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Colon targeted drug delivery systems: A boon for the treatment of inflammatory bowel disease

Laxmi Bhumarkar and Umesh Patil

Abstract
Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. It is a spectrum of chronic, inflammatory conditions of the gastrointestinal (GI) tract. It is conventionally divided into two main subtypes: CD and UC. If inflammation affects the entire digestive tract called CD and if inflammation affects only in the large intestine called UC. Medications are used to treat symptoms caused by bacteria H. Pylori; highly acidic environment in bowel, foreign substances (Antigens) may be the direct cause of inflammation, changes in the endothelial blood vessel lining. It is an anti-inflammatory drug that works by lowering the inflammation in the colon. Sustained release, dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing therapeutic agents over an extended period of time after administration of a single dose. The basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and nontoxic for an extended period of time. Systems provide medication over an extended period.

Keywords: Colon targeted drug delivery, intestinal microflora, Crohn's disease, IBD

Introduction
Ongoing research in the area of oral delivery of drugs, a discipline which has basked in the spotlight of pharmaceutical sciences for the past 70 years, has led to improved and profound insights into the physiology, biology and physical chemistry (pharmacokinetics, partitioning phenomenon) of organs, compartments, cells, membranes, cellular organelles and functional proteins (e.g. transporters) associated with absorption processes of drugs in the gastrointestinal tract (GIT). Majority of the research has focused on delivery of drug to the small intestine. The large intestine, however, because of its remoteness and relatively different physiology acquired the status of an outcast. From last two decades, interest in area development of oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders (Rubinstein A *et al*., 2005) [41]
Colonic delivery offers several potential therapeutic advantages as a site for drug delivery:

a) The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.
b) The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.
c) The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
d) Reduced proteolytic activity in the colon may be helpful in achieving reasonable absorption of certain drugs that are enzymatically labile in small intestine.
e) Reduced fluid motility and motility in the colon when compared with small intestine is advantageous formulation consists of multiple components such as permeation enhancers that must reach epithelial layer to achieve close spatial proximity with each other.
f) The colonic region has somewhat less hostile environment with less diversity and less intensity of activity as compared to stomach and small intestine. (Ashford M *et al*., 2005),

Targeting of drugs to the colon is of increasing importance for local treatment of inflammatory bowel diseases (IBD) of the colon such as ulcerative colitis and crohn's disease (CD). (Ashford M *et al*., 2005), The prevalence of ulcerative colitis and CD ranges from 10 to 70 per 100,000 people, but recent studies in Manitoba, Canada, and Rochester, have shown prevalence a high as 200 per 100,000 people. (Loftus EV Jr, *et al*., 2005),

If the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted on the colon. Site-specific means of drug delivery could also allow oral administration of peptide and protein drugs, which normally become inactivated in the upper parts of the gastrointestinal tract. (Yang, *et al*., 2005), CTDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis Colonic drug delivery can be achieved by oral or rectal administration. With regard to rectal route, the drugs do not always reach the specific sites of the colonic disease and the sites of colonic absorption. To reach the colon and to be able to specifically deliver and absorb the drug there, the dosage form must be formulated taking into account the obstacles of gastrointestinal tract. (Crcarevska MS, *et al*., 2005).

Factors to be considered in designing CTDDS: Formulations for colonic delivery are, in general, delayed-released dosage forms which may be designed either to provide a 'burst release' or a sustained / prolonged / targeted. Factors to be considered for designing CTDDS are explained below:

(A) Anatomy and physiology of colon: (Bauer KH, *et al*., 2005),

Parts: the duodenum, the jejunum, and the ileum. Enzymes and other substances made by intestinal cells, the pancreas, and the liver are secreted into the small intestine and breakdown starches, sugars, fats, and proteins. Absorption of nutrients occurs through the millions most digestion and absorption occurs in the small intestine. The small intestine has 3 of tiny fingerlike projections called villi and the even tinier projections on the villi called microvilli. Any undigested material moves to the large intestine. The large intestine has 3 parts: the cecum, the colon, and the rectum. The main function of the large intestine is to remove water and salts (electrolytes) from the undigested material and to form solid waste (feces) that can be excreted. The remaining contents of the large intestine move to the rectum, where feces are stored until they leave the body through the anus as a bowel movement (Fig. 1 shows anatomy of GI Tract).

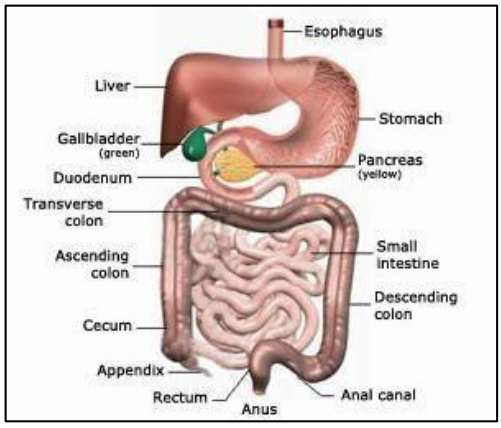

Fig 1: Anatomy of Gastrointestinal tract (Myers D. *et al*., 2005)

In mammals colon is further subdivided into the ascending colon, transverse colon, the descending colon and the sigmoid colon. The colon from cecum to the mid transverse colon is also known as the right colon. The remainder is known as the left colon. The location of the parts of the colon is either in the abdominal cavity or behind it in the retro peritoneum.

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

Transverse colon

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

Descending colon

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

Sigmoid colon

The sigmoid colon is the part of the large intestine after the descending colon and before the rectum. The name sigmoid means S-shaped. The walls of the sigmoid colon are muscular, and contract to increase the pressure inside the colon, causing the stool to move into the rectum.

(B) pH of the colon

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

(C) Colonic micro flora: (Kapoor VK, *et al*., 2005)

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, theses enzymes are derived from

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

Intestinal microflora count: 103 CFU/ml. Colonic microflora count: 1012 CFU/ml.

Classification of CTDDS: CTDDS can be classified as follows

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

1) pH dependent systems: (Spitael J, *et al*., 2005)

pH of human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to 7-8 in the distal ileum.

The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the Ileocecal junction.

These processes distribute the drug throughout the large intestine and improve the potential of CTDDS.

Disadvantages of pH dependent systems:

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

2) Time dependent systems: (Kinget R, *et al*., 2005)

Strategy of time released system is to resist the acidic environment of stomach and release the drug after predetermined lag time, after which release of drug take place.

Factors affecting release from time dependent systems:

Residence time plays a key role here along with it Fed and fasted state of the subject and the Interdigestive phase may prolong emptying time of stomach.

- Residence time of stomach (approx.) – 2 h.
- Small intestine (approx.) – 2 to 4 h

Disadvantages of time dependent systems:

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

3) Bacterial enzyme dependent system:

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

4) Covalent linkage of the drug with a carrier: (Chourasia MK, *et al*., 2005)

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine.

This approach chiefly involves the formation of prodrug, which is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug. Fig. 2 shows Colon targeting by prodrug approach. The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon. Site specific drug delivery through site specific prodrug activation may be accomplished by the utilization of some specific property at the target site, such as altered pH or high activity of certain enzymes relative to the non-target tissues for the Prodrug conversion.

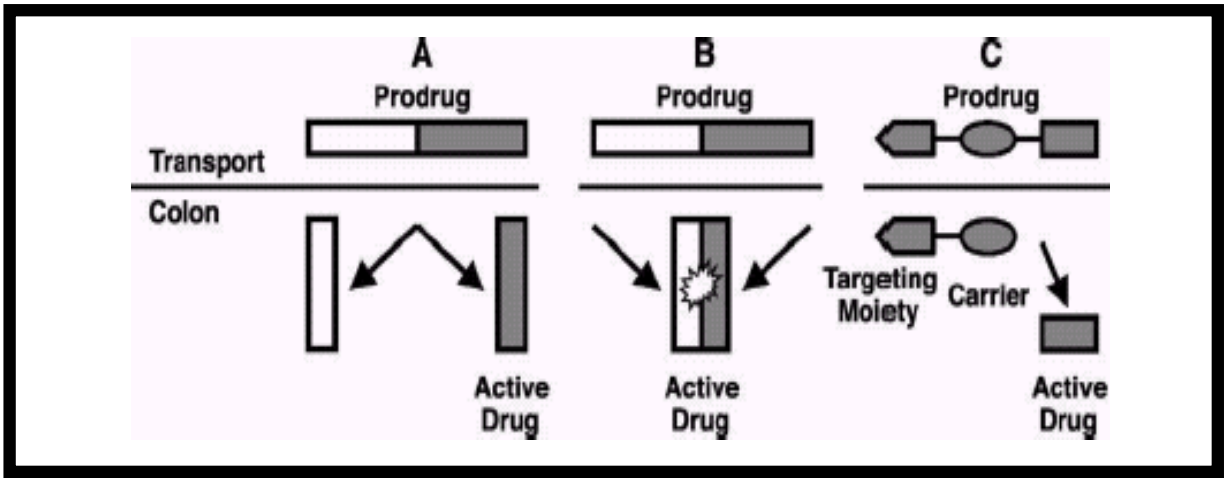

Fig 2: Colon targeting by Prodrug approach (Chourasia MK, *et al*., 2005)

5) Redox sensitive polymers

Under anaerobic conditions, bacterial azo reduction by enzymatically generated reduced flavins where the initial substrate thought to be involved in cellular electron transport requires the presence of NADPH as its electron source.

As NADPH is oxidized, the electron mediator (reduced flavins) acts as an electron shuttle from the NADPH dependent flavoprotein to the azo compound.

Reduction of the azo bond to the hydroazo intermediate requires a low electron density within the azo region, and thus substitution of electron-withdrawing groups will favor this reaction.

Redox potential is an expression of the total metabolic and bacterial activity in the colon and it is believed to be insensitive to dietary changes.

The mean redox potential in proximal small bowl is - 67 90 mv, in the distal small bowl is -196 97 mv and in the colon is -145 72 mv.

Microflora-induced changes in the redox potential can also be used as a highly selective mechanism for targeting to the colon.

6) Bio adhesive systems

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Dissolution of dosage form and simultaneous absorption from upper GIT lead to low Intracolonic drug concentration as well as absorption of drugs result in the generation of side effects. Bio adhesion is a process whereby drug remains in contact with a particular organ for a longer period of time. It may be used for improved absorption of poorly absorbable drugs. Polymers: polycarbophils, polyurethanes and poloxamers. (Chickering DE, *et al*., 2005)

7**) Coating with micro particles:** (Mathiowitz E, *et al*., 2005) It consists of small silica particles (5-10 µm in diameter) covalently linked to a drug.

8) Osmotic controlled drug delivery: (Mirelman D, *et al*., 2005)

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

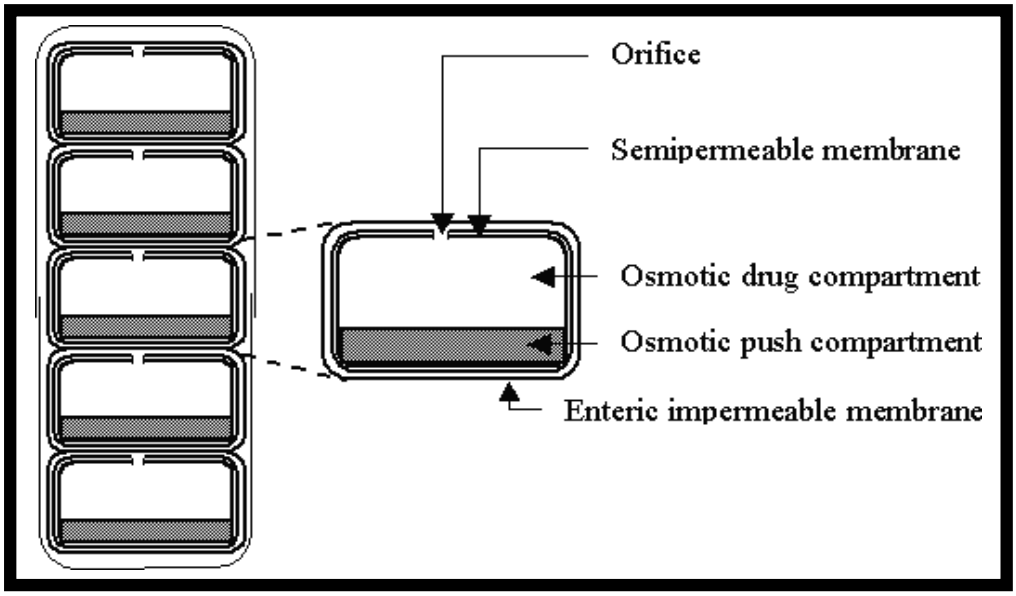

Fig 3: Osmotically controlled CTDDS (Jain SK. *et al*.)

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

It is well recognized that peptides and proteins are well absorbed intact from the gastrointestinal tract, but the bioavailability is invariably extremely low, with exceptions, such as di and tripetide analogues and cyclosporine. (Smith PL, *et al*., 2005)

Crohn's Disease (CD) And Ulcerative Colitis (UC)

BD is a group of inflammatory conditions of the colon and small intestine. It is a spectrum of chronic, inflammatory conditions of the gastrointestinal (GI) tract. It is conventionally divided into two main subtypes: CD and UC. If inflammation affects the entire digestive tract called CD and if inflammation affects only in the large intestine called UC.

Fig. 4 shows colon in normal condition and infected condition in UC. Some organizations such as World Gastroenterology Organization (WGO), American Gastroenterological Association (AGA), International Organization for the Study

of Inflammatory Diseases (IOIBD) and the European Crohn's and Colitis Organization (ECCO) etc. estimate that as many as 5 million people worldwide are living with IBD. Both UC and CD can affect individuals of any age but they are mostly diagnosed in patients aged between 15 and 30 years. (Daniel C. Baumgart *et al*. 2011) In the Western world, the number of new cases of IBD diagnosed each year (incidence rate) has been estimated to be about seven per 1,00,000 (Ghosh *et al*., 2000) [16], with over 200 people per 100,000 living with UC at any given time. A various number of dosage forms such as powders, granules, tablets, capsules etc. are used to deals with IBD.

Etiology

Despite of scientific efforts during the last decades, etiology and pathogenesis of the major inflammatory bowel diseases, namely

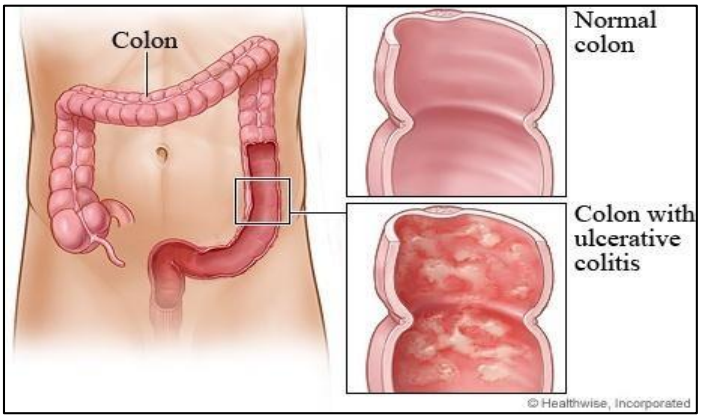

Fig 4: Shows normal colon and UC infected colon.

Crohn's disease and ulcerative colitis, remain rather unclear. Fig. 5 showed main causes of IBD. Three characteristics define the etiology of inflammatory bowel disease (IBD): (Schmidt C *et al*. 2005) [42]

1) Genetic predisposition;
2) An altered, dysregulated immune response; and
3) An altered response to gut microorganisms.

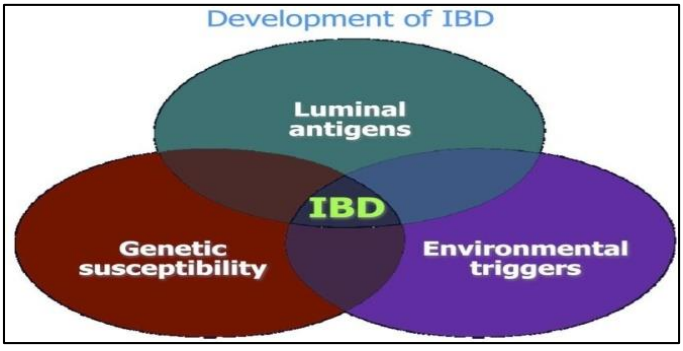

Fig 5 Causes of IBD

No mechanism has been found as the primary cause, but many postulates are described such as

1. **Immune system:** Bacteria may stimulate the immune system to produce inflammation. An inappropriate and excessive response to dietary triggers, unidentified infectious agents or the normal colonic bacterial population (Kovvalin and Das, 2005) by an inadequately regulated mucosal immune system are thought to play a major path physiological role in the chronic inflammation and manifestation of symptoms of UC and CD.
2. **Hypercoagulability:** Abnormality of Blood Coagulation that increases the risk of Thrombosis, and chronic infection of sub mucosal endothelium of the intestines with the measles virus. Changes in the Endothelial blood vessel lining.(Wakefield *et al*. 1998)
3. Various environmental and host factors (e.g. Genetic, epithelial, immune and non- immune) are involved in the pathogenesis of IBD, even though the exact mechanism by which the intestinal mucosa loses tolerance to its bacterial neighbors remains elusive.
4. In addition to environmental factors, genetic predisposition, stronger in CD than in CD, also seems nowadays to play a key role in the pathology. The genetic aspect of research is quite focused on numerous chromosomal loci. Important insights into pathogenesis also have emerged from genetic analyses of CD.
5. **Genetic predisposition:** More than 100 potential susceptibility genes identified. Genes involved in the ability to recognize bacteria (e.g., NOD2) nucleotide-binding oligomerization domain-2 (NOD2/CARD15).and autophagy (e.g., ATG16L1) is an intracellular element responsible for the indirect recognition of bacterial peptidoglycan through the binding of muramyl dipeptide, thereby playing an important role in the natural immunity to bacterial pathogens (Hugot *et al*., 2001).
6. **Environmental triggers:** Foreign substances (antigens) may be the direct cause of inflammation. (Dalwadi *et al*. 2001).
7. Pseudomonal protein I2 and a flagellin protein, respectively, as dominant super antigens that induce the TH1 response in Crohn's disease. Lodes *et al*. (2004), thus, these converging experimental approaches are generating new insights into the pathogenesis of Crohn's disease that soon may translate into novel therapeutic approaches to IBD.

8. Other approaches are

Other early ''vaccines,'' based on a specific infectious etiology of IBD, included injections of

- Polyvalent anti dysentery vaccine (AF Hurst, Guy's Hospital, London) and typhoid vaccine.
- With the advent of antibiotics, the idea of a bacterial etiology was pursued with great optimism but only temporary benefit at best.
- Numerous other specific bacterial agents have been advanced as the causative agent of IBD, including Pseudo monas maltophilia, and Helicobacter hepaticas or pylori species. Those specific infectious agents, more recently, which gained support based on some evidence includes Mycobacterium avium par tuberculosis (MAP) and measles. MAP has been proposed by numerous groups as the causative agent of CD. (Joshua R.*et al*. 2005) [20]

Pathogenesis Approach in Cd & Uc

CD may irregularly affect the entire GI tract, even though most commonly the small intestine and the area adjacent to the ileocecal valve. The inflammation in CD is not necessarily confluent and its transmural nature may lead to fibrosis and strictures or, alternatively, to fistulas formation. Conversely, UC is characterized by confluent mucosal inflammation of the colon starting at the anal verge and extending proximally for a variable extent (e.g. colitis, left- side colitis, pan colitis). From

a histological point of view, the transmural lesions in CD exhibit marked infiltration of lymphocytes and macrophages, granuloma formation and sub mucosal fibrosis, whereas the superficial lesions in UC have lymphocytic and neutrophilic infiltrates. Within the diseased bowel in CD, the cytokine profile includes increased levels of interleukin- 12 (IL-12), interferon-γ, and tumor necrosis factor-α (TNF-α), findings characteristic of T- helper 1 (TH1)–mediated inflammatory processes.

Clinical Signs and Symptoms

IBD is a chronic, intermittent disease. Symptoms range from mild to severe during relapses and may disappear or decrease during remissions. In general, symptoms depend on the segment of the intestinal tract involved.

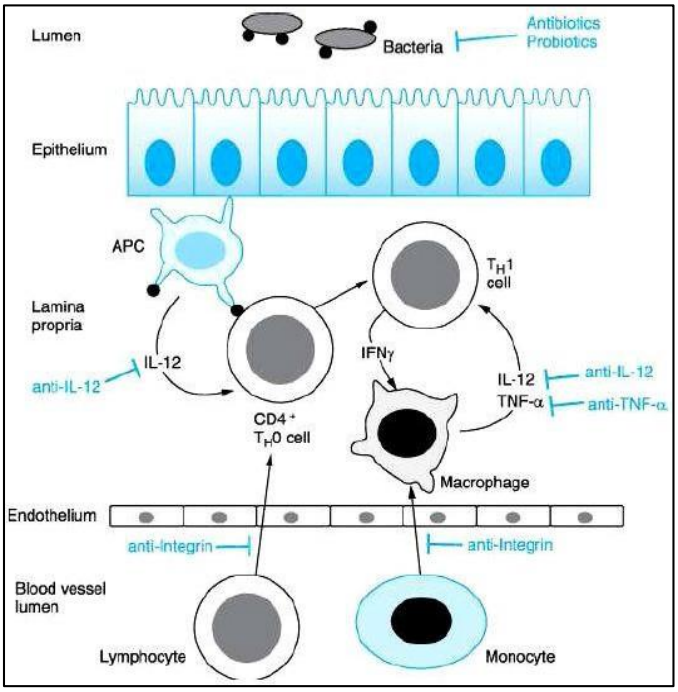

Fig 6: Proposed pathogenesis of IBD and target sites. (Sellin *et al*., 2006.) [43].

Symptoms related to IBD in the digestive tract

- Diarrhea- Stool may contain mucus or blood.
- Constipation.
- Pain or rectal bleeding with bowel movement.
- Severe bowel movement urgency.
- Abdominal cramps and pain- In the right lower quadrant of the abdomen common in CD, or around the umbilicus, in the lower left quadrant in moderate to severe UC
- Nausea and vomiting may occur, but more so in CD than UC. (Charles N. Bernstein *et al*. 2009) [5].
- General symptoms associated in CD and UC:
- Fever.

Loss of appetite

- Weight loss.
- Fatigue.
- Night sweats.
- Growth retardation.
- Rectal Bleeding.
- Abdominal Pain.
- Severe internal cramps/muscle spasms in the region of the pelvis.
- Anorexia, Nausea, Vomiting.
- Anemia is the most prevalent extra intestinal complication of inflammatory bowel disease.
- Associations with Deep vein thrombosis (DVT) and Bronchiolitis obliterans organizing pneumonia (BOOP).

IBD Management &Treatments

The following interventions were considered:

- Oral 5-ASA drugs (e.g., sulfasalazine, mesalamine)
- Oral traditional corticosteroids (e.g., prednisone or prednisolone)
- Immunosuppressive therapy (e.g., azathioprine, 6-mercap-topurine (6-MP),
- Biological therapies (e.g., infliximab, adalimumab, etanercept, certolizumab)
- Antibiotic therapy (e.g., antimycobacterial drugs, metronidazole)
- Diarrhea - bulking agent, loparamide, cholestyramine
- Pain/cramping - dicyclomine/bentyl, donnatal, and hyoscyamine.
- Constipation - bulking agent, milk of magnesia.
- Identify and correct precipitating factors (lactose intolerance, anxiety disorder, etc).
- Diet therapy.
- Drug therapy – In this Therapy used various solid dosage forms such as - Pellets, Tablets, Capsules, and Granules etc. In overall therapies Granule therapy is Most Convenient Therapy for Sustained Release of drug. (Nicholas J. *et al*. 2011)

Sustained Release (SR) Of Dosage Form - Concept

- Sustained release, dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing therapeutic agents over an extended period of time after administration of a single dose.
- The basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. (Girish K Jani, 2009). Systems provide medication over an extended period. With the goal of maintaining therapeutic blood levels.
- In the case of orally administered forms, the period is measured in hours and critically depends on the residence time of the dosage form in the gastrointestinal (GI) tract. SR systems include any drug-delivery system that achieves slow release of drug over an extended period of time. (Navin Dixit *et al*. 2005)

Merits of SR system

Following merits of sustained release system over conventional system

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient.
- The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced, because a more even blood level can be maintained.
- Better control of drug absorption can be attained, since the high blood level peak that may be observed after administration in an extended action form
- The characteristic blood level variations due to multiple dosing of conventional dosage form can be reduced.
- The total amount of drug administration can be reduced, thus

a) Maximizing availability with minimum dose.

b) Minimize or eliminate systemic side effects.
c) Minimize drug accumulation with chronic dosing 8 Improve efficacy in treatment.
- Cure or control condition more promptly
- Improve/ control i.e. reduce fluctuation in drug level.
- Avoid problems of drugs have a narrow therapeutic index - (small difference between toxic level and therapeutic level)

✓ Requires multiple dosing.
✓ Poor patient compliance.

- Avoid danger of systemic toxicity with more potent drugs.
- Targeted delivery is possible.
- The total amount of drug administered can be reduced, thus maximizing availability with a minimum dose.
- Minimize drug accumulation.
- Increasing the duration of drug action.
- Decreasing the frequency of dosing.
- Decreasing the required dose employed.
- Providing uniform drug delivery.
- Improve bioavailability (Navin Dixit *et al*. 2005)

SR Granulation/Pelletization

Granulation is size enlargement process which converts fine or coarse particles into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity. (Leuenberger H. *et al*. 2007) [29]. The term ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum’’ meaning ‘grained’.

These granular dosage forms are used to a prolonged therapeutic effect by continuously releasing therapeutic agents over an extended period of time after administration of a single dose.

Properties

(1) More stable when compared to powders
(2) Convenient to administration
(3) Be coated in order to Sustained Release

Reasons to Granulate & Spheronize

- Improve flow.
- Dansify materials.
- Improve content uniformity.
- Improve compression characteristics.
- Control the rate of drug release.
- Facilitate metering or volume dispensing.
- Decrease dust generation and reduce employee exposure to drug product.
- Improve the appearance of the tablet. (Leuenberger H. *et al*. 2007) [29].

Desirable Granule/Pellets Properties

- Controlled Size Distribution.
- Specific Granule Void age – Intragranular Porosity.
- Specific Bulk Density
- Suitable Structural Stability.
- Physical Strength. (Litster J. *et al*. 2007) [29].

Various Techniques for Preparing Granules/Pellets- various techniques has been used to preparing granules:

Conventional Technologies

- Granulation by Crystallization.
- Spray Drying.
- Melt Granulation techniques.
- Fluid-Bed Granulation.
- Wet Granulation.
- Dry Granulation (Roller Compaction → Milling).
- Spray Drying.
- Melt Granulation/Spray Congealing.
- Physical Mixture etc. (Litster J. *et al*. 2007) [29].

Novel Technologies

- Pneumatic Dry Granulation (PDG).
- Freeze granulation Technology.
- Foamed Binder Technologies (FBT).
- Steam Granulation.
- Moisture Activated Dry Granulation (MADG).
- Granulex® Technology.
- Thermal Adhesion Granulation Process (TAGP) etc. (Himanshu. K. Solanki *et al*. 2010) [17].

Most convenient methods used in laboratory scale -

The classical granulation process using either wet or dry methods is employed in the process industries

Wet Granulation

Wet granulation is the oldest and most common granulation technique and can be accomplished using different types of equipment, including high-shear, fluid-bed, and twin-screw granulators. While wet granulation is used for a large number of pharmaceutical drugs, it does have the drawback of being a high-energy process, because drying is necessary once the wet granulation process is complete. It involves blending at high and/or low shear forces with the addition of a liquid. The greatest potential of the wet-granulation methods because it is a robust, continuous process (Cvnthiachallener *et al*. 2013)

Dry Granulation

This method involves simple blending of active pharmaceutical ingredient (API) with other ingredients and direct compaction of the resultant mixture. The particle size is enhanced by aggregating the particles by roller compaction and then milling to the desired size, resulting in improved content uniformity, dissolution times, and stability. Do not utilize any liquid. (Gowtham Kumar *et al*.2013).

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