FORMULATION AND EVALUATION OF GASTRO-RESISTANT TABLET CONTAINING LOCALLY ACTING STIMULANT LAXATIVE

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1.0. INTRODUCTION

1.1. DRUG DELIVERY SYSTEM

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term **drug delivery** can be defined as techniques that are used to get the therapeutic agents inside the human body.

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in figure-1.To overcome these problems, controlled drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies[1].

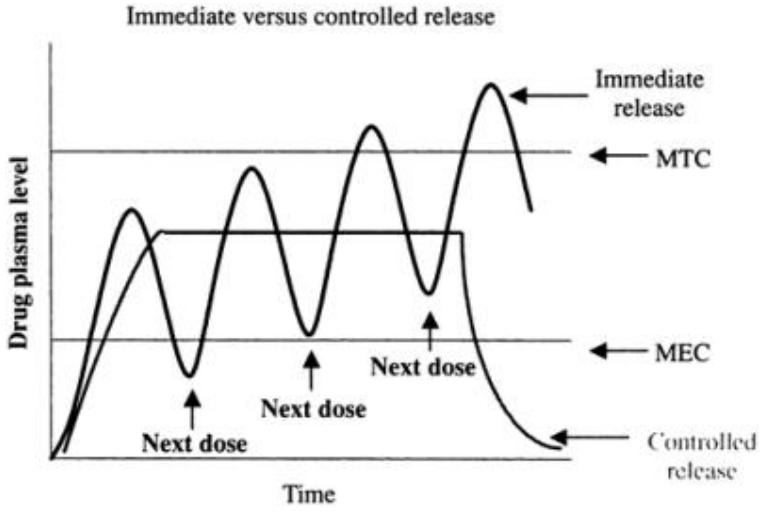


Figure-1 Drug levels in the blood with Conventional drug delivery systems and Controlled drug delivery systems

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying Pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized[2].

Several types of modified-release drug products are recognized:

1. **Extended-release drug products**. A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

2. **Delayed-release drug products**. A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products

3. **Targeted-release drug products**. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

1.2 DELAYED RELEASE SYSTEMS

The two types of delayed release systems are:

1. Intestinal release systems
2. Colonic release system,

1. **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.

2. **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 and

b) Systemic absorption of protein and peptide drugs

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

i) Destroyed in the stomach or by intestinal enzymes

ii) Known to cause gastric distress

iii) Absorbed from a specific intestinal site or

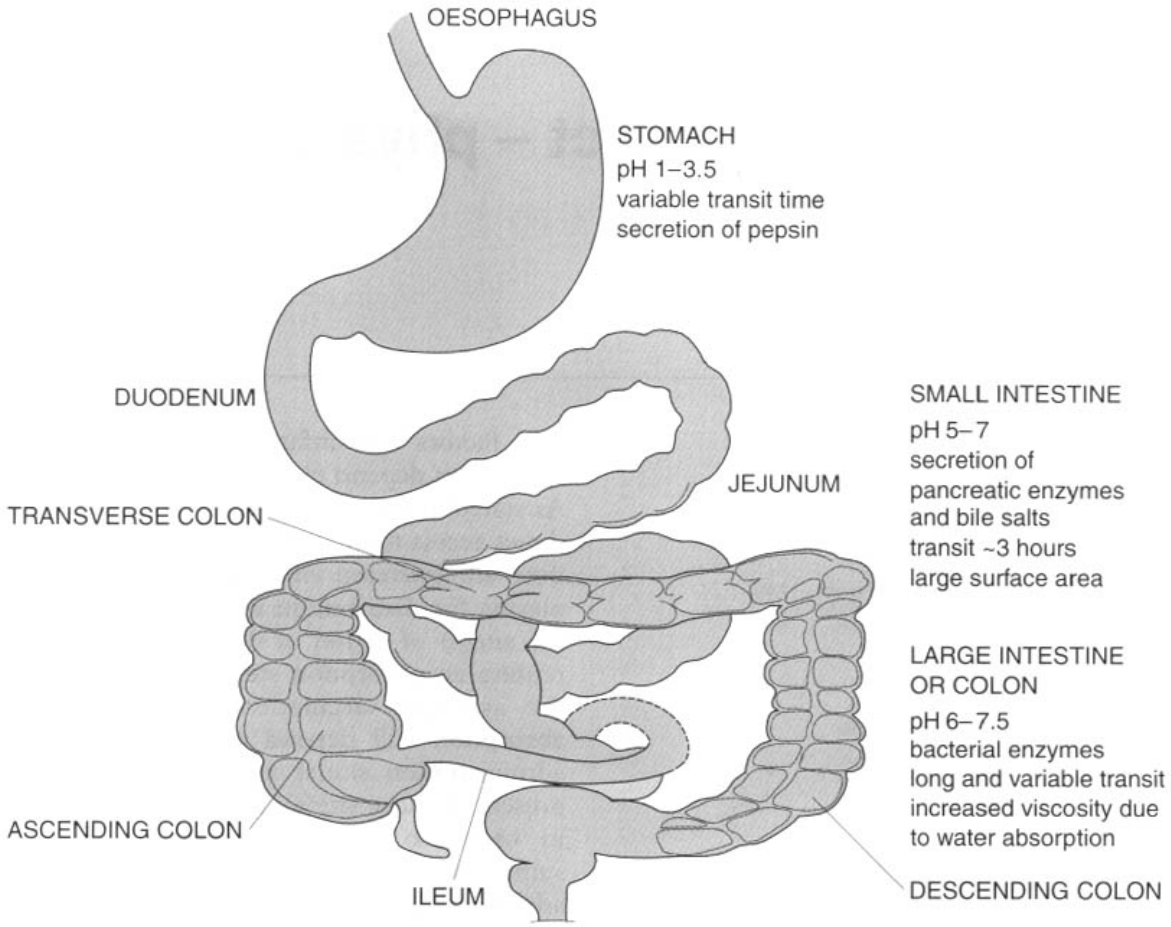
iv) Meant to exert local effect at a specific gastrointestinal site

As a result, new strategies of drug delivery have been developed to overcome obstacles encountered by oral delivery. Among these strategies, colon-specific delivery has been extensively studied for the last two decades. Colon, an area where protein drugs are free from the attack of numerous proteases, is thought to be an ideal location to direct drugs into the bloodstream and the immune system. New formulations of different delivery vehicles from synthetic and natural polymers, which are either hydrophilic or hydrophobic, have been tested for these purposes. The challenge in the design of oral drug delivery vehicles which effectively carry drugs to the colon site is to meet a certain criteria. Firstly, they need to remain intact when traveling through the upper GI tract in order to protect the incorporated drugs from chemical and enzymatic degradation. Secondly, they should be able to release the incorporated drugs immediately upon reaching the colon segment of the lower GI tract. Furthermore, the released drugs need to be absorbed at an efficient rate in the GI tract in order to be therapeutically effective[3].

1.3 PHYSIOLOGY OF THE GASTROINTESTINAL TRACT[4]

The gastrointestinal tract is a muscular tube approximately 6 m in length with varying diameters. It stretches from the mouth to the anus and consists of four main anatomical areas: the oesophagus, the stomach, the small intestine and the large intestine or colon. The luminal surface of the tube is not smooth but very rough, thereby increasing the surface area for absorption.

Figure-2 - Physiology of the Gastrointestinal Tract



1.3.1The oesophagus

The mouth is the point of entry for most drugs (so called peroral - via the mouth - administration). At this point contact with the oral mucosa is usually brief. Linking the oral cavity with the stomach is the oesophagus. This is composed of a thick muscular layer approximately 250 mm long and 20 mm in diameter. It joins the stomach at the gastro esophageal junction, or cardiac orifice as it is sometimes known.

The oesophagus, apart from the lowest 20 mm which is similar to the gastric mucosa, contains a well differentiated squamous epithelium of non-proliferative cells. Epithelial cell function is mainly protective: simple mucous glands secrete mucus into the narrow lumen to lubricate food and protect the lower part of the oesophagus from gastric acid. The pH of the oesophageal lumen is usually between 5 and 6.

1.3.2 The stomach

The stomach is the most dilated part of the gastrointestinal tract and is situated between the lower end of the oesophagus and the small intestine. Its opening to the duodenum is controlled by the pyloric sphincter. The stomach can be divided into four anatomical regions, namely the fundus, the body, the antrum and the pylorus.

The stomach has a capacity of approximately 1.5 L, although under fasting conditions it usually contains no more than 50 ml of fluid, which are mostly gastric secretions. These include:

- Acid secreted by the parietal cells, which maintains the pH of the stomach between 1 and 3.5 in the fasted state;
- The hormone gastrin, which itself is a potent stimulator of gastric acid production. The release of gastrin is stimulated by peptides, amino acids and distension of the stomach;
- Pepsins, which are secreted by the peptic cells in the form of its precursor pepsinogen. Pepsins are peptidases which break down proteins to peptides at low pH. Above pH 5 pepsin is denatured;

- Mucus, which is secreted by the surface mucosal cells and lines the gastric mucosa. In the stomach the mucus protects the gastric mucosa from auto digestion by the pepsin-acid combination[5].

1.3.3 The small intestine

The small intestine is the longest (4-5 m) and most convoluted part of the gastrointestinal tract, extending from the pyloric sphincter of the stomach to the ileocaecal junction where it joins the large intestine.

Its main functions are:

- Digestion: the process of enzymatic digestion, which began in the stomach, is completed in the small intestine.
- Absorption: the small intestine is the region where most nutrients and other materials are absorbed. The small intestine is divided into the duodenum, which is 200-300 mm in length, the jejunum, which is approximately 2 m in length, and the ileum, which is approximately 3 m in length.

The surface area of the small intestine is increased enormously, by about 600 times that of a simple cylinder, to approximately 200 m2 in an adult, by several adaptations which render the small intestine such a good absorption site:

- Folds of Kerckring: these are sub mucosal folds which extend circularly most of the way around the intestine and are particularly well developed in the duodenum and jejunum. They are several millimeters in depth.
- **Villi:** these have been described as finger-like projections into the lumen (approximately 0.5-1.5 mm in length and 0.1 mm in diameter).They are well supplied with blood vessels. Each villus contains an arteriole, a venule and a blind ending lymphatic vessel (lacteal). The structure of a villus.
- **Microvilli:** approximately 600-1000 of these brush-like structures (~ 1 μm in length and 0.1 μm in width) cover each villus, providing the largest increase in surface area. These are covered by a fibrous substance known as glycocalyx. The luminal pH of the small intestine increases to between about 6 and 7.5.

1.3.4 The colon [6, 7]

Irrespective of therapy desired for local (colonic) or systemic delivery of drug, the development and aim of the drug delivery to colon remain same, that is

- The drug must not absorb from other regions of the gastro intestinal tract (GIT).
- It should only suffer negligible degradation in the small intestine lumen.
- The release of the drug in the colon should be at quantitatively controlled rate and the released drug in the colon should be absorbed from the lumen of the large intestine without any appreciable degradation.

Parts of the Colon:

The colon is actually just another name for the large intestine. The shorter of the two intestinal groups, the large intestine, consists of parts with various responsibilities. The parts of the colon are; transverse colon, ascending colon, appendix, descending colon, sigmoid colon, and the rectum and anus. The transverse, ascending, and descending colons are named for their physical locations within the digestive tract, and corresponding to the direction food takes as it encounters those sections. Within these parts of the colon, contractions from smooth muscle groups work food material back and forth to move waste through the colon and eventually, out of the body. The intestinal walls secrete alkaline mucus for lubricating the colon walls to ensure continued movement of the waste. The ascending colon travels up along the right side of the body. Due to waste being forced upwards, the muscular contractions working against gravity are essential to keep the system running smoothly. The next section of the colon is termed the transverse colon due to it running across the body horizontally. Then, the descending colon turns downward and becomes the sigmoid colon,

followed by the rectum and anus. The ileocecal valve is located where the small and large intestines meet. This valve is an opening between the small intestine and large intestine allowing contents to be transferred to the colon. The cecum follows this valve and is an opening to the large intestine. The rectum is essentially a storage place for waste and is the final stop before elimination occurs. When elastic receptors within the rectum are stimulated, these nerves signal that defecation needs to occur.

The anus is the last portion of the colon, and is a specialized opening bound with elastic membranes, sensitive tissues, and muscles and nerves allowing it to stretch for removing bowel movements of varying sizes.

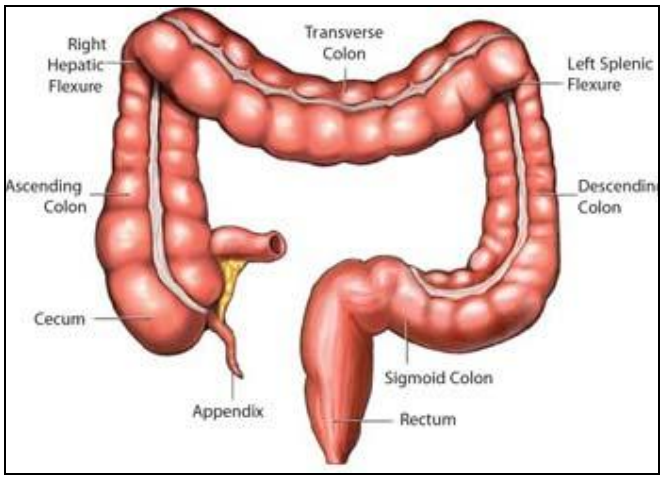


Fig: 3 Anatomy of the Colon

Advantages of colon specific drug delivery

- A near neutral pH, a much longer transit time and a much greater responsiveness to absorption enhancers.
- Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn's disease etc.)
- By producing the 'friendlier' environment for peptides and proteins when compared to upper gastrointestinal tract.
- Minimizing extensive first pass metabolism of steroids.
- Preventing the gastric irritation produced by oral administration of NSAIDS.
- Targeting the drug required in amoebiasis to the colon.
- Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.

Limitations of colon specific drug delivery

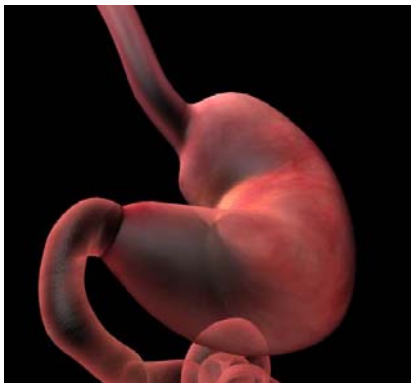
- The location at the distal portion of the alimentary canal, the colon is difficult to access.
- Successful delivery requires the drug to be in solution before it arrives in the colon, but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.[2]

1.4 COATING

1.4.1 Enteric coating[8]:

An enteric coating is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. Enteric refers that the drug releases in to the small intestine. Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. For example, they will not dissolve in the acidic juices.

Acidic pH (pH ~3) in stomach, Alkaline pH (above pH 7-9) environment present in the small intestine. Drugs which have an irritant effect on the stomach 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 (intestine's pH 5.5 and above) where they do not degrade, and give their desired action .Recently, some companies have begun to utilize enteric coatings on fish oil (omega 3 fatty acids) supplements.



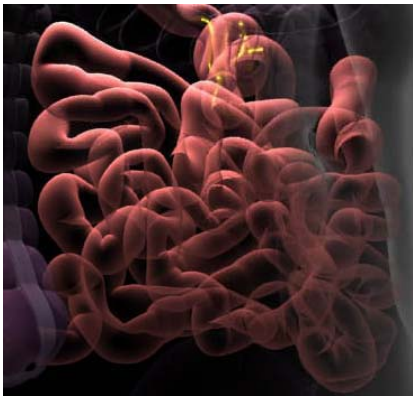


Fig.4 Highly Acidic Gastric secretion pH 1-4 **Fig.5 Duodenum pH 6.8**

Reasons for enteric coating:

- To protect acid-liable drugs from the gastric fluid
- To protect gastric distress or nausea due to irritation from drug
- To deliver drugs intended for local action in the intestines.
- To deliver drug that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To provide a delayed release component to repeat actions.
- Protect the drugs from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media.

COMPOSITIONS OF COATING

- Cellulose acetate phthalate (cap)
- Methyl Acrylate-Methacrylic acid copolymers
- Cellulose acetate succinate
- Hydroxy propyl methyl cellulose phthalate
- Hydroxy propyl methyl cellulose acetate succinate
- Polyvinyl Acetate Phthalate (PVAP)
- Methyl Methacrylate Methacrylic acid copolymers
- Sodium alginate and Stearic acid

Advantages of Coating:

1. High productivity /faster coating High film adhesion-produces much better tablet finish with improved tablet gloss.

2. Easy processing, Low requirement of energy

3. Improvement in efficiency of other production operations e.g. packaging of tablets on high speed packaging machines.

4. Environmental friendly system-eliminates the use of organic solvents.

5. Low cost.

1.4.2 Sugar-Coating

Compressed tablets may be coated with colored or uncolored sugar layer. The coating is water soluble and quickly dissolves after swallowing. The sugar coat protects the enclosed drug from the environment and provides a barrier to objectionable taste or odour. The sugar coat also enhances the appearance of the compressed tablet and permit imprinting manufacturing's information. Sugar coating provides a combination of insulation, taste masking, smoothing the tablet core, coloring and modified release. The disadvantages of sugar coating are the time and expertise required in the coating process and thus increases size, weight and shipping costs.

- Sugar coating process involves five steps

I. Sealing/Water proofing: Provides a moisture barrier and harden the tablet surface.

II. Sub-coating: Causes a rapid buildup to round off the tablet edges.

III. Grossing/Smoothing: Smoothes out the sub-coated surface and increases the tablet size to predetermine dimension.

IV. Coloring: Gives the tablet its color and finished size.

V. Polishing: Produces the characteristics gloss.

I. Sealing/Water proofing.

Prior to applying any sugar/water syrup, the tablet cores must be sealed, thoroughly dried and free of all residual solvents. The seal coat provides a moisture barrier and hardness to the surface of the tablet in order to minimize attritional effects. Core tablets having very rapid disintegration rates conceivably could start the disintegration process during the initial phase of sugar coating. The sealants are generally water-insoluble polymers/film formers applied from an organic solvent solution. The quantities of material applied as a sealing coat will depend primarily on the tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Hence, one or more further application of resin solution may be required to ensure that the tablet cores are sealed effectively.

Common materials used as a sealant include Shellac, Zinc, Cellulose acetate phthalate (CAP), Polyvinyl acetate phthalate, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose etc.

II. Sub-coating:

Sub-coating is the actual start of the sugar coating process and provides the rapid buildup necessary to round up the tablet edge. It also acts as the foundation for the smoothing and color coats.

- Generally two methods are used for sub-coating:
  i. The application of gum based solution followed by dusting with powder and then drying. This routine is repeated until the desired shape is achieved.
  ii. The application of a suspension of dry powder in gum/sucrose solution followed by drying.

Thus sub-coating is a sandwich of alternate layer of gum and powder. It is necessary to remove the bulk of the water after each application of coating syrup.

Table No. 1 - Typical Binder Solution Formulation for Sub-coating

Materials	**%W/W**	**%W/W**
Gelatin	6	3.3
Gum acacia (powdered)	8	8.7
Sucrose (powdered)	45	55.3
Distilled water	To 100ml	To 100ml

Table No. 2 - Typical Dusting Powder Formulation for Sub-coating

Materials	**%W/W**	**%W/W**
Calcium carbonate	40.0	-
Titanium dioxide	5.0	1.0
Talc, asbestos free	25.0	61.0

Sucrose(powdered)	28.0	38.6
Gum acacia (powdered)	2.0	-

III. Grossing/ smoothing:

The grossing/smoothing process is specifically for smoothing and filing the irregularity on the surface generated during sub-coating. It also increases the tablet size to a predetermined dimension.

If the sub-coating is rough with high amount of irregularities then the use of grossing syrup containing suspended solids will provide more rapid buildup and better filling qualities. Smoothing usually can be accomplished by the application of a simple syrup solution

(Approximately 60-70 % sugar solid). This syrup generally contains pigments, starch, gelatin, acacia or opacifier if required. Small quantities of color suspension can be applied to impart a tint of the desired color when there are irregularities in coating.

IV. Color coating:

This stage is often critical in the successful completion of a sugar coating process and involves the multiple application of syrup solution (60-70 % sugar solid) containing the requisite coloring matter. Mainly soluble dyes were used in the sugar coating to achieve the desired color, since the soluble dye will migrate to the surface during drying. But now a day the insoluble certified lakes have virtually replaced the soluble dyes in pharmaceutical tablet coating. The most efficient process for color coating involves the use of a pre-dispersed opacified lake suspension.

V. Polishing

Sugar-coated tablets needs to be polished to achieve a final elegance. Polishing is achieved by applying the mixture of waxes like beeswax, Carnauba wax, candelila wax or hard paraffin wax to tablets in polishing pan.

1.5 SCIENTIFIC PRINCIPLES OF STABILITY TESTING[9-13]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. Therefore, stability studies provide data to justify the storage condition and shelf-life of the drug product. For drug substance, such studies establish the retest date in addition to the storage condition of raw material.

Stability of a drug substance or drug product during drug synthesis, formulation, and storage must be ascertained. Instability could lead to chemical degradation and loss of drug potency and the possible formation of new chemical species with potential toxic side effects. Therefore, early evaluation of a drug substance should include elucidation of stability under a number of environmental conditions. To aid in the prediction of drug stability, forced or accelerated degradation is performed to elucidate potential degradation products, determine their safety, and develop analytical procedures to quantitate these new chemical species. These forced degradation studies may be predictive of the degradation pathways of the drug under normal conditions. In fact, information learned from studying the kinetics of

degradation may be used to extrapolate rates of degradation which might apply during normal storage conditions and could be utilized to predict long-term stability under these normal storage conditions.

The development of appropriate analytical methods will then aid in the development of purification schemes to remove degradants and to allow the development of drug impurity profiles which will be used for setting purity specifications and for defining the drug which is to be utilized in pre-clinical animal and later human studies.

The analytical procedures to assess stability must encompass the elements common to validating analytical assays. The methods must be validated according to the parameters of accuracy, precision, robustness and specificity, limits of detection and quantitation, linearity of active ingredient assays, degradants, and other reaction products.

These stability studies will expose the drug to potentially degrading conditions including moisture, oxygen, pH, temperature, and light. Discovery that a drug has a very restricted stability range will affect process and packaging development, and labeling for long-term shelf-life.

Sensitivity to such environmental factors may also dictate the necessity for inclusion of stabilizers in the formulation and will dictate the choice of dosage form and packaging. It may turn out that such restricted stability and associated developmental costs to remedy the situation will be sufficient to eliminate a potentially viable drug product. For products which are expected to be sold and used worldwide, attention

must be given to differing climate zones when considering expiry dating and long-term stability.

For solid dosage forms, the solubility, efficacy, and stability of a drug may depend on the particular crystalline state of the drug. Many crystalline drugs can exist in different crystalline states called polymorphs. It is expected that characterization of the solid dosage forms include not only the chemical identity but the polymorphic distribution as well. The polymorphic content may be characterized by techniques such as x-ray powder diffraction, Raman and infrared spectroscopy. The sensitivity to environmental conditions of different polymorphs of the same drug entity may differ and therefore polymorphic composition may play an important role in determining a drug's stability.

Once the drug sensitivities are determined and the product development process addresses these issues and defines the product, then the long-term official stability studies may begin. The conditions and protocols for these studies are well defined by FDA and ICH guidelines

Requirements of stability program

Written program must include:

_ Sample size and test intervals,

_ Storage conditions for samples,

_ Reliable, meaningful, and specific test methods,

_ Testing of drug product in marketed container,

_ Testing of drug product for reconstitution at dispensing time and reconstituted time.

2.0. AIM, OBJECTIVE AND PLAN OF WORK

The aim and objective of the present study was to formulate and evaluate delayed release dosage form of local acting agent i.e., Stimulant laxative.

2.1 OBJECTIVE:

- To formulate the various prototype formulation trials and evaluate.
- To optimize the formulation with reference product by using different manufacturing techniques to observe the process variation.
- To carry out Drug-Excipient compatibility studies.
- To evaluate and compare the properties of developed pharmaceutically test product with reference product by uniformity of drug content and related substance.
- To evaluate and match the disintegration time of the reference product in different phosphate buffer.
- To carry out stability studies of developed product as per ICH guidelines.

2.2 SCOPE:

Stimulant laxative used for the treatment of constipation and bowel evacuation. It acts mainly in the large intestine following oral administration.

Bisacodyl was recently subjected to carcinogenicity testing and was shown to be free of carcinogenic/ mutagenic potential and therefore, from a safety perspective is the stimulant laxative of choice.

However Bisacodyl (API) is directly irritant to the intestinal mucosa of the upper intestine and can cause griping and epigastric pain. To reduce the incidence of such effects drug is conventionally administered as enteric- coated tablets. Enteric-coated formulations are suitable vehicles to modify the release of active substances such that release at specific target areas within the GI tract can be affected.

A major aim of enteric coating is protection of drugs that are sensitive or unstable at acidic pH. This is particularly important for drugs such as enzymes and proteins, because these macromolecules are rapidly hydrolyzed and inactivated in acidic medium.

The advantage of sugar coating is to protect the enclosed drug from the environment and provide a barrier to objectionable taste or odour. It also enhances the appearance of the compressed tablet and permit imprinting manufacturing information.

2.3. PLAN OF WORK

2.3.1 PREFORMULATION STUDY

a) DRUG EXCIPIENT COMPATIBILITY STUDIES.

b) EVALUATION OF PRE-COMPRESSION PARAMETERS

- Angle of repose
- Bulk density and tapped density
- Compressibility index
- Particle size distribution.

2.3.2 FORMULATION DESIGN

Preparation of delayed release tablets using different techniques

- Direct compression

2.3.3 EVALUATION OF DELAYED RELEASE TABLETS

- Weight variation
- Thickness
- Hardness
- Friability
- Disintegration test
- Dissolution
- Drug content estimation
- Related substance.

3.0. LITERATURE REVIEW
3.1 GASTRO-RESISTANT TABLET

Patel Gayatri C.*, et al[14]:

Enteric coatings are pH sensitive and can be considered as a pulsatile drug delivery system because of the lag time is essential for the drugs that undergo degradation in gastric acidic medium which irritate the gastric mucosa. The present study explores the comparative utility of the enteropolymers (enteric-coated polymers) such as acrycoat L-100, acrycoat S-100, ethyl cellulose (EC) and cellulose acetate phthalate (CAP) in developing a suitable dosage form, exhibiting a minimum drug release in the upper regions of the gastrointestinal tract (GIT) on order to provide site specificity as well as time controlled formulation. Core tablets of diclofenac sodium (DS) were prepared by wet granulation and coated with one of the coating polymers to a varying coating level. From the dissolution data obtained, it was found that the dissolution rate was inversely proportional and lag time was directly proportional to the coating level applied. Comparative dissolution data revealed that, of all the various polymers at varying coating level used, a 15% acrycoat S 100 and EC was most suitable for pulsatile drug delivery. Moreover, such study also provides a site specific drug delivery.

Anroop B Nair*,et al[15]:

The present study was an attempt to formulate and evaluate 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%.

Vishal V. Rajguru*,et al[16]:

Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. Formulation coated with enteric polymers releases drug, when pH move towards alkaline range while as the multicoated formulation passes the stomach, the drug is released after a lag time of 3-5 hours that is equivalent to small intestinal transit time. Drug coated with a bioadhesive polymer that selectively provides adhesion to the colonic mucosa may release drug in the colon. The review is aimed at understanding Pharmaceutical approaches to colon targeted drug delivery systems for better therapeutic action without compromising on drug degradation or its low bioavailability.

Sateesh kumar et al[17]:

Oral administration of different dosage forms is the most commonly used method due to greater flexibility in design of dosage form and high patient acceptance, but the GIT presents several formidable barriers to drug delivery. Colon specific drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides.

Sharma Anuj et al[18]:

Although oral delivery has a become a widely accepted route of administration of therapeutic drugs, the GIT presents several formidable barrier to drug delivery. The delivery of drugs to the colon has a number of therapeutic implications in the field of drug delivery. In the recent times, the colon specific drug delivery system is also gaining importance not only for local drug delivery of drugs but also for the systemic delivery of protein and peptide drugs. The various approaches that can be exploited to target the release of drug to the colon including prodrug formation, coating with PH sensitive polymer, coating with biodegradable polymers, embedding in biodegradable matrices, hydrogel time release system, osmotic and bio-adhesive for achieving colon specific drug delivery.

Dinesh Kaushik et al[19]:

Oral or non parental drug delivery systems are widely used for the administration of therapeutic drugs. However, the gastro intestinal tract present several barriers to anti cancer drugs in targeting colon cancer. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local disease associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. To achieve successful colonic delivery, which is considered to be the optimum site for colon-targeted delivery of drugs, colon targeting is of prime importance for the topical treatment of disease of colon such as chorn's diseases, ulcerative colitis, colorectal cancer, and amebiasis.

Kerl G.wagner et al[20]:

Enteric coated bisacodyl pellets were compressed in to divisible disintegrating tablets on a high speed rotary tablet press and investigated for pellet damages. The degree of pellet damages was examined via the bisacodyl dissolution during the acid treatment of the drug release test for enteric coated articles according to USP 23. The damages depended on the type of filler-binder used and the settings of the press. Avicel PH 101 proved to be the most suitable filler-binder, effecting homogenous distribution of the pellet.

Ohno, shigeru et al[21]:

Enteric coatings are provided on a solid pharmaceutical dosage forms by a method comprising covering the dosage form with an aqueous solution of a polymeric substance having carboxyl groups in the water soluble salt form and contacting the thus coated dosage forms with an inorganic acid to convert the polymeric substance in to the water-insoluble acid form. The coating solution includes no organic solvent, and this method is safe.

3.2 REVIEW OF LITERATURE ON EUDRAGIT POLYMERS

Many pharmaceutical dosage forms irritate the stomach mucosa due to their chemical properties. Others undergo chemical changes in gastric acid and through the action of enzymes, thus becoming less effective. In order to protect the stomach from irritation and/or to protect drugs from degradation in gastric acid /enzymes, enteric coated dosage forms are regularly formulated. The Eudragit grades for enteric coatings are based on anionic polymers of methacrylic acid and methacrylates. They contain –COOH as a functional group. They dissolve at ranges from pH5.5 to7.The different products are available as aqueous dispersions, powders and organic solvents.

Table No. 3. Eudragit polymers with different dissolution properties:

Applications	Eudragit Grades	Availability	Functionality	Dissolution Properties
Drug delivery in Duodenum	EUDRAGIT L100-55	Powder	Anionic polymers with Methacrylic Acid as a functional group	Dissolution above pH 5.5
	EUDRAGIT L30D-55	Aqueous dispersion 30%		
Drug delivery in Jejunum	EUDRAGIT L100	Powder		Dissolution above pH 6.0
Drug delivery in Ileum	EUDRAGIT S100	Powder		Dissolution above pH 7.0
Colon delivery	EUDRAGIT FS30D	Aqueous dispersion 30%		Dissolution above pH 7.0

Ceballos A et al[22]:

Extended-release theophylline (TP) matrix tablets were prepared by direct compression of drug and different pH-dependent (Eudragit L100, S100 and L100-55) and pH-independent (Eudragit RLPO and RSPO) polymer combinations. The influence of varying the polymer/polymer (w/w) ratio and the drug incorporation method (simple blend or solid dispersion) was also evaluated. Drug release, monitored using the Through Flow Cell system, markedly depended on both the kind of Eudragit polymer combinations used and their relative content in the matrix. Maintaining a constant 1:1 (w/w) drug/polymers ratio, the selection of appropriate mixtures of pH-dependent and pH-independent polymers enabled achievement of a suitable control of TP release. In particular, matrices with a 0.7:0.3 w/w mixture of Eudragit L100-Eudragit RLPO showed highly reproducible drug release profiles, with an almost zero-order kinetic and allowed 100% released drug after 360 min. As for the effect of the drug incorporation method, simple blending was better than the solid dispersion technique, which not only did not improve the release data reproducibility, but also caused, unexpectedly, a marked slowing down in drug release rate.

Guo HX et al[23]:

The enteric-coated dosage forms are designed to resist the acidic environment of the stomach and to disintegrate in the higher pH environment of the intestinal fluid. Polymers for enteric coating can be applied to solid dosage forms (granules, pellets**,** or tablets**)** from aqueous latex or pseudo latex dispersions, aqueous solutions of alkali salts, or organic solvent solutions**.**

M.Zahirul I Khan et al[24]:

Lactose-based placebo tablets were coated using various combinations of two methacrylic acid copolymers, Eudragit® L100-55 and Eudragit® S100, by spraying from aqueous systems. The Eudragit® L100-55–Eudragit® S100 combinations (w/w) studied were 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5 and 0:1. The coated tablets were tested in vitro for their suitability for pH dependent colon targeted oral drug delivery. The same

coating formulations were then applied on tablets containing mesalazine as a model drug and evaluated for in vitro dissolution rates under various conditions. The results also demonstrated that a combination of Eudragit® L100-55 and Eudragit® S100 can be successfully used from aqueous system to coat tablets for colon targeted delivery of drugs and the formulation can be adjusted to deliver drug at any other desirable site of the intestinal region of the GI tract on the basis of pH variability. For colon targeted delivery of drugs the proposed combination system is superior to tablets coated with either Eudragit® L100-55 or Eudragit® S100 alone.

Poonam Kushwaha et al[25]:

In the recent year colonic drug delivery has gained importance for delivery of drug for the treatment of local diseases associated with colon and systemic delivery of therapeutic peptides and proteins. This article gives an overview on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery. This article also discusses advantages and limitations of the approaches applied and work has been done in the field of site specific drug delivery to colon.

Xue Duan et al[26]:

Layered double hydroxides (LDHs) or so-called anionic clays consist of cationic brucite-like layers and exchangeable interlayer anions. Because of their biocompatibility, these layered inorganic solids can be used as host materials to create drug–LDH host–guest supramolecular structures. Because of the basicity of LDHs however, LDHs as drug delivery system will be limited for use in the stomach where pH is 1.2. A core-shell material has been prepared therefore in this work. A non-steroidal anti-inflammatory drug, Fenbufen-intercalated LDHs as the core was coated with enteric polymers, Eudragit® S 100 or Eudragit® L 100 as a shell, giving a composite material which shows controlled release of the drug under in vitro conditions which model the passage of a material through the gastrointestinal tract.

Davis et al[27]:

The subject invention involves pharmaceutical compositions in dosage unit form, for peroral administration of bisacodyl to a human or lower animal having a gastrointestinal tract, with a lumen there through, with a small intestine and a colon with a junction there between, comprising:

(a) A safe and effective amount of rapidly-dissolving bisacodyl means; and

(b) A delivery means which prevents the release of bisacodyl from the dosage form into the lumen of the gastrointestinal tract during transport of the dosage form through the lumen until the dosage form is near the junction between the small intestine and the colon and which then releases the bisacodyl in the lumen near the junction between the small intestine and the colon.

Hiroto Bando et al[28]:

Theophylline was found to dissolve completely from pellets coated with Eudragit® S100:L100 (1:1) plasticized with 50% TEC at pH 6.0 after 2 h. The shape of the pellets was maintained during dissolution testing. In conclusion, the plasticizer content in the film coating influenced the dissolution profile of theophylline from pellets coated with Eudragit® S100:L100 (1:1). A large amount of the TEC was leached from the enteric films before drug release was initiated and a TEC level of approximately 30% in the films, based on the polymer weight, was the critical amount of TEC for initiating drug release during dissolution testing at pH 6.0. While enteric films are more soluble and dissolve faster at higher pH values, the kinetics of plasticizer release was one of the important factors controlling the dissolution of drugs at pH 6.0, at which pH the enteric polymers were insoluble.

Zeitoun,paul et al[29]:

Coated compress tablets for oral administration are disclosed which substantially disintegrate specially at the level of the colon. The tablets comprise a compressed center piece containing an active agent which center piece is coated by a first coating layer which is comprised of a mixture of pharmaceutically acceptable film forming organic polymer materials which is non-deteriorated by a neutral or a alkaline aqueous medium and a second coating layer which is comprised of pharmaceutically acceptable Enteric organic polymer coating material.

Allwood,Michael et al[30]:

Delayed release compositions comprising an active compound and glassy amylose. A variety of different types of active compound may be employed in the compositions. The compositions are particularly adapted for achieving the selective release of medicaments in to the colon.

Iamartino et al[31]:

Orally administrable pharmaceutical preparation containing an active ingredient to be released in the lower part of the gastrointestinal tract, i.e., in the large intestine and especially colon, consisting of a core containing a therapeutically active substance and coated with three protection later of different solubility.

Gary Robert et al[32]:

The present invention relates to a pharmaceutical composition in a unit dosage form for peroral administration in a human or lower animal, having a gastrointestinal tract comprising a small intestine and a colon with a lumen there through having an inlet to the colon from the small intestine, comprising;

a. A safe and effective amount of rapidly dissolving Bisacodyl incorporated into compressed, bi-convex tablets.
b. A non-PH dependent smoothing coat applied to the tablet to provide a smooth tablet surface free from edges and sharp curves; and
c. An enteric polymer coating material comprising at least one inner coating layer and only one outer coating layer; where in the rapidly dissolving Bisacodyl is released at a point near the inlet to, or within the colon; each of the inner coating layer(s) is an enteric polymer that begins to dissolve in an aqueous media at a PH between about 5 to about 6.3; and the outer coating layers is an enteric polymer that begins to dissolve in an aqueous media at a pH between about 6.8 to about 7.2

John T.Fell et al[33]:

The effect of a pH-dependent polymer coating, Eudragit S100 on its ability to protect a model drug and control its release from rapidly disintegrating tablets has been examined Invitro conditions were chosen to mimic those likely to occur during transit from the mouth to the colon. Dissolution was affected by coating thickness and pH. At a given pH, the nature of the buffer system dramatically affected dissolution

and disintegration profiling experiments involving PH changes and mimicking the extremes of conditions prevailing in vivo indicated that release of drug may commence in the duodenum or not at all.

Jain D, Panda AK et al[34]:

He investigates the Eudragit S100 entrapped insulin microspheres for oral delivery. They were found that insulin loaded Eudragit S100 microspheres retard the release of insulin at low pH. And release insulin at pH 7.4 in the colon.

Kelm et al[32]:

The present invention relates to a pharmaceutical composition in a unit dosage form for peroral administration in a human or lower animal, having a gastrointestinal tract comprising a small intestine and a colon with a lumen there through having an inlet to the colon from the small intestine, comprising:

a. A safe and effective amount of rapidly dissolving Bisacodyl incorporated in to or coated on the surface of a dosage form selected from the group consisting of a spherical substrate, an elliptical substrate, a hard capsule, or a compressed tablet, with a maximum diameter of about 3mm to about 10mm;and
b. An enteric polymer coating material.

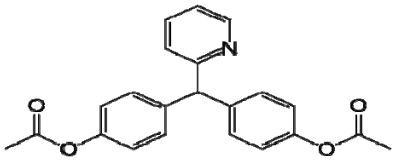
The enteric polymer coating material has a coating thickness of at least about 250 micrometers.

4.0. DRUG PROFILE[35-36]

Description: The drug is the derivatives of diphenylmethane, are stimulant laxatives used to treat constipation. It is administered either orally as a tablet or rectally as an enema or rectal suppository.

Chemical Name: 4, 4- (prydinyl-2-methylene) diphenyl diacetate.

Molecular Structure:



(pyridin-2-ylmethanediyl)dibenzene-4,1-diyl diacetate
OR
4,4'-(pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate

Molecular formula: $C_{22}H_{19}NO_4$.
Molecular weight: 361.4.
CAS NO: 603-50-9.
Description: A white or almost white crystalline powder.
Solubility: Practically insoluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute mineral acids.
pH: 6-7 (10%w/v suspension in water)
Melting point: 131-135^{0}c

Loss on Drying: 0.18 %w/w.

Mechanism of Action: Stimulant laxatives are believed to produce laxation by directly stimulating peristaltic movement of the intestine via local mucosal irritation, thus increasing motility. More recent studies suggest that stimulant laxative (drug) promotes evacuation of the colon by altering intestinal fluid and electrolyte absorption. This causes a net intestinal fluid accumulation and produces laxation.

Pharmacokinetics: Drug is administered either orally or rectally. Drug is minimally absorbed (15%), and the onset of action of the drug begins 6-8 hours after an oral

dose and 15- 60 minutes after rectal administration. Drug distributes locally, and the circulating drug undergoes hepatic metabolism and is then excreted in the urine.

Pharmacokinetic Data

Bioavailability	**15%**
Metabolism	**Hepatic(CYP450-mediated)**
Half life	**16 Hours**
Excretion	**Primarily in the feces, systemically absorbed drug is excreted in the urine**

CONTRAINDICATIONS/PRECAUTIONS:

All laxatives are contraindicated in patients with appendicitis, GI obstruction, abdominal conditions requiring surgery, or undiagnosed abdominal pain.

Stimulant laxatives, such as drug (API) are most likely to cause GI irritation, fluid and electrolyte loss, nausea, vomiting, or diarrhea.

Laxative dependence can occur with long-term or excessive laxative therapy.

Drug administration can exacerbate ulcerative colitis, rectal fissures, ulcerative lesions of the colon, and fecal impaction. Therefore, the drug is contraindicated in patients with these conditions.

Prolonged Drug therapy can cause potassium depletion.

The safety of Drug usage during pregnancy has not been determined, so use of the drug should be avoided in women of child bearing age or during pregnancy, unless the potential benefits outweigh the risks.

DRUG INTERACTIONS: Concomitant use of Drug as oral tablets and antacids, milk, or other drugs that cause an increase in gastric pH levels can cause the enteric coating of the drug to dissolve prematurely, leading to possible gastric or intestinal irritation.

ADVERSE REACTIONS: Stimulant laxatives, such as Drug (API) are most likely to cause GI irritation, fluid and electrolyte loss, or diarrhea. Short-term usage (at normal dosages) typically results in abdominal pain or cramps, faintness, nausea/vomiting, or mild abdominal discomfort.

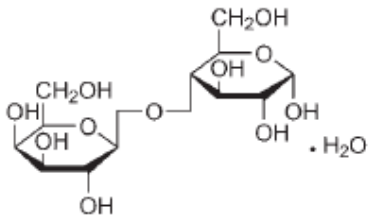
- Prolonged usage of drug can cause hypokalemia.
- Prolonged use of stimulant laxatives can result in dependence, leading to constipation when use is interrupted.

5. 0 EXCIPIENTS PROFILE[37]

5.1. LIST OF API AND EXCIPIENTS USED:

S. No.	MATERIALS	SUPPLIERS	CATEGORY
1	Bisacodyl API	Dhisman pharmaceuticals	Drug
2	Lactose monohydrate (tabletose100)	Meggle excipient & Technology	Diluent
3	Microcrystalline Cellulose (AVICEL PH101)	FMC Biopolymer	Adsorbent; suspending agent
4	Klucel LF hydroxyl propyl cellulose	Aqualon	Coating agent; viscosity-increasing Agent
5	Maize starch B 5%	Roquttee	Binder/Disintegrant
6	Pregelatinized starch (Lycatab)	Roquttee	Binder
7	HPMC E5	Dow chemicals	Film coating
8	Eudragit L100	Evonik	Enteric coating polymer
9	Eudragit S100	Evonik	Enteric coating polymer
10	TEC	Vertillus performance materials Inc	Plasticizer
11	Magnesium Stearate	Ferro-Portugal	Lubricant
12	Sucrose	MB Sugars & pharma	Sweetening & Bulking agent
13	HPMC E15	Dow chemicals	Film coating
14	Purified talc	Luzenac pharma	Glidant
15	Iron oxide yellow	Roha Dye Chem	Coloring agent
16	IPA	Merck	Non aqueous solvent
17	Titanium dioxide	Krons-Germany	Opacifier
18	Carnauba wax	Quality Chemical industries, Mumbai	Polishing agent

5.2. Lactose Monohydrate

Nonproprietary names	Lactose (BP), Lactose Monohydrate (PhEUR, USP-NF).
Synonym	CapsuLac, GranuLac, Lactochem, lactosum monohydricum, onohydrate, Pharmatose, PrismaLac, SacheLac, SorboLac, pheroLac, SuperTab 30GR, Tablettose.
Chemical Name and CAS Registry Number	O-b-D-Galactopyranosyl-(1!4)-a-D-glucopyranose monohydrate, [10039-26-6]
Empirical Formula and molecular weight	**1.** Formula: $C_{12}H_{22}O_{11}$·H2O. 2. **2.** MW: 360.31
Description	In solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. α-lactose monohydrate, β-lactose anhydrous and α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder, it is odorless and slightly sweet-tasting.
Structural formula	
pH	5.5-8.9.(1%w/w aqueous solution at 25°)
Solubility	Insoluble in chloroform, ethanol, ether. Soluble in water in ratio of 1 in 5
Melting point	201–202^{0}C (for dehydrated a-lactose monohydrate)
Moisture content	Lactose monohydrate contains normally has a range of 4.5–5.5% w/w water content.
Functional Category	Dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler.

Applications in Pharmaceutical formulation or technology	Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is added to freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose to prepare sugar-coating solutions. It may also be used in intravenous injections. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Direct-compression grades of lactose monohydrate are available as spray-dried lactose and anhydrous lactose.
Incompatibilities	A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, amfetamines and lisinopril.
Stability and storage conditions	Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show mutarotation. Lactose should be stored in a well-closed container in a cool, dry place.
Safety	Lactose is widely used as a filler and filler-binder in orals and injections. Adverse reactions to lactose are largely attributed to lactose intolerance, results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence

5.3 Microcrystalline cellulose (Avicel PH101)

Synonyms	Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel ; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.
Description	Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.
Functional categories	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
Solubility	Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
pH	5.0–7.5
Density (bulk) **Density (tapped)**	0.32 g/cm3 0.45 g/cm3
Stability and storage conditions	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Microcrystalline cellulose is incompatible with strong oxidizing agents.
Safety	Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.
Applications	Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and

	direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

5.4 Hydroxy propyl cellulose Klucel KF

Synonyms	Cellulose, hydroxypropyl ether; E463; hyprolose; Klucel; Methocel; Nisso HPC; oxypropylated cellulose.
Description	Hydroxypropyl cellulose is a white to slightly yellow-colored, odorless and tasteless powder
Functional categories	Coating agent; emulsifying agent; stabilizing agent; suspending agent; tablet binder; thickening agent; viscosity-increasing agent.
Solubility	soluble 1 in 10 parts dichloromethane; 1 in 2.5 parts ethanol (95%); 1 in 2 parts methanol; 1 in 5 parts propan-2- ol; 1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons; aromatic hydrocarbons; carbon tetrachloride; petroleum distillates; glycerin; and oils.
pH	5.0–8.5 for a 1%w/v aqueous solution.
Density (bulk)	0.5 g/cm3
Stability and storage conditions	Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0, with the viscosity of solutions being relatively unaffected. However, at low pH aqueous solutions may undergo acid hydrolysis, resulting in chain scission and hence a decrease in solution viscosity. Ultraviolet light will also degrade hydroxypropyl cellulose and aqueous solutions may therefore decrease slightly in viscosity if exposed to light for several months. Aqueous hydroxypropyl cellulose solutions have optimum stability when the pH is maintained at 6.0–8.0, and also when the solution is protected from light, heat, and the action of microorganisms.

	Hydroxypropyl cellulose powder should be stored in a well closed container in a cool, dry place.
Incompatibilities	Hydroxypropyl cellulose in solution demonstrates some incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose solutions. The compatibility of hydroxypropyl cellulose with inorganic salts varies depending upon the salt and its concentration
Safety	Hydroxypropyl cellulose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. Hydroxypropyl cellulose is generally regarded as an essentially nontoxic and nonirritant material. However, the use of hydroxypropyl cellulose as a solid ocular insert has been associated with rare reports of discomfort or irritation, including hypersensitivity and edema of the eyelids. Adverse reactions to hydroxypropyl cellulose are rare.
Applications	Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations. In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release matrix former. Concentrations of hydroxypropyl cellulose of 2–6% w/w may be used as a binder in either wet-granulation or dry, direct-compression tableting processes. Concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

5.5. Maize Starch:

Synonyms	Amido, amidon, amilo, amylum.
Description	It is as an odorless & tasteless, fine, white color powder comprising very small spherical/ovoid granules whose size & shape are characteristic for each botanical variety.
Functional categories	Glidant, tablet & capsule diluent, tablet & capsule disintegrant, tablet binder.
Solubility	Practically insoluble in cold ethanol (95%) & in cold water.
pH	5.5-6.5
Density (bulk) **Density (tapped)**	0.462 g/cm^3 0.658 g/cm^3
Stability and storage conditions	Dry, unheated starch is stable if protect from high humidity. When use as diluent/disintegrant in solid dosage form, starch is consider to be inert under normal storage condition. However , heated starch solution/past are physically unstable & readily attacked by microorganism to form a wide verity of starch derivatives & modified starch that have unique physical properties. Starch should store in airtight container in & dry place.
Incompatibilities	_
Safety	Starch is widely used as excipient in pharmaceutical formulations, particularly oral tablet. It is inedible food substance & generally regarded as a nontoxic and nonirritant material. However, oral consumption of massive doses can be harmful owing the formation of starch calculi, which cause bowel obstruction.
Applications	It is an excipient primarily in oral solid dosage formulations where it is utilized as a binder, diluent & disintegrant. As a diluent, starch is use for preparation of standardized triturates colorants or blending process in manufacturing operations. it is use as disintegrant at concentration of 3-15%w/w. unmodified starch does not compress well and tends to increase the tablet friability and capping in high concentration.

5.6. Pregelatinized starch

Nonproprietary Names	BP: Pregelatinized starch PhEur: Amylum pregelificatum UspNF: Pregelatinized starch.
Synonyms	Compressible starch, Instastarch, Lycatab, Merigel, Lycatab PGS;
Chemical Name and CAS Registry Number	PG [9005-25-8]
Emperical formula and molecular weight	$(C_6H_{10}O_5)_n$ where n= 300-1000
Functional category	Tablet and capsule diluent; Tablet binder; tablet and capsule disintegrant;
Description	Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.
Typical properties	
Angle of repose	40.7
Density(bulk).(tapped)	0.586g/cm3 (0.879g/cm^3)
Density(true)	1.516g/cm3
Flow ability	18-23%.
Solubility	Practically insoluble in organic solvents slightly soluble in cold water, depending up on the degree of Pregelatinization.
Safety	Pregelatinized starch and starch are widely used in oral solid dosage formulations. PG starch is generally regarded as a non toxic and non irritant excipient. However, oral

	Consumption of large amount of PG starch may be harmful.
Stability and storage conditions	PG starch is stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.
Applications	PG starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, disintegrant. In comparison to starch grades of PG starch may be produced with enhanced flow and compression characteristics such that the PG material may be used as a tablet binder in dry compression or direct compression processes. In such process, PG starch is self-lubricating

5.7. Sucrose:

Nonproprietary Names	BP: Sucrose. JP: Sucrose. PhEur: Saccharum USPNF: Sucrose
Synonyms:	Beet Sugar, Cane sugar, Saccharose, Sugar.
Chemical Name and CAS Registry Number	Beta-D-fructofuranosyl-alpha-D-glucopryanoside[57-50-1]
Emperical Formula and molecular weight	$C_{12}H_{22}O_{11}$ 342.30
Functional category	Coating agent, granulating agent, tablet binder, tablet filler, and tablet-capsule diluent.
Description	Sucrose occurs as colorless crystals, as crystalline masses or blocks or as a white crystalline powder; it is odorless and has a

	sweet taste
Typical properties	
Bulk density	0.60g/cm^3.
Tapped density	0.82g/cm^3.
True density	1.6g/cm^3
Flowability	Crystalline sucrose is free flowing, where as powdered sucrose is a cohesive solid.
Stability and Storage conditions	Sucrose has good stability at room temperature and at moderate relative humidity. It absorbs up to 1% moisture, which is released up on heating at 90°C.
Safety	Sucrose is hydrolyzed in the small intestine by the enzyme sucrase to yield dextrose and fructose, which are then absorbed when administered intravenously, sucrose is excreted unchanged in the urine
Applications	Sucrose is widely used in oral pharmaceutical formulations. Tablets that contain large amounts of sucrose may harden to give poor disintegration. Sucrose syrups are used as tablet coating agents at concentration between 50% and 67%w/w.

5.8. Carnauba wax:

Nonproprietary Name	BP: Carnauba wax JP: Carnauba wax. PhEur: Cera carnauba. USPNF: Carnauba wax.
Synonyms	Brazil wax ; Caranda wax ; E903
Chemical Name and CAS Registry Number	Carnauba wax [8015-86-9]
Functional Category	Coloring agent
Description	It occurs as a light brown to pale yellow colored powder, flakes, or irregular lumps of a hard brittle wax. It has a characteristic bland odor and practically no taste.
Solubility	Soluble in warm chloroform and in warm toluene; slightly soluble in boiling ethanol (95%); practically insoluble in water
Safety	Carnauba wax is widely used in oral pharmaceutical formulations, cosmetics, and certain food products. It is generally regarded as an essentially non-toxic and non-irritant material.
Stability and storage conditions	Carnauba wax is stable and should be stored in a well-closed container, in a cool, dry place.
Applications:	Carnauba wax is widely used in cosmetics, certain foods and pharmaceutical formulations. It is the hardest and highest melting of the waxes commonly used in the

	pharmaceutical formulation and is used primarily as a 10% w/v aqueous emulsion to polish sugar coated tablets. The carnauba wax coating produces tablets of good luster without rubbing. Carnauba wax may also be used in powder form to polish sugar coated tablet

5.9. Talc:

Synonyms	Hydrous magnesium calcium silicate, hydrous magnesium silicate, talcum, Luzenac Pharma, magnesium hydrogen metasilicate, purtalc, superiore.
Description	Very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
Functional categories	Anti-caking agent, glidant, tablet and capsule Diluent, tablet and capsule lubricant.
Solubility	Practically insoluble in dilute acids and alkalis, organic solvents, and water.
Ph	7-10 (20% w/v aqueous dispersion)
Stability and storage conditions	Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. Should be stored in well closed container in a cool and dry place.
Incompatibilities	Incompatible with quaternary ammonium compound.
Safety	Talc is not adsorbed systematically following oral injection and therefore regarded as an essentially nontoxic material.
Applications	Anti-cocking agent, glidant, tablet and capsule Diluent, tablet and capsule lubricant

5.10. Titanium Dioxide:

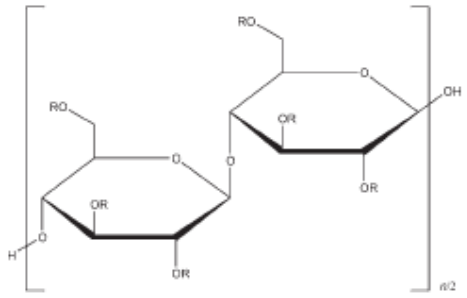
Synonyms	Anatase titanium dioxide, brookite titanium dioxide, color index number 77891, E1701, rutile titanium dioxide.
Description	White, amorphous, odorless and tasteless non hygroscopic powder. Titanium dioxide may occur in several different crystalline for: rutile, anatase and brookite.
Functional Categories	Coating agent, pigment and opacifier.
Solubility	Practically insoluble in dilute sulfuric acid, hydrochloric acid, nitric acid, organic solvent and water. Soluble in hydrofluoric acid and hot conc. sulfuric acid.
Stability and storage conditions	Titanium dioxide is extremely stable at high temperature due to the strong bond between the tetravalent titanium ion and the bivalent oxygen ions. Stored in a well closed container, protect from light, in a cool, dry place.
Incompatibilities	Titanium dioxide may interact with certain active substances. it has also been shown to induce photo oxidation of unsaturated lipids.
Safety	Titanium dioxide is widely used in foods and oral and topical pharmaceutical formulations. It is generally regarded as essentially nonirritant and nontoxic excipient.
Applications	Titanium dioxide is widely used in confectionary, cosmetics, foods, and topical and oral pharmaceutical formulation as a white pigment. Titanium dioxide is also used in dermatological preparations and cosmetics such as sunscreens.

5.11. Eudragit

Synonyms	Eastacryl 30D, Eudragit, Kollioat, Polymeric methacryl
Description	Polymethacrylates are the cationic and anionic polymers of the methacrylic acids Eudragit E:- Cationic polymer, soluble in gastric fluid upto pH=5 Eudragit L, S: - Anionic copolymer of methacrylic acid and methyl methacrylate Eudragit L:-Carboxyl group : Ester group = 1:1 Eudragit S:- Carboxyl group : Ester group = 1:2 White free flowing powders, resistant to gastric media soluble in intestinal fluid pH 6 – 7 Eudragit RL,RS = Ammonio methacrylate copolymer Methacrylate with amine like odour
Functional categories	Film former, tablet binder, tablet diluents
Loss on drying	50%
Stability and storage conditions	Dry powder stable at temperature less than 30^0 C Dispersions sensitive to extreme temperature and phase separation occurs below 0^0C
Incompatibilities	Coagulation may occur by soluble electrolytes, organic solvents and extreme temperature
Applications	It is used as enteric coating film former resistant to gastric juice and dissolves readily above pH 5.5

5.12. Hydroxy propyl methyl cellulose

Nonproprietary Names	Hypromellose (BP, JP, PhEur, USP)
Synonyms	Benecel, hydroxypropyl methylcellulose, HPMC, hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, pharmacoat.
Chemical Name	Cellulose hydroxypropyl methyl ether
Empirical Formula	Hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose.

Molecular weight	10000–1500000
Structural Formula	 where R is H, CH_3, or $CH_3CH(OH)CH_2$
Description	Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder
Typical Properties	
pH	5.0–8.0 (2% w/w solution)
Loss on drying	45.0%
Residue on ignition	41.5%
Density	1. Density (bulk) 0.341 g/cm3. 2. Density (tapped) 0.557 g/cm3. 3. Density (true) 1.326 g/cm3.
Melting point	190–200^{0}C
Moisture content	Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.
Solubility	Soluble in cold water, practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol.
Specific gravity	1.26
Nominal viscosity (mPas)	3 - 100000 (2%w/w solution at 20^{o}C) The different commercial grades are available with varying in viscosities, Methocel K4M 4000 mPas Methocel K15M 15000 mPas

	Methocel K100M 100000 mPas
Functional Category	Bioadhesive material; coating agent; controlled-release agent; emulsifying agent; extended-release agent; film-forming agent; modified-release agent; solubilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent.
Applications in Pharmaceutical Formulation or Technology	Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. It is also widely used in cosmetics and food products.
Stability and Storage Conditions	It is a stable material, although it is hygroscopic after drying. It should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	It is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.
Safety	It is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect.

5.13. Magnesium Stearate

Nonproprietary names	Magnesium Stearate (BP, USP-NF, PhEUR).
Synonym	Dibasic magnesium stearate, magnesium distearate, magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid.
Chemical Name and CAS Registry Number	Octadecanoic acid magnesium salt, [557-04-0].
Empirical Formula and molecular weight	Formula: $C_{36}H_{70}MgO_4$. MW: 591.24. Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$
Description	Magnesium stearate is a very fine, light white, precipitated or milled poorly flowing, cohesive powder, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin
Solubility	Practically insoluble in ethanol, ether and water, slightly soluble in warm benzene and warm ethanol (95%).
Melting point	117–150^{0}C.
Functional Category	Tablet and capsule lubricant.
Applications in Pharmaceutical formulation or technology	Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
Stability and storage conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Safety	Magnesium stearate is non-toxic for oral administration and larger consumption may result in laxative effect and mucosal irritation.

5.14. Iron oxide yellow:

Synonyms	Iron oxide yellow, hydrated ferric oxide, yellow ferric oxide, mapico yellow;
Chemical Name and CAS Registry Number	Iron oxide yellow monohydrate [51274-00-1]
Emperical Formula and molecular weight	1. Formula- $Fe_2O_3.H_2O$ 2. Mol Wt.- 177.70
Functional Category	Colorants
Description	Iron oxides occur as yellow, red, black or brown powder. The color depends on the particle size and shape, and the amount of combined water.
Stability and storage conditions	Iron oxides should be stored in well-closed containers stored in a cool, dry place
Incompatibilities	Iron oxides have been reported to make hard gelatin capsules brittle at high 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 in to gelatin material
Safety	Iron oxides are widely used in cosmetic, foods and oral and topical pharmaceutical applications. They are generally regarded as non-toxic and non-irritant excipients
Applications	Iron oxides are widely used in cosmetics food and pharmaceutical applications as colorants and UV absorbers

5.15. Isopropyl Alcohol:

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.
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.
Empirical Formula & Molecular Weight	Formula - C3H8O MW - 60.1
Solubility	Solubility Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solutions. Forms an azeotrope with water, containing 87.4% w/w isopropyl alcohol (boiling point 80.378C).
Functional category	Disinfectant; solvent.
Auto ignition temperature	42.5°C
Dielectric constant D20 = 18.62	D20 = 18.62
Boiling point	82.4°C
Stability and storage conditions	Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

Incompatibilities	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
Safety	LD50 (dog, oral): 4.80 g/kg(9) LD50 (mouse, oral): 3.6 g/kg LD50 (mouse, IP): 4.48 g/kg LD50 (mouse, IV): 1.51 g/kg LD50 (rabbit, oral): 6.41 g/kg LD50 (rabbit, skin): 12.8 g/kg LD50 (rat, IP): 2.74 g/kg.
Applications	Used in cosmetics and pharmaceutical formulations, primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity.

6.0 EXPERIMENTAL WORK

6.1. EQUIPMENTS USED

Table No.4 List of Equipments

Sr. No.	Name of instrument	Manufacturing Company
1	Digital weighing balance	Essae digi DS-450SS
2	Common weighing balance	Essae Teraoka Ltd
3	Stirrer	REMI motors Ltd
4	Neocota	Kevin
5	Compression Machine 27 station	Cadmach
6	Blender 2 liters	Gansons
7	Sieves(ASTM)	Jayant Scientific Ltd
8	Heating Mantle	SUNBIM
9	Vernier Calipers	Mitutoyo corp
10	Hardness tester	Benchsaver series VK200
11	Disintegration test apparatus	Electro lab
12	Friabilator	Electro lab EF2
13	Moisture Analyser	Essae MB45
14	Digital pH meter	Mettler Toledo
15	Bulk density apparatus	Campbell electronics
16	HPLC	Agilent Technologies.1200 series

6.2 INNOVATOR PRODUCT CHARACTERISATION :

Innovator product is characterized for its various parameters as follows:

- **Manufactured by:** Boehringer Ingelheim Limited, France.
- **Batch Number: 18973.**
- **Expiry date: June 2013.**

- **Dosage form**: Tablets.
- **Coated/uncoated:** coated, Enteric coated, Sugar coated.
- **Embossing:** upper punch –None, Lower punch—None.
- **Color:** yellow Colored.
- **Shape:** Biconvex Shaped (round).
- **Diameter (mm) Initial:** 5.92, 5.82, 5.96, 5.89, 5.88, 6.03.
- **After DT in 0.1N HCl for 2hrs:** 5.58, 5.64, 5.59, 5.55, 5.68, 5.56.
- **Thickness (mm) Initial:** 3.63, 3.51, 3.55, 3.59, 3.50, 3.62.
- **After DT in 0.1NHCl for 2hrs:** 3.18, 3.27, 3.10, 3.04 3.15, 3.20.
- **Hardness(N):** 41—51
- **Weight Initial (mg):**100.7, 95.7, 101.2, 99.7, 101.0, 96.7.
- **After DT in 0.1NHCL for 2hrs:** 77.3, 74.5, 77.6, 75.8, 79.4, 73.5.

✓ **Disintegration Time(min' sec'');**

- **After DT in 0.1NHCL for 2hrs:** In pH 6.4 up to 2hrs the tablet was not disintegrating. In pH 7.6 -33mins was taken to disintegrate the tablets.
- **Pack:** Blister pack.

- **Storage:** Do not store above 25^0C

6.3. PREFORMULATION STUDIES[38]

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

Preformulation studies relate to pharmaceutical and analytical investigation carried out-processing and supporting formulation development efforts of the dosage form of the drug substance preformulation yields basic knowledge necessary to develop suitable formulation for toxicological use. It gives information needed to define the nature of the drug substances and provide a dosage form. Hence, the following preformulation studies were performed for the obtained sample of drug. (Leon Lachman et. al.)

6.3.1.Organoleptics properties:

a) Color: A small quantity of Bisacodyl powder was taken in butter paper and viewed in well-illuminated place.

b) Taste and Odor: Very less quantity of Bisacodyl Aspirin powder was used to get taste with the help of tongue as well as smelled to get the odor.

6.3.2. Physical Characteristics:

a) Loss on drying: This is employed in IP, BP, and USP. Although the loss in weight in the samples so tested, principally is due to water, small amount of other volatile material will contribute to the weight loss the moisture balance combines both the

drying presses and weight recording, it is suitable where large numbers of sample are handled and where a continuous record of loss in weight with time is required.

Procedure:

Placed about 1gm of API in the plate of digital moisture balance instrument. Set the temp 105^{o}C and run up to constant weight finally read out the percentage loss on drying automatically.

% LOD = loss on drying/total sample × 100

b) Angle of repose: In this method weighed 20gm of bulk powder, passed it through sieve no 40 mesh size .Then allowed to flow under gravity though funnel and angle of incline of the formed. By measuring the height and having a fixed base i.e. diameter. Put the value into following formula;

Angle of Repose $\theta = \tan^{-1} h/r$

$\tan \theta = h/r$

Where
h = height of peak
r = radius of peak base

Table No. 5 - Angle of repose.

Angle of repose (degrees)	Flow ability
25-30	Excellent
31-35	Good
36-45	Passable
>46	Very Poor

c) Determination of Density:

Bulk Density:

Determined by pouring bulk drug pre sieved by 40 mesh size in to a graduated, cylinder via large funnel in and measuring the volume and weighed. The tapped density is determined by placing a graduated cylinder containing a known mass of drug or formulation on a mechanical tapper apparatus USP 1. This is operated for a fixed 100 taps. The powder bed volume has reached minimum.

Then quantities put in formula:

Bulk density: Bulk mass / Bulk volume

True density: Bulk mass / tapped volume

d) Compressibility index:

It is determined by taking tapped density and bulk density which has been put in the formula given below and determined compressibility index using following formula.

$$\text{Compressibility index} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \text{X} 100$$

Table No. 6 - Compressibility index limits

% Compressibility	Flowability
5-12	Excellent
12-16	Good
18-21	Fair
23-25	Poor
33-38	Very poor
More than 40	Very, very poor

d. Hausner Ratio: It is the ratio of tapped volume or tapped density to bulk density.

Hausner Ratio = Vb/ Vt

Table No. 7 - Hausner Ratio index limits:

Hausner Ratio	Flowability
1.2-1.3	**Excellent**
1.3-1.4	Good
1.4-1.5	Fair
1.6-1.9	Poor

e. Particle Size: Sieving method

The particle size distribution and shapes affect various chemicals and physical properties of drug substance. The effect is not only on the physical properties of solid drug but also, in some instances, on their biopharmaceutical behavior. E.g. the bioavailability of griseofulvin and phenacetin is directly related to the particle size distribution of these drugs.

Size also plays a role on the homogeneity of the final tablet size can also be a factor in the stability, fine materials are relatively and are open to attack from the diluents and active raw materials several tools are commonly employed to monitor the size for quantities particle size distribution analysis of material that range upward from about 50mm, sieving or screening is appropriate. Most pharmaceutical powders, however, range in size from 1 to 120 μm.

In the sieving process the powder is passed over a preferred screen, so that particle sufficiently small will pass through, while those that are over size will be retained on the sieve. Sieve is therefore, a simple 'go/no go' test which divides the powder into fraction above and below a specified size.

Method:

This test was performed with the help of sieve of different size. They were fitted in the platform of sieve shaker in such a way that the coarse sieve was placed on top corresponding to the finer sieves. Placed 10 gm of the Drug X on top and run the machine to separate out the powder and after some time off the machine and took the weight of the

powder remained on the sieve (s) finally, calculated the % of powder retained on each sieve by the following equation.

$$\% \text{ Powder retained} = \frac{\text{Amount of powder retained}}{10} \times 100$$

6.3.3. Solution Properties

a) Solubility:

Solubility measured by shaking an excessive previously weighed solid solute in the presence of the solvent, in sealed container at a temperature i.e. 25^0C. After equilibration a sample is withdrawn. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles. The solubility is expressed in turns of ratio of solute and solvent.

b) pH:

Weighed and transferred accurately about 1.0g of sample in a 20 ml clean and dried volumetric flask, dissolved in carbon dioxide free water and made up the volume to 20 ml with same solvent, mixed. Determined the pH of freshly prepared solubility by using precalibrated pH meter.

c) Melting Point: -

It is one of the parameters to judge the purity of crude drugs. In case of pure chemicals or phytochemicals, melting points are very Sharp and constant. Since the crude drug contains the mixed chemicals, they are described with certain range of melting points.

6.3.4. Identification of Drug and compatibility study:

In 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-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

Drug-Excipient Compatibility studies

Procedure:

- Taken weighed quantity of drug and excipients according to ratio given in literature.
- Poured drug in individual vials.
- Then drug plus individual excipient poured in to separate vials according ratio. Labeled every vial.
- Finally keep all vials at 25^0 C/60%R.H and 50^0C/75% R.H for 1 Month.
- Before keeping vials for exposure initial appearance of powder mixture were noted down. Then sealed the vials with rubber closure.
- After 1 month vials were removed from exposure and observed for physical appearance only.
- Results are mentioned in result and discussion.

The blend of the active pharmaceutical ingredient and excipients were subjected to accelerated conditions of temperature and humidity viz. 25ºC / 60% RH, 50ºC / 75% RH and refrigeration 4 - 8ºC. As per ICH guidelines to evaluate the compatibility by

observing, the physical parameters of the physical mix with a view to narrow down on the probable excipients to be used.

The evaluation was carried out for 4 weeks and the samples from 25ºC and 60% RH, 50ºC and 75% RH incubation chambers were observed for any physical change such as Colour, odour etc. by comparing with samples stored in refrigeration 4 - 8ºC.

The API was compatible with the excipients tested. The ingredients identified for developing Bisacodyl was limited to generally regarded as safe commonly used excipients viz.: - Lactose Monohydrate, Pregelatinized Starch, Magnesium state, Talc, Sucrose, HPMC E15, MCC105, Mannitol, Eudragit L100, Eudragit S100, TEC

During the development, trials were conducted by varying the ratios of the excipients in the blend to optimize the formula by measuring the physical characteristics such as average weight, hardness, friability and thickness.

6.4. FORMULATION TABLES:

Experimental work: Delayed Release Tablets

6.4.1. Formula for core tablet

Batch no: F1 – F5

Table No 8. Formula for core tablet

Sr. No.	Ingredients	Amount (mg/ per tablet) Formulation No.				
		F1	F2	F3	F4	F5
1	API	5	5	5	5	5
2	Lactose Monohydrate	40.1	35.1	35.1	35.1	25
3	Maize Starch	3.0	5.0	8.3	8.3	-
4	Pre gelatinized starch	0.5	3.5	1.5	1.5	19.9
5	Magnesium Stearate	1.4	1.4	0.1	0.1	0.1
	Total	50.00	50.00	50.00	50.00	50.00
	Conclusion	Check Feasibility Properties	Capping was observed	Unity of drug content was not in limit	Unity of drug content was not in limit	Core tablet was optimized

According to above trials the F-5 was the optimized formula for the core tablet. It complies all the parameters for core tablet.

So this formulation was selected further study. Selected formulation was taken for seal coating with HPMC 5cps as seal coating polymer and enteric coating with Eudragit S100 and Eudragit L100 as enteric coating polymer.

Preparation of Core Tablets (direct compression):

Step I: **Shifting** - the weighed quantity of API, Lactose monohydrate, maize starch, PG Starch sieved through 40# size.

Step II: Blending

The above shifted materials were mixed using 2ltr blender for 10min.

Step III: Lubrication

Finally the above shifted materials were lubricated with Magnesium Stearate for 3 min in octagonal blender. These blended materials were ready for compression.

Step IV: Compression of blend material:

- **Compression machine parameter: (for core tablet**)

Table No 9. Compression machine parameter

Punch	5 mm deep concave shape
Machine	27 Station B tooling
Relative Humidity	50 %
Temperature	27 %

- **Tablet parameters**:-

Table No 10. Tablet parameters

Weight of core tablet	50.0 mg
Diameter	5±0.2mm
Thickness	2.3±0.2mm
Hardness	NLT 2 kp
Friability	NMT 1.0%
Disintegration	NMT 15 min in distilled water at ±37^{o}C

6.4.2. Seal Coating:

Seal coating layer is done to protect drug and for increasing the stability of a drug. Mechanical strength of tablets also increased. In order to prevent interaction between active drug & enteric coating solution, the seal coating solution made up of cellulose derivatives. Hydroxyl propyl methyl cellulose polymer used for seal coating.

a) Application of separating layer

1. Separating layer is done to protect drug and for increasing the stability of a drug.
2. Moisture protection
3. Good storage stability
4. Improved passage of the dosage form
5. Smooth and glossy surfaces
6. Prevent interaction between active drug & enteric coating solution.

b) Procedure for preparation of seal coating solution:

1. Dispensed all the ingredients as per manufacturing formula**.**

2. Then take purified water & dissolved HPMC-5 cps for continuous stirring to 45 min.

3. Finally, above solution can be filter through #100 & use for spraying.

c) Seal Coating Parameters:

Table No 11. Seal Coating Parameters

Coating pan RPM	8 to 16
Atomization Pressure	Less than 1.8 Kg / cm^2
Inlet Air Temperature	40° to 55^o C

Spray RPM	3 to 10
Spray Gun	0.8 mm nozzle
Exhaust Temperature	42 to 50

d) Formulation for seal coating:

Batch no: F5A

Table No 12. Formulation for seal coating

Sr. No.	Ingredients	Formulation No. F5A
1.	Weight of uncoated tablets	50mg
2.	H.P.M.C.-5cps	7.5mg
3.	Purified Water	Q.S
4.	% w/w Subcoating solution	5%
5.	Theoretical weight of tablets	57.5mg
6.	Practical weight of tablets	57.8mg
7	% Build up	15%
	Conclusion	Seal coating was optimized.

After giving seal coat on core tablet to all formulation. It was decided to give enteric coat on the same tablets. For this the enteric coating polymer Methacrylic acid co-polymer was selected. Initially 9 % was selected randomly as initial concentration for enteric coating .After spraying coating solution on tablet bed determined required parameters. The increased polymer concentration was increased until the required parameters for enteric coating tablet was obtained.

6.4.3. Enteric Coating solution preparation[39]:

a) Procedure for Enteric coating solution

1. Dispense all the required quantity of ingredients as per manufacturing formula.
2. Dispense total quantity of solvent (IPA + water) and mix it properly.
3. To 50% of solvent, add talc &TEC slowly later mix it for 10-15min with high shear.
4. Take another 50% of solvent & add EudragitS100, EudragitL100 slowly under stirring condition in another Stainless Steel vessel & Stir it up to completly dissolve in 45-60min.
5. Add Talc &TEC solution to the Eudragit solution &mix it for 10min & spray the solution with suitable parameters.

b) Enteric Coating Parameters:

Table No 13. Enteric Coating Parameters

Coating pan RPM	8to 16
Inlet Air Temp	30° to 35° C
Exhaust temperature	32° to 34°C
Spray Gun	0.8 mm nozzle
Spray RPM	3to5
Atomization Pressure	1 to 1.5kg/ cm^2

c) **Enteric Coating- Batch no: F5B to F5G**

Table No 14. Enteric coating Formulation

Sr. No.	Ingredients	Formulation No.					
		F5B	F5C	F5D	F5E	F5F	F5G
1	Initial Weight of Tablets Bead	57.5mg	57.8mg	57.6mg	57.4mg	57.5mg	57.7mg
2	Eudragit L100	0.89mg	0.99mg	1.09mg	1.19mg	1.29mg	1.48mg
3	Eudragit S100	2.94mg	3.27mg	3.59mg	3.92mg	4.25mg	4.90mg
4	TEC	0.58mg	0.64mg	0.71mg	0.77mg	0.84mg	0.97mg
5	Talc	0.77mg	0.86mg	0.94mg	1.03mg	1.11mg	1.28mg
6	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
7	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
8	% w/w Enteric coating Solution	15%	15%	15%	15%	15%	15%
9	Theoretical weight of tablets	62.6mg	63.5mg	63.9mg	63.7mg	64.5mg	64.9mg
10	Final weight of tablets (Enteric Coated)	63.0mg	63.4mg	64.0mg	64.0mg	64.8mg	64.8mg
11	% Build up	9%	10%	11%	12%	13%	15%
	Conclusion	Swelling was observed	DT not matched	DT not matched	DT slightly matched	Enetric coating was optimized	DT not matched
Note – Q.S (Quantity Sufficient) & NOTE: IPA: WATER=80:20							

Finally the polymer concentration for enteric coating of tablet to pass the all required parameters was obtained. From this was concluded the final formulation is **F5F**

6.4.4. Sugar coating solution preparation:

a) Procedure for sugar coating solution:

1. Dispense all the ingredients as per manufacturing formula.
2. Take required quantity of water and boil it &add slowly HPMC E15 to it until to get a clear solution.
3. Take required quantity of water &boil it, and add sucrose to it to get a sucrose solution
4. Shift sucrose solution to HPMC E15 solution and kept in a homogenizer under stirring condition.
5. To the above solution add talc and magnesium stearate and continue stirring for 45 min.
6. Filter the solution through #100 and spray the solution with suitable parameters.
7. Take 2% of sub-coating solution add titanium dioxide, iron oxide yellow under stirring condition up to 30min to get color solution.
8. Filter the solution through #100 and spray the solution with suitable parameters.

b) Sugar coating parameters: Table No. 15

Coating pan RPM	10 to 20
Inlet Air Temperature	50 to 60
Exhaust Air Temperature	47 to 52
Spray RPM	3 to 10
Spray Gun	0.8mm nozzle.
Atomization Pressure	Less than 1.8 kg/cm^2

b) Sugar Coating- Batch no F5F1-F5F5

Table No 16. Sugar Coating Formulation

S.NO	Ingredients	Amt mg/tablet				
		Formulation Numbers				
		F5F1	**F5F2**	**F5F3**	**F5F4**	**F5F5**
	Sub-coating					
1	Sucrose	97.5	22.4	22.4	19.04	19.04
2	HPMC E15	-	6.40	6.40	5.43	5.43
3	MCC 105	7.31	-	-	-	-
4	Mannitol	13.0	-	-	-	-
5	HPMC E5	2.43	-	-	-	-
6	Talc	-	3.2	10.0	8.50	8.50
7	Magnesium Stearate	-	-	1.5	1.28	1.28
	Color or Smooth coating					
8	Opadry yellow	6.25	3.0	-	-	-
9	Opagloss Yellow	-	-	3.5	-	-
10	Iron Oxide Yellow	-	-	-	0.40	0.40
11	Titanium dioxide	-	-	-	0.065	0.065

	Polish Coating					
12	Opagloss clear	2	2	-	-	-
13	Carnauba Wax	-	-	-	0.50	0.50
14	IPA	-	-	-	Q.S	Q.S
	Conclusion	Roughing surface, color not match	Physical appearance color not matching	Physical appearance color not matching	Slightly matched but color not matching	Sugar coating was optimized

6.5. EVALUTION OF TABLETS[38]:

a) Description: Poured 10 tablets in to the Petri dish and visualized it manually.

b) Weight variation tests: The 20 tablets were selected randomly and weighed. The average weights were compared with individual tablet weight. The percentage weight variation was calculated. As per British pharmacopoeia specification, tablets with an average weight 102 mg, the percentage deviation should not be more than 7.5 %.

Table No. 17 – Weight Variation test

Average Weight of tablets(mg)	Maximum % difference allowed
Less than 80	10
80-250	7.5
Above 250	5

$$\%\text{Deviation} = \frac{\text{Tablet Weight-Average weight}}{\text{Tablet Weight}} \times 100$$

c) Friability test:

Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum was rotated at a speed of 25 rpm for 4 minutes and reweighed the tablets. % friability was calculated by the following formula.

$$\%\,\text{Friability} = \frac{\text{Initial weight - Final Weight}}{\text{Initial weight}} \text{X}\,100$$

d) Diameter & thickness:

Twenty tablets were selected randomly and determined its diameter & thickness by using vernier caliper and reading were noted.

e) Hardness:

10 tablets were determined for hardness by using Monsanto hardness tester instrument. The force applies up to breaking of tablets. Results were noted down the force required to break the tablet.

f) Acid Uptake Test:

In this method take 6 tablets and note the initial weight of each tablets and immersed in 0.1N HCl for 2hrs, after that remove the tablets and dry it and again check the weight i.e., final weight. The following formula is used to calculate the % acid uptake of tablets.

$$\%\text{Acid uptake} = \frac{\text{Final weight-Initial weight}}{\text{Initial weight}} * 100$$

g) Disintegration test[40-41]:

Placed one tablet in each tube of the basket, using 0.1 N HCl maintained at 37^0 C±2^0C as immersion fluid for 2 hrs. Noted if the tablets were remaining intact or not. Later placed same tablet in each tube of the basket, using different pH phosphate buffer maintained at 37^0C±2^0C as immersion fluid for tablet disintegration. Noted down the time to complete disintegration.

h) Assay[42]:

Determined by liquid chromatography.

Bisacodyl 5mg Gastro-Resistant Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of $C_{22}H_{19}NO_4$

Solvent mixture.

4 volumes of glacial acetic acid, 30 volumes of acetonitrile and 66 volumes of water.

Test solution:

Weighed and powder 20 tablets. Weighed a quantity of powdered tablet containing 10mg of Bisacodyl with 40ml of solvent mixture, dilute to 50ml and filter. Dilute further 1 volume to 4 volumes with solvent mixture. (0.05% w/v)

Chromatographic System: A stainless steel column 25cm x 4.6mm packed with octadecylsilyl silica gel (5µm).

Mobile Phase: A mixture of 45 volumes of acetonitrile and 55 volumes of 0.025M ammonium formate adjusted to pH 5.0 with anhydrous formic acid.

Flow Rate: 1.5 ml per minute.

- Use a detection wavelength of 265nm.
- Inject 50µl of each solution.

Standard preparation:

Dissolved an 75mg weighed quantity of Bisacodyl standard in 100ml mixture of 99ml of acetonitrile and 1ml of formic acid. (British Pharmacopoeia, 2009)

Formula for Calculate the % of Assay

$$\%Assay = \frac{\text{Area of Sample}}{\text{Area of Standard}} \times \frac{\text{Dilution of Standard}}{\text{Dilution of Sample}} \times \frac{\text{Avg. Wt. of Tab.}}{\text{LC}} \times \frac{\text{Potency}}{100} \times 100$$

Formula for Calculate the % of Impurity:

$$\text{Impurity} = \frac{\text{Area of impurity}}{\text{Area of dil. Standard}} \times \frac{\text{Dilution of dil. Standard}}{\text{Dilution of Sample}} \times \frac{\text{Avg. Wt. of Tab.}}{\text{LC}} \times \frac{\text{Potency}}{100} \times \frac{1}{\text{RRF}} \times 100$$

LC – Label Claim
RRF- Relative Response factor of impurity.

i) Dissolution:

Acid Stage: Dissolution Conditions:
Apparatus: Paddle
Medium Volume: 900ml
Medium: 0.1M Hydrochloric Acid
RPM: 100
Time Interval: 2 hours
Temperature: $37^0C+ 0.5^0C$

Buffer Stage: Dissolution Conditions:
Apparatus: Paddle
Medium Volume: 900ml
Medium: Phosphate Buffer pH – 6.8, 7.4, 8.0.
RPM: 100
Time Interval: 2 hours
Temperature: $37^0C+ 0.5^0C$

Chromatographic Conditions: as per Assay method

6.6. STABILITY STUDY[9]:

An overall view

Purpose

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of Pharmaceutical products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. On the ICH Harmonized Tripartite Guidelines on Stability testing of New Drug substances and products, fundamental recommendations are summarized.

According to the ICH guidelines, long term (12 months) and accelerated stability studies (at least 6 months) have to be carried out.

Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. In general case, how the study done was shown by the below Table.18

Stability study (General case)

Table No. 18 - Stability study Conditions

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60%RH ±5% RHor30°C ± 2°C/65%RH ±5% RH	12 months
Intermediate	30°C ± 2°C/65%RH ±5% RH	6 months
Accelerated	40°C ± 2°C/75%RH ±5% RH	6 months

It is up to the applicant to decide whether long term stability studies are performed at 25°C ± 2°C/60%RH ±5% RH or 30°C ± 2°C/65%RH ±5% RH . If 30°C ± 2°C/65%RH ±5% RH is the long term condition, there is no intermediate condition. If long term studies are conducted at 25°C ± 2°C/60%RH ±5% and significant change occurs at any time during 6 months testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria.

For drug products packaged in impermeable containers (Aluminum tubes), semi permeable container (LDPE pouches, bottles etc), drug products intended for storage in a refrigerator , in a freezer and below –20°C, the study , storage condition and minimum time period covered by data at submission, are different not like as in general case. (ICH Q 1A9 R2 Stability testing guidelines)

Testing Frequency

For long term studies frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0,3 and 6 months) , form a 6- month study is recommended.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition , a minimum of four time points including the initial and final time points (e.g. 0, 6, 9, 12 months) form a 12 month study is recommended.

Joel Davis test

According to Joel Davis Test , if the product holds up for 3 months under accelerated condition i.e. 40°C and 75%RH (chemical stability, dissolution , physical characteristics) , then in an ANDA , the generic company will be given a two year expiration date but must follow up with real time data to substantiate the dating . The method is however, also used by ethical companies in the development of new drug entities. If the product does not pass the Joel Davis test, then conventional stability testing at room temp for prolonged periods (eighteen months) must accompany the NDA or the ANDA to satisfy the stability requirements of the submission.

Generally Acceptable Design considerations for Tablets and Capsules

Tablets: A stability study should include tests for the following characteristics of the tablet: Appearance, friability, hardness, color, odor, moisture, strength and dissolution.

Capsules: A stability study should include tests for the following characteristics, strength, moisture, color, appearance, shape, brittleness, and dissolution.(ICH Q 1A9 R2 Stability testing guidelines)

Procedure:

Packing material: Alu- PVDC blisters Packing.

Bisacodyl 5mg Gastro-resistant Tablets were exposed at: 40^{O} C/75% RH, 50^{O} C/75%RH conditions

The Tablets were withdrawn and analysed for following parameters:

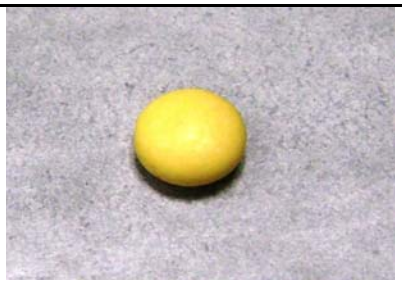
- Physical parameters of Tablets
- Related substances
- Assay (ICH Q 1A9 R2 Stability testing guidelines)
- Dissolution

7.0. RESULTS AND DISCUSSION

7.1. REVERSE ENGINEERING OF REFERENCE PRODUCT & COMPARISON WITH TEST PRODUCT

PARAMETERS	RESULTS	
	Reference Product	**Test Product**
Product	Dulcolax	Bisacodyl 5 mg Gastro-resistant Tablets
Description	Yellow colored biconvex Shaped tablets, plain on both the sides.	Yellow colored biconvex shaped tablets, plain on both the sides
Lot Number:	018973	BGR-TX0005-F005
Expiry date:	June 2013	Not Applicable
Manufactured	Boehringer Ingelheim Limited, France	Genovo Development Service Ltd

STAGE 1 : FINISHED PRODUCT

PARAMETERS	RESULTS	
Description	**Reference Product**	**Test Product**
	Yellow coloured biconvex shaped Tablets, plain on both the sides.	Yellow coloured biconvex shaped tablets, plain on both the sides.
Weight	97.5 mg	98.456 mg (theoretical target weight)
Thickness	3.52 mm	3.77mm
Diameter	5.95 mm	5.90mm
Fig.6 Photograph of the Tablet		

STAGE 2 : TABLET WITH ENTERIC COATING (AFTER DISSOLVING OUTER SUGAR COATING LAYER)

PARAMETERS	RESULTS	
Description	**Reference Product**	**Test Product**
	White biconvex tablet with the waxy appearance or little shiny appearance.	White biconvex tablet with shiny appearance
Weight	76.4 mg	63.25mg
Thickness	3.19 mm	3.16mm
Diameter	5.65 mm	5.31mm
Inference	The mean sugar coating weight may contributes to 25 mg – 30 mg.	The mean sugar coating (sub coating with color coating & polishing) weight Contributes 35.215mg.
Fig.7 Photograph of the Tablet		

STAGE 3: TABLET AFTER REMOVAL OF ENTERIC COATING LAYER

PARAMETERS	RESULTS	
Description	White biconvex tablet with the waxy appearance	White biconvex tablet with the shiny appearance
Weight	62.5 mg	57.5mg
Thickness	2.80 mm	3.07mm
Diameter	5.37 mm	5.19mm
Inference	The mean enteric layer weight may contribute to 14 mg – 15 mg. The core with the seal coating layer may contributes to weight of 62 to 65 mg.	The mean enteric layer weight contributes to 5.75 mg. The core with the seal coating layer may contributes to weight of 57.5 mg.
Fig.8 Photograph of the Tablet		

STAGE 4 : DISINTEGRATION OF THE ABOVE TABLET IN PURIFIED WATER (i.e. Tablet after removing the enteric layer)

PARAMETERS	RESULTS	
	Reference Product	**Test Product**
Description	The DT of the above tablet shows that there is a presence of another layer which was peeled of during the agitation on the media (water) using a spatula. The film layer is seen in the photograph below. The time taken by the film to break was 3'30" sec (Figure 1).After the removal of the film the tablet disintegrated completely with in a minute. (Figure 2).	DT of the seal tablet shows that film layer disintegrates same pattern as reference product and the time taken by the film to break was 4'04" sec (Figure 1). After the removal of the film the tablet disintegrated completely with in a 40 secs. (Figure 2).
Media/ Volume	100 ml water	

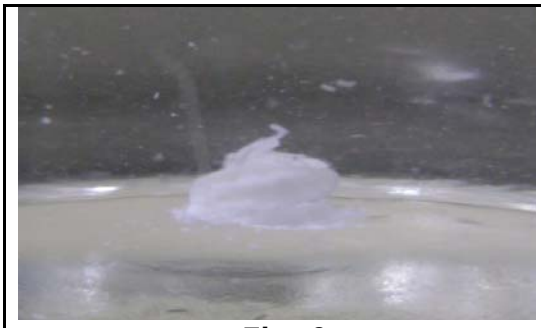


Fig: 9

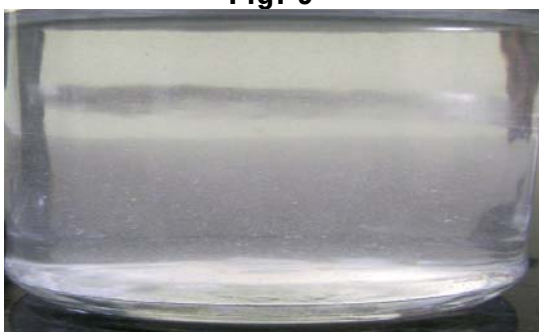
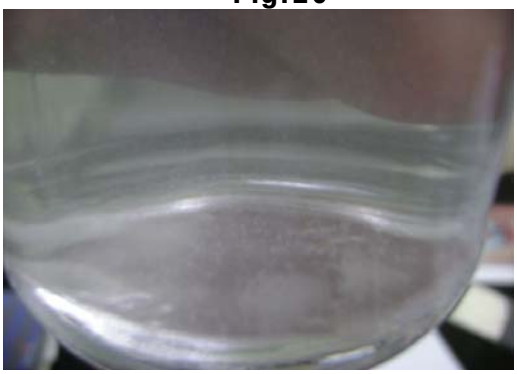


Fig:10



Photograph of Disintegration of the Tablets

7.2. PREFORMULATION STUDY[38]:

7.2.1. Organoleptic Properties

These test performed as per procedure given in experimental work chapter and results are illustrated in following table.

Table No. 19: Organoleptic properties:

Test	Specification	Observation
Color	White crystalline powder.	White, crystalline powder
Taste	Tasteless	Tasteless
Odour	Odourless	Odourless

The above result shows all parameters are within Specification

7.2.2. Loss on drying:

These test performed as per procedure given in experimental work chapter the results are illustrated in following table.

Table No 20. Loss on drying

Test	Specification	Observation
Loss on drying	Not more than 0.5%	0.18%

The above result shows all parameters are within Specification

7.2.3. Angle of Repose:

These test performed as per procedure given in experimental work chapter. The results are illustrated in following table

Table No 21. Angle of Repose- API

Sr. No.	Material	Angle of repose	Average angle of repose
1	API	83.70	$83^0.52'$
2		83.09	
3		83.79	

7.2.4. Bulk Density and tapped density:

These test performed as per procedure given in experimental work chapter. The results are illustrated in following table.

Table No. 22: API - Bulk Density and tapped density

S.No.	Material	Bulk density (gm/cc)	Average bulk density (gm/cc)	Tapped density (gm/cc)	Average tapped density (gm/cc)
1	API	0.21	0.20	0.28	0.32
2		0.20		0.33	
3		0.20		0.35	

Table No. 23: Blend - Bulk Density and tapped density

S.No.	Material	Bulk density (gm/cc)	Average bulk density (gm/cc)	Tapped density (gm/cc)	Average tapped density (gm/cc)
1	Blend	0.6	0.6	0.8	0.84
2		0.59		0.85	
3		0.61		0.88	

The bulk density and tapped density of active material and blend ready for compression were determined and calculated by using the formula,

$$\text{Bulk density} = \frac{\text{Weight of substance}}{\text{Final volume of substance}} \quad \text{(gm/cc)}$$

$$\text{Tapped density} = \frac{\text{Weight of substance}}{\text{Final volume of substance after tap}} \quad \text{(gm/cc)}$$

The above result shows that drug have low density.

7.2.5. Compressibility index:

These test performed as per procedure given in experimental work chapter. The results are illustrated in following table.

Table No 24. Compressibility index

Material	Compressibility index	Hausner ratio
API	42.86	1.75

The above result shows that drug has very poor **compressibility index.**

Table No 25.Sieve analysis:

Sieve no	Empty sieve(gm)	Sample sieve(gm)	Weight of sample (gm)	%Retained	%Cumulative Retained
#40	399.8	420.6	20.8	51.23	51.2
#60	393.4	412.2	18.8	46.30	97.5
#80	383.8	384.2	0.40	0.985	98.5
#100	384.4	384.4	0.40	0.985	99.5
#120	376.4	376.6	0.20	0.492	99.9
#140	374.8	374.8	0	0	99.9
#200	374.4	303.2	0	0	99.9
Receiver	377.4	359.0	0	0	99.9

Weight of sample=41.0gm.

NOTE: Agglomerates are formed.

7.2.6. pH:

These test performed as per procedure given in experimental work chapter. The results are illustrated in following table.

Table No. 26 pH of API

Test	Specification	Observation
Bisacodyl	6-7	7

The above result shown all parameters complies.

7.2.7. Melting Point:

These tests were performed as per procedure given in experimental work chapter. The results are illustrated in following Table No.27

Table No 27. Melting Point of API

S.No.	Material	Melting point range
1	Bisacodyl	131-135°C

The result of table indicates that the Bisacodyl was pure one.

7.2.8. Drug-excipient compatibility study:

It was determined as per procedure given in experimental work chapter. The results are illustrated in following Table

Table No 28. Drug-excipient compatibility study

Sr. No.	Name of the Excipient + drug	Initial	Exposed to 25^0C/60% RH	Exposed to 50^0C/75% RH	Comment
1	Drug X	White color	No change	No change	Compatible
2	API + Lactose monohydrate	White color	No change	No change	Compatible
3	API + Maize starch	White color	No change	No change	Compatible
4	API +Pregelatinized starch	White color	No change	No change	Compatible
5	API + Talc	White color	No change	No change	Compatible
6	API + Magnesium stearate	White color	White color	No change	Compatible
7	API +HPMC E5	White color	No change	No change	Compatible
8	API + Eudragit L100&S100	White color	No change	No change	Compatible
9	API + HPMC 15 cps	White color	No change	No change	Compatible
10	API + TEC	White color	No change	No change	Compatible
11	API+ Titanium dioxide	White color	No change	No change	Compatible
12	API + Sucrose	White color	No change	No change	Compatible
13	API + Iron oxide yellow	Yellow color	No change	No change	Compatible
14	API+ Carnauba wax	White color	No change	No change	Compatible
15	API+ Opadry yellow	Yellow color	No change	No change	Compatible

7.3. FORMULATION TABLE RESULTS:

F=Formulation

F1-> This trial is to check the physical feasibility of ingredients with the reference product.

F2-> In this trial Direct Compression technique was used and capping is observed due to high content of lubricant.

F3-> The granules are shifted through #24, but UOD was not in a specific limit.. Sticking observed due to Humidity

F4-> Humidity Adjusted to 50% by dehumidification. In this trial UOD is not in a specific limit.

F5-> In this trial we consider the direct compression method, by increasing the % of binding agent, proper hardness was observed.

F5A-> In this trial seal coating was optimized.

F5B-> In this trial 7% of enteric coating solution was considered, but swelling of tablets was observed. Hence enteric coating is further optimized to get better gastric resistance.

F5C-> In this trial 9% of enteric coating solution was considered, but DT is not optimized when compared to the reference product.

F5D-> In this trial 10% of enteric coating solution was considered, but DT is not optimized when compared to the reference product.

F5E-> In this trial 11% of enteric coating solution was considered. DT was slightly matched with the reference product by showing 10-11 minutes variation.

F5F-> In this trial 13% of enteric coating solution was considered. DT was optimized with the reference product.

CONCLUSION:

By the above trials we observed that **F5E & F5F** DT was matched with the reference product, among them **F5F** was optimized for enteric coating.

SUGAR COATING:

F5F1-> In this trial required % of sugar coating solution was considered, but the tablet surface was found rough, particles was settled at the edges of tablets. Hence sugar coating needs to be optimized.

F5F2-> In this trial % of sugar coating solution was taken, but physical feasibility was not matching with the reference product.

F5F3-> In this trial % of sugar coating solution was taken, but physical feasibility was not matching with the reference product.

F5F4-> In this trial sugar coating was slightly matching with the reference product, but color coating needs to be optimized.

F5F5-> In this trial sugar coating was optimized.

7.4. EVALUATION OF TABLETS - RESULTS:

7.4.1. FOR CORE TABLET[38]: (BATCH NO F1-F5)

a) Description:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

It is a yellow colored, circular, biconvex tablets.

b) Individual Weight variation Test:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No.29: Weight variation Test of Core Tablet				
51.2	50.0	49.8	50.1	50.4
50.2	50.7	50.0	49.9	50.0
50.3	50.1	50.4	50.0	49.8
50	50.4	50.1	50.1	50.0
Weight of 20 tablets = 869.5mg.				
Average wt of tablet = 102.4 mg.				
Minimum wt of tablet = 50.0mg.				
Maximum wt of tablet = 50+2mg. The above result show all parameters complies				

c) Friability:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No. 30 - Friability of Core Tablet

Friability in %w/w= (W1 – W2) X 100/W1 (Limit NMT 1.0%)		
Before rotation (W1)	**After rotation (W2)**	**Friability in %**
6.808gm	**6.799gm**	**0.12**

The above result shows that the tablets have good mechanical strength

d) Thickness of core tablet:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No. 31: Thickness of 20 tablets in mm

2.3	2.37	2.37	2.39	2.38	2.38	2.3	2.40	2.39	2.40
2.35	2.32	2.34	2.4	2.38	2.32	2.36	2.37	2.3	2.36

Maximum Thickness = 2.40 mm.

Minimum Thickness = 2.30mm.

The above result shows the tablet diameter.

e) Diameter of core tablets:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No. 32: Diameter of 20 tablets mm

5.02	5.04	5.06	5.04	4.95	4.99	4.98	5.01	5.00	5.01
4.96	4.98	4.97	4.99	5.00	4.98	4.96	5.00	4.98	5.00

Maximum Diameter =5.00 mm.

Minimum Diameter = 4.90 mm.

The above result shows that the tablets have uniform thickness.

f) Hardness of core tablets:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No. 33: Hardness of tablets

Hardness of 10 tablets in kp									
2.1	**2.9**	**3.2**	**3.4**	**3.4**	**3.6**	**3.0**	**4.0**	**2.7**	**3.6**
Maximum Hardness = 4 kp									
Minimum Hardness = 2.5 kp The above result shows that the tablets have good mechanical strength.									

g) Disintegration[41-42]:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Medium: Purified water

Time limit: within 30 minutes

Apparatus: disintegration tester (USP)

Table No. 34: Disintegration Test

Disintegration time	10-15 sec.

The above result shows that the tablets disintegrate within time limit.

h) Assay[42] :(Estimation of Bisacodyl by liquid chromatography)

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Bisacodyl was estimated as per procedure given in method section, the following table illustrated the result.

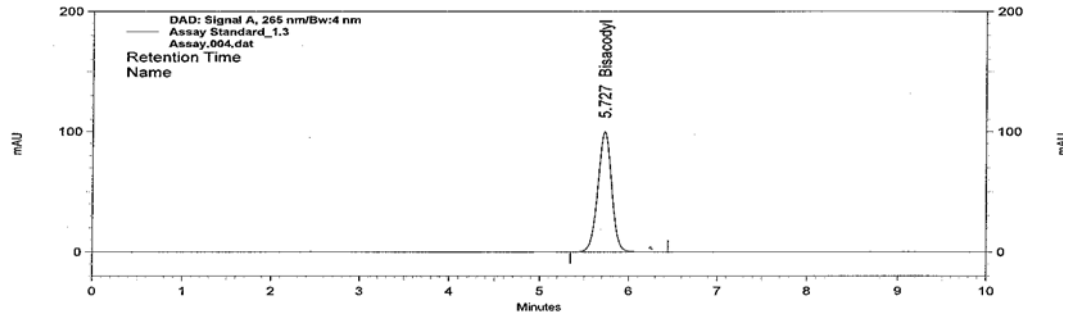
Limit: Bisacodyl Gastro-resistant tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of **$C_{22}H_{19}NO4$**

Table No. 35: Estimation of Bisacodyl Core Tablet

Sample No.	Weight of sample (mg)	Area of Bisacodyl peak from assay preparation chromatogram	%of Bisacodyl	Average % Of Bisacodyl
1	50.10	2265739	100.0	100.0
2	50.10	2261809	100.0	100.0

The above result shows that tablets have uniformity in content.

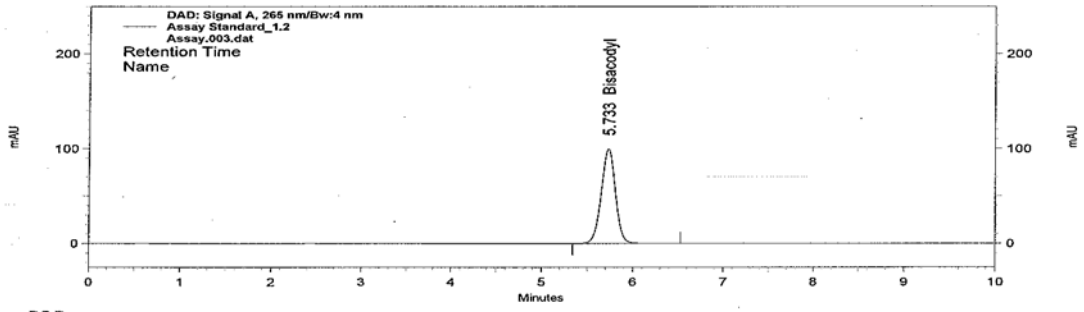
Fig.11.Assay Standard - Chromatogram



DAD: Signal A, 265 nm/Bw: 4 nm Results

Pk #	Name	RT	Area	%Area	Height	Theoretical plates (USP)	Asymmetry
1	Bisacodyl	5.727	2263904	100.00	209494	6471	1.01
Totals			2263904	100.00	209494		

Fig.12.Assay Test - Chromatogram



DAD: Signal A, 265 nm/Bw: 4 nm Results

Pk #	Name	RT	Area	%Area	Height	Theoretical plates (USP)	Asymmetry
1	Bisacodyl	5.733	2261809	100.00	209246	6515	0.98
Totals			2261809	100.00	209246		

FOR CORE TABLET BATCH (F1 TO F5):

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No.36: Evaluation of core tablets

Parameters	Formulation No.				
	F1	F2	F3	F4	F5
Average Weight of core tablet (mg)	50mg	50mg	50mg	50mg	50mg
Weight for 20 tablets(gm)					
Diameter (mm)	5.0	4.98	4.9	5.0	5.0

Thickness (mm)	2.4	2.3	3.2	3.2	3.6
Friability (%)	0.163	0.517	0.264	0.337	0.12
Hardness (Kg/cm^2)	2.4	3.3	2.9	3.2	3.0
Disintegration time (sec) (Purified water)	7sec	33sec	10sec	12sec	8sec

The above F5 batch result shows all parameters complies.

7.4.2. FOR ENTERIC COATED TABLETS:

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No.37: Evaluation of Enteric coated tablet

Parameters	**Formulation No.**				
	F5B	**F5C**	**F5D**	**F5E**	**F5F**
Average Weight (mg)	61.5mg	62.mg	63.5mg	63.9mg	64.9mg
Weight for 20 tablets (gm)					
Diameter (mm)	5.36	5.40	5.39	5.41	5.32
Thickness (mm)	3.15	3.17	3.15	3.17	3.17

The above result shows all parameters of F5F batch are complies.

Evaluation for Enteric Coated Tablet :(Formulation No.F5F)

a) Individual Weight variation of 20 tablets (mg)

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No. 38: Weight variation of Enteric Coated Tablet (mg)

64.9	64.5	64.9	65.0	64.8
64.8	64.9	64.9	65.0	64.7
64.9	65.0	65.1	64.8	64.9
64.7	64.7	64.8	64.9	64.9

Weight of 20 tablets = 2296 mg

Average wt of tablet = 114.8 mg

Minimum wt of tablet = 115.7 mg

Maximum wt of tablet = 112.7 mg

Appearance of all tablets = white colored, circular, biconvex enteric coated tablets. Above result shows tablets were uniform in weight.

b) Diameter of 10 tablets in(mm):

It was determined as per procedure given in Evaluation of tablets in experimental work chapter . The following table illustrated the result.

Diameter of Tablet

5.27	5.32	5.32	5.27	5.26	5.30	5.31	5.32	5.32	5.32

Maximum Diameter = 6.65 mm

Minimum Diameter = 6.63 mm

The above result shows that tablet have uniformity in diameter

c) Thickness of 20 tablets (mm)

It was determined as per procedure given in Evaluation of tablets in experimental work chapter . The following table illustrated the result.

Thickness of Tablets

3.15	3.15	3.17	3.17	3.15	3.16	3.18	3.20	3.17	3.17
3.18	3.15	3.17	3.20	3.20	3.17	3.18	3.15	3.17	3.17

Maximum Thickness = 3.55 mm

Minimum Thickness = 3.45 mm

The above result shows that the tablet has uniformity in thickness.

7.4.3. EVALUATION FOR SUGAR COATED TABLET:

(FORMULATION NO.F5F5)

a) Individual Weight variation of 20 tablets (mg)

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Table No. 39: Weight variation of Sugar Coated Tablet (mg)

97.2	100.8	101.2	97.3	94.1
97.2	100	100.3	100.2	101.1
99.8	99.9	101	100	100.5
99.9	100	100.4	100.2	100.1

Weight of 20 tablets = 2296 mg

Average wt of tablet = 114.8 mg

Minimum wt of tablet = 115.7 mg

Maximum wt of tablet = 112.7 mg

Appearance of all tablets = white colored, circular, biconvex enteric coated tablets. Above result shows tablets were uniform in weight.

b) Diameter of 10 tablets in(mm):

It was determined as per procedure given in Evaluation of tablets in experimental work chapter . The following table illustrated the result.

Diameter of Tablet

5.94	5.89	5.88	5.90	5.89	5.91	5.94	5.93	5.89	5.91

Maximum Diameter = 6.65 mm

Minimum Diameter = 6.63 mm

The above result shows that tablet have uniformity in diameter

c) Thickness of 20 tablets (mm)

It was determined as per procedure given in Evaluation of tablets in experimental work chapter . The following table illustrated the result.

Thickness of Tablets

3.80	3.77	3.79	3.80	3.77	3.78	3.76	3.79	3.78	3.75
3.79	3.80	3.79	3.77	3.77	3.78	3.79	3.80	3.80	3.79

Maximum Thickness = 3.55 mm

Minimum Thickness = 3.45 mm

The above result shows that the tablet has uniformity in thickness.

d) **Disintegration[40]:**

It was determined as per procedure given in Evaluation of tablets in experimental work chapter. The following table illustrated the result.

Acid Medium:

Medium: Acid (0.1N HCl Purified 800ml).

Time limit: Tablets remain intact for 120 minutes.

Apparatus: Disintegration Tester (USP).

Table No. 40: Disintegration in Acid Medium of Enteric coated tablet

Disintegration time	Tablet remain intact for 120 min.

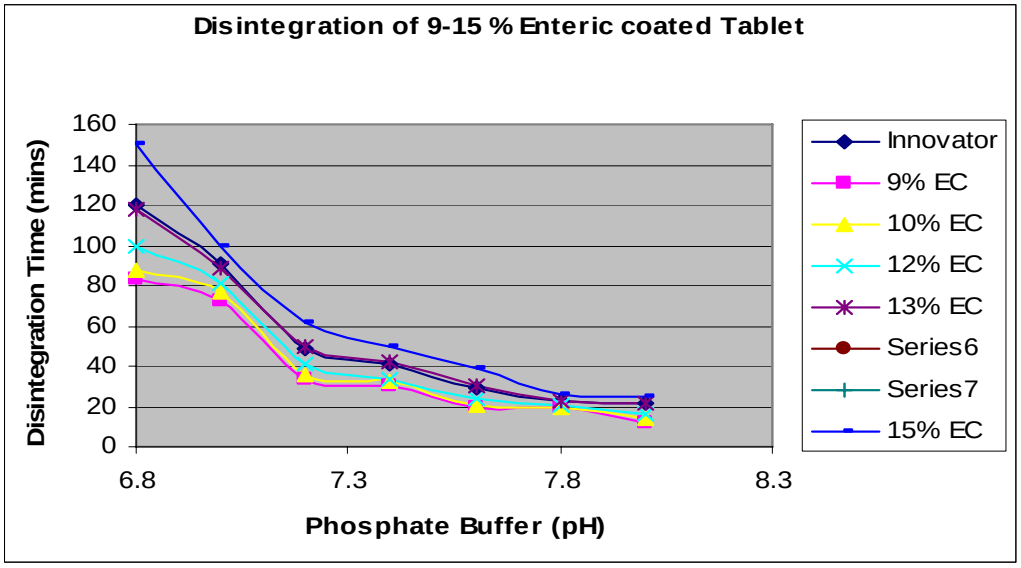
The above result shows that tablet doesn't disintegrate in acidic pH

Disintegration of Different percentage of Enteric coated tablet in Phosphate Buffers

Table No. 41:

Media		Disintegration time in Minutes					
0.1N HCl	**PHOSPHATE BUFFER**	**Reference Product**	**Test Product (9%)**	**Test Product (10%)**	**Test Product (12%)**	**Test Product (13%)**	**Test Product (15%)**
0.1N HCl (2hrs)	6.8	120	83	88	99	118	150
	7.0	91	72	77	81	89	100
	7.2	49	34	36	41	50	62
	7.4	41	30	32	34	42	50
	7.6	29	20	21	24	30	39
	7.8	23	19	20	21	23	26
	8.0	22	12	14	16	22	25

Fig.13. Disintegration of 9-15% Enteric Coated Tablet



Note: All disintegration tests are performed in 0.1N HCl for 2 hours followed by Phosphate buffer.

The above result shows that Innovator and 13% Enteric coated Bisacodyl Tablet has similar Disintegration time in Phosphate Buffer pH 6.8- to pH -8.0

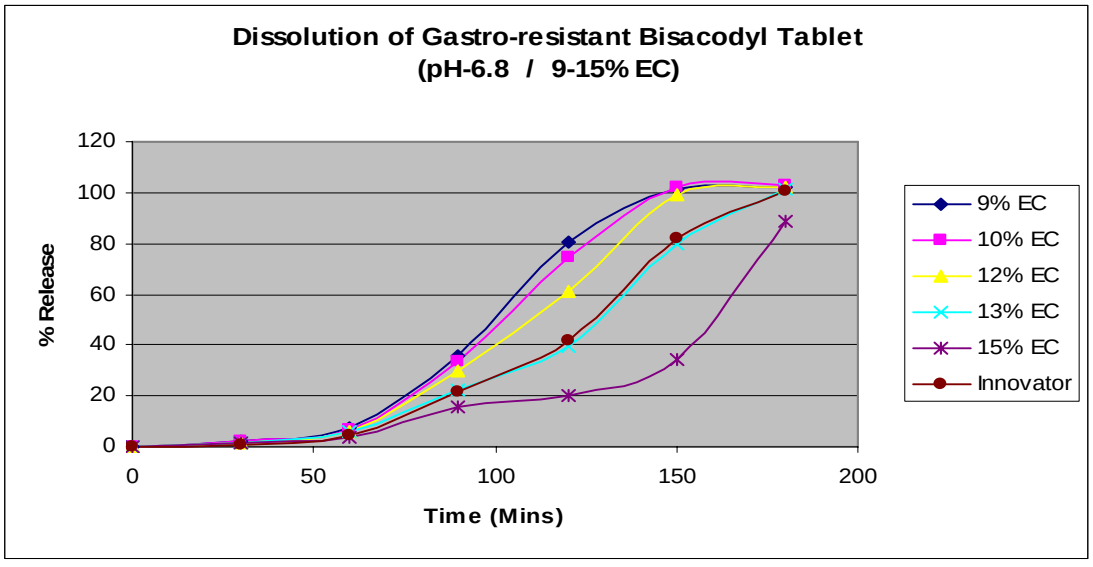
e) Dissolution[43-45]

- **Dissolution of Different percentage of Enteric coated tablet in Phosphate Buffers**

Table No. 42: Phosphate buffer pH-6.8

Sno.	Enteric coating %	0.1N Hcl	% Release ↓	Range (min) →					
			0	30	60	90	120	150	180
1	9%	2hrs	0	2.40	7.40	35.60	80.30	101.20	102.40
2	10%		0	2.00	6.90	33.51	74.42	101.80	102.69
3	12%		0	1.75	6.00	30.10	61.20	99.22	102.32
4	13%		0	1.50	5.60	22.55	39.58	79.45	101.81
5	15%		0	1.37	3.75	15.87	20.39	34.48	88.99
6	Innovator		0	1.10	4.30	21.37	41.71	82.22	100.36

Fig.14. Dissolution of 9-15% Enteric Coated Tablet in pH-6.8 Phosphate buffer

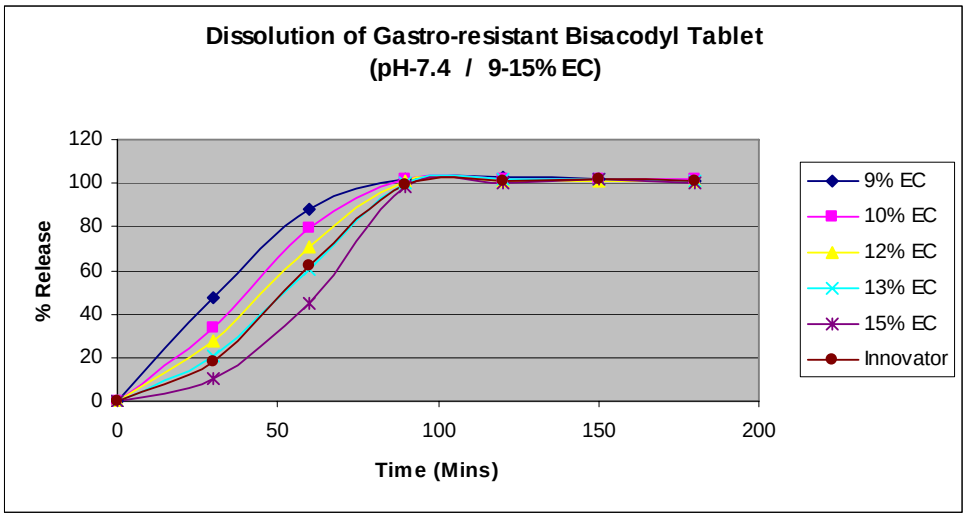


The above result shows that Innovator and 13% Enteric coated Bisacodyl Tablet has similar release patterns in Phosphate Buffer pH 6.8

Table No. 43: Phosphate buffer pH-7.4

Sno.	Enteric coating %	0.1N Hcl	% Release ↓	Range (min) →					
			0	30	60	90	120	150	180
1	9%	2hrs	0	47.20	88.30	102.20	102.40	101.50	101.40
2	10%		0	33.55	79.70	101.86	101.46	101.80	101.69
3	12%		0	27.64	71.20	101.30	101.20	101.41	101.32
4	13%		0	20.46	60.70	100.35	101.58	101.79	100.69
5	15%		0	10.40	44.50	98.30	100.39	101.48	100.39
6	Innovator		0	18.40	62.30	99.44	100.02	101.1	99.8

Fig.15 Dissolution of 9-15% Enteric Coated Tablet in pH-7.4 Phosphate buffer

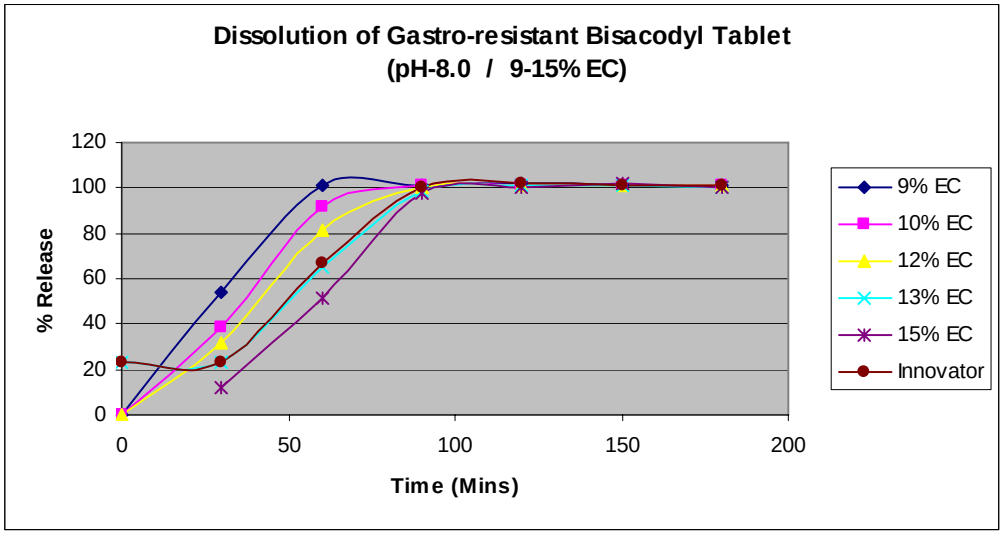


The above result shows that Innovator and 13% Enteric coated Bisacodyl Tablet has similar release patterns in Phosphate Buffer pH 7.4

Table No. 44: Phosphate buffer pH-8.0

Sno.	Enteric coating %	0.1N Hcl	% Release ↓	Range (min) →					
			0	30	60	90	120	150	180
1	9%	2hrs	0	54.25	101.49	101.10	102.28	101.33	101.24
2	10%		0	38.56	91.61	101.24	101.52	101.28	101.29
3	12%		0	31.77	81.84	100.10	101.27	101.54	101.32
4	13%		0	23.52	65.20	98.90	101.38	101.47	100.42
5	15%			11.95	51.15	97.53	100.29	101.61	100.29
6	Innovator		23.01	23.01	67.10	100.34	101.61	101.20	100.84

Fig.16 Dissolution of 9-15% Enteric Coated Tablet in pH-8.0 Phosphate buffer



The above result shows that Innovator and 13% Enteric coated Bisacodyl Tablet has similar release patterns in Phosphate Buffer pH 8.0

Table No. 45 f_2 and f_1 values for dissolution of F5F (13%) vs Innovator

Medium	f_2	f_1
0.1 N HCl - pH 1.2	**95.14**	**0.35**
Phosphate buffer - pH 6.8	**97.08**	**0.68**
Phosphate buffer - pH 7.4	**91.77**	**0.76**
Phosphate buffer - pH 8.0	**94.60**	**0.49**

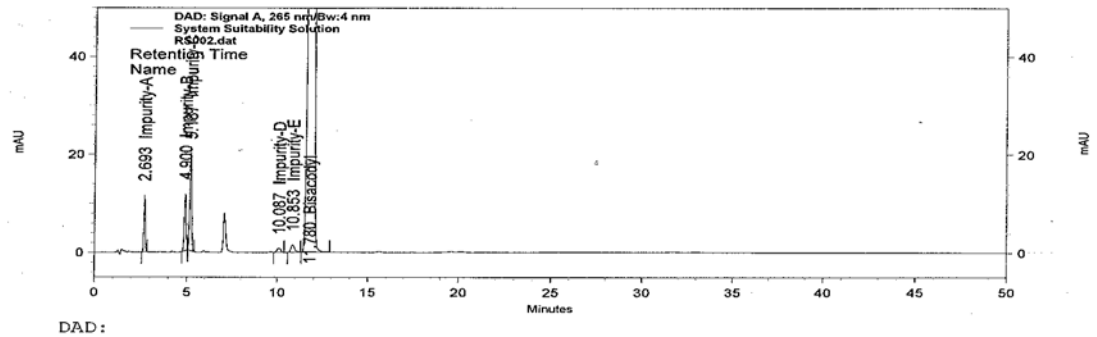
f1 (Dissimilarity Factor) = NMT 15
f2 (Similarity Factor) = NLT 50

f) Related Substance (RS):

It was determined as per procedure given in Evaluation of Tablet in Experimental work chapter. The following table illustrated the result.

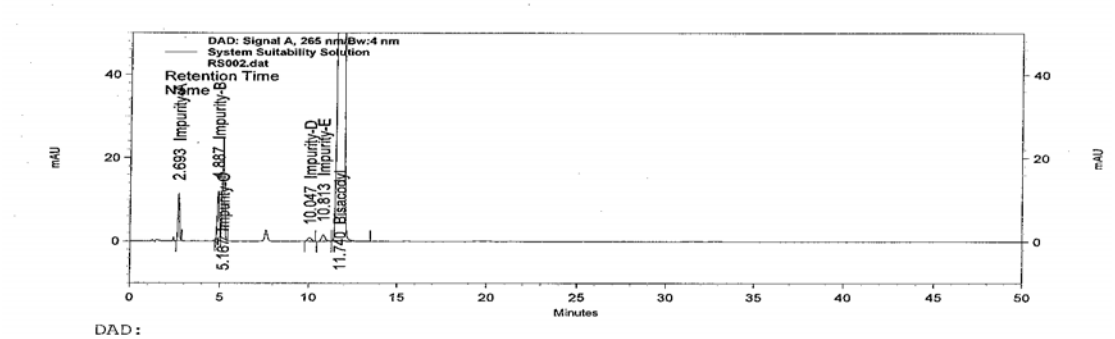
Bisacodyl was estimated as per procedure given in method section, the following table illustrated the result.

Fig.17 Initial RS for Core Tablet – Chromatogram



DAD: Signal A, 265 nm/Bw:4 nm Results

Pk #	Name	RT	Area	%Area	Resolution (USP)
1	Impurity-A	2.693	124337	0.495	0.000
2	Impurity-B	4.900	170062	0.677	13.740
3	Impurity-C	5.187	294006	1.171	1.530
4	Impurity-D	10.087	26268	0.105	16.815
5	Impurity-E	10.853	45126	0.180	2.062
6	Bisacodyl	11.780	24449226	97.372	2.591
Totals			25109025	100.000	



DAD: Signal A, 265 nm/Bw:4 nm Results

Pk #	Name	RT	Area	%Area	Resolution (USP)
1	Impurity-A	2.693	135541	0.519	0.000
2	Impurity-B	4.887	173048	0.663	12.683
3	Impurity-C	5.167	386722	1.481	1.401
4	Impurity-D	10.047	27757	0.106	16.204
5	Impurity-E	10.813	48558	0.186	2.013
6	Bisacodyl	11.740	25334179	97.044	2.494
Totals			26105805	100.000	

Fig.18 Initial RS for Final coated tablets– Chromatogram

The RS results are within the limits

7.5. STABILITY STUDY RESULT:

(For Formulation No: F5F5)[11-13]

a) DESCRIPTION:

It was determined as per procedure given in Evaluation of tablets in Experimental work chapter. The following table illustrate the result.

Table No.46: Stability Description of Final Product – Color Coated Tablet

S.No.	Storage condition	Period	Appearance
1	$25^0C \pm 2^0C$ /60%±5%RH & $40^0C \pm 2^0C$ /75%±5%RH	1 months	Yellow colored , biconvex ,circular shape Intact.

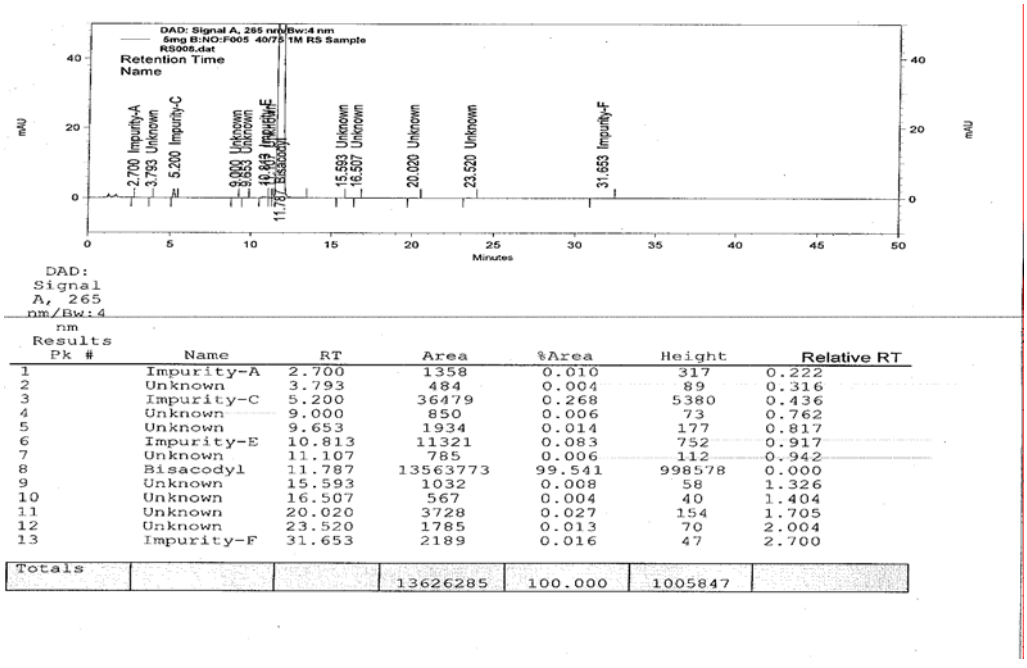
b) ASSAY:

It was determined as per procedure given in Evaluation of tablets in Experimental work chapter. The following table illustrated the result.

Table No.47: Assay- 1 Month Stability

Storage Condition	Storage period	Specification	Inference
$25^0C \pm 2^0C$ /60%±5%RH & $40^0C \pm 2^0C$ /75%±5%RH	1months	NLT 95.0% and NMT 105.0% of labeled amount of --	100.52%

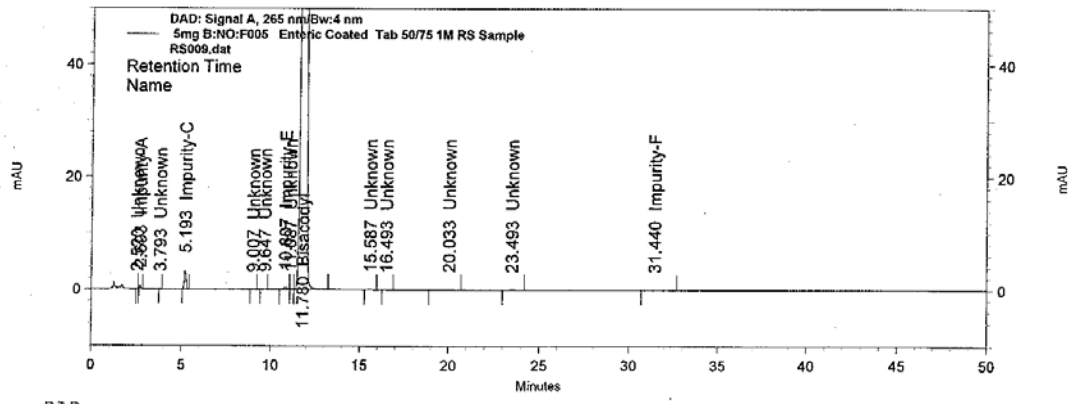
Fig.19 RS for Final Product at 25^0C /60%RH, 1 Month Stability Conditions



DAD: Signal A, 265 nm/Bw:4 nm
Results

Pk #	Name	RT	Area	%Area	Height	Relative RT
1	Impurity-A	2.700	1358	0.010	317	0.222
2	Unknown	3.793	484	0.004	89	0.316
3	Impurity-C	5.200	36479	0.268	5380	0.436
4	Unknown	9.000	850	0.006	73	0.762
5	Unknown	9.653	1934	0.014	177	0.817
6	Impurity-E	10.813	11321	0.083	752	0.917
7	Unknown	11.107	785	0.006	112	0.942
8	Bisacodyl	11.787	13563773	99.541	998578	0.000
9	Unknown	15.593	1032	0.008	58	1.326
10	Unknown	16.507	567	0.004	40	1.404
11	Unknown	20.020	3728	0.027	154	1.705
12	Unknown	23.520	1785	0.013	70	2.004
13	Impurity-F	31.653	2189	0.016	47	2.700
Totals			13626285	100.000	1005847	

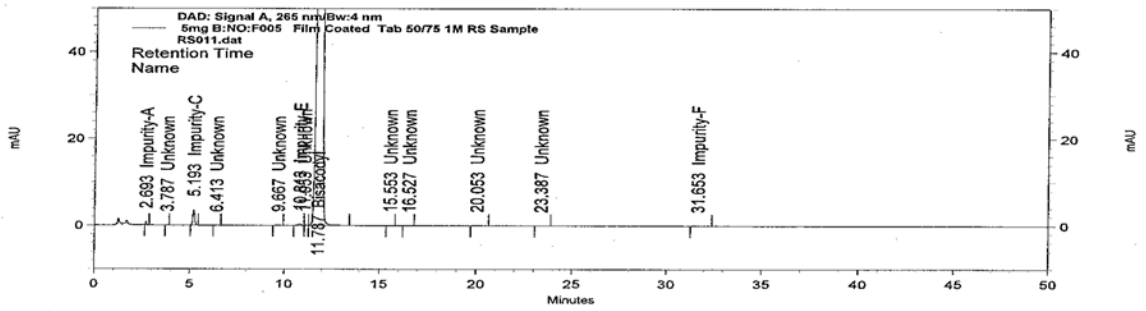
Fig.20 RS for Final Product at 40^{0}C /75%RH, 1 Month Stability Conditions



DAD: Signal A, 265 nm/Bw:4 nm
Results

Pk #	Name	RT	Area	%Area	Height	Relative RT
1	Unknown	2.520	434	0.003	142	0.207
2	Impurity-A	2.693	6375	0.042	1398	0.222
3	Unknown	3.793	425	0.003	91	0.316
4	Impurity-C	5.193	46552	0.307	6934	0.436
5	Unknown	9.007	616	0.004	58	0.763
6	Unknown	9.647	1391	0.009	122	0.817
7	Impurity-E	10.807	11914	0.079	786	0.917
8	Unknown	11.087	911	0.006	128	0.941
9	Bisacodyl	11.780	15057994	99.453	1108379	0.000
10	Unknown	15.587	1495	0.010	81	1.326
11	Unknown	16.493	754	0.005	43	1.404
12	Unknown	20.033	6671	0.044	197	1.707
13	Unknown	23.493	3011	0.020	88	2.003
14	Impurity-F	31.440	2211	0.015	40	2.683
Totals			15140754	100.000	1118487	

Fig.21 RS for Final Product at 50^{0}C /75%RH, 1 Month Stability Condition



DAD: Signal A, 265 nm/Bw: 4 nm
Results

Pk #	Name	RT	Area	%Area	Height	Relative RT
1	Impurity-A	2.693	6931	0.050	1555	0.222
2	Unknown	3.787	478	0.003	96	0.315
3	Impurity-C	5.193	49520	0.359	7312	0.436
4	Unknown	6.413	826	0.006	60	0.540
5	Unknown	9.667	2264	0.016	194	0.819
6	Impurity-E	10.813	10546	0.077	704	0.917
7	Unknown	11.053	1041	0.008	112	0.937
8	Bisacodyl	11.787	13705283	99.419	1007303	0.000
9	Unknown	15.553	703	0.005	53	1.322
10	Unknown	16.527	790	0.006	41	1.406
11	Unknown	20.053	3720	0.027	145	1.707
12	Unknown	23.387	1955	0.014	66	1.993
13	Impurity-F	31.653	1335	0.010	39	2.700
Totals			13785392	100.000	1017680	

Table No.48 – Related substance of Final Product at 25^{0}C /60%RH, 40^{0}C /75%RH, 1 Months (Stability Studies) and 50^{0}C /75%RH, 1 month (Degradation Study)

S.NO	RELATED SUBSTANCE	LIMITS
1	**IMP A,B**	NMT 0.1%
2	**IMP C,E**	NMT 0.5%
3	**IMP D**	NMT 0.2%
4	**IMP F**	NMT 0.3%
5	**UNSPECIFIED IMPURITIES**	NMT 0.1%
6	**DISREGARD IMPURITIES**	NMT 0.05%
7	**TOTAL IMPURITIES**	NMT 1.0%

7.6. DISCUSSION

The objective of the study is to formulate and evaluate Bisacodyl Gastro-resistant tablets compared to the innovator product.

Formulations of enteric coated and sugar coated tablets of Bisacodyl were developed by preparing core tablets using Lactose monohydrate as diluent and Pregelatinized starch as binder and varying the compositions of enteric coating using Eudragit, and sugar coating using HPMC E15, titanium dioxide. The core tablets were prepared by direct compression method.

The results indicated that the finished product formulations F5F fulfilled all the specifications of the physical properties and chemical properties are comparable to the innovator product. Formulation F2 failed to compress as tablets due to capping problem. In Formulation F5B acid resistance test was failed due to insufficient enteric coating. Enteric coated formulations F5C to F5E Disintegration test was not matched when compared to the reference product.

Enteric coated formulation F5F fulfilled all the specifications prescribed for Bisacodyl Gastro-resistant tablets and comparable to the innovator product

8.0. SUMMARY AND CONCLUSION

SUMMARY

The objective of present work is to formulate and evaluate Gastro-resistant Tablet of bisacodyl.

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 peristaltic movement occurs.

Preformulation studies were compared with British pharmacopoeia (BP) specification for Bisacodyl. The physical properties such as Organoleptic characteristics, loss on drying, angle of repose, compressibility, density, solution properties like pH, melting point of the solution were evaluated.

Drug excipients compatibility study performed at 25^{o}C /60% RH and 50^{O}C/75% RH for 1month. The physical and chemical compatibility was determined.

Lactose monohydrate, Pregelatinized starch are used to prepare a blend for direct compression method. The prepared blends were lubricated with Magnesium stearate. To protect the drug form degradation in acidic environment tablet formulation coated with pH dependant solubility polymers Eudragit L100 & S100 (Enteric coating polymer).

Blends were compressed on tablet compression machine by using 5 mm punch. Finally optimized formulation for core tablet i.e. F5 is obtained. It gives all required parameters for core tablet. F5 formulations were selected for seal coating and finally enteric coating with Eudragit having optimized polymer 13% coating.

These selected formulations were evaluated for tablet parameters i.e. Weight variation, diameter & thickness, hardness, disintegration in 0.1 M HCl for 120 min and different phosphate buffers was used, pH-7.6 phosphate buffer showed better disintegration of tablet.

Assay performed by HPLC method to determine content of drug per tablet and related substance also performed by HPLC method.

Alu-P.V.D.C blister strip used as packing material. This finally packed tablet kept for stability at different storage condition.

Stability studies were carried out for optimized formulation at 25^0C /60%RH, 40^0C /75%RH, 1 Months (Stability Studies) and 50^0C /75%RH, 1 month (Degradation Study). After completion of time period, assay and related substance for every storage condition was determined. On completion of all the study, selected formulation was decided as a final product which complies with reference product parameters.

8.0. CONCLUSION

Preformulation results comply with Pharmacopoeial specification.

Drug-Exipients compatibility studies found that API was compatible with the excipients and test results directs the further development of formulation.

Bisacodyl core tablet was made by direct compression techniques and optimized using Pregelatinized starch as Binder – (Formulation F5).

A seal coat of 15% weight gain using H.P.M.C.-5cps (Formulation F5A) was sufficient to protect the tablets from the acid coat of the enteric layer.

Enteric coating was done using Eudragit L100: Eudragit S100 (1:3 ratios) to achieve 9, 10, 11, 12, 13 and 15% weight gain. Formulation F5F with 13% enteric coating found similar with innovator by the results.

Sugar coating and Color coating Formulation F5F5 optimized to achieve the Physical feasibility.

Disintegration time for Innovator and 13% enteric coating found similar in 0.1N HCl for 2 hours and Phosphate buffer pH – (6.8 – 8.0).

Dissolution of Innovator and 13% enteric coating in 0.1N Hydrochloric acid – 2 hours and Phosphate Buffer pH – 6.8, 7.4, 8.0 found similar with f1 – NMT15 and f2 – NLT50.

Bisacodyl Gastro-resistant (Enteric coated) Tablet with packing materials Alu- PVDC blisters Packing found as stable formulation in different stability conditions. After the stability study all physical, assay, related substance, and dissolution test have done and shows no change compared to the initial test.

Based on the results of different trials, F5F5 formulation is satisfactory and can be taken for Scale-Up and Bio-Study

9.0. REFERENCES

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