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FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM

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1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. For sustained as well as controlled drug delivery system, the oral route of administration has received the most attention, because of ease in dosage form design for oral than parentral routes, quit high patient acceptance, relatively safe route of drug administration and minimal damage at the site of administration. An ideal or advanced drug delivery system is that, which precisely control the rate, time and site of drug delivery independently of normal physiological variables such as p^H of GI tract, digestive state of GI tract, peristaltic movement and circadian rhythm.[1] An ideal dosage regimen in the drug therapy of any disease in the one which immediately attains the desired therapeutic concentration of drug in plasma and maintains it constant for entire duration of treatment .This is possible through administration of a convention dosage form in a particular dose and at a particular frequency .The frequency of administration or the dosing interval of any drug depends upon its half life or mean residence time and its therapeutic index.[2]

Colon Targeted Drug Delivery System

Colon drug delivery system refers to targeted delivery of drug in to the lowerpart of GI tract, mainly large intestine. To overcome this difficulty, colon-specific drug delivery systems have been broadly analyze during the last two decades. By definition, a colonic delivery refers to delivery of drugs accurately into the lower GI tract (by avoiding the drug release in upper GIT), which occurs primarily in the large intestine (i.e. colon). Rectal

administration is another route used for colon targeting, but it shows less compliance (uncomfortable) and becomes difficult to reach the colon. Conventional dosage forms that are used in the prevention of colon diseases (ulcerative colitis,crohn's diseases, amoebiasis) are failing as an improper amount of drug reaches site of action.

The aim of a targeted drug delivery system is to provide a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site. Itis suitable and required for the drugs having instability, low solubility, short half-life, a large volume of distribution, poor absorption, low specificity, and therapeutic index. Targeting may provide maximum therapeutic activity (by preventing degradation or inactivation of drug).

Ongoing research in the area of oral delivery of drugs, a discipline which has basked in the spotlight of pharmaceutical sciences for the past 70 years, has led to improved and profound insights into the physiology, biology and physical chemistry (pharmacokinetics, partitioning phenomenon) of organs, compartments, cells, membranes, cellular organelles and functional proteins (e.g. transporters) associated with absorption processes of drugs in the gastrointestinal tract (GIT). Majority of the research has focused on delivery of drug to the small intestine. The large intestine, however, because of its remoteness and relatively different physiology acquired the status of an outcast. From last two decades, interest in area development of oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders.

Colonic delivery offers several potential therapeutic advantages as a site for drug delivery, (a) The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. (b) The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. (c) The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. (d) Reduced proteolytic activity in the colon may be helpful in achieving reasonable absorption of certain drugs that are enzymatically labile in small intestine. (b) Reduced fluid motility and motility in the colon when compared with small intestine is advantageous formulation consists of multiple components such as permeation enhancers that must reach epithelial layer to achieve close spatial proximity with each other. (e) The colonic region has somewhat less hostile environment with less diversity and less intensity of activity as compared to stomach and small intestine.[2-4]

Advantages of colon targeted drug delivery system

The following advantages can be obtained on CTDDS.[2,3]

1. One of the potential advantage for CTDDS to treat disease in colon eg., inflammatory bowel disease by delivering the drug to colon, smaller size dose ofdrug is required.
2. By CTDDS the frequency of dose is reduced. So, lower the cost of expensive drugs.
3. By decreasing the dose and frequency as mentioned above, possibly lead to a reduced incidence of side effects and drug interactions.
4. The colon is an attractive site where poorly absorbed drug molecules may have an enhanced bioavailability, because CTDDS has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
5. Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
6. By pass initial first pass metabolism.
7. Extended daytime or night time activity; that mean can be used to prolong the time of drug delivery and this improve patient compliance.

Limitations of colon targeting drug delivery system

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

The most useful applications of colon targeted drug delivery system

1. The following applications show the potential advantages of CTDDS: Colon is a site where local and systemic drug delivery could be achieved, local treatment of inflammatory bowel disease, for example Ulcerative colitis and Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine.
2. CTDDS can be used for drugs used to treat asthma, and arthritis to prevent early morning attacks.
3. Formulations for CTDDS are also suitable for drugs which are polar and susceptible to chemical and enzymatic degradation in the upperGIT and highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

4. Other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively, if drugs were targeted to the colon.[4]

Why Colon Targeted Drug Delivery needed?

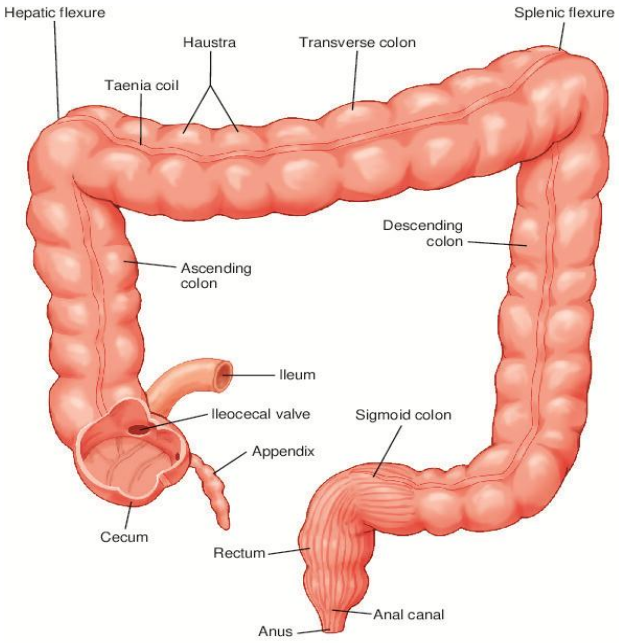
To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's Disease.

Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism, in particular, therapeutic proteins and peptide.

Anatomy And Physiology Of Colon

In GIT, large intestine starts from the ileocecal junction to the anus having a length of about 1.5m (adults) and is divided into three parts, viz. colon, rectum and anal canal. The colon consists of caecum, ascending colon, transverse colon, descending colon and sigmoid colon. Colon is made up of four layers, serosa, muscularis externa, submucosa and mucosa. The epithelium consists of a single layer of cells, which lines the crypts and covers the surface of the mucosa. Three major cell types found in the epithelium are the columnar absorptive cells, goblet (mucous) cells and entero endocrine cells. Adjacent columnar absorptive cells are attached to one another near apical margins by a junctional complex.[5]

Mucus production in the colon is a function of goblet cells and the proportion of goblet cells increases in the elderly. The colon and the rectum have an anatomic blood supply. The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon. The venous drainage is via the superior (proximal colon) and inferior (distal colon) veins. The arterioles and capillary branches pass to the epithelial surface between the crypts and form an extensive network of capillary plexi. The mucus lining of GIT forms a barrier against bacterial invasion of the gutwall.



Ascending colon

The ascending colon is on the right side of the abdomen. It is the part of the colon from the cecum to the hepatic flexure (the turn of the colon by the liver). It is retroperitoneal in most humans. In grazing animals the cecum empties into the spiral colon.

Transverse colon

The transverse colon is the part of the colon from the hepatic flexure (the turn of the colon by the liver) to the splenic flexure (the turn of the colon by the spleen). The transverse colon hangs off the stomach, attached to it by a wide band of tissue called the greater omentum. On the posterior side, the transverse colon is connected to the posterior abdominal wall by a mesentery known as the transverse mesocolon. The transverse colon is encased in peritoneum, and is therefore mobile (unlike the parts of the colon immediately before and after it). As the path progresses from intestine the the solid content increases as water gets absorbed.[6]

Descending Colon

The descending colon is the part of the colon from the splenic flexure to the beginning of the sigmoid colon. It is retroperitoneal in two-thirds of humans. In the other third, it has a (usually short) mesentery.

Sigmoid Colon

The sigmoid colon is the part of the large intestine after the descending colon and before the

rectum. The name sigmoid means S-shaped. The walls of the sigmoid colonare muscular, and contract to increase the pressure inside the colon, causing the stool to move into the rectum.

pH of the colon

High pH gradient exists between the different parts of GIT. pH gradient between saliva and gastric juice and between gastric juice and intestinal juice is considerably high but that between different parts of intestine is low. The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state, and food intake influence the pH of the gastrointestinal fluid. The change in pH along thegastrointestinal tract has been used as a means for targeting drug to the colon. There is a pH gradient in the gastrointestinal tract with value ranging from1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. The pH difference between the stomach and the small intestine has historicallybeen exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in the pH on the entry into the colon due to the presence of shortchain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermanted by colonic bactertia to produce large amounts of lactic acid resulting in drop in the pH to about 5.0.

Colonic microflora

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, theses enzymes are derived from gut Microflora residing in high number in the colon. Colon consists of a more than 500 different types of enzyme liberating symbiotic anaerobes. These enzymes derived from microbes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent i.e. release drug from the polymeric prodrugs. There is a vast difference in the microflora count of intestine and cecum. This is due to the retardation of movement of the contents within the gastro intestinal tract due to widening of the intestinal lumen as it moves from the ileum to the cecum and to the ascending colon. These facts and the bag shaped nature of the cecum make this site the favourite region for microbial settlement.

Intestinal microflora count : 10 3 CFU/ml10 power 3 correction.

Colonic microflora count: 1012 CFU/ml 10 power 12.

During illness and antibiotic therapy there is reversible destruction of microbes. The most important anaerobic bacteria are bacteroides, Bifidobacterium, Eubacterium, Peptococcus,

Peptostreptocococcus, Ruminococcus, Propionibacterium andClostridium.

Transit time to colon

Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. Arrival time of a drug or dosage form in the colon is subject to the vagaries of the gastric emptying and intestinal transit time. Under normal conditions transit time to colon is between 5 to 7 h.

Approximate transit time of different organs.Stomach - 2 h

Upper small intestine - 1 hLower small intestine - 2 h

So, overall transit time is approximately 5 h.

But this transit time varies with fed and fasted state of GIT. Under fasted state transit time is between 3 to 5 h and in fed state it is between 6 to 10 h. The movement ofmaterials through the colon is slow and tends to be highly variable and influenced by a number of factors other than diet like mobility, stress, disease state and presence of other drugs. In the healthy young and adult males, dosage forms such as tablets pass through the colon in approximately 20-30 h, although the transit time of a few hours to more than 2 days can occur. Diseases affecting colonic transit have important implications for drug delivery: diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant.[7]

Anatomy of the Colon

The colon is not labeled very creatively—most of the labels for the colon correspond to their anatomical location and flow of stool. Your large intestine is broken down into six sections including the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and the rectum. The colon begins at the end of the small intestine, where it is called the cecum, and ends at the rectum. Cancers of the large intestine are casually referred to as colon, rectal or colorectal cancer.

The cecum is anatomically located in the lower right sight of your abdomen approximately where your appendix is attached. The cecum is the widest part of your entire colon and is approximately 5 centimeters long, or a third as long as a pen. Between 15 and 20 percent of all colon cancers occur in the cecum. The ascending colon heads up vertically from the cecum to the transverse colon. The juncture between the cecum and transverse colon is

called the right colic flexure, or the hepatic flexurefor its proximity to your liver (hepatic system). Anatomically, the ascending colon is about 10 centimeters long and is seated on the right side of your abdomen.

FUNCTIONS OF THE COLON

The major function is the consolidation of the intestinal contents into feaces by the absorption of water and electrolytes. The absorptive capacity is very high. In healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted. Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements caused by circularmuscle and causing the appearance of the sac-like haustra, predominate and resulting in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle, is less common and occurs an averageof three or four times daily.[8]

Barriers To Colonic Drug Absorption

Drug absorption through the colon can be limited by number of barriers. In the lumen itself, specific and non-specific drug binding can occur through the interaction of drug with dietary components and products released from bacteria residing in the colon. The mucus barrier at the epithelial surface can present a formidable physical barrier to uptake as a result of specific and non-specific drug binding. Mucus-drug incompatibility can be compounded if the delivered drug stimulates the mucus secreting goblet cells because the transit through mucus is diffusion limited, the greater the thickness of this barrier, longer the time required for an individual molecule to reach the epithelial surface. The unstirred water layer (the space between mucus layer and epithelial cells) presents another barrier to colonic absorption, particularly for lipophilic drugs. A pH gradient may also exist across the unstirred water layer. This lower pH at the colonocyte surface may dramatically alter drug solubility and since drug transport within the unstirred layer is driven by chemical potential, altered drug solubility can affect absorption. Probably the most significant barrier to epithelial transport of drugs in the colon occurs at the level of the epithelium. Here, the lipid bilayers of the individual colonocytes and the occluding junctional complex (OJC) between these cells provide a physical barrier to drug absorption.[8,9]

Colonic Absorption

As absorption capacity of colon is very high which is attributed to the colon transit time, which can be as long as 20-35 hours, hence it is ideally suited for absorption. The absorption

is influenced by the transport of water, electrolytes and ammonia across the mucus and it is more in the proximal colon than the distal colon. Drug molecules pass from the apical to basolateral surface of epithelial cells by.

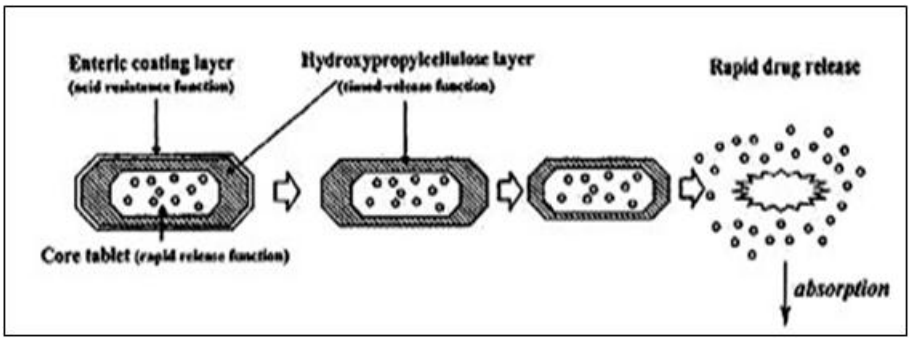


Figure.2: Design of enteric coated coated timed release press coated table (ETP Tablet).

- Passing through colonocytes (trans cellular transport), or
- Passing between adjacent colonocytes (para cellular transport)

Small amphipathic drugs may pass this barrier through transcellular transport. Paracellular transport may be the most promising means of general drug absorption in colon. Additionally, carrier mediated uptake of the drug in the colon is not extensive and usually related to the metabolic events of the resident bacteria. Receptor mediated endocytosis and pinocytosis could, however lead to transcellular transport of drug.

The transverse colon connects your ascending and descending colon, traveling lengthwise across your abdomen. The transverse colon lies close to your stomach, liver, and gallbladder and is approximately 50 centimeters long.

FACTORS AFFECTING COLONIC DRUG DELIVERY

There are many factors that influence the drug delivery to colon. They include.[10]

1. Transit through GIT

In order to reach colon in an intact form, the drug delivery systems should surpass the barriers in the stomach and small intestine. Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction. During this period the dosage form is exposed to enzymes present in small intestine. Compared to the other region of GIT, movement of material through the colon is slow. The

colonic transit time of a capsule in adult is 20-35 hrs. Improved residence time with subsequent longer transit time and the contact of dosage form with micro flora in colon govern the release and absorption of drug from dosage form.

2. Gastric emptying

Once the dosage form enters the stomach, the primary concern is how long it will remain there before being discharged into the duodenum. Emptying generally completes in 5-10 min up to 2 hours depending on phase of the stomach at the time of drug administration. It is preferable for a colonic delivery system to spend little time inthe stomach. Such system may release the drug at a distant locus from the colon.

3. Stomach and intestinal pH

The pH of GIT must be considered when enteric coatings (bioerodiblepolymers) are used to deliver drugs to colon. Since, in such systems, GIT pH gradient is used to trigger drug release.

4. Colonic microflora

Microflora of the colon has a number of implications in health and the treatment of diseases such as IBD. The concentration of gut microflora rises considerably in the terminal ileum to reach extraordinarily high levels in the colon. The gut bacteria are capable of catalysing a wide range of metabolic events. Many colon-specific drug delivery systems rely on enzymes unique to gut microflora to release active agents in the colon. However, only two or three enzyme systems namely azoreductases and glycosidases (including glucuronidase) have been explored in this area. A large number of polysaccharides are actively hydrolysed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases (including glucuronidases). The main bacterial groups responsible for β- glycosidases activity arelactobacilli, bacteroides and bifidobacteria.

5. Gastrointestinal Disease State

Gastrointestinal diseases such as IBD (inflammatory bowel disease), crohn's disease, constipation, diarrhoea and gastroenteritis may affect the release and absorption of drug from colon-specific drug delivery system.

Classification of CTDDS

CTDDS can be classified as follows:

1) pH dependent systems.
2) Time dependent systems.
3) Bacterial enzyme dependent system.
4) Covalent linkage of a drug with a carrier
5) Redox release system.
6) Bioadhesive systems.
7) Coating with microparticles.
8) Osmotic controlled drug delivery.

1) pH dependent systems

pH of human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and itincreases to 7-8 in the distal ileum. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. These processes distribute the drug throughout the large intestine and improve the potential of CTDDS.[11]

Disadvantages of pH dependent systems

- Lack of consistency in the dissolution of polymer at the desired site.
- Moreover, many factors such as the presence of short chain fatty acids, residues of bile acids, carbon dioxide or other fermentation products can reduce the colonic pH to approximately 6 which can certainly affectthe release of drug in the colon.
- Certain disease state does alter the pH of the colon.

2) Time dependent systems

Strategy of time released system is to resist the acidic environment of stomach and release the drug after predetermined lag time, after which release of drug take place. Factors affecting release from time dependent systems Residence time plays a key role here along with it Fed and fasted state of the subject and the interdigestive phase may prolong emptying time of stomach. Residence time of stomach (approx.) – 2 h. small intestine (approx.) – 2 to 4 h.

Disadvantages of time dependent systems

Individual to individual variation arises due to health, pathologic state, concomitant medication which causes Premature / Delayed drug release.

3) Bacterial enzyme dependent system

The bioenvironment inside the human GIT is characterized by the presence of complex microflora especially the colon that is rich in microorganisms that are involved in the process of reduction of dietary component or other materials. Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, have been exploited in designing drugs for colon targeting.

Actually, upon passage of the CTDDS through the GIT, it remains intact in the stomach and small intestine where very little microbially degradable activity is present that is quiet insufficient for cleavage of polymer coating. Release of the drugs from polysaccharide based formulation is supposed to take place after degradation of polysaccharide by the enzymes released from bacterias present in the colonic microflora.

4) Covalent linkage of the drug with a carrier

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biologicalenvironment to release the active drug. The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon. Site specific drug delivery through site specific prodrug activation may be accomplished by the utilization of some specific property at the target site, such as altered pH or high activity of certain enzymes relative to the non-target tissues for the prodrug-drug conversion.

5) Redox sensitive polymers

Novel polymers that hydrolyzed nonenzymatically by enzymatically generated flavins are being developed for colon targeting. Under anaerobic conditions, bacterial azo reduction by enzymatically generated reduced flavins where the initial substrate thought to be involved in cellular electron transport requires the presence of NADPH as its electron source. As NADPH is oxidized, the electron mediator (reduced flavins) acts as an electron shuttle from

theNADPH dependent flavoprotein to the azo compound. Reduction of the azobond to the hydroazo intermediate requires a low electron density within the azo region, and thus substitution of electron-withdrawing groups will favor this reaction. Redox potential is an expression of the total metabolic and bacterial activity in the colon and it is believed to be insensitive to dietary changes. The mean redox potential in proximal small bowl is - 67 90 mv, in the distal small bowl is -196 97 mv and in the colon is -145 72 mv. Microflora-induced changes in the redox potential can also be used as a highly selective mechanism for targeting to the colon.

6) Bioadhesive systems

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Dissolution of dosage form and simultaneous absorption from upper GIT lead to low intracolonic drug concentration as well as absorption of drugs result in the generation of sideeffects. Bioadhesion is a process whereby drug remains in contact with a particular organ for a longer period of time. It may be used for improved absorption of poorly absorbable drugs. Polymers: polycarbophils, polyurethanes and poloxamers.

7. Osmotic controlled drug delivery

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units each 4mm in diameter, encapsulated with in a hard gelatin capsule. Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves.

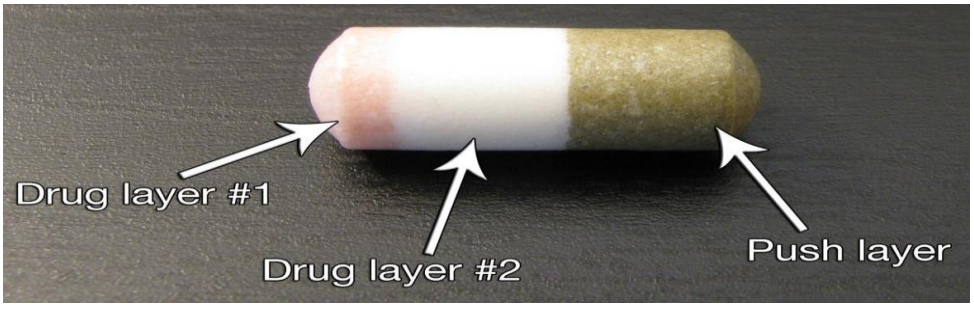


Figure 3: An illustration of the different inner components of a tablet of Concerta, a PSOP OROS design.

Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach and hence no drug is delivered. As the unit enter the small intestine, the coating dissolve in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine.

Bio pharmaceutics classification system

The Biopharmaceutics Classification System (BCS) is a system used to differentiate the drugs on the basis of their solubility and permeability, and it is considered as guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. The fundamental basis for the BCS wasestablished by Gordon Amidon.

According to the BCS the drugs can be characterized into four classes depending on in vitro solubility and in vivo permeability data as represented in table. Among the four classes, class II drugs show poor solubility and high permeability. Therefore, their low ability to dissolve is a limitation to their overall rate and extent of absorption over their ability to permeate through the membrane. Hence, theformulation design for oral delivery of class II compounds should focus on theenhancement of aqueous solubility or dissolution rate. Once these drugs dissolve, they rapidly pass through biological membranes such as the GIT membrane.[12]

Table. 1: USP and IP solubility criteria.

Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Descriptive term Part of solvent required per part of solute.

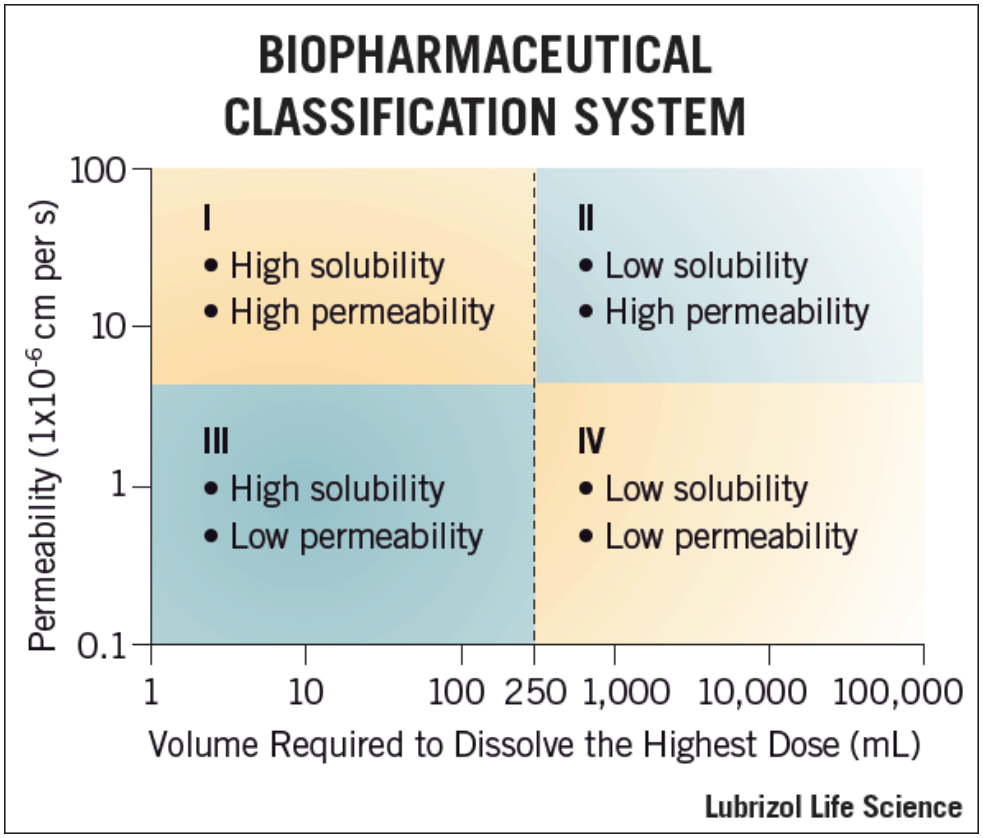


Table.1 Class Aqueous solubility Permeability.

There are successive two processes that can be identified to describe the oral absorption of drugs from solid dosage forms: dissolution of the drug in vivo to produce a solution and transport of the dissolved drug across the gastrointestinal membrane. The particle size of the drug is of great importance in the transport fromthe GIT to the site of action by increasing the dissolution rate in the GIT. The techniques that are generally employed for solubilization of drug include micronization, pH adjustment, chemical modification, solid dispersion, cosolvency, complexation, micellar solubilization and hydrotropy and others. The pharmacopoeia lists solubility in terms of solvent required to dissolve 1g of solute. The pharmacopoeia provides general terms to describe a given range as shown in table.[13,14]

DISEASES OF COLON

Inflammatory bowel disease (IBD) results from the interaction between genetic and environmental factors which influence the immune responses. Inflammatory bowel diseases are mainly divided into ulcerative colitis (UC) and Crohn's disease (CD). Crohn's disease is similar to UC, both of which have been classified as chronic IBD and which cause digestive disorders and inflammation in the gastrointestinal tract. Some of the symptoms of CD and UC include diarrhea, abdominal pain, rectal bleeding, and weight loss. They are mainly

characterized by inflammation. Both the diseases may occur in adolescents and adults and affectmen and women equally. Despite the similarity between the symptoms of these two diseases, there are some differences between the symptoms of CD and UC.[15]

Crohn's disease is one of the IBDs that occur in patients between ages 15-35 years. Unlike other inflammatory diseases, IBDs could not be suppressed easily. Consequently, the immune system is stimulated, and part of the intestine is destroyed. It causes pain, diarrhea, fever, and other symptoms. In addition to the serious effect on the lower part of the small intestine, CD can also occur in parts of the digestive tract including the large intestine, stomach, esophagus, or even mouth.

Crohn's disease affects the mouth, anus, and the entire layers of the intestine. Ulcerative colitis affects the mucosal layer of the colon. The lesions occur in the rectum and the intestine. The symptoms are mild to severe and may threaten life. The symptoms of CD and UC are very similar. Malnutrition is very common in CD because the small intestine is responsible for the absorption of nutrients, and CD damages the small intestine.[16]

Ulcerative colitis is associated with blood in stool, severe pain, and diarrhea, while in CD there is also a risk of bleeding in severe cases. Rectal bleeding is less common in CD, while UC is commonly associated with rectal bleeding. More than 50% of people with CD suffer from folate and vitamin D deficiency, while more than 50% of people with UC suffer from iron deficiency.

The affected areas of the digestive tract vary in these diseases. For example, CD often affects the ileum and a part of the large intestine. It may affect any part of the gastrointestinal tract (GI) including mouth, esophagus, stomach, small intestine, rectum, and anus. In CD, the small intestine often becomes inflamed, while UC is limited to the colon and is found mostly in some parts of the large intestine including colon and rectum. In UC, the large intestine becomes inflamed and the small intestine works naturally.

Ulcerative colitis only affects the innermost part of the colon, while CD occursin all layers of the bowel wall. By understanding the fact that CD and UC are both major categories of IBD, it could be pointed out that CD can cause serious problems particularly for skin and biliary stones, and UC will be associated with osteoporosis and possibly colon cancer if it lasts over 8–10 years. Crohn's disease is mostly associated with abdominal pain and

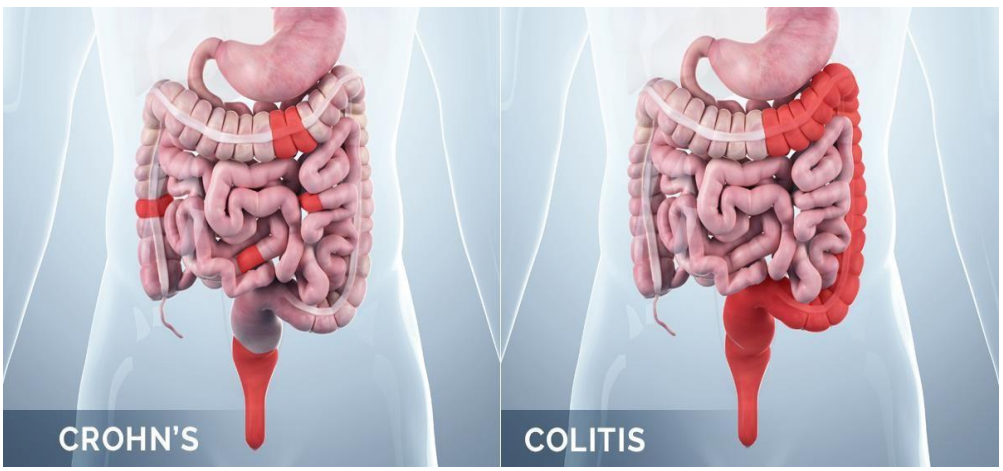
problems such as fistula and rectal lesions. In contrast, people with UC usually suffer from intermittent pain consistent with bowel movements.

It affects both children and adults. It is estimated that UC affects 2.6 million in Europe and 1.2 million people in North America. Approximately 25% of these patients are diagnosed before the age of 18 years. The disease often begins in adolescence and approximately 25% of patients with IBD are younger than 20 years.[17,18]

SIGNS AND SYMPTOMS OF ULCERATIVE COLITIS

The most common signs and symptoms of ulcerative colitis are diarrhea with bloodor pus and abdominal discomfort. Other signs and symptoms include.[19]

- An urgent need to have a bowel movement
- Nausea or loss of appetite
- Weight loss
- Fever
- Anemia is a condition in which the body has fewer red blood cells than normal Less common symptoms include
- Joint pain or soreness
- Eye irritation
- Certain rashes
- The symptoms a person experiences can vary depending on the severity of the inflammation and where it occurs in the intestine. When symptoms first appear,
- Most people with ulcerative colitis have mild to moderate symptoms
- About 10 percent of people can have severe symptoms, such as frequent, bloody bowel movements, fever and severe abdominal cramping.



CAUSES OF ULCERATIVE COLITIS

The exact cause of ulcerative colitis is unknown. Researchers believe the following factors may play a role in causing ulcerative colitis.[20]

- Overactive intestinal immune system
- Genes
- Environment

Overactive intestinal immune system.

Scientists believe one cause of ulcerative colitis may be an abnormal immune reaction in the intestine. Normally, the immune system protects the body from infection by identifying and destroying bacteria, viruses, and other potentially harmful foreign substances. Researchers believe bacteria or viruses can mistakenly trigger the immune system to attack the inner lining of the large intestine. This immune system response causes the inflammation, leading to symptoms.[21,22]

Genes.

Ulcerative colitis sometimes runs in families. Research studies have shown that certain abnormal genes may appear in people with ulcerative colitis. However, researchers have not been able to show a clear link between the abnormal genes and ulcerative colitis.

Environment

Some studies suggest that certain things in the environment may increase the chance of a person getting ulcerative colitis, although the overall chance is low. No steroidal anti-inflammatory drugs, antibiotics, and oral contraceptives may slightly increase the chance of developing ulcerative colitis. A high-fat diet may also slightly increase the chance of getting ulcerative colitis.[22,23]

Some people believe eating certain foods, stress, or emotional distress can cause ulcerative colitis. Emotional distress does not seem to cause ulcerative colitis. A few studies suggest that stress may increase a person's chance of having a flare- up of ulcerative colitis. Also, some people may find that certain foods can trigger or worsen symptoms. North America and uncommon in most of the developing Asian countries. The incidence/prevalence of ulcerative colitis varies not only according to geographical region but also with race and ethnicity.[24]

INCIDENCE AND PREVALENCE OF ULCERATIVE COLITIS

- Ulcerative colitis occurs worldwide. It is considered common in most of Europe and Lab tests.
- Endoscopies of the large intestine.[25]

a. Medical and Family History

Taking a medical and family history can help the health care provider diagnose ulcerative colitis and understand a patient's symptoms. The health care provider will also ask the patient about current and past medical conditions and medications.

b. Physical Exam

A physical exam may help diagnose ulcerative colitis. During a physical exam, the health care provider most often checks for abdominal distension, or swelling listens to sounds within the abdomen using a stethoscopetaps on the abdomen to check for tenderness and pain.

c. Lab Tests

A health care provider may order lab tests to help diagnose ulcerative colitis, including blood and stool tests.

d. Blood tests

A blood test involves drawing blood at a health care provider's office or a lab. A lab technologist will analyze the blood sample. A health care provider may use blood tests to look for.

- Anemia
- Inflammation or infection somewhere in the body
- Markers that show ongoing inflammation
- Low albumin, or protein common in patients with severe ulcerative colitis

e. Stool tests

A stool test is the analysis of a sample of stool. A health care provider will give the patient a container for catching and storing the stool at home. The patient returns the sample to the health care provider or to a lab. A lab technologist will analyze the stool sample. Health care providers commonly order stool tests to rule out other causes of GI diseases, such as infection.[19,26]

f. Endoscopies of the Large Intestine

Endoscopies of the large intestine are the most accurate methods for diagnosing ulcerative colitis and ruling out other possible conditions, such as Crohn's disease, diverticular disease, or cancer. Endoscopies of the large intestine include.[27]

- Colonoscopy
- Flexible sigmoidoscopy

g. Colonoscopy

Colonoscopy is a test that uses a long, flexible, narrow tube with a light and tiny camera on one end, called a colonoscope or scope, to look inside the rectum and entire colon. In most cases, light anesthesia and pain medication help patients relax for the test. The medical staff will monitor a patient's vital signs and try to make him or her as comfortable as possible. A nurse or technician places an intravenous (IV) needle in a vein in the patient's arm or hand to give anesthesia. For the test, the patient will lie on a table or stretcher while the gastroenterologist inserts a colonoscope into the patient's anus and slowly guides it through the rectum and into the colon. The scope inflates the large intestine with air to give the gastroenterologist a better view. The camera sends a video image of the intestinal lining to a monitor, allowing the gastroenterologist to carefully examine the tissues lining the colon and rectum. The gastroenterologist may move the patient several times and adjust the scope for better viewing. Once the scope has reached the opening to the small intestine, the gastroenterologist slowly withdraws it and examines the lining of the colon and rectum again.[28]

A colonoscopy can show irritated and swollen tissue, ulcers, and abnormal growths such as polyps extra pieces of tissue that grow on the inner lining of the intestine. If the gastroenterologist suspects ulcerative colitis, he or she will biopsy the patient's colon and rectum. A biopsy is a procedure that involves taking small pieces of tissue for examination with a microscope. A health care provider will give patients written bowel prep instructions to follow at home before the test. The health care provider will also give patients information about how to care for themselves following the procedure.[29]

h. Flexible sigmoidoscopy

Flexible sigmoidoscopy is a test that uses a flexible, narrow tube with a light and tiny camera on one end, called a sigmoidoscope or scope, to look inside the rectum, the sigmoid colon, and sometimes the descending colon. In most cases, a patient does not need

anesthesia. For the test, the patient will lie on a table or stretcher while the health care provider inserts the sigmoidoscope into the patient's anus and slowly guides it through the rectum, the sigmoid colon and sometimes the descending colon.

The scope inflates the large intestine with air to give the health care provider a better view. The camera sends a video image of the intestinal lining toa monitor, allowing the health care provider to examine the tissues lining the sigmoid colon and rectum. The health care provider may ask the patient to moveseveral times and adjust the scope for better viewing. Once the scope reaches theend of the sigmoid colon, the health care provider slowly withdraws it while examining the lining of the colon and rectum again. The health care providerwill look for signs of bowel diseases and conditions such as irritated and swollen tissue, ulcers, and polyps.[30]

TABLETS

Tablets are solid dosage forms each containing a unit dose of one or more medicaments. They are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersed in water before administration and some are retained in the mouth where the active ingredient is liberated. Because of their composition, method of manufacture or intended use, tablets present a variety of characteristics and consequently there are several categories of tablets.

Tablets are usually solid, the end surfaces of which are flat or convex and the edges of which may be bevelled. They may exist in other shapes like triangular, rectangular, etc also. They may have lines or break-marks and may bear a symbol or other markings. They are sufficiently hard to withstand handling without crumbling or breaking.[31]

Advantages of Tablets

- They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- They are in general the easiest and cheapest to package and strip of all oral dosage forms.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such asenteric or delayed release products.

- They are better suited to large-scale production than the other unit oral forms.
- They have the best-combined properties of chemical.
- Cost is low.
- Lighter and compact.
- Easy to swallowing with least tendency for hang- up.
- Sustained release product is possible by enteric coating.
- Objectionable odour and bitter taste can be masked by coatingtechnique.[32,33]
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional stepswhen employing an embossed and or monogrammed punch face.

Disadvantages of the tablets

- Some drugs resist compression in to dense particles, owing to theiramorphous nature or flocculent, low density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features are very challenging for the formulators.
- Difficult to swallow in case of children and unconscious patients.
- Bitter tasted drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.[34]

Various Types of Tablets

Based on the route of administration or the function, the tablets are classified as follows.[35]

1) Tablets ingested orally.

a) Compressed tablets

b) Multiple compressed tabletsI) Layered tablets

II) Compression coated tablets

c) Repeat action tablets

d) Delayed action and enteric coated tablets

e) Sugar and chocolate coated tablets

f) Film coated tablets

g) Chewable tablets

2) Tablets used in the oral cavity.

a) Buccal tablets

b) Sublingual tablets

c) Troches and Lozenges

d) Dental cones

3) Tablets administered by other routes.

a) Implantation tablets

b) Vaginal Tablets

4) Tablets used to prepare solution.

a) Effervescent tablets

b) Dispensing tablets

c) Hypodermic tablets

d) Tablets triturates

PHARMACEUTICAL INGREDIENTS USED IN THE FORMULATION OF TABLETS

1. Acive ingredients

A drug substance is the Active Pharmaceutical Ingredient (API) or component that produces pharmacological activity.

2. Fillers/diluents

Diluents are used as excipients for direct compression formulas have beensubjected to prior processing to give them flow ability and compressibility.

Eg: Lactose, Dibasic calcium phosphate, Dextrose, Calcium carbonate, Magnesium carbonate, Starch, Sucrose, Mannitol.

3. Binders

Binders are agents which are used to impart cohesive qualities to the powdered material. Binders are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressedtablets.

Eg: Povidone, Acacia, Gelatin, HPMC, Polyvinyl pyrrollidone, Hydroxypropylcellulose.

4. Disintegrants

Disintegrants are substances or a mixture added to a tablet formulation tofacilitate its breakup

or disintegration of the tablet after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow rapid dissolution.[36,37]

Eg: Microcrystalline cellulose, Starch, Crosscarmellose sodium, Sodium starch glycolate.

5. Lubricants

During compression lubricants acts as to reduce the interface between the face of the die and the surface of the tablet and act to reduce the friction at this interface during ejection of the tablet from the tablet press. Inadequate lubrication of this interface results in the production of tablets with a pitted surface and is due to their ability of the tablet surface to detach from the surface of the tablet die. There are two main categories of lubricants: (1) insoluble and(2) soluble. Insoluble lubricants are added to the final mixing stage prior to the tablet compression.

Eg: Magnesium stearate, Stearicacid, Glycerylpalmitostearate. Soluble lubricants are principally employed to overcome the possible deleterious effects of their insoluble counterparts on the time required for tablet disintegration and drug dissolution.

Eg: Polyethylene glycol, Polyethylene stearate, Lauryl sulphate salt.

6. Glidants

Glidants are added to the formulation in order to improve the flow properties of the material to be fed into the die and sometimes aid in particle rearrangement within the die during the early stages of compression. They may act by interposing their particles between those of the other components and so, by virtue of their reduced adhesive tendencies, lower the overall interparticulate friction of the system.

Eg: Talc, Colloidal silicon dioxide.

7. Adsorbents

Adsorbents are used whenever it is required to include a liquid or semisolidcomponent, e.g. a drug or a flavour, within the tablet formulation. As the production of tablets requires solid components, the liquid/semisolid constituent is adsorbed on to a solid component which, in many cases, may be one of the other components in the tablet formulation (e.g. diluent) during mixing. If this approach is not possible, an adsorbent is specifically included in the formulation.Eg: Magnesium oxide/Carbonate, kaolin/Bentonite.

8. Sweetening agents/flavours

Sweetening agents and flavours (in accordance with other dosage forms) are employed to

control the taste and hence the acceptability of tablets. These agents are of particular importance if the conventional tablet contains a bitter drug or, more importantly, if the tablet is a chewable tablet.

Eg: Aspartame, Sucralose, Sucrose, Glycerine, Mannitol, Sorbiltol, Acesulfame potassium. Flavouring agents are incorporated into the formulation to give the tablet a more pleasant flavouror mask an unpleasant one.

Eg: Chocolate, Peppermint, Pineapple and Vanilla flavour.

9. Colours

Colorants do not contribute to the therapeutic activity and to improve the product bioavailability or stability. Their main role is to facilitate identification and to enhance the aesthetic appearance of the product. All colorants used in pharmaceuticals must be approved and certified by the FDA. Some commonly used Pharmaceutical colorants.[37]

Eg: Erythrosine, Tartrazine, Sunset Yellow, Brilliant blue.

TABLET PROCESSING

Pharmaceutical products are processed all over the world using the direct compressing, wet granulation, or dry granulation methods. Method chosen depends on the ingredients, individual characteristics like flow property, compressibility etc. Right choice of method requires thorough investigation of each proposed ingredient in the formula for comprehensive approach for intractions and stability.[38]

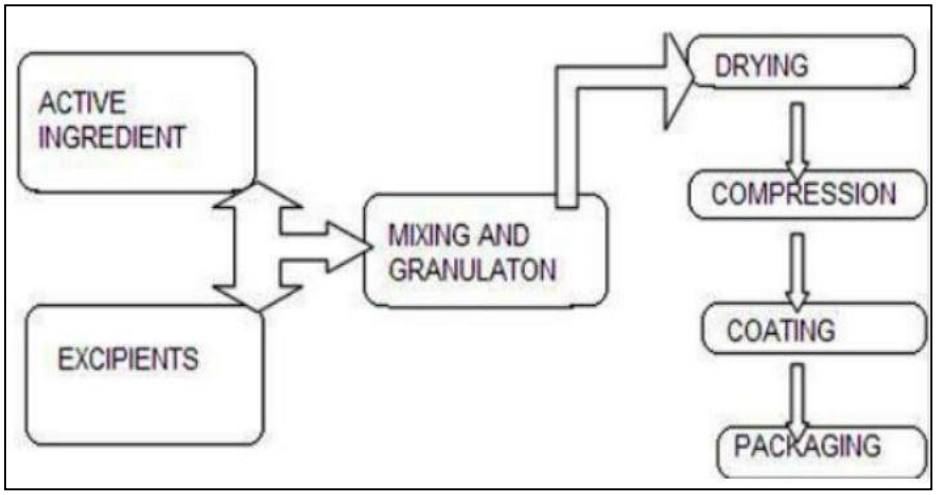


Figure 4: Various unit operation sequence in Tablet Manufacturing.

Tablet Coating

Coating is a process by which an essentially dry, outer layer of coating material is applied to

the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it.

Coating may be applied to multiple range of oral solid dosage form, including tablets, capsules, multi particulates and drug crystals. When coating composition is applied to a batch of tablets in a coating pan, the tablet surfaces become covered with a tacky polymeric film. Before the tablet surface dries, the applied coating changes from a sticky liquid to tacky semisolid and eventually to a non-sticky dry surface pans. The entire coating process is conducted in a series of mechanically operated acorn-shaped coating pans of galvanized iron stainless steel or copper. The smaller pans are used for experimental, developmental, and pilot plant operations, the larger pans for industrial production.[39]

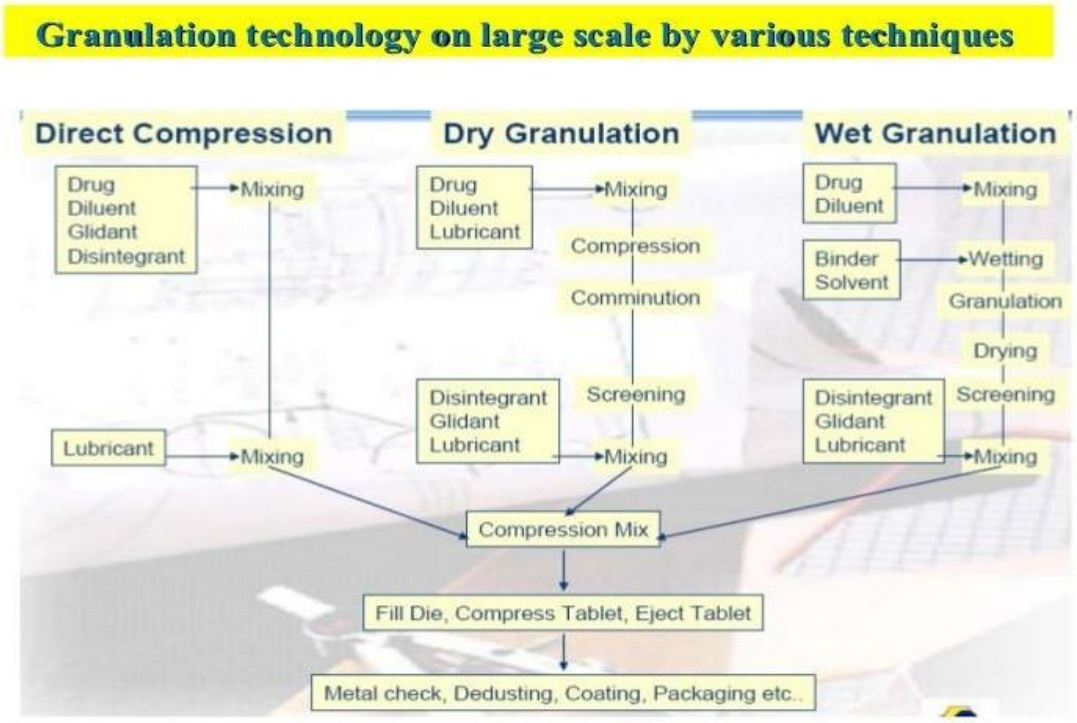


Fig. 5: Granulation Technology on large scale by various techniques.

Primary components involved in tablet coating

- Tablet properties
- Coating process
- Coating equipments
- Parameters of the coating process
- Facility and ancillary equipments
- Automation in coating processes.[40]

The application of coating is usually based on one or more of the following

- To mask the taste, odour or colour of the drug.
- To provide physical and chemical protection to the drug.
- To control the release of the drug.
- To protect the drug from the gastric environment of the stomach with an acid resistant coating.
- To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibility or to provide sequential drug release.
- To provide pharmaceutical elegance by use of special colour.[41]

Types of Coating

- Sugar Coating,
- Film Coating,
- Enteric Coating,
- Controlled release
- Coating, Specialized Coating,
- Compressed Coating,
- Electrostatic coating,
- Dip Coating,
- Vacuum Coating.

ENTERIC COATING

Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intensionis to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa. The coatings thatare used now a day to produce enteric effects are primarily mixed acid functionality and acid ester functionality, synthetic, or modified natural polymers. The most extensively used polymers are Cellulose acetate, polyvinyl acetate,polyhydroxy propyl methyl cellulose, Methacrylic acid copolymers. All these polymers have the common feature of containing the dicarboxylic, pthalic acid in partially esterified form.

These polymers, being acid esters are insoluble in gastric media that have the pHof about 4. And then leave the stomach and enter into the duodenum (pH 4-6) and further along the small intestine, where the pH is increased to a range of (pH 7-8). The primary mechanism, by which these polymers lose their integrity, is there by admitting the releasing drug to the intestinal fluid. In this ionization of the residualcarboxyl groups on the chain and subsequent hydration.[42]

- There are four **reasons** for putting such a coating on a tablet or capsule ingredient:
- Protection of active pharmaceutical ingredients, from the acidic environment of the stomach (e.g. enzymes and certain antibiotics).
- To prevent gastric distress or nausea from a drug due to irritation (e.g. sodium salicylate).
- For the delivery of drugs that are optimally absorbed in the small intestine to their

primary absorption site in their most concentrated form.

- To provide a delayed-release component for repeat action.
- Required for minimizing first pass metabolism of drugs.

Ideal enteric coating materials should have the following properties

- Resistance to gastric fluids.
- Ready susceptibility to or permeability to intestinal fluids.
- Compatibility with most coating solution components and the drug substrates.
- The film should not change on aging.
- Formation of continuous film.
- Non-toxicity.
- Low cost.
- Ease of application.

Enteric Coating Materials

Enteric coatings polymers are selectively insoluble substances. They won't dissolve in the acidic juices of the stomach, but they will when they reach the higher pH of the small intestine. Most enteric coatings won't dissolve in solutions with a pH lower.

Commonly-used enteric coating polymers

- Methacrylic acid copolymers
- Cellulose acetate (and its succinate and phthalate version)
- Polymethacrylic acid/acrylic acid copolymer
- Hydroxypropyl methyl cellulose phthalate (HPMCP)
- Polyvinyl acetate phthalate (PVAP)
- Hydroxy ethyl cellulose phthalate
- Cellulose acetate tetra hydro phthalate

The earliest enteric coatings utilized formalized gelatin, this was unreliable because of the polymerization of gelatin could not be accurately controlled. Another was shellac, disadvantage was polymerization with time, and resulting in poor dissolution of the coating. The most extensively used polymers are CAP, PVAP. The most recently used polymers are HPMCP, Methacrylic acid copolymers.[43]

- **Cellulose Acetate Phthalate (CAP)**

Effective enteric coating, it only dissolves above pH 6 and may delay drug release longer than desired. It is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

- **Poly Vinyl Acetate Phthalate (PVAP)**

Less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrates at pH5.

- **Hydroxy Propyl Methyl Cellulose Pthalate (HPMCP)**

It is available in two grades HP50 and HP55. HP55 solutions are more viscous than HP50. HP50 disintegrates at pH5 and HP55 disintegrates at pH5.5. It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require Plasticizer.

- **Methacrylic acid copolymers**: Two grades are available A, B and C which differs in the ratio of free carboxyl to ester groups therefore:

Type A - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio 1: 2: 0.2 and soluble in intestinal fluid from pH 6.

Type B - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio of 1:2:0.1 and soluble in intestinal fluid frompH 7.

Type C - Poly (methacrylic acid, ethyl acrylate) 1:1 and soluble in intestinal fluid from pH 5.5.

Table 2: Common polymer Used in enteric Coating formulation.

Common Polymers Used in Enteric Coating Formulations	
Examples	**Dissolution pH**
Cellulose acetate phthalate (CAP)	6.2
Cellulose acetate trimellitate (CAT)	5.0
Hydroxypropyl methylcellulose acetate succinate (HPMCAS)/ Hypromellose acetate succinate	> 6.0
Hydroxypropyl methylcellulose phthalate (HPMCP)	4.5 – 5.5
Polyvinyl acetate phthalate (PVAP)	5.0
Poly (methacrylic acid co-methyl methacrylate)	5.5 – 7.0
Shellac (esters of aleurtic acid)	7.0

Dissolution controlled extended release system can also be obtained by covering drug particles with a slowly dissolving coating. The release of the drug from such unit occurs in two steps, Criteria for selection of Drugs for.

1. The liquid that surrounds the release unit dissolves the coating.
2. The solid drug is exposed to the liquid and subsequently dissolves.

Sustained release oral product employing dissolution as the rate-limiting step arein principle then simplest to prepare. A drug with a slow dissolution rate is inherently sustained. Some examples of these drug includes digoxin, griseofulvin, and salicylamide. Other such as aluminium aspirin, ferrous sulphate and benzphetamine paomate, produce such forms when in contact with the absorption pool contents. Steroids have been reports to undergo transformation into less soluble polymorphs during dissolution in the absorption pool.

For those drug with high water solubility and therefore high dissolution rate, can decrease solubility through appropriate salt of derivative formation. Unfortunatelyforms such as these do not meet the criterion of constant availability rate because their surface area decreases with time. Nevertheless, sustained drug release can beachieved by coating drug particles or granules with materials of varying thickness or by dispersing them in a polymeric matrix.[44]

The basic principle of dissolution control is “If the dissolution process is diffusion layer controlled, where the rate of diffusion from the solid surfacethrough an unstirred liquid film to the bulk solution is rate limiting ”the flux J is given by.

$J = -D(dc/dx)$ 1.1

Where D is the diffusion coefficient and dc/dx is the concentration gradient from the solid surface to the bulk solution.

The flux can also be defined as the flow rate to material (dm/dt) through a unitarea (A), thus equation becomes

$J = (1/A)\, dm/dt$ 1.2

Where Cs is the concentration at the solid surface and Cb is the concentration Ithe bulk solution. By combining the above equation, the flow rate of material is given by

$dm/dt = -(DA/h)(Cb-Cs) = Ka(Cs-Cb)$. 1.3

Where k is the intrinsic dissolution rate constant.

The above equation predicts constant dissolution rate. If the surface area, diffusion co-efficient, diffusion layer thickness, and concentration difference are kept constant. However, as dissolution proceeds parameters like the surface area especially, may change.

Most suitable dosage froms for this mechanism is compressed tablets containing coated particles. E.g. Ethyl cellulose, Nylon, Acrylic resins. Release depends on drug solubility and pore structure membrane. Constant release resulted whengastrointestinal fluid passes through barrier to dissolve drug.

2. Diffusion Controlled Release Systems

There are basically two types of diffusion controlled systems which have been developed over the past two decades: reservoir devices and matrix devices. In diffusion controlled extended release system the transport by diffusion of dissolved drug in pores filled with gastric or intestinal juice or in a solid phase is the release controlling process. Depending on the part of the release unit in which the drug diffusion takes place, diffusion controlled release systems are divided into matrix systems and reservoir systems. The release unit can be tablet or a nearly spherical particale of about 1mm in diameter. In both cases the release unit should stay more or less intact during course of the release process.

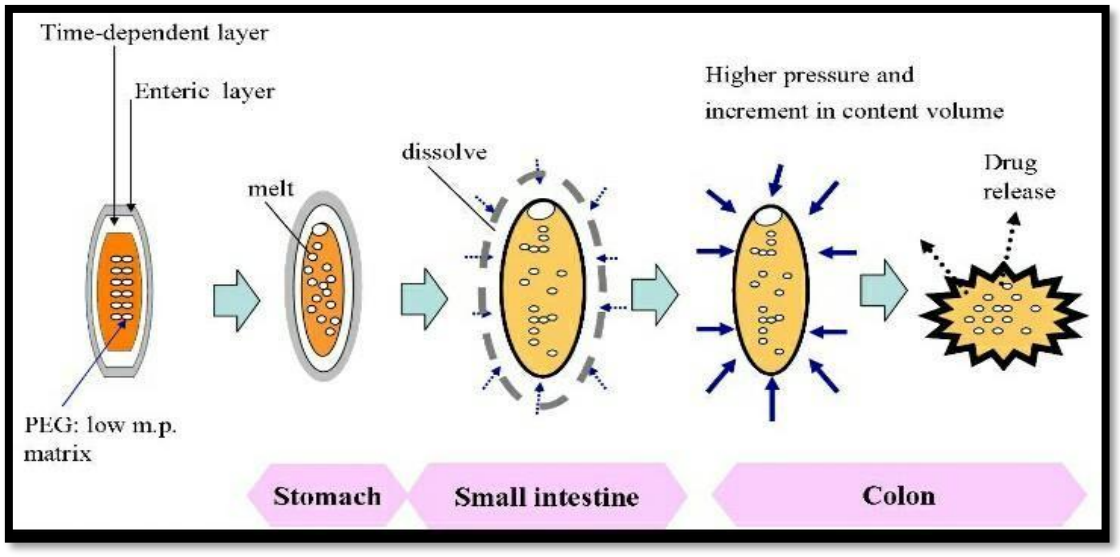


Fig 7: Dissolution controlled release system.

In matrix system diffusion occurs in pores located within the bulk of the release unit, and in reservoir system diffusion take place in a thin water-insoluble film or membrane, often about

5-20um thick, which surrounds the release unit. Diffusion through the membrane can in pores filled with fluid or in the solid phase thatforms the membrane.[45]

Drug is release from a diffusion controlled release unit in two steps

1. The liquid that surround the dosage from penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.
2. The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released, and alternatively the dissolved drug will partition into the membrane surrounding the dose unit and diffusion in the membrane

A dissolution step is thus normally involved in the release process but the diffusion step is the rate controlling step. The rate at which diffusion will occur depends on four variables:

- The concentration gradients over the diffusion distance.
- The area.
- The distance over which diffusion occurs.
- The diffusion co-efficient of the drug in the diffusion medium. Some of these variables are used to modulate the release rate in the formulation.[46]

Reservoir system

In a reservoir system the diffusion occurs in a thin a film surrounding the release unit. This film is normally formed a high molecular weight polymer. The diffusion distance will be constant during the course of the release and, as long a constant drug concentration gradient is maintained, the release rate will be constant, i.e. a zero order release. One possible process for the release of the drug from a reservoir system involves partition of the drug dissolved inside the release unit to the solid membrane, followed by transport by diffusion of the drug within the membrane.Finally, the drug will partition to the solution surrounding the release unit. The driving force for the release is the concentration gradient of dissolved drug over the membrane.

In this system, a water-insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surroundingthe particle or tablet. Additional drug will enter in the membrane, diffuse to the periphery, and exchange with the surrounding media.

Coefficient, which is defined as the concentration of drug in the membrane over the concentration of drug in the core. If the partition coefficient is high, the core will be depleted of drug in a short time so that zero order release will be observed only over a short segment of the time course of drug release.[47]

Matrix Devices

In matrix system the drug is dispersed as solid particles within a porous matrix formed of a water insoluble polymer, such as polyvinyl chloride. Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter, drug particles at successively increasingly distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. Thus, the diffusion distance of dissolved drug will increase as the release process proceeds. The drug release, in terms of the cumulative amount of drug (M) release from a matrix in which drug particles are suspended is proportional to th e square root of time i.e. $M = kt^{1/2}$. The main formulation factors by which the release rate from a matrix system can be controlled are.

- The amount of drug in the matrix,
- The porosity of the release unit, The length of the pores in the release unit (dependent on the size of the release unit and pore tortousity),
- The solubility of the drug (which regulates the concentration gradient). The characteristics of the pore system can be affected by the addition of soluble excipients and by the compaction pressure during tabletting.

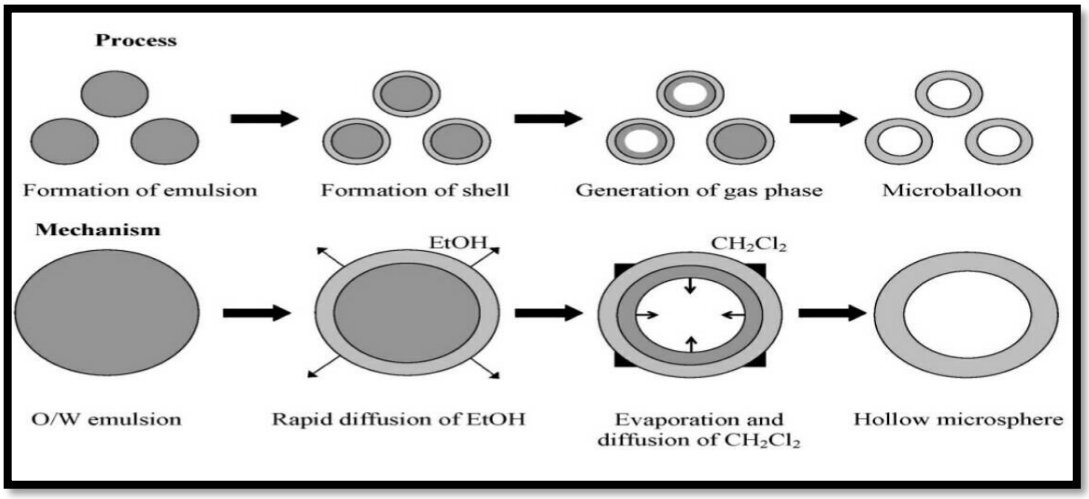


Fig. 8: Diffusion control release system.

3. Dissolution and Diffusion Controlled Products

In these systems, the drug core is coated with a partially soluble membrane. Pores are thus formed due to dissolution of parts of the membrance, which permit entry of aqueous medium into the core and release of dissolved drug by diffusion.[48,49]

For weak bases

$St = So(1+H^{+}/Ka) = So(1+10^{pka-pH})$

If a poorly soluble drug was consider as a suitable candidate for formulation into sustained release system. Since weakly acidic drugs will exist in the stomach pH 1-2 primarily in the unionized from their absorption will be favoured from this acidic environment on the other hands weakly basic drugs same site, their absorption will be poor in the upper portion of the small intestine the pH is more alkaline pH 5-7 and the reverse will be expected for weak acids.

Drug stability

The stability of the drug in environment to which is exposed, is another physiochemical factor to be considered in design at sustained can be placed in slowly soluble. Forms or have their release delayed until they reach the small intestine.orally administered drug can be subjected to both acid, base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugsin the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation. However for same drugs which are unstable in small intestine are undergo extensive Gut-Wall metabolism have decreased the bioavailability. When these drugs are administered from a sustained dosage form to achieve better bioavailability, at different routes of the drugs administered should be chosen. The presence of metabolism enzymesat the site or pathway can be utilized.

Protein Binding

It is well known that may drugs bind to plasma protein with the influence on duration of action. Drug –protein binding serve as a depot for drug producing a prolonged release profile, especially it is high degree of drug binding occurs. Extensive binding to plasma protein will be evidenced by a long half life of elimination for drug and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of

binding to plasma protein also might bind to biopolymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on dug molecule also increases the binding potential. The binding of the drugs to plasma protein result in retention of the drug into the vascular space the drug protein complex canserves as reservoir in the vascular space for sustained drug release to extra vascular tissue but only for those drugs that exhibited a high degree of binding. The main force of attraction are Wander-vals forces, hydrogen binding,electrostatic binding. In general charged compound have a greater tendency to bind a protein then uncharged compound, due to electrostatic effect.[50]
Eg. Amitryp;ine, cumarin, diazepam, digoxide, dicaumarol, novobiocin.

Colon Targeted Drug Delivery System (CTDDS) may be following the concept of Controlled or Sustained drug Delivery System. For CTDDS oral route of administration has received most attention. Local delivery allows topical treatment of inflammatory bowel disease. Colon is highly desirable for localtreatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease,colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs.[51,52]

For effective and safe therapy of these colonic disorders, colon specificdrug delivery is necessary i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. Today, colon specific drug delivery is challenging task to pharmaceutical technologist. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons.[53]

A. Less diversity

B. Intensity of digestive enzymes.

Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CTDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Coating of the drugs with pH-sensitive polymers provides simple approach for colon-specific drug delivery.[54]

The bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the reaches the colon. Because the colon has a long residence time 72 hours and high water content it favors absorption of poorly absorbed drug molecule may have an improved bioavailability, CTDDS has been employ to achieve following objectives.

LITERATURE REVIEW

1. Y. Zhou et al., (2017)[55] Designed a new colon-targeted drug delivery system based on chitosan.The properties of the films were studied to obtain useful information about the possible applications of composite films. The composite films were used in a bilayer system to investigate their feasibility as coating materials. However, the drug release from a bilayer-coated tablet in SCF increased over time, and the drug was almost completely released after 24h. Overall, colon-targeted drug delivery was achieved by using a chitosan/gelatin complex film and a multilayer coating system.

2. V. Gadhave et al., (2017)[56] Reported pectin–Chitosan compression coated core tablets of Mesalamine for colonic delivery. The system was designed based on the gastrointestinal transit time concept, under the assumption of colon arrival times of 6 h. It was found that pectin alone was not sufficient to protectthe core tablets and Chitosan addition was required to control the solubility of pectin. The optimum Chitosan concentrationwas 1 and such system would protect the cores up to 6 h and after that under the influence of pectinase the system wouldd degrade faster and delivering 5-ASA to the colon. The pectin– Chitosan (10:1) envelope was found to be a promising drug delivery system for those drugs to be delivered to the colon.

3. A. Amidon et al., (2015)[57] Drugs such as proteins and peptides that are known to degrade in the extreme gastric pH, if delivered to the colon intact, can be systemically absorbed by colonic mucosa. In order to achieve effective therapeutic outcomes, it is imperative that the designed delivery system specifically targets the drugs into the colon. Several formulation approaches have been explored in the development colon- targeted drug delivery systems. These approaches involve the use of formulation components that interact with one or more aspects of gastrointestinal (GI) physiology, such as the difference in the pH along the GI tract, the presence of colonic microflora, and enzymes, to achieve colon targeting.

4. P. Ratnaparakhi et al., (2013)[58] This review mainly compareed the primary approaches for CDDS (Colon Specific DrugDelivery) namely prodrugs, pH and time

dependent systems, and microbial triggered systems, whichachieved limited success and had limitations as compared with newer CDDS namely pressure controlledcolonicdelivery capsules, CODESTM, and osmotic controlled drug delivery (ORDS-CT) which are uniquein terms of achieving in vivo site specificity, and feasibility of manufacturing process. Treatment could bemore effective if it is possible for drug to be directly delivered to colon.

5. K. Malleswari et al., (2013)[59] New developments in field of colon specific drug delivery system. Colonic drug delivery was gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. New systems and technologies had been developed for colon targeting and to overcome pervious method's limitations. Colon targeting holds a great potential andstill need more innovative work.

6. A. Basit et al., (2012)[60] A variety of delivery strategies and systems had been proposed for colon targeting. These generally rely on the exploitation of one or more of the following gastrointestinal features for their functionality: pH, transit time, pressure or microflora. Coated systems that utilise the pH differential in thegastrointestinal tract and prodrugs that rely on colon bacteria for release had been commercialised. Both approaches have their own inherent limitations. Many systems in development have progressed no further than the bench, while others are expensive or complex to manufacture, or lack the desired site-specificity. The universal polysaccharide systems appear to be the most promising because of their practicality areexploitation of the most distinctive property of the colon, abundant microflora.

7. A. Philip et al., (2010)[61] The colon was a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs could be targeted directly into the colon, thereby reducing the systemic side effects. This review, mainly compares the primary approaches for CDDS (Colon Specific Drug Delivery) namely prodrugs, pH and time dependent systems, and microbially triggered systems, which achieved limited success and had limitations as compared with newer CDDS namely pressure controlled colonic delivery capsules, CODESTM, and osmotic controlled drug delivery which are unique in terms of achieving in vivo site specificity, and feasibilityof manufacturing process.

8. R. Dhawle et al., (2018)[63] The blessings of tablet coating are flavour covering, smell overlaying, bodily and chemical protection, protects the drug from the gastric surroundings and so on.Enteric coated tablets are solid unit dosage forms which are designed to bypass the stomach and release the drug in small intestine and are meant for oral administration. The word "enteric" indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coating works by presenting a surface that is stable at the highly acidic pH found in stomach, but breaks down rapidly at a less acidic pH. For e.g. they will not dissolve in the acidic juices of the stomach (pH-3), but will in the alkaline (pH7-9) environment present in the small intestine. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibres.

9. G. Prasanna Laxmi et al., (2019)[64] Esomeprazole tablets were successfully prepared using enteric coated polymers ethyl cellulose and HPMC pthallate by first preparing the core tablets and then press coated with polymers. study of the preformulation characteristics and FTIR studies indicates that there was no interaction between Esomeprazole and excipients used in the formulation. Invitro release profiles of optimized form of F6 were found to showed delayed release pattern in a very customized manner which was very much required for the colon specific drug delivery. In vitro release profiles of optimized formulation of Esomeprazole controlled release tablets (F-6) were found to be improvised and followed zero - order kinetics, hence the release of the drug from the dosage form was independent of concentration and followed Higuchi model, and hence release of drug from press coated tablet was by diffusion mechanism. The drug delivery system was designed to deliver the drug at such a time when it was needed nocturnal.

10. S. Nareskumar et al., (2019)[65] Bumadizone Calcium is an acetic acid derivative, having irritation in stomach. Bumadizone Calcium has short half-life (4hrs) and undergoes first pass metabolism. It is pH-dependent. This research work was carried out to improve the bioavailability, patient compliance on oral colon targeted drugdelivery. Bumadizone Calcium sustained release enteric coated pellets were prepared, which minimize the release of drug in stomach for treatment of IBD formulated by Extrusion Spheronization process.

11. G. Ratnam et al., (2017)[66] Mesalamine is 5-amino salicylic acid used as a topical anti-inflammatory agent and prednisolone is a synthetic glucocorticoid used for the treatment of various types of inflammatory and autoimmune conditions. Pectin was used as an enzyme

dependent polymer. Eudragit S 100 was used to enteric coat the compression coated tablets to avoid prerelease of the drug into the upper gastrointestinal tract. In vitro release study was carried out at various pH (1.2, 6.8 and 7.4) and in the presence of the pectinolytic enzyme. Therapeutic efficacy of the prepared tablets was evaluated in trinitrobenzene sulfonic acid-induced rabbit colitis model.

12. S. Vemula et al., (2009)[67] In oral colon-specific drug delivery system, colon has a large amount of lymphoma tissue (facilitates direct absorption in to the blood), negligible brush boarder membrane activity, and much less pancreatic enzymatic activity as compared with the small intestine. Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. Different approaches are designed based on prodrug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure etc to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes for colon targeting. The efficiency of drug delivery system is evaluated using different in vitro and in vivo release studies.

13. Shivkumar et al., (2019)[68] have prepared the pH sensitive multi-particulate system of diltiazem hydrochloride for colon targeting. The particles were prepared using Eudragit S-100 by extrusion spheronization method. The In-vitro dissolution study of the pellets performed following pH progression method showed that the drug release was depended on the coat weight applied and pH of the dissolution media.

14. Varshosaz et al., (2018)[69] Developed mesalazine chitosan microspheres for colon specific delivery. As 5-ASA is rapidly absorbed from the small intestine and it was necessary to develop a colon-specific delivery system for it, coated chitosan microspheres prepared by an emulsion-solvent evaporationtechnique. They reported that chitosan microspheres with good bioadhesive properties can attach to colon tissue and release slowly in zero order mode.

15. Kabra AO et al., (2012)[70] have used 10% (w/w) solution of polymethacrylates. Eudragit L100 and Eudragit S100 been prepared in isopropyl alcohol: water (9:1) mixture. The ratios of Eudragit S100: Euragit L100 were 1:4. The resulted suspension was coated on matrix tablet using coating pan. Coated tablets were removed from the apparatus when the coating loads reached 20% (w/w). It shows the release of drug to the colon.

16. Prasanta kumar choudhury et al., (2012)[71] Developed the matrix tablets of Ornidazole were prepared by wet granulation method using matrix forming natural polymers like Guar gum and Xanthan gum in combination with different proportions. The further effect of enteric coat on the matrix tablets for colon specific drug release was investigated. The Ornidazole optimized matrix formulation OM1 showed drug release around 32.37±0.33% in 2 hrs. So it was further enteric coated with 5% Eudragit S100 and coded as OME1 which showed 44.09±0.16% of drug release after 12 hrs. All formulations were subjected to Hardness test, Friability test, determination of uniform diameter and thickness, drug content for optimization and further evaluation. In-vitro dissolution studies indicated that the drug release in upper part of GIT from matrix tablets of Ornidazole can be prevented by enteric coating with pH sensitive polymer (Eudragit®S100), which releases the drug specifically in colonic region to achieve target delivery. All the parameters were found to be within the limits. Formulation OME1 showed 44.09% of drug release at the end of 12 hrs and emerged as best formulation.

DRUG PROFILE

Name

Prednisolone

Accession Number

DB00860 (APRD00197)

Type

Small Molecule

Groups

Approved, Vet approved

Description

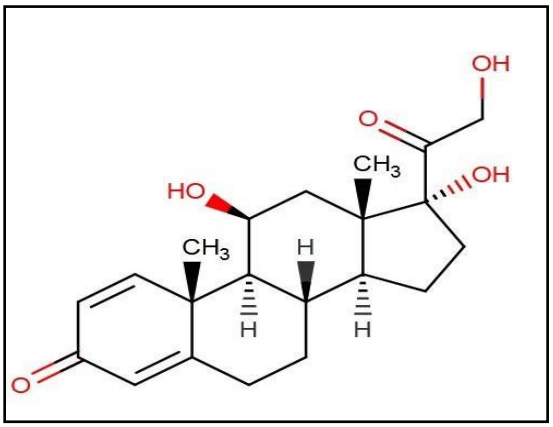
Prednisolone is a glucocorticoid similar to cortisol used for its anti- inflammatory, immunosuppressive, anti-neoplastic, and vasoconstrictiveeffects.

Prednisolone was granted FDA approval on 21 June 1955.

Chemical Name

The **chemical name** for **prednisone** is pregna-1,4-diene-3,11,20- trione, 17,21-dihydroxy- and its **molecular** weight is 358.43.

Structure



Chemical Formula

$C_{21}H_{28}O_5$

Weight

Average: 360.444

Monoisotopic: 360.193674006

Storage: Store at 20° to **25°C** (68° to **77°F**) Dispense in a tight, light-resistant container as defined in the USP.

Solubility

Prednisolone is very slightly **soluble in water** (1 g dissolves in 1000–10000 mL). 20 An aqueous **solubility** ranging from 0.22 to 0.24 mg/mL has been reported (without indicating the tempera- ture), 23,24 which is in accordance with a value of 243 mg/mL that was measured at 258C.

Indication

Prednisolone is indicated to treat endocrine, rheumatic, and hematologic disorders; collagen, dermatologic, ophthalmic, respiratory, and gastrointestinal diseases; allergic and edematous states; and other conditions like tuberculous meningitis.

Pharmacodynamics

Corticosteroids bind to the glucocorticoid receptor, inhibiting pro- inflammatory signals, and promoting anti-inflammatory signals. Prednisolone has a short duration of action as the half life is 2.1-3.5 hours. Corticosteroids have a wide therapeutic window as patients make require doses that are multiples of what the body naturally produces. Patients taking corticosteroids

should be counselled regarding the risk of hypothalamic-pituitary-adrenal axis suppression and increased susceptibility to infections.

Mechanism of action

The short term effects of corticosteroids are decreased vasodilation and permeability of capillaries, as well as decreased leukocyte migration to sites of inflammation. Corticosteroids binding to the glucocorticoid receptor mediates changes in gene expression that lead to multiple downstream effects over hours to days.

Glucocorticoids inhibit neutrophil apoptosis and demargination; they inhibit phospholipase A2, which decreases the formation of arachidonic acid derivatives; they inhibit NF-Kappa B and other inflammatory transcription factors; they promote anti- inflammatory genes like interleukin-10.

Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. High doses of glucocorticoids for an extended period bind to the mineralocorticoid receptor, raising sodium levels and decreasing potassium levels.

Uses

Prednisone is used to treat conditions such as arthritis, blood disorders, breathing problems, severe allergies, skin diseases, cancer, eye problems, and immune system disorders. Prednisone belongs to a class of drugs known as corticosteroids. It decreases your immune system's response to various diseases to reduce symptoms such as swelling and allergic-type reactions.

Side Effects

Nausea, vomiting, loss of appetite, heartburn, trouble sleeping, increased sweating, or acne may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly. Remember that your doctor has prescribed this medication because he or she has judgedthat the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Tell your doctor right away if any of these unlikely but serious side effects occur: muscle pain/cramps, irregular heartbeat, weakness, swelling hands/ankles/feet, unusual weight gain, signs of infection (such as fever, persistent sore throat), vision problems (such as blurred vision), symptoms of stomach/intestinal bleeding (such as stomach/abdominal pain,

black/tarry stools, vomit that looks like coffee grounds), mental/mood changes (such as depression, mood swings, agitation), slow wound healing, thinning skin, bone pain, menstrual period changes, puffy face, seizures, easy bruising/bleeding.

This medication may rarely make your blood sugar rise, which can cause or worsen diabetes. Tell your doctor right away if you have symptoms of high blood sugar such as increased thirst/urination. If you already have diabetes, check your blood sugar regularly as directed and share the results with your doctor. Your doctor may need to adjust your diabetes medication, exercise program, or diet.

A very serious allergic reaction to this product is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

This is not a complete list of possible side effects. If you notice other effects not listed above, contact your doctor or pharmacist.

Precautions

Before taking prednisone, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: current/past infections (such as fungal infections, tuberculosis, herpes), heart problems (such as heart failure, recent heart attack), high blood pressure, thyroid problems, kidney disease, liver disease, stomach/intestinal problems (such as ulcer, diverticulitis), bone loss (osteoporosis), mental/mood disorders (such as psychosis, anxiety, depression), eye diseases (such as cataracts, glaucoma), diabetes, mineral imbalance (such as low level of potassium/calcium in the blood), seizures, blood clots, bleeding problems.

Using corticosteroid medications for a long time can make it more difficult for your body to respond to physical stress. Therefore, before having surgery or emergency treatment, or if you get a serious illness/injury, tell your doctor or dentist that you are using this medication or have used this medication within the past 12 months. Tell your doctor right away if you develop unusual/extreme tiredness or weight loss. If you willbe using this medication for a long time, carry a warning card or medical ID bracelet that identifies your use of this

medication.

Before having surgery, tell your doctor or dentist about all the products you use (including prescription drugs, nonprescription drugs, and herbal products).

This medication may mask signs of infection. It can make you more likely to get infections or may worsen any current infections. Therefore, wash your hands well to prevent the spread of infection. Avoid contact with people who have infections that may spread to others (such as chickenpox, measles, flu). Consult your doctor if you have been exposed to an infection or for more details.

The liquid form of this medication may contain sugar and/or alcohol. Caution is advised if you have diabetes, liver disease, or any other condition that requires you to limit/avoid these substances in your diet. Ask your doctor or pharmacist about using this product safely.

This medication may cause vaccines not to work as well. Do not have immunizations/vaccinations without the consent of your doctor. Avoid contact with people who have recently received live vaccines (such as flu vaccine inhaled through the nose).

This medicine may cause stomach bleeding. Daily use of alcohol while using this medicine may increase your risk for stomach bleeding. Limit alcoholic beverages. Consult your doctor or pharmacist for more information.

Older adults may be more sensitive to the side effects of this drug, especially bone loss/pain, stomach/intestinal bleeding, and mental/mood changes (such as confusion).

This medication may slow down a child's growth if used for a long time. Consult the doctor or pharmacist for more details. See the doctor regularly so your child's height and growth can be checked.

During pregnancy, this medication should be used only when clearly needed. It may rarely harm an unborn baby. Discuss the risks and benefits with your doctor. Infants born to mothers who have been using this medication for an extended period of time may have hormone problems. Tell your doctor right away if you notice symptoms such as persistent nausea/vomiting, severe diarrhea, or weakness in your newborn.

This medication passes into breast milk but is unlikely to harm a nursing infant. Consultyour

doctor before breast-feeding.

Interactions

Drug interactions may change how your medications work or increase your risk for serious side effects. This document does not contain all possible drug interactions. Keep a list of all the products you use (including prescription/nonprescription drugs and herbal products) and share it with your doctor and pharmacist. Do not start, stop, or change the dosage of any medicines without your doctor's approval.

If your doctor has directed you to take low-dose aspirin for heart attack or stroke prevention (usually at dosages of 81-325 milligrams a day), you should continue taking it unless your doctor instructs you otherwise. Ask your doctor or pharmacist for more details.

EXCIPIENT PROFILE

Microcrystalline cellulose

I. Nonproprietary Names

BP: Microcrystalline Cellulose **JP:** Microcrystalline Cellulose.

PhEur: Cellulose, Microcrystalline **USP-NF:** Microcrystalline Cellulose.

2. Synonyms

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum;Celphere; Ceolus KG; crystalline cellulose; E460; Emceed; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

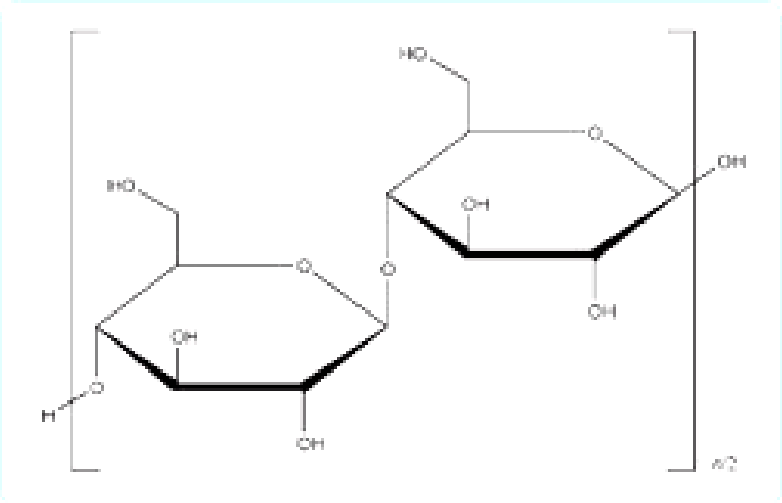
3. Chemical Name and CAS Registry Number

Cellulose [9004-34-6]

4. Empirical Formula and Molecular Weight

(C6H1005)n _36 000 where n 220.

5. Structural Formula



6. Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7. Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulationswhere it is used in both wet- granulation and direct-compression processes.(1-7) In addition to its use as a binder/diluent, and microcrvstallinecellulose also has some lubricant(8) and disintegnuttproperties that make it useful in table ting. Microcrystalline cellulose is alsoused in cosmetics and food products.

8. Description

Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particle. It is commerciallyavailablein different Particle sizes and moisture grades that have different properties and applications.

9. Typical Properties

Density (bulk) : 0.337 g/cm3;0.32 g/cm3,for Avicel PH-101.

Density (tapped) : 0.478 g/cm3, 0.45 g/em3 for Avicel PH-101

Density (true) : 1.512-1.668 g/cm3.

Angle of repose : 498 for Colus KG;34.48 for Embowel 90M.

Flow ability : 1.41 g/s for Emcocel 90M

Melting point : Chars at 260-2708°C.

10 Moisture content: Typically less than 5% wav. However, different grades maycontain varying amounts of water. Microcrystalline cellulose is hygroscopic.

11 Particle size distribution: Typical mean particle size is 20-200 mm.Different grades may have a different nominal mean particle size.

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

Specific surface area : 1.06-1.12m2/g

12 Stability and Storage Conditions.

Microcrystalline cellulose is a stable though hygroscopic inaterial. The hulk material lace• should be stored in a well-dosed container in a cool, dry place.

CROSCARMELLOSIC SODIUM

Non-proprietary Names

BP: Croscarmellose Sodium **JP:** Croscannellose Sodium **PhEur:** Croscarmellose Sodium **USP-NF:** Croscannellose Sodium 2

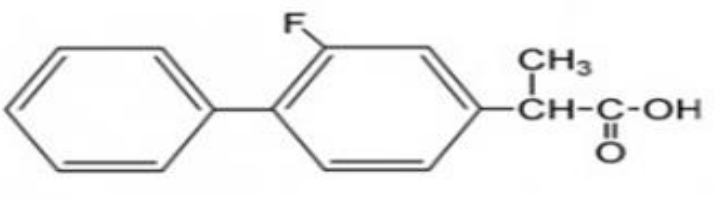
2. Synonyms

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nyincel ZSX; Pharmacy XL; Primellose; Solutab; Vivasol.

3 Chemical Name : Cellulose, carboxymethyl ether, sodium salt, cross linked 4 CAS **Registry Number :** [74811-65-7] S.

Empirical Formula and Molecular Weight : Croscarmellose sodium is a cross linked polymer of carboxymethylcellulose sodium.

6 Structural Formula



7. Functional Category.

Tablet and capsule disintegrate.

8 Applications in Pharmaceutical Formulation or Technology

cmammicllose Sodium is used in oral phannaccutical formulations as a &ante for apsaic,,(1.2) tablets,(3-13) and granules. ln tablet formulations, croscarmellose sodium may be tad in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the Process (infra- and extra granutarly so that the wicking and swelling ability of the disintegrate is best utilized.(11,12) Croscarmellosc sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

9 Description: Croscarmellose sodium occurs as an odorless, white or grayish white powder.

10 Particle size distribution: Ac-Di-Sol not more than 2% retained on a #200 (73.7 mm)mesh and not more than 10% retained on a #325 (44.5 mm)mesh.

Solubility: Insoluble in water, although croscarmellose sodiumrapidly swells to 4-8 times its original volume on contact withwater. Practically insoluble in acetone, ethanoland toluene.

Specific surface area : 0.8 I-0.83m2/g

11 Stability and Storage Conditions.

Croscamiellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 308°C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

AEROSIL

I Nonproprietary Names

BP: Colloidal Anhydrous Silica

JP: Light Anhydrous Silicic Acid

PhEur: Silica, Colloidal Anhydrous

USP-NF: Colloidal Silicon Dioxide

2. Synonyms

Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica;fumed silicon dioxide; hochdisperses silicum dioxid; SAS; silica colloidalis anhydrica; silica sot; silicic anhydride; silicon dioxide colloidal; silicon dioxide fumed; synthetic amorphous silica; Wacker HDK.

3. Chemical Name **:** Silica.

4. CAS Registry Number **:** [7631-86-9]

5. Formula **:** Si02

6. Molecular Weight **:** 60.08

7. Functional Category

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

8. Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface' area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting(2-4) and capsule filling. Colloidal silicon dioxideis also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to Promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent aspersing_ agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also an adsorbent during the preparation of wax microspheres as a thickeningagent for ng of used as EePleal preparations and has been used to aid nanocapsules and nanosphere suspensions.

9. Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

10 Stability and Storage Conditions: Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0-7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosityin creasing properties of colloidal silicon dioxide are reduced; and at a p1-1 greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.(14) Colloidal silicon dioxide powder should be stored in a well-closed container.

TALC

1. Non-proprietary Names: BP: Purified Talc. **JP**: Talc

PhEur: Talc

USP : Talc

2. Synonyms

Altaic; E553b; hydrous magnesium calcium silicate; hydrousmagnesium silicate: Imperial; Luzenac Pharma; magnesium hydrogenmetasilicate; Mag,sil Osmanthus; Magsil Star, powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore; talcum.

3. Chemical Name: Talc.

4. CAS Registry Number: [14807-96-6]

5. Empirical Formula: Mg6(Si205)4(014)4

6. Functional Category: Anticaking agent; glidant; tablet and capsule diluent; tablet andcapsule lubricant.

7. Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as alubricant and diluent, although today it is lcsscomnnonly used. However, it is widely sed c o u asuse a dissolution retardant in the development of controlled-release products.(4-6) Tal is alsd as a lubricant in tablet formulations in a novel powder coating for extended-release pcllets.

8. Description

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

9. Stability and Storage Conditions "Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. may also be sterilized by exposure to ethylene oxide or gamma irradiation-(10) Talc should be stored in a well-closed container in a cool. dry place.

MAGNESIUM STEARATE

1 Nonproprietary Names

Bp: Magnesium Stemma **JP**: Magnesium Stearate **PhEur**: Magnesium Stearate **USP-NF**: Magnesium Stearate.

2. Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia steams; magnaium octadecanoate; octadecanoie acid, magnesium salt; stearic acid, magnesium salt; Synpro 90.

3. Chemical Name : Octadecanoic acid magnesium salt

4. CAS Registry Number: [557-04-0]

5. Empirical Formula: C36H70Mg0

6. Molecular Weight: 591.24

7. Structural Formula: [CH3(C112)16C00]2Mg

8. Functional Category: Tablet and capsule lubricant.

9. Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant incapsule and tablet manufacture at concentrations between 0.25%and 5.0% w/w. It is also used in barrier creams.

10. Description: Magnesium stearate is a very fine, light white, precipitated ormilled, impalpable Powder of low bulk density, having a faint odor of stearie acid and a

characteristic taste. The Powder is greasy to the touch and readily adheres to the skin.

AIM AND OBJECTIVE

Aim

Formulation and Evaluation of colon targeted Drug Delivery System.

Objectives

1. To reduce dosing frequency.

To delay delivery to the colon to achieve high local concentrationin the treatment of disease.

2. To protect the drug from being released in the stomach and small intestine.
3. To enhance patient compliance.
4. To targeted drug release in colon.

PLAN OF WORK

The present work was carried out to formulate the colon targeted tablets of Prednisolone and to evaluate the various parameters. It wasplanned to carry out this work as outlined below.

- To carry out the Preformulation studies to maximize the chances in formulating an acceptable, safe, efficacious and stable product.

a) Evaluation of API

- Description
- Solubility
- Melting point
- Particle size distribution
- Loss on drying

b) Drug excipient compatibility studies

- Physical observation
- FT-IR studies.

- Formulation of uncoated tablets by direct compression method.
- Evaluation of the granules such as

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index

- Hausner's ratio

➢ Evaluation of physical parameters for compressed tablets.

- Weight variation
- Thickness
- Hardness
- Friability
- Disintegration
- Determination of drug content

➢ Evaluation of the coated tablet.

➢ Evaluation of the most satisfactory formulation.

➢ In-vitro Drug Release Studies.

➢ To carry out the stability studies for the best formulation.

Table No. 3: MATERIAL AND EQUIPMENTS.

Table Material In The Investigation.

Sr. no.	Name of ingredients	Category	Manufacturing
1	prednisolone	Active ingredient	Yarrow cam lab, Mumbai.
2	Microcrystallinecellulose	Binder, Diluent	FMC International
3	Croscarmellosesodium	Superdisintegrant	DFE Pharm
4	Aerosil	Asorbent, Anticakingagent, Disintegrant	Cabot Sanmor
5	Talc	Thicking agentlubricant	Vijay Mineral
6	Magnesium Stearate	Lubricant	Sunshine Org.

Equipment

Sr. No.	Instruments	Manufacturer
1.	Weighing balance	shimadhu
2	Bulk density apparatus	Thermonik
3	Compression machine	Accura
4	Coating pan	Electro lab
5	Hardness tester	Thermonik
6	Thickness tester	japan
7	Friability tester	Electro lab
8	Disintegration apparatus	Lab india
9	Dissolution apparatus	Electro ab
10	PH Analyzer	Lab india
11	UV spectrophotometer	Shimadhu
12	Electromagnetic shaker	Electro pharma

EXPERIMENT

Materials

prednisolone IP, microcrystalline cellulose,cross carmellose sodium, sodium starch glycollate, aerosil, isopropyl alcohol, talc, magnesium stearate, Eudragit L100, Eudragit S 100, DEP, TIO2. All the material was provided by Lincoln Pharmaceutical Ltd. Equipments used included: Rotary tablet machine, Roche friabilator, Bulk Density measuring apparatus (Electro lab B.D/T.D. measuring apparatus), Monsanto Hardness Tester.

Table 4: Tablet formulation.

Sr. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
1	Drug	20	20	20	20	20	20	20	20
2	Microcrystalline cellulose	62	65	65	68	63	63	64	64
3	Sodium Starch Glycollate	8	4	6	2	6	7	6	7
4	Cross Carmellose Sodium	4	5	3	4	5	4	4	3
5	Aerosil	2	2	2	2	2	2	2	2
6	Talc	2	2	2	2	2	2	2	2
7	Magnesium Stearate	2	2	2	2	2	2	2	2

METHOD

Preparation of core tablets

The core tablet of prednisolone 100 mg were prepared by direct compression method of manufacture using MCC (AVICEL) as the main constituent. Prednisolone, MCC, SSG, Cross carmellose sodium were passed through sieve no #40 and thoroughly mixed in a polythene bag (approx. 10 min). Loss on Drying (LOD) was measured by halogen moisture balance (Mettler Toledo). Above mixer was lubricated granules were lubricated with talc,aerosil and Magnesium stearate which were already passed through sieve no # 60 and compressed in to tablets on a 35 station single rotary machine using 8/32 inch Standard concave, Plain/Plain punch. The compression pressure level was kept constant for all the batches by adjusting the pressure control knobs to the same setting.

Table 5: Composition of coating solution.

Sr. No	Ingridents	SF1 (5%)	SF2 (5%)	SF3 (7%)	SF4 (7%)	SF5 (7%)	SF6 (10%)	SF7 (10%)	SF8 (10%)
1	Eudragit L100	30	15	30	25	20	30	25	20
2	Eudragit S100	20	35	20	25	30	20	25	30
3	DEP	2.5	2.5	3	3	4	4	4	4
4	TIO2	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
5	Acetone	150	150	150	150	150	150	150	150
6	IPA	350	350	350	350	350	350	350	350

Coating of the tablets

It was done by using the standard coating pan, where fixed numbers of tablets were coated each time by atomizing the polymeric coating solution through the means of spray gun. The scale-up variables including pan loading, pan speed, number of spray guns, spray rate, and inlet airflow etc. were considered. About 500 tablets of prednisolone tablet were taken and allow to coatings in pan coater at 30 rpm and 50^{o}Ctemperature. Coating was carried out with praying method and dried with same.

Evaluation of pharmaceutical powder properties

Micromeretic propertic (Bulk Density and Tapped Density**)**

Flow properties (Angle of repose, Compressibility index, Hausner ratio**)**

Bulk Density

Bulk density was determined according to usp method 1. Accurately weighed quantity of powder, which was previously passed through sieve 18 and carefully poured into graduated cylinder. Then the cylinder the powder bed was made uniform without disturbing. Then the volume measure was called as the bulk volume and the bulk density is calculated by following formula.

Bulk density = Weight of powder/Bulk volume.

Tapped Density

Tapped density was determined by usp method 2. The powder sample under test was screened through sieves no 18 and tablet blend was filledmin 100ml cylinder after measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tapped density apparatus was set to 250tap drops per minutes and operated for 500 tap. Volume was noted as and and again tapped for 750 times and volume was noted as. The tapped density is calculated by the following formula.

Tapped density = Weight of poweder/Tapped volume

Carrs index

Compressibility index are mrasure of the propensity of a powder to be compressed. As such they are mresure of relative importance of interparticulate interaction. It is one of the most important parameter to characterize the nature of powders and granules. At can be calculated from the following formula, Carrsindex=Tappeddensity–Bulkdensity/ Tappeddensity *100.

Hausner Ratio

Housner ratio is an important character to determine the flow property of powder and granules. This can be be calculation by the following formula,

Hausner Ratio = Tapped density/Bulk density

Angle of Repose

It is a direct measure of flow property of powders. The tangent of angle repose is equal to the coefficient of friction between the particles. Angle of repose was determined using funnel to pour the powder on the powder on the surface from a fixed height of 2 cm, the radius base of a pile was measured at5 different point and average was teken for calculataing angle of repose using following formula

Tan = h/r

The prepared tablets were evaluated for the following parameters Hardness, measured by tablet hardness tester; schleuniger in kp (Kilo Pascal), Weight variation (Average weight of ten tablets by electronic weighing balance), Thickness which was measured by Vernier Caliper in millimeter (mm), Friability was checked by USP apparatus (Roche friabilator) for 100 rpm.

Table 6: Evaluation of uncoated tablet.

Formulation	Hardness	Friability (%)	Thickness (mm)	Weight variation(Mg)	Average Weight (Mg)
SF1	7.5	0.3	2.72	0.2	100
SF2	9.4	0.6	2.86	0.4	100
SF3	9.2	0.4	2.79	0.3	100
SF4	11.6	0.7	2.8	0.2	100
SF5	8.7	0.3	2.76	0.4	100
SF6	9.3	0.5	2.92	0.3	100
SF7	8.3	0.2	2.9	0.6	100
SF8	9.7	0.4	2.84	0.5	100

In-vitro drug release studies

The in-vitro dissolution studies were carried out using USP dissolution apparatus type II in different medium.

Acid stage: Two hours in 900 ML 0.1N HCL at 75 rpm.

Buffer stage: Three hour in 900 ML pH 4.5 phosphate buffers at 75 rpm, 1 hour in 900 ML pH 7.2 simulated colonic fluid at 75 rpm. Dissolution test was carried out for a total period of 6 hours. Analysis for prednisolone was done by UV detected at 247 nm. Table no**.** 4 shows

the results of in vitro drug release studies.

Table 7: Cumulative percentage drug release of prednisolone P^H dependentTablets.

Time(hr)	1	2	3	4	5	6
pH	1.2		4.5		7.2	
SF1	5.48	9.82	10.9	15.04	19.1	102.4
SF2	3.84	4.73	8.09	12.1	16.2	97.13
SF3	2.76	9.34	11.56	15.79	18.96	101.4
SF4	1.6	2.7	5.2	6.36	11.56	91.86
SF5	2.1	3.2	5.4	7.5	12.1	94.8
SF6	2.1	2.7	5.7	9.2	10.4	95.4
SF7	1.08	2.2	3.3	4.5	6.7	98.2
SF8	1.08	2.1	3.4	4.6	5.6	99.11

RESULTS AND DISCUSSION

Organoleptic characteristics

The physical appearance of sample of Prednisolone was carried out as per USP. It shows that off-white in color, odorless and the melting point was carried out by capillary method and it was found to be 235^0C.

Table No. 8: Organoleptic characteristics.

Sr. No.	Characteristics	Result
1	Colour	off-white
2	Odour	Odorless
3	Melting point	235 °C
4	Boiling Point	570.6±50.0 °C at 760 mmHg

PREFORMULATION STUDY

Determination of wavelength maxima (λ_{max}) of Prednisolone

The solution of 10µg/ml in phosphate buffer pH 6.8 (few drops of ethanol) was prepared and scanned in the range of 200-400 nm and wavelength maxima was determined at 315 nm by using shimandzu U.V. spectrophotometer.

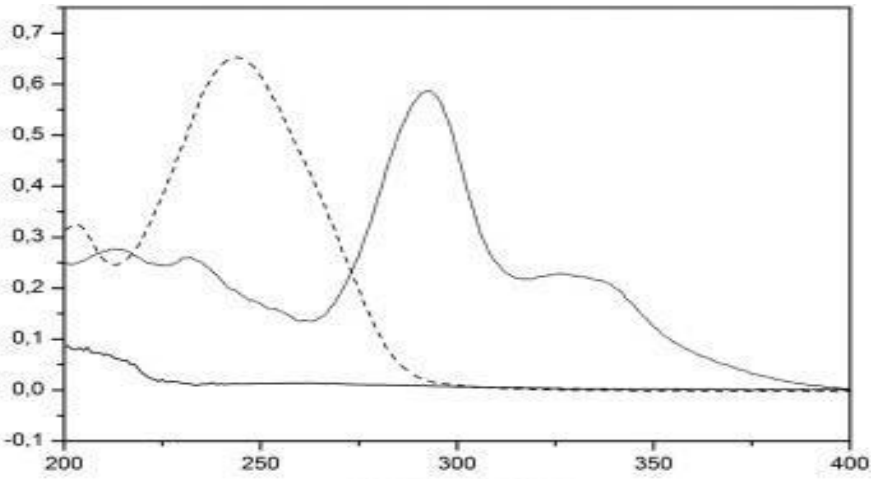


Figure 10: Maximum absorbance spectra of Prednisolone.

Preparation of standard calibration curve

The method for the estimation for the drug Prednisolone showed maximum absorbance at wavelength 315nm in phosphate buffer pH 6.8and when subjected to regression analysis, the value of regression coefficient was found to be 0.9979, which showed linear relationship between concentration and absorbance.

Table No. 9: Standard calibration curves for Prednisolone

Sr. No.	Concentration (µg/ml)	Absorbance
1	10	0.243
2	20	0.446
3	30	0.565
4	40	0.721
5	50	0.988

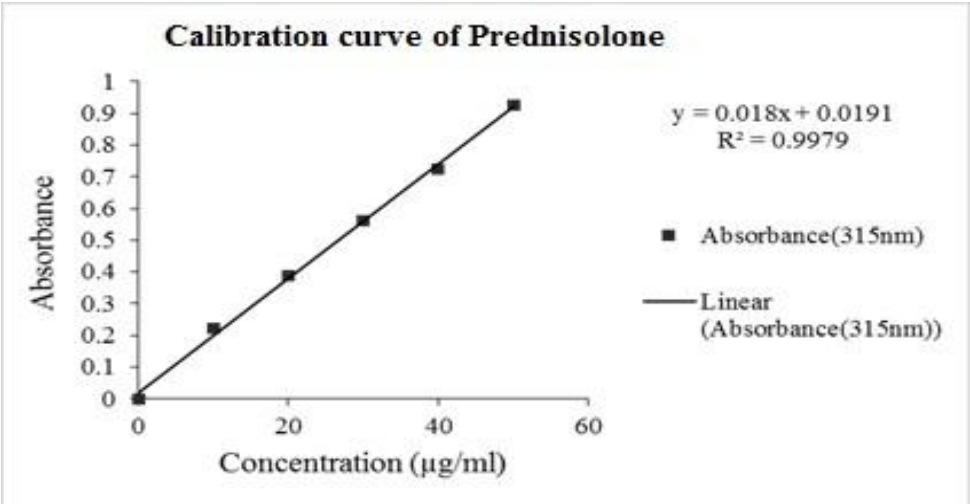


Figure 11: Standard calibration curve of Prednisolone in phosphate bufferpH 6.8.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

The FTIR spectrum of Prednisolone was shown below which complies with standard functional group frequencies.

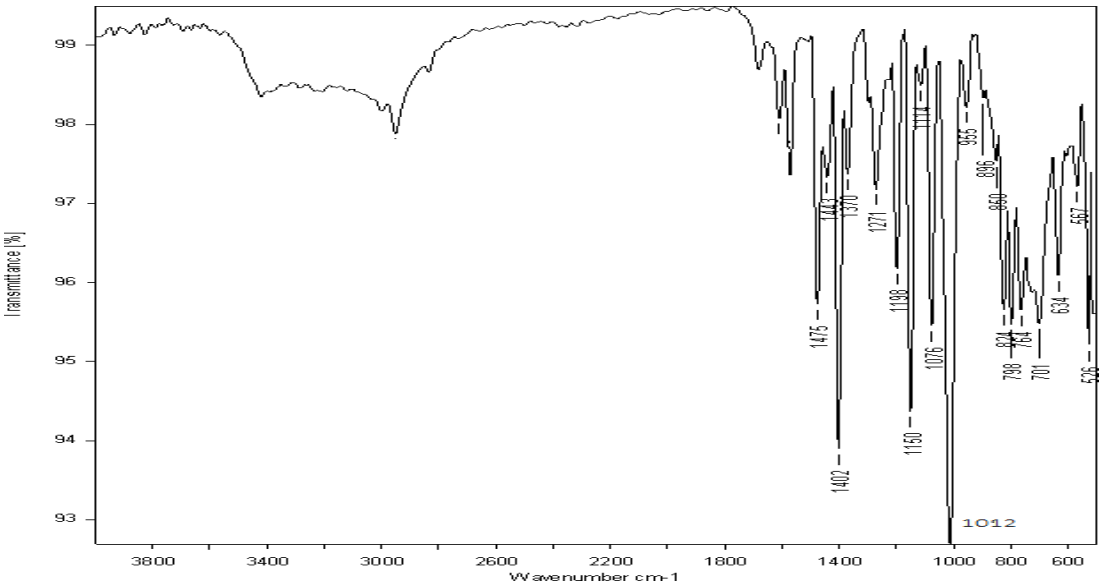


Figure 12: FTIR spectrum of pure drug Prednisolone.

Table No.10: IR frequencies of Prednisolone.

Functional group	Characteristic wave number (cm^{-1})	Prednisolone observed wave number(cm^{-1})	Prednisolone wave number(cm^{-1})
C-C stretching (in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1150
C-O-C stretching	1100-900	1076	1071
S=O	1050-800	1012	1013

The peaks analyzed in the Table indicate the most characteristic frequencies of the functional group of Prednisolone which are C-C stretching, C-N stretching, C-O-C stretching, the presence of S=Oetc. were confirmed compared to the reported frequencies.

Compatibility between drug and polymer

The FTIR spectrum of Prednisolone with excipients are shown in figure.

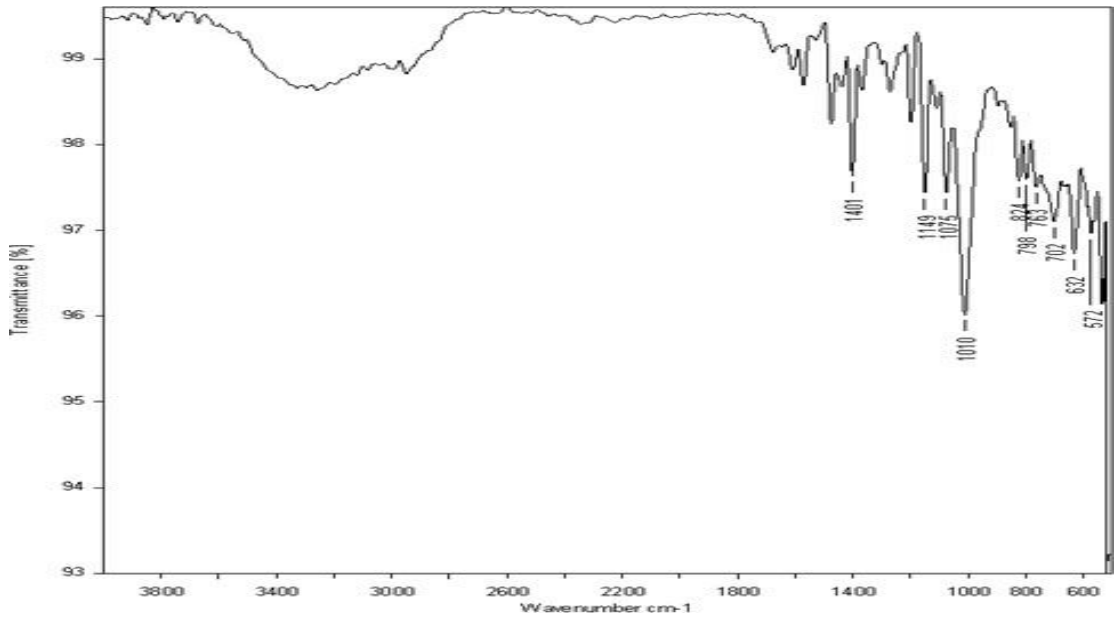


Figure 13: FTIR spectrum of the physical mixture of Prednisolone + Croscarmellose sodium+ Microcrystalline cellulose.

Table No.11: IR frequencies of Prednisolone + Croscarmellose sodium+ microcrystalline cellulose.

Functional group	Characteristic wave number (cm^{-1})	Prednisolone observed wave number(cm^{-1})	Prednisolone - excipient mixture wavenumber (cm^{-1})
C-C stretching (in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1150
C-O-C stretching	1100-900	1076	1071
S=O	1050-800	1012	1013

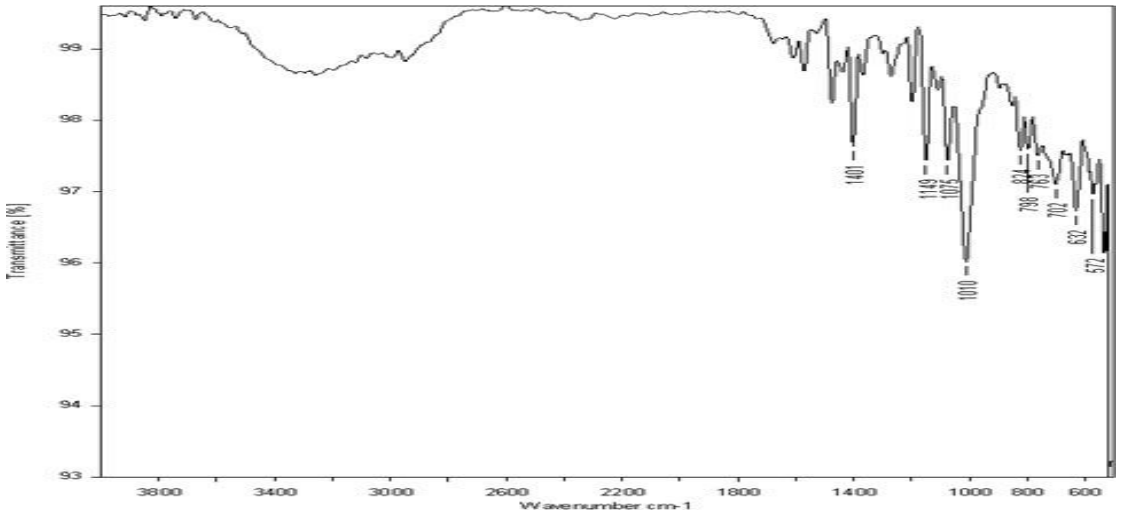


Figure 14: FTIR spectrum of the physical mixture of Prednisolone+ Sodium starchglycollate + Microcrystalline cellulose.

Table No.12: IR frequencies of Prednisolone+ Sodium starch glycollate + Microcrystalline cellulose.

Functional group	Characteristic wavenumber (cm^{-1})	Prednisolone observed wave number (cm^{-1})	Prednisolone - excipient mixture wave number (cm^{-1})
C-C stretching (in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1149
C-O-C stretching	1100-900	1076	1075
S=O	1050-800	1012	1010

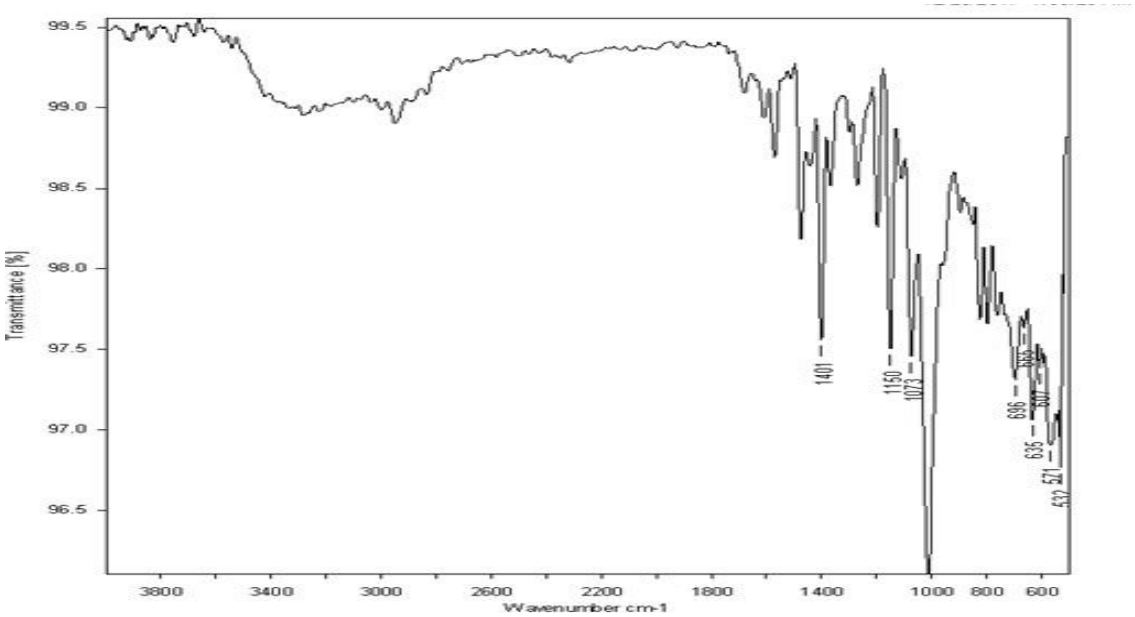


Figure 15: FTIR spectrum of the physical mixture of Prednisolone + Aerosil+ Microcrystalline cellulose.

Table No.13: IR frequencies Prednisolone + Aerosil + Microcrystalline cellulose.

Functional group	Characteristic wave number(cm^{-1})	Prednisolone observedwave number(cm^{-1})	Prednisolone - excipientmixture wave number(cm^{-1})
C-C stretching(in a ring)	1500-1400	1402	1401
C-N stretching	1360-1150	1150	1150
C-O-C stretching	1100-900	1076	1073
S=O	1050-800	1012	1012

The compatibility between drug-polymer was carried out by using FT-IR peak matching method. All major peaks present in the spectrum of a pure drug were observed in the spectrum of the drug-polymer mixture. This suggests that the drug remains in its normal structure and hence this confirmed the absence of any chemical interaction or complexation

between drug and polymers.

FORMULATION OF COLON TARGETED TABLET

Colon targeted tablet of Prednisolone was prepared by direct compression method, using various superdisintegrants such as Sodium starch glycolate, Croscarmellose sodium, Aerosil4 in different ratios and directly compressible Microcrystalline cellulose as diluent.

PRE-COMPRESSION PARAMETERS

Table No. 14: Physical characteristics evaluation of powder mixture (n=3).

Formulation code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	An angle ofrepose (°)	Compressibilityindex (%)	Hausner's ratio
F1	0.312±0.032	0.390±0.068	32.55±1.25	20.51±1.230	1.25±0.103
F2	0.297±0.018	0.368±0.050	31.72±1.28	19.23±1.115	1.23±0.102
F3	0.340±0.034	0.416±0.061	29.04±1.19	18.18±1.196	1.22±0.112
F4	0.326±0.026	0.394±0.075	33.54±1.17	17.39±1.479	1.21±0.015
F5	0.312±0.020	0.375±0.049	30.10±1.11	16.60±1.146	1.20±0.105
F6	0.310±0.011	0.387±0.052	30.85±1.29	20.01±1.188	1.25±0.113
F7	0.312±0.045	0.371±0.047	33.35±1.35	16.01±1.050	1.19±0.107
F8	0.283±0.069	0.330±0.036	27.40±1.18	14.28±0.986	1.16±0.110
F9	0.389±0.046	0.518±0.043	34.32±1.31	25.12±1.137	1.33±0.116
F10	0.364±0.013	0.478±0.015	31.75±0.14	23.80±0.956	1.31±0.104
F11	0.356±0.007	0.440±0.054	29.44±0.23	19.04±1.543	1.23±0.117
F12	0.318±0.019	0.418±0.013	34.46±0.36	24.33±1.678	1.31±0.111

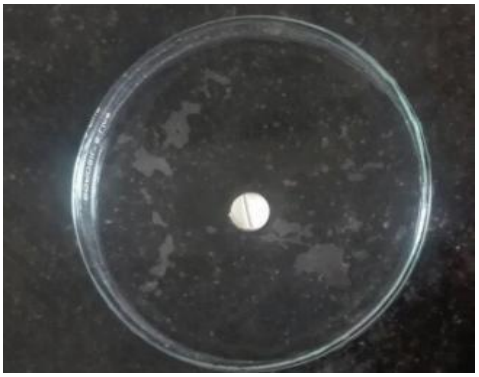
POST-COMPRESSION PARAMETERS

Table No. 15: Evaluation of formulated tablet (n=3).

Formulationcode	Average weight (gm)	Thickness (mm)	Hardness (kg/cm^2)	% Friability	Wetting time(sec)	Water absorption ratio (%)	Content uniformity (%)	Disintegration time (sec)
F1	201±1.15	2.68±0.12	4.2±0.17	0.932±0.16	13±1.11	65.00±0.20	92.58±0.24	63±1.14
F2	204±2.05	2.47±0.24	4.2±0.15	0.866±0.28	12±1.15	71.42±0.40	93.94±0.11	63±1.16
F3	199±1.17	2.33±0.36	4.4±0.18	0.943±0.11	12±1.10	77.27±0.30	91.64±0.18	54±1.21
F4	204±1.13	2.62±0.14	4.2±0.10	0.834±0.24	12±1.15	80.00±0.63	94.45±0.15	38±1.15
F5	201±2.58	2.77±0.18	4.3±0.12	0.816±0.30	13±1.14	76.19±0.48	93.94±0.19	41±1.25
F6	204±2.31	2.83±0.39	4.6±0.19	0.910±0.29	12±1.17	83.33±0.32	90.80±0.16	39±1.16
F7	201±1.97	2.36±0.50	4.0±0.21	0.934±0.15	12±1.20	85.00±0.44	97.65±0.25	32±1.18
F8	200±2.10	2.73±0.19	4.5±0.25	0.934±0.26	10±1.13	90.90±0.11	98.19±0.16	24.±1.10
F9	199±3.15	2.11±0.29	4.3±0.09	0.866±0.33	24±1.11	57.5±0.17	96.28±0.23	68±1.23
F10	207±1.48	2.54±0.64	4.4±0.28	0.919±0.17	22±0.16	60.00±0.21	91.97±0.38	65±1.29
F11	207±1.29	2.63±0.10	4.4±0.13	0.778±0.14	22±1.19	61.90±0.27	90.24±0.30	59±1.24
F12	201±2.11	2.14±0.25	4.1±0.14	0.834±0.18	20±1.12	78.94±0.16	94.45±0.26	40±1.31

For weight variation test, ten tablets were randomly selected from each formulation and evaluated. The average weight of each formulation values are almost uniform and was within

the specifications. Thus all the formulations passed the test for weight variation. The thickness value of tablet ranges from 2.11 to 2.83mm. The hardness values range from 4.0 to 4.6kg/cm^2. The friability values of tablets ranged from 0.778 to 0.943 %. All the values are below 1% indicating that the tablets of all formulations are having good friability property. Wetting time of formulations are ranged from 10 to 24 sec. The water absorption ratio of the formulations ranges from 57.5 to 90.90% respectively. The content uniformity of the prepared formulations values ranged from 90.24 to 98.19%. The disintegration time of formulations values ranged from 24 to 68sec.



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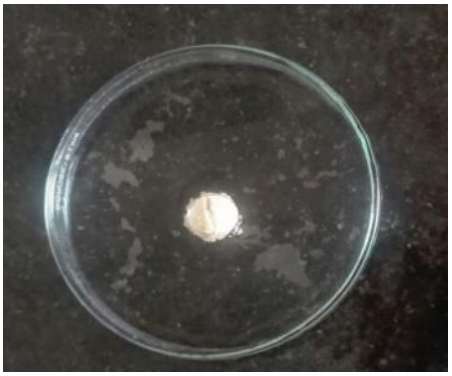

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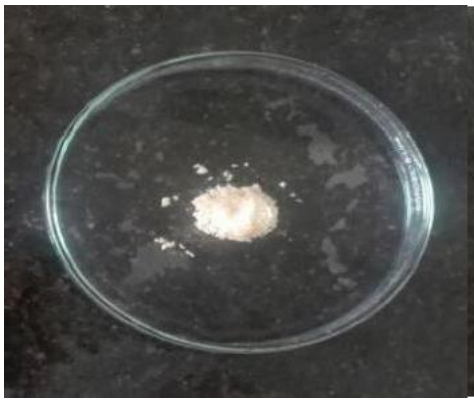

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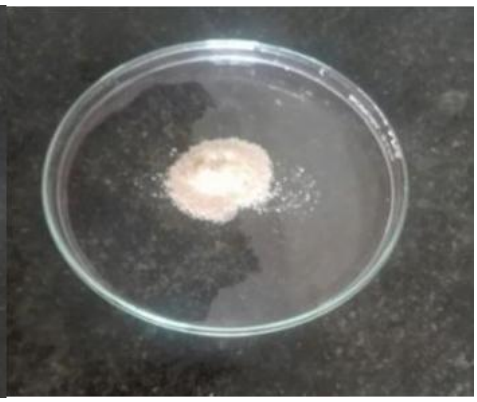

18sec

23sec

Figure 16: Disintegration time of F8.

In-vitro dissolution studies

Table No.16: Percentage cumulative drug release data for formulations F1-F4, (n=3).

Time (min)	F1 %CDR	F2 %CDR	F3 %CDR	F4 %CDR
0	0	0	0	0
1	30.86±0.31	33.13±0.24	41.54±0.18	30.53±0.42
2	35.25±0.15	36.08±0.16	44.05±0.13	41.54±0.56
5	42.20±0.23	51.54±0.67	57.56±0.61	58.55±0.38
10	44.94±0.46	56.68±0.55	66.57±0.52	69.56±0.17
15	46.79±0.59	71.04±0.39	75.58±0.40	72.07±0.29
20	58.33±0.11	73.99±0.48	86.59±0.23	86.90±0.45
25	78.38±0.18	83.68±0.14	91.10±0.09	92.25±0.10
30	86.52±0.25	87.90±0.10	92.35±0.27	94.60±0.21

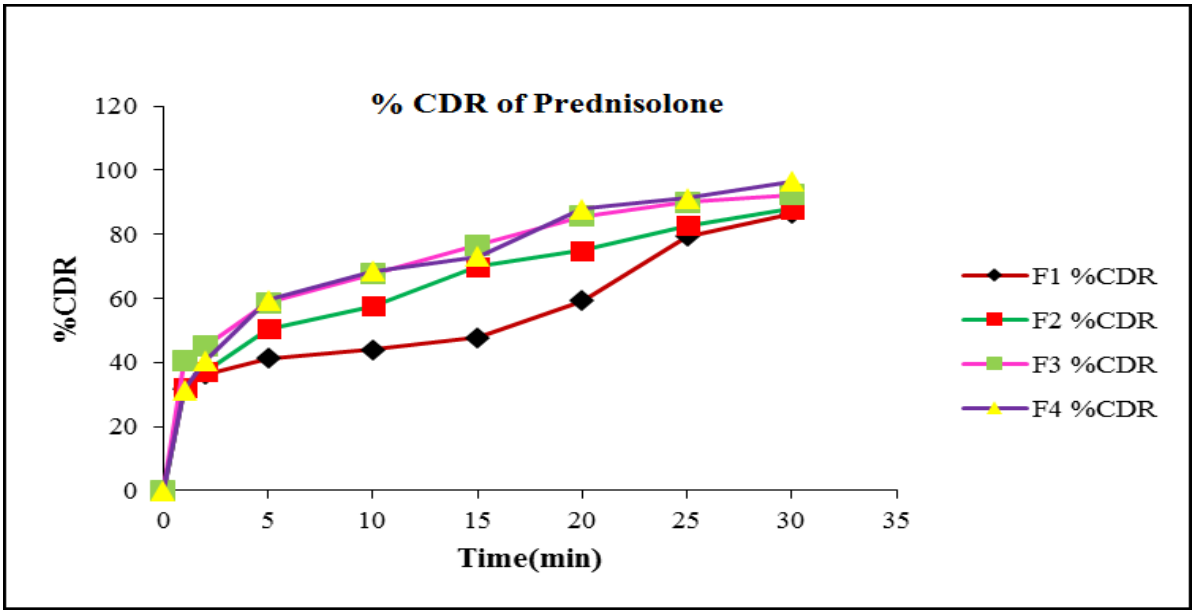

Figure 17: Percentage cumulative drug release profile of formulations F1-F4.

Table No. 17: Percentage cumulative drug release data for formulations F5-F8, (n=3)

Time (min)	F5 %CDR	F6 %CDR	F7 %CDR	F8 %CDR
0	0	0	0	0
1	26.03±0.34	30.06±0.16	34.94±29	28.25±0.40
2	41.54±0.11	42.56±0.41	45.40±0.68	31.25±0.57
5	44.55±0.57	54.06±0.26	66.71±0.14	44.05±0.17
10	55.06±0.49	60.81±0.19	68.19±0.27	71.45±0.14
15	57.56±0.23	72.08±0.53	74.34±0.38	81.57±0.33
20	66.57±0.16	78.83±0.21	82.85±0.45	88.05±0.19
25	75.58±0.70	86.53±0.10	92.45±0.12	95.05±0.64
30	85.59±0.25	93.35±0.29	96.85±0.08	97.07±0.59

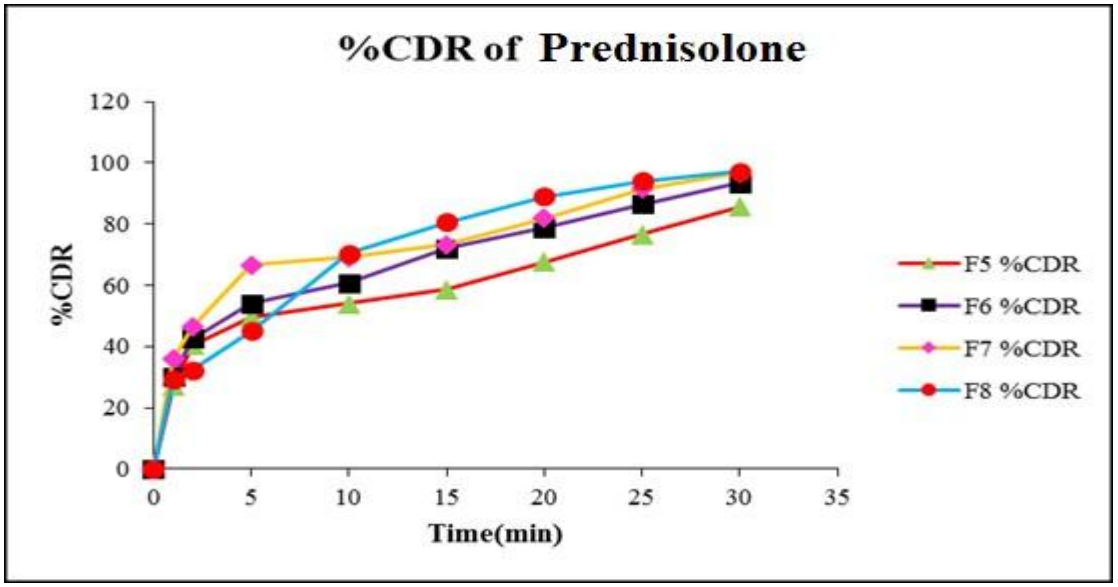

Figure 18: Percentage cumulative drug release profile of formulations F5-F8.

Table No. 18: Percentage cumulative drug release data for formulations F9-F12, (n=3)

Time (min)	F9 % CDR	F10 %CDR	F11 % CDR	F12 %CDR
0	0	0	0	0
1	31.45±0.29	35.15±0.17	33.03±0.07	32.31±0.35
2	34.15±0.18	38.27±0.23	37.80±0.13	38.18±0.16
5	44.97±0.43	51.26±0.51	44.20±0.60	56.58±0.27
10	65.74±0.15	58.50±0.33	54.28±0.28	67.30±0.25
15	71.97±0.38	61.43±0.25	65.74±0.17	72.51±0.71
20	74.36±0.56	71.14±0.43	74.61±0.69	79.66±0.53
25	83.84±0.49	83.68±0.10	84.15±0.51	82.95±0.42
30	95.01±0.11	90.10±0.19	88.17±0.23	91.19±0.09

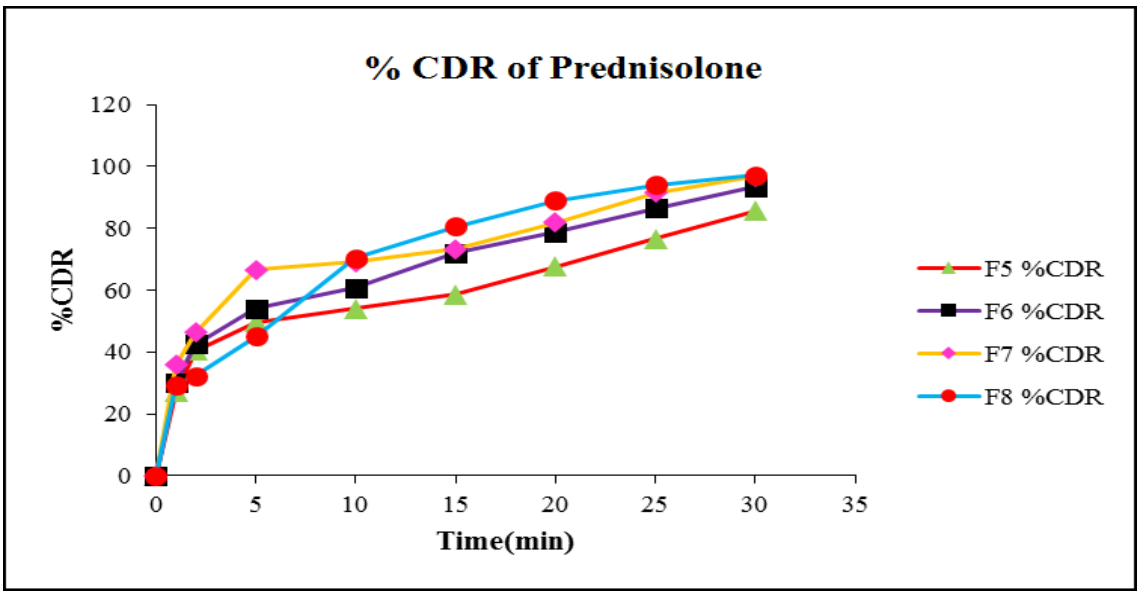

Figure 19: Percentage cumulative drug release profile of formulations F9-F12.

Kinetics of in-vitro drug release

The in-vitro drug release data of all the Prednisolone tablet formulations were subjected to the goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release.

Table No.19: Kinetic study of formulations

Formulation code	Release Kinetics				
	Zero-order R^2	First order R^2	Higuchi R^2	Pep pas	
				R^2	N
F1	0.851	0.875	0.893	0.814	0.262
F2	0.823	0.974	0.954	0.992	0.297
F3	0.765	0.974	0.922	0.993	0.254
F4	0.797	0.972	0.951	0.984	0.319
F5	0.812	0.931	0.935	0.951	0.295
F6	0.824	0.964	0.957	0.985	0.303
F7	0.749	0.921	0.911	0.965	0.268
F8	0.857	0.993	0.977	0.978	0.390
F9	0.842	0.919	0.968	0.987	0.334
F10	0.821	0.931	0.933	0.957	0.264
F11	0.857	0.969	0.966	0.976	0.307
F12	0.784	0.954	0.944	0.990	0.308

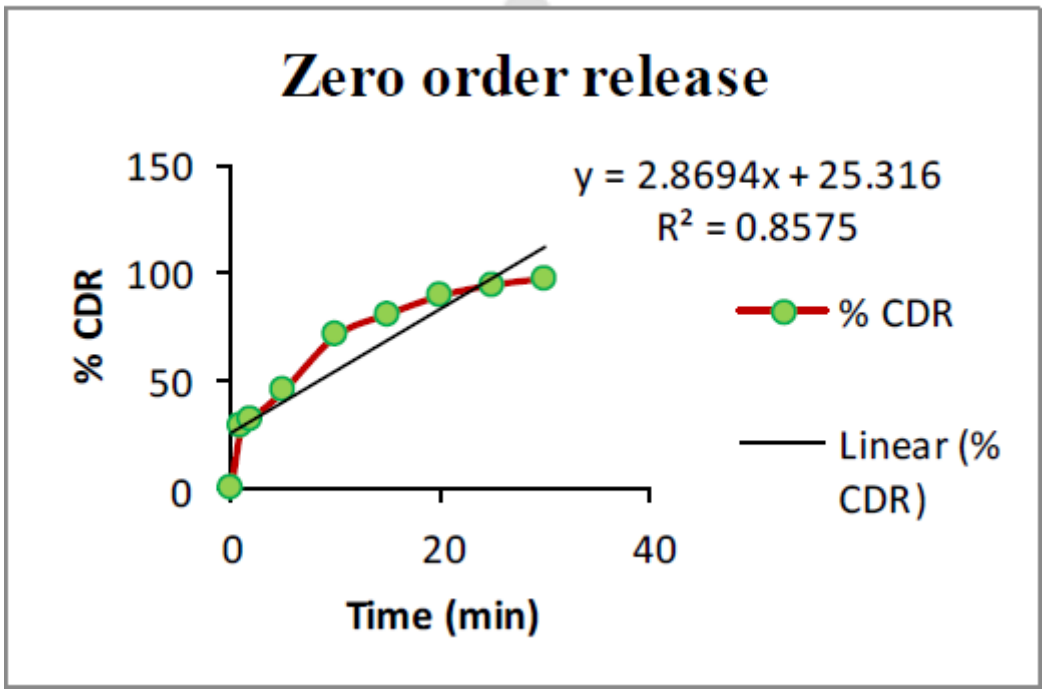

Figure 20: Zero-order release kinetics profile ofoptimiz.

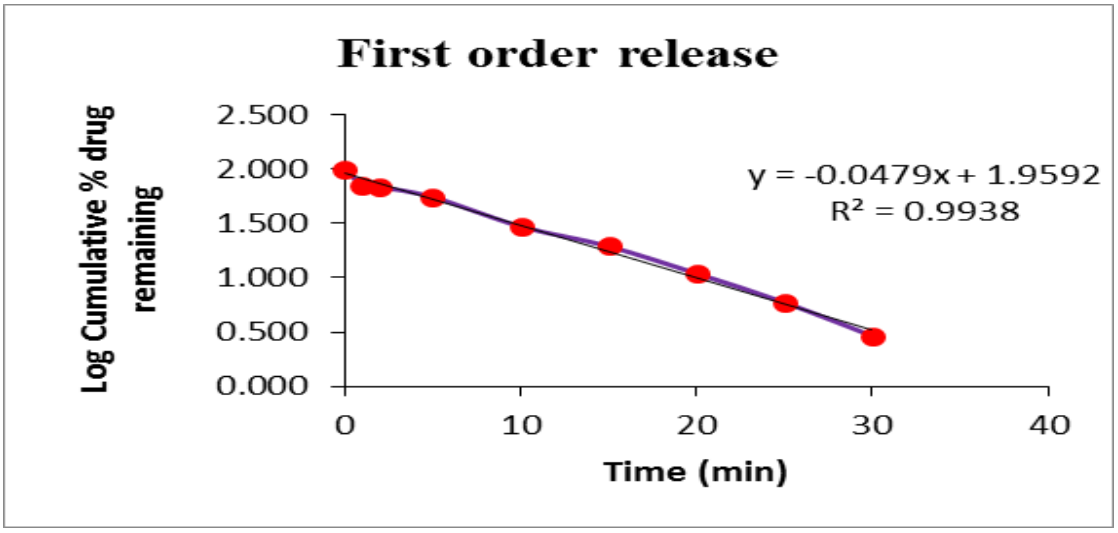

Figure 21: First order release kinetic profile of optimized formulation F8.

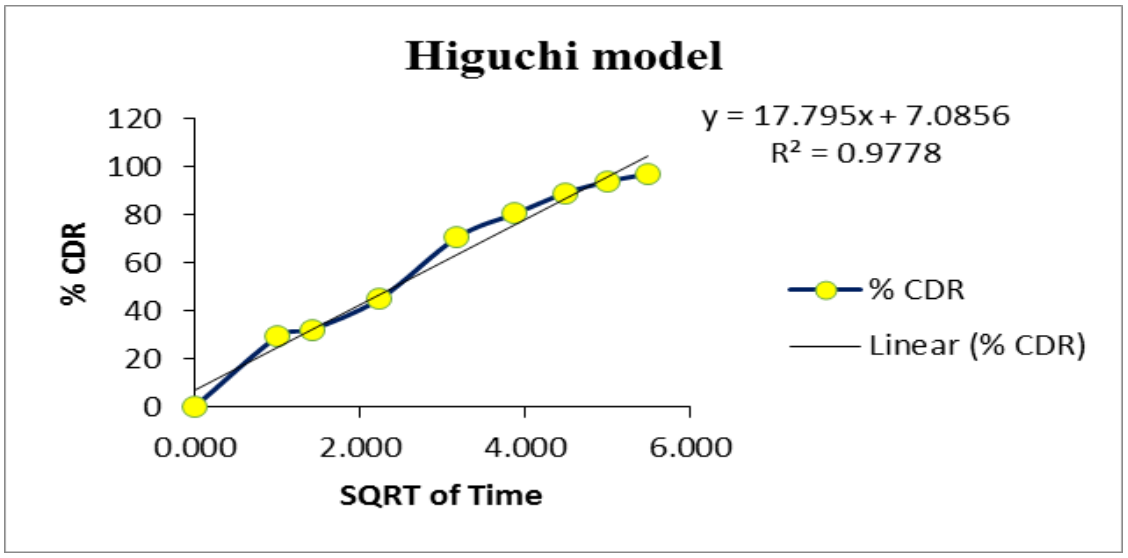

Figure 22: Higuchi release kinetics profile of optimized formulation F8.

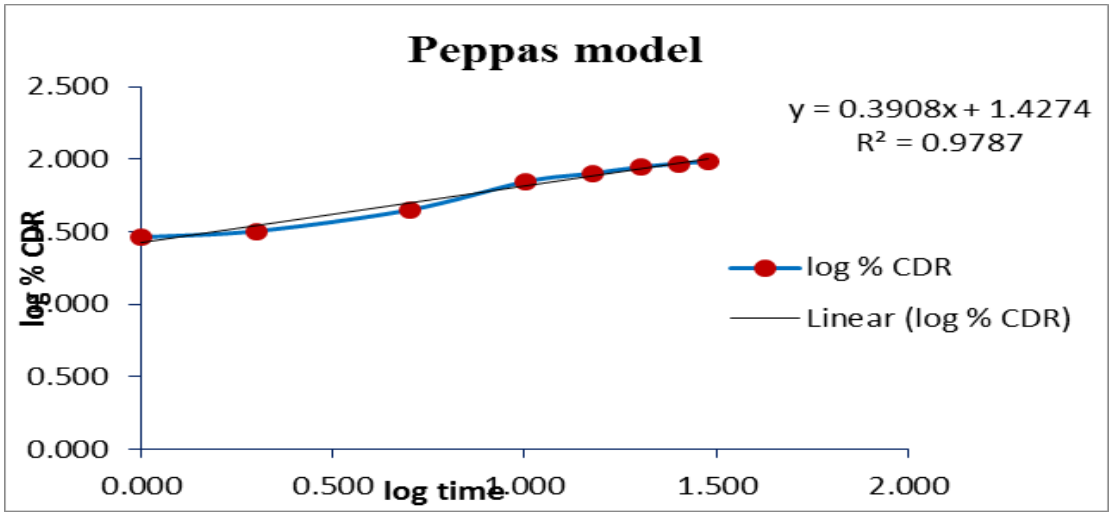

Figure 23: Peppas release kinetics profile of optimized formulation F8.

From the above data, it was concluded that the formulation F8 follows first-order kinetics with R^2 value 0.993. The in-vitro drug release data as log % CDR versus time were fitted to Korsmeyer equation in order to understand the mechanism by which Prednisolone was released from this formulation. Value of exponent n was found to be 0.254-0.390. The Korsmeyer-Peppas model yields n values <0.45 indicating that the diffusion mechanism from the formulation followed Quasi-Fickian diffusion.

Stability studies

Stability studies were carried out on optimized formulation F8 for a period of one month. The comparison of the parameters before and after stability studies was represented in a table No. 26.

Table No. 20: Comparison of parameters before and after stability studies

Parameters	Before stability studies	After stability studies
Appearance	Off-white color	Off-white color
Wetting time (sec)	10±1.13	10±0.23
Water absorption ratio (%)	90.90±0.11	89.50±0.14
Disintegration time (sec)	24±1.10	24±1.05
%CDR	98.19±0.16	97.12±0.29

The results obtained from the stability studies showed that the optimized formulation F8showed only a slight decrease in the wetting time, water absorption ratio, the disintegration time of Prednisolone tablet at 40°C after 1 month of storage. The in vitro drug release also slightly decreased after the stability period. There was no change in the appearance of the formulation. From the stability studies, it was confirmed that the optimized formulation of Prednisolone remained stable at 40°C and 75% relative humidity.

The expected in vitro release pattern selected for the colon targeting was not morethan 10% of drug release up to the end of 5hrs.Eudragit L-100 and Eudragit S-100 were used in different concentration; 5%, 7% and 10% coating level. The batch SF1 and SF2 with 5% coating showed a release of more than 10% in less than five hours i.e. 19.1 % & 16.2 % respectively, which is not acceptable. Hence these formulations were excluded from further studies. However the SF7 and SF8 formulation showed a release of less than10% in the first five hour of dissolution study.

The drug release was directly related to the concentration of polymer in solution and the % coating level. Percent of drug release vs. time plot shows that the dissolution rate was

inversely proportional to the coating level applied. A significant difference was observed in the percentage of drug released for different coating level. All the coated tablets with variable coating level showed a nearly complete drug release in the 6 hr.

In the formulation SF3,SF4 and SF5 where 7% polymer coating was applied in the ratio 3:2,1:1,2:3. The % drug release after 5hr was 18.96 %, 11.56 %, 12.1 % respectively. The solubility of the films from various combinations of Eudragit L100– Eudragit S100, and the release rate of drug from the coated tablets in various pH media could be controlled by varying the ratios of the two polymers.

For formulation SF6, SF7 and SF8 where, 10% coating in the ratio 3:2, 1:1, 2:3; was applied. The drug release at 5th hr and 6th hour 10.4% 95.4% respectively in the formulation SF5 observed. In the SF7 & SF8 polymer was able to control the drug releaseafter 5th hr the drug release was well within the desired limits of less than 10% i.e. 6.7% and 5.6%. The drug released from these formulations at the end of dissolution run was 98.2% & 99.1%. It was observed that the drug release was controlled by increase the coating level. Based on the above studies, the optimum formulation, formulation SF8 coated with Eudragit L100–Eudragi S100 at a combination ratio of 2:3 and at the coating level of 10%, was chosen for studying the effect of pH of the buffer media on the release profiles, as shown in Figure. As anticipated, the release profiles were obviously faster in pH 7.2 than in pH 4.5 buf fer media.

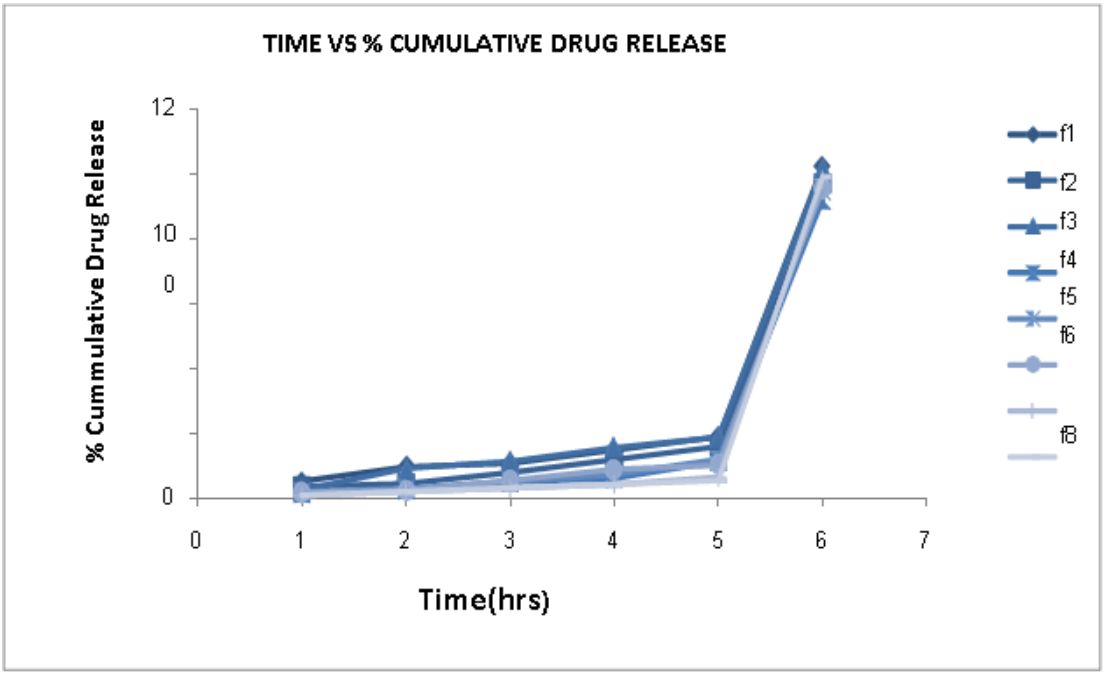

Figure 24: Comparative in vitro release profiles for coated prednisolone tablets.

CONCLUSION

The present study was carried out to investigate the ability of targeting the drug release in colon. From results obtained in the present study, it was concluded that the resulted optimum formulation was the one coated. The in vitro studies showed that this formulation successfully deliver the maximum amount of drug in intact form to the colon. The combined action of the super disintegrant; cross carmellose sodium and sodium starch glycollate have been contributed to such a fast disintegration property. It prevents the drug release in the stomach and intestine so we can solve the problem of side effect of anti inflammatory drug in this area & also prevents ulcerative colitis.

The Prednisolone tablets were successfully formulated by direct compression method using the selected excipient quantities. The formulated tablets were evaluated for both pre-compression and post-compression parameters as per requirements of standards. And the results were complied with the pharmacopoeia specification. The formulated Prednisolone tablets were coated with enteric by pancoating method.

Drug delivery to the diseased colon are advantageous in reducing systemic side effects, lower dose of drug, supply of the drug only when it is required and maintainance of the drug in its intact form as close as possible to the target site. Better colonic delivery could be achieved by protecting the drug from absorption and /the environment of the upper GIT and then abruptly released in to proximal colon, which isthe site for colonic targeted delivery of drugs. All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbed drugs. The colon is rich in microflora which can be used to target the drug release in the colon.

Colon targeted based tablets of prednisolone coated were successfully prepared by the wet granulation technique and optimized using full factorial design. DSC studies indicated compatibility of drug with other excipients. As the amount of HEG in the tablet formulations increases, the drug release decreases and as the percentage coat weight gain increases, the drug release also decreases. From the results of full factorial design formulation F9 containing 30% HEG and 9% CWG evolved as optimized formulation and it released only 10.09% of drug in upper part of GIT. The accelerated stability studies established physical integrity of the formulation and chemical stability of the drug. The present study corroborates colonic delivery of prednisolone tablets dually coated with Eudragit L100 and Eudragit S100 (1:4) to be a potential system so as to restrict the release of drug to colon with the merits of

reduced systemic exposure and enhanced potency.

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