FORMULATION AND EVALUATION OF COLON TARGATED PREDNISOLONE COMPRESSION COATED TABLET

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
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In partial fulfillment of the requirements for the award of the Degree of

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Submitted by

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THE CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF COLON TARGATED PREDNISOLONE COMPRESSION COATED TABLET"** was submitted to **THE TAMIL NADU Dr. M. G. R. MEDICAL UNIVERSITY, CHENNAI-600032** by **VIGNESH E (Reg. No. 261710013)** under the guidance of **Dr. Grace Rathnam, M.Pharm., Ph.D., Professor, Department of Pharmaceutics** in partial fulfillment of the requirements for the award of the Degree of **MASTER OF PHARMACY** in **PHARMACEUTICS.** The project was carried out at C. L. Baid Metha College of Pharmacy, Chennai-600097 under my supervision in the Department of Pharmaceutics during the academic year 2018-2019.

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DECLARATION

I hereby declare that the dissertation work entitled **"FORMULATION AND EVALUATION OF COLON TARGATED PREDNISOLONE COMPRESSION COATED TABLET"** has been originally carried out by me at C. L. Baid Metha College of Pharmacy Chennai-600097, under the guidance and supervision of **Dr. Grace Rathnam, M.Pharm., Ph.D.,** Professor, Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2018-2019.

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CONTENTS

ABBREVIATIONS AND SYMBOLS

IR	Immediate Release
MS	Magnesium Stearate
CCT	Compression Coated Tablets
TDDS	Targeted Drug Delivery System
IV	Intra-venous
DDS	Drug Delivery System
CTDDS	Colon Targeted Drug Delivery System
GIT	Gastro-Intestinal Tract
IBS	Irritable Bowel Syndrome
FGIDs	Functional gastro-intestinal disorders
°C	Degree Celsius
cps	Centipoise
g	Gram
mg	Milligram
ng	Nanogram
BP	Blood Pressure, British Pharmacopoeia
IP	Indian Pharmacopoeia
PhEur	European Pharmacopoeia

USP	United States Pharmacopoeia
JP	Japanese Pharmacopoeia
API	Active Pharmaceutical Ingredients
M.W	Molecular Weight
θ	Theta
º	Degree
%	Percentage
cum.	Cumulative
RPM	Revolution Per Minute
RH	Relative Humidity
Vis	Visible
USFDA	United States Food and Drug Administration
cm	Centimeter
mm	Millimeter
nm	Nanometer
ml	Millilitre
h	Hours
min	Minutes
sec	Seconds
L	Litre
UV	Ultra violet

INTRODUCTION

1. 1TARGETED DRUG DELIVERY SYSTEM[1]

1.1.1. COLON TARGETED DRUG DELIVERY SYSTEM:

Colon-targeted drug delivery has been the focus of numerous studies in recent years due to its potential to improve treatment of local diseases affecting the colon, while minimizing systemic side effects. Some examples of diseases states which impact the colon include crohn's diseases (CD), ulcerative colitis (UC), and irritable bowel syndrome (IBS)

Some of the frequently used drugs for the treatment of these ailments include:

- Sulfasalazine
- Dexamethasone
- Hydrocortisone
- Metronidazole
- Prednisolone and others

The delivery of these drugs specifically to the colon without being absorbed first in the upper gastrointestinal (GI) tract allows for a higher concentration of the drug to reach the colon with minimal systemic absorption. The colonic contents have a longer retention time (up to 5 days), and the colonic mucosa was known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery. A drug can be delivered to the colon *via* the oral, or the rectal route. Oral dosage forms are the most preferred delivery route for colon-specific delivery due to their convenience. Oral dosage forms also allow for a greater degree of flexibility in their manufacturing, design, improved patient adherence, relatively safe administration, and they do not require sterile preparation. Direct rectal delivery of drugs was challenging with respect to targeting a drug to specific sites within the colon. Additionally, the extent of drug distribution varies for different rectal dosage forms depending on their spreading capacity and retention time.

The success of a colon-specific drug delivery system (CDDS) depends on the drug's physic-chemical properties, the type of delivery system, all other factors which may influence the GI transit time, as well as the degree of interaction between the drug and the GI tract. It was essential for oral CDDS to protect the drug from being released in the stomach and small intestine. Thus, the approaches used in developing a CDDS are aimed at delaying the drug release until the system reaches the colon, with some strategies demonstrating better success than others.

Advantages:

- Ideal site for the delivery of active agents to cure the colon diseases (ulcerative colitis, chron's diseases, amoebiasis, etc.).
- Smaller drug quantities should be required for local treatment.
- Less side effects and drug interactions occurs.
- Dosage frequency was less so, cost effective.
- The long retention time of colon, improved bioavailability of poorly absorbed drug molecules (up to 5 days)
- Bypass initial first pass metabolism.
- Extended daytime or night time activity.

Limitations of colon targeting drug delivery system:

- The location of drug at the distal portion of the alimentary canal, the colon was difficult to access.
- 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 was lower and more viscous than in upper GIT, which was the limiting factor for poorly soluble drugs.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa into the systemic circulation.

1.1.2. ANOTOMY AND PHYSIOLOGY OF COLON[1-2]:

The GI tract was divided into stomach, small intestine, and large intestine. The longest part of the GIT was small intestine where most enzymatic digestion and absorption occur. The

large intestine was the last major portion of the GIT (starts from the distal end of the ileum to the anus) and was about 1.5 m long.

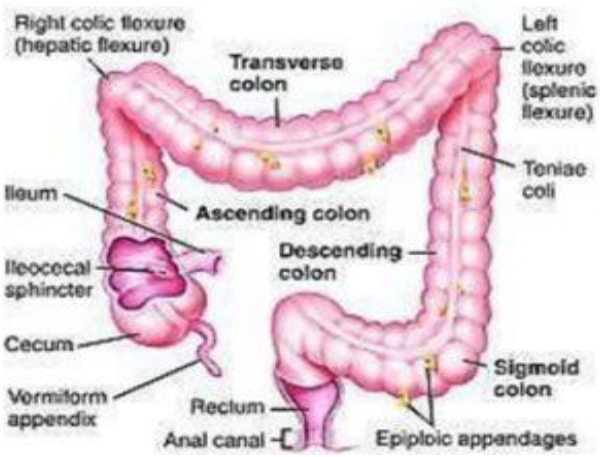


Fig: 1 Structure of Colon.

Colon was upper five feet of the large intestine and mainly situated in the abdomen. Colon was a cylindrical tube that was lined by a moist, soft pink lining called mucosa. The cecum was the first part of the colon and leads to the right colon or the ascending colon followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal. The right colon was made up of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon and left colon was made up of the left half of the transverse colon, splenic flexure, descending colon, and sigmoid. The colon does not have villi unlike small intestine, but due to the presence of plicaese-milunares (crescentic folds) the intestinal surface of the colon was increased to approximately 1300 cm^2.

Function of Colon:

- The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and storage of feces until excreted from the body.
- To provide a favorable environment for the growth of colonic microorganisms.
- Absorption of H_2O and Na^+ from the lumen, and secretion of K^+ and HCO_3

1.1.3. PHYSIOLOGICAL FACTORS[2]:

Colonic pH:

The pH of the gastrointestinal tract was subject to both inter and intrasubject variations. This pH variability of the GIT has been used as a means for targeted colon drug delivery and influenced by some factors like diet, diseases state and food intake. Due to the presence of short chain fatty acids (bacterial fermentation of poly saccharides8), fall in pH into the colon as been seen in table 1

Table: 1Colonic pH Range.

Part of GIT	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small Intestine	6.6-7.5
Colon **Ascending Colon** **Transverse Colon** **Descending Colon**	 6.4 6.6 7.4

1.1.4.Colonic Micro Flora and their Enzymes[3]:

In colon around 400 distinct bacterial species have been found with concentration 1011-1012 CFU/ml, of which 20-30% belongs to genus *Bacteroides*. Variety of microorganism present throughout the GIT, which further produces enzymes for a metabolic activity like hydrolysis, decarboxylation, dealkylation as shown in Table 2. The bacterial count (colony forming unit CFU/ml) in different regions of the GITwas 0-103CFU/ml in stomach, 0-105 CFU/ml injejunum and 103-107 CFU/ml in ileum.

Table: 2 Colonic Micro flora and their Enzymes.

Enzymes	Microorganism	Metabolic Reaction catalyzed
Nitroreductase	E. coli, Bacteroides	Reduction of aromatic and heterocyclic nitro compounds
Azoreductase	Clostridia, Lactobacilli, E. coli	Reductive cleavage of azo compounds
N-Oxide reductase, Sulfoxide reductase	E. coli	Reduce N-Oxide and sulfoxides
Hydrogenase	Clostridia, Lactobacilli	Reduce carbonyl groups and aliphatic double bonds
Esterases and Amidases	E. coli, P. vulgaris, B. subtilis, B. mycoides	Cleavage of esters or Amidases of carboxylic acids
Glucosidase	Clostridia, Eubacteria	Cleavage of , β-glycosidase of alcohols and phenols

1.1.5. Diseases of colon:

Inflammatory bowel diseases: Crohn's diseases and ulcerative colitis are two inflammatory bowel diseases that cause chronic inflammation in the GIT. That can treat efficiently using CTDDS.

Inflammatory Bowel Diseases:

Crohn's diseases and ulcerative colitis are inflammatory bowel diseases that cause chronic inflammation and damage in the gastrointestinal (GI) tract. The GI tract was responsible for digestion of food, absorption of nutrients, and elimination of waste. Inflammation impairs the ability of affected GI organs to function properly, leading to symptoms such as persistent diarrhoea, abdominal pain, rectal bleeding, weight loss and fatigue. While ongoing inflammation in the GI tract occurs in both crohn's diseases and ulcerative colitis, there are important differences between the two diseases.

Irritable Bowel Syndrome:

Irritable bowel syndrome was the condition that affects the function and behavior of the intestines. In this condition, the muscles lining the intestines intermittently contract and relax to move food along the digestive tract. In IBS, This pattern resulting in uncomfortable symptoms. 40 million people around the world are affected by IBS. Patients with IBD can also have IBS.

Crohn's Diseases:

Crohn's diseases can affect any part of the GI tract from the mouth to the anus. It most commonly affects the end of the small intestine (the ileum) where it joins the beginning of the colon. crohn's diseases may appear in "patches," affecting some areas of the GI tract while leaving other sections completely untouched. In crohn's diseases, the inflammation may extend through the entire thickness of the bowel wall.

Ulcerative Colitis:

Ulcerative colitis was limited to the large intestine (colon) and the rectum. The inflammation occurs only in the innermost layer of the lining of the intestine. It usually begins in the rectum and lower colon, but may also spread continuously to involve the entire colon.

1.2. COLON TARGETED DRUG DELIVERY SYSTEM (CTDDS)[4]:

Colon targeted drug delivery system (CTDDS) maybe follow the concept of sustained or controlled drug delivery system, for CTDDS oral route of administration has received most attention. This was because of the flexibility in dosage form designed for oral than parenteral route because

- Patient acceptance for the oral administration of the drug was quite high.
- It was relatively safe route of drug administration compared with parenteral route and potential damage at site of administration was minimal.
- Most of the conventional drug delivery systems for treating the colonic disorder such as Inflammatory bowel diseases i.e. Ulcerative colitis, cohn's diseases, colon cancer and amoebiasis are failing as drug do not reach the site of action in appropriate concentration. For effective and safe therapy of these colonic disorders, colon specific drug delivery was necessary. Today, colon specific drug delivery was challenging task to pharmaceutical technologists.
- Therapeutic advantages of targeting drug to the diseases organ include:
- The ability to cut down the conventional dose
- Reduced the incidence of adverse side effects
- Delivery of drug in its intact form as close as possible to the target sites.
- Colon specific drug delivery systems are also gaining importance for the delivery of protein and peptides due to several reasons as follow
- Rapid development of biotechnology and genetic engineering resulting into the availability of protein and peptide drugs at reasonable cost.
- Proteins and peptide drugs are destroyed and inactivated in acidic environment of the stomach or by pancreatic enzymes in small intestine.
- Parental route was expensive and inconvenient.
- Longer residence time, less peptidase activity and natural absorptive characteristics make the colon as promising site for the delivery of protein and peptide drug for systemic absorption.
- Less diversity and intensity of digestive enzymes.

- Comparative proteolytic activity of colon mucosa was much less than observed in the small intestine, i.e. CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to higher systemic bioavailability.

Table 3: Transit times of various dosage forms.

Dosage form	Transit time (h)		
	Stomach	Small intestine	Total
Tablet	0.7±1.5	3.1±0.4	5.8
Pellet	1.2±1.3	3.4±1.0	4.6
Capsule	0.8±1.2	3.2±0.8	4.0
solution	0.3±0.07	4.1±0.57	4.4

Advantages: Drugs are directly available at the target site.

- Comparatively lesser amount of required dose.
- Decreased side effects.
- Improved drug utilization.

1.2.1. Advantages of CTDDS over Conventional Drug Delivery:

Chronic colitis, namely ulcerative colitis, and crohn's diseases are currently treated with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushinoid symptoms, and bone resorption. Thus, selective delivery of drugs to the colon could not only lower the required dose but also reduce the systemic side effects caused by high doses

Criteria for Selection of Drug for CDDS: CTDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhoea, and colon cancer are prominent for local colon delivery. Drugs used for local effects in colon against GIT diseases drugs poorly absorbed from upper GIT

- Drugs for colon cancer that degrade in stomach and small intestine
- Drugs that undergo extensive first pass metabolism
- Drugs poorly absorbed from upper GIT drugs for targeting

1.2.2. Approaches for colon targeted drug delivery system[5-6]

A. Covalent linkage of drug with carrier

1. Prodrug Approaches: -

Prodrug was a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site.

This was approach involves covalent linkage between the drug and its carrier in such a manner that oral administration the moiety remains intact in the stomach and small intestine and after reached in the colon, enzymatic cleavage regenerates the drug.

When synthesizing prodrugs, the choice of carrier depends on the functional group available on the drug molecule for conjugation with the carrier e.g., the hydroxyl group present on the corticosteroids can enter into a glyosidic linkage with various sugars and the carboxyl group of biphenyl acetic acid forms an ester/amide conjugate with cyclodextrin.

Generally, a prodrug was successful as a colon drug carrier if it was hydrophilic and bulky to minimize absorption from the upper GIT, and if once in the colon, it was converted into a more lipophilic drug molecule, which was then available for absorption.

- Azo bond conjugate
- Glycoside conjugation
- Glucuronide conjugates
- Cyclodextrin conjugate
- Dextran conjugate
- Amino acid conjugation
- Polymeric prodrugs

B. Approaches to deliver intact molecule to colon[8]

2. pH dependent approach:

This was approach utilizes the existence of pH gradient in the GIT that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).

By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.

Coating of the drug core with pH sensitive polymers.

Table 4: Various pH dependent coating polymers.

Polymer	Threshold P.H
Eudragit L100	6.0
Eudragit S100	7.0
Eudragit L-30D	5.6
Eudragit FS 30D	6.8
Eudragit L 100-55	5.5

3. Embedding in pH-sensitive matrices: -

The drug molecules are embedded in polymer matrix. Extrusion spheronization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it was not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness. Citric acid promoted the pelletization process resulting in a narrower area distribution however, Eudragit S100 could not cause statistically significant delay in the drug release at lower pH.

Some market formulations:

Asacol® Proctor & Gamble Pharmaceuticals, USA Delayed-release tablets containing mesalazine and coated with Eudragit® S-100 are marketed in a number of countries (Asacol). These tablets dissolved at pH 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon.

4. Time dependent delivery:-

It also known as delayed release or sigmoidal release system. This approach was based on the principle of delaying the release of the drug until it enters into the colon.

Although gastric emptying tends to be highly variable, small intestinal transit time was relatively constant or little bit variation can be observed. The strategy in designing timed-released systems was to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place.

The lag time in This case was the time requires to transit from the mouth to colon. A lag-time of 5 hours was usually considered sufficient since small intestine transit was about 3-4 hours, which was relatively constant and hardly affected by the nature of formulation administration

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms.

Disadvantages of this system:

Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea and the ulcerative colitis. Therefore, time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Time-dependent drug delivery includes:

- Pulsincap
- Time clock
- Time-controlled- explosion drug-delivery system (pulsatile system based on rupturable coating)
- Colon targeted delivery capsule based on pH sensitivity and time-release principles chronotropic® system
- PORT system

5. Microbially triggered drug delivery to colon:

The microflora of colon was in the range of 10 11 -10 12 CFU/ml, consisting mainly of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc.

This vast microflora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri- saccharides, polysaccharides etc.

For This fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.

Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon- specific drug delivery seems to be a more site-specific approach as compared to other approaches.

These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon.

On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer.

Table 5: Different polymers used for CDDS based on Microbial drug delivery system.

Classes	Example
Disaccharides	Lactose, Maltose, Cyclodextrins, Lactulose, Raffinose, Stachyose
Polysaccharides	Alginates, Amylose, Cellulose, Chitosan, Starch, Chondroitin sulphate, pectin, xanthan gum, etc.

6. Bioadhesive systems:

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bioadhesion was a process by which a dosage form remains in contact with particular organ for an augmented period of time.

This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems.

Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have been investigated as materials for bioadhesive systems. Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

7. Pressure controlled system:

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion was higher in the colon compared to pressure in the small intestine, which was attributed to the difference in the viscosity of luminal contents.

In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content was significantly increased due to reabsorption of water from the lumen and formation of faces.

It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. Takaya et al. (1995) have developed pressure controlled colon delivery capsules prepared using an ethyl cellulose, which was insoluble in water. In such systems drug release occurs following disintergration of a water insoluble polymer capsule as a result of pressure in the lumen of the colon.

The thickness of the ethyl cellulose membrane was the most important factor for disintergration of the formulation. The preferred thickness of the capsule wall was about 35-60 μm [27]. The system also appeared to depend on capsule size and density.

In pressure-controlled ethyl cellulose single unit capsules the drug was in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.

8. Osmotic controlled drug delivery:

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 within a hard gelatin capsule. Each push-pull unit was bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle, semipermeable membrane was permeable to the inward entry of water and aqueous GI fluids and was impermeable to the outward exit of the drug. An orifice was drilled into the semipereable membrane to the drug layer. The outside surface of the semipermeable membrane was then coated by eudragit® S100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤7. As a result, water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit was designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine.

Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hr. in the colon or can deliver drug over an internal as short as 4 hours.

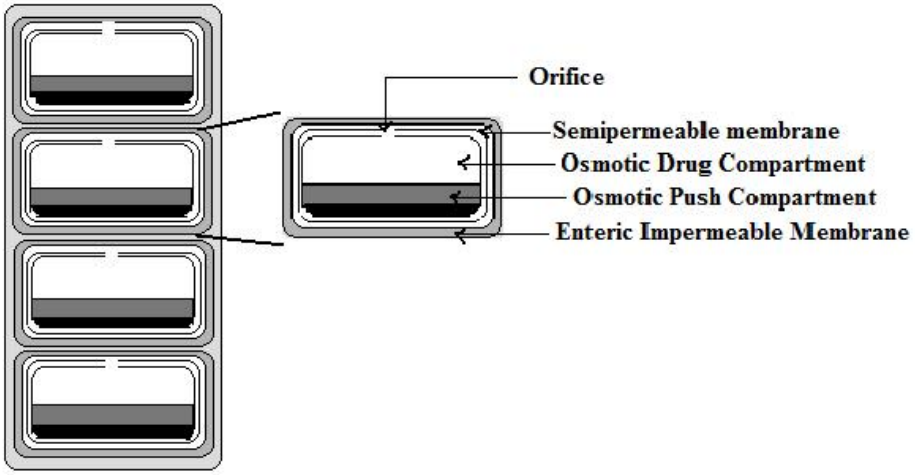


Fig 2: Osmotic controlled drug delivery.

9. **Multiparticulate systems**:

Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintergration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Report suggests that drug carrier systems larger than 200 μm possess very low gastric transit time due to physiological condition of the bowel in colitis. For This reason and considering the selective uptake of micron or submicron particles by cancerous and inflamed cells/ tissues a multiparticulate approach was expected to have better pharmacological effect in the colon. Recently, much emphasis was being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like,

- Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the
- Ascending colon for a relatively long period of time and hence increased bioavailability. Because of their smaller particle size as compared to single unit dosage forms these systems are
- Capable of passing through the GI tract easily, leading to less inter and intrasubject variability. Moreover, multiparticulate systems tend to be more uniformly dispered in the GI tract and also
- Ensure more uniform drug absorption. Reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.
- Multiparticulate approaches tried for colonic delivery include includes formulations in the form of pellets, granular matrix, beads, micro spheres, nano particles.

1.2.3. Enteric coating[9]:

An enteric coating was a barrier applied to oral medication that controls the location in the digestive tract where it was absorbed. Enteric refers to the small intestine; therefore, enteric coating on the dosage form prevents the release of drug before it reaches the small intestine.

Most enteric coatings work by presenting a surface that was stable to highly acidic pH of stomach, but breaks down rapidly at a less acidic (relatively more basic) pH.

Necessary enteric coating-:

Enteric coating was suitable for:

Drugs that have irritant effect in stomach (like aspirin), drugs which are unstable in acidic pH of stomach.

Thus, enteric coating was aimed to prevent the formulations from gastric fluid in the stomach and Release the drug component in the intestinal region or once it has passed into the duodenum.

Some of the most important reasons for the application of enteric coating to the dosage form are as follows:

- To protect the acid-labile drugs from the acidic pH of gastric fluid. Example: enzymes and certain
- Antibiotics. To prevent gastric distress or nausea due to irritation caused by certain drugs. Example: Sodiumsalicylate.
- To deliver drugs intended for the local action in intestines. Example: intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach.
- To deliver 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 to repeat action tablets.

An ideal enteric coating material should possess the following properties:

- Resistance to gastric fluids.
- Ready susceptibility to or permeability to intestinal fluids.
- Compatibility with most of the coating solution components and the drug substances.
- Stability alone and in the coating solutions i.e. the film should not change upon aging.

- Formation of a continuous film on the dosage form.
- Non-toxic and non-irritant
- Low cost.
- Ease of application without specialized equipment.
- Ability to be readily printed or to allow film to be applied to debossed tablets

Polymers used for enteric coating:

Table 6: Different polymers used for enteric coating.

Polymer	Dissolution pH
Shellac(esters of aleurtic acid)	7.0
Cellulose acetate phthalate(CAP)	6.2
Poly(methcrylic acid-co-methyl methacrylate)	5.5-7.0
Cellulose acetate trimellate(CAT)	5.0
Poly(vinyl acetate phthalate)(PVAP)	5.0
Hydroxypropyl methylcellulose phthalate(HPMCP)	4.5-5.5

1.3. Compression coating method[10-11]:

- Compression coating has been introduced during the period 1950-1960 to formulate incompatible drugs.
- Compression coating was becoming more popular and formulation scientists are showing interest to produce the modified release products owning to the advantages over solvent coating, since the process does not need the use of solvents, requires a relatively short manufacturing process and allows greater weight gain to the core tablet.
- Compression coating method involves the compression of coating materials around a preformed core tablet using conventional or specially designed tablet compression machine and it doesn't require use of any special solvent for coating purpose. Hence it was also known as press coating or solvent-less coating technique or dry coating technique.

- By composition, compression coated tablet has two parts: internal core and surrounding coat. The core tablet was small porous tablet and prepared on one turret and to prepare compression coating of core tablet, another turret with a bigger die cavity was used.
- Compression coated tablets are prepared by putting half of the quantity of the coating material in the die cavity, then the core tablet was carefully placed in the centre of the die cavity and finally it was filled with the other half of the coating material to surround the core tablet and compress the powder, which has the core tablet inside. Getting a reproducible central positioning of the core tablet within compression coated tablet was the major limitation for this method

1.3.1. Advantages of compression coating[12]:

- Compression coating was considered as the absolute dry coating without use of solvent and heat.
- Compression coating has no limitation for the cores and overcomes the adhesion problem found in spraying methods.
- This method eliminates the time-consuming and complicated solvent coating and also improves the stability of the drug by protecting it from moisture.
- This method has many advantages because no special coating solvent or coating equipment are needed for coating of tablet and manufacturing speed was faster
- It reduces the cost by eliminating the tedious and expensive processes of solvent disposal/treatment.
- It can significantly reduce the processing time by eliminating drying and evaporation step and the entire process was done without any heat and thus can provide an alternative technology to coat temperature sensitive drugs.

1.3.2. Limitations of compression coating:

- Compression coating involves the multistep processes and multiple compressions.
- Reproducible central positioning of the core tablet within compression coating was a major challenge for large scale industrial manufacturing.

- In some cases, difficulties in achieving good friability values after compression coating of immediate release powder onto controlled release tablet.
- It was difficult to coat using poor compressible polymers like guar gum and other gum materials.
- For large scale industrial manufacturing of compression coated tablets, the core material should possess the ability to flow into a die during production.

1.3.3. Applications of compression coating:

From the last two decades, for pharmaceutical formulation scientists, compression coating becomes a significant tool for tablet coating to develop the modified drug release tablets as well as site-specific drug delivery systems. However, compression coating technique has some drawbacks recently, the common manufacturing problems for compression-coated tablets, such as central positioning of the core in the compression-coated tablets and absence of core in coat, have been overcome by applying a novel one-step dry coated tablet (OSDRC) method invented by Ozeki et al. Some of the pharmaceutical aspects of compression-coated tablets in dosage form development are:

- To protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs.
- To separate incompatible drugs from each other and achieve sustained release.
- To protect the gastric mucosa from drugs like NSAIDs that cause gastric upset.
- To modify the drug release pattern delayed and/or sustained release tables.
- To achieve the site-specific drug delivery like colon specific compression coated tablets.
- To develop the pulsatile and programmable release for different drugs in one tablet and to prepare the multilayer tablets.

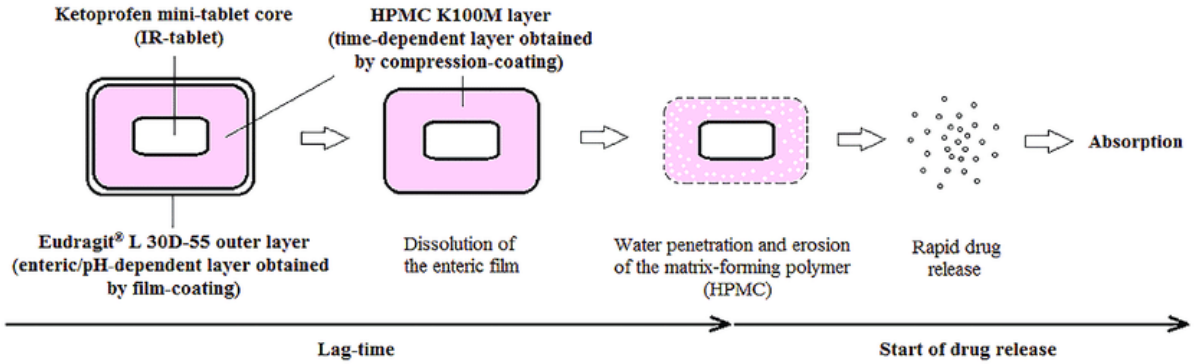


Fig 3: compression coating

2. LITERATURE REVIEW:

Seth Amidon *et al.*[13] stated that the colon-specific drug delivery systems (CDDS) are desirable for the treatment of a range of local diseases such as ulcerative colitis, crohn's diseases, irritable bowel syndrome, chronic pancreatitis, and colonic cancer. In addition, the colon can be a potential site for the systemic absorption of several drugs to treat non-colonic conditions. 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 was 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. This article highlights the factors influencing colon-specific drug delivery and colonic bioavailability, and the limitations associated with CDDS. Further, the review provides a systematic discussion of various conventional, as well as relatively newer formulation approaches/technologies currently being utilized for the development of CDDS

Anita *et al.* [14] stated that the colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like crohn's diseases, ulcerative colitis, *etc*. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs, and anti-diabetic agents. This review article discusses, in brief, the introduction of the colon, factor affecting the colonic transition, colonic diseases and the novel and emerging technologies for colon targeting.

Anil K*et al.* [15] stated that the colon was a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel diseases. However, treatment can be made effective if the drugs can 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 feasibility of manufacturing process.

Libo Yang*et al.* [16] **s**tated that the necessity and advantages of colon-specific drug delivery systems have been well recognized and documented. In the past, the primary approaches to obtain colon-specific delivery achieved limited success and included prodrugs, pH- and time-dependent systems, and microflora-activated systems. Precise colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological conditions particular to the colon. Hence, continuous efforts have been focused on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accommodate different therapeutic needs. Among the systems developed most recently for colon-specific delivery, four systems were unique in terms of achieving in vivo site specificity, design rationale, and feasibility of the manufacturing process (pressure-controlled colon delivery capsules (PCDCs), CODES™, colonic drug delivery system based on pectin and galactomannan coating, and Azo hydrogels). The focus of this review was to provide detailed descriptions of the four systems, in particular, and in vitro/in vivo evaluation of colon-specific drug delivery systems, in general.

Amwash Ashvinkumar Dangi*et al.* [17] developed and evaluated colon specific sustained release tablet using levetiracetam (LEV), microbially degradable polymeric carrier (pectin), coating material and matrix forming polymers. The colon targeted tablet was prepared by wet granulation technique using different percentage of pectin as matrix carrier, starch mucilage as a binding agent, HPMC K-100 as swellable polymer and coated with Eudragit polymers. Pectin, drug and physical mixture were evaluated for incompatibility study by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). All the batches of matrix tablet (F1-F4) were subjected for in-vitro dissolution in various simulated gastric fluids for suitability for colon specific drug delivery system. Tablets were evaluated for micromeritic properties of granules, physical properties, drug content, water uptake and erosion characteristics. F2 was optimized and subjected to coating based on evaluation results. The dissolution study of F2 revealed, in simulated intestinal fluid (SIF) release was 40.48% at the end of 6h and in simulated colonic fluids (rat caecal content) was 102.88% after degradation at the end of 8h. The colon targeted matrix tablet of LEV showed no change either in physical

appearance, drug content or dissolution pattern after performing stability study for 3 months. The studies confirmed that, the designed formulation could be used potentially for colon delivery by controlling drug release in stomach and the small intestine.

LinShuLiua*et al.* [18] developed pectin-derived matrices are now being examined and tested for controlled drug delivery. Pectin was intact in the upper gastrointestinal tract and degraded by colonic microflora. The composition of this microflora remains relatively consistent across a diverse human population. Thus, pectin-derived drug carriers provide promising potential for colon-specific drug delivery. This paper reviews recent developments in pectin-derived formulations. Subjects reviewed include gelation of pectin, calcium cross-linked pectinate, composites of pectin and other polymers, technologies to fabricate pectin into useful drug delivery vehicles, and methods to evaluate release kinetics of incorporated drugs. This article discusses advantages, limitations, and possible future developments in pectin-based formulations with particular emphasis on the field of colon-specific drug delivery
Abraham Rubinstein

Raphael Radai*et al.* [19] showed that the Calcium pectinate (CaP)—the insoluble salt of pectin—can potentially be used as a colon-specific drug delivery system. The use of CaP as a carrier was based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon but that it retains its integrity in the physiological environment of the small bowel. The biodegradation of the carrier was characterized by monitoring the percent cumulative release of the insoluble drug indomethacin, incorporated into pectin or CaP matrices. Compressed tablets of pectin and indomethacin were analyzed for degradation in the presence of pectinex 3XL, a typical pectinolytic enzyme mixture, and in the presence of the human colonic bacterium *Bacteroides ovatus*. The degradation of CaP-indomethacin tablets was assessed in the presence of Pectinex 3XL and in rat cecal contents. The release of indomethacin was significantly increased (end-time percentage cumulative release vs control) in the presence of pectinex 3XL (89 ± 20 vs 16 ± 2 for CaP tablets), *Bacteroides ovatus* (12 and 22 vs 5.2 for pectin tablets), and rat cecal contents (61 ± 16 vs 4.9 ± 1.1 for CaP tablets). The weight loss of tablet mass was significantly higher (end-time dry weight vs control) in the presence of pectinex 3XL (0 vs 75 ± 6% of initial weight for CaP tablets). These findings indicate the potential of

CaP, compressed into tablets with insoluble drug, to serve as a specific drug delivery system to the colon.

Abraham Rubinstein*et al.* [20] developed the human gastrointestinal tract consists of a highly complex ecosystem of aerobic and anaerobic microorganisms that plays a significant role in the metabolism of nutrients as well as drugs. In the colon, bacteria ferment various types of substrates that are not susceptible to digestion in the small intestine. This arouses interest in specific drugs, drug delivery systems, and prodrugs that escape small bowel digestion, arrive intact, and are absorbed or degraded in the large bowel. For the past forty years, experience has been gained with the azo prodrug of 5-amino salicylic acid, salazopyrine, which was cleared by colonic bacteria to its parent drug. Some laxative drugs were also reported to degrade into active metabolites in the colon. Lately equally interesting and more sophisticated microbial controlled delivery systems, have been developed based on similar principles.

H. bronsted *et al.* [21] stated that the new types of synthetic water soluble polymeric systems for the treatment of colon diseases are described. These systems are based on the concept of binding of polymeric carriers containing carbohydrate moieties complementary to colonic mucosal lectins and on the concept of site-specific release of drug (5-aminosalicylic acid) from the polymeric carrier by the degradingaction of microbial enzymes present in the colon. New synthetic pathways have been developed for the synthesis of *N*-(2-hydroxypropyl)methacrylamide copolymers containing high amounts of both the bioadhesive moiety (fucosylamine) and 5-aminosalicylic acid. Fucosylamine containing copolymers bind to the colonie mucosa of guinea pigs. The higher the content of fucosylamine, the higher the binding. The binding can be inhibited by unbound fucose indicating the presence of specific lectin-like structures in the guinea pig colon. New biodegradable hydrogels containing both acidic comonomers and enzymatically degradable azoaromatic crosslinks were synthesized. These hydrogels are suitable for site-specific delivery of peptides (proteins) into the colon. In the low pH range of the stomach, the gels have a low equilibrium degree of swelling and the drug was protected against digestion by enzymes. The degree of swelling increases as the hydrogel passes down the gastrointestinal tract due to increased pH. In colon, the hydrogels have reached a degree of swelling that makes the crosslinks accessible to azoreductases and mediators. The rate of degradation depends on the structure of the hydrogels. Total dissolution in vivo canbe

achieved in less than 48 h. Brush border membrane and luminal enzymes were isolated from guinea pig small intestine and colon. Their enzymatic activity towards insulin and insulin B-chain was compared. It was shown that the extent of peptide degradation was substantially lower with colonic enzymes when compared to those isolated from the small intestine.

M. Zahirul I. Khan*et al.* [22] developed tablets containing mesalazine as a model drug were coated using various combinations of two methacrylic acid copolymers, (Eudragit® L100 and Eudragit S100) by spraying from aqueous systems. The Eudragit L100–Eudragit S100 (w/w) combinations studied were 1:0, 4:1, 3:2, 1:1, 2:3, 1:4, 1:5, and 0:1. The coated tablets were tested in vitro for their suitability for pH-dependent colon-targeted oral drug delivery. The dissolution profiles of the drug obtained from the studied tablets demonstrate that the release of the drug could be manipulated by changing the Eudragit L100–Eudragit S100 ratios in the combinations within the pH range between 6.0 and 7.0 in which the individual polymers are soluble, and a coating formulation consisting of a combination of the two polymers can overcome the was issue of high gastrointestinal (GI) pH variability among individuals. The results also demonstrate the feasibility of using aqueous dispersions of Eudragit L100–Eudragit S100 combinations for coating tablets for colon-targeted delivery of drugs, and that the formulation can be adjusted to deliver drug(s) at any other desirable site of the intestinal region of the GI tract in which pH of the fluid was within the range 6.0 to 7.0. For colon-targeted delivery of drugs, the proposed combination system was superior to tablets coated with either Eudragit L100 or Eudragit S100 alone.

Murat Turkoglu *et al.* [23] developed pectin–HPMC compression coated 5-Amino Salicylic Acid Tablets for colonic delivery. They prepared 5-ASA Core Tablets by wet granulation method using PVP (K 29-32). Each 100 mg Core Tablet contained 5-ASA and was compression coated at 20 kN or 30 kN using 100% pectin, 80% Pectin–20% HPMC and 60% pectin–40% HPMC at two different coat weights as 400 or 500 mg. Drug dissolution/system erosion/degradation studies were carried out in pH - 1.2 and 6.8 buffers using a pectinolytic enzyme. HPMC addition was required to control the solubility of pectin. The optimum HPMC concentration was 20% and such system would protect the cores up to 6 h that corresponded to

25–35% erosion and after that under the influence of pectinase the system would degrade faster and delivering 5-ASA to the Colon.

Sateesh Kumar Vemula *et al.* [(24)] formulated and evaluated colon-specific double compression coated mini-Tablets of Ketorolac tromethamine. Double compression coated tablets were prepared based on time-controlled Hydroxypropyl methylcellulose K100M inner compression coat and pH-sensitive Eudragit S-100 outer compression coat. 6 formulations were done. From the *in-vitro* drug release studies, F6 Tablets was considered as the optimized formulation, which retarded the drug release in stomach and small intestine (3.51 + 0.15% in 5 h) and progressively released to colon (99.82 + 0.69% in 24 h). The release process followed supercase-II transport with zero order release kinetics. From the pharmacokinetic evaluation, the Compression coated tablet Core Mini-Tablets reached peak plasma concentration (C-max of 4532.68 + 28.14 ng/ml) at 2 h T-max and Colon targeted Tablets showed C-max of 3782.29 + 17.83 ng/ml at 12 h T-max. The area under the curve and mean resident time of Core Mini-Tablets were found to be 11,278.26 + 132.67 ng.h/ml and 3.68 h respectively while 17,324.48 + 56.32 ng.h/ml and 10.39 h for Compression Coated Tablets.

Patel Rushikesh Chandubhai *et al.* [(25)] formulated and evaluated an oral Time-controlled drug delivery System of Flurbiprofen, based on chronotherapeutic approach for the treatment of Rheumatoid arthritis (RA). In This study, Flurbiprofen CCT was prepared by compression coating the Core Tablet with different polymers like HPMC K4M, HPMC K15M and HPC in various proportions. Different ratios of polymers were selected to achieve suitable lag time for the treatment of RA. The CCT were evaluated for their hardness, thickness, friability, weight variation, drug content uniformity and core erosion ratio. The *in-vitro* drug release profile of the formulations was performed in simulated gastric and intestinal pH conditions up to 8 h. The desired lag time of 6 h was obtained for selected formulations and burst release was obtained after the lag time, which was consistent with the demands of chronotherapeutic drug delivery.

Srikanth S et al .[(26)]formulated and evaluated microbially activated osmotic drug deliverysystem for colon targeted tinidazole tablets and concluded that all the physical

characteristics of the formulations like thickness, hardness, friability, drug content, and in-vitro dissolution study were found to be well within the limits and official standards.

Mehta T Jet al .[27]formulated, developed and optimized metronidazole compression coated tablets and found that the amount of chitosan and carbopol showed significant effect on the release of metronidazole from the colon specific tablet formulation.

Dr. S.S. Khadabadi *et al.* [28] formulated and evaluated the press coated tablet of Ketoprofen. The PCT containing Ketoprofen in the inner core were formulated by direct compression method. SSG was used as a super disintegrant in core tablet. The HPMC K4M was used as a coating material to modify the release in outer coat. Totally 9 formulations were made by varying amounts of SSG and HPMC K4M. Evaluations were done. The release profile of PCT exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 32 factorial design considering two independent factors at three levels. The optimized batch F6 gave a lag time of 6 h and drug release of 95.74% which consisted of 40% HPMC K4M and 2% SSG.

Ganesh D K et al. [29] formulated and evaluated colon targeted drug delivery of aceclofenac and showed that compression coated tablet with guar gum: xanthan gum was most likely to provide targeting of aceclofenac for local action.

Soad A Y et al. [30] formulated budesonide compression-coated tablets for colonic delivery and proved that Budesonide compression-coated with 75% pectin may be beneficial in the treatment of inflammatory bowel diseases.

Krwashnaveni.G *et al* .[31] developed and evaluated Pulsatile Drug Delivery System containing Montelukast Sodium by press coated tablet using natural polysaccharides. Totally 9 different Montelukast sodium core tablet formulations were prepared by direct compression method using different concentrations of SSG, CCS, Crospovidone. Then the optimized F3 formulation was coated with a natural polymers such xanthan gum, guar gum and mixture of it respectively. The evaluations were done. Formulation P5-F3 shows great ideal in pulsatile drug delivery. The release data from the formulation was found to fit in peppas model with r2 of

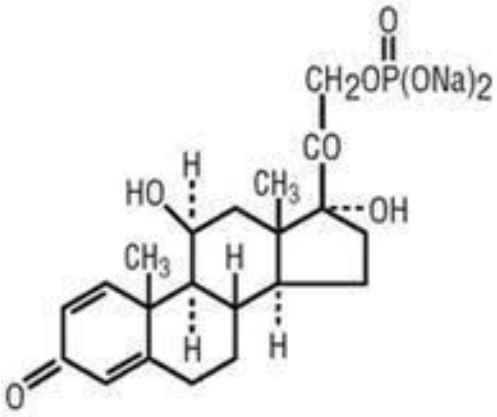
0.983. Stability studies also performed for 3 months at 40ºC and 55ºC at 75% RH as per ICH guidelines for optimized formulation and it was found to be stable.

Purushotham R et al. [32] prepared naproxen-pectin-based matrix tablets for colon drug delivery and concluded that addition of hydroxy ethyl cellulose along with pectin coated with ethyl cellulose and cellulose acetate phthalate will be an ideal carrier for colon targeted drug delivery.

3. DRUG PROFILE[15-16]

SYNONYM: Prednisolone

CHEMICAL NAME: pregna-1, 4-diene-3, 20-dione,11, 17-dihydroxy-21- (phosphonooxy), disodium salt(11ß)-



THE EMPIRICAL FORMULA: $C_{21}H_{27}Na_2O_8P$

THE MOLECULAR WEIGHT: 484.39

PHYSICAL PROPERTIES

COLOR: White or slightly yellowish

STATE/FORM: Friable granules or powder

SOLUBILITY: It was freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; and very slightly soluble in acetone and in dioxane.

PHARMACOKINETICS:

ABSORPTION: Absorbed from GIT bioavailability: Found to be about 62%. The fraction of the dose recovered in the urine as the hydroxylated metabolites of prednisone and prednisolone was lower after the oral prednisone dose, suggesting that poor absorption of prednisone was the main cause of the low bioavailability. Plasma binding: 70-90%

ELIMINATION: Eliminated from the plasma with a half-life of 2 to 4 hours. It was metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

DOSE: Available in strengths containing 13.4 mg, 20.2 mg, and 40.3 mg prednisolone (equivalent to 10 mg, 15 mg, or 30 mg prednisolone base, respectively).

USES: It was used for treatment of severe inflammatory conditions including allergies, arthritis, asthma, or skin reactions. It may also be used to treat certain blood, adrenal gland, eye, respiratory, or bowel conditions. It may also be used for other conditions as determined by your doctor. Orapred ODT was a corticosteroid. It works by modifying the body's immune response to various conditions and decreasing inflammation.

HOW TO USE: This medication was swallowed through the mouth, whole with water. And then it enter into the systemic circulation.

DRUG INTERACTIONS: Drugs such as barbiturates, phenytoin, ephedrine, and rifampin, which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisoloneand require that the dosage of orapred be increased.

Increased activity of both cyclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Estrogens may decrease the hepatic metabolism of certain corticosteroids thereby increasing their effect.

Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60% leading to an increased risk of corticosteroid side effects.

Co administration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Concomitant use of aspirin (or other non-steroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics, amphotericin-B), patients should be observed closely for development of hypokalemia. Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Due to inhibition of antibody response, patients on prolonged corticosteroid therapy may exhibit a diminwashed response to toxoids and live or inactivated vaccines. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. If possible, routine administration of vaccines or toxoids should be deferred until corticosteroid therapy was discontinued.

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required. Corticosteroids may suppress reactions to skin tests.

STORAGE: Store at room temperature between 68-77^{0}F (20-25^{0}C) away from light and moisture. Keep all medicines away from children and pets.

4. POLYMER PROFILE:

4.1. PECTIN[17-19]

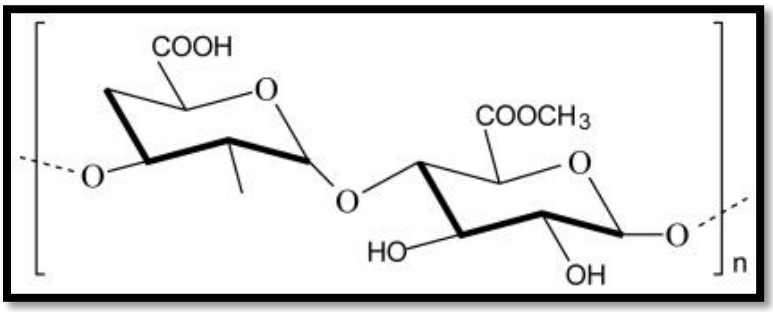
SYNONYM: PECTIN

NON-PROPRIETARY NAME: pectin

CHEMICAL NAME AND CAS REGWASTRY NUMBER: pectin [9000-65-5]

FUNCTIONAL CATEGORY: Absorbent, emulsifying agent, gelling agent, thickening agent, stabilizing agent

STRUCTURAL FORMULA:



MOLECULAR WEIGHT: 30,000-100,000

DESCRIPTION: pectin occurs as coarse or fine, yellowish-white odorless powder that has mucilaginous taste.

SOLUBILITY: Soluble in water, insoluble in ethanol (95%) and other organic solvents

INCOMPATIBILTIES:-

STABILITY AND STORAGE CONDITIONS: Pectin was a non-reactive and stable material; it should be store in a cool and dry place

SAFETY: Pectin was used in oral pharmaceutical formulation and as food product, and was generally regarded as essential non-toxic and non-irritant material.

Low toxicity by subcutaneous rout as been reported.

LD_{50} (mouse/SC):6.g/kg

APPLICATION IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY:

- Pectin has promwasing pharmaceutical uses such as in controlled release dosage forms, it acts as a carrier and a number of techniques such as ionotropic gelation and gel coating have been used to fabricate the pectin based delivery systems
- Pectin hydrogels have been reported to act as binding agents in controlled-release matrix tablet formulations. Also it acts as an encapsulating agent in sustained release dosage forms alone or in combination with gelatin
- As delivery vehicles, the pectin complex hydrogels have shown great potential in carrying the encapsulated drugs to the colon and specifically releasing them at the site
- Pectin has been used as an absorbent and bulk forming agent, and was present in multi-ingredient preparation for management of diarrhea, constipation, and obesity
- It has also been used as an emulsion stabilizer
- Pectin have been used as a component in the preparation of mixed polymer microsphere systems with the intention of producing controlled release tablets

POLYMER PROFILE:

4.1.2. HYDROXYPROPYLMETHYLCELLULOSE[20]

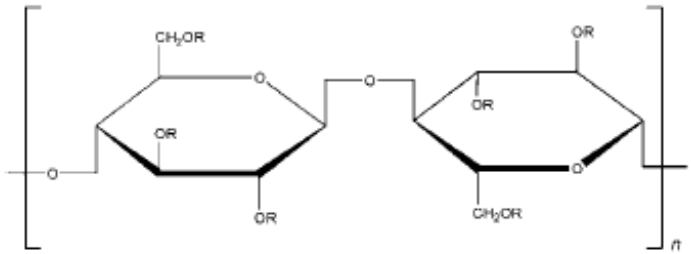
SYNONYMS: Methocel, Metolose, Tylopur, Benecel MHPC

CHEMICAL NAME: Cellulose hydroxypropylmethyl ether

CAS R. NUMBER: 9004-65-3

DESCRIPTION: White or creamy- fibrous or granular Odorless and tasteless, powder.

FORMULA:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

FUNCTIONAL CATEGORY:

- Coating agent
- Stabilizing agent
- Tablet binder
- Rate-controlling polymer for SR
- Film-former
- Suspending agent

TYPICAL PROPERTIES:

- **Acidity/alkalinity**: for a 1% w/w aqueous solution pH = 5.5–8.0.
- **Ash:** 1.5–3.0%, as per grade and viscosity.
- **Auto ignition temperature**: 360°C
- **True density** : 1.326 g/cm3
- **Bulk density** (BD): 0.341 g/cm3
- **Tapped density** (TD): 0.557 g/cm3
- **Specific gravity**: 1.26

MOISTURE CONTENT: HPMC take up moisture from the damp air; the amount of water taken up depends upon the initial moisture, temperature and relative humidity of the atmosphere.

MELTING POINT: Chars at 226–230°C. Browns at 191–200°C; Glass transition

- Temperature was 171–180°C.

SOLUBILITY: In cold water- Soluble, Forms viscous colloidal solution; In chloroform, ethanol (95%), and ether, practically insoluble but in mixtures of methanol and dichloromethane; ethanol and dichloromethane and water and alcohol, it was soluble.

VISCOSITY (DYNAMIC): A wide vary of viscosity sorts are available in market for commercial purpose. Generally aqueous solutions are prepared, though HPMC may additionally bed dissolved in alcohols like ethanol and propan2ol provided the where alcohol content was< 50% w/w. Methylene chloride and ethanol mixtures may additionally used to prepare viscous Hydroxypropylmethylcellulose solutions. Solution's victimization in organic solvents tend to be additional viscous; increasing concentration conjointly produces additional viscous solutions.

STABILITY AND STORAGE CONDITIONS: HPMC in powder form was usually a stable excipient, but it becomes hygroscopic after drying. Rise in heat decreases the viscosity of prepared solutions. HPMC experiences a vice-versa sol–gel transformation when heated and cooled, respectively. Liquid preparations are stable at pH 3–11. The temperature at which it converts in to gel- gel point was 51–90°C, based on the type of grade and concentration. (Banker et al., 1982) HPMC solutions prepared in aqueous are reasonably enzyme-resistant, giving good stability (of viscosity) while storage for long-term. However, solutions prepared in aqueous are accountable to microbial spoilage and while preserving it, requires antimicrobial preservative: when HPMC was used as a viscosity-enhancing agent in solutions for ophthalmic preparation, the most commonly used preservative was benzalkonium chloride. HPMC solutions prepared in aqueous may also be autoclaving for sterilization; if polymers get coagulated, it must be shake when cooled to redispered.

HPMC dry powder should be, stored in well-closed bottles, in a dry & cool place.

INCOMPATIBILITIES: Hydroxypropylmethylcellulose was not compatible with few oxidizing agents. Since HPMC are nonionic, it will not complex with ionic organics or metallic salts to and will not prepare non-soluble precipitates.

SAFETY: HPMC was widely and extensively used in oral and topical formulations. It was used extensively also in food products and cosmetics. HPMC was normally viewed as a safe and nonirritant material, even though extreme oral ingesting may produce laxative effect. The WHO has not stated the satisfactory daily consumption for HPMC since the stages consumed were not measured to signify a hazard to health, (FAO/WHO, 1990).

Mouse: LD50 (IP): 5 g/kg
Rat: LD50 (IP): 5.2 g/kg

APPLICATIONS IN FORMULATION: As Emulsifier and stabilizing agent in ointments; HPMC was extensively being used,

In oral products,

- As a tablet binder (2% and 5% w/w, wet or dry)
- In film-coating (2–20% w/w)
- As a matrix (10–80% w/w) for use in XR tablets and capsules
- High-viscosity grades, better retard the release

In topical formulations,

- Suspending and thickening agent
- Stabilizing agent

In ophthalmics,

- Thickening agent (0.45–1.0% w/w)

POLYMER PROFILE:

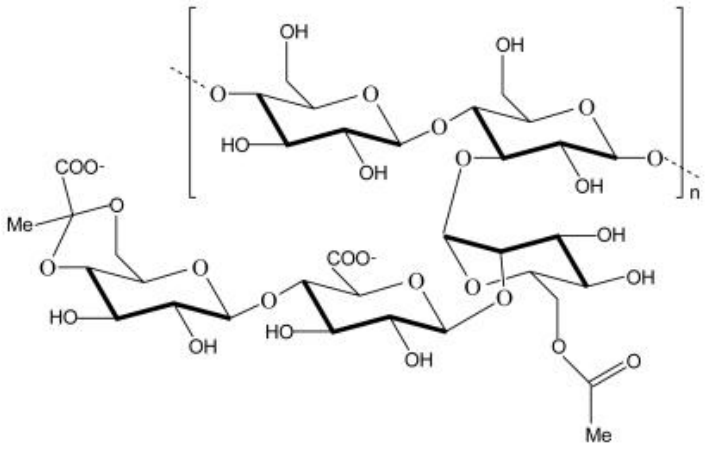
1.1.1. XANTHAN GUM[21]

NON-PROPRIETARY NAME: USP NF: Xanthan gum

SYNONYMS: Corn sugar gum, E415, Keltrol, Merezan, Polysaccharide B-1459, Rhodigel, and Xanthum gum.

CHEMICAL NAME: Xanthum gum [11138-662]

CHEMICAL STRUCTURE:



FUNCTIONAL CATEGORY: Stabilizing agent, suspending agent, viscosity increasing agent, matrix making agent in preparation of oral sustained released tablets.

APPLICATION IN PHARMACEUTICAL FORMULATION: Widely used in oral and topical pharmaceutical Formulation, cosmetics, and food as a suspending and stabilizing agent.

It was non-toxic, compatible with other pharmaceutical ingredient and has good stability and viscosity properties over a wide pH and temperature range. It was also used in preparation of matrix tablets.

DESCRIPTION: Cream or white colored, odorless, free-flowing and fine powder.

TYPICAL PROPERTIES: -

ACIDITY/ALKALINITY: pH 6- 8 for a 1% w/v aqueous solution.

SOLUBILITY: Practically insoluble in ethanol, soluble in cold/ warm water.

VISCOSITY: 1200-1600mPas (1200-1600cP) for a 1% w/v aqueous solution.

STABILITY AND STORAGE CONDITION: It was a stable material. The bulk material should be stored in a well-closed container in a cool and dry place

5. EXCIPIENT PROFILE:

5.1.1. MICROCRYSTALLINE CELLULOSE[23]

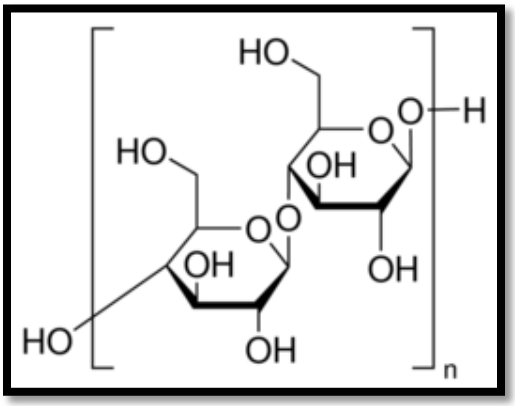
NAME: MICROCRYSTALLINE CELLULOSE

SYNONYMS: Avicle pH, cellets, cellulose gel, ceolus KG, crystalline cellulose, emcocel, tabulose, fibrocel.

FUNCTIONAL CATEGORY: Adsorbent, suspending agent, tablet disintergration, tablet and capsule diluents

CHEMICAL NAME: cellulose [9004-34-6]

STRUCTURAL FORMULA:



DISCRIPTION: microcrystalline cellulose was purified, partially depolymerized cellulose that occurs as a white, odorless, crystalline powder composed of porous particles.

TYPICAL PROPERTY:

- Angle of repose – 49^0 for ceolus Kg
- Density (bulk) – 0.337 g/cm^3
- Density (tapped) – 0.478 g/cm^3
- Density (true) – 1.420-1.460 g/cm^3 for avicel pH-102
- Melting point chars at 260-270^0c
- Moisture content typically less than 5%w/w. However, different grades ma contain varying, amount of water. Microcrystalline cellulose was hygroscopic
- Solubility slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents
- Specific surface area – 1.21-1.30m^2/g for Avicel pH-102

STABILITY AND STORAGE CONDITION: Microcrystalline cellulose was a stable though hygroscopic material. The bulk materials should stored in a well-closed container in a cool, dry place.

INCOMPATIBILITIES: Microcrystalline cellulose was in compatible with strong oxidizing agent.

APPLICATION IN PHARMACEUTICAL FORMULATION AND TECHNOLOGY:

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

EXCIPIENT PROFILE:

5.1.2. MAGNESIUM STEARATE[23]

NAME: MAGNESIUM STEARATE

NON-PROPRIETARY NAMES:

- BP : Magnesium stearate
- PhEur : Magnesium stearate
- US : Magnesium stearate

SYNONYMS: Magnesium octadecanoate; stearic acid magnesium salt; octadecanoic acid, magnesium salt.

CHEMICAL NAME AND CAS REGWASTRY NUMBER: Octadecanoic acid magnesium salt [557-04-0]

STRUCTURAL FORMULA: [CH3(CH2)16COO]2 Mg

FUNCTIONAL CATEGORY: Tablet and capsule lubricant

DESCRIPTION: Fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder was greasy to the touch and readily adheres to the skin.

TYPICAL PROPERTIES:

- Crystalline forms: high purity Magnesium sterate has been isolated as a trihydrate, a dihydrate and an anhydrate.

- Bulk density: 0.159 g/cm3
- Flow ability: poorly flowing, cohesive powder.
- Melting range: 117-150^{0}c (commercial samples) 126-130^{0}c (high purity Mg. stearate.)
- Solubility: Practically insoluble in ethanol, ethanol (95%), ether and H2O, slightly soluble in warm benzene and warm ethanol (95%).

STABILITY AND STORAGE CONDITIONS: Magnesium sterate was stable and should be stored in a well-closed container in a cool, dry place.

INCOMPATIBILITIES: Incompatible with strong acids and iron salts, can't be used in products containing aspirin, some vitamins and most alkaloid salts.

APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY:

Magnesium sterate was widely used in cosmetics, foods and pharmaceutical formulations. It was primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25- 5.0%. It was also used in barrier creams.

6.0 DISEASE PROFILE[13]

6.1.1. Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome is a part of a family of functional gastrointestinal disorders (FGIDs) in which there is disturbance of gastrointestinal functions in the absence of any known pathology changes. It is a chronic relapsing disorder characterized by abdominal pain, distension and disturbed bowel habit. Diagnosis depends mainly on symptom evaluation and clinical criteria and on ruling out the presence of other organic causes. There is currently no specific diagnosis test for IBS.

The symptoms of the IBS are cramping, abdominal pain, diarrhoea, constipation or a combination of both diarrhoea and constipation, mucus discharge along with stools, bloating, straining at defecation, urgency and feeling of incomplete evacuation. It is chronic nature, signs and symptoms which vary periodically from mild to severe have many negative effects on the quality of life for the sufferer. Therefore the appropriate treatment of these patients is highly important. Depending on the predominant bowel symptoms, IBS can be classified as

- Constipation predominant IBS (IBS-C)
- Diarrhoea predominant IBS (IBS-D)
- IBS with mixed constipation and diarrhoea (IBS-M)

IBS is also known as **Irritable Colon, Spastic Colon, And Nervous Colon.**

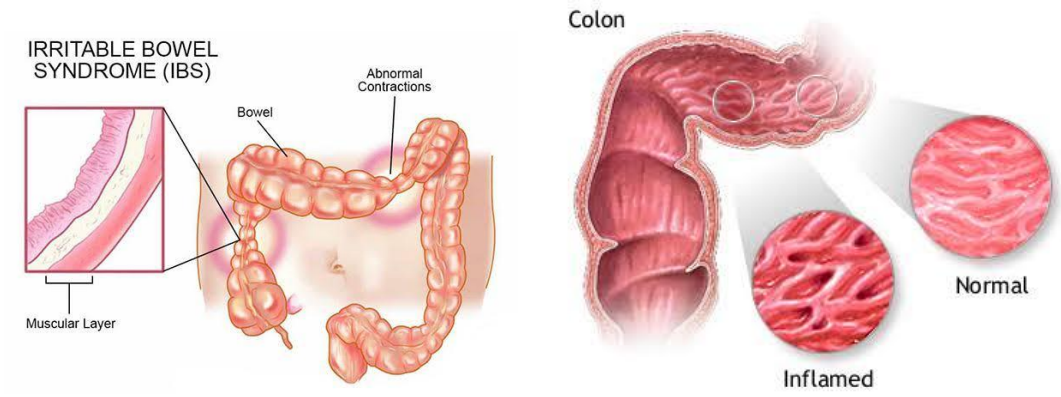


Fig 3: Colon in IBS.

6.1.2. Etiology of IBS

The exact Etiology of IBS remains to be determined. The debate remains whether it is caused by hereditary or environmental factors. It is possibly due to complex interaction between both. A number of mechanisms have been described in the etiology of IBS as summarized below,

- **Visceral hypersensitivity**

It is an important mechanism for abdominal pain in IBS. It is caused by heightened sensitivity of both peripheral and CNS due to inflammatory and non-inflammatory agents.

- **Abnormal gut motility**

A cardinal feature of IBS is change in bowel pattern which is due to abnormality of gut motility. Sympathetic and parasympathetic nerves control the function of enteric nervous system via. A variety of mediators and receptors such as serotonin. Activation of 5-HT3 and 5-HT4 receptors enhances gut motility while inhibition of 5-HT3 delays transit time. Gut motility is also regulated by psychogenic, somatic and immune stress.

- **Autonomic nervous system dysfunction**

There appears to be an imbalance resulting from increased sympathetic and decreased parasympathetic activity. Vagal and adrenergic dysfunctions are associated mainly with constipation and diarrhoea respectively.

- **Small intestine bacterial overgrowth**

Up to 84% patients with IBS have been found to have Small intestinal bacterial overgrowth (SIBO). Antibiotic treatment with non-absorbable antibiotics, e.g. Rifaximin leads to clinical improvement of IBS. Two studies suggest the prevalence of SIBO to be 11% in India. However, villous atrophy with bacterial overgrowth (tropical enteropathy) is also common in India. It is presently unclear whether SIBO is the cause or effect of IBS.

- **Microscopic inflammation**

Microscopic inflammation has been documented in some patients. This concept is important because IBS has previously been considered to have no demonstrable pathologic alterations. Immuno histochemical studies reveal mucosal immune system activation in a subset of patients with IBS-D.

- **Post-infectious Irritable Bowel Syndrome**

Post-infectious IBS affects 10% of IBS patients. This subtype is consequent to previous bacterial gastroenteritis and raises the importance of bacterial infections in causation of IBS. A longer duration of the diarrhoeal episode, younger age, female sex, bloody stools, depression, etc., increases the risk of development of IBS. Interestingly, some studies in India suggest a protective effect of previous exposure to amebic infection.

- **Food intolerance and allergy**

Hypersensitivity reactions lead to mast cell degranulation with production of local and systemic proinflammatory Leukotrienes and Histamine which act on smooth muscles. Sugar and gluten intolerance have also been implicated but seem to be unlikely cause of IBS although may contribute to bloating.

- **Psychosocial factors**

Emotions affect gut motility and patients with history of physical or sexual abuse, loss and separation during childhood, and conflicting maternal relationship are all associated with development of IBS.

- **Genetic factors**

There is some evidence to suggest a genetic factor in causation of IBS. One study found that 33% of patients with IBS had a positive family history. Also, first-degree relatives are twice likely to have IBS

6.1.3. PATHOPHYSIOLOGY[13]

The pathophysiology of IBS is poorly understood. Till now there is no single clear pathophysiology has been demonstrated. Theories includes;

- **Altered bowel motility**

Instead of the normal muscular activity (motility) of digestion, IBS patients may experience spasms and cramping. If the motility is too fast, it may result in diarrhoea and if it is too slow, it might result in constipation. These two conditions may also produce abdominal discomfort or pain in IBS patients. Abnormal motility can also be associated with abdominal cramping, belching, urgency or other unpleasant GI symptoms.

- **Visceral hypersensitivity**

For IBS patients, there can also be increased sensitivity of the nerves in the GIT. This can develop after a gastrointestinal infection or an operation that causes injury to the nerves in the intestine. This result in a lower threshold for experiencing intestinal sensations, leading to abdominal discomfort or pain. In those with visceral hypersensitivity, the stretch put on the intestines from eating even small amounts of food may produce discomfort.

- **Imbalance of neurotransmitters**

Serotonin is synthesized and released by Enterochromaffin cells in the GIT and plays an important role in regulation of GI-motility, sensation and secretion. Excess released serotonin is mopped up by the serotonin reuptake transporter (SERT). Several studies have indicated a noted imbalance in the functioning of 5-HT due to an impairment in its release and reuptake mechanisms by SERT in functional GI disorders which has in particular been shown be true IBS. Upto 60 % of patients with IBS have psychiatric co-morbidities including depression, anxiety, somatization and functional disorders such as chronic fatigue syndrome.

6.2. RISK FACTORS[14]

1. Gender and age

Younger age was found to be an independent risk factor for IBS development. IBS usually begins during the late teens or early 20's. According to the American College of Gasteroenterology more than 80% of the IBS patients are women.

2. Stress

Stress induced release of Corticotrophin - Releasing Factor (CRF) may be responsible for mast cell activation and mediator release. It will lead to CRF infusion in IBS patients evokes an exaggerated colonic motor response.

3. Food Allergy

The symptoms of IBS are often made worse by eating, and this leads many patients to conclude that they are suffering from some form of dietary allerg. There is little evidence to suggest that immediate type mediated.

4. Smoking

A single study showed smoking to be associated with Postinfective-IBS (PI-IBS) development. However, smoking can be a marker for psychological distress, hence associating with PI-IBS, which makes it harder to draw any conclusions based on the limited evidence.

6.2.1. SYMPTOMS

Symptoms associated with IBS are;

- Chronic abdominal pain
- Altered bowel habits
- Painful Diarrhoea and Painful Constipation
- Mucus discharge along with stools
- Straining at defecation
- Feeling of incomplete evacuation
- Upper GI symptoms include gastro-esophageal reflux, dysphagia, early satiety, intermittent dyspepsia, nausea and non-cardiac chest pain are noted as being common
- Patient may also frequently complain of abdominal bloating and an increase in gas production in the form of flatulence or belching
- Extra-intestinal symptoms include impaired sexual function, dysmenorrhea, dyspareunia, increase in the frequency and urgency to urinate, hypertension and asthma, fibromyalgia

6.3. MANAGEMENT OF IBS[14]

The IBS management is done in following steps;

1. Dietary interventions
2. Pharmacological therapy
   - Anti-spasmodic agents
   - Peppermint oil
   - Anti-diarrhoeal agents
   - Corticosteroids
   - Selective serotonin reuptake inhibitors (5-HT3 Antagonist)
   - 5-HT4 Agonist
3. Probiotics
4. Biopsychosocial modifying therapies:
   - Hypnotherapy

- Cognitive behavioral therapy
- Yoga
- Acupuncture

6.3.1. Dietary interventions

Dietary interventions form an important strategy in managing children with IBS. Constipation is a common complaint in patients with IBS. The commonest dietary recommendation made to patients with IBS is to increase the intake of dietary fibre. Fruit and vegetable contain substantial amounts of both soluble (pectins, hemicelluloses) and insoluble (cellulose, lignin) fibre. Fibre supplementation with naturally derived concentrated non starch polysaccharides such as bran, ispaghula husk, methylcellulose and sterculia increases faecal mass and may accelerate transit.

6.3.2. Anti-spasmodic agents

Anti-spasmodics are believed to inhibit contractile pathways in visceral muscle walls and thus reduce abdominal pain. Anti-spasmodics can be classified in three major subclasses

2. Anti-cholinergic / Anti-muscarinic agents
    - Dicyclomine Hydrochloride
    - Hyoscyamine Sulfate
    - Cimetropium Bromide
    - Otilanium Bromide
    - Octylonium Bromide
    - Prifinium Bromide
    - Zamifenacin
    - Darifenacin

2. Smooth muscle relaxants

- Mebeverine
- Papaverine-like agents

3. Calcium channel blockers

- Pinaverium Bromide

6.3.3. Peppermint oil:

It exerts an Anti-spasmodic action via. menthol and act as a calcium antagonist and results in Anti-flatulent action, the exact mechanism of which currently remains unexplained.

6.3.4. Anti-diarrhoeal agents

It is useful for the treatment of IBS-D but has little effect on abdominal pain. The opioid analogues stimulate inhibitory presynaptic receptors in the enteric nervous system resulting in inhibition of peristalsis and secretion. Eg. Loperamide and Diphenoxylate. It has a better safety profile, since it does not cross the blood brain barrier like other opiates.

6.3.5. Corticosteroids

Corticosteroid drugs — including cortisone, hydrocortisone and prednisone — are useful in treating many conditions, such as rashes, inflammation and asthma. Corticosteroids mimic the effects of hormones your body produces naturally in your adrenal glands, which are small glands that sit on top of your kidneys. When prescribed in doses that exceed your body's usual levels, corticosteroids suppress inflammation. This can reduce the signs and symptoms of inflammatory conditions, such as Irritable Bowel Syndrome

- Hydrocortisone
- Cortisone.
- Ethamethasoneb
- Prednisone
- Prednisolone (Orapred, Prelone)
- Triamcinolone

In some times Tricyclic Anti-depressants are effective in the treatment of IBS patients at low doses. They are particularly used to treat severe IBS-D (not those with constipation, since this is a side effect of Anti-depressants).

TCAs include;

- Amitriptyline
- Imipramine
- Desipramine
- Nortriptyline

PREDNISOLONE

Prednisolone is a steroid that prevents the release of substances in the body that cause inflammation.

Prednisolone is used to treat many different inflammatory conditions such as arthritis, Irritable Bowel Syndrome, ulcerative colitis, allergic disorders, gland (endocrine) disorders, and conditions that affect the skin, eyes, lungs, stomach, nervous system, or blood cells.

Prednisolone may also be used for purposes not listed in this medication guide.

6.4. Yoga

Yoga can be considered as a form of behavioral therapy and consist of general relaxation exercises, breathing exercises, focused training for abdominal relaxation and positive reinforcement by focusing thoughts on a single topic and good experiences.

6.5. Acupuncture

This is considered to relieve pain by release of endogenous opiates and triggering of serotoninergic inhibitory pathways. A study compared differences in the therapeutic effect of Tianshu acupuncture, Dachangshu acupuncture and western medication with Trimebutine maleate. Acupuncture was found to relieve symptoms of IBS.

7. AIM AND OBJECTIVE

For the past 30 years, corticosteroids have been the mainstay of therapy in patients with moderate to severe active inflammatory bowel disease. Initial treatment is prednisone, 40 to 60 mg per day. In severely ill hospitalized patients, reasonable initial therapy is prednisolone, administered intravenously every eight hours. Intravenous therapy generally produces rapid improvement of symptoms, with maximal benefit occurring when the corticosteroid has been administered for six to eight days.

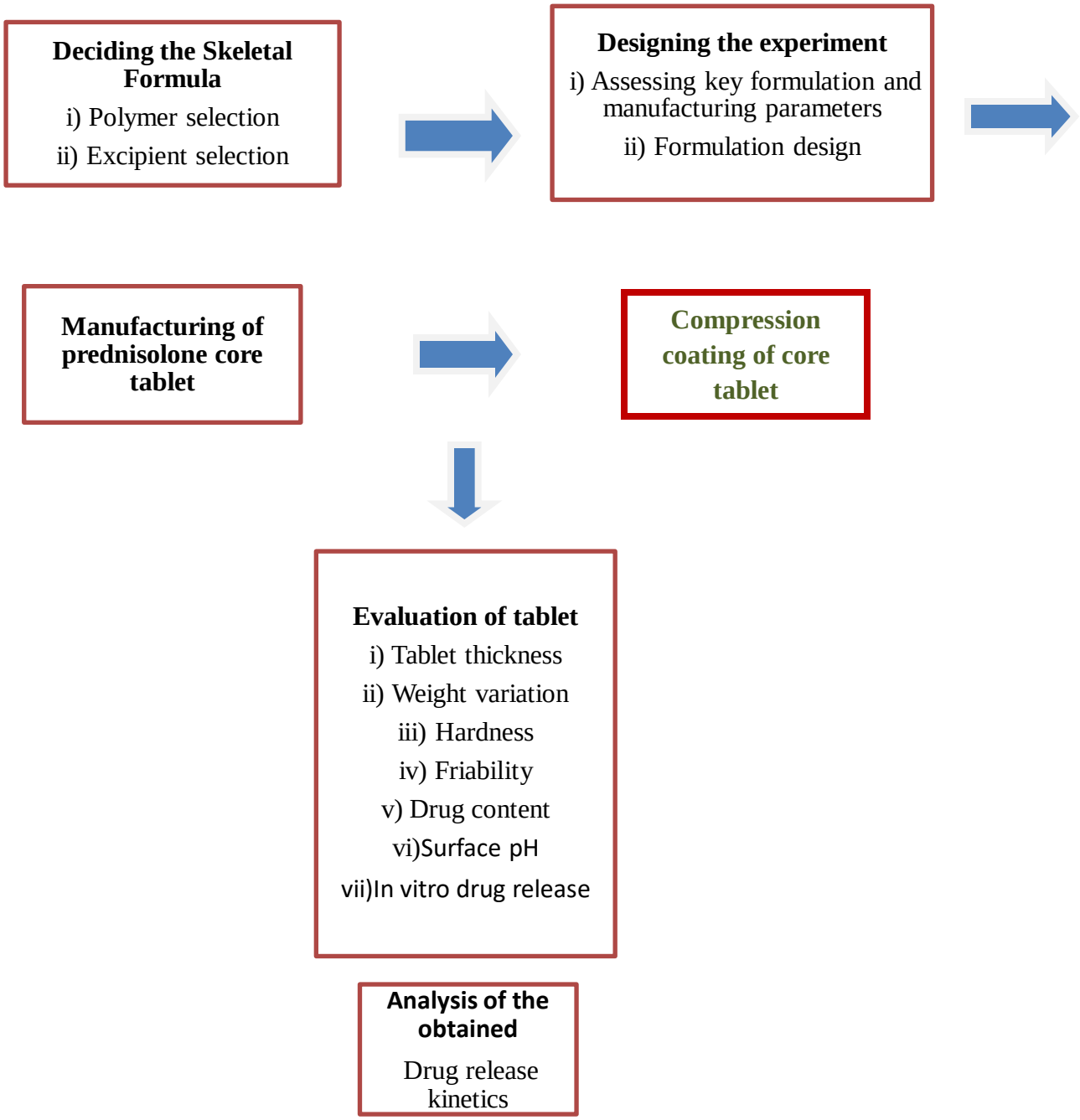
Once improvement has occurred, prednisone is tapered by 5 to 10 mg per week until the dosage is 15 to 20 mg per day. This dosage is then tapered by 2.5 to 5 mg per week until the drug is discontinued

The objective of this study was to design compression coated tablets of prednisolone for an effective and safe therapy of ulcerative colitis and inflammatory bowel disease using pectin and xanthan gum and HPMC as carriers. The core tablets of prednisolone were coated with combination of pectin: HPMC and xanthan gum: HPMC.

PLAN OF WORK

The present study focused on the formulation of pednisolone core compression coated tablet.

Flow of work



8. MATERIALS AND METHOD:

Table 7: List of Materials and their application in formulation.

S.NO.	Name of the material	Manufacturer / Supplier	Use in formulation
1	Prednisolone	Fourrts (india) Laboratories Pvt. Ltd.,	Active pharmaceutical ingredient
2	Microcrystalline cellulose	Fourrts (india) Laboratories Pvt. Ltd.,	Binding agent
3	Magnesium steate	Loba Chemie Pvt.Ltd.,	Lubricant
4	Talc	Loba Chemie Pvt.Ltd.,	Glidant
5	Xanthangum	Loba Chemie Pvt.Ltd.,	Natural polymer
6	Hydroxypropylmethylcellulose (HPMC K100)	Loba chemie Pvt.Ltd.,	Flim – forming agent
7	Pectin	Lab Chemicals	Natural polymer

Table 8: List of Equipments used.

S.No.	Equipments / Instruments	Manufacturer / Supplier
1	Electronic weighing balance	Asha Scientific Company, Mumbai
2	10 station compression machine	Cadmach India Ltd.,
3	Vernier caliper	Mitutoya, Japan
4	Monsanto Hardness tester	Standard Steel, India
5	Friabilator	Electrolab, India
6	pH Meter	MC Dalal, Chennai
7	Dissolution tester	Campbell, India
8	UV-Visible Spectrophotometer	Schimadzu, Japan.
9	Disintergration Apparatus	Electrolab, India

9.0. PREFORMUALTION STUDIES[25]

The preformulation studies are conducted to establish the physicochemical characteristics of the drug and its compatibility with the various excipients utilised in the formulation. The preformulation studies are necessary for obtaining stable, safe and effective dosage form. .

9.1.2. CALIBRATION CURVE[26]

Calibration curve of Prednisolone in Phosphate buffer pH 6.8

100 mg of Prednisolone was taken in 100 ml standard flask and it was dissolved in 5 ml of ethanol, shaken well and then the volume was made up with phosphate buffer pH 6.8. From this, dilutions were made using phosphate buffer pH 6.8to get concentrations from 2 to16 µg/ml. The absorbance of the resulting solutions were measured at 239 nm using UV visible Spectrophotometer (Shimadzu, Japan). Calibration curve was plotted in a graph using concentration in x-axis and absorbance in y-axis

9.2. FORMULATION DEVELOPMENT

9.2.1. Formulation of compression coated Core Tablets of Prednisolone

The core tablets of Prednisolone were prepared as per ingredients given in Table 9 by using direct compression method. Predinisolone was dry blended with microcrystalline cellulose and talc and compressed into tablet using Cadmach 8 station rotary tablet press.

The core tablet was then compression coated with different granular coat formulation in different ratios. Xanthan gum and HPMC were used in the ratio 1:1 and 1:2 for F1 and F2 and for F3 and F4, pectin and HPMC were used in the ratio 1:1 and 1:2. The coat formulation pellets were prepared by blending the materials and wetting it with alcohol. The wet coherent mass was then passed through sieve No.22 and dried in hot air oven at 50^0C for 2 h.

For compression coating about 45% of the coat weight granular material was first placed in the die cavity. Then the core tablet was positioned manually in the center which was then filled with the remainder 55% of the coat granular material. The coating was then compressed around the core tablet by using round flat and plain punches.

Table 9: Formulation of Prednisolone Compression Coated Tablets.

S.No.	Ingredients	Formulation Quantity per tablet (mg)			
		F1	**F2**	**F3**	**F4**
1	Prednisolone	10	10	10	10
2	Microcrystalline cellulose	39	39	39	39
3	Magnesium stearate	0.5	0.5	0.5	0.5
4	Talc	0.5	0.5	0.5	0.5
5	Xanthangum	120	140	_	_
6	Hydroxypropylmethylcellulose (HPMC K100)	30	30	30	30
7	Pectin	_	_	120	140

9.4. POST COMPRESSION STUDIES

a) General appearance

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters are shape and colour was evaluated visually.

b) Uniformity of Weight

Twenty tablets were randomly selected and weighed individually. The average weight was also measured. The percentage deviation of tablets was calculated and compared with standard specifications.

Table10: Uniformity of weight.

S.NO.	Average weight of Tablet	% Deviation
1	80mg or less	10
2	80mg to 250mg	7.5
3	More than 250mg	5

c) Thickness and Diameter

The thickness and diameter were measured to determine the uniformity of size and shape. Thickness and diameter of the tablets were measured using Vernier caliper.

d) Hardness

Hardness was defined as the force required for breaking a Tablet at diametric compression test and it was termed as "Tablet Crushing strength". Hardness of the prepared formulations was determined using Monsanto Hardness Tester. It was expressed in kg/cm^2.

e) Friability

Friability of the prepared formulations was determined by using Roche friabilator. Pre-weighed sample of Tablets was placed in the friabilator, which was then operated for 100 revolutions, Tablets were de-dusted and re-weighed. The friability of the tablets was calculated using the formula mention below,

$$\%\text{Friability} = \frac{(\text{Initial weight of tablet} - \text{final weight of the tablet})}{\text{Initial weight of tablet}} \times 100$$

f) *In-vitro* drug release study

For Prednisolone core tablet

The *in-vitro* drug release study of core tablets were done by using USP Type-II (Paddle) Dissolution apparatus under sink condition. 900 ml of phosphate buffer pH 6.8 was used as a dissolution medium. Stirring rate was maintained at 75 RPM and the temperature was 37ºC±0.5ºC. The samples were withdrawn from the dissolution medium at various time intervals and the same volume of fresh medium was replaced for each and every sampling. Then the

samples were analyzed by UV-Visible Spectrophotometer(Shimadzu, Japan)using phosphate buffer pH 6.8 as blank at 234 nm.

For Prednisolone compression core tablet

The ability of the prepared compression-coated tablet formulation to prevent or remain intact with respect to time in the physiological environment of stomach and small intestine in pH conditions prevailing in stomach and small intestine was assessed by in vitro drug release in the USP dissolution test apparatus.

The USP paddle method at 37ºC±0.5ºC, 75 rpm were used to determine dissolution profile of the tablet using two consecutive media: 900 ml of 0.1 N hydrochloric acid for 2 h, followed by 900 ml of pH 6.8phosphate buffer solution in the presence and absence of rat cecal content (4%).

Preparation of rat cecal medic.

Rats were anesthetized and killed. The abdomen were opened, ceca were traced, ligated at both the ends, dissected and contents were pooled and added to the pH 6.8 phosphate buffer. The solutions were finally added to the dissolution media to give a final cecal dilution of 4% w/v.

9.4.1. APPLICATION OF RELEASE RATE KINETICS TO DISSOLUTION DATA

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into Zero order, First order, Higuchi, Hixson-Crowell release model and Korsmeyer-Peppas release model.

1. Zero order equation

The zero order release can be obtained by plotting cumulative % percentage drug release versus time. It was ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C=K_0t$$

Where, K_0 = Zero order constant

t = Time in hours

2. First order equation

The graph was plotted as log % cumulative drug remaining vs time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where, C_0 = Initial concentration of drug

K = First order

t = Time in hours

3. Higuchi kinetics

The graph was plotted with % cumulative drug release vs. square root of time

$$Q = Kt^{½}$$

Where, K = constant reflecting design variable system (differential rate constant)

t = Time in hours

4. Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppasequation as log cumulative % of drug released (vs) log time.

$Mt/M\alpha = Ktn$

Where,

$Mt/M\alpha$= Fraction of drug released at time t

t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

Table11. Release mechanisms based on n-value

Release mechanisms	**n-value**
Fickian diffusion	$n<0.5$
Non-Fickian transport	$0.45<n<0.89$
Case II transport	$n=0.89$
Super case II transport	$n>0.89$

The n value obtained is used to characterize different release mechanisms for cylindrical shaped matrices.

5. Hixson and Crowell erosion equation

$$\mathbf{Q_o^{1/3} - Q_t^{1/3} = K_{HC} t}$$

Where,

Q_t = Amount of drug released at time t

Q_o = Initial amount of drug

K_{HC} = Rate constant for Hixson Crowell equation

10. RESULT AND DISCUSSION

10.1. CALIBRATION CURVE OF PREDNISOLONE

Linearity and Calibration- The linearity of the calibration curve was estimated by plotting the graph of absorbance (nm) (y) versus concentration (µg/ml) (x) in the concentration range 2-16 µg/ml. A calibration curve was prepared by measuring the absorbance at 239 nm. The results are shown in Table 12 and represented graphically in Fig. 4.

Values of linear regression analysis gave the equation for the line of best fit as y = 0.051x + 0.031. Linearity was observed in the concentration range between 2 to 16 µg/ml. The R^2 values are 0.995.

Table 12: Data for Calibration Curve of Prednisolone.

Concentration (mcg/ml)	Absorbance
0	0
2	0.142
4	0.264
8	0.456
12	0.654
16	0.842

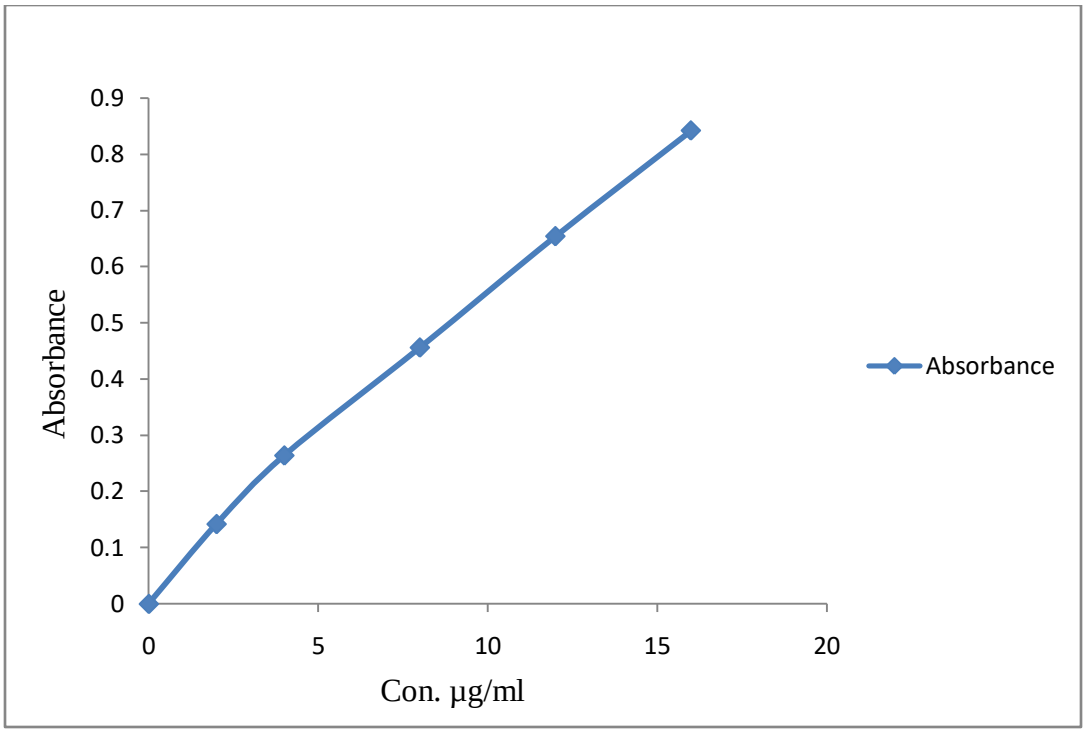


Fig 4: Standard curve of prednisolone in pH 6.8

10.1.2. POST COMPRESSION STUDIES:

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated Tablets was given in Table 13

Table 13: Uniformity of weight for each tablet

S.NO.	Formulation code	Uniformity of weight* (mg)
1	F1	197.8±3.62
2	F2	221.5±3.99
3	F3	200.6±2.98
4	F4	223.1±2.12

THICKNESS:

The Thickness of the formulated Tablets was given in the table 14.

Table 14: Thickness for each tablet

S.NO.	Formulation code	Thickness (mm)
1	F1	2.5±0.125
2	F2	2.7±0.254
3	F3	2.6±0.546
4	F4	2.7±0.234

HARDNESS

The Hardness of the formulated Tablets was given in the Table15.

Table 15: Hardness of formulated prednisolone tablet

S.NO.	Formulation code	Hardness (kg/cm^2)
1	F1	5.2±0.046
2	F2	5.9±0.057
3	F3	5.5±0.057
4	F4	5.8±0.054

The formulated Tablets have uniform Thickness

FRIABILITY

The Friability of the formulated Tablets was given in the Table16.

Table 16: %friability of formulated tablet

S.NO.	Formulation code	Friability (%)
1	F1	0.164
2	F2	0.025
3	F3	0.127
4	F4	0.235

The percentage friability of all the formulation was within the Pharmacopoeial limits.

DRUG CONTENT

The Drug content of the formulated Tablets was given in the Table17.

Table 17: % Drug content of formulated tablet

Formulation	Drug content (%)
F1	98.04±0.256
F2	99.30±0.102
F3	98.91±0.77
F4	97.05±0.084

The percentage drug content of all the formulations ranges from 95.04 % w/w to 99.30 % w/w. It complies with the official monograph of the drug

All the tablets met the IP requirements for weight variation, friability and drug content. They were within the compendial limits.

10.2. IN VITRODRUG RELEASE STUDY CORE TABLET

The in vitro drug release study of core formulations of prednisolone using buffer pH 6.8 are given in the Table18.

Table 18: Drug release study of formulated core tablet

Time (min)	Core tablet
0	0
30	12.21
60	29.05
90	36.68
120	45.79
150	58.56
180	72.18

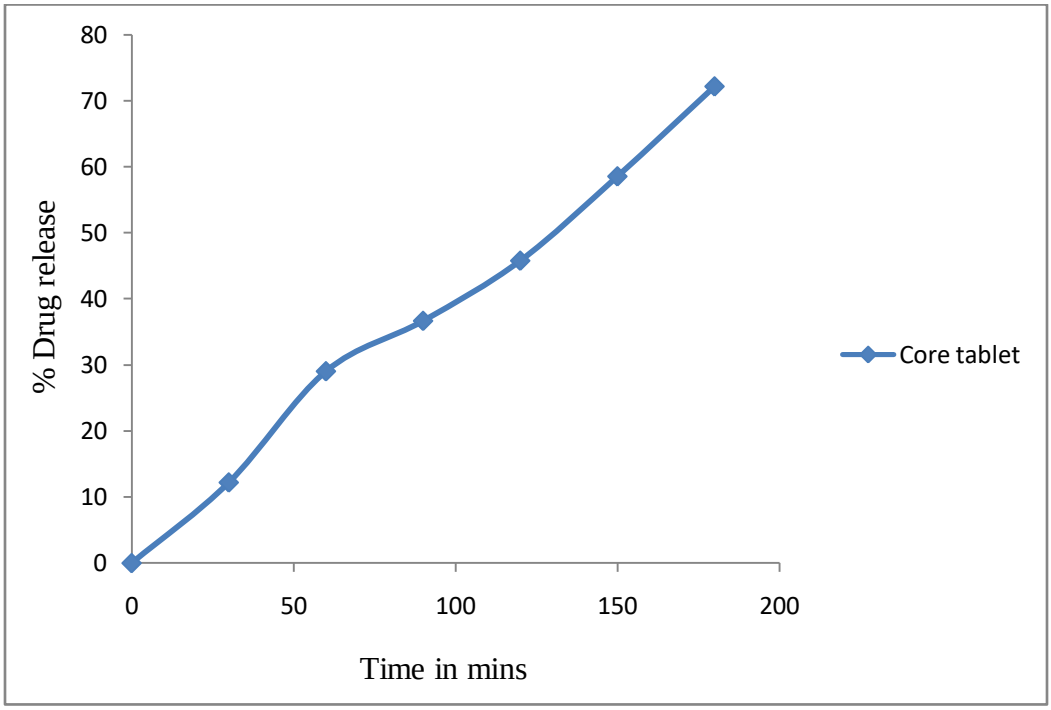


Fig 5: In vitro study of prednisolone core tablet in pH6.8

The in vitrodrug release study of formulations of predisolone using 0.1N hydrochloric acid and buffer pH 6.8without rat cecal content are given in the Table 19.

Table 19: Drug release of formulated tablet

Time (Hrs)	**Percentage drug release (%)**			
	F1	F2	F3	F4
0	0	0	0	0
1	5.25	4.38	5.50	3.51
2	10.42	9.56	10.89	10.46
3	18.05	17.81	21.10	19.82
4	21.14	25.11	29.21	26.24
5	32.43	30.54	36.81	35.68
6	40.30	40.07	47.88	45.01

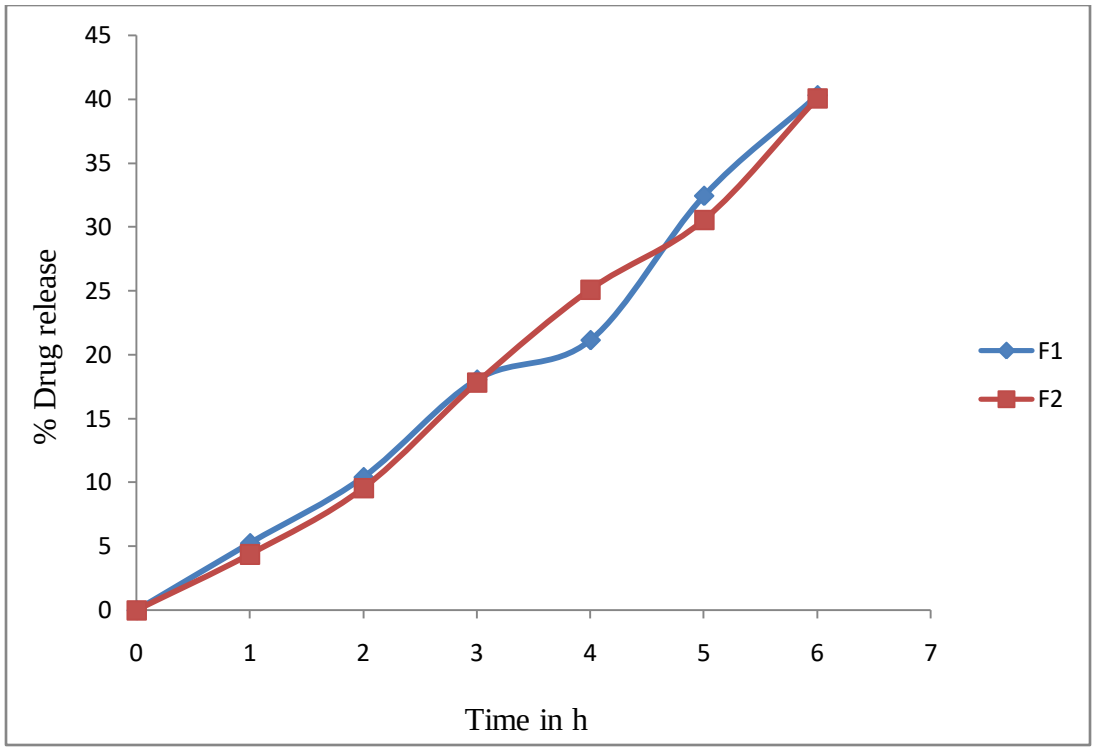


Fig 6: In vitro study of prednisolone in 0.1N hydrochloricacid and pH 6.8 buffer

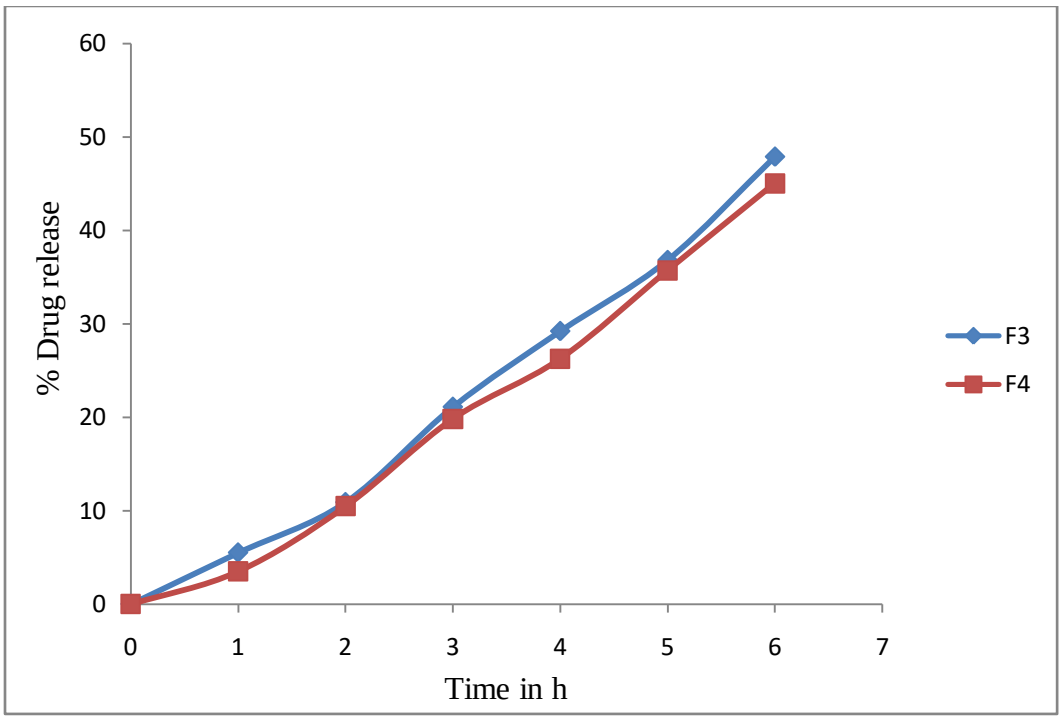


Fig 7: In vitro drug release study of prednisolone using 0.1N hydrochloricacid and buffer pH6.8

The *in-vitro* drug release study of compression coated formulations of prednisolone using rat caecal with buffer pH 6.8is given in the Table 20.

Table20: Drug release of formulated tablet in rat caecal content

Time (Hrs)	**Percentage drug release (%)**			
	F1	F2	F3	F4
0	0	0	0	0
1	5.91	5.32	6.24	4.50
2	7.87	7.15	8.75	8.01
3	38.75	43.29	40.5	45.71
4	50.75	55.69	52.5	62.03
5	58.7	60.7	68.32	73.97
6	62.3	65.12	80.34	88.22

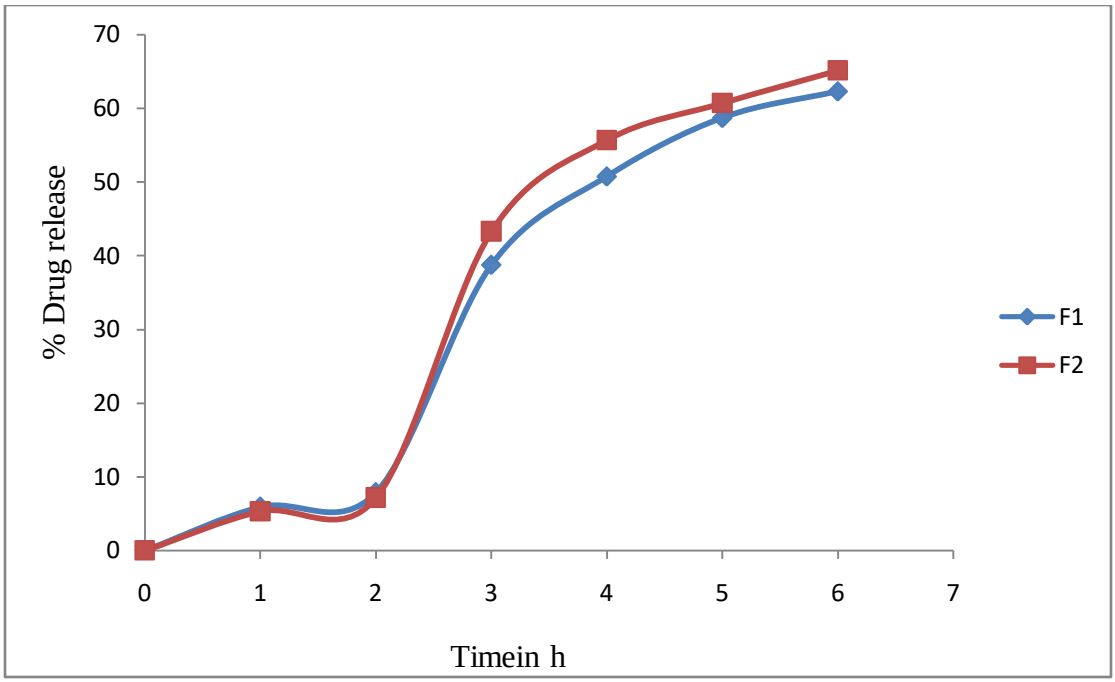


Fig 8: In vitro %drug release in rat caecal with buffer pH 6.8

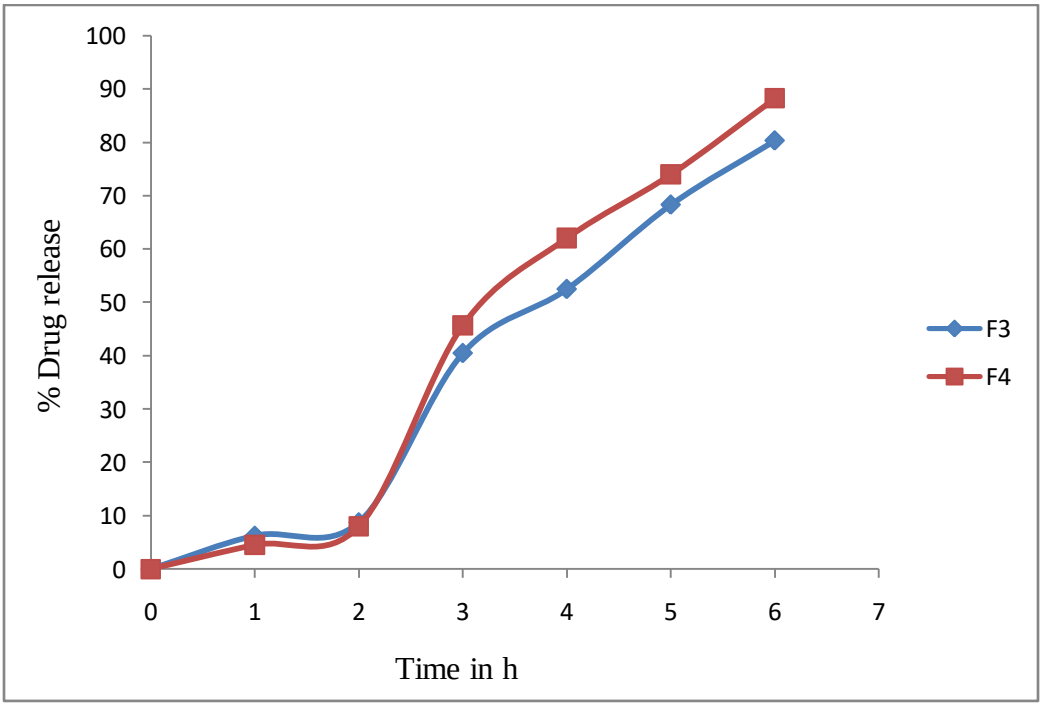


Fig 9: In vitro %drug release in rat caecal with buffer pH 6.8

The drug release from the core formulation in pH 6.8 buffer was 72.18 % in 3 h. The mean drug release from the tablets F1, F2, F3 and F4 after the first 2 h was between 9.56 to

10.89 % respectively. At the end of 6 h the mean % drug release was respectively in pH 6.8 buffer was between 40.3 to 52.01%. While in rat caecal medium at 6 h the mean % drug release was increased to 88.22 % respectively for F4. The maximum drug release after 6 h in rat caecal medium was significantly higher ($p< 0.05$) in comparison with the drug release in control medium. This can be explained as the release of prednisolone in the physiological environment of colon is due to pectinolytic enzyme. The results showed that the degradation was very efficient with pectinolytic enzyme.

The addition of HPMC also helped in the significant increase in the mean % drug release in the presence of rat caecal content in formulation mainly with pectin. The increase in drug release could be explained due to HPMC which creates a porous structure of the coat and consequently increase drug leaching and release. F4 was chosen for kinetic studies. The release kinetic parameters are listed in Table 21.

Table21: Release kinetics and mechanism

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon-crowell (R^2)	Korsmeyer-Peppas		Possible drug release mechanism
					(R^2)	N	
F4	0.938	0.911	0.9835	0.799	0.9465	0.521	Non Fickian transport

10.3. RELEASE KINETICS AND MECHANISM

The formulated colon targeted release dosage form provides the burst release after 2 h when the pH of the medium becomes 6.8. The kinetics of drug release for the prednisolone compression coated tablet F4 was helpful to know whether the maximum amount drug reaches to the colon from the formulated tablets which pass through the upper part of GIT in a controlled manner or not. The release kinetics of F4 is shown in the Table 21. In zero order plot the r^2 value obtained is 0.938 and first order gave 0.911 describing the drug release rate relationship with concentration of drug. The best linearity was found in Higuchi's equation plot with r^2 indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion. The values of n was 0.521 which is closer to 0.5 indicates Fickian diffusion.

11. SUMMARY AND CONCLUSION

Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are needed most, and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine. The drugs used in the treatment of Irritable bowel syndrome, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection.

Compression coating has gained increased interest in the recent years for creating modified released products. It involves the compaction of granular materials around a preformed tablet core using specially designed tableting equipment. Compression coating is a dry process. This type of tablet (compression coated tablet) has two parts, internal core and surrounding coat. The core is a small porous tablet and prepared on one turret. For preparing the final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied.

Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that involve chronic inflammation of your digestive tract. Types of IBD include:

- **Ulcerative colitis.** This condition causes long-lasting inflammation and sores (ulcers) in the innermost lining of your large intestine (colon) and rectum.
- **Crohn's disease.** This type of IBD is characterized by inflammation of the lining of your digestive tract, which often spreads deep into affected tissues.

Both ulcerative colitis and crohn's disease usually involve severe diarrhea, abdominal pain, fatigue and weight loss.

IBD can be debilitating and sometimes leads to life-threatening complications.

For the past 30 years, corticosteroids have been the mainstay of therapy in patients with moderate to severe active inflammatory bowel disease. Initial treatment is prednisone, 40 to 60 mg per day. In severely ill hospitalized patients, reasonable initial therapy is hydrocortisone, 100 mg administered intravenously every eight hours. Intravenous therapy generally produces rapid improvement of symptoms, with maximal benefit occurring when the corticosteroid has been administered for six to eight days.

Once improvement has occurred, prednisone is tapered by 5 to 10 mg per week until the dosage is 15 to 20 mg per day. This dosage is then tapered by 2.5 to 5 mg per week until the drug is discontinued

The objective of this study was to design compression coated tablets of Prednisolone for an effective and safe therapy of ulcerative colitis and inflammatory bowel disease using pectin and xanthan gum and HPMC as carriers. The core tablets of Prednisolone coated with pectin: HPMC in the ratio 1:1 and 1:2 and xanthan gum: HPMC in the ratio 1:1 and 1:2 .

Pectin: HPMC coated pellets offer a greater degree of protection from premature drug release in the upper GI tract than pectin alone. The pectin is still available for enzymatic degradation, which allows greater drug release under conditions that may be expected to pertain in the colon. It is possible by careful formulation of the compression coated tablet to have different drug release profiles, whereby an increase in the amount of drug released can be induced by the action of pectinolytic enzymes. By changing the other variables such as the pectin and HPMC ratio or the molecular weight of the polymers, it may be possible to produce a system with a release profile, which is tailored to meet the particular requirements of any individual drug. From the results it can be concluded that pectin: HPMC coated tablets could be used to treat the inflammatory conditions of the colon.

Natural polysaccharides such as xanthan gum, are not digested in the human stomach or small intestine, but are degraded in the colon by resident bacteria. HPMC delayed the drug release in the small intestine, but was degraded by colonic bacterial enzymes thereby releasing the drug. Xanthan gum is a high molecular weight extracellular polysaccharide. The molecule consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymer, which until recently had been limited for use in thickening,

suspending and emulsifying water based systems. It appears to be gaining appreciation for fabrication of matrices, as it not only retards drug release, but also provides time- independent release kinetics with added advantages of biocompatibility and inertness.

Based on drug release in the colon compressed coated tablets with mixture of pectin was more successful to produce a drug targeting to the colon with minimum amount released in the other parts of gastro intestinal tract.

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