ejpmr, 2023,10(3), 53-65

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

FORMULATION VARIABLES AND PROCESS VARIABLES IN COLON TARGETED CAPSULE DOSAGE FORM

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Article Received on 26/12/2022 **Article Revised on 16/01/2023** **Article Accepted on 06/02/2023**

ABSTRACT

Recent studies show its ability to target certain drugs and/or peptides to the colonic region for the treatment of several diseases while avoiding systemic absorption and potential side effects, colon drug delivery has become a field of research of growing interest. Anything which is taken orally will start to dissolve very quickly. Capsule is one of them which includes medication enclosed in a shell. When this shell breaks down in the digestive tract and the medication is absorbed into the bloodstream then drug is distributed and metabolized in similar pattern to the tablet. In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Many drugs are unstable at the acidic pH of stomach therefore many of the tablets and capsules carries a special gastro-resistant coating. Various factors that can affect this targeting and drug release are reviewed in this article. Formulation variables and process variables are critical parameters need to be controlled for optimized drug delivery to the colon. Formulation ingredients play a key role in releasing drug in a controlled manner or to the target site. Local or systemic effect and immediate or prolonger drug release can be possible by varying the type and amount of polymers used in the formulation and also by various approaches such as pH-dependent systems, enzyme-activated systems, receptor-based systems, magnetically activated systems and combination approaches such as Phloral™ technology are also responsible for release of the drug to the target site like colon. This review focuses on Formulation variables and process variables in colon targeted capsule dosage form.

KEYWORDS: Formulation variable, Process variable, Colon targeted, Capsule, Enteric coating, Phloral, Encap, Encode.

INTRODUCTION

The digestive system is mainly consisting of stomach, small intestine and large intestine. Colon is the large part of large intestine starts from the ileocecal junction and extend to anus. Faecal contents are stored in colon and also has a very high absorption capacity. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects.

ENCODE stands for Encap Colonic Delivery and is the bringing together of a suite of complementary or alternative technologies that can be selected and used to target a drug to the colon for local effect or systemic absorption. Targeting to the colon can be achieved by a variety of formulation strategies, and many have been attempted over the years. The optimal strategy will depend on the specific drug product. Colon targeted drug delivery systems are designed to selectively release a drug in response to the colonic environment without premature drug release in the upper GI tract. Therefore, it is important to consider the physiological properties of the colon and the microenvironment surrounding disease site(s) for the successful development of colon-targeted drug delivery systems. In general, GI tract undergoes dynamic changes in motility, fluid contents, enzymatic activity, and pH from the stomach to the intestine.[1] The colonic contents have a longer retention time up to 5 days, and the colonic mucosa is known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery. A drug can be delivered to the colon via the oral, or the rectal route. Anything which is taken orally will start to dissolve very quickly, so many of the tablets and capsules have a special "gastro-resistant" coating. This makes sure the drug is released in the right part of the digestive system – usually the small intestine (small bowel) or large intestine (colon). This is why it can be important to swallow tablets or capsules whole and not to break or crush them.[2]

Inflammatory bowel diseases including irritable bowel syndrome, ulcerative colitis and Crohn's disease are considered as serious colonic disorders. Various strategies have been explored including pH-dependent systems, enzyme-activated systems, receptor-based systems, and magnetically activated systems to achieve more efficient colonic drug delivery.[3] This review article specifically focuses on formulation variables and processing variables that may affect targeting of capsule to the colon and release of active at the desired site.

Formulation variables

The formulation factors that influence colonic drug delivery and bioavailability includes physicochemical properties of the drugs, the dose, and the dosage form factors. Due to the lower amount (1 ml to 44 ml) of colonic fluid available for dissolution, the solubility and the dose of a drug become important factors for its colonic bioavailability.

1. **General:** Parameters that can critically influence target specificity, drug release and such others are to be considered when formulating a colon targeted capsule dosage form (CTCDF)
2. **Specific:** Individual formulation ingredient might affect the drug release to the target site

In general, following formulation variables needs due consideration when developing a capsule dosage form for colon targeting.

1. Drugs used as active in dosage form

A predominant and an obvious challenge is the fact that the colon is located in the distal part of the gastrointestinal tract (GIT). An orally administered dosage form has to traverse the entire alimentary canal in order to reach the target site. The GIT physiology is complex and has a variation of pH, fluid volumes, and transit time throughout the entire path. Moreover, the presence of food and metabolic enzymes also increases the physiological complexity. These factors are an obstacle to the reliable and efficient delivery of drugs to the colon.[4]

Selection of a drug for a colon-specific delivery

Drug candidates should fulfill at least one of the following physico-chemical/therapeutic criteria to make them incorporated into a colon-specific delivery system.[5,6] First, these drugs should exhibit local effects in the colon to treat intestinal diseases. Peptide drugs like amylin and non-peptide drugs such as oxyprenolol are the examples of agents with these effects. Secondly, these drugs may show a sub-optimal absorption in the upper gastrointestinal tract. This includes antianginal drugs such as isosorbide dinitrate. Agents used in the treatment of colon or rectal cancers (*e.g.*, 5-flurouracil and capecitabine) are also ideal candidates for CDDS. The remaining criteria include a high likelihood of the drug's degradation in the stomach by the acidic environment or enzymes (*e.g.*, peptide drugs like insulin and gonadotropin), or a high risk for first-pass metabolism (*e.g.*, corticosteroids). It is believed that a colon is the suitable absorption site for peptides and protein drugs. Reasons may be one of the following: 1) intensity of digestive enzymes and less diversity, 2) decreased proteolytic activity of colon mucosa leading to better protection from enzymatic degradation in duodenum and jejunum and hydrolysis, 3)greater systemic bioavailability and 4) long residence time(5day) of colon and responsiveness is high to absorption enhancers.[7] Vancomycin which is amphoteric glycopeptide antimicrobial substance produced by the growth of certain strains of ***Streptomyces orientalis*** used to treat enterocolitis caused by *Staphylococcus aureus* and antibiotic associated pseudomembranous colitis caused by *Clostridium difficile* Vancomycin being a peptide in nature is a good candidate for colon targeted drug delivery.[8]

A. Active/Inactive form used: Mostly drugs are active in their unionized form**.** Prodrugs are inactive derivatives of a drug molecule which release the active ingredient once they are hydrolysed by enzymes such as those in the colon.[9,10] In order to optimize drug delivery specific to the colon, the extent of this hydrolysis should be minimal in the upper portions of the gastrointestinal tract and much more extensive in the colon. Azo conjugates are one of the most researched groups of compounds that fall into this category.[11,12] However, this is not a very flexible method because it relies on the functional groups of the drug molecule.[13] Kim *et al.* synthesized a prodrug of metronidazole, which was metabolized to the active drug, metronidazole when placed in rats' cecal contents.[14] Unlike metronidazole, this prodrug did not metabolize in the small intestine, and the systemic absorption of this prodrug was also found to be much lower compared to that of oral metronidazole. In another study, Kim *et al*. prepared a prodrug of metronidazole, using a sulfate group, and showed that this formulation remained intact in the upper intestine, but was cleaved in the presence of rat cecal contents and active metronidazole was released. Similar to the first prodrug, much less of the conjugated prodrug was degraded and absorbed in the small intestine compared to the active drug after oral administration. Therefore, a minimal amount was absorbed into systemic circulation.[15] Vaidya *et al.* utilized the prodrug approach by conjugating metronidazole with pectin and compared the drug release from this formulation to that from pectin microspheres which physically entrapped the drug.[16] The pectin-metronidazole (PT-ME) prodrug showed significantly reduced drug release in the upper GIT compared to pectin microspheres containing metronidazole. *In vitro* and *in vivo* studies revealed that conjugating the drug to pectin can successfully target its delivery to the colon since no drug release occurred at an acidic pH from the PT-ME prodrug while nearly 100% of the

metronidazole physically entrapped in pectin microspheres was released in this same environment. A significantly higher fraction of the drug was released from the PT-ME prodrug in the colon.

a. **Dose:** As we have variable sized capsules available for human use, no matter with the dose as it would be as per the prescribed dose for colonic conditions to be treated. Physician can prescribe one or two capsules at a time if needed.

b. **Dilution ratio with polymer and other excipients:** This depends on the formulation approach selected for the formulation development. Dilution ratio predominantly considered in time dependent drug delivery system. As we increase the proportion of polymer hindering the drug release we get sustained release or extended release pattern from the dosage form.

c. **Content filled in capsule:** Finally, the technology used in the dosage form development can also influence the colonic bioavailability of drugs. Useris® and Entocort EC® are currently approved budesonide products for the treatment of Ulcerative colitis and Crohn's disease, respectively.[17] Useris® is a multi-matrix (MMX)-based delayed-release tablets, which ensures the drug release in the colon, while Entocort EC® is a capsule which releases the drug in the ileum to treat Crohn's disease. Unigel technology allows to put a soft gel within a soft gel, a tablet within a soft gel, granules within a soft gel or any other combinations thereof. Unigel™, a first-to-market technology, developed and patented by Procaps, is designed to combine multiple API formulations into one single soft gelatin capsule, offering different release modes, bioavailability enhancement, lower manufacturing costs (vs. two separate doses) and superior adherence to different therapies.[18]

Solid: Minitablet, fine powder, granules, spansules, coated granules, graules with variable release pattern, granules and powder mix, powder/granule and minitablet mix, microspheres, beads, pellets all may be filled in capsule as per the desired release pattern. Form selected for colon targeting should deliver drug to the target site for the desired treatment and rate of drug release required at the site of action. Solid may be matrix or coated dosage forms like hydrogel tablet, enteric coated tablet and capsules, enteric coated granules and so on.

Giselle oliveira et al.,(2010) carried out study on Chitosan–pectin multiparticulate systems associated with enteric polymers for colonic drug delivery. Multiparticulate systems showing simultaneously specific biodegradability and pH-dependent drug release were prepared based on chitosan (CS), amidated pectin (PC), and calcium ions, using triamcinolone (TC) as model drug. The addition of CAP and HPMCP resulted in the highest control over the drug release in all media. CAP:TC formulation presented the slowest drug release rate, of only 1.33%, in acidic medium after 2 h, while the control formulation released 45.52% after the same time.[19]

Liquid: Many vitamins and oils are dispensed in liquid form by using soft gelatin capsules. Suspension emulsion and other such dispersed systems also may be a part of capsule content. Liquid form impart good absorptivity which is suitable for immediate release dosage forms. For specific action to the colon, liquid filled capsules should only release liquid drug to the target site and this can be achieved by enteric coating of the capsule shell.

Semisolid: Pastes, ointments, gels, creams, lotions are such preparations when required in small amounts capsules are best-fit dosage form to supply them particularly in saloons and spa. Formulation development of such capsule might be tedious and time consuming.

d. **Size of particles/globules:** Surface area available to disperse/dissolve and then to diffuse drug particle or liquid globule in colonic fluid depends on its size. As the size decreases surface area increases and hence is the solubility and absorption.

e. **Stability:** Stability of drug in colon can be a matter of concern. The non-specific interactions of the drug with the colonic content *e.g.*, dietary residues, intestinal secretions, mucus, or fecal matter can have a negative influence on the stability of the drug. [20] In addition, the colonic bacterial enzymes may also degrade the drug, rendering it ineffective.

f. **Solubility:** Due to a low colonic luminal fluid volume, higher viscosity, and a neutral pH, the solubilization of the drug could be a rate-limiting factor for colonic absorption. Although the highly potent drug budesonide (dose, 9 mg) has a lower aqueous solubility, it is absorbed well in the colon and is used successfully in the treatment of Ulcerative Colitis. [21] Mesalamine has a significantly higher solubility (3.64 mg/ml) compared to budesonide (0.24 mg/ml); however, it also has a significantly higher dose (4.8 g daily) which becomes a rate-limiting factor for its colonic absorption. [22]

B. Polymer used in formulation

Polymer type was the main factor influencing the capsule sealing and disintegration time. The most difficult challenge has been the development and scale-up of the pH polymer and the starch-based coatings. Interest in the biodegradable polymers is increasing day by day because they are safe, non-toxic, and economic and are chemically compatible with the other excipients in the formulation. Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic in acidic pH. Various bacteria present in

the colon secretes many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. C-D-galactosidase, amylase, pectinase, C-Dglucosidase, dextranase, D-D-xylosidase. Pectin, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in dosage forms. These polymers are inexpensive and are available in a variety of structures. Linear polysaccharides remains intact in stomach and small intestine but the bacteria of human colon degrades them and thus make them potentially useful in colon targeted drug delivery systems.[23]

a. pH Sensitivity:

In the stomach, pH ranges between 1 and 2 during fasting but increases after eating.[24] The pH is about 6.5 in the proximal small intestine, and about 7.5 in the distal small intestine.[25] From the ileum to the colon, pH declines significantly. It is about 6.4 in the cecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers.[26] The pH in the transverse colon is 6.6 and 7.0 in the descending colon. pH ranges of GI tract can be significantly altered by diet, disease state, water intake, and microbial metabolism.[27] Use of pH dependent polymers is based on these differences in pH levels. The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises.[28] Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor.[29] The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-cecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations. pH dependent polymers provide protection from degradation and this enteric coating helps by either protecting drugs from the acidity of the stomach, the stomach from the detrimental effects of the drug, or to release the drug after the transit of drug delivery system from stomach. To prevent oral medications dissolution in the gastric environment a polymer barrier is applied to oral medication is called enteric coating. Many drugs are unstable at the acidic pH of stomach so, needs protection from degradation and this enteric coating helps by either protecting drugs from the acidity of the stomach, the stomach from the detrimental effects of the drug, or to release the drug after the transit of drug delivery system from stomach. To modify the drug release rate, hard gelatine capsule halves can be coated with the use of enteric polymer. Chitosan is a nontoxic, biodegradable, biocompatible and bioactive polymer. It is used for the colon targeted drug delivery because it has a tendency to dissolve in acidic pH of stomach but get swollen in the intestinal pH. Chitosan capsules were used for colonic delivery of an antiulcerative colitis drug.[30] The shellac coating layer remains intact during the passage of the stomach and the small intestine until it reaches the colon with its higher pH. This allows the transport of drugs into the colon for a topical treatment of colonic diseases. Moreover, the peptidase activity in the colon is lower than in the upper GI tract allowing for an oral delivery of peptide drugs such as insulin.[31] F. Bigucci et al.,(2008) carried out study on Chitosan/pectin polyelectrolyte complexes: Selection of suitable preparative conditions for colon-specific delivery of vancomycin. The influence of polyelectrolyte complexes composed of chitosan and pectin on the release behavior of vancomycin has been investigated. *In vitro* swelling, cohesion and release tests were performed in order to investigate the chitosan/pectin complex ability in the delivery of vancomycin in the gastro-intestinal tract. The results confirmed the formation of polyelectrolyte complexes between pectin and chitosan at pH values in the vicinity of the pK_a interval of the two polymers. The particular composition of these complexes improved vancomycin availability at alkaline pH on the bases of an enzyme-dependent degradation as confirmed from release studies performed in presence of beta-glucosidase. [32]

b. Digestibility/Metabolism of polymer by gut microbes or enzymes:

The digestive system is mainly consisting of stomach, small intestine and large intestine. Colon which is the large part of large intestine starts from the ileocecal junction and extend to anus. Faecal contents are stored in colon and also has a very high absorption capacity.[33] The colon is known to consist of over 400 different species of aerobic and anaerobic microorganisms like *Escherichia coli* and *Clostridium* species,respectively.[34] These bacteria contain several hydrolytic and reductive metabolizing enzymes.[35] The colonic enzymes catalyze a range of reactions, including the metabolism of xenobiotics (*e.g.*, drugs) and other biomolecules (*e.g.*, bile acid), deactivation of harmful metabolites as well as carbohydrate and protein fermentation.[36] Polysaccharides such as chitosan, guar gum, pectin, *etc.*, are commonly employed as release rate-controlling components in colon-targeted dosage forms. These polysaccharides are known to be resistant to gastric and intestinal enzymes, but are metabolized by anaerobic bacteria in the colon.[37,38,39] Drugs are also known to be susceptible to biotransformation by colonic enzymes. The metabolism of drugs by the colonic enzymes may result in the formation of metabolites that are pharmacologically active, inactive, or sometimes even harmful.[40,41] Formation of a pharmacologically active metabolite by the colonic metabolism of drugs is a commonly used "prodrug" approach for the colon-specific drug delivery systems.[42] Pectin is almost completely degraded by the colonic bacterial enzymes to produce a series of soluble oligalactorunates.[43,44] Monovalent cations (alkali metal) salt of pectinic and pectic acids are soluble in water; di- and tri-valent cations salts are weakly soluble or insoluble. If used alone it swells, when it comes in contact with aqueous fluids of GI tract and causes the release of entrapped drug through diffusion mechanism. Pectin has been used

in the pharmaceutical industry for a wide range of applications. Guar gum is used in colon targeted drug delivery systems due to its drug release retarding property and susceptibility to microbial degradation in large intestine. Guar gum has a gelling property which retards the release of drug from the dosage form, making it more likely that degradation will occur in the colon. Guar gum was found to be a colon-specific drug carrier in the form of matrix and compression coated tablets as well as microspheres. Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate mainly by B. thetaiotaomicron and B. ovatus species in large intestine. Cyclodextrins remains intact during their passage throughout the stomach and small intestine of the GI tract. However, in colon, they undergo fermentation in the presence of vast colonic microfloras into small monosaccharide and thus absorbed from these regions.[45,46] Dextran gets degraded by microbial enzyme dextranases which is found in colon.[47]

The microflora of the colon is in the range of 1011 -1012 CFU/mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc.[48] This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine, e.g. di- and tri-saccharides, polysaccharides etc.[49,50] For this fermentation, the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.[51] Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches.[52] These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism, or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength.[53,54,55,56,57] They are then unable to hold the drug entity any longer.[58]

c. Nature and form

Natural:

Natural polysaccharides are now extensively used for the development of solid dosage forms for colon drug delivery. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose, and locust bean gum. Guar gum and pectin are reported to be potential carriers for colon-specific drug delivery. These studies have shown the drug release retarding property of guar gum in the upper GIT and its degradation by the anaerobic bacteria in the colon.[59,60,61] Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs. Alginate and their derivates have many unique properties such as biocompatibility, biodegradability, low toxicity, non-immunogenicity, water solubility, relatively low cost, gelling ability, stabilizing properties, and high viscosity in aqueous solutions.[62] Studies on the polysaccharides done by Raghavan et al. (2002) proved that the combination of locust bean gum and chitosan, as a coating material, is capable of protecting the core tablet containing mesalazine during the condition mimicking mouth to colon transit. The coating was susceptible to the colonic bacterial enzymes which causes the release of drug. It was concluded that the formulation containing locust bean gum and chitosan in the ratio of 4:1 held a better dissolution profile, higher bioavailability and hence a potential carrier for drug targeting to colon.[63] Amylose is resistant to pancreatic amylases but it gets degraded by the bacteroids, bifidobacterium.[64] Addition of ethylcellulose to amylose gives a suitable polymer mixture for colon targeting. Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. Inulin is not hydrolyzed by the endogenous secretions of human digestive tract.[65] However, bacteria harbouring in the colon and more specifically Bifido bacteria are able to ferment inulin. Vervoort et al, developed inulin hydrogels for colonic delivery of drugs and swelling property of these hydrogels was investigated.[66]

Synthetic:

There are various synthetic polymers which are used for colon targeted drug delivery. These can also be called as pH dependent polymers. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose. For colonic drug delivery, drug core is coated with pH sensitive polymers. The drug are includes tablets, capsules, pellets, granules, micro-particles and nanoparticles.[67] The pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. Eudragit products are pH-dependent carboxyl group containing methacrylic acid polymers. The number of esterified carboxyl groups affects the pH level at which dissolution takes place. When sites of disintegration of Eudragit S-coated single-unit tablets were investigated using a gamma camera they were found to lie between the ileum and splenic flexure. Eudragit L coatings have been used in single-unit tablets to target 5-ASA on the colon in patients with ulcerative colitis or Crohn's disease.[68] Xanthan gum solutions offer very good stability. They are least affected by changes in pH and are stable in both alkaline and acidic conditions.[69] Hideyuki tozaki et al., carried out a study with objective of to estimate colon-specific insulin delivery with chitosan capsule. The japan pharmacopoeia carried out in vitro drug release experiments from chitosan capsule which contain carboxyfluorescein rotating basket method with some slight modification. The absorption of insulin in intestine was evaluated by measuring plasma insulin levels and its

hypoglycemic effects after administrated orally of the chitosan capsule contains insulin. After administration the hypoglycemic effect start after 8 hour of administration of capsule when it entered in colon, which is evaluated by the transit time experiment.so the finding of this study suggests that chitosan capsule may be used as a colon-specific drug delivery of peptide including insulin.[70]

C. Capsule

Encapsulation using a premoulded, two-piece hard capsule is just one of a multitude of drug delivery systems in practice and is extremely effective in delivering active pharmaceutical ingredients (APIs). Standard pharmaceutical hard capsules are generally manufactured from gelatin. However, religious and ethical objections to the use of animal-based material in capsules forced pharmaceutical companies to consider alternatives. This has led to several alternatives to the gelatin capsule being developed and available on the market, most notably Shionogi Quali-V and Capsugel V-Caps.[71,72,73] Both of these capsules are based on hypromellose (HPMC) and studies have shown that HPMC capsules are promising as far as regulatory, manufacturing, religious and dietary issues are concerned.[74] Gelatin and HPMC capsules are designed to dissolve in the stomach, releasing the encapsulated contents for absorption in the intestine following gastric emptying. Capsules are gelatin shells filled with the ingredients that make up an individual dose. Capsules include medication that's enclosed in an outer shell. This outer shell is broken down in the digestive tract and the medication is absorbed into the bloodstream and then distributed and metabolized in much the same way as medication from a tablet.[75] Capsules are used for filling different materials like powder, granules, beads, tablets, caplets and pastes. The term enteric coating refers to ''the coating that is designed to sustain the gastric pH and disintegrate in the intestine.

The intestinal-colonic transit time plays an important role in the performance of CDDS and the colonic bioavailability of drugs. The transit times are also influenced by colonic disease states such as UC and CD. Patients with UC are known to have shorter colonic times (~24 h) compared to healthy subjects (~52 h).[76] Similarly, Rana *et al*. showed that in patients with IBD, the orocecal transit time was delayed.[77] The transit of dosage forms generally depends on the time of administration, presence/absence of food, and the type of dosage form. Stubbs *et al*. studied the effect of dawn and dusk on the motility of dosage forms in the colon. The results showed that colonic transit was delayed during sleep, and larger dosage forms, *e.g*., capsules transited faster compared to smaller dosage forms, *e.g*., dispersed particles.[78]

- **Type of capsule:**

Alan et al. have created polymer film formulations that can be used to form capsule shells and that are resistant to acid for up to 2 h, providing the possibility to deliver drugs or other substances to the intestine without the need to coat the capsule or the API. The major advantages of these capsules are: no coating process is required; all materials are from non-animal origin.[79]

A comparative study on different enteric-coated hard capsules was performed. The influence of different formulation factors like choice of enteric polymer, triethyl citrate (TEC) concentration (plasticizer), talc concentrations (anti-tacking agent), and different coating process parameters on the sealing performance of the capsule and the disintegration time were investigated. Furthermore, the influence of different disintegration test methods (with disc vs. without disc and 50 mM U.S. Pharmacopoeia (USP) buffer pH 6.8 vs. biopredictive 15 mM phosphate buffer pH 6.5) was evaluated.[80] Around 92% of the Hard capsules and 77% of the soft gels used by the drug industries are made with gelatin. There have not been a lot of suppliers in the soft gel technology area.

i. HGC

Sumit sharma et al., (2017) carried out study on Liquid Nano size Emulsion-Filled Enteric-Coated Capsules for Colon Delivery of Immunosuppressant Peptide. The aim of the study was to solubilizing slightly water-soluble peptide into a nano size emulsion to be filled in the hard gelatin capsule in form of preconcentrate. For colon targeting the capsule which is filled with liquid was dip coated with ethyl cellulose and eudragit S100. A and B formulation showed immediate release after 5 to 6 hours, which represent ileo-ceacal transit time. The nano size emulsion was confirmed by electron microscopy.[81] Nishant sing et al.,(2012) carried out a potential approach on Colon targeted drug delivery systems. To introduce colon along with the novel and emerging technologies for colon targeting of drug molecule. CDD has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, and many more but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. For colon targeting and to overcome previous method's limitation, the new system and technologies have been developed. Colon targeting holds a great potential but still need more innovative work.[82] Karl thoma et al., wrote a book on enteric coated hard gelatin capsules in which it shows that to protect the stomach from a potentially irritant drug substance or to administer acid labile drug pharmaceuticals develop an enteric coated hard gelatin capsule during early stages. Study reviewed other therapeutic applications of enteric coated pharmaceutical dosage forms. It describes the properties of the various enteric film forming agents along with plasticizers and other excipients and formulation with each polymer system are suggested. Book also reveals about general difficulties of enteric coating dosage forms and those specific to hard gelatin capsules as well as aspect on stability of product. And it shows that coating

process is most commonly used method in pharmaceuticals.[83] Ewart cole et al.,(2002) carried out a study on Enteric coated HPMC capsules designed to achieve intestinal targeting. The aim of the study was to investigate the enteric coating of HPMC capsules containing paracetamol. Eudragit® L 30 D-55 and Eudragit® FS 30 D two enteric polymers were studied to achieve properties and colonic release. For HPMC units coated with Eudragit® L 30 D-55, complete disintegration occurred predominately in the small bowel in an average time of 2.4 h post dose. For HPMC capsules coated with Eudragit® FS 30 D, complete disintegration did not occur until the distal small intestine and proximal colon in an average time of 6.9 h post dose.[84] Peter watts et al., describes, for site specific delivery of drugs in the digestive tract and, in particular, targeted release into the colonic region TARGIT technology is designed. For application the key area is the delivery of therapeutic agents for lower gastrointestinal disorders treatment. This technology have base on the application of Ph-sensitive coatings onto injection-moulded starch capsules. The generated data showing reliable in vivo performance of the capsule. In total 90% of TARGIT capsules delivered their contents to the target site of the terminal ileum and colon.[85]

ii. SGC

In normal individuals, the level of fluid available for conventional dosage form (tablet and dry powder-filled capsules) disintegration and dissolution is limited, with some reports of free water levels to be no more than a few tens of milliliters. Encap believes that there could be an advantage if we can deliver the drug to the colon in liquid form, via a liquid-filled hard capsule.[86]

Encap has established itself as a world leader in the field of liquid and hot melt filled hard capsules.

- **Thickness of capsule shell**

Gamest et al. prepared and evaluated enteric coated capsules having Eudragit S100 coating for the thickness attained by coating. The changes in thickness indicated that the final Eudragit coating acquired by the capsules when the thickness was measured by Digimatic caliper. The thickness measurement was performed to check uniform deposition of enteric coat on capsule shell body because it is necessary for the capsule to stay intact in acidic media for entire duration of residence in stomach. Finding said that the coating attained by the capsule shell evaluated to be 0.0643 mm.[86]

- **Coating of capsule**

Method of coating works effectively for HPMC capsules and to some extent gelatin capsules, but in the case of gelatin capsules, poor adhesion of the coat to the smooth gelatin surface can be a problem causing the capsule shell to become brittle.[87,88] Degree of gap closure seems to be at least one of the critical parameters influencing the degree to which the coat capsule is acid-proof. As reported by Maoqi Fu, formulation based on HPMCAS-MG shows a higher acid uptake compared to formulations based on HP-50 and HP-55 even though the SEM did not reveal tangible differences in the degree of gap closing. Subcoating the capsules with an immediate release polymer material helps to properly coat the cap–junction interface to seal the gap without a need to apply a too-thick enteric coat. This can also help to improve enteric coat adhesion which is an issue for gelatin rather than hydroxypropyl methylcellulose capsules. A single step enteric coating is more attractive and feasible, particularly for HPMC capsules owing to the good film adhesion on their surfaces. [89]

- **Coating composition**

Effect of coating composition on enteric-coated capsule disintegration times was reported by Maoqi Fu. [80]

- **Viscosity of coating solution**

Among the HPMCP series, HP-55S shows the smoothest structure of the coating and the best sealing of the junction between the cap and body of the capsule. This is most probably related to its higher degree of polymerization (reflected by higher viscosity) resulting in greater entanglement and accordingly superior film formation. [80]

- **Material to be filled in capsule**

Carrier:

Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule.[17] For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.[90] In the small intestine drug carrier will be delivered to the target side, and drug release will begin at a predetermined time point after gastric emptying. Another way to assist a drug formulation to remain intact as it passes through the stomach and small intestine is for it to be covalently linked to a carrier. A drug can bind to carrier molecules such as cyclodextrin, glucuronide, dextran, and amino acids. It can also be linked to a carrier through an azo bond. All of these bonds are broken down by colonic bacteria or enzymes.[91] Modasiya *et al.* studied the use of sodium alginate (Na-Alg) and hydroxypropyl methylcellulose (HPMC) as carriers for the successful delivery of matrix, enteric-coated, and compression-coated tablets of curcumin to the colon.[92] The *in*

vitro results showed that the drug release was rapid from the matrix, and from the enteric-coated tablets in conditions representing the stomach and small intestine. It was also observed that increasing HPMC levels significantly restricted the release of curcumin in the upper GIT and assisted in the delivery of curcumin specifically to the colon.

Plasticizer:

Sumit s. lal et al., describes, materials which are protein based have a special attention to the growth of polymer films and protein based coating. Study focus on efficiency of kafirin film and its effect as an enteric coating for release of drug. Study tested the cast films with varying plasticizer concentrations for mechanical tests and after that analyzed with use of DSC and TGA analysis. FTIR and swelling behavior were performed to ensure medium uptake and intra- and inter-related molecular structural changes. For enteric coating paracetamol which is filled in capsule were dip coated in kafirin solution with 20,30 and 40% of PEG plasticizer of drug related study. The plasticizer concentration effect was noticeable in the case of HPMC capsules, and release of drug declined with the increase in content of plasticizer. An increasing amount of Triethyl citrate resulted in a smoother and brighter surface. [80] But in case of gelatin opposite results were obtained. This study shows that kafirin protein has a potential for use as an enteric coating of drug delivery application.[93]

Process variables

1. Process selected

a. pH activated DDS
b. Enzymatically activated DDS
c. Receptor mediated DDS
d. Phloral Technology

Another novel (patented) technology has been developed by the School of Pharmacy, London (now University College London). The formulation, known as Phloral™, is designed to work through a combination of pH and enzymatic release.

e. Magnetically activated DDS

Changxuan, Wang, et al.(2019) carried out a study on Superparamagnetic Chitosan Nanoparticles for a Vancomycin Delivery System: Optimized Fabrication and *In Vitro* Characterization. To develop a vancomycin-loaded superparamagnetic chitosan nanoparticles (Vm-SPMCNs) system for the treatment of chronic pyogenic osteoarthrosis to avoid the critical side effects caused by the systemic administration of vancomycin. The results of *in vitro* release tests suggested that the Vm-SPMCNs could constantly release vancomycin to maintain the concentration above the minimum inhibitory concentration for ten days, and noninvasive external magnetic stimulation could modulate the release profile according to the actual therapeutic requirements.[94]

f. Temperature
g. Inlet and Outlet processing temperatures

2. Coating of capsule

a. Preparation of coating solution
b. Cap-body junction (Gap) closing after coating
c. Spray rate
d. Coating time

James Matthews et. al., (1989) carried out a study on Process for coating gelatin capsules. The rationale for the study was to investigate a new gelatin capsule formulation and sub coating for producing hard gelatin capsule. Hard gelatin capsule having better mechanical strength and an improved capacity for adhering to known coating composition. It suggests that sub coating may also be used to manufacture improved enteric coated hard gelatin The finished capsule shell formulation comprises glycerin 22%-25%, gelatin 65%-70%, and water 8%-10% and the sub coating is a suspension of hydroxypropyl methylcellulose.[95]

Young jeong et. al., (2001) carried out a study on Evaluation of an intestinal pressure-controlled colon delivery(PCDC) capsules prepared by a dipping method. For dipping process, a new method of preparation for PCDCs was developed. After oral administration of the test PCDC preparations containing 30 mg of Fluorescein, blood samples were obtained from the jugular vein and serum FL levels were measured. The thickness of the EC membrane layer varied in both the capsule body and cap. HPMCAS PCDCs had 62.1±5.0 (S.E.) μm (body) and 49.7±3.3 μm (cap) with thicker ones and 55.7±6.6 μm (body) and 46.8±6.2 μm (cap) with thinner ones. HPMCP PCDCs had 28.1±3.3 μm (body), 30.9±1.0 μm (cap) with thinner ones and 43.1±9.8 μm (body), 42.4±8.2 μm (cap) with thicker ones.[96]

Harpreet kaur et. al., (2013) carried out a study on enteric coated 5-fluorouracil capsules designed to achieve intestinal targeting. The purpose of the present study was to achieve successful delivery especially to colon using shellac as coat over the hard gelatin capsule. Gp1 shows a release of 12.14% in first 5 hours but, on twenty four hours Gp1 shows a maximum release of 98.75%. So the capsule with probiotic was found to be more effective than without probiotics.[97]

Thanaphat chartpitak et. al., (2018) carried out a study on Vancomycin-impregnated polymer on Schanz pin for prolonged release and antibacterial application. This study is to apply enteric coating on vancomycin with dip coating method to prevent its release in stomach and to sustain in colon. Results show that vancomycin release from the coating was able to provide the growth inhibition of *Staphylococcus aureus* up to 1 month. These results demonstrate that the surface coating of vancomycin and poly (lactic acid) was successful in inhibiting the growth of gram-positive bacteria on Schanz pins.[98] S.k.bajpai et. al., (2003) describes, hard gelatin capsules, which contain riboflavin -loaded polyacrylamide cylindrical hydrogels were chemically modified by treating with an aqueous formaldehyde solution with the purpose to delayed release of drug

along the digestive tract. Capsule's disintegration time was studied as a function of concentration of formaldehyde solution and the time of treatment. Dynamic release of vitamin B_2 was focused as a function of crosslinking ratio of the hydrogels. The current device study seems to have potential to be used for colon - targeted drug delivery.

Coating parameters which can critically affect the process

Process variable in dip coating

a. Gun geometry[99]

Gun to gun distance, gun to bed distance, is important for uniform spray and spray pattern. Gun calibration to be done before commencing of each operation. The gun-to-bed distance is an important process parameter that often times does not receive its due attention. It refers to the distance between the tip of the nozzle and an imaginary flat surface on the cascading bed of substance or capsules.

As the droplets move in this region, the solvent can evaporate, leading to a decrease in size, or the droplets can coalesce, thus increasing in size. In general, a reduction in droplet size is observed. However, since the pattern air flattens the spray, there is also a significant droplet coalescence occurring (and the size of the droplet hitting the capsule surface is dependent on process parameters.

If the gun-to-bed distance is too large, spray drying can be observed where smaller droplets dry completely before hitting the tablet surface, which in turn can lead to lower process efficiency and capsule defects such as rough surface.

On the other hand, if the spray nozzle is placed too close to the tablet bed, relatively large droplets may reach the tablets, creating an over-wetted surface and thus increasing the chance for tablet defects, including twinning and surface dissolution. Another factor to consider is the viscosity of droplets hitting the capsule. If the droplets have the appropriate viscosity right before they hit the capsule surface, they coalesce to the tablet substrate and form a good quality film. The residual water is evaporated by conduction of heat from the capsule to the droplet at a rate dictated by the bed temperature.

b. Atomization air pressure[99]

It coverts suspension to fine droplets or mist. High air pressure can cause spray drying and less air pressure may cause defects like sticking and picking due to formation of large droplet size. The atomization air pressure used in coating processes dictates the droplet size and velocity of the solution. The pattern air on the other hand flattens out the spray cone and enables better and more uniform spray coverage across the capsule bed. The pattern air can cause additional collision between droplets and result in an increase in droplet size. The size of the spray droplet impacts the drying kinetics as the droplet moves from the nozzle toward the tablet cores. A narrow droplet size distribution is desirable for good process control. Excessive atomization air pressure can result in the production of smaller droplets that dry completely before reaching the capsule surface, On the other hand, a low atomization air pressure can lead to ineffective atomization of the coating suspension, leading to bigger droplets that may not get spread and dried appropriately after they contact the capsule substrate.

c. Pan pressure

Kept negative based on the supplier's standard recommendation.

d. Pan speed

Pan speed was adjusted so as to ensure uniform mixing of capsules throughout the coating process which is based on the capsule shape and size. A dry run without spray was performed at pan speed of 2.1 rpm, to observe the capsule mixing pattern.

e. Spray rate[100]

Spray rate is one of the most important coating process parameters. At one extreme, a high spray rate may cause coating defects such as twinning, picking and sticking, whereas at the other extreme, a low spray rate may cause spray drying and a loss in coating efficiency. Inappropriately high spray rate may cause inadequate drying, twining and sticking. Thus spray rate will have a significant impact on surface roughness and weight gain. The optimization of spray rate is needed.

f. Inlet air temperature

Water evaporation and uniformity of coating is highly depended on inlet air temperature. High inlet air temperature may cause over drying and spray resulting rough surface, low inlet air temperature can lead to sticking of, twining and increase moisture content thus may impact the stability of the product. The inlet air (flow rate, T, and RH) dictates the drying kinetics of the spray droplets as they travel from the spray nozzle to the tablet surface and thus is another critical processing parameter in film coating. [101]

g. CFM: Though CFM is very important parameter for coating process. In this case, the machine selected has a good cfm capability and CFM value achieved is as per equipment supplier CFM recommendation i.e. 1500 cuft/min.

h. Out let air temperature

Outlet air temperature depends upon the amount of inlet air temperature; inlet CFM, spray rate and atomization are pressure.

i. The humidity and temperature inside

They are critical to solvent evaporation and film formation, especially with polymeric dispersions.

j. Exhaust temperature

Process control based upon adjustment of inlet air temperature to maintain a desired exhaust temperature is commonly used. The factors affecting the required inlet air temperature include spray rate, percent solids in coating solution, inlet airflow rate, and inlet air RH. The exhaust temperature is one of the process parameters that are generally kept constant during the pan coating process scale-up.[102,103]

CONCLUSION

A colonic targeted approach found to be effective in minimizing uncertain side effects. So, the colon, as a site for drug delivery, offers distinct advantages on account of near neutral pH, a much longer transit time, relatively low proteolytic enzymatic activity and offers a much greater responsiveness to absorption enhancers. Colon specific delivery systems should prevent the release of drug in upper part of GIT and require a triggering mechanism to release the drug on reaching the colon. The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

List of Abbreviation

CAP: Cellulose acetate phthalate
HPMC: Hydroxypropyl methylcellulose
API: active pharmaceutical ingredient
HGC: Hard gelatin capsule
SGC: Soft gelatin capsule
FTIR: Fourier-transform infrared spectroscopy.

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