CHAPTER 1

INTRODUCTION
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1.1. INTRODUCTION

Pharmaceutical industry, nowadays, is confronting several issues and challenges owing to global competition and increasing demand for better products. The existing trend in pharmaceutical industry is to develop marked formulations of old active molecule with the support of latest formulation technologies on account of high expenses and longer duration requirement in the new drug development. Substantial attention is being laid to expand the advanced systems in delivery of active pharmaceutical ingredients (API). The word ‘advanced system’ denotes investigating for something out of necessity and is intended to minimize the limitations related with existing dosage form there by leading to optimizing the therapy (Harani et al., 2009). In spite of extraordinary advancements in drug delivery, the oral systems are believed as the suitable and better to administrate the therapeutic agents. This is due to the low cost involved for and also the aspect of easiness involved in administration that leads to superior degree conformity to patient (Yadav et al., 1999).

The main stream oral delivery systems allow a definite amount of API levels in plasma devoid of any control over the delivery of drug. Therefore the oral administration of a medication by way of preplanned or orderly release drug delivery systems should render it capable for enable the release rate of API at a intended, anticipated way and in a controlled manner to gain the required plasma levels and to retain them
steady for a prolonged period of time (Chien et al., 1992). Devising of modified release formulation technologies becomes an efficient concept for utmost use of the bioavailability and dosing frequency of dosage forms. The term ‘modified release’ denotes both delayed and extended release systems for oral administration as well as oral delivery systems particularly planned to change the release of poorly water-soluble drugs and the fast dissolving dosage forms for which absorption occurs principally in different positions of gastrointestinal tract (GIT) (Ohara, 2005).

Development of site specific drug delivery and/or targeted drug delivery to a particular and intended part or organ is to improve the therapeutic efficacy by increasing therapeutic drug concentrations at desired site of action, and also to reduce the side effects and cost by reducing the dose and dosing frequency (Krishnaiah et al., 1998). During the last twenty years, the pharmaceutical scientists extensively probed in the area of colonic region for targeted drug delivery system. The significant hurdles for the colonic drug release are the absorption and deactivation ways in the stomach and small intestine. However, a systematically designed colon-targeted system can get over these obstacles. Targeting drugs to the colon has been turned out to be quite valuable in a variety of disorders, and the colon has been found to be a potential site for local as well as systemic administration of drugs (Libo et al., 2002). Colon targeting is done mainly to treat the ailments of colon,
to cure the diseases such as asthma, angina and rheumatoid arthritis those are sensitive to circadian rhythms and for drugs like proteins, peptides and steroids (Vemula et al., 2009 and Asghar et al., 2006). The major role of colon is for water and electrolytes absorption and for provisional storage of stools. However, now days, colon is largely acknowledged as one of the sites for drug delivery because of the following preferential benefits (Ganesh et al., 2010, Girish et al., 2006 and David, 2005).

- Colon is considered as the entryway for the drugs to enter the systemic circulation for treatment.
- Colon contains only fewer amounts of digestive enzymes and diminishes the possibility of drug degradation and considered as safe when compared to small intestine.
- Colon targeting gives the efficient treatment of the disease at lesser dose with minimum side effects.
- Colonic drug delivery facilitates chronotherapy in case of asthma and rheumatoid arthritis.

Targeted drug delivery systems to the colon provide the following therapeutic advantages (Brahma et al., 2010 and Chourasia et al., 2003):

- Reduces the adverse effects and improves efficacy in case of treating the diseases related to colon.
- By producing well-disposed environment in colon for peptides and proteins when compared to upper GIT.
- Minimizes extensive first pass metabolism of steroids
- Prevents the gastric irritation produced by non-steroidal anti-inflammatory drugs (NSAIDS) upon oral administration.
- Colon targeting provides the delayed release of drugs, to treat angina, asthma and rheumatoid arthritis.

An ideal drug delivery system specifically to the colon avoids the drug release in stomach and small intestine, but begins delivery at the beginning of the large bowel where conditions are most favorable for drug dispersion and absorption. To achieve successful colon targeting, it should overcome the following limitations (Luppi et al., 2008 and Aurora et al., 2006)

- The colon is difficult to access due to its location is at the distal portion of the alimentary canal.
- Successful delivery of the drugs require the solution form prior to appearance in colon, but the low watery content of the colon gives more viscous form than in the upper GIT, which is difficult for water insoluble drugs.
- Colon can limit drug transport across the mucosa in to the bloodstream due to lower surface area and relative tightness of the tight junctions of colon.
1.1.1. ANATOMY AND PHYSIOLOGY OF COLON

Irrespective of therapy desired for local or systemic dispensation of drug, the development and objective of the drug delivery to colon continues to be same i.e.,

- The drug must not be absorbed from other areas of the gastrointestinal tract (GIT).
- It should only undergo negligible degradation in the upper GIT.
- The colonic drug release should be at quantitatively coordinated rate and it should be taken in from the lumen of the large intestine without any substantial degradation.

In order to meet these objectives, a comprehensive knowledge of the structure as well as functioning of GIT is needed. In GIT, the part between ileocecal junction and anus is considered as large intestine that is composed of colon, rectum and anal canal. First part of the large intestine is called as colon, which is a mucosa lined cylindrical tube and is divided into cecum, ascending colon, transverse colon, descending colon and sigmoidal colon. The colon does not possess villi, but due to existence of plicae semilunares (crescentic folds), the intestinal surface of the colon is increased to approximately 1300 cm². The major factors governs release rate of drug from different designs of Colon-specific drug delivery system (CDDS) are pH, transit time and the microbial environment of the colon. Different properties of GIT are given in Figure 1.1 and Table 1.1 (Vyas, 2006 and Yang et al., 2002).
Major functions of the colon are (Mahkam, 2007 and Vincent et al., 2002):

- Generates the suitable atmosphere for the development of microbes of colon.
- Acts as reservoir/ temporary storage of stools.
- Segmenting colonic movements are accountable for assimilation of luminal contents, which stimulated by circular muscles while propulsive movements origin by longitudinal muscles are related to defecation.
Table 1.1 Properties of Gastro Intestinal Tract

<table>
<thead>
<tr>
<th>Region of GIT</th>
<th>Property</th>
<th>Measured value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GIT</td>
<td>Surface area</td>
<td>2-10^6 cm^2</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Length</td>
<td>20-30 cm</td>
</tr>
<tr>
<td>-Duodenum</td>
<td></td>
<td>150-250 cm</td>
</tr>
<tr>
<td>-Jejunum</td>
<td></td>
<td>200-350 cm</td>
</tr>
<tr>
<td>-Ileum</td>
<td></td>
<td>2-10^6 cm^2</td>
</tr>
<tr>
<td>Large intestine</td>
<td>Length</td>
<td>6-7 cm</td>
</tr>
<tr>
<td>-Cecum</td>
<td></td>
<td>20 cm</td>
</tr>
<tr>
<td>-Ascending colon</td>
<td></td>
<td>45 cm</td>
</tr>
<tr>
<td>-Descending colon</td>
<td></td>
<td>30 cm</td>
</tr>
<tr>
<td>-Transverse colon</td>
<td></td>
<td>40 cm</td>
</tr>
<tr>
<td>-Sigmoid colon</td>
<td></td>
<td>12 cm</td>
</tr>
<tr>
<td>-Rectum</td>
<td></td>
<td>3 cm</td>
</tr>
<tr>
<td>-Anal canal</td>
<td></td>
<td>3 cm</td>
</tr>
<tr>
<td>Small intestine</td>
<td>Internal diameter</td>
<td>3-4 cm</td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
<td>6 cm</td>
</tr>
<tr>
<td>Stomach</td>
<td>pH</td>
<td>1-3.5</td>
</tr>
<tr>
<td>Duodenum</td>
<td></td>
<td>5-7</td>
</tr>
<tr>
<td>Jejunum</td>
<td></td>
<td>6-7</td>
</tr>
<tr>
<td>Ileum</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Colon</td>
<td>Redox potential</td>
<td>- 415</td>
</tr>
<tr>
<td>-Right</td>
<td></td>
<td>- 400</td>
</tr>
<tr>
<td>-Mid</td>
<td></td>
<td>- 380</td>
</tr>
<tr>
<td>-Left</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.1.2. COLONIC ABSORPTION OF DRUGS

The small surface area of the colon is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 h).

- Passes through colonocytes (Trans cellular transport)
- Passes between adjacent colonocytes (Para cellular transport)

Most of the lipophillic drugs absorbed by trans cellular transport because of the passageway of drugs through cells, where as hydrophilic drugs absorbed by paracellular transport due to the convey of drug through the tight junctions between the cells (Vyas and Roop, 2006). Drugs that have sound absorption in colon comprise diclofenac, ibuprofen, oxyprenolol, metoprolol and theophylline. While drugs having poor absorption are pyretanide, buflomedel, furosemide, hydroclorthiazide, and ciprofloxacin (Masataka et al., 2006 and Sarasija et al., 2000).

1.1.3. DEVELOPMENT OF COLONIC FORMULATIONS: COMMON DELIBERATIONS

Most of the colonic delivery systems of various drugs are delayed release dosage forms that may be designed either to endow with a burst/fast release or a sustained/prolonged release in the region of colon. The righteous selection of a formulation approach for colon targeting depends on the following factors:

- In case of localized treatment, Pathophysiology of the colon/ affected parts of the lower GIT and nature of the disease, where as the
physiological composition of the healthy colon if the formulation is for 
 systemic action not for the local action.

- Nature of the drugs such as physicochemical and biopharmaceutical 
  properties at the particular site of delivery i.e., colon.
- The physiological factors like pH, transit time of the GIT that governs 
  the design of colonic formulations.
- The desired release pattern of the API.

1.1.4. DRUGS SUITABLE FOR CDDS

Founded on literature review, various categories of drugs suitable for 
 colon drug delivery are given hereunder (Vincent et al., 2002 and Vyas et 
 al., 2006).

- Drugs used to treat irritable bowel disease (IBD) need local delivery at 
  drug to colon e.g. sulfasalazine, olsalazine, mesalazine, steroids like 
  fludrocortisone, budanoside, prednisolone and dexamethasone.
- Drugs to treat colonic cancer require local delivery e.g. 5-fluorouracil, 
  doxorubicin, and methotrexate.
- Protein and peptide drugs which eliminate drug degradation e.g. 
  growth hormones, calcitonin, insulin, interleukin, interferon and 
  erythropoietin.
- Drugs to treat infectious diseases (amoebiasis & helminthiasis) - 
  requires site specific delivery e.g. metronidazole, mebendazole and 
  albendazole,
Drugs to treat rheumatoid arthritis (NSAIDS), nocturnal asthma, angina require delay in absorption due to circadian rhythms.

Drugs indicative of more selective absorption in colon than small intestine due to small extent of paracellular transport e.g. glibenclamide, diclofenac, theophylline, ibuprofen, metoprolol, and oxyprenolol.

1.1.5. COLON-SPECIFIC DRUG DELIVERY: FORMULATION TECHNOLOGIES

Different types of formulations aimed to achieve the colon targeting are chiefly cataloged into four types (Kumar et al., 2010). They are

(i) Prodrug approach

(ii) pH-dependent (Delayed release) system

(iii) Time-dependent (Timed release) system

(iv) Microbial-dependent (Microbial controlled) system

1.1.5.1. Prodrug approach

A pharmacologically dormant derivative of the original drug that needs spontaneous in vivo enzymatic transformation on the way to liberate the original physiologically active drug in the specific site is called as prodrug (Sinha et al., 2001 and Samyn et al., 1995). This system involves covalent bonding linking the API and its conjugate to form a prodrug, which should stable in upper GIT but release the drug in colonic environment upon the enzymatic cleavage/hydrolysis due to microbial colonic environment (Etienne et al., 1996).
This biotransformation is undertaken by different colonic enzymes such as azo-reductase, nitro-reductase, glycosidase deaminase and β-galactosidase etc. An ideal prodrug should be bulky and hydrophilic to minimize absorption from the stomach and small intestine and it is renovated into a lipophilic drug molecule accessible for absorption in the colon. Different types of conjugates to form prodrug for colon targeting are given in Table 1.2 (Lee et al., 2007, Nagpal et al., 2006, Zou et al., 2005, Chavan et al., 2001, Soodabeh et al., 1997, Kaneto et al., 1997 and Harold et al., 1997). The challenging conception of prodrug formation is that the covalent linkage will result harmless and efficient liberation of the drug with smallest amount of oscillation in the specific region i.e., colon (Jung et al., 2006).

1.1.5.2. pH-dependent systems

The key theory concerned with pH-dependent systems is the usage of various pH sensitive polymers to coat the dosage forms (Table 1.2). These are intended not only to generate delayed release but also to furnish security from GI fluids. Assortment of suitable polymer is a critical issue in this method. The selected polymers must be capable to resist the pH of upper GIT to facilitate colon targeting (Davaran et al., 2001). In case of solid formulations for colon specific delivery systems found on pH-dependency, the release mechanism of API is same as usual enteric-coated dosage forms except the site specificity. Contrary to the established enteric-coated formulations, pH-dependent systems for colon
delivery are aimed to release the APIs to the terminal part of ileum and colonic region by utilizing higher threshold pH enteric polymers (Sriamornsak et al., 2007).

In this approach, the majority of regularly used polymers belong to methacrylic acid and cellulosic derivatives, which have the capability to stand firmly for a number of hours in the atmosphere varying from acidic pH (~1.2) to neutral pH (~7.5). Evidently, retaining the integrity of colonic delayed release for pH-dependent systems in passage through the upper GIT is very important until it reaches the colon. The most frequently used polymers for colon targeting are methacrylic acid esters (Rodriguez et al., 2001 and Cheng et al., 2004). Eudragit S100 and L100 are the preferred polymers for colonic formulations as L100 is withstand up to pH 6 or above while S100 up to pH 7 (Skalsky et al., 2003). The major disadvantage of this method is early release of API in the stomach and small intestine that leads to decreasing the therapeutic efficiency of formulation due to disintegrating of coat in the small intestine. Applying higher coating levels of enteric polymers is somewhat significant method to overcome this problem.

1.1.5.3. Time-dependent systems

Time-dependent formulations are able to deliver the API both at predetermined times when patient required and at a desired and specific site i.e., colon. The main principle implied in this approach is delivering
the API after a predetermined lag time to reach the colon at correct period in precise quantity (Arora et al., 2006).

A lag time incorporated in the formulations is comparable to the transit time from mouth to colon to give colon specific release i.e., 5 h (Cheng et al., 2004). In this method, the thickness of the surface coating layer of the delivery system using various polymers (Table 1.2) will demonstrate the time needed to release the drug (Sinha et al., 2006 and Wu B et al., 2007). The most challenging factor of this approach to formulator is controlling the drug release up to predetermined lag time that depends on the concentration and thickness of the polymer in the matrices/coating layer. Perfectly, systems based on this approach are intended that the individual variations in the gastric emptying time, upper GIT pH or bacterial environment in the colon are not influenced the delivery site. In the therapy of diseases depend on circadian rhythms, time-dependent systems are highly suitable for efficient therapy. (Ziyaus et al., 2006 and Fukui et al., 2000).

1.1.5.4. Microbial-controlled systems

The fundamental law engaged in microbial-controlled systems is microbial or bacterial enzymatic degradation of polymers presented in/on the dosage forms to release the API in the colon. This is due to the atmosphere within the human GIT is illustrated with existence of multifaceted microorganisms, specifically the colonic region (Patel et al., 2009 and Sinha et al., 2003). The efficacy of this approach is depending
on the nature of polymers incorporated i.e., biodegradability. When this system passing through stomach and small intestine, the dosage form is maintaining its integrity due to minimum microbial degradable activity that is inadequate for degrade the polymer (Sinha et al., 2002).

The list of polymers (polysaccharides) used in this approach is given in Table 1.2 (Wei et al., 2007, Sinha et al., 2007, Mundargi et al., 2007, Song-Qi et al., 2006, Das et al., 2006, Liu et al., 2006, Chambin et al., 2006, Kashappa, 2005, Atyabi et al., 2005, Parisa et al., 2004, Libo et al., 2003, Norihito et al., 2003, Paola et al., 2003, Norihito et al., 2002, Masataka et al., 2002, Shinji et al., 2001, Hideki et al., 2001, Krishnaiah et al., 2001, Lee et al., 2000, Irit et al., 2000, Nykanen et al., 1999, Khaled et al., 1999, Irit et al., 1998, Hideyuki et al., 1997, Munjere et al., 1997 and Snezana et al., 1996). The colonic formulations based on this approach are believed safe since the polymers used are belongs to dietary fiber. But the major limitation of these systems is hydrophilicity of these materials leads to soluble/disperses or swells in the aqueous environment present in the GIT.
Table 1.2 Materials used in Formulation of CDDS

<table>
<thead>
<tr>
<th>Prodrug conjugates</th>
<th>pH-sensitive polymers</th>
<th>Time-dependent polymers</th>
<th>Microbial degradable polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azo bond conjugates</td>
<td>Eudragit L-100 and S-100</td>
<td>Hydroxy Propyl Methyl Cellulose</td>
<td>Guar gum, Chitosan and Pectins</td>
</tr>
<tr>
<td>Amino acid (polypeptide) conjugates</td>
<td>Eudragit L-30 D, FS 30 D and L-100-55</td>
<td>Hydroxy Ethyl Cellulose</td>
<td>Cyclodextrins and Dextrans</td>
</tr>
<tr>
<td>Glycoside conjugates</td>
<td>Poly Vinyl Acetate Phthalate</td>
<td>Ethyl Cellulose</td>
<td>Inulin and Lactulose</td>
</tr>
<tr>
<td>Glucuronide conjugates and Sulphate conjugates</td>
<td>Hydroxy Propyl Methyl Cellulose Phthalate 50 and 55</td>
<td>Microcrystalline Cellulose</td>
<td>Amylose and Alginates</td>
</tr>
<tr>
<td>Polymeric conjugates</td>
<td>Hydroxy Propyl Ethyl Cellulose Phthalate</td>
<td>Hydroxy Propyl Methyl Cellulose Acetate Succinate</td>
<td>Locust bean gum and Boswellia gum</td>
</tr>
<tr>
<td>Cyclodextrin and Dextran conjugates</td>
<td>Cellulose Acetate Phthalate and Trimellate</td>
<td>Lactose/Behinic acid</td>
<td>Chondroitin sulphate</td>
</tr>
</tbody>
</table>
1.2. LITERATURE REVIEW

Maroni et al 2012: This review gives a brief introduction to the physiology of the colon and discusses the necessity for oral colonic drug delivery. The authors reviewed elaborately on the approaches of colon targeting like pH-sensitive, time-controlled and microbial activated methods. Although the review is based on insulin delivery it gives a general review of colonic drug delivery systems.

Kumar et al 2011: They explained elaborately about constraints and challenges involved in the development of colonic formulations. Approaches like microbially triggered delivery, targeted prodrug design, pH and time sensitive systems, pressure and osmotically controlled methods were discussed. Pulsatile drug delivery was covered extensively in this review.

Philip et al 2010: The topical, local and systemic actions of drug delivery systems were discussed in this review. A specific disease condition requires a specific drug delivery system depending up on whether the disease condition requires topical delivery, local action or systemic action of the drug. The drug delivery systems targeting colon are divided into primary approaches and newer approaches. Conventional colon specific systems include prodrugs, pH and time dependent delivery systems and microbially triggered systems. The newly developed methods include delivery systems based on osmosis and pressure.
Shukla et al 2012: The carbohydrate polymers like guar gum, pectin, chitosan, dextran and alginates are explored for the application in colon specific drug delivery. Similarly carbohydrate mixtures, carbohydrate eudragit mixtures were also used in delivery systems specific to colon. Polysaccharide modification boosts the applicability to achieve colon targeting. This review also touches upon the industrial patents and marketed formulations.

Maroni et al 2009: The main objective of the study by Maroni et al is to assess the feasibility of time-controlled proposal, chronotopic, to deliver the insulin specifically to colon. Insulin loaded core tablets were coated with HPMC for time dependent release to the colon. Stability studies (accelerated as well as long term) were conducted on selected formulation. The conclusions from the study include that the manufacturing process has minimal effect on the stability of insulin and long term stability tests suggested that the stability of insulin in the formulation.

Rujivipat et al 2010: The aim of this investigation is to acquire desire release profiles using HPMC compression coating of the tablets with progressive time. Drugs with different solubility were incorporated into the core of the tablet and compression coated with HPMC so as to know the feasibility and difficulties of the compression coating. A distinct lag time was observed with all the formulations containing different drugs, but the release rates afterwards were determined by the solubility
of the drug. Molecular weight of the HPMC in the compression coat significantly influenced the release pattern of poorly soluble drugs but there was no effect was observed in case of soluble drugs dissolution profiles.

Liew et al. 2006: The natural polymers, alginates have a significant role in development of various formulations. The key properties that influence the release rate of drug from matrices contains alginate include chemical nature, viscosity and particle size etc. The present study studied the effect of above properties on release profile.

Mastiholimath et al 2007: Present study employed time dependent and pH dependent approaches to gain the specific release of theophylline to the colon. This system contains an insoluble hard gelatin capsule body loaded with theophylline-eudragit microcapsules then plugged using hydrogel seal. This is then coated with enteric polymer to avoid release variability to achieve colon specific release.

Belgamwar et al. 2008: Pulsatile release systems are the quick as well as momentary drug release after a predetermined lag time. Pulsatile drug delivery is beneficial in diseases which show circadian rhythms in their pathophysiology and for drugs which need protection in the upper GIT. Present article discusses about the diseases requiring pulsatile delivery of the drugs and delivery approaches which facilitate pulsatile drug delivery.
Neekhra et al 2010: In the present investigation developed the colon drug delivery system of ketorolac tromethamine capsule. In this, capsules were fabricated using combination of guar gum and cellulose acetate phthalate. This study revealed that combination of pH dependent approach and microbial activated approach was suitable for colon targeting.

Mura et al 2006: This study was intended to develop a simple matrix tablets for colon targeting. In this study Mura et al explained the advantage of combination of microbial degradation approach and pH sensitive method to achieve the successful drug delivery specifically to colon. The present investigation deals with the preparation of enteric coated pectin matrix tablets using theophylline as model drug and achieved the colon specific release.

Sinha et al 2006: This study is about the preparation of pH-sensitive polymer coated fast released tablets for colonic delivery. The amount of super disintegrant and coat weight were varied to get an optimized formulation that releases the drug specifically in the colon. In the same article authors described another approach, osmogen based delivery to achieve colon-specific release. Both approaches succeed to release the celecoxib specifically in the colon.

Viriden et al 2011: They studied the influence of HPMC chemical diversity on the release rate of API from hydrophilic matrices. The release profile of model drugs methyl paraben and butyl paraben from the HPMC
matrix was studied. The results suggested that the more hydrophobic butyl paraben interacted closely with HPMC and the release was slower in comparison to the methyl paraben which interacted at lower extent and the release was faster. Substituent heterogeneity of the HPMC is a significant factor that affects the release rate of drug from matrices.

Escudero et al 2008: Development of HPMC matrices using different viscosity grades were studied in this study and introduced a new polymer i.e., hydroxylpropyl cellulose-methyl methacrylate. The dissolution rate was controlled by the swelling rate, porosity and capillary action from hydrophilic matrix. From the study, freeze dried polymer mixtures required low pressure, showed superior plasticity and easy way to prepare tablets when compared with oven dried polymer blendes. Diffusion and erosion controlled release mechanisms were observed in the study.

Gohel et al 2009: The present investigation deals with development of new delivery system of ibuprofen specifically to colon. In this, the capsules made with HPMC filled with ibuprofen and pregelatinized starch then gave inner ethyl cellulose coat and outer eudragit S100 coat to gain colon targeting.

Paharia et al 2007: The intention of this study was to formulate colon targeted 5-fluorouracil eudragit coated pectin microspheres. Emulsion dehydration method was used to prepare the microspheres by
incorporating pectin and coated with eudragit. From the results it was found that the colonic release of 5-fluorouracil from microspheres.

Mandal et al 2010: In this study, matrix tablets of diltiazem were prepared using sodium alginate and polyacrylamide-grafted- copolymer. The effect of proportions of copolymer and sodium alginate on the dissolution rate was determined and it was chiefly depending on the swelling capacity and the viscosity of matrix.

Sriamomsak et al 2007: Modified drug release behavior of alginate system was studied by incorporating the metronidazole as a model drug. Direct compression method was employed to prepare the alginate matrix tablets of different grades. From this study it was concluded that the drug release from alginate matrices is due to combination effect of swelling and erosion phenomena.

Krishnaiah et al 1998: In the present study indomethacin-guar gum colon specific compression coated tablets were developed. Guar gum is compression coated on indomethacin core tablets to retard the drug release in the upper GIT. The tablets showed negligible drug release in the upper GIT but progressive release showed in the colonic region.

Ugurlu et al 2007: Nisin compression coated tablets with pectin and HPMC mixture were formulated for colon-specific release. Different ratios of pectin to HPMC were used in the compression coat. From this study it was found that pectin/HPMC envelopes offers colonic delivery of nisin.
Kabra et al 2011: This article explained the efficacy of hydrophilic polymers like HPMC and sodium alginate as colon specific release polymer. In this investigation 5-amino salicylic acid enteric coated matrix tablets were developed to achieve successful colon targeting.

Zou et al 2008: The present article studied the development of a time controlled colon targeting wax matrix tablet and coated with eudragit NE 30D then investigated for in vitro drug release profile and for in vivo pharmacokinetics. Wax matrix tablets showed more stable release than the tablets without wax matrix. With Eudragit coating of the wax matrix tablets the lag time of 3h was achieved.

Krishnaiah et al 2001: Present study is carried out using 20% guar gum in a matrix tablet for colonic delivery of albendazole. The authors developed the guar gum matrix tablets and explained the effect of metronidazole and tinidazole on albendazole release. The dissolution studies conducted using 4% w/v rat ceacal contents. From the results guar gum present in the matrices degraded due to the effect of microbial environment.

Akhlaq et al 2011: Once-daily ethyl cellulose-flurbiprofen (100 mg) matrix tablets were developed by direct compression method based on controlled release mechanism. Effect of other excipients like HPMC, starch and CMC, was studied on the release behavior of the tablets. The developed formulation showed a better release profile than the marketed formulation.
Krishnaiah et al 2003: Mebendazole-guar gum colon specific tablets were compared with conventional tablets of same in human volunteers to study the pharmacokinetics using cross over design. The dose of mebendazole was 50 mg in both tablets. From the study, fast release of Mebendazole was shown by conventional tablets while guar gum tablets gave 5 h lag time to reach the plasma indicating the delayed release for colon targeting.

Krishnaiah et al 2003: This experiment deals with the comparison between the 5-fluorouracil colon specific guar gum tablets and conventional tablets of same. Pharmacokinetic studies were done in 12 healthy humans by giving 50 mg tablets. The appearance of drug in plasma was observed after 6 h lag time in case of guar gum tablets while quick appearance within 30 min was shown by conventional tablets after oral administration. Colon specific tablets were succeed to retard the drug release in upper GIT and prolonged release in colon in contrast to conventional tablets of 5-fluorouracil.

Al-saidan et al 2004: The authors carried out the pharmacokinetic study in six human volunteers using metoprolol tartrate three layer guar gum matrix tablets. From this investigation it was found to be delay in the T_max and unchanged bioavailability with extended half life in case of colon specific tablet in contrast to conventional tablet demonstrated a slow and extended metoprolol tartrate release in the colon.
Wang et al 2007: Sustained-release pellets of flurbiprofen were prepared to reduce the administration frequency. The absorption of flurbiprofen sustained-release capsules were compared with those of immediate release tablets. A novel HPLC analytical method was developed and utilized to analyze the flurbiprofen from rat plasma samples. UV detector was used and the mobile phase was methanol and phosphoric acid solution (70:30 v/v). This method was used to evaluate the pharmacokinetics of sustained and immediate release tablets.

Bhaskar et al 2009: The authors developed the flurbiprofen solid lipid nanoparticles and nanostructured lipid carriers and incorporated into the hydrogels for transdermal delivery to enhance the bioavailability. The pharmacokinetic parameters of flurbiprofen solid lipid nanoparticles in rats were evaluated using a HPLC method analyzed at 245 nm using the mobile phase containing 60% acetonitrile and 40% aqueous phase (pH 2.6). Using this method it was proved that the transdermal gels were more bioavailable than the oral formulation.

Radwan et al 2010: this study aimed to develop the polyethylcyanoacrylate nanoparticles as biodegradable carriers for ketorolac oral systems. Polymerization technique at room temperature was employed to prepare the nanoparticles in a continuous aqueous phase to achieve 76–96% of ketorolac. A novel ultra-performance liquid chromatography tandem mass spectrometry was developed and used for the quantization of plasma levels of ketorolac in rats.
1.3. DRUG PROFILE-FLURBIPROFEN

Chemical name: 2 Fluoro-α-methyl-(1,1-biphenyl)-4-acetic acid.

Structure:

\[
\text{Molecular formula: } C_{15}H_{13}FO_2. \\
\text{Molecular weight: } 244.30. \\
\text{Description: } A \text{ colorless crystalline solid. Flurbiprofen (FLB) is a } \text{derivative of propionic acid that is analgesic and antipyretic belongs to nonsteroidal antiinflammatory drugs (NSAID). Flurbiprofen is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen.} \\
\text{Solubility: Freely soluble in most of the organic solvents and moderately soluble in water.} \\
\text{Melting point: About } 110^\circ \text{C.} \\
\text{Partition coefficient: Log P (octanol/water), 4.2.} \\
\text{Mechanism of action: Flurbiprofen is a non selective COX inhibitor and is one of the most effective NSAIDs to hinder the prostaglandin. Like other NSAIDs, the antiinflammatory effects of flurbiprofen happen}
through inhibition of cyclooxygenase enzyme that is accountable for the alteration of arachidonic acid to prostaglandin G2 and to prostaglandin H2. Then it is diminish the prostaglandins responsible for inflammation, pain, swelling and fever.

**Volume of distribution:** 0.1 L/kg.

**Clearance:** 0.3 ml/min/kg.

**Biological half-life:** 2 to 6 h (≈3.5 h).

**Protein binding:** 99% in plasma.

**Pharmacokinetics:** After oral administration, flurbiprofen has quick and complete absorption and reached \( C_{\text{max}} \) within 30 min to 4h. About 95% of administered dose is under gone to urine excretion mainly as 4-hydroxy, 3, 4-dihydroxy, and 4-methoxy metabolites, which are excreted partly as conjugates; about 25% dose is excreted in unchanged form.

**Dosage forms:** FLB tablets having 50 mg and 100 mg dose exist and ophthalmic solutions containing 0.33% and store at controlled room temperature and in tightly closed containers.

**Dose:** Daily 150-300 mg.

**Toxicity:** General undesirable effects of FLB are stomachache, constipation-diarrhea, stomach upset, ulcer formation, nausea-vomiting, renal and liver aberrations and headache.
1.4. DRUG PROFILE-KETOROLAC TROMETHAMINE

Chemical Name: (±)-5-benzoyl-2,3-dihydro-lH-pyrrolizine-1-carboxylic acid.2-amino-2-[hydroxymethyl]-1,3 propanediol.

Structure:

Molecular formula: C₁₅H₁₃NO₃. C₄H₁₁NO₃.

Molecular weight: 376.40.

Description: Ketorolac Tromethamine (KTM) is a analgesic and antiinflammatory drug that is alkaline salt of a slightly acidic drug belongs to pyrrolo-pyrrole group of non-steroidal antiinflammatory drugs (NSAIDs).

Solubility: It is freely water soluble drug and also in methanol, but moderately soluble in ethanol and it is completely insoluble in methylene chloride.

Melting point: 160-161°C.

Partition coefficient: 2.32 [in octanol/water],.
Mechanism of action: KTM acts through inhibition of cyclooxygenase enzyme in metabolism of arachidonic acid and consequently reducing synthesis of prostaglandin to demonstrate distinct analgesic effect.

Volume of distribution: 0.15-0.33 L/kg.

Plasma half-life: 4-6 h.

Bioavailability: Oral bioavailability after administration of an oral solution is up to 81-100%.

Pharmacokinetics: Ketorolac is well absorbed after oral administration and also through intramuscular route and reached $C_{\text{max}}$ within 0.5-1.0 h. It is converted in the liver to metabolites like glucoronic acid conjugates and para-hydroxy derivatives and excreted primarily in urine.

Dosage forms: KTM tablets having 10 mg and 30 mg/ml IM injections exist and also obtained in the form of ophthalmic formulations.

Dose: 10 to 40 mg daily.

Toxicity: KTM produces the side effects if plasma levels are exceeding 5 mg/L. The common incidences are headache, nausea, rash oedema and hypertension.
1.5. EXCIPIENT PROFILE

1.5.1. HYDROXYPROPYL METHYLCELLULOSE (HPMC)

Chemical name: Cellulose, 2-hydroxypropyl methyl ether

Synonyms: Methyl Hydroxy Propyl cellulose, Propylene Glycol ether of methylcellulose, Methylcellulose, Methylcellulose propylene, Glycol ether, Methocel, Metolose, E464, Pharmacoat, Culminal MHPC.

Structural formula:

![Structural formula of HPMC](image)

Where R is H, CH₃ or CH₃-CH(OH)-CH₂

Molecular weight: 10,000-15,000,000

Description: HPMC is colorless to cream white and odour less and taste less powder, which is granular in nature. The density of the powder is 0.3 to 1.3 g/ml and specific gravity is 1.26.

Solubility: Soluble in cold water, completely insoluble in chloroform, ethanol and ether but has solubility in ethanol and dichloromethane mixture.

Viscosity: HPMC-K4M-3,000-5600 mPas, K15M-2,000-21,000 mPas and K100M: 80,000-1, 20,000 mPas

Melting point: HPMC browns in the range of 190-200°C temperature, chars at 225°C and glass transition temperature is 170-180°C.
**Functional category:** It has a wide range of functions in the pharmaceuticals and acts as a coating polymer, film forming agent, controlled release polymer and also used as binding agent to make tablets, suspending agent and viscosity enhancer.

**Application:** Concentration between 2.0 to 5.0 % w/w may be used as a binder in both wet and dry granulation process. High viscosity grades act as release retarders for water-soluble drugs. Concentration at 0.45-1% w/w acts as thickening agent and as vehicle designed for eye drops. HPMC is also acts as a binder in plastic bandage. It has wide applications in food and cosmetic preparations. In addition, it acts as emulgent, suspending agent and stabilizer in topical preparations.

**Stability and storage:** It is slightly hygroscopic. The bulk substance must be stored in tightly closed packing in dry but cool place. Increased in temperature reduces the viscosity of the solution.

**Effect of viscosity:** Drug release profile is stoutly controlied by viscosity of the gel barrier that forms on the tablet surface due to hydration of HPMC. Higher concentrations in matrices and the higher molecular weight grades exhibit high viscous gels.
1.5.2. SODIUM ALGINATE

Source: In nature alginates are available in large amounts. It is originate as a structural constituent of brown algae such as *Macrocystis pyrifera*, *Ascophyllum nodosum*, *Laminaria hyperborean* found in the marine.

Structure: Alginic acid, a linear, anionic block copolymer heteropoly saccharide containing monomers of β-D-mammuronic acid and its epimer, α-L-guluronic acid residues connected together through 1,4-glycosidal linkages.

Solubility: Alginic acid is moderately water soluble and insoluble in most of the organic solvents. It is reacting with alkali metal ions to form alginates (salt forms) that are hydrophilic, soluble in cold water. Sodium alginate (SA) is slowly soluble in cold water to form viscous solution/gel and is insoluble in alcohol.

Gel properties: The aqueous solution of SA is capable to form gels in the presence of Ca$^{2+}$, Sr$^{2+}$, Ba$^{2+}$, Fe$^{3+}$ and Al$^{3+}$ ions by replacing Na$^{+}$ ion that is called as electrostatic interaction. This property of SA is widely applied in pharmaceutical preparations.

Viscosity: A variety of viscosity grades of SA are available, producing 1% aqueous solutions of different viscosity within a range of 20-400 cp at 20°C. These solutions are pseudo plastic in nature.

Stability: SA is highly hygroscopic in nature. The stability Sa powder is excellent when it is stored in a tightly closed container at room temperature. In solution form it is having high stability at 4-10 pH range.
Viscosity of SA solutions reduces at above 10 pH and at high temperatures.

**Functional category:** It has different roles in the pharmaceutical formulations due to its natural origin and low toxicity. It acts as a

- Viscosity enhancer.
- Controlled release matrix forming agent.
- Binding agent.
- Thickening agent
- Suspending agent.

**Application:** 5.0 % w/w SA is acting as binding agent in both wet and dry granulation process. High viscosity grades form matrices that controlled the release rate. It is widely used suspending/thickening agent.
1.5.3. EUDRAGIT

EUDRAGIT S 100 (ED) is the aqueous dispersion of methacrylate copolymer. ED is practically insoluble in acidic media (low pH), but dissolves through salt formation at above pH 7.0. Apart from its enteric properties, its dissolution at a higher pH value allows site specific delivery of drugs.

Structure:

```
R1
[CH3—CH2] n
| R2
| C—O
| R3
| n
| R4
| C—O
| CH2CH2N*(CH3) Cl–
```

R1 = CH3, H; R2 = CH3; R3 = COOH; R4 = CH2CH2N+(CH3) Cl–;

Advantages of Eudragit coating:

- pH-sensitive release of APIs.
- Protection of gastric mucosa and protection of drugs sensitive to gastric fluid/acidic environment.
- Enhance the drug efficacy and good storage stability.
- GI and colon targeting.

Applications:

- Conventional application is acting as coating polymer.
- Used as controlled release matrix forming agent.
- Used to modify the release rate of pH sensitive drugs.
- Used in taste masking.
1.6. OBJECTIVES OF THE STUDY

The current investigation is aimed to formulate new anti-inflammatory colon-targeted tablets of Flurbiprofen and Ketorolac Tromethamine using time-dependent systems and combining the time-controlled and pH sensitive approaches. In the present study Hydroxypropyl methylcellulose and Sodium alginate were employed as time-dependent polymers and Eudragit S100 was employed as pH sensitive material to formulate matrix and compression coated tablets.

The major objectives of the present study are as follows:

- Development of the HPLC analytical method for flurbiprofen and ketorolac tromethamine and plot the standard graphs in different pH media using UV-Visible spectroscopy.
- Selection of the suitable additives/excipients.
- To execute preformulation studies like solubility studies in different solvents, solution stability, flow properties etc.
- To perform drug excipient interaction studies using FTIR and DSC techniques.
- To prepare colon specific matrix tablets of flurbiprofen and ketorolac tromethamine using different polymers.
- To evaluate various physical parameters like weight variation, hardness, friability and drug content of tablets.
- To plan the *in vitro* drug release studies of prepared tablets using USP XXIV dissolution equipment in simulated GI fluids.
To study the effect of polymers like hydroxypropyl methylcellulose and sodium alginate and effect of viscosity grade of hydroxypropyl methylcellulose on drug release.

To evaluate the eudragit S100 coating on optimized matrix tablet formulation and select the optimized formulation.

To determine the drug release mechanism of matrix tablets using various kinetic models.

To prepare and evaluate the flurbiprofen fast disintegrating tablets and select the optimized formulation as core tablet for compression coating.

To prepare and evaluate the core tablets of ketorolac tromethamine and select the optimized formula for compression coating.

To prepare colon specific compression coated tablets of flurbiprofen and ketorolac tromethamine using different polymers.

To evaluate various physical parameters like weight variation, hardness, friability and drug content of tablets.

To plan the in vitro drug release studies of prepared tablets using USP XXIV dissolution equipment in simulated GI fluids.

To study the effect of polymers like hydroxypropyl methylcellulose and sodium alginate and effect of viscosity grade of hydroxypropyl methylcellulose on drug release to select optimized formulation.

To incorporate the eudragit S100 in optimized compression coated formulation to study its effect to select optimized formulation.
• To determine drug release mechanism of compression coated tablets using dissolution data in various kinetic models.

• To carry out the stability studies of optimized tablets at 45 °C and 75% RH for six months.

• To plan the in vivo x-ray studies for optimized tablets of both drugs in human volunteers.

• To compare the drug release rate of final optimized formulation with control conventional formulation for two drugs.

• To plan the in vivo studies of final optimized tablets of both drugs in human volunteers in comparison with the control conventional formulation for pharmacokinetic evaluation.

• To assess the in vitro-in vivo correlation.
1.7. PLAN OF RESEARCH WORK

- Literature review
- Procurement of drugs and polymers
- Analytical method development
- Selection of excipients
- Selection of method and polymers for colon delivery
- Preparation of matrix and compression coated tablets
- Physical characterization of tablets
- *In vitro* dissolution studies
- Study the effect of Eudragit S 100
- Drug-polymer interaction studies
- Stability studies
- *In vivo* x-ray imaging studies
- *In vivo* pharmacokinetic evaluation
- Documentation of the results
- Conclusion of the study