alter their bioavailability. Therefore, the tablets are to be evaluated before dispensing to ensure their stability and bioavailability throughout their shelf life. Evaluation of tablets can be carried out by the following test.

Pre-compression Parameters

- ✓ Loss on drying
- ✓ Bulk density
- ✓ Tapped density
- ✓ Carr's index
- ✓ Hausner's ratio

Evaluation of Tablets

- ✓ Tablet appearance
- ✓ Hardness
- ✓ Thickness
- ✓ Friability

- ✓ Weight variation test
- ✓ Disintegration test
- ✓ Drug content
- ✓ *In-vitro* Dissolution test

1.5. MODIFIED DRUG DELIVERY SYSTEM[26,27,28]

Modified release DDS include systems with pH–dependent, extended, delayed or pulsed drug release. Sustained, extended or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery.

1.5.1. CLASSIFICATION

The USP and NF have defined a modified release dosage forms as one in which the drug release characteristics of time course and location are chosen to accomplish therapeutic objectives not offered by conventional dosage forms.

a. Sustained Release

A sustained-release dosage form is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. These systems try to mimic zero-order release by providing drug in a slow first-order fashion.

b. Controlled Release

The term “Controlled release” has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. These systems deliver drugs in a zero-order fashion.

c. Repeat Action

Alternative method of sustained release in which multiple doses of a drug are contained within a dosage form and each dose is released at a periodic interval.

d. Site-specific and receptor targeting

For receptor release, target is particular receptor for a drug within an organ or tissue.

1.5.2. DELAYED RELEASE SYSTEM

The design of such system involves release of drugs only at a site in the gastrointestinal tract. The drugs contained in such a system are those that are:

a) Destroyed in the stomach or by intestinal enzymes
b) Known to cause gastric distress
c) Absorbed from a specific intestinal site or
d) Meant to exert local effect at a specific gastrointestinal site.

The two types of delayed release systems are:

- **Intestinal release systems**

  A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pH etc.

- **Colonic release systems**

  Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons.

  a) Local action in the treatment of ulcerative colitis
  b) Systemic absorption of protein and peptide drugs

1.5.3. DELAYED RELEASE SOLID ORAL DOSAGE FORMS

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micrometric or macrometric proprerties of materials during manufacture and for providing a desired drug delivery system[29]. The most commonly used pharmaceutical delayed release solid dosage forms today include tablets, capsules, granules, pellets.

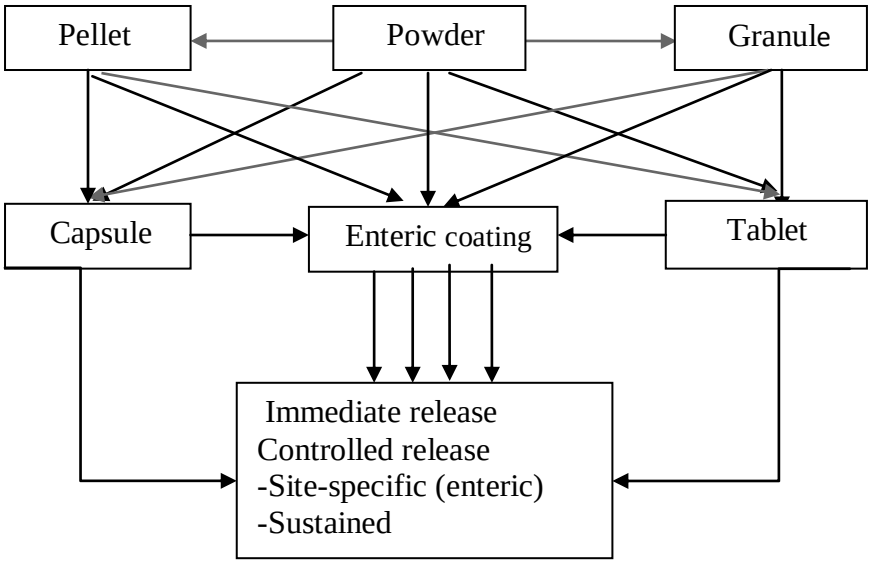


Figure 2: Relationship of Pharmaceutical Delayed Release Solid Dosage Forms

1.5.3.1. CLASSIFICATION OF DELAYED RELEASE SOLID ORAL DOSAGE FORMS

Delayed release solid oral dosage forms are available either as single unit (non divided formulations–tablets,capsules) or as multiple unit (divide formulations-pellets, mini -tablets) forms.

- **Single unit dosage forms**

The single-unit dosage forms usually refer to diffusion controlled systems which include monolithic systems. Where the diffusion of a drug through a matrix is the rate limiting step reservoir or multilayered matrix systems[30]. Where the diffusion of the drug through polymer coating or layer of the system is the rate limiting step. However , generally, release of drugs will occur by a mixture of these two mechanisms.

- **Multi unit dosage forms[31,32]**

Types of multi unit dosage forms comprise,

a. Granules
b. Pellets
c. Microparticles (microspheres or microcapsules) and Nanoparticles.
d. Mini tablets and mini depots (dispersed and distributed throughout the gastro intestinal tract when the capsule or tablet disintegrates).
e. Multi unit tablets (divided at ingestion without loss of the depot effect, as the sub unit act as a self contained depots).

Therapeutic Advantage of Multi units over single units

When taken orally, multi unit dosage forms

- Disperse freely in the gastro intestinal tract.
- Provides less risk of dose dumping.
- Reduces localized concentration of irritative drugs.
- Reduce risk of inter and intra patient variability.
- Improves safety and efficacy of a drug.
- Maximize drug absorption, reduce peak plasma fluctuations, minimize local irritation of the mucosa by certain irritant drugs and minimize potential side effects without appreciably lowering drug bioavailability.

CHAPTER 2

AIM AND PLAN OF WORK

2. AIM AND PLAN OF WORK

2.1. AIM AND OBJECTIVE

The aim of the present investigation was to prepare delayed release i.e., enteric coated tablets of Rabeprazole sodium by using Methacrylic acid copolymer and to optimize coating process parameters by Direct compression method.

Rabepeazole sodium is used in the treatment of acid related gastro duodenal disorders by reducing gastric acid secretion. Proton pump inhibitors are substituted benzimidazoles and all share a similar core structure and mode of action, but differ in substituent groups.

Delayed release dosage form is best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation, or are absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer.

2.2. PLAN OF THE WORK

The present work was carried out to formulate delayed release tablets of Rabeprazole sodium and to evaluate the tablets for various parameters. It was planned to carry out this work as outlined below.

1. To Study the drug and excipient compatibility by FT-IR.

2. To carry out the Pre-compression parameters of the powder blend such as
    - Angle of repose
    - Bulk Density
    - Tapped density
    - Compressibility Index
    - Hausner's ratio

3. To formulate delayed release tablets of Rabeprazole sodium by "Direct Compression Method" using methacrylic acid as as a copolymer.

4. Evaluation of Compressed tablets
    - Hardness
    - Thickness
    - Friability
    - Weight variation
    - Estimation of drug content
    - Disintegration time
    - *In-vitro* release studies

5. Evaluation of Enteric Coated tablets
    - Thickness
    - Weight variation
    - Estimation of drug content
    - Disintegration time (Acid & Alkali Buffer)
    - *In-vitro* release studies using buffers
    - Optimized formulation Vs Marketed sample Comparison

5. To perform stability study for the best formulation at 25^0C ± 2/60% ± 5%RH and 40^0C ± 2/75% ± 5%RH for 3 months.

CHAPTER 3
LITERATURE REVIEW

2. LITERATURE REVIEW

G Sridhar Babu *et al.*,[33] formulated and evaluated the delayed release tablets of Rabeprazole sodium, an anti ulcer drug like peptic ulcer and duodenal ulcer. Rabeprazole was class-I Proton pump inhibitor to gain FDA approval. Rabeprazole sodium Delayed release tablets were prepared by Direct Compression method using different excipients as well as with varying concentration of polymer proportions using HPMC Phthalate 55 (HPMCP 55) as enteric coating material. All the excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. During compression tablet appearance, average weight, hardness, thickness, friability, disintegration time was evaluated and enteric coated tablets were evaluated for Hardness, thickness and *In-vitro* drug release studies. From the results F8 fulfilled all the specifications of the physical properties and *in-vitro* release and is comparable to the innovator product.

Anroop B Nair *et al.*,[34] formulated and evaluated the enteric coated tablets for Esomeprazole magnesium trihydrate. Different core tablets were prepared and formulation (F-1) was selected for further enteric coating, based on the disintegration time. Seal coating was applied to achieve 3% weight gain using opadry. Enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and Acryl-EZE to achieve 5% weight gain. Disintegration studies showed that the formulations failed in 0.1 N HCl media. Hence the quantity of enteric coating was increased to 8% w/w. *In vitro* analysis of the developed tablets was carried out. Results from disintegration time and dissolution rate studies indicate that all the Esomeprazole enteric tablets prepared possess good integrity, desirable for enteric coated tablets. Among the polymers studied, the methacrylic polymers exhibited better dissolution rate than the cellulose polymers. Stability studies indicate that the prepared formulations were stable for a period of three months. This study concluded that enteric coated tablets of esomeprazole can be prepared using any of the enteric coating polymer studied using a minimal weight gain of 8%.

Sourav Tribedi *et al.*,[35] formulated and evaluated of enteric coated tablets of Pantoprazole Pantoprazole is a proton pump inhibitor, belongs to group of benzimidazole, Pantoprazole sodium were prepared by direct compression method using different concentration of, microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, crosscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. Direct compression is economic compare to wet granulation since it requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, Eudragit L100 and by dip coating method. The *in vitro* release was studied using acidic buffer pH 1.2 and phosphate buffer pH 6.8. Prepared all batch's C2F9 was found best, with hardness 6.3 ± 0.14 (Kg/cm2**)**, drug content 98.54 ± 0.12(%), disintegration time 6.02± 0.21(min), and percentage cumulative drug released which started after 120 min and reached 99.72 after 180 min. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40 °C / 75% RH for a period of 3 month.

Farha Amna Shaik *et al.*,[36] formulated and evaluated Rabeprazole delayed release enteric tablets comparable to the innovator product. Five formulations of enteric coated tablets of Rabeprazole were developed by preparing core tablets using mannitol as diluents and Crospovidone as super disintegrant in different proportions and varying the compositions of sub coating and enteric coating using opadry white and enteric yellow .The core tablets were prepared by direct compression method. In the preformulation studies the micromeritic flow properties of the API were assessed by determining angle of repose, compressibility index, Hausner ratio. The results indicated good free flow of Rabeprazole. As such formulation F5 developed is considered as an efficient delayed release formulations of Rabeprazole comparable to the innovator product. Thus the study fulfilled the objective of developing efficient Rabeprazole delayed release tablets.

Rabia Bushra *et al.*,[37] formulated the enteric coated tablet of Ibuprofen (200 mg) using an aqueous dispersion system Ibuprofen is a propionic acid derivative that belongs to the class NSAIDs. Major adverse reactions associated with Ibuprofen are related to GIT and include peptic and mucosal ulcers, dyspepsia, severe gastric pain and bleeding, that results in excessive treatment failure. The goal of this study was to develop 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. Enteric coated formulation was subjected to disintegration and dissolution tests by placing in 0.1 M hydrochloric acid for 2 h and then 1 h in phosphate buffer with a pH of 6.8. About 0.04% of drug was released in the acidic phase and 99.05% in the basic medium. These results reflect that Ibuprofen can be successfully enteric coated in order to prevent its release in the stomach and facilitate rapid release of the drug in the duodenum, due to the presence of superdisintegrant. Formulated this enteric coated tablets could increase patient compliance by decreasing adverse drug reactions (ADR_S) associated with Ibuprofen therapy.

Mohammed Sarfaraz *et al.*,[38] developed immediate-release enteric-coated time release tablets of Salbutamol sulphate for the treatment of nocturnal asthma. Nocturnal asthma is an asthma phenotype marked by nighttime increases in airway inflammation, airway hyper responsiveness, and expiratory airflow limitation. The occurrence of nocturnal asthma is associated with increased morbidity and inadequate asthma control, and has an important negative impact on quality of life. Formulation of enteric-coated time release tablets with suitable lag time could address the problems associated with asthma. To achieve this goal, immediate release tablets were prepared by direct compression method using superdisintegrants that contribute to the faster disintegration of tablet and thereby improved solubility of the drug. Different disintegrants like cross caramellose sodium, crospovidone and sodium starch glycolate in different concentrations (2.5% to 7.5%w/w) were tried in order to further improve disintegration time. The formulation, which showed best disintegration and dissolution profile, was coated with ethyl cellulose as inner layer and Eudragit S100 as outer enteric-coating polymer which does not dissolve at gastric pH

but dissolve at intestinal pH, releasing the drug immediately in the alkaline medium. The optimized enteric-coated formulation E6 containing 2.5%w/w of Eudragit S 100 and 30%w/w of ethyl cellulose as coating system inhibited the release of the drug in 0.1 N HCl, and whereas 99.04% of drug was released in the intestinal medium. Thus, dissolution profiles indicated that E6 tablet may be better alternative in the treatment of nocturnal asthma which overcomes the problems of conventional forms.

N. Damodharan *et al.*,[39] developed the small intestine targeting tablets of Doxycycline hydrochloride by wet granulation method and enteric coating of tablets (conventional standard coating technique).This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers .Polymers like Eudragit and HPMC Phthalate are selected where dissolution is above pH 6 and pH 6.4 respectively. Preformulation studies like angle of repose, bulk density, tapped density, porosity, Carr's index, Hausner's ratio were performed. Six batches (F1 to F6) were formulated and evaluated for hardness, friability, weight variation, drug content, disintegration and in-vitro dissolution. Among the six batches, batch F4 was showing 94% drug release and was considered to be best formulation.

M. Kishore *et al.*,[40] formulated and evaluated the fabricated olsalazine sodium enteric coated tablets in ulcerative colitis and also compare the In-vitro dissolution profile of optimized Olsalazine sodium enteric coated tablets in the presence of β- glycosidase at targeted colonic region.The present study was fabricated to observe the drug release of Olsalazine sodium enteric coated tablets at targeted site specific colon region. These tablets were formulated from F1-F8 by selecting time dependent and release retard biodegrable polymers such as ethyl cellulose-chitosan composite by combining with different concentrations by wet granulation. This composite was included in this study to control the solubility of premature drug release in gastrointestinal fluid and in this regard, the above formulation F6 was optimized and coated with Eudragit-S 100 as enteric polymer as to retard the drug release at specified site colon by changing suitable concentration as like 1, 3, 5, and7 %. From which F6 containing 5% Eudragit-S 100 was shown only 75.6 % drug release in 24 hrs and also it was compared with dissolution medium containing β-glycosidase. In which enzymatic condition the above formulation enhanced the drug release i.e, 98.3% was founded in 24 hrs.

Muthuirulappan Thirumaran *et al.*,[41] formulated the Paroxetine controlled release enteric coated tablet and its *in-vitro* release kinetics and stability studies. Paroxetine core tablets were prepared by wet granulation process using HPMC K4M and K100M as matrix forming hydrophilic polymers. Instacoat En II (10%) in Isopropyl alcohol (90%) was used as an enteric coating solution. *In vitro* dissolution study was performed for all the formulations by using Tris buffer as dissolution medium. Different dissolution models were applied to evaluate release mechanisms and its kinetics. The result suggests that F11 formulation showed uniform (zero order) release of drug from the matrix tablet with good correlation value for 12 hours. The effect of paddle RPM in kinetic study was also done for F11 formulation. The stability studies were conducted for F11 at $40^{o}C \pm 2^{o}C$ / 75% RH ± 5% for a period of 3 months. No significant differences were observed in the release profile of different batches of each enteric coated paroxetine CR tablet. The similarity and dissimilarity factors for F11 were 0.68 and 95.62 respectively. The best fit with higher correlation was found in the linear regression graph with the Hixon-crowel cube root law for selected formulation F11 and innovator brand. The present study concluded that the formulation F11 was stable and exhibited appreciable controlled release of an enteric coated paroxetine matrix tablet for reproducible and commercial manufacturing.

B.Rama *et al.*,[42] developed pharmaceutically equivalent and stable enteric-coated tablets of Rabeprazole sodium comparable to innovator product. Different Formulations of Rabeprazole core tablets were developed using mannitol as diluent and croscarmellose as super disintegrant in different proportions. Further optimized formulation was coated with varying the compositions of sub coating and enteric coating using opadry white and enteric yellow. Compatibility studies were performed for drug, physical mixture tablet which shows no interaction. From the dissolution the formulation F6 shows highest percentage of drug release. The kinetics of drug release for F6 & Innovator followed first order and 'n' value ($0.5>n<1$) shows that the mechanism may be erosion control rate release. The f1 and f2 were found to be 3.03 and 72.01 respectively for formulation F6 and innovator product. Hence these two products were considered similar and comparable. In the accelerated stability testing carried out at 40°c and 75% RH for three months, no significant change in the physical properties, drug content, and dissolution rate of formulation F6 was observed. From this it can be concluded that formulation

F6 developed is found to be an efficient delayed release formulations of Rabeprazole comparable to the innovator product.

B.Shibu *et al.,*[43] formulated and evaluated the enteric coated Serratiopeptidase tablets by wet granulation method. Serratiopeptidase is derived from bacteria belonging to genus Serratia. Serratiopeptidase tablets used in the treatment of viral diseases and hepatitis. Serratiopeptidase were formulated using HPMC phthalate as enteric coating polymer in different concentrations to optimize delayed drug release profile and to target the drug release in the small intestine regions. The present work was made to develop enteric coated tablets containing Serratiopeptidase tablets were made by direct compression method. The tablets were evaluated for physical characterization, in vitro release study and stability studies. Results of in vitro release profile indicated that formulation F1 was the most promising formulation as the extent of drug release from this formulation was optimum and match with the In-house Specification when compared to other formulations.

Sanjay R. *et al.,*[44] developed and evaluated the enteric coated tablets of Rabeprazole sodium by using Methacrylic acidcopolymer (Colorcoat EC4S) and to optimize coating process parameters which implicate more significant effects on tablet coating process. The different batches of uncoated tablets were prepared by both wet granulation and direct compression method. Batch B6 of uncoated tablets prepared by direct compression method shown good results of evaluation parameters compared to other batches. Results of the preliminary trials indicated that process parameters individually affected the quality of coated tablets. At this point of time it was seen that spray rate, inlet air temperature and hence to study the combined effect of this factors on the coating process, full factorial design was applied. Comparative study of dissolution profile of final batch with market preparations was conducted and it was concluded that final formulation F shown good similarity with market products. The results of the accelerated stability of final formulation F for 3months revealed that storage conditions were not found any significant changes in final formulation F. The photo instability of the Rabeprazole sodium showed by the photo stabilty studies indicated that special care to avoid exposure of the drug to the light effects must be taken during the manufacture and storage of the pharmaceutical preparations.

Rupesh S. Kamble. ***et al.,***[45] formulated and evaluated Enteric Coated Dosage Form using Ketorolac Tromethamine. Reduction of side effects while prolonging its action by using controlledrelease of oral dosage forms is highly desirable. In the present study direct compression method is used for the preparation of fabricated batches and EudragitL100 is used as coating polymer for enteric coating. In vitro release profiles of batches F1-F4 shows that Ketorolac Tromethamine drug:polymer ratio with Guar gum, Xanthan Gum, Ethyl cellulose and Sodium alginate give 79.32%, 91.52%, 88.35%and 92.19% drug release respectively in 12 hours. In vitro release profile of batches F5-F8 shows f 85.21%, 95.52%, 93.50%, 97.24% respectively in 12 hours. In vitro release profile ofbatches F9-F12 shows that Ketorolac Tromethamine in ratio 1:3 with Guar gum, Xanthan Gum, Ethylcellulose and Sodium alginate gives release of 89.50%, 98.25%, 95.22%, 100.27% respectively in 12hours. 2 and then showed higher increase in phosphate buffer of pH 6.0 up to 12 hours. All these batches follow near zero order kinetic. This indicates that the Guar Gum, Xanthan Gum and Ethyl cellulose and Sodium alginate at minimum concentration is not only able to sustain but also control the drug release.

Subramaniam Kannan *et al.,*[46] formulated and evaluated the enteric coated aspirin tablets.The delayed release tablet is intended to release the drug after some delay or after tablet pass GI tract. The enteric coating is common example of this tablet. All enteric coated tablets are delayed release tablet but all delayed release tablet are not enteric coated tablets.1 Aspirin delayed release tablet is used to increase bioavailability and to reduce risk of hospitalization for heart failure, coronary thrombosis deliver drug at a near constant rate for 24hr. The 2 and 10 keeping these factors in view it is aimed to formulate, evaluate and stabilize Aspirin (75mg) DR tablet to provide a controlled and predictable release of Aspirin and which is used in the treatment of Coronary Thrombosis (heart disease) for once in day administration. The half life of Antiplatelet agent is 6 Hours which makes it suitable candidate for delayed release formulation. The present work aims to avoid degradation of drug in acidic environment of stomach. So due to enteric coating drug releases in to the small intestine so that drug gets larger surface area for absorption. Micro crystalline cellulose, maize starch, cross carmilose sodium is a disintegrent used to prepare a blend for direct compaction method. Aspirin anti-platelet compounds which suppress or inhibit the cyclooxygenase enzyme which is responsible for the formation of thromboxane A2 thus block the formation of thromboxane A2. Thromboxane A2 is a activator

of platelet aggregation. Hence our present study was performed on these formulations as aspirin delayed release tablet.

Sumit Chakraborty, *et al.*,[47] formulated and evaluated the pantoprazole sodium enteric coated tablets .This compound inhibits gastric acid formation and thereby it is very efficient for the treatment of gastric and duodenum ulcers. In aqueous media more acidic than pH 4 it suffers a practically complete decomposition within a period shorter than 10 minutes. Even in solid state it is sensitive to heat,light and especially to substances containing an acidic group. Pantoprazole which is an acid labile drug it degrade on the stomach pH can be coated with a substance that will only dissolve in the small intestine. For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action.

CHAPTER 4

MATERIALS AND METHODS

LIST OF MATERIALS

4.1 LIST OF CHEMICALS

Table 1: LIST OF CHEMICALS AND THEIR MANUFACTURERS.

S.No	Materials	Manufacturers
1	Rabeprazole sodium	Metrochem API Pvt. Ltd., Hyderabad ,India
2	Mannitol anhydrous	Qingdao Bright Moon Seawood Group Co.Ltd., China
3	Copovidone	Boai NKY Pharmaceutials Ltd., China
4	Crospovidone	Boai NKY Pharmaceutials Ltd., China
5	Light magnesium oxide	Par drugs & chemicals pvt. ltd,vadodara,india
6	Methyl paraben	Rasula pharmaceuticals and fine chemicals, Hydrabad,India
7	Propyl paraben	Rasula pharmaceuticals and fine chemicals, Hydrabad,India
8	Magnesium stearate	Par drugs & chemicals pvt. ltd,vadodara,india
9	Instacoat moist shield white	Ideal Cures Pvt. Ltd., Mumbai, India
10	Protectab Enteric M1	Bharat Coats, Chinna Salam, Kanchipuram , India
11	Insta coat glow	Ideal Cures Pvt. Ltd., Mumbai, India
12	Lake of ironoxide yellow	koel colours pvt ltd. mumbai , india
13	Lake of Ironoxide red	Koel colours pvt ltd. mumbai , india
14	Isopropyl alcohol	Deepak Fertilisers And Petrochemicals Corporation Limited Pune,India
15	Methylene dichloride	Chemplast Sanmar Plant II, Mettur Dam, Salem,Tamil Nadu,India.

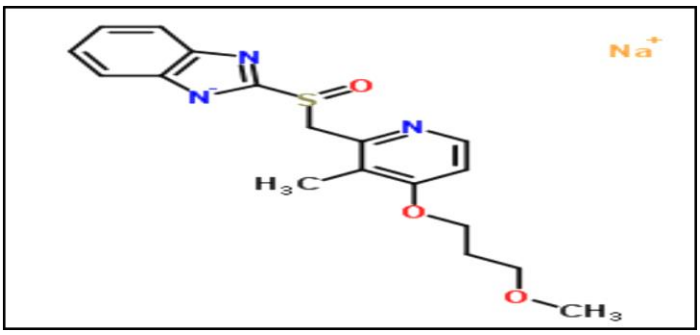
DRUG PROFILE

4.2. DRUG PROFILE

4.1.1. RABEPRAZOLE SODIUM[47-49]

Rabeprazole sodium : Rabeprazole sodium is an antiulcer drug in the class of proton pump inhibitors. It is a prodrug - in the acid environment of the parietal cells it turns into active sulphenamide form. Rabeprazole inhibits the H+, K+ATPase of the coating gastric cells and dose-dependent oppresses basal and stimulated gastric acid secretion.

Chemical structure :



IUPAC Name : 2-({[4-(3-Methoxypropoxy)-3-methyl-2 pyridyl] methyl} sulfinyl) -1*H*-benzimidazole sodium**.**

Molecular formula : $C_{18}H_{20}N_3NaO_3S$.

Molecular weight : 381.42.

Description : A White or almost white powder.

Melting point : 170-173 °C.

Solubility	:	Soluble in water.
Half life	:	1-2 hours (in plasma).
Absorption	:	Absolute bioavailability is approximately 52%.
Volume of distribution	:	160 litre.
Protein binding	:	96.3% (bound to human plasma proteins).
Pharmacodynamics	:	Rabeprazole prevents the production of acid in the stomach. It reduces symptoms and prevents injury to the esophagus or stomach in patients with gastroesophageal reflux disease (GERD) or ulcers. Rabeprazole is also useful in conditions that produce too much stomach acid such as Zollinger-Ellison syndrome. Rabeprazole may also be used with antibiotics to get rid of bacteria that are associated with some ulcers. Rabeprazole is a selective and irreversible proton pump inhibitor, suppresses gastric acid secretion by specific inhibition of the H^+, K^+ - ATPase, which is found at the secretory surface of parietal cells. In doing so, it inhibits the final transport of hydrogen ions (via exchange with potassium ions) into the gastric lumen.
Mechanism of action	:	Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H^+/K^+ATPase (hydrogen-potassium adenosine

triphosphatase) at the secretory surface of the gastric

parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied in vitro, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds.

Metabolism : Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. In vitro studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole). The thioether metabolite is formed by reduction of rabeprazole.

Route of elimination : Approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites.

Adverse reactions : In general, rabeprazole treatment has been well-tolerated in both short-term and long-term trials. The adverse events rates were generally similar between the 10 and 20 mg doses.

Dosage and administration : Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD):

The recommended adult oral dose is one 20 mg delayed-release tablet to be taken once daily for four to eight weeks. For those patients who have not healed after 8 weeks of treatment.

Healing of Duodenal Ulcers:

The recommended adult oral dose is one 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

Stability and storage : Prevent from oxidising agents. Store in a cool, dry place. Store in a tightly closed container. Store at $2\text{-}8^0$ C.

EXCIPIENTS PROFILE

4.3. EXCIPIENTS PROFILE

4.2.1. METHACRYLIC ACID COPOLYMER[50,51]

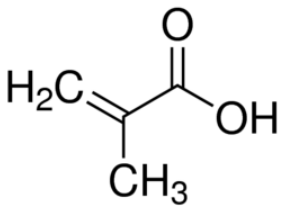
Nonproprietary Names : BP: Methacrylic acid-ethyl acrylate copolymer (1:1). PhEur: Acidum Methacrylicum et ethylis acrylas, Polymerisatum 1:1, Acidum methacrylicum ethylis arcylas polymersatum 1:1 dispersio 30 per centum. USPNF: Ammonio methacrylate copolymer, methacrylic acid copolymer, methacrylic acid copolymer dispersion.

Synonyms : Acryl-EZE, Acryl-EZE MP, Eastacryl 30D, protetab entric $m_{1;}$ bharth coat, polymeric methacrylic acid.

Chemical Name : Poly (methacrylic acid, ethyl acetate)1:1.

Molecular Weight : About 2,50,000.

Structural Formula



Description : Synthetic cationic and anionc polymers of dimethyl amino ethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratio.

Acid Value : 300-330.

Density (Bulk) : 0.390 g/cm^3.

Density (Tapped) : 0.424 g/cm^3.

Density (True) : 1.062-1.072 g/cm^3.

Solubility : Miscible in acetone and alcohols, 1N HCL , Petrolium ether.

Viscosity (Dynamic) : Dispersions are sensitive to extreme temperature and phase separation occurs below 0^oc. Dispersions should therefore be stored at temperature between 5 to 25^oc and are stable for at least 18 months after shipping from the manufactures warehouse if stored in a tightly closed container.

Applications : Poly methacrylates are primarily used in oral capsule and tablet formulations at film –coating agents.

Incompatibilities : Depends upon ionic and physical properties of the polymer and solvent.

4.2.2. METHYLENE DI CHLORIDE[52,53]

Chemical Name	:	Dichloromethane.
Synonyms	:	F30, r30, R30, HCC30, CH2Cl2, Freon30, Nevolin, Driverit.
Molecular Formula	:	CH_2C_{l2}.
Molecular weight	:	84.93.
Chemical structure	:	
Melting point	:	-97 °C.
Boiling point	:	39.8-40 °C mm Hg (lit.)
Vapour density	:	2.9
Solubility	:	Miscible in ethyl acetate, alcohol, hexanes, methanol, diethyl ether, n-octanol, acetone.
Description	:	Colorless, transparent, volatile liquid with pungent smell similar to ether. Soluble in water of about 50 times the volume, soluble in phenol, aldehyde, ketone, acetic acid, triethyl phosphate, ethyl acetoacetate, cyclohexylamine. Miscibile with other chlorinated hydrocarbon, solvent ethanol
Category	:	Pesticide.

Toxicity : Its oral toxicity is moderate.

Uses : The most important use of dichloromethane is solvent. It is largely used in the manufacture of safe film, polycarbonate, the rest used as paint solvents, metal degreasing agent, gas aerosol spray, polyurethane foam, mold release agent, paint remover. It is also used as the reaction medium in the pharmaceutical industry for the preparation of ampicillin, ampicillin and cephalosporin. Dichloromethane is inert because of the stereoscopic electron effect, and usually does not participate in the chemical reaction. But under certain conditions it can also participate in the reaction. Explosion accident occurred in industry because of the generation of diazomethane methane when residual dichloromethane and sodium azide reacted in N, N-dimethyl formamide. Dichloromethane is mainly used in film production and medicine in China. Film production accounts for 50% of the total consumption, medicine accounts for 20%, the cleaning agent and chemical industry accounts for 20%, and others accounts for 10%.

4.2.3. COPOVIDONE[52,53]

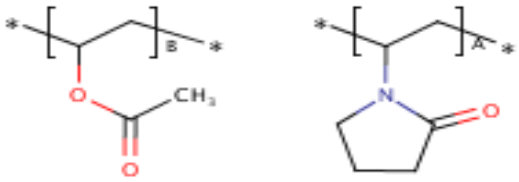
Nonproprietary Names : BP: Copovidone.
PhEur: Copovidone.
USP-NF: Copovidone.

Synonyms : Acetic acid vinyl ester, polymer with 1-vinyl-2-pyrrolidinone; copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 3 : 2 by mass; copolyvidone; copovidonum; Kollidon VA 64; Luviskol VA; Plasdone S-630; poly(1-vinylpyrrolidone-co-vinyl acetate); polyvinylpyrrolidone-vinyl acetate copolymer; PVP/VA; PVP/VA copolymer.

Chemical Name : Acetic acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone [25086-89-9]

Embrical Formula and Molecular Weight : $(C_6H_9NO)n . (C_4H_6O_2)m$ (111.1)n. (86.1)m

Structural Formula :



Functional Category : Film-forming agent; granulation aid; tablet binder.

Description : Copovidone is a white to yellowish-white amorphous powder. It is typically spray-dried with a relatively fine particle size. It has a slight odor and a faint taste.

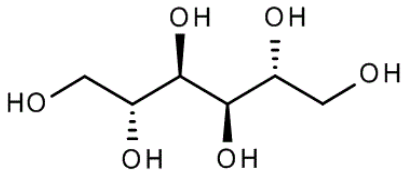
Applications : Copovidone is used as a tablet binder, a film-former, and as part of the matrix material used in controlled-release formulations. In tableting, copovidone can be used as a binder for direct compression(1–3) and as a binder in wet granulation.(4,5) Copovidone is often added to coating solutions as a film-forming agent. It provides good adhesion, elasticity, and hardness, and can be used as a moisture barrier.

4.2.4. MAGNESIUM OXIDE[52,53]

Nonproprietary Names	**:**	BP: Heavy Magnesium Oxide. Light Magnesium Oxide. JP: Magnesium Oxide. PhEur: Magnesium Oxide, Heavy Magnesium Oxide, Light. USP: Magnesium Oxide.
Synonyms	**:**	Calcined magnesia; calcinated magnesite; Descote; E530; Magcal; Magchem 100; Maglite; magnesia; magnesia monoxide; magnesia usta; magnesii oxidum leve; magnesii oxidum ponderosum; Magnyox; Marmag; Oxymag; periclase.
Chemical Name	**:**	Magnesium oxide.
Empirical Formula	**:**	MgO.
Molecular Weight	**:**	40.30
Structural Formula	**:**	MgO.
Functional Category	**:**	Anticaking agent; emulsifying agent; glidant; tablet and capsule diluent.

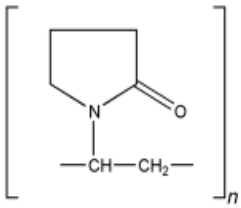
Description	**:**	Fine, white, odorless amorphous powder.
Applications	**:**	Magnesium oxide is used as an alkaline diluent in solid-dosage forms to modify the pH of tablets. It can be added to solid-dosage forms to bind excess water and keep the granulation dry. In combination with silica, magnesium oxide can be used as an auxiliary glidant. It is also used as a food additive and as an antacid, either alone or in conjunction with aluminum hydroxide. Magnesium oxide is additionally used as an osmotic laxative and a magnesium supplement to treat deficiency states.

4.2.5. MANNITOL ANHYDROUS[52,53]

Non-Proprietary Names	**:**	BP: Mannitol. JP: D-Mannitol. PhEur: Mannitol. USP: Mannitol.
Synonyms	**:**	Cordycepic acid, Emprove, Manna sugar, D-mannite, Mannite, Mannitolum; Mannogem, Pearlitol.
Chemical Name	**:**	D-Mannitol.
Empirical Formula	**:**	$C_6H_{14}O_6$.
Molecular Structure	**:**	
Molecular Weight	**:**	182.17g/mol.
Melting Point	**:**	166-168°C.
Solubility	**:**	Soluble in alkalis and practically insoluble in ether.
Description	**:**	Mannitol occurs as a white, odorless, crystalline powder or free-flowing granules.

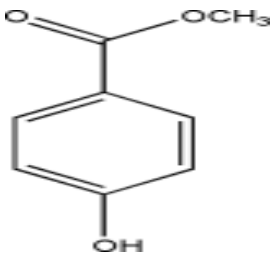
Functional Category	**:**	Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent and tonicity agent.
Applications	**:**	Mannitol is widely used in Pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available or in wet granulations.
Stability And Storage Conditions	**:**	Mannitol is stable in the dry state and in aqueous solutions. The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	**:**	Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

4.2.6. CROSPOVIDONE[52,53]

Non-Proprietary Names	**:**	BP: Crospovidone. PhEur: Crospovidonum. USPNF: Crospovidone.
Synonyms	**:**	Crosslinkedpovidone, Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyvinylpolypyrrolidone.
Chemical Name	**:**	1-Ethenyl-2-pyrrolidinone homopolymer.
Empirical Formula	**:**	$(C_6H_9NO)_n$.
Molecular Structure	**:**	
Molecular Weight	**:**	2.5 g/mol.
Melting Point	**:**	150^0C.
Solubility	**:**	Practically insoluble in water and most common organic solvents.
Description	**:**	Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

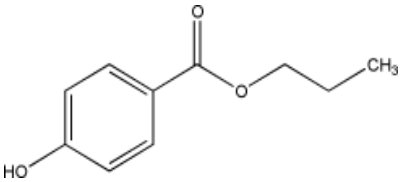
Functional Category	**:**	Tablet disintegrant.
Applications	**:**	Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Crospovidone can also be used as a solubility enhancer.
Stability And Storage Conditions	**:**	Crospovidone is hygroscopic; it should be stored in an airtight container in a cool, dry place.
Incompatibilities	**:**	Crospovidone is compatible with most organic and inorganic Pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

4.2.7. METHYL PARABEN[52,53]

Non-Proprietary Names	**:**	BP: Methyl hydroxybenzoate. JP: Methyl parahydroxybenzoate. PhEur: Methylisparahydroxybenzoas. USPNF: Methylparaben.
Synonyms	**:**	4-hydroxybenzoic acid methyl ester, methyl p-hydroxybenzoate, Nipagin M.
Chemical Name	**:**	Methyl-4-hydroxy benzoate.
Empirical Formula	**:**	$C_8H_8O_3$.
Molecular Structure	**:**	
Molecular Weight	**:**	152.15 g/mol.
Melting Point	**:**	125–128^0 C.
Solubility	**:**	Soluble in water when heated.
Description	**:**	Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

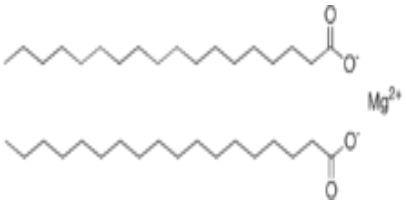
Functional Category	**:**	Antimicrobial preservative.
Applications	**:**	Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products and Pharmaceutical formulations.
Stability And Storage Conditions	**:**	Aqueous solutions of methyl paraben at pH 3–6 may be sterilized by autoclaving at 120^0 C for 20 minutes, without decomposition. Methylparaben should be stored in a well-closed container in a cool, dry place.
Incompatibilities	**:**	The antimicrobial activity of methylparaben and other parabens is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization. Methylparaben is discolored in the presence of iron and is subject to hydrolysis by weak alkalis and strong acids.

4.2.8. PROPYL PARABEN[52,53]

Non-Proprietary Names	**:**	BP: Propyl hydroxybenzoate. JP: Propyl parahydroxybenzoate. PhEur: Propylisparahydroxybenzoas. USPNF: Propylparaben.
Synonyms	**:**	4-hydroxybenzoic acid propyl ester, Nipasol M, Propyl p-hydroxybenzoate; Propyl parasept, Solbrol P.
Chemical Name	**:**	Propyl 4-hydroxybenzoate.
Empirical Formula	**:**	$C_{10}H_{12}O_3$.
Molecular Structure	**:**	
Molecular Weight	**:**	180.20 g/mol.
Melting Point	**:**	96-99^{o}C.
Solubility	**:**	Soluble in water when heated.
Description	**:**	Propylparaben occurs as a white, crystalline, odorless and tasteless powder.
Functional Category	**:**	Antimicrobial preservative.

Applications	**:**	Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products.
Stability And Storage Conditions	**:**	Propylparaben is stable under normal conditions. It decomposes on heating. Stored in a tightly closed container.
Incompatibilities	**:**	The activity of propylparaben can be adversely affected by the presence of other excipients or active ingredients, such as atropine, essential oils, iron, magnesium trisilicate, talc, polysorbate and other nonionic surfactants, sorbitol, weak alkalis and strong acids.

4.2.9. MAGNESIUM STEARATE[52,53]

Non-Proprietary Names	**:**	BP: Magnesium stearate. JP: Magnesium stearate. PhEur: Magnesiistearas. USPNF: Magnesium stearate.
Synonyms	**:**	Magnesium octadecanoate, Octadecanoic acid, Magnesium salt, Stearic acid and Magnesium salt.
Chemical Name	**:**	Octadecanoic acid magnesium salt.
Empirical Formula	**:**	$C_{36}H_{70}MgO_4$.
Molecular Structure	**:**	
Molecular Weight	**:**	591.34 g/mol.
Melting Point	**:**	117-150^{0}C.
Solubility	**:**	Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol.
Description	**:**	Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

Functional Category	**:**	Tablet and capsule lubricant.
Applications	**:**	Magnesium stearate is widely used in cosmetics, foods and Pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at a concentration between 0.25% and 5.0% w/w. It is also used in barrier creams.
Stability And Storage Conditions	**:**	Magnesium stearate is stored in a well closed container in a cool dry place.
Incompatibilities	**:**	It incompatible with strong acids, alkalis and iron salts. It cannot be used be used in products containing aspirin, vitamins and alkalodial salts.

4.2.10. LAKE IRON OXIDE RED[52,53]

Nonproprietary Names	**:**	None adopted.
Synonyms	**:**	Iron oxide yellow monohydrate: E172; hydrated ferric oxide; iron (III) oxide monohydrate, yellow; pigment yellow 42; yellow ferric oxide. Iron (III) oxide hydrated: Bayferrox 920Z; CI 77492; ferric hydroxide; ferric hydroxide oxide; ferric hydrate; ferric oxide hydrated; Ferroxide 510P; iron hydrate; iron hydroxide; iron hydroxide oxide; Mapico Yellow EC; Sicovit Y10; yellow ochre; yellow iron oxide.
Chemical Name And CAS Registry Number	**:**	Iron oxide red [51274-00-1] (monohydrate); [20344- 49-4] (hydrate)
Empirical Formula And Molecular Weight	**:**	Fe_2O_3H2O - 88.85
Structural Formula	**:**	Iron oxides are defined as inorganic compounds consisting of any one of or combinations of synthetically prepared iron oxides, including the hydrated forms.
Functional Category	**:**	Colorant.
Description	**:**	Iron oxides occur as yellow, red, black, or brown

		powder. The color depends on the particle size and shape, and crystal structure.
Solubility	**:**	Soluble in mineral acids; insoluble in water.
Applications	**:**	Applications in Pharmaceutical Formulation or Technology Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs. However, iron oxides also have restrictions in some countries on the quantities that may be consumed, and technically their use is restricted because of their limited color range and their abrasiveness.
Stability And Storage Conditions	**:**	Iron oxides should be stored in well-closed containers in a cool, dry place.
Incompatibilities	**:**	Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules, and will limit the amount that can be incorporated into the gelatin material.

4.2.11. ISOPROPYL ALCOHOL[52,53]

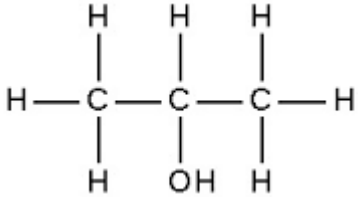
Nonproprietary Names : BP: Isopropyl Alcohol
JP: Isopropanol
PhEur: Isopropyl Alcohol
USP: Isopropyl Alcohol

Synonyms : Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol; rubbing alcohol. 3 Chemical Name and CAS Registry Number Propan-2-ol [67-63-0]

Empirical Formula : C_3H_8O.

Molecular Weight : 60.1.

Structural Formula :



Functional Category : Disinfectant, solvent.

Description : Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

Solubility	**:**	Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt.
Stability and Storage Conditions	**:**	Isopropyl alcohol should be stored in an airtight container in a cool, dry place.
Incompatibilities	**:**	Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

LIST OF EQUIPMENTS/ INSTRUMENTS

4.4 LIST OF EQUIPMENTS

Table 2: LIST OF EQUIPMENTS AND THEIR MANUFACTURERS.

S.No	Instruments	Manufacturers
1	Single pan electronic balance	Sartorious,Germany
2	12 Station D/B Tooling compression Machine	Fluid pack, Ahmedabad,India
3	R&D Mini coater	Ideal cure pvt ltd ,Mumbai, India
4	Vernier calipers	Mitutoyo, Japan
5	Dissolution Test Apparatus	Electro Lab, Mumbai, India
6	Hardness Tester	Monsanto,Mumbai,India
7	Friability Test Apparatus	Electro Lab, Mumbai, India
8	Sieves	Jayant Scientific Ind, Mumbai,India
9	Disintegration Test Apparatus	Electro Lab, Mumbai, India
10	FTIR	Shimadzu, Japan
11	HPLC	Waters, USA
12	Stability Chamber	Labtop, Mumbai, India
13	Blister Packing Machine	Elmach packages pvt ltd, Mumbai, India

METHODOLOGY

4.5. METHODOLOGY

4.4.1. PREFORMULAION STUDY[54]

Preformulation studies are designed to determine the compatibility of initial excipients with the active substance for a biopharmaceutical, physicochemical and analytical investigation in support of promising experimental formulations. Successful formulations take into account a drug's interactions with the physicochemical properties of other ingredients [and their interactions with each other] to produce a safe, stable, beneficial and marketed product. The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance. The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available prior to initiating a formulation development activity.

4.4.1.1. DESCRIPTION

It is the initial evaluation during preformulation studies which assess the colour and taste of the substance. This was only a descriptive test.

4.4.1.2. SOLUBILITY[55]

Aqueous solubility is an important physicochemical property of drug substance, which determines its systemic absorption and in turns its therapeutic efficacy.

Table No.3: Solubility Specifications

Descriptive terms	**Approximate volume of solvent in milliliters per gram of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

4.4.1.3. DRUG EXCIPIENT COMPATIBILITY STUDY

The tablet dosage form the drug is in intimate contact with one or more excipients, the latter could affect the stability of the drug. Knowledge of drug-excipients interactions therefore is very useful to the formulators in selecting appropriate excipients. This information may already be in existence for known drug.

Method

Compatibility was performed by preparing compatibility blends at different ratio of different excipients with API, based on the tentative average weight. The blends were stored at accelerated condition of 40°C ±2°C/ 75% ±5% RH for 30 days. The samples were compared with initial samples data after the 2^{nd} and 4^{th} week of the study.

Table No.4: Drug excipients compatibility study

S. No.	Composition	Ratio (Drug : Excipient)
1	Rabeprazole sodium	-
2	Rabeprazole sodium + Mannitol anhydrous	1:1
3	Rabeprazole sodium + Copovidone	1:1
4	Rabeprazole sodium + Crospovidone	1:1
5	Rabeprazole sodium + Light magnesium oxide	1:1
6	Rabeprazole sodium + Methylparaben	1:1
7	Rabeprazole sodium + Propylparaben	1:1
8	Rabeprazole sodium + Magnesium stearate	1:1
9	Rabeprazole sodium + Instacoat moist shield white	1:1

4.4.1.4. DRUG – EXCIPIENT INTERACTION STUDIES BY FT-IR

Infra red spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tones pressure. It was scanned from 4000 to 150 cm^{-1} in a shimadzu FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

4.4.2. FORMULATION OF RABEPRAZOLE SODIUM UNCOATED TABLETS

Delayed release tablets of Rabeprazole sodium (20 mg) were prepared through direct compression method as per the composition shown in Table: The formulation codes, F-I to F-VII, were prepared by direct compression method. Various steps (sieving, dry mixing, lubrication and compression) involved in the tablet production by direct compression method were mentioned below.

Sieving

The active ingredient was passed through the sieve # 40 followed by the other ingredients (details of the formulation codes F-I to F-VII in Table: were passed through the same sieve.

Dry mixing

All the materials (including the active ingredient) were taken in poly bag and mixed for 10 minutes for uniform mixing.

Lubrication

The magnesium stearate and talc were passed through the sieve # 60 and mixed together with the powder mixture in a polybag for 5 minutes to get a uniform blend.

Compression

Finally, the powder mixture was compressed into tablets using 7.14 mm round shape punches and dies, by using single rotary tablet compression machine.

Packing Details

The prepared tablets were packed with following specification: 10 tablets were packed in Alu-Alu Blister packing.

4.4.3. COATING FORMULA

Seal Coating

Accurately weighed ethyl cellulose and dissolved in acetone and milled for 20 minutes.

Moisture Prior Coating

The solid material of insta coat moisture shield white was dissolved in isopropyl alcohol and then mixed with methylene dichloride. Milled for 30 minutes.

Enteric Coating

Protectab enteric M1 barath coat (methacrylic acid co polymer) powder was mixed with isopropyl alcohol. Iron oxide red was added to this solution.

Table No. 5: Composition of Rabeprazole Sodium Delayed Release Tablets

Ingredients	Quantity per tablet (mg)						
	F-I	**F-II**	**F-III**	**F-IV**	**F-V**	**F-VI**	**F-VII**
Rabeprazole sodium	20	20	20	20	20	20	20
Mannitol anhydrous	173	169	165	161	161	161	161
Copovidone	-	4.00	4.00	4.00	4.00	4.00	4.00
Crospovidone	-	-	4.00	8.00	8.00	8.00	8.00
Light magnesium oxide	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Methylparaben	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Propylparaben	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Magnesium stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Average weight of the un coated tablets	**200**	**200**	**200**	**200**	**200**	**200**	**200**
Seal coating							
Instacoat moist shield white	-	-	-	3.80	3.80	3.80	3.80
Isopropyl alcohol	-	-	-	25.00	25.00	25.00	25.00
Methylene dichloride	-	-	-	50.00	50.00	50.00	50.00
Lake of iron oxide red	-	-	-	0.20	0.20	0.20	0.20
Enteric coating							
Protectab Enteric M1	-	-	-	4.80	9.80	14.80	19.80
Isopropyl alcohol	-	-	-	25.50	51.00	76.50	102.00
Methylene dichloride	-	-	-	25.50	51.00	76.50	102.00
Lake of Ironoxide red	-	-	-	0.20	0.20	0.20	0.20
Polish coating							
Insta coat glow	-	-	-	1.00	1.00	1.00	1.00
Isopropyl alcohol	-	-	-	3.50	3.50	3.50	3.50
Methylene dichloride	-	-	-	3.50	3.50	3.50	3.50
Average weight of the Enteric coated tablets	-	-	-	**210.00**	**215.00**	**220.00**	**225.00**

Coating parameters

Table No. 6: Coating Parameters

Specifications	Enteric coating range
Pan diameter	12
Speed of pan revolution	10-12 rpm
Distance of spray gun	5-6
Spray nozzle diameter	1.2 mm
Spray rate	1.5 -2.0 ml /min
Dry air temperature	50 $\pm$ 5^0C / 30 mins
Coating time	4 hours
Bed temperature	30-40^0C

4.4.4. EVALUATION OF PRECOMPRESSION PARAMETERS

Angle of repose[56]

The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where,

h = Height of the powder cone.

R = Radius of the powder cone.

Table No. 7: Flow properties and corresponding angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-40
Passaple	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

Bulk density and tapped density[56,57]

Both Bulk density (BD) and tapped density (BD) was determined. A quantity of 2 gm of API powder from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

Compressibility index[58]

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\textbf{Compressibility index}(\%) = [\frac{TD - BD}{TD}] \times 100$$

BD= Weight of the powder blend/Untapped Volume of the packing

TD= Weight of the powder blend/Tapped Volume of the packing

Hausner's ratio[59]

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio was calculated from the bulk and tapped density using the following formula,

$$\textbf{Hausner's ratio} = \frac{\textit{Tapped density}}{\textit{Bulk density}}$$

Table No. 8: Scale of flowability

Flow character	Compressibility index (%)	Hausner's ratio
Excellent	<10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very poor	32 – 37	1.46 – 1.59
Extremely poor	>38	>1.60

4.4.5. EVALUATION OF POST COMPRESSION PARAMETERS

The compressed tablets were evaluated for the following parameters.

General appearence

The formulated tablets color, shape and dimension were measured through organoleptic testing methods and the same is reported in table:

Hardness[60]

Tablet requires a certain amount of mechanical strength to withstand the shock of handling in its manufacture, packaging, shipping and dispensing. It may be especially important to monitor the tablet hardness for sustained release drug products or other products that possess real or potential bioavailability problems or sensitive to variations in drug release profile.

The crushing strength that just causes the tablet to break is recorded by means of Monsanto hardness tester. The tablet is placed vertically in between the lower and upper plungers. The initial reading was taken immediately after placing the tablet onto the lower plunger. The upper plunger was then forced against a spring by turning a threaded bolt until

the tablet fractured. As the spring was compressed, a point moves along a gauge in the barrel to indicate pressure.

Thickness[61]

Once the tablet size and shape have been established, tablet thickness remains the only overall dimensional variable. Thickness should be controlled within 5% or less of an established standard value. Excessive variation in tablet thickness can result in problems with packaging as well as consumer acceptance. Variation in tablet thickness can also indicate force. The thickness of the individual tablets was measured with vernier caliper.

Weight Variation[62]

The weight variation test of the tablets was done as per the guidelines of Indian Pharmacopoeia. 20 tablets were selected at random and its individual weight was noted and from then, the mean weight of the tablet was calculated. Percentage deviation of each tablet from the mean was determined Table No. 7:

Table No. 9: Percentage Deviation of Tablets

S. No.	Average weight of tablet (mg)	Percentage deviation
1	130 or less	± 10.0
2	130-324	± 7.5
3	More than 324	± 5.0

Not more than 2 of the individual weights deviate from the average weight by more than 5% and none deviates by more than twice that percentage.

Friability[63]

Friability is the measure of a tablet's ability to withstand both shock and abrasion without crumbling during the handling of manufacturing, packing, shipping and consumer use. Tablets that tend to powder, chip, and fragment when handled lack elegance, and hence, consumer acceptance. The weight of 10 tablets was noted and placed them in Roche type friabilator. The device subjects the tablets to the combined effect of shock and abrasion by

utilizing a plastic chamber which revolves at 25 rpm, rolling the tablets a distance of 6 inches with the revolution. The pre-weighed tablet sample is removed after 100 revolutions, dusted and reweighed. Tablets that loose less than 0.5 to 1 percent in weight are generally considered acceptable.

Disintegration test

The disintegration test was carried out according to IP procedure on six tablets using disintegration test apparatus with discs in 0.1N HCL (pH 1.2) maintained at 37°C ± 2°C for 2 hours. After 2 hours 0.1N HCL was replaced with phosphate buffer 6.8 pH. A disc was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

Drug Content Determination by UV[64]

Solvent preparation

Methanol:Purified water (80:20). 300 ml methanol added into 700 ml of purified water to make 1000 ml of diluent.

Sample Preparation

Accurately weighed crushed tablet power equivalent 100mg of Rabeprazole sodium was placed into a clean 100 ml volumetric flask and 50 ml of diluents was added. Mixed well and sonicated for 20 minutes. Then make up to 100 ml with diluents. Filtered and diluted 1 ml to 100 ml and from this, 5 ml was diluted to 10 ml.

Standard preparation

Accurately weighed 100 mg of Rabeprazole sodium working standard in a clean, 100 ml volumetric flask and dissolved into 50 ml of diluents. The volume was making up to 100 ml with diluents. 1 ml of this solution was diluted to 100 ml with diluents. From this, 5 ml of the resulting solution was diluted to 10 ml with diluents.

Procedure

The absorbance of both the standard and sample preparations was measured at 284 nm using diluents as a blank. The drug content of prednisolone present per tablet was calculated by using the following expression.

$$Drug\ content = \frac{absorbance\ of sample}{absorbance\ of\ standard} \times \frac{weight\ of\ standard}{100} \times \frac{1}{100} \times \frac{5}{10} \times \frac{100}{weight\ of\ sample} \times \frac{100}{1} \times \frac{10}{5} \times \frac{purity\ ot\ standard}{average\ weight} \times 100$$

$$Assay = \frac{drug\ content}{label\ claim} \times 100$$

***In vitro* Drug Release Studies[65]**

Drug release studies were carried out using a USP type II paddle dissolution test apparatus at 50 rpm for 2 hr in 0.1 N HCl (900 ml) maintained at 37°C ± 0.5°C. 10 ml of sample was taken and sample was analyzed using UV spectrophotometer at 284 nm. Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for drug release for 45 minutes at 37°C ± 0.5°C temperature and 75 rpm speed. After 10, 20, 30 and 45 minutes, 10 ml of the samples were taken out and 10 ml Volume of fresh phosphate buffer pH 7.4 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer 284 nm.

STABILITY STUDIES OF THE TABLETS[66,67,68]

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product is not complete without proper stability analysis, carried out on it to assess the physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance of drug product varies with time. Under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted.

The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of new drug substances and product" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

- Long –term testing: $25 \pm 2°C/60\% \pm 5\%$ RH for 12 months.
- Accelerated testing: $40 \pm 2°C/75\% \pm 5\%$ RH for 6 months.

Stability studies was carried out at 25°C/60% RH and 40°C/75% RH for optimized formulation (F-VII) for 12 weeks.

Method

The selected clear Alu-Alu packed formulations stored at 25°C/ 60% RH and 40°C/75% RH for 3 months and evaluated for their physical appearance and drug content at specified intervals of every month. The formulations were further scanned to observe any possible spectral changes.

CHAPTER 5
RESULTS AND DISCUSSION

5. RESULTS AND DISCUSSION

5.1. PREFORMULATION STUDIES

5.1.1. DESCRIPTION

Table No. 10: Description of Rabeprazole Sodium

S. No.	Tests	Results
1	Colour	White
2	Odour	Unpleasant
3	Nature	Crystalline
4	Taste	Bitter

Discussion:

The colour, odour, nature and taste of the API were evaluated. It was found to be as per the monograph.

5.1.2. SOLUBILITY

Table No. 11 Solubility of drug

Raw material	Solubility
Rabeprazole sodium	Soluble in water,
	Soluble in methanol
	Soluble in ethanol

Discussion:

Thus the results revealed that the drug was soluble in water, methanol and ethanol.

5.1.3. DRUG - EXCIPIENT COMPATIBILITY STUDY

Table No. 12: Drug Excipients Compatibility Study

S. No.	Composition	Description		
		INITIAL PERIOD	2nd WEEK	4th WEEK
1	Rabeprazole sodium	white to off white powder	NCC	NCC
2	Rabeprazole sodium + Mannitol anhydrous	white to off white powder	NCC	NCC
3	Rabeprazole sodium + Copovidone	white to off white powder	NCC	NCC
4	Rabeprazole sodium + Crospovidone	white to off white powder	NCC	NCC
5	Rabeprazole sodium + Light magnesium oxide	white to off white powder	NCC	NCC
6	Rabeprazole sodium + Methylparaben	white to off white powder	NCC	NCC
7	Rabeprazole sodium + Propylparaben	white to off white powder	NCC	NCC
8	Rabeprazole sodium + Magnesium stearate	white to off white powder	NCC	NCC
9	Rabeprazole sodium + Instacoat moist shield white	white to off white powder	NCC	NCC

Note: NCC – No Characteristic change

Discussion:

From the drug excipients compatibility study, it was observed that there was no change between drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Rabeprazole sodium.

5.1.4. COMPATIBILITY STUDIES BY FT-IR

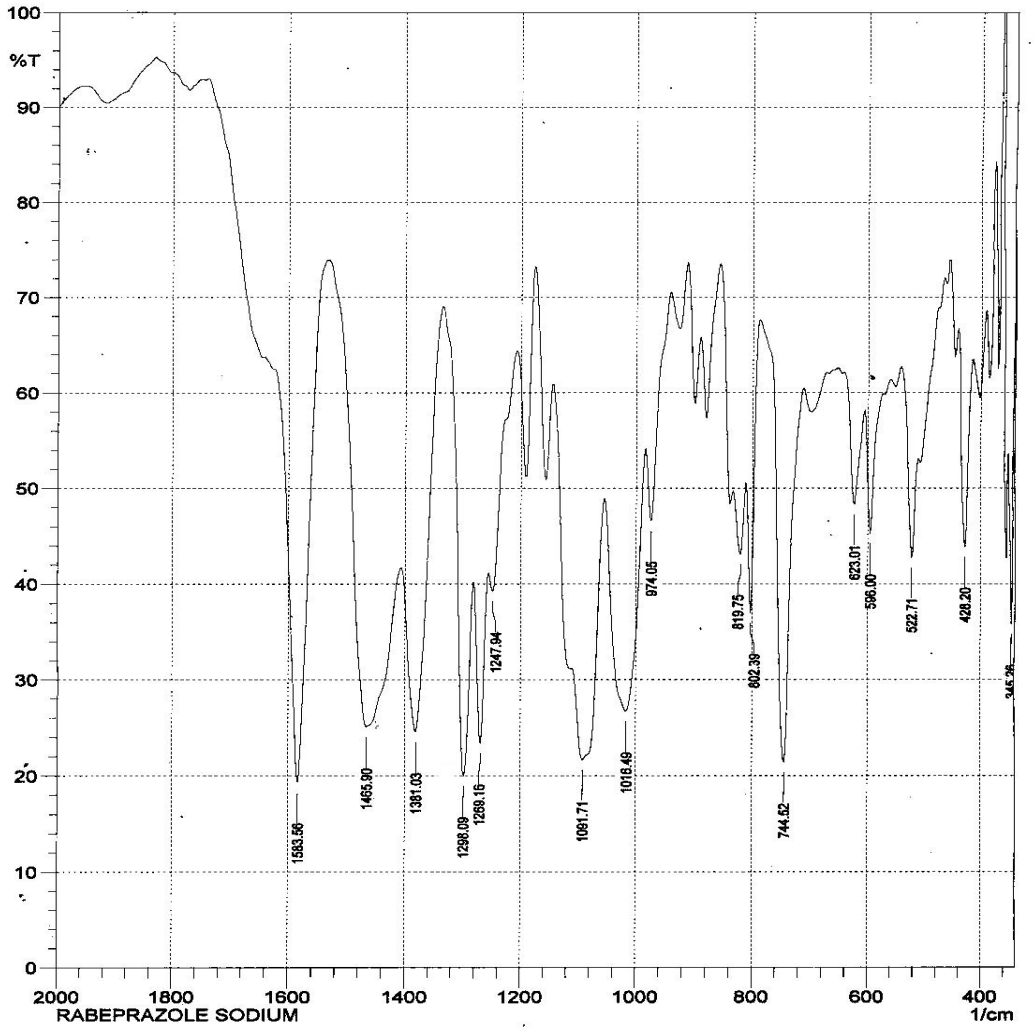


Figure 3: FTIR Spectra of Rabeprazole Sodium

FTIR Spectral Data of Rabeprazole Sodium

Table no.13

S. No	Wave Number (cm^{-1})	Functional Group
1.	1083	N-H Bending of Primary Amines
2.	1298	N-O Symmetric stretching of Nitro compounds
3.	1460	C-N Stretching
4.	1583	C-C Stretching of Benzene

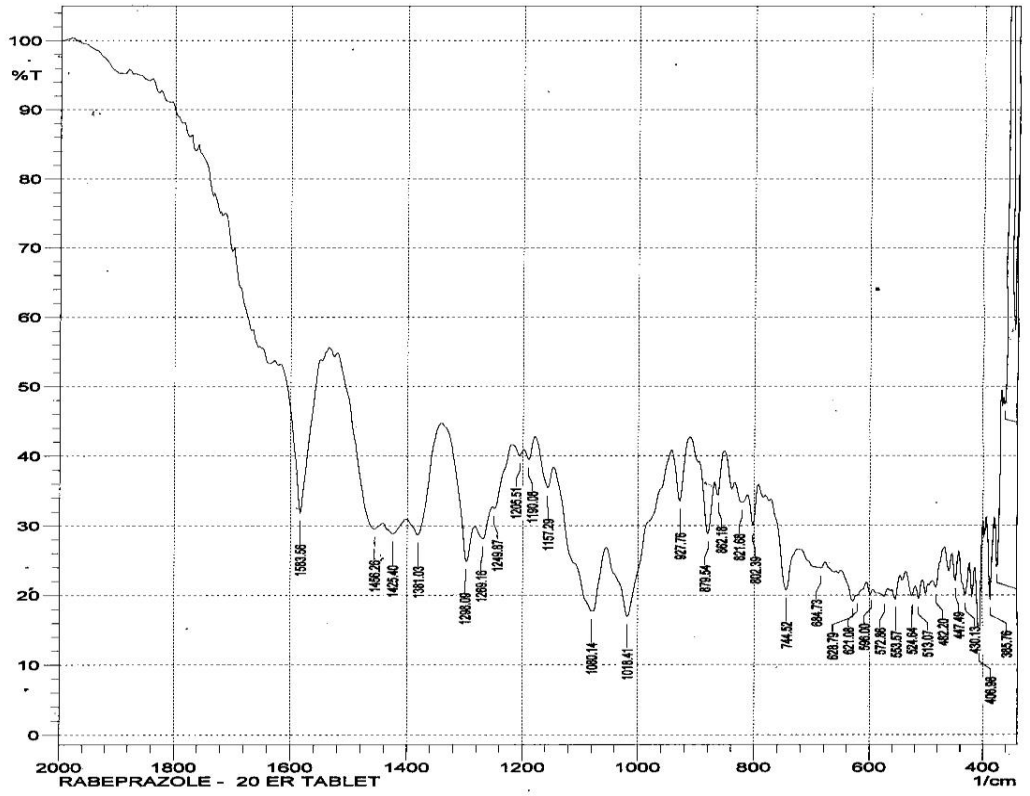


Figure 4: FTIR Spectra of Rabeprazole Sodium Enteric Coated Tablets

FTIR Spectral Data of Rabeprazole Sodium Enteric Coated Tablets

Table no.14

S. No	Wave Number (cm^{-1})	Functional Group
1.	1080	N-H Bending of Primary Amines
2.	1298	N-O Symmetric stretching of Nitro compounds
3.	1456	C-N Stretching
4.	1583	C-C Stretching of Benzene

Discussion:

In FTIR spectra the peaks of physical mixture were compared with the Pharmacopoeia reference spectra. Same peaks were observed, indicates no possible molecular interaction between the drug and the Excipients.

5.2. EVALUATION OF PRECOMPRESSION PARAMETERS

Table No. 15: Precompression Parameters of Rabeprazole Sodium Powder

Formulation Code	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility index (%)	Hausner's ratio
F-I	27.9±0.3	0.31±0.1	0.37±0.3	16.0±0.1	1.19±0.3
F-II	29.9±0.3	0.31±0.3	0.37±0.1	15.8±0.3	1.19±0.2
F-III	24.0±0.2	0.31±0.1	0.37±0.4	15.1±0.6	1.19±0.2
F-IV	29.5±0.1	0.31±0.2	0.36±0.1	16.5±0.2	1.16±0.1
F-V	27.6±0.4	0.32±0.2	0.37±0.2	15.5±0.7	1.15±0.2
F-VI	26.1±0.3	0.32±0.1	0.37±0.4	15.3±0.5	1.15±03
F-VII	25.0±0.2	0.31±0.4	0.36±0.2	15.85±0.3	1.16±0.2

* All the values are expressed as mean ± SD; n=3.

Discussion:

The angle of repose was found to be in the range of 24.0 ± 0.2 to 29.9 ± 0.3 for all formulations. If the angle of repose was within 30^o, it shows excellent flow properties. The result proved that all the formulations showed excellent flow properties.

The bulk density of all formulations was measured by using bulk density apparatus. The bulk density was in the range 0.31 ± 0.1 to 0.32 ± 0.2 g/cm^3.

The tapped density of all formulations was measured by using tapped density apparatus. The tapped density was found in the range of 0.36 ± 0.1 to 0.37 ± 0.3 g/cm^3.

The compressibility index was in the range of 15.1 ± 0.6 to 16.5 ± 0.2 %. It proved that the flow behaviours and compressibility of the granules are good. The hausner's ratio lies in the range of 1.15 ± 0.2 to 1.19 ± 0.3. Hence the flow properties of all formulations were good.

5.3. EVALUATION OF POST COMPRESSION PARAMETERS

Table No.16: Evaluation of Rabeprazole sodium Uncoated Tablets

Formulation Code	Average Thickness (mm)	Hardness (kg /cm^2)	Weight Variation (%)	Friability (%)	Drug Content (%)
F-I	3.32± 0.042	7.50± 0.32	202±1.42	0.01±0.002	100.50±1.30
F-II	3.30± 0.014	7.20± 0.29	200±1.39	0.06±0.001	99.32±2.69
F-III	3.28± 0.030	7.00± 0.27	201±2.78	0.28±0.001	98.65±3.05
F-IV	3.38 ± 0.022	7.60± 0.49	205±0.19	0.46±0.003	101.96±1.78
F-V	3.42 ± 0.020	7.10± 0.24	200±3.10	0.32±0.005	100.72±1.39
F-VI	3.30± 0.054	7.50± 0.21	202±1.90	0.20±0.002	99.21±2.87
F-VII	3.40± 0.020	7.50± 0.22	201±2.30	0.15±0.004	102.63±2.51

* All the values are expressed as mean ± SD; n=3.

Discussion:

General Appearance

The formulated tablets were evaluated for their organoleptic characters. The tablets are round in shape and red in colour. All the tablets showed elegance in appearance.

Thickness

Thickness of the tablets was found to be in the range of 3.28 ± 0.030 mm to 3.42 ± 0.020 mm. The results showed that the thickness of all formulated tablets was found to be uniform.

Hardness

The hardness of the tablets was measured by Monsonto hardness tester. The hardness of all the formulations was found to be in the range of 7.00 ± 0.27 to 7.60 ± 0.49 kg/cm^2. It indicates all the tablets have adequate mechanical strength.

Weight variation test

Twenty tablets of each formulation were selected for weight variation test. The accepted percentage deviation was ±7.5 for 130-324mg weight tablets. The results showed that weight variation was ranging from 200 ± 1.39 to 205 ± 0.19mg. It was within the I.P. limit and all the tablets passed the weight variation test.

Friability test

Friability test was carried out by Roche friabilitor. The maximum weight loss should be not more than 1%. The maximum and minimum friability values among 7 formulations were found to be in the range of 0.01 ± 0.002 to 0.46 ± 0.003% respectively. Hence all the tablets passed the friability test.

Drug content

The assay of Rabeprazole sodium delayed release tablets were found in the range between 98.65±3.05 and 102.63±2.51. The acceptable limit of Rabeprazole sodium content as per I.P. is 90 to 110%. The results revealed that the assay of Rabeprazole sodium was within the acceptable limits.

5.4. EVALUATION OF COATED TABLETS

Table No. 17: Evaluation of Rabeprazole sodium Delayed Release Tablets.

Formulation Code	Thickness (mm)	Weight Variation (%)	Disintegration test		Drug Content (%)
			Acid medium (mins)	Buffer medium Mins / sec	
F-IV	3.50 ± 0.032	211.05±0.19	35	-	101.96±1.78
F-V	3.58 ± 0.071	214.86±3.10	75	-	100.72±1.39
F-VI	3.65± 0.046	221.34±1.90	103	-	99.86±2.87
F-VII	3.72± 0.026	225.57±2.30	120	10.50''	102.63±2.51
Marketed sample	2.90± 0.055	210.00±2.50	120	15.20''	99.02±1.65

* All the values are expressed as mean ± SD; n=3.

Discussion:

In F-IV to F-VI formulations, the disintegration time in acid medium was found to be 35, 75 and 103 minutes. It was not within the limit. The disintegration time for F-VII formulation in acid medium was found to be within the limit. When compared with marketed sample, it showed better disintegration time.

5.5. *IN VITRO* DRUG RELEASE STUDIES

Table No. 18: *In vitro* Drug Release of Rabeprazole sodium Delayed Release Tablets

Dissolution media	Sampling time	% Drug release				
		F-IV	F-V	F-VI	F-VII	Marketed sample
(0.1 N HCl)	2 hrs	2.57± 0.67	2.08± 0.12	1.8± 0.12	1.6 ± 0.50	1.7 ± 0.58
(6.8pH Phosphate buffer)	5 mins	4.89± 0.38	2.44± 0.43	6.2± 0.67	7.34 ± 0.33	7.10 ± 0.12
	10 mins	7.5± 0.12	5.10± 0.43	14.23± 0.14	19.77 ± 0.67	18.25 ± 0.24
	15 mins	28.22± 0.14	29.45± 0.21	30.32± 0.22	40.37 ± 0.58	39.45 ± 0.36
	20 mins	32.54± 0.67	34.23± 0.58	52.22± 0.12	75.28 ± 0.38	73.32 ± 0.14
	30 mins	40.22± 0.58	46.06± 0.43	72.32± 0.12	87.19 ± 0.22	85.56 ± 0.43
	45 mins	44.62± 0.12	59.62 ± 0.43	86.21± 0.36	99.98 ± 0.12	98.68 ± 0.21

* All the values are expressed as mean ± SD; n=3.

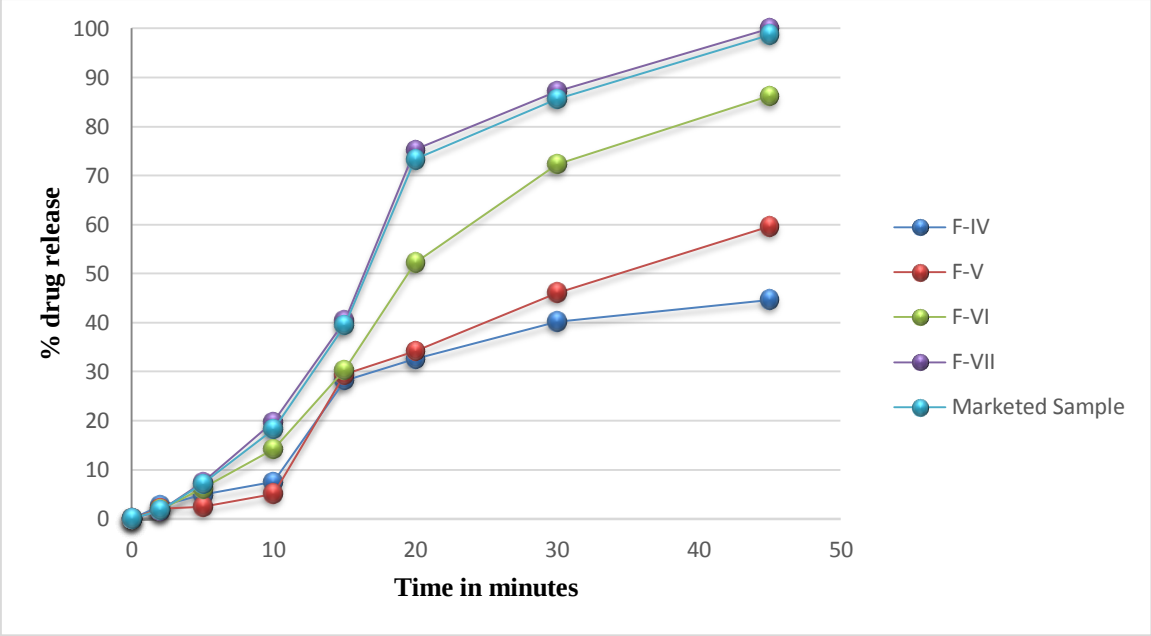


Figure 5: Comparative Dissolution Profile Study of Rabeprazole sodium Delayed Release Tablets

Discussion:

The results revealed that the drug released from marketed product was fairly matching with the drug release from Rabeprazole sodium delayed release tablet formulation F-VII. Based on this, F-VII was selected as best formulation other than F-IV,F-V,F-VI and subjected for stability studies.

5.6. STABILITY STUDIES

Table No. 19: Stability studies for F-VII Rabeprazole sodium Delayed Release Tablets

Parameters	$40^{o}C \pm 2^{o}C$/ 75% RH ± 5%RH			
	Initial Period	1st Month	2nd Month	3rd Month
Description	Round shaped red colour	Round shaped red colour	Round shaped red colour	Round shaped red colour
Average weight (mg)	225.57±2.30	226.48 ± 2.13	226.89 ± 1.98	227.02 ± 1.84
Hardness (kg/cm^2)	7.50± 0.22	7.48 ± 0.23	7.45 ± 0.20	7.43 ± 0.41
Thickness (mm)	3.72± 0.02	3.71 ±0.02	3.68 ± 0.2	3.68 ± 0.08
Disintegration time (mins)	130.50''	131.34''	131.57''	132.14''
Assay (%)	102.63±2.51	101.98 ± 2.14	101.56 ± 2.04	101.13 ± 1.34

* All the values are expressed as mean ± SD; n=3.

Discussion:

F-VII formulation was kept for stability studies. No physical changes were observed at end of 1st, 2nd and 3rd month. But average weight gradually increased every month, this may be due to increase in moisture content. Assay data showed no significance variation during stability studies.

Table No. 20: Stability study dissolution data for F-VII formulation

Dissolution media	Sampling time	Storage condition $40^oC \pm 2^oC$ / 75% RH ± 5% RH			
		Initial period	1st Month	2nd Month	3rd Month
Simulated gastric fluid (0.1 N HCl)	2 hrs	1.6 ± 0.50	1.6 ± 0.75	1.7 ± 0.42	1.7 ± 0.87
Simulated intestinal fluid (6.8pH Phosphate buffer)	5 mins	7.34 ± 0.33	7.35 ± 0.17	7.24 ± 0.41	7.31 ± 0.28
	10 mins	19.77 ± 0.67	18.84 ± 0.51	19.54 ± 0.28	19.69 ± 0.46
	15 mins	40.37 ± 0.58	40.58 ± 0.44	40.14 ± 0.29	41.21 ± 0.34
	20 mins	75.28 ± 0.38	74.84 ± 0.24	75.45 ± 0.49	74.67 ± 0.35
	30 mins	87.19 ± 0.22	87.25 ± 0.24	88.41 ± 0.31	88.12 ± 0.21
	45 mins	99.98 ± 0.12	99.96 ± 0.14	98.98 ± 0.22	98.94 ± 0.34

* All the values are expressed as mean ± SD; n=3.

Discussion:

F-VII was kept for stability studies. The *in vitro* dissolution profile was remained without any significant changes at the end of 1st, 2nd and 3rd months. Hence it was concluded that the formulated Rabeprazole sodium delayed release tablets were stable.

CHAPTER 6
SUMMARY AND CONCLUSION

6. SUMMARY AND CONCLUSION

SUMMARY

Formulation and evaluation of delayed release tablets of Rabeprazole sodium was carried out by performing the preformulation studies, formulation of Rabeprazole sodium delayed release tablets, evaluation parameters, *in vitro* drug release studies and stability studies.

The preformulation studies of API and drug excipients compatibility studies were carried out.

- IR spectroscopic analysis of drug with excipients was showed that the drug was compatible with excipients which were used in the formulation.
- Rabeprazole delayed release tablets were prepared by direct compression method and coated with Protectab Enteric M1 as coating polymer in different concentrations.
- The prepared powder blend was evaluated for precompression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner ratio. The obtained results indicated that it has good flow property for direct compression method.
- The prepared tablets were evaluated for hardness, thickness, weight variation, friability, assay and disintegration time. All these parameters were found to be within the pharmacopoeial limits in F-VII formulation.
- *In vitro* dissolution study was carried out for F-VII formulation. The drug release was found to be 99.98 ± 0.12% at 45 mins.
- Comparative *in vitro* dissolution study of F-VII formulation showed better drug release than the marketed product.
- The accelerated stability studies of F-VII formulation (F7) at 40^{o}C/75% RH for a period of 3 months indicated that there was no significant change in description, disintegration time, drug content and *in vitro* dissolution profiles. The result shows that the F-VII formulation was stable.

CONCLUSION

Formulation and evaluation of Delayed release tablets of Rabeprazole sodium for the effective treatment of duodenal ulcer was successfully carried out.

The preformulation studies, formulation of Rabeprazole sodium delayed release tablets, selection of the best formulation based on disintegration time and *in vitro* studies for delayed release tablets and stability studies were performed. The final product was correlated with the marketed product.

From all the above observations it was concluded that the F-VII formulation was better one compared to the other formulations. Thus the study concluded that delayed release tablets of Rabeprazole sodium prepared by direct compression method. The tablets were coated with Protectab Enteric M1 as a polymer for the effective therapy for duodenal ulcer.

CHAPTER7
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BIBLIOGRAPHY

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