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Oral Controlled Release Drug Delivery System: A Promising Approach for the Treatment of Ulcerative Colitis

Ankita Sharma, Ankush Kumar Sharma, Saurabh Sharma and Neeraj Mishra*

Department of Pharmaceutics, I.S.F. College of Pharmacy, Moga, Punjab, India

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ABSTRACT

Ulcerative colitis is an idiopathic, chronic and relapsing intestinal inflammatory disorder of digestive tract which is represented by bloody diarrhoea, tenesmus, anaemia, bowel distension. In Western Europe and in the USA, ulcerative colitis has a proportion of approximately 6 to 8 cases per 100,000 peoples and an approximated prevalence of around 70 to 150 per 100,000 peoples. Proper local targeting is the major challenge in the treatment of ulcerative colitis. To minimize these challenges oral controlled drug delivery system seem to be a promising approach for colon targeting. The main motive of this article is to explore the role of oral controlled drug delivery systems in ulcerative colitis for appropriate targeting of drug entities to the colon. The increased demand of these dosage forms is because of the alertness to toxicity and ineffectiveness of oral conventional approach in the form of capsules and tablets. Generally, conventional formulations create fluctuation in drug concentration in the tissues and bloodstream with ensuing undesirable toxicity and poor efficacy. These limitations of conventional treatment such as fluctuation in drug concentration, the inappropriate drug at the target site and repetitive dosing could be overcome by the oral controlled drug delivery system. The present article contains brief review on the pathophysiology of ulcerative colitis and several formulation approaches used for colon targeting by using the oral controlled drug delivery system.

Keywords: Oral controlled release drug delivery; Formulation approaches; Colon targeting

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INTRODUCTION

Inflammatory Bowel Disease

Inflammatory bowel diseases (IBD), is an idiopathic, chronic and relapsing intestinal inflammatory disorder of gastrointestinal tract, which mainly comprises ulcerative colitis and Crohn's disease [1,2]. Small intestine and large intestine or colon is the major parts involved in inflammatory bowel diseases, which are marked by the chronic inflammation in distinct mucosal or transmural region [3]. Proper local targeting is the major challenge in the treatment of ulcerative colitis. For better localization, a well-designed drug delivery system is favourable to improve therapeutic efficacy [4,5]. A major threat in developing therapeutically efficacious products for IBD is the focus of disease on the delivery system of the drug [6]. Targeted drug delivery into the colon is highly preferable for local treatment of different inflammatory bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, and colonic cancer [7]. Oral controlled release drug delivery is only a system that serves as continuous oral delivery of drugs at predictable and uniform kinetics for a predetermined time throughout the manner of GI transit and also the system that target the delivery of a drug to a distinct area within the digestive tract for either a local or systemic action [8].

The oral route is the most beneficial and suitable route for local treatment of a variety of bowel diseases. Rectal administration offers the precise route for targeting drugs to the colon. Though reaching the proximal region of colon through rectal administration is tough. Rectal administration can also be awkward for patients and compliance may be less than optimal range [7].

At present, the etiology of the disease is not fully cleared but it has been considered that several factors such as genetic, Gut/environmental, psychosomatic, autoimmune, epidemiological are mainly involved in the evolution of disease [9]. Gut/environmental factors hold immune/epithelial interactions, bacterial infections, and epithelial blockade actions. Epidemiological survey consists of dietary routine, smoking habits, intake of drugs, hormonal condition, diversity due to different climates, and variations due to social circumstances. The inflammatory aspects can be evaluated through several cell signalling pathways, inflammatory mediators such as tumour necrosis factor α (TNF- α), Interleukin-1, Interleukin-6, Interleukin-12, Interleukin-4, Interleukin-10 and Interleukin-11, Eicosanoids profiles etc. [10] The serious form of ulcerative colitis turns to colon cancer. Chronic inflammation developed by the generation of reactive oxygen species turns to induce dysplasia, which further leads into CAC, i.e. colitis-associated colorectal cancer, which is the serious form of ulcerative colitis [11]. Thus, there are huge chances of colon cancer in patients which are suffering from ulcerative colitis [12]. This possibility is increasing each year. Urban and western industrialized areas are mainly affected by these disorders as compared to rural areas [13]. An inflammatory bowel disease (IBD) is a common term for a group of chronic inflammatory diseases of unknown etiology involving the digestive tract characterized by abdominal pain and Diarrhoea [2]. UC is restricted to the colon, characterized by prolonged inflammation, constantly involving the rectum and is classified according to its proximal limit. Further, variant CD, inflammation in UC is confined to the mucosal surface [14]. Meanwhile, UC and CD share a lot of inflammatory similarities, such as epithelial barrier dysfunction, genetic susceptivity etc. IBD may results in significant morbidity and mortality, with negotiable and life expectancy [2]. UC is a case in which inflammatory response and morphologic changes remain restricted to the colon. The rectum is involved in 95% of patients, with changeful degrees of proximal extension [15]. It involves only the deepest lining or mucosa, manifesting as continuous regions of inflammation, ulceration, oedema and haemorrhage onward the length of the colon. The most consistent aspect of UC is the existence of blood and mucus fused with stool, accompanied by lower abdominal pain which is most excessive during the passage of bowel movements [16]. There are several conventional and unconventional remedies used for the treatment of ulcerative colitis hold aminosalicylates, glucocorticoids, immunomodulators, etc. These need to be administered periodically to patients, which lowers patient compliance and can originate systemic side-effects. Thus, oral drug delivery is found to be an auspicious approach for controlled and targeted drug delivery, which reduces dosage frequency and enhance patient compliance.

Sign and Symptoms of Ulcerative Colitis

The major first symptoms of ulcerative colitis include abdominal pain, tenesmus, anorexia, bloody or mucous diarrhoea as compared to Crohn's disease, which does not display bloody diarrhoea [17]. The serious cases of ulcerative colitis include various symptoms such as weight reduction, tachycardia, fever, anaemia and bowel distension [18]. It is generally related with full remission of symptoms in the interim. Both male and female sexes are equally affected [19]. In Western Europe and in the USA, ulcerative colitis has a proportion of approximately 6 to 8 cases per 100,000 peoples and an approximated prevalence of around 70 to 150 per 100,000 peoples. The peak incident of ulcerative colitis is mainly in the ages of 15 to 35 [20]. Inflammatory bowel disease can influence at an individual of any age and can permanent throughout their whole life as it does not have any continuous treatment [21]. In Ulcerative colitis, sites of inflammation broaden to the more proximal areas of the colon over time. Generally, the rectum is also involved. While in CD, site of inflammation is commonly distal ileum [22]. Figure 1 represents a schematic flow chart which specifies ulcerative colitis.

Epidemiology and Risk Factors

Ulcerative colitis is more common in persons as compared to Crohn's disease. North America and northern Europe have the maximum pervasiveness and incidence proportion of ulcerative colitis, with incidence changing from 9 to 20 cases per 100 000 people-years, and pervasiveness proportions from 156 to 291 cases per 100 000 humans. Ulcerative colitis has a bimodal arrangement of incidence, with the major commencement peak between ages 15 and 30 years and a second shorter peak between ages 50 and 70 years. Despite both sexes are equitably affected; Ulcerative colitis is somewhat more common in males, while Crohn's disease is hardly more frequent in women [23], It is predicted that 1-2 million Americans endure from IBD; relatively half of these have ulcerative colitis. UC can arise anytime in life, but it is generally diagnosed prior to age 30. The disease arrives to affect men and women uniformly. Almost 20 percent of people with UC have a nearly relative with IBD. Individuals have a higher prevalence of UC, with Jewish people of European descent 3-6 times extra likely to evolve the disease. Areas with a low prevalence of UC hold Asia, Africa, Japan and South America. Breast feeding, appendicectomy, and smoking are related to decreased risk of UC. Expenditure of a "Western diet," left-handedness, and depression may increase the possibility for ulcerative colitis [14].

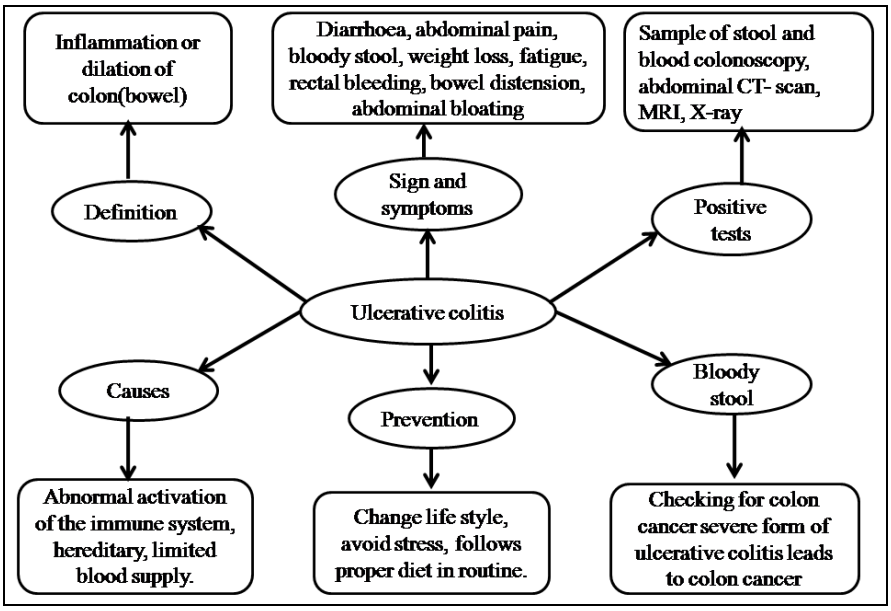

Figure 1: Schematic flow chart for ulcerative colitis

Pathogenesis of Ulcerative Colitis

Ulcerative colitis is a case in which the inflammatory return and morphologic diversity remain restricted to the colon. The rectum is included in 95% of peoples which are suffering from ulcerative colitis, with alterable degrees of proximal expansion. Inflammation is confined primarily to the mucosa and comprises of continuous involvement of inconstant severity with ulceration, edema, and haemorrhage onward the length of the colon. Acute and chronic inflammation of the mucosa is the major histologic conclusions by polymorphonuclear leukocytes and mononuclear cells, crypt abscesses, intorsion of the mucosal glands, and goblet cell reduction [15]. Figure 2 represents the factors responsible for ulcerative colitis.

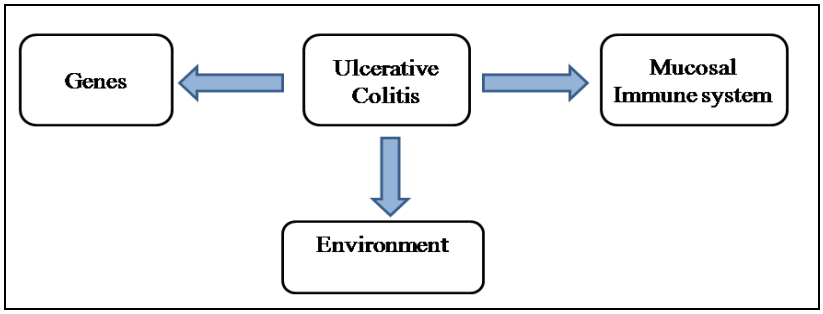

Figure 2: Factors responsible for ulcerative colitis

Factors Responsible for Ulcerative Colitis

Although extensive analysis over various decades, a simple description of cause of these diseases has not been emerged. It is likely that the pathophysiology of inflammatory bowel disease is more complicated than a single cause and consequence relation, and possibly represents an interaction between genetic predisposing aspects, exogenous and endogenous triggers, and modifying aspects. The conclusion of these interactions is an automatically reverting and remitting inflammatory course, in which tissue injury is resolved by the immune system. Till the predisposing and trigger aspects have been precisely examined therapeutic and preventive approaches for these conditions must be established on interrupting the immunopathogenic mechanisms involved. Thus, I shall focus on the potential immunologic processes and mediators of tissue damage in ulcerative colitis [24]. Cytokines are abundantly originated by the cells of the gut correlated immune system. These short, cell-signaling protein molecules act in a paracrine, autocrine, or endocrine style and affect the activity of the immune system in a number of ways. Subsequently, cytokines coordinate the dispatch between immune and non-immune cells of the intestinal area and reform acute and chronic inflammatory reactions both at the local and the systemic regions.

Thus, it is of no amazement that cytokines have been the major therapeutic targets in recent advances for the management of ulcerative colitis [25]. Ulcerative colitis has multifarious aetiology that may result in either primary immunological malfunction or an improper pathological immunological feedback to an environment. e.g. commensal intestinal microorganisms. The primary cause is the dysfunction of the immune system which further leads to enormous immune responses to normal microflora. Secondly, epithelial cell deformities and diversity in the composition of gut microflora promote an anomalous mucosal immune response [26]. Thirdly, defective gene expression i.e. mutation of a gene named CARD15/ NOD2, placed on Chr 16 and another gene named OCTN 1 and 2 on Chr 5, in the case of Crohn's disease [27].

Two decades back, a classification of immune return has been recommended, which was established on the cytokine profile that was significant in different situations. The actual scheme consists of the T helper 1 (Th1) vs. T helper 2 (Th2) paradigm along former being controlled by the manufacturing of interleukin-12 (IL-12)/IFN-γ and another by the excretion of IL-4, IL-5, and IL-13. A considerable shift in this archetype appeared following the examination of a third effector population, which is described by high IL-17A excretion, thus its classification as the Th17 response [28]. In addition, it has become identified that not only specialized CD4+ lymphocytes play an effector character but also a managerial one, expressing suppressive function, governing effector pathways, and dampening inflammatory feedback [29]. These regulatory cells also consist of various subgroups but generally act via the excretion of IL-10 and TGF-β1. The purpose of this approach in mucosal immunology resulted in the evaluation of ulcerative colitis as a Th2-mediated situation. However, for certain years this was usually linked to the lack of enhanced IFN-γ expression comparatively to the rise of IL-4, the Th2-defining cytokine [30]. In fact, the recent is not monitored at the mucosal level in ulcerative colitis. However, there is increased IL-5, thus the term "atypical Th2-status" that was coined to ulcerative colitis. Figure 3 represents Interactions of T-helper cells and cytokines in normal mucosa and in inflamed mucosa of IBD patients.

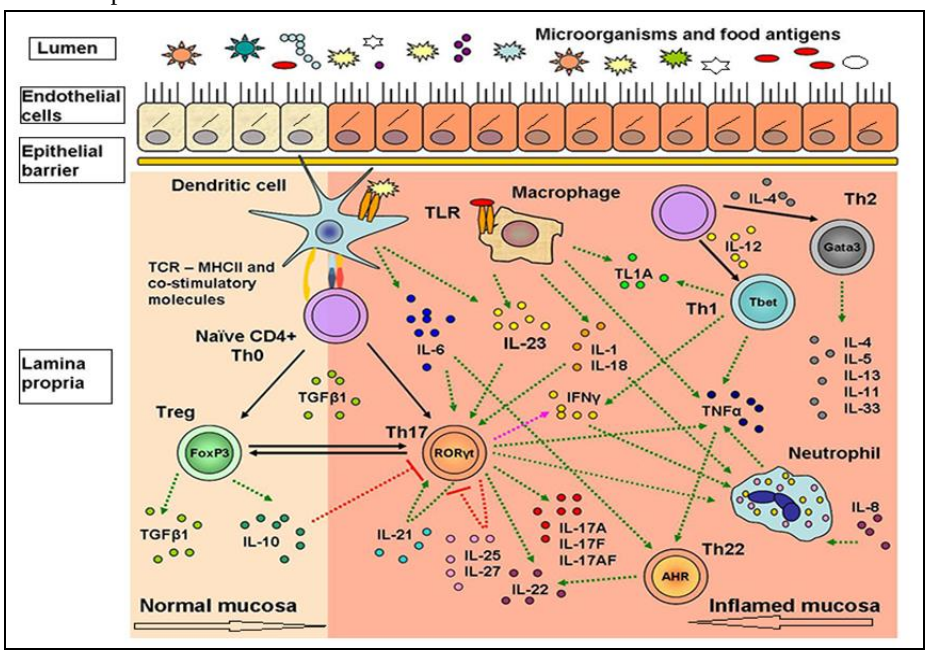

Figure 3: Interactions of T-helper cells and cytokines in normal mucosa and in inflamed mucosa of IBD patients

In addition, studies have demonstrated that the cytokine expression arrangement in the colon of patients suffering from ulcerative colitis and also of patients suffering from Crohn,s disease do not correlate to terminally specialized immune return. Particularly the "rigid polarization" model of Th1 vs. Th2 does not arise to be completely applicable in IBD [31,32]. Alternately, an overabundance of effector and managerial pathways is reported in ulcerative colitis, which is definitely affected by various factors such as the stage of the disease (acute or severe), the contribution of innate immunity pathways, the involvement of epithelial cells, and the effect of treatments against inflammation. Within this complex and distinct chain of cytokines, extensive earlier research has determined molecular destination that not only could be essential for disease pathology but also will offer different therapeutic chances [33]. Certain of these pathways, the most significant example being TNF-α, have been broadly examined in latest IBD history and will not be comprised herein [34,35]. Table 1 represents list of various drugs used for the treatment of ulcerative colitis.

Table 1: List of drugs used for the treatment of ulcerative coliis

Drugs	Brand name	Marketed formulation	Site of release	Standard dose	References
Budesonide	Cortiment	Multi-matrix prolonged release tablet	Terminal ileum, colon	9 mg daily	[36]
Beclometazone dipropionate	Clipper	Sustain release tablet	Terminal ileum, colon	5 mg daily	[37]
Prednisolone	Deltasone	Delayed release tablet	Duodenum, jejunum, ileum, colon	20-40 mg daily	[38]
Dexamethazone	Dexazone	Delayed release tablet	Colon	0.25-6 mg daily	[37]
Hydrocotisone	Colifoam	10% foam	Colon	One dose once or twice daily	[39]
Sulphasalazine	Azulfidine	Gastro-resistant tablet	Jejunum, ileum, colon	1 g -2 g four times daily	[40]
Mesalamine	Asacol	Coated tablet	Terminal ileum, colon	2.4–4.8 g daily	[41]
Balsalazide	Colazide	Capsule	Jejunum, ileum, colon	2.25 g three times daily	[42]
Olsalazine	Dipentum	Modified-release tablet	Colon	1 g daily in divided doses	[43]
Azathioprine	Imuran	Film-coated tablet	Terminal ileum, colon	50 mg daily	[44]
Methotrexate	Rheumatrex	The solution given i.v.	Jejunum, ileum, colon	25 mg/ml daily	[10]
Infliximab	Remicade	Powder for intravenous injection	Terminal ileum, colon	100 mg	[45]
Adalimubab	Humira	Prefilled glass syringe	Colon	20 mg/0.4 ml and	[45]
Ciprofloxacin	Cipro	Extended release tablet	Terminal ileum, colon	500 mg twice daily	[10]

Role of Oral Controlled Drug Delivery System in Colon Targeting

For impressive treatment of ulcerative colitis delivery route play very important role. The cure of ulcerative colitis should be such that patient should offer limited pain, decreased cross infections. For attaining such conditions, the most beneficial route of drug delivery is the oral route, specifically for those severe conditions in which revised drug delivery is required. But with the profits of this route, there are also some drawbacks. This route is not suitable for the delivery of protein and polypeptide drugs because of the gastric environment and limited absorption. These drugs are more prone to gastric enzymes and get deteriorate on contact with this environment. Thus, for the safety of drugs from gastric environment novel strategies have been developed. Among these approaches, oral colon specific drug delivery has established to be an interesting alternative beyond systemic drug delivery [46]. Colon is the best acceptable absorption site for poorly soluble drugs because it offers almost long residence time and neutral pH for drugs. There is several modified release approaches has been developed for the effective release of drug in colonic site. Absorption of electrolytes and water takes place in the colonic region, but still, there is the possibility of various diseases such as inflammatory bowel diseases i.e. Crohn's disease and ulcerative colitis and other diseases like helminths, colorectal cancer and irritable bowel syndrome [47]. Oral colon targeted drug delivery system is an innovative technology is having a lot of advantages by targeted drug delivery to colonic region by utilizing combination of one or more sustained release mechanisms, which protects the release of drug in upper part of the digestive tract but releases drug moiety in lower part of the digestive tract by following oral administration. Therefore it improves safety and decreases side-effects when treating systemic or local diseases [48]. Most of the severe conditions could be cured efficaciously on local release of drug moiety to the target site. Conventional drug delivery system fails to achieve target drug delivery or suitable concentration of drug at the target site. Therefore, target drug delivery is a big threat to the pharmaceutical industry. Thus, there is the demand of developing such delivery system which transfers the drug specifically to colon and thus cures the colonic disorders like ulcerative colitis, irritable bowel syndrome and Crohn's disease. Rectal dosage forms like enemas and suppositories can also be utilized but both the formulations are efficacious in different parts of the colon and create discomfort to patients. Thus, these drawbacks can be reduced by utilizing oral site-specific pH-dependent drug delivery system which prevents the active drug moiety in the upper digestive tract and first pass effect. Thus, targeting drug entities in its intact form to the colon decreases dosage frequency, avoids mucosal metabolism and reduces side effects [49].

The delivery of these drugs particularly to the lower part of digestive tract without being absorbed initially in the upper part of digestive tract allows for a maximum amount of the drug moiety to reach the colon with minor systemic absorption. The colonic contents have a higher retention time and the colonic mucosa is known to promote the absorption of various drugs, making this region an ultimate site for delivery of drugs [50]. The oral and rectal route can be used to deliver the drug entity to the colon. Oral controlled drug delivery is the most favoured delivery route for target delivery to colon due to their effectiveness and convenience. The rectal route for the delivery of drugs is most challenging due to patient discomfort [51]. Moreover, the degree of drug distribution changes for various rectal dosage forms depending on their dispersal capacity and retention time. The achievement of target drug delivery to the lower part of digestive tract depends on the physicochemical properties of the drug, all factors which may improve digestive transit time as well as the extent of interaction between drug moiety and digestive tract [52]. It is important for the oral controlled drug delivery system to prevent the drug moiety from being released in the

upper part of the digestive tract. Therefore, the approaches used for the development of site-specific drug delivery to the colon are meant at sustaining the release of drug till the formulation reaches to the colon, with a number of schemes representing great success as compared to others.

Oral Controlled Release Drug Delivery System

Oral drug administration is the most suitable and beneficial approaches as the oral route contribute greater active surface area as compared to all drug delivery system for delivery of various drugs. The drug release pattern of the oral controlled release delivery system controls the level of plasma drug concentration within the therapeutic level, through a definite rate and time, resulting in constant therapeutic activity [53]. The significance of these dosage forms because of attention to toxicity and inefficiency of drugs when delivered through oral conventional technique in the mode of tablets and capsules. In comparison, the conventional oral drug delivery has several drawbacks such as, greater tendency of fluctuations in plasma drug concentration, elevation in the dosage frequency, less time for drug efficacy at the specific site of action, limited drug at the site of action and limited oral bioavailability of some drugs because of the interaction with food, number of side effects due to high dosage of drug. Controlled release oral drug delivery is a scheme that serves endless oral delivery of drugs at predetermined and reproducible kinetics for a predictable period all over the system of digestive tract transit and also the approach that targets the drug to a specific area within the digestive tract for either a systemic or local activity [8]. Research on oral controlled release drug delivery with either further advancement in the delivery pattern or innovation in the formulation of the drug is ongoing work for several formulation scientists [54]. The most important specifications for the novelty of a drug delivery system are, first, is controlled release drug delivery, and second is the passage of the active entity to the specific site for its activity. Formulation scientists have been used various approaches to attain this challenging innovation in oral drug delivery, either by encapsulating drug into a carrier system or by controlling the release of drug in the blood to achieve the designed target [55,56]. Oral controlled release drug delivery systems can play important role in controlled release of drugs. Therefore, the controlled oral drug delivery system is the most commonly used approach for controlling the release of drugs which are given orally [57]. Several complementary terms such as prolonged release, sustained release, extended release, modified release are used to evaluate controlled release drug delivery systems that are designed to sustain the rate of release of drugs over an elongated period of time [58]. Innovation in the drug dosage form is essential for attaining a useful controlled oral release drug delivery system. Figure 4 represents modified release oral drug delivery system.

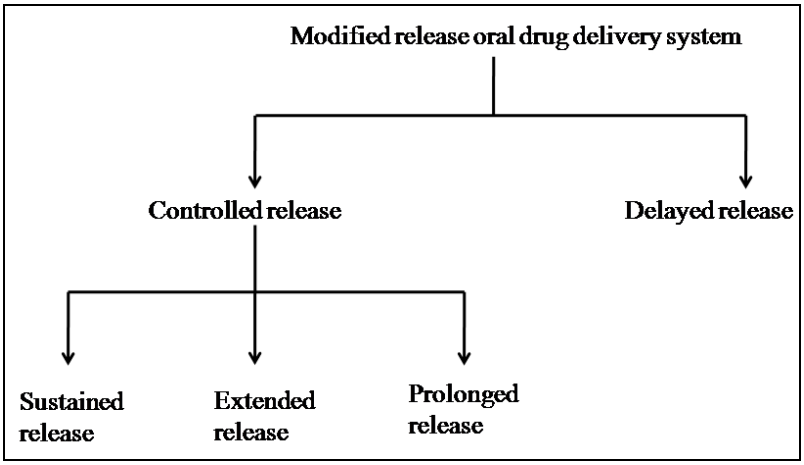

Figure 4: Modified release oral drug delivery system

Advantages of Oral Controlled Release Drug Delivery Systems

Oral controlled release drug delivery system offer many advantages, such as:

- Approximately constant drug level at the specific site of action
- Protection of peak-trough fluctuations
- Reduction in dose of drug
- Decreased dosage frequency
- Reduced side effects
- Improved patient compliances
- Taste masking
- Enteric prevention

- Colon targeting
- Sustained pH-independent release pattern
- Pulsatile release pattern
- Enhancement in bioavailability of some drugs due to spatial control [59,60]

Figure 5 represents approaches of oral controlled release drug delivery system

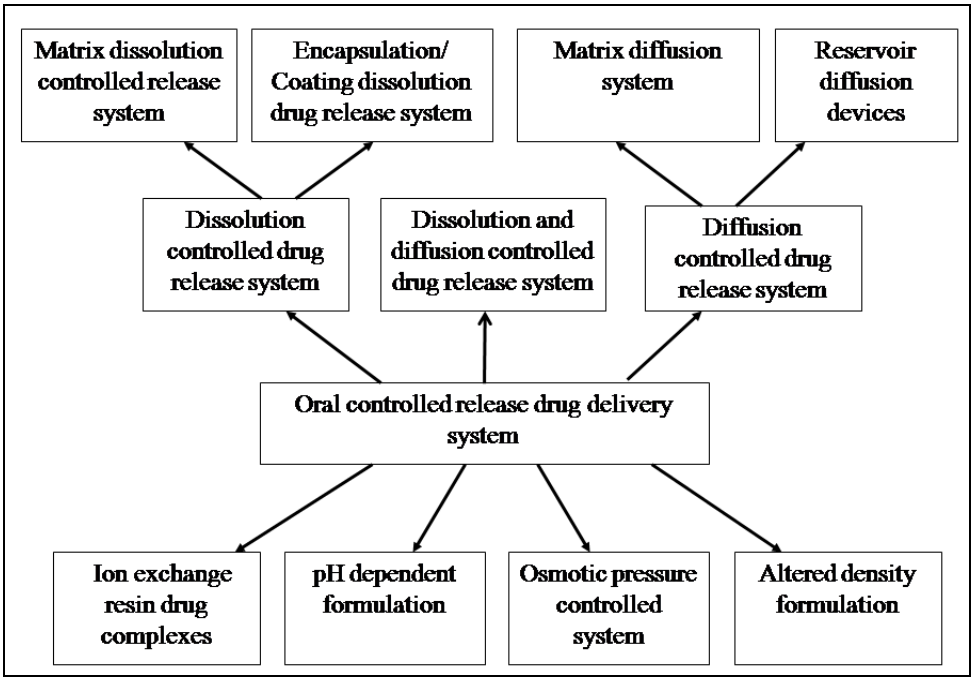

Figure 5: Approaches of oral controlled release drug delivery system

1. Dissolution Controlled Drug Release System

Drugs having a limited rate of dissolution will acquire sustaining properties, as the rate of dissolution obstructs the drug release from the system. Thus it looks possible to establish the sustained-released formulation by reducing the rate of dissolution of drugs which are hydrophilic in nature [61]. Delayed release oral product operating dissolution as the rate-limiting step is a major aspect which involved in this system. To attain this type of system, the particles of drug can be coated with a material of deviating thickness or by encapsulating them in a matrix made up of the polymer. A drug entity with a limited dissolution rate is inherently extended and for those drugs with greater water solubility, one can reduce dissolution through convenient salt or derivative development [62]. For the formation of enteric coated dosage forms, these approaches are most widely employed.

For the protection of stomach from the side effects of drugs entities such as Aspirin, a coating that liquefies in the natural or basic medium is used. This suppresses the release of drugs from the drug formulation till it reaches the greater pH of the intestine. In many cases, enteric coated dosage forms are not exactly sustaining in nature, but serve as a significant function in supervising the release of the drug to a target site. The same scheme can be employed for materials that are degraded by the severe conditions found in the gastric area [63]. Dissolution is defined as solid material dissolved in a given solvent.

It is a rate limiting step when liquid is dispersing from the solid substance. Various theories explain dissolution such as:

1. Surface renewal theory
2. Diffusion layer theory
3. Limited solvation theory

Figures 6 and 7 represents common forms of dissolution controls formulation.

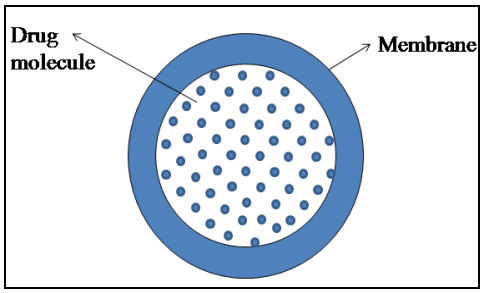

Figure 6: Dissolution control of drug release depends on dissolution rate ans thickness of the membrane coating

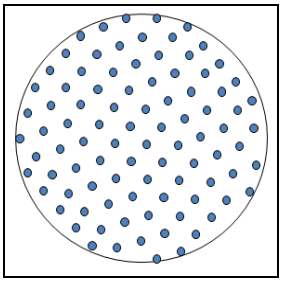

Figure 7: Dissolution control of drug release depends on polymer core erosion

a) Matrix dissolution controlled drug release system

The drug is equally distributed all over the polymer matrix. Drug particles are released as the polymer matrix dissolves. The release rate of drug reduces as the size of the matrix decreases. The release of the drug is nonzero-order. Both spherical matrix systems and micro matrix Systems Small are prepared by microencapsulation technique. Macromatrix Systems Tablets comprises of an outer core, and inner coat, and a film coat [64]. Matrix dissolution controlled drug release system is also called as monolithic dissolution controlled system. In this system, dissolution is controlled by various aspects such as varying porosity of tablet, reducing its wet ability and dissolving at a slower rate. This system follows first-order drug release pattern. The dissolution rate of the polymer can also be determined the release of drug particles. In this system, another scheme is to compress the drug entity with a slow dissolving carrier. In this approach release rate of the drug is controlled by the rate of penetration of the dissolution medium into the matrix, porosity, existence of hydrophobic excipients and the wetting capacity of the system and surface of the particle [65]. Figure 8 represents matrix dissolution controlled drug release system.

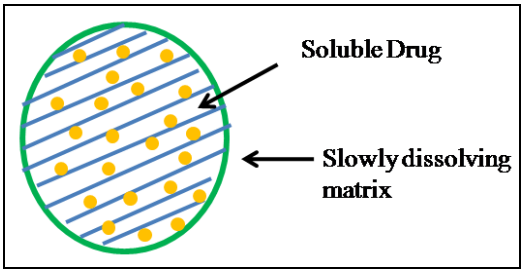

Figure 8: Matrix dissolution controlled drug release system

b) Encapsulation/coating dissolution controlled drug release system

The method includes the coating of granules or particles of the drug with the slow solubilising material. This system is also called as coating dissolution controlled system till the drug encapsulated, with slowly dissolving material like cellulose, PEG (polyethene glycol), waxes and PMA (polymethylacrylate). The dissolution rate of coating depends on stability and thickness of coating material [66]. The drug particles which are subjected to coating can be compressed directly in tablet compression machine for the production of tablets or capsules. The process of microencapsulation controlled the rate of dissolution of the drug moiety. When the coating is properly dissolved, the drug becomes free for the process of dissolution. By changing the thicknesses of the coating material and its composition, controlled release pattern of the drug can be achieved. A major advantage of encapsulated pellet products is that the absorption is less conscious to stomach emptying. The entry of the pellets products into the small

where the absorption of various drug entities occurs is consistently more uniform as compared to non-disintegrating delayed-release tablet formulations [67]. Figure 9 represents the reservoir dissolution controlled drug release system.

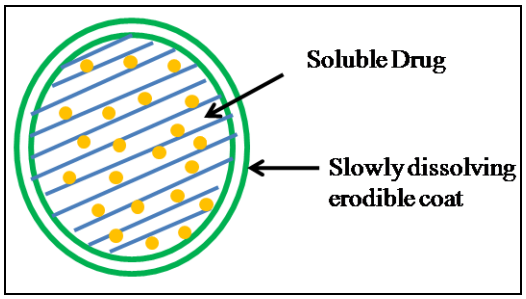

Figure 9: Reservoir dissolution controlled drug release system

2. Diffusion Controlled Drug Release System

On contact with aqueous liquids in the digestive tract, water diffuses into the internal side of the drug entity. Due to this process drug dissolution occurs and the solution which contains drug diffuse across the released coating to the outer side [68]. It is a significant process for absorption in which energy requirement is not necessary. In this system drug particles diffuse from an area of higher concentration to lower concentration till equilibrium is acquired with a magnitude which is directly proportional to the concentration gradient across the membrane. In this system rate of drug release is determined from its diffusion rate through a water-insoluble polymer [69].

a) Matrix diffusion system

The matrix system is described as a well-mixed composite which contains gelling agent with one or more drugs i.e. water soluble polymers. Matrix systems are generally used for extending the rate of release of the drug. This is a release system which extends and controls the rate of release of the drug that is dispersed or dissolved in the matrix. A solid drug entity is dispersed or dissolved in an insoluble matrix and the rate of release of the drug only depends on the rate of drug diffusion, not on the rate of solid material dissolution [70]. In this system, the drug is dispersed or dissolved as solid material within a penetrable matrix made up of a non-aqueous polymer. The drug particles which are present at the surface of the release moiety will be dissolved first and immediately drug will release. After this drug molecule at a successively rising gap from the exterior of the release moiety will be dissolved and then release by diffusion mechanism in the pores to the outer side of the release moiety. Therefore, the diffusion gap of dissolve drug entity will rise as the release process is going on [71]. Figure 10 represents diffusion type matrix system.

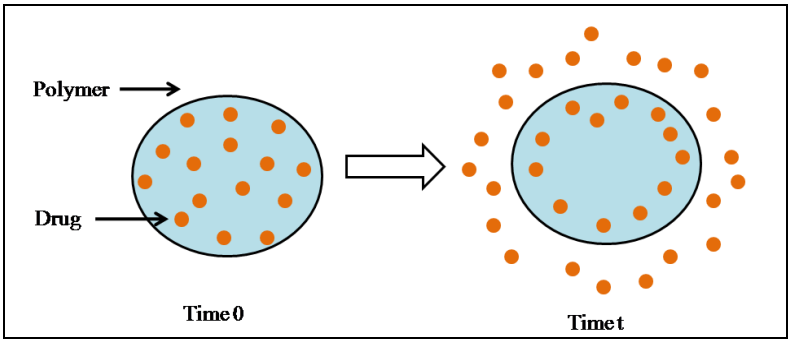

Figure 10: Diffusion type of matrix system

b) Reservoir diffusion system

In this system, the drug is covered by the non-aqueous polymeric material. The drug will differentiate into the membrane with the liquid surrounding the molecule or tablet. The additional drug will come in the polymer and then diffuse to the outer surface after this exchange with the surrounding liquid will occur. The rate of drug release depends upon the diffusion mechanism [72]. Figure 11 represents diffusion type reservoir system.

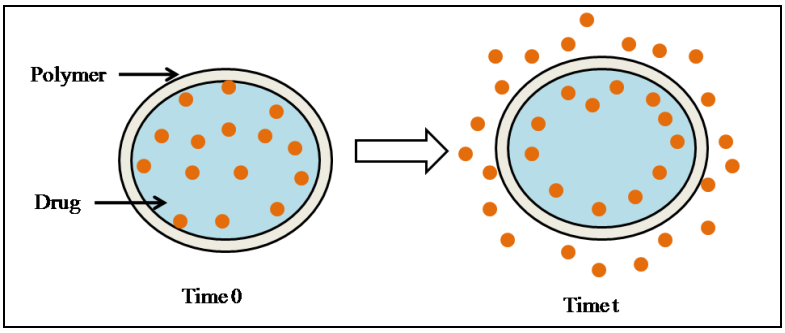

Figure 11: Diffusion type reservoir system

3. Dissolution and Diffusion Controlled Drug Release System

The major factor of this release system is that the drug core is enfolded with a fractionally soluble membrane. Firstly drug is enfolded in a fractionally soluble membrane and pores are formed due to the dissolution of regions of the membrane. It permits passage of aqueous fluid into core and drug is diffused or dissolved outside of the system. Polyvinylpyrrolidone (PVP) and ethyl cellulose mixture dissolves in water and produced pores of insoluble ethyl cellulose [73].

4. Ion Exchange Resin Drug Complexes

In this type of system, the resins used are non-aqueous cross-linked polymers bringing functional groups and comprises of a salt-forming group at distinct positions on the polymeric chain [74]. The utilized resins are generally polymers with unified ionic entities which have an ability to produce exchangeable counter-ions between the solid and the liquid phase. After administration of the resin drug complex, the release of drug occurs in the existence of a large amount of the polyelectrolyte's counter ions in the gut medium. The drug particles are shuffled, diffused out and finally transferred into digestive fluids [75]. The capability of the resin to interchange ions is evaluated by the ionizable group. Thus, ion exchange resins are classified on the basis of ionisable group. There are various types of ion exchange resins like weak acid cation exchange resins, strong acid cation exchange resins, weak base anion exchange resins and strong base anion exchange resins [76]. These all types of ion− exchange resins can be utilized to bind drugs. Ion exchange resins are mainly utilized in the oral controlled drug delivery system. But this system can also be utilized for several ways of drug administration like nasal, topical and transdermal drug delivery systems [77]. Various studies have reported the application of ion exchange resin for delivery of drugs in clinical medicine like carboxylic and sulfonated resins with a backbone containing polystyrenes [78]. Cross-linked polymers polymethacrylate and polystyrene are considered the most accepted resins utilized in pharmaceutical industry. Another reported study described that the rate of drug release can be controlled by modifying the coating of polymer in the ion exchange complex system with non-aqueous polymers such as waxes or ethyl cellulose [79].

5. pH-dependent Formulation

Maximum drugs entities are either weak bases or weak acids. The release of drug from the controlled system is pH dependent. Despite, buffers like the salt of citric acid, amino acid phthalic acid, tartaric acid or phosphoric acid can be added to the system to help to manage a constant pH for the development of pH-dependent system [80]. A buffered system is produced by mixing an acidic or basic drug with the buffering agent for the maintenance of pH, granulating with convenient pharmaceutical excipients and coating with digestive fluids passable film producing a polymer. When digestive fluid passes through the membrane, then agents which are used for the maintenance of pH arrange the fluid inside to useful constant pH to achieve a constant rate of drug release [79].

6. Osmotic Drug Delivery System

In this type of approach, an osmotically active polymeric material is used for the production of osmotic drug delivery system. Therefore, the process of osmosis released the drug at a predictable zero-order kinetic rate for a constant and prolonged period of time till the amount of polymer in the matrix starts decreasing under the saturation solubility of the drug entity in the liquid [61,81]. The encapsulated drug in the system starts degrading through a cavity on the semi-permeable membrane of the osmotic pump. The rate of drug release will be controlled by a constant hydrostatic pressure and by osmotic pressure differences on all sides of the semi-permeable membrane. Negligible impact on this system can occur by different physiological factors in the inner side of the gut lumen. The release aspects of the drug can, therefore, be easily predictable from the known characteristics of the drug entity and

the dosage form [82]. This osmotic drug delivery system is mainly divided into two parts which are enclosed in the double layered core. The upper layer consists of an active drug moiety and the downward layer consists of an osmotically active polymeric material. The rigid semi-permeable membrane is used for the coating of the double layered core. The drug moiety is compacted in the core and which will be released by the cavity present on the semi-permeable membrane of the osmotic pump [83,84]. Therefore osmotic drug delivery system is a significant approach for achieving controlled release of drugs. The osmotic drug delivery systems are mainly classified into two types of osmotic systems i.e. type-A and type-B.

In the type-A osmotic system, the core contains both, the electrolytes and drug entities. The electrolytes supply osmotic pressure and manage the drug release. In the type-B osmotic system, the solution of drug entity is present in a semi-permeable membrane encircled by the electrolytes [85]. Figure 12 represents type-A and type-B osmotic pump.

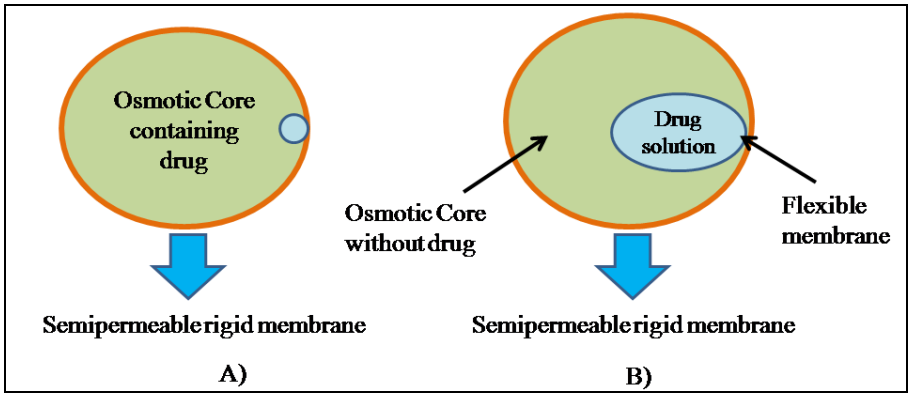

Figure 12: Type-A and Type-B osmotic systems

7. Altered Density Formulation

Various approaches have been prepared to sustain the residence time drug formulation in the digestive tract. The first approach is the bioadhesion approach which is based on the adherence of polymeric material to the epithelial surface of the digestive tract. Another approach is to modify the formulation's density by utilizing either low or high-density pellets.

(1) High-density approach

In this system density of pellets always exceed that of normal content of stomach and thus it should be at least 1.4 g/cm^3. In developing such kind of formulations, drugs can be coated on the bulky core or mixed with bulky inert materials such as barium titanium dioxide, zinc oxide and barium sulphate, iron powder. The membrane which controls the rate of diffusion can be used to cover the weighted tablets.

(2) Low-density approach

In this system apparent density is less than that of gastric liquids can be utilized as a carrier of the drug for controlled release of the drug. Pop rice, popcorn and even poly styrol are all the candidates used as a carrier. The covering of these empty shells is undercoated by using sugar or a polymeric compound such as cellulose acetate phthalate and meth acrylic polymer. Then undercoated shell is coated with a drug mixture with polymers such as hydroxypropyl cellulose and ethyl cellulose. The final product floats on gastric medium for a delayed period, while slowly releasing drug [86,87].

CONCLUSION

With rising new technologies, an important growth has been made in producing a truly suitable approach for targeting drug moiety to a specific site of action in ulcerative colitis. The progression of oral controlled drug delivery systems for colon targeting has attained growing attention among formulation scientists in current years. As discussed above, oral controlled drug delivery systems offer great therapeutic benefits to the patients in terms of effectiveness, patient compliance and safety. Factors including the physicochemical properties of the drug moiety, process variables and formulation as well as the digestive physiological factors impact, and may present a threat to the successful formulation of an oral controlled drug delivery system for colon targeting. The formulation approaches used to reduce these threats majorly focus on bypassing the complicated pH environment of the upper digestive tract by the dosage form, delivery mechanism of the drug, protecting release of drug and absorption of drug in the upper digestive tract, and releasing the drug moiety in the lower part of the digestive tract [88]. The

metabolizing capability of the colon enzymes is also being analyzed as a scheme to site-specific drug delivery in the colonic region. To ensure equilibrium between target-specificity, price, effectiveness and patient compliance, it arrives that a combination of conventional and novel approaches is the key to the development of oral controlled drug delivery systems. Moreover, oral controlled release drug delivery system has cheap price as compared to oral conventional drug delivery system which makes it more economical option for patients.

REFERENCES

[1] F Talaei; F Atyabi; M Azhdarzadeh; R Dinarvand; A Saadatzadeh. *Eur J Pharm Sci.* **2013**, 49, 712-722.
[2] Y Yan. Pathogenesis of inflammatory bowel diseases. *INTECH Open Access Publisher*. **2012**.
[3] DR Friend. *Adv Drug Deliv Rev.* **2005**, 57, 247-265.
[4] EM Collnot; H Ali; CM Lehr. *J Control Release.* **2012**, 161, 235-246.
[5] M Rashid; V Kaur; SS Hallan; S Sharma; N Mishra. *Saudi Pharm J.* **2014**.
[6] RA Keraliya; VH Shah. *Int Res J Pharm Sci.* **2014**, 5, 4-9.
[7] AK Philip; B Philip. *Oman Med J.* **2010**, 25, 79-87.
[8] AA Rao; VN Rao; AS Devi; K Anil; VV Naik; A Rajesh. *Int J Pharm Chem Res.* **2015**, 1, 6-15.
[9] NA Molodecky; GG Kaplan. *Gastroenterol Hepatol.* **2010**, 6, 339-346.
[10] M Rashid; V Kaur; SS Hallan; S Sharma; N Mishra. *Saudi Pharm J.* **2016**, 24, 458-472.
[11] G Rogler. *Cancer Lett.* **2014**, 345, 235-241.
[12] U Navaneethan; R Jegadeesan; NG Gutierrez; PG Venkatesh; JP Hammel; B Shen; RP Kiran. *J Crohn's Colitis.* **2013**, 7, e684-e691.
[13] BS Thippeswamy; S Mahendran; MI Biradar; P Raj; K Srivastava; S Badami; VP Veerapur. *Eur J Pharmacol.* **2011**, 654, 100-105.
[14] KA Head; JS Jurenka. *Altern Med Rev.* **2003**, 8, 247-283.
[15] BA Hendrickson; R Gokhale. JH Cho. *Clin Microbiol Rev.* **2002**, 15, 79-94.
[16] P Rutgeerts; WJ Sandborn; BG Feagan; W Reinisch; A Olson; J Johanns; S Travers; D Rachmilewitz; SB Hanauer; GR Lichtenstein. *New Engl J Med.* **2005**, 353, 2462-2476.
[17] JK Lee; DH Tang; L Mollon; EP Armstrong. *Best Pract Res Cl Ga.* **2013**, 27, 949-960.
[18] J Meier; A Sturm. *World J Gastroenterol.* **2011**, 17, 3204-3212.
[19] S Ardizzone. Ulcerative colitis. Orphanet encyclopedia, **2003**.
[20] J Burisch. *Dan Med J.* **2014**, 61, B4778-B4778.
[21] J Cosnes; C Gower Rousseau; P Seksik; A Cortot. *Gastroenterol.* **2011**, 140, 1785-1794.
[22] VA Botoman; GF Bonner; DA Botoman. *Am Fam Physician.* **1998**, 57, 57-68.
[23] SB Hanauer. *Inflamm Bowel Dis.* **2006**, 12, S3-S9.
[24] F Shanahan. *Lancet.* **1993**, 342, 407-411.
[25] S Danese; S Rutella; S Vetrano. *Gut.* **2013**, 62, 1098-1099.
[26] W Strober; I Fuss; P Mannon. *J Clin Invest.* **2007**, 117, 514-521.
[27] S Ardizzone; GB Porro. *J Intern Med.* **2002**, 252, 475-496.
[28] K Maloy; M Kullberg. *Mucosal Immunol.* **2008**, 1, 339-349.
[29] EK Boden; SB Snapper. *Curr Opin Gastroen.* **2008**, 24, 733-741.
[30] IJ Fuss; M Neurath; M Boirivant; JS Klein; C De La Motte; SA Strong; C Fiocchi; W Strober. *J Immunol.* **1996**, 157, 1261-1270.
[31] KO Arseneau; H Tamagawa; TT Pizarro; F Cominelli. *Curr Gastroenterol Rep.* **2007**, 9, 508-512.
[32] G Bamias; MR Nyce; A Sarah; F Cominelli. *Ann Intern Med.* **2005**, 143, 895-904.
[33] G Bamias; M Mishina; M Nyce; WG Ross; G Kollias; J Rivera-Nieves; TT Pizarro; F Cominelli. *P Natl Acad Sci Usa.* **2006**, 103, 8441-8446.
[34] A Andoh; Y Yagi; M Shioya; A Nishida; T Tsujikawa; Y Fujiyama. *World J Gastroenterol.* **2008**, 14, 5154-5161.
[35] G Bamias; G Kaltsa; SD Ladas. *Discov Med.* **2011**, 11, 459-467.
[36] V Criscuoli; E Sinagra; M Cottone. *Gastroenterol.* **2013**, 144, e23.
[37] G Van Assche; F Manguso; M Zibellini; JLC Nuño; A Goldis; E Tkachenko; G Varoli; D Kleczkowski; V Annese; F D'heygere. *Am J Gastroenterol.* **2015**, 110, 708-715.
[38] T Gabbani; N Manetti; S Bagnoli; V Annese. *Expert Opin Orphan Drugs.* **2015**, 3, 87-96.
[39] S Bar-Meir; HH Fidder; M Faszczyk; GB Porro; GC Sturniolo; O Mickisch; R Müller; R Greinwald; Y Chowers; V Groβ, *Dis Colon Rectum.* **2003**, 46, 929-936.
[40] AA Khan; D Howes; J Piris; S Truelove. *Gut.* **1980**, 21, 232-240.

[41] M Ham; AC Moss. *Expert Rev Clin Pharmacol.* **2012**, 5, 113-123.
[42] WT Elliott, J Chan. Balsalazide Disodium Capsules (Colazal—Salix Pharmaceuticals), AHC Media, **2000**.
[43] MV Singer; H Schmausser; G Schönfeld. *Hepato-gastroenterology.* **2005**, 53, 317-321.
[44] A Hawthorne; R Logan; C Hawkey; P Foster; A Axon; E Swarbrick; B Scott; J Lennard-Jones. *BMJ.* **1992**, 305, 20-22.
[45] G Järnerot; E Hertervig; I Friis-Liby; L Blomquist; P Karlén; C Grännö; M Vilien; M Ström; Å Danielsson; H Verbaan, PM Hellström; A Magnuson; B Curman. *Gastroenterology.* **2005**, 128, 1805-1811.
[46] L Liu; ML Fishman; J Kost; KB Hicks. *Biomaterials.* **2003**, 24, 3333-3343.
[47] A Basit; J Bloor. *Pharm Technol.* **2003**, 185-190.
[48] G Cheng; F An; MJ Zou; J Sun; XH Hao; YX He. *World J Gastroentero.* **2004**, 10, 1769.
[49] Y Krishnaiah, S Satyanarayan, N Jain. *A*dvances in Controlled and Novel Drug Delivery. CBS Publishers and Distributors, New Delhi, India, **2001**, 89-119.
[50] A Bhattacharjee. *Int J Life Sci Pharm Res.* **2012**, 1, 31-39.
[51] S Amidon; JE Brown; VS Dave. *AAPS PharmSciTech*. **2015**, 16, 731-741.
[52] M Chourasia; S Jain. *J Pharm Pharm Sci.* **2003**, 6, 33-66.
[53] K Moodley; V Pillay; YE Choonara; LC du Toit; VM Ndesendo; P Kumar; S Cooppan; P Bawa. *Int J Mol Sci.* **2011**, 13, 18-43.
[54] RA Keraliya; C Patel; P Patel; V Keraliya; TG Soni; RC Patel; M Patel. *ISRN Pharm.* **2012**, 2012.
[55] A Pandita; P Sharma. *ISRN Pharm.* **2013**, 2013.
[56] P Khirwadkar; D Sisodiya; K Dashora. *Int J Biomed Adv Res.* **2012**, 3, 149-161.
[57] M Arafat. *Int J Pharm Pharm Sci.* **2015**, 7, 16-21.
[58] D Bhowmik; K Kumar; A Dutta; S Paswan. *Crit Rev Pharm Sci.* **2012**, 1, 20-33.
[59] D Bhowmik; H Gopinath; BP Kumar; S Duraivel; KS Kumar. *Pharm Innov.* **2012**, 1.
[60] JA Fix. *Pharm Res.* **1996**, 13, 1760-1764.
[61] S Gupta; RP Singh; R Sharma; R Kalyanwat; P Lokwani. *Int J Compr Pharm.* **2011**, 2, 1-8.
[62] NK Jain. Controlled and novel drug delivery. CBS Publishers and Distributors, India, **1997**.
[63] RK Mamidala; V Ramana; G Sandeep; M Lingam; R Gannu; MR Yamsani. *Int J Pharm Sci Nanotech*. **2009**, 2, 583-594.
[64] D Wise. Handbook of Pharmaceutical Controlled Release Technology, CRC Press, USA **2000**, 1, 435-440.
[65] HW Hui. In: Controlled Drug Delivery: Fundamentals and Applications, 2nd edition, CRC Press, USA, **1987**, 373-432.
[66] S Ummadi; B Shravani; NR Rao; MS Reddy; B Sanjeev. *System.* **2013**, 7.
[67] JR Robinson; VH Lee. Controlled drug delivery: fundamentals and applications. CRC Press, USA, **1987**.
[68] N Dey; S Majumdar; M Rao. *Trop J Pharm Res.* **2008**, 7, 1067-1075.
[69] K Patel. Rensselaer Polytechnic Institute, **2008**.
[70] R Kar; S Mohapatra; B Barik. *Asian J Pharm Clin Res.* **2009**, 2, 5461.
[71] ME Aulton, KM Taylor. Aulton's pharmaceutics: the design and manufacture of medicines. Elsevier Health Sciences, Nertherland, **2013**.
[72] T Salsa; F Veiga; M Pina. *Drug Dev Ind Pharm.* **1997**, 23, 929-938.
[73] M Gibaldi. Biopharmaceutics and clinical pharmacokinetics. 4th edition, Lea and Febiger, Philadelphia, **1977**.
[74] A Bilandi; A Mishra. *Int Res J Pharm.* **2013**, 4, 65-74.
[75] V Sharma; H Chopra. *Int J Pharm Pharm Sci*. **2010**, 2, 4.
[76] S Vijay; V Sharma; L Singh. *Int J Pharm Sci Rev Res.* **2011**, 61, 10-13.
[77] J Mahore; K Wadher; M Umekar; P Bhoyar. *Int J Pharm Sci Rev Res.* **2010**, 1, 8-13.
[78] S Pande; M Kshirsagar; A Chandewar. *Int J Adv Pharm Sci.* **2011**, 2.
[79] JR Robinson, GM Jantzen. In: Modern Pharmaceutics, Fourth Edition, CRC Press, USA, **2002**.
[80] L Allen, HC Ansel. Ansel's pharmaceutical dosage forms and drug delivery systems, Lippincott Williams and Wilkins, Philadelphia, **2013**.
[81] B Mishra; C Sankar; C Dilip; V Pravitha; AST Arun Raj. *Der Pharmacia Letter.* **2010**, 2, 21-27.
[82] CA Babu; MP Rao; JV Ratna. *Asian J Pharm Res Health Care.* **2010**, 2, 114-126.
[83] S Herrlich; S Spieth; S Messner; R Zengerle. *Adv Drug Deliv Rev.* **2012**, 64, 1617-1627.
[84] D Prabakaran; P Singh; P Kanaujia; SP Vyas. *Int J Pharm.* **2003**, 259, 173-179.
[85] K Imran; A Priyanka; R Deepti; F Fiza. *Indo Am J Pharm Res.* **2013**, 3, 3147-3157.
[86] M Srikanth; S Sunil; N Rao; M Uhumwangho; KR Murthy. *J Scic Res.* **2010**, 2, 597.
[87] S Kamboj; G Gupta; J Oberoy. *Pharmainfo*. **2009**, 7.
[88] A Beloqui; R Coco; PB Memvanga; B Ucakar; A des Rieux; V Préat. *Int J Pharm.* **2014**, 473, 203-212.