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AN UPDATE OVERVIEW OF RECENT ADVANCES ON FORMULATION DEVELOPMENT FOR COLON TARGETING

Beena Kumari [1], Prabhat Kumar Upadhyay [2], Manish Kumar [* 3], Sonia Narwal [4], A. Pandurangan [3] and Anuj Malik [3]

Department of Pharmaceutical Sciences [1], IGU, Meerpur, Rewari - 123401, Haryana, India.
Institute of Pharmaceutical Research [2], GLA University, Mathura - 281406, Uttar Pradesh, India
M. M. College of Pharmacy [3], Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala - 133203, Haryana, India.
Department of Pharmaceutical Sciences [4], PDM University, Bahadurgarh - 124507, Haryana, India.

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Correspondence to Author:
Dr. Manish Kumar

Professor,
M. M. College of Pharmacy,
Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala - 133203, Haryana, India.

E-mail: manish_singh17@rediffmail.com

ABSTRACT: In targeted drug delivery systems, there is one of the most important drug delivery systems is colon targeting drug delivery system. This system is mainly used in the treatment of diseases like colonic cancer, ulcerative colitis, Crohn's disease. For local treatment of various bowel diseases colon is highly desirable. For the systemic action of nonpeptide drugs *i.e.*, cardiovascular and antiasthmatic agents and protein-peptide drugs such as insulin, calcitonin, colon targeting is apparently useful. There are various approaches that have been proposed for targeted colon delivery; they include the pH, pressure controlled, time-controlled, microflora, osmotic controlled, and multi-particulates and novel techniques. The carriers used in this system are microsphere, synthetic polymers, liposomes and nanoparticles, matrix tablets and compression coated tablets *etc.*

INTRODUCTION:

Oral Drug Delivery Systems: The oral route is considered to be the most convenient route for the administration of drugs to patients. Normally drugs dissolve in stomach fluid or intestinal fluid and are absorbed from these regions of GIT. For a specified period of time-controlled drug delivery is one of the systems that deliver the drug locally or systemically at a predetermined rate. Throughout the course of GIT at predictable & reproducible kinetics, it provides the continuous oral delivery of drugs for predetermined period [1].

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Drug delivery systems which take into consideration the carrier, route and the target, have been evolved on the strategy of processes or devices designed to enhance the efficacy of therapeutic agents through controlled release. This may involve enhanced bioavailability, improved therapeutic index or improved patient acceptance [2].

Limitations of Conventional Dosage Forms:

- With short half-life and increased chances of missing the dose of the drug due to which frequent administration is necessary so, poor patient compliance.
- The manifest fluctuations of dose may lead to under medication or over medication.
- The accomplishment of a steady-state condition makes difficult due to typical peak-valley plasma concentration time profile.

- Precipitation of adverse effects may leads due to fluctuations in drug levels, especially whenever over medication occur of a drug with small Therapeutic Index (TI) [3].

Controlled Drug Delivery Systems: This system is capable of controlling the drug delivery rate, targeting the delivery of the drug to tissue and sustaining the duration of therapeutic activity. Modified drug delivery or a controlled drug delivery system is classified into four types.

1. Delayed-release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, this system can be defined as sustained drug action by maintaining a relatively constant, effective drug level in the body at a predetermined rate with concomitant minimization of undesirable side effects [4]. Various factors are responsible for designing a controlled drug delivery system as polymer used, nature of the drug, nature of the polymer, target site, route of drug delivery, disease, patients and many other biopharmaceutical factors. Out of these factors, the route of drug delivery has a significant impact on the therapeutic outcome of the drug. Additionally, it may be possible to deliver the drug at a controlled rate and to the target organs *i.e.,* targeted controlled drug delivery. The targeting of a drug to the site of action can be divided into three different types [5].

- First-order targeting (delivery to the discrete organ).
- Second-order targeting (targeting the specific cell type within a tissue or organ, *e.g.,* tumor cells).
- Third-order targeting (delivery to a specific intracellular compartment in the cells, *e.g.,* lysosomes).
- Advantages of controlled drug delivery systems [1, 6].
- Improved patient compliance due to decreased dosing frequency.
- Reduced the total amount of dose as a result of targeting.
- More uniform drug effect.
- Enhanced efficacy at the desired site by modifying the carrier to the target site.
- Better patient acceptance & compliance.
- Less fluctuation at plasma drug levels.
- Disadvantages of controlled drug delivery systems [6].
- Chances of dose missing.
- For accurate dose adjustment reduced potential.
- Additional need for patient education.
- Increased cost.
- Technology intense, patented systems.

Colon Targeted Drug Delivery: For local treatment of various bowel diseases such as colonic cancer, ulcerative colitis, crohan's disease amebiosis targeted drug delivery to the colon is highly desirable. For systemic action of nonpeptide drugs such as cardiovascular and antiasthmatic agents and protein-peptide drugs such as insulin, calcitonin, colon targeting is apparently useful [7]. In the systemic absorption of drugs like Nifedipine and isosorbide, the colonic delivery is also useful. The protection of a drug requires *via* the gastrointestinal tract from being released in the stomach and small intestine for the successful delivery of drugs to the colon [1].

TABLE 1: OPTIMUM PH OF COMMONLY USED POLYMERS

Polymers	Optimum pH for dissolution
Eudragit L100	6.0
Eudragit S100	7.0
Eudragit L30 D	5.6
Eudragit FS30 D	6.8
Eudragit L100-55	5.5
Polyvinyl acetate phthalate	5.0
Hydroxyl propyl methyl cellulose phthalate	4.8
Hydroxyl propyl methyl cellulose phthalate 50	5.2
Hydroxyl propyl methyl cellulose phthalate 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0
Shellac	7.0

By the application of thicker layers of a conventional enteric coating or extremely slow releasing matrices, slower release rates or longer release duration is obtained in this easiest method for targeting of drugs to the colon. For colon drug targeting there are several methods or techniques such as; formation of the prodrug, coating with biodegradable polymers, coating with pH-sensitive polymers, designing formulations using

polysaccharides, timed released systems, osmotic pressure controlled systems. A simple approach for colon-specific drug delivery is provided by a coating of the pH-sensitive polymers **Table 1** [8].

Need for Colon Targeted Drug Delivery: [9]

- Direct treatment at the disease site, lower dosing, and less systemic side effects may be ensured by targeted drug delivery to the colon.
- Oral administration of peptide and protein drugs may be done by site-specific or targeted drug delivery systems.
- To prolong the drug delivery colon-specific formulation could also be used.
- The colon is a site where topical treatment, local or systemic drug delivery could be achieved *i.e.* treatment of bowel disease, ulcerative colitis or crohan's disease. Inflammatory conditions are usually treated using glucocorticoids and sulphasalazine.
- By targeting drugs to colon a number of other serious diseases of the colon may also be treated more effectively *e.g.* colorectal cancer.
- Formulations that are highly affected by hepatic metabolism, polar or susceptible to chemical and enzymatic degradation in the upper GI tract, are also suitable for colonic delivery [10].
- Advantages of colon drug delivery systems [11].
- Lower cost of expensive drugs due to less reduced dose frequency.
- Reduced incidence of side effects and drug interactions due to site targeting.
- Prolonged day or night time activity.
- Enhances the absorption of poorly absorbed drugs because of longer retention time.
- Better patient compliance.
- Bypass early first-pass metabolism.
- Decreases gastric irritation.
- Peptides, oral vaccines, insulin, growth hormones, can be given through this route due to less peptidase activity.
- Oral delivery of drugs to the colon is valuable in the treatment of diseases of the colon (ulcerative colitis, Chron's disease, carcinomas and infections).
- The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies, and this helps in efficient vaccine delivery.
- The colon is attracting interest as a site where poorly absorbed drug molecules may have improved bioavailability.
- Disadvantages of colon drug delivery systems [12].
- Multiple manufacturing steps.
- Incomplete release rate.
- The resident microflora could also affect colonic performance *via* metabolic degradation of the drug.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form *in-vitro*.
- Bioavailability of drugs may be low due to the potentially binding of the drug in a nonspecific way to dietary residues, mucus or fecal matter.

Approaches to Colon Target Drug Delivery:

1. Primary Approaches for Colon Targeted Drug Delivery:

1. pH-sensitive polymer coated drug delivery systems
2. Delayed-release drug delivery systems
3. Microbially triggered drug delivery

a. Prodrug approach
b. Azo polymeric prodrug
c. Polysaccharide based systems

2. Novel Approaches for Colon Targeted Drug Delivery:

1. Pressure controlled drug delivery systems (PCDDS)
2. Novel colon targeted delivery systems (CODESTM)

3. Osmotic controlled drug delivery systems (OROS-CT)
4. Pulsatile

a. Pulsincap systems
b. Port systems

5. Azo hydrogels
6. Multi particulate system based drug delivery nanoparticles

Primary Approaches for Colon Targeted Drug Delivery:

I. pH-Sensitive Polymer Coated Drug Delivery to Colon: The pH-dependent CTDDS exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), small intestine (pH 6-7) at the site of digestion and it increases to (pH 7-8) in the distal ileum [13]. The coating of pH-sensitive polymers to the tablets delayed-release provided by using capsules or pellets and protect the active drug from the gastric fluid. Lower pH values of the stomach and proximal part of the small intestine are maintained by using the polymers used for colon targeting as shown in **Table 1** and these are also should be able to disintegrate at the neutral or slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction. The potential of the colon targeted delivery system is improved by distributing the drug throughout the large intestine. There is no real substitute for endorsing reliable performance *in-vivo* in man while this release pattern can be studied *in-vitro*. The technique of gamma scintigraphy has become the most popular method to investigate the gastrointestinal performance of pharmaceutical dosage forms [14].

II. Delayed-Release Drug Delivery to Colon: This system based on the principle that after a scheduled lag time drug releases at the desired time and site of action. For colon targeting drug delivery system lag time, 5 h is considered acceptable. The time for the release of drugs in the colon is influenced by the coated polymer or mixture of polymers. The colon influx time of the dosage form cannot be predicted exactly because the gastric emptying rate differs from person to person. However, in the treatment of some diseases based on circadian rhythms these systems are useful. A time-controlled system in the form of capsules and bilayer tablets are described. The release time of drug from the dosage form is controlled by the steadiness between the amount of swellable excipients and thickness of lipidic membrane [15]. The disadvantages of this system are:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- The gastrointestinal transit of the drug is influenced by peristaltic movements or contractions that occur in the stomach.
- This influence is mainly observed in IBD, diarrhea, ulcerative colitis type diseases.

Thus, the targeted drug delivery to the colon may be improved by the integration of pH and time-release systems in a dosage form and also the passage of dosage forms in small intestine is less influenced (2-4 h). The period of lag phase is controlled either by the weight or composition of the polymer (HPMC) layer. The polymers used for this delayed-type system are Microcrystalline Cellulose (MC), Hydroxyl Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Methyl Cellulose Acetate Succinate, Hydroxy Ethyl Cellulose (HEC), Ethyl Cellulose (EC), Lactose/Behinic acid *etc.* [10, 15]

III. Microbially Triggered Drug Delivery: The system is based on the principle of the microflora of the colon that causes degradation of the polymers coated on the dosage form. Colon has a complex range of microflora which is responsible for fermentation of the substrate such as polysaccharides that present in the intestinal region. A wide variety of enzymes are produced by these micro flora and these enzymes metabolize the substrates like polysaccharides, carbohydrates and proteins that result in the escape of digestion in upper GIT. To control the drug release from the dosage form pectin is used in large quantities if used alone but it was used in combination with chitosan and HPMC it was found very useful to control the drug release in the stomach and very efficiently releasing the drug in the colon. The microbially degradable polymers are pectin, dextran, chitosan, inulin, lactulose, guar gum, cyclodextrin, alginates, amylose and locust bean gum [16]. The Microbially triggered drug delivery includes mainly the three approaches mentioned below.

A. Prodrug Approach: Prodrugs are the pharmacologically inactive compound that converts into an active form by the spontaneous or enzymatic transformation *in-vivo* in order to release the active drug. In this method, the covalent linkage exists between the drug and its carrier, it remains as such in the upper GIT and this linkage breaks in the colon followed by releasing the drug. A number of linkages of drugs with hydrophobic moieties like glucose, cellulose, amino acids, glucoronic acid and galactose *etc.* have been prepared which are succeptible to hydrolysis in the colon. For chemical linkage in prodrug approach has major limitation is that for its design and present on the drug moiety, development of the functional group plays a very important role. An example of prodrug that was found stable in upper GIT and hydrolysed by ceacal to release 5-ASA is conjugated with glycine by amide linkage is 5- ASA [17].

B. Azo-Polymeric Prodrugs: The different polymers as carrier of drugs are used in this new technique for the colonic delivery. By using sub synthetic polymers, drug and polymers are designed by linkage with an azo group or known as azo linkage. Degradation of the drug in upper GIT is protected by polymer cross-linkage with azo aromatic group when coated and by breakage of these azo bonds released in the colon, where the azo bonds were broken. Segmented polyurethane-coated over the pellets of budesonide is an example of azo polymer-based drug delivery system [18].

C. Polysaccharide Based Approach: Due to easy availability, their abundance and inexpensiveness, naturally occurring polysaccharides are widely in use for drug targeting. They are highly stable, most safe, non-toxic, gel-forming, biodegradable and hydrophilic. Chitosan, Pectin, Chondroitin sulphate and Alginates are some natural polymers which are obtained from plants, microbes, animals and algae and novel forms of dosage forms used with drug and polymer-carriers are given in **Table 2**.

These polysaccharides are breaks into simpler ones by the Colonic microflora. For the colon drug delivery, chitosan is used mainly in the form of capsule forming material [10].

TABLE 2: LIST OF SOME COLON TARGETED DOSAGE FORM WITH THEIR POLYMER CARRIER USED

Drugs	Polymer carrier	Dosage form	Reference
Levetiracetam	Pectin	Tablet	24
Mesalamine	Pectin and chitosan	Coated core tablets	25
Celecoxib	Chitosan	Microspheres	18
Prednisolone	cellulose acetate phthalate (CAP)	Coated tablet	26
Metronidazole	Eudragit® S 100 (ES) and ethyl cellulose (EC)	Mini-tablets	29
Acetylharpagide	Microcrystalline cellulose, sodium carboxymethyl starch hydroxypropyl methylcellulose (HPMC)	Tablet	30
Hydrocortisone	microcrystalline cellulose, Eudragit® L100	Tablet	31
Ornidazole	HPMC K100M and Ethylcellulose	Tablet	
Flurbiprofen	HPMC and K4M Sodium Alginate	Tablet	32
Camptothecin	PLGA, Chitosan	Nanoparticles	33
Prednisolone	ε-polylysine (SPL)	Silica nanoparticles	34
5-fluorouracil	guar gum/Eudragit FS30D	Granules	35
Icariin	alginate-chitosan	Microspheres	36
Meloxicam	Eudragit® S100	Microspheres	37
Meloxicam	EudragitRS100	Microsponges	38
Prednisolone	Eudragit S-100	Smedds	39

2. Novel Approach:

1. Pressure-Controlled Drug-Delivery System: Higher pressures are encountered in the colon than in the small intestine as a result of peristalsis. By using ethyl cellulose, which is insoluble in water pressure controlled colon-delivery capsules are prepared. Drug release occurs by following the disintegration of water-insoluble polymer capsule in such systems and as a result of pressure in the lumen of the colon. The most important factor for the disintegration of the formulation the thickness of the ethylcellulose membrane. This system depends on capsule size and density. The viscosity of luminal content is more in the colon than the small intestine because of water reabsorption water from the colon. In the context of colon drug

delivery systems, the drug dissolution in the colon could create a problem. The drug is in a liquid form in pressure-controlled ethyl cellulose single-unit capsules. Lag times of 3-5 h in relation to drug absorption were noted when these capsules were administered to humans shown in **Fig. 1** [13, 14].

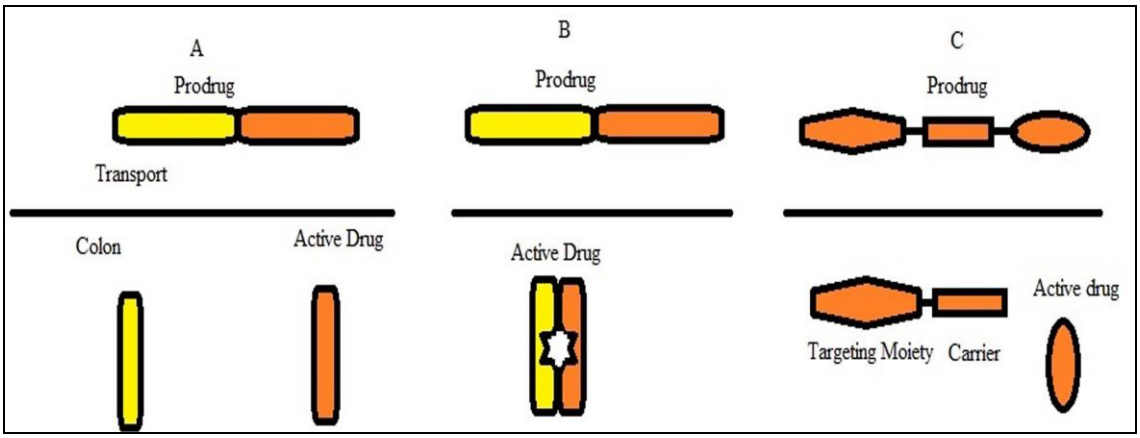

FIG. 1: SCHEMATICS OF PRESSURE CONTROLLED DRUG DELIVERY SYSTEM

2. Novel Colon Targeted Delivery System: Problems related to pH and time-dependent drug delivery systems are minimized by using this method. The pH-sensitive polymers and polysaccharides are degraded by the present bacteria of the intestine. A three-layer coated core tablet of polymer coatings constitutes this system. The external coating is done by using the polymer Eudragit-L. Once the tablet passes through the pyloric and duodenums the coating gets dissolved and exposes the next coating which is composed of Eudragit E. The lactulose present in the internal core is released by this layer. The surrounding pH is lowered where the Eudragit E layer dissolves by the unconstrained lactulose gets which metabolized into short-chain fatty acids. The dissolving of Eudragit E consequences in the revelation of the drug. Along with the drug other polysaccharides are also used in the core tablet such as; manitol, maltose *etc.* For the degradation of polysaccharides, bacteria is responsible and this degradation results in organic acid formation that decreases the pH of the tablet surrounding shown in **Fig. 2** [18].

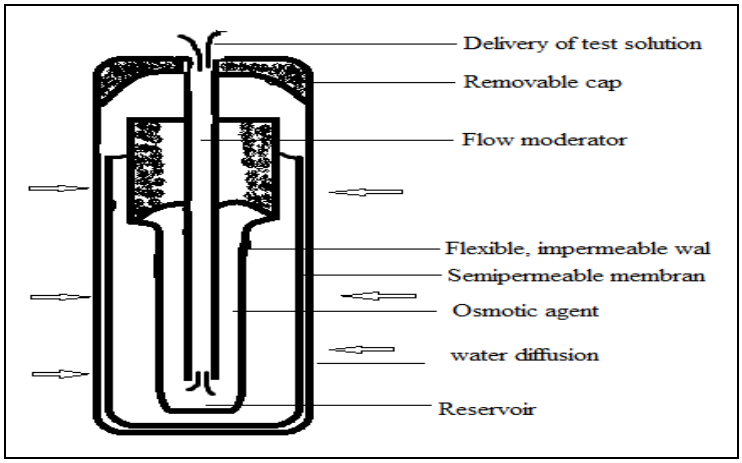

FIG. 2: SCHEMATICS OF CONCEPTUAL DESIGN OF CODESTM

3. Osmotically Controlled Colon Targeted Drug Delivery System: This system comprises of osmotic units that used either single or in a combination of five to six push-pull units which are encapsulated in the hard gelatin capsule. These push-pull units are double layered with outer layer as enteric impermeable membrane and inner layer as semi-permeable membrane. The push-pull consists internal or central part of the drug layer and push layer. The next layer to the drug is semi-permeable membrane which consists of an orifice and through this orifice drug contents are expelled during the course of time. After administration, the capsule, immediate dissolution occurs of body

enclosing this push-pull units. During the passage of the push-pull units through the GIT, the enteric impermeable membrane prevents the water absorption into the unit. The coating gets dissolved once it reaches the small intestine due to a pH greater than 7. Push layer gets swell due to entering the water through the semi-permeable membrane swelling of the push compartment forces the drug into the surrounding environment through the orifice. The drug can be delivered at a constant rate up to 24 h by osmotically controlled drug delivery systems [19].

4. Pulsatile Colon Targeted Drug Delivery:

A. Pulsincap System: The formulation is filled in a capsule form in this system. The release of the drug is controlled by the plug located in the capsule. To seal the drug contents swellable type hydrogels are used. When the capsule comes in contact with the dissolution fluid it gets swelled and plug gets pushed off after the lag time and it causes the drug release. In hydrogel plug, the polymer used are; hydroxyl propyl methylcellulose (HPMC), PVA and polymethyl methacrylate. By the length and point of intersection, the lag time is controlled of the plugin the capsule body as shown in **Fig. 3** [19].

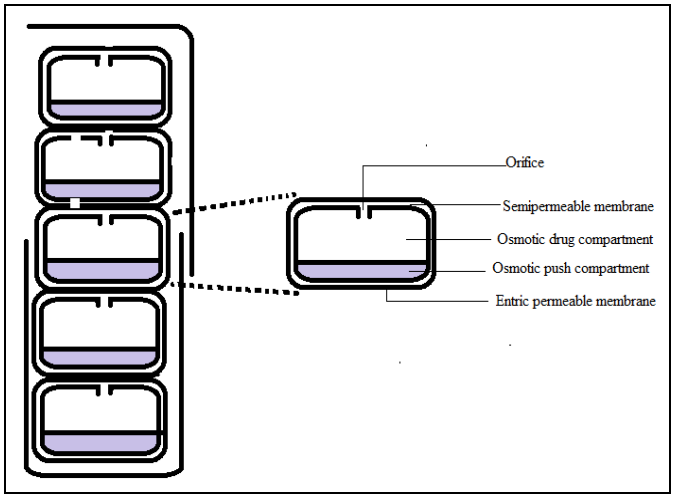

FIG. 3: PULSINCAP SYSTEM

B. Port System: In this system, the capsule body is enclosed in a semi-permeable membrane. An insoluble plug consisting of osmotically active agents and drug formulation is enclosed in the capsule body. The semi-permeable membrane allows the flow of fluid into the capsule when it comes in contact with the dissolution fluid resulting in the expansion of pressure in the capsule body and due to expelling of the plug, it leads to drug release. At regular intervals, the drug is released with a time gap between the successive intervals [20].

5. Azo Hydrogels: In the hydrogel, the pH-sensitive monomers and azo cross-linking agents produce the colon specificity. These hydrogels swell as the pH increases during their passage through the GIT. The release of drugs entrapped in the hydrogel is because of the hydrogel swelling which slashes the cross-links in the network of the hydrogel. By cross-linking polymerization of N-tert- butyl acrylamide, N- substituted (meth) acrylamides and acrylic acid with 4, 4-di methacryloylamino azobenzene as cross-linking agents, these hydrogels are prepared. By polymer-polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH_2 groups and cross-linking polymeric precursors, the hydrogels are also prepared. The degradation rate of the hydrogel is associated with the degree of swelling and inversely proportional to the cross-linking density [21].

6. Multi-particulate System: The numerous advantages of multi-particulate systems are reduction in local irritation and systemic toxicity while increased bioavailability. The several multi-particulate techniques are pellets formation, micro-particles preparation, granules and nanoparticle formation. Multi-particulates approaches are desired over single unit dosage forms such as tablets because the multi-particulate systems enable the drug to reach the colon rapidly and retained in colon for a long duration. Due to small/fine size, these systems pass through the GIT easily. In the GIT multi, particulate systems are dispersed more uniformly than single units and resulting in more drug absorption [22].

Nanoparticles: The nanoparticle preparation is very easy, simple. This formulation results in high stability due to the protection of protein and peptide drugs from the chemical and enzymatic degradation in GIT due to which the absorption *via* the intestinal epithelium is also increased. There are numerous techniques to prepare polymeric nanoparticles which involve the use of agitation, organic solvents and heat such as polymerization, nanoprecipitation and inverse microemulsion. As

heat, agitations both are harmful to proteins and peptide drugs thus it is the main limitation of these techniques. So, for such types of drugs such as proteins and peptide drugs Ionic gelation technique is the most commonly used method [23]. For inflammatory bowel disease treatment Tumor necrosis factor-alpha (TNF-α) is usually regarded as a potential target. A promising strategy targeting the intestinal inflammation based on the interaction of the single chain of triple-helical β-glucan (s-LNT) with poly-deoxyadenylic acid [poly (dA)], and the colon-specific degradation of chitosan-alginate (CA) hydrogel for effective delivery of phosphorothioated antisense oligodeoxyribo-nucleotide of TNF-α (PS-ATNF-α) is reported. For the oral delivery of antisense oligonucleotides to attenuate inflammatory response strategy demonstrating a notable potential for clinical applications in the intestine, inflammation targeted therapy [24].

Another example of conventional oral drug formulations for the treatment of colonic diseases was developed by loading a large amount (ca. 34% w/w) of prednisolone into 3-aminopropyl-functionalized mesoporous silica nanoparticles (MCM-NH_2) and by coating the nanoparticle with succinylated ε-polylysine (SPL) targeting prednisolone release to the colon. To deliver the dye intracellularly to RAW 264.7 macrophages the SPL-coated nanoparticles are used and also used for diseases of the colon such as inflammatory bowel disease and colorectal cancer which offers a highly promising and novel drug delivery system [25].

Tablets: One of the most suitable and widely used dosage forms are tablets or solid oral dosage forms for the delivery of the therapeutic active drug to treat any disease [26]. The conventional tablet dosage form provides a minimal amount of drug in the colon due to variation in the transit time with undesirable adverse effects [27, 28]. Hence, there is a need to develop colon targeted drug delivery systems to target the drug directly to the site of action in the colon, which will enhance the therapeutic drug level and increases the bioavailability of medicament and reduce the dose concentration [29-31].

Microsphere: Through conjugate-receptor inter-actions site-specific targeting of drugs to a biological surface can also be achieved. Labeling polymeric drug carriers surface *i.e.* microspheres, with appropriate conjugates facilitates targeting of surface receptors on selected cell types [32]. When such types of systems contacts the appropriate surface receptor, being retained at the cell surface they can interact potentially. Direct delivery of drugs to the site of interest instead of untargeted can result in both cost savings and reduction of unwanted side effects due to the lower required dose [33]. In preference to a single unit, dosage forms the use of multiparticulate drug delivery systems for colon targeting showed that this enabled the drug to reach the colon quickly and were retained for a relatively long period of time in the ascending colon. These systems are capable of passing through the GIT easily, followed by less inter and intrasubject variability because of their smaller particle size as compared to single unit dosage forms [34]. Moreover, these systems tend to be more uniformly dispersed and absorbed. The methods used for drug targeting into colon are drug release based on:

- Variation on pH,
- Gastrointestinal transit,
- The presence of colonic microflora and;
- Pressure controlled drug delivery systems [35-37].

Self-micro Emulsifying Drug Delivery System (SMEDDS): Another formulation used for colon targeting is the self-micro emulsifying drug delivery system (SMEDDS). These types of formulation are used for colon-specific drug delivery for effective treatment of colonic diseases. For example, a formulation is prepared using a Ternary phase diagram that was used to optimize the level of oil, surfactant and co-surfactant to optimize SMEDDS and were evaluated for percent transmittance, emulsification time, *in-vitro* release, myeloperoxidase (MPO) activity and intestinal accumulation. The spray-dried SMEDDS were filled in capsules that were enteric-coated with Eudragit S-100 at 10% weight gain to ensure SMEDDS delivery at the colon. The spray-dried SMEDDS were also evaluated for IR, DSC, XRD, SEM and stability study. In the ternary phase diagram, Capmul MCM C8 and Capmul PG12 NF with surfactant (Tween 20) and co-surfactant (PG) in ratio 2:1 and 3:1, respectively, showed

maximum emulsification area. These liquid SMEDDS show maximum transmittance, globule size of 90-30 nm. The spray-dried SMEDDS with diluents show good flow property and overall all good properties [38, 39].

CONCLUSION: In the present study, considerable attention has been focused on the study of colon targeted drug delivery systems (CTDDS). These days much of the activity has been centered on the potential to produce new and improved pharmaceutical dosage forms in the form of various carriers so that the therapeutic efficacy of the existing drugs can be improved. Various approaches have been proposed for targeted colon delivery include the pH-, time-controlled, micro flora-, pressure controlled, osmotic controlled, and multi-particulates drug delivery systems. These carriers include synthetic polymers, liposomes, microsphere and nanoparticles, matrix tablets and compression coated tablets.

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