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MICROSPHERES AS DRUG CARRIERS FOR TARGETED DRUG DELIVERY: A REVIEW

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ABSTRACT

Microsphere is having free- flowing powder properties that are incorporate proteins and synthetic or natural polymer. This polymer is biodegradable in nature and particle size having less than 200 µm. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, niosomes etc which modulates the release and absorption characteristics of the drug. Microspheres play a very important role as particulate drug delivery system because of their small size and other efficient properties. Microspheres have been proved to be a suitable bridge to scale the distance over to formulate an effective dosage form, to simulate controlled drug release. Microspheres having particle size in range between 0.1-200 µm, can be delivered by several routes like oral, parentral, nasal, ophthalmic, transdermal, colonal etc. Various recent advancement in case of microspheres like mucoadhesive, hollow, floating, microballons, magnetic have been contributed to overcome the various problems that are associated with the use of microspheres, which includes site specific targeting and improved release kinetics. In future by combining various new strategies, microspheres will find a central place in novel drug delivery, particularly in diseased cell sorting, genetic materials, safe, targeting and effective drug delivery.

KEYWORDS: Nanotechnology, Microsphere, Microadhesive, Natural polymer, Targeted drug delivery system.

1. INTRODUCTION

1.1. Oral route for drug delivery system

With gradual advancement detected in the field of biopharmaceutics, several useful corners have been evolved for discussion on designing and fabrication of drug delivery systems. Several useful information collected upto date directed modern research to have accuracy and rationality with sufficing every possible need of pharmaceutical technology. Dosage form development has rendered some new useful aspects of reliable drug carrier system with their conventionally popular counterpart. Of several developed drug administration methods, oral route has found its way to prove potential convenience to offer the greatest potential for more effective therapeutics, but they do not facilitate drug that easily cross mucosal surfaces and biological membranes; they are easily denatured or degraded, prone to rapid clearance in the liver and other body tissues and require precise dosing. At present, susceptible drugs are usually administered by injection but this route is less pleasant and also poses problems of oscillating blood drug concentrations. Despite the barriers for successful drug delivery that exist in the gastrointestinal tract (such as acid-induced hydrolysis in the stomach, enzymatic degradation throughout the gastrointestinal tract by several proteolytic enzymes, bacterial fermentation in the colons), the oral route is still the most intensively investigated as it offers advantages of convenience and economic in administration, and potential manufacturing cost savings. The design of oral control drug delivery systems (DDS) should be primarily aimed to achieve more predictable and increased bioavailability.[1] Historically, oral drug administration has been recognized as the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissues and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[2] However the oral route of drug administration presents its own unique set of problems and constraints. The time frame, or “window,” for absorption is limited to the total GI residence time. Taking into account gastric emptying and small and large intestine transit time, it would seem that a reasonable duration in the GI tract is approximately 24 hours. The absorption, distribution and elimination of drugs are normally simplified by considering them all to be simple first-order processes. Given the average 24-hour residence time and high individual variability in the GI tract, only drugs with relatively short elimination half-lives should be considered for membrane-controlled reservoir systems.

1.2. Controlled drug delivery system

Controlled drug release and subsequent biodegradation are important for developing successful formulations of targeted and/or controlled drug delivery system. The principles, theories and devices in chemical engineering can be modified and further developed to meet the challenges in the design of drug delivery systems. Therefore, controlled drug delivery can become a major possibility for chemical engineering to make significant contributions to human health care.[3] Novel approach for drug delivery is the method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is achieved and concentrations above or below this range can be toxic or produce no therapeutic benefit at all, on the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. Novel drug delivery system uses both physical and biochemical mechanism.[4] Controlled-release dosage forms are gaining rapid popularity in clinical medicine. The more sophisticated systems are used to alter the pharmacokinetic behavior of drugs in order to provide twice- or once-a-day dosage. Other applications include enteric coatings for the protection of drugs from degradation within the GI tract or the protection of the stomach from the irritating effects of the drug, and the delivery of drugs to absorption windows or specific targets within the GI tract, particularly the colon. In classical mechanisms of drug release, drug molecules are released from solid polymeric NPs by several mechanisms which is shown in **Figure-1.1.a**

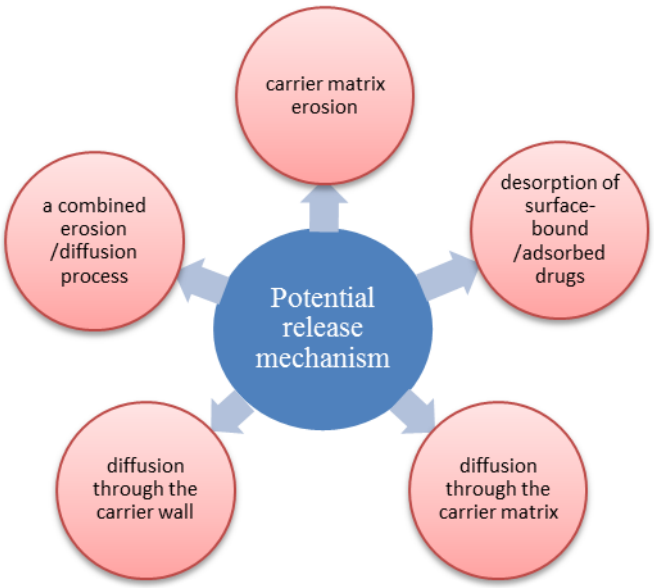

Figure 1.1: Mechanism of Potential release.

All these mechanisms employ physical transformation of constituents involved in the system when they are put into a biological environment. Although there are feasible chemically driven drug delivery systems, they involve chemical modifications with active agents and carrier vehicles for which regulatory approval and adequate toxicology and safety profiles are needed before reaching final application. For such reasons, simpler systems with approved active agents and excipients are often utilized in the preparation of the controlled drug delivery systems used for medical applications. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion, out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature).[6]

1.3. Targeted drug delivery system

Targeted drug delivery is an advanced method of delivering drugs to the patients in such a targeted sequences that increases the concentration of delivered drug to the targeted body part of interest only (organs/tissues/ cells) which in turn improves efficacy of treatment by reducing side effects of drug administration. Basically, targeted drug delivery is to assist the drug molecule to reach preferably to the desired site to direct the drug loaded system to the site of interest. Thus targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body

relative to others.[4] Targeted drug delivery system is preferred over conventional drug delivery systems due to three main reasons. The first being pharmaceutical reason conventional drugs have low solubility and more drug instability in comparison to targeted drug delivery systems. Secondly conventional drugs also have poor absorption, shorter half-life and require large volume of distribution. These constitute its pharmacokinetic properties. The third reason constitutes the pharmacodynamic properties of drugs. The conventional drug delivery systems have low specificity and low therapeutic index as compared to targeted drug delivery system. The targeted or site- specific delivery of drugs is indeed a very attractive goal because this provides one of the most potential ways to improve the therapeutic index of the drugs. To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development.[7] Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the drug while reducing side effects. Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs exclusively.[8] Targeting is the ability to direct the drug-loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest as second order targeting whereas for third order intracellular molecules are more specifically targeted.[9] Passive targeting refers to the accumulation of drug or drug carrier system at a specific site such as anti-cancerous drug whose explanation may be attributed to physicochemical or pharmacological factors of the disease. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.[10] Targeted drug delivery is a kind of smart drug delivery system which is miraculous in delivering the drug to a patient. This conventional drug delivery system is done by the absorption of the drug across a biological membrane, whereas the targeted release system is that drug is released in a dosage form.[11] Carrier is one of the special molecule or system essentially required for effective transportation of loaded drug up to the pre-selected sites. These are engineered vectors which retain drug inside or onto them either via

encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell.[12] Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation.[13]

Antibiotics, either are cytotoxic or cytostatic to the micro-organisms, allowing the body's natural defences, such as the immune system, to eliminate them. They often act by inhibiting the synthesis of a bacterial cell, synthesis of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), by a membrane disorganizing agent, or other specific actions.[14] Antibiotics may also enter the cell wall of the bacteria by binding to them, using the energy-dependent transport mechanisms in ribosomal sites, which subsequently leads to the inhibition of the protein synthesis.[15]

To combat against infections or microbes, undoubtedly antibiotics are a blessing to human civilization that has saved millions of people.[16] Multiple varieties of the antibiotics have been used for therapeutic purposes over time. Antibiotics were seen as the 'wonder drug' in the mid-20th century. At the time, there was an optimistic belief that communicable disease was nearly coming to a complete halt. The beginning of modern "antibiotic era" was synonymously associated with two names Alexander Fleming and Paul Ehrlich.[17]

Researchers have designed a new kind of hydrogel microsphere that can slowly release ciprofloxacin hydrochloride, a widely used antibiotic. They prepared the microspheres using xanthan gum (a bacterial polysaccharide) and polymers. This microsphere will be very useful for delivering the antibiotic in order to treat various bacterial infections. Xanthan gum is a polysaccharide secreted by the bacterium *Xanthomonas campestris*. It is used as a food-thickening agent in salad dressings and as a stabilizer in cosmetic products to prevent ingredients from separating. It is also used in the oil industry to thicken drilling mud. Researchers synthesized an interpenetrating polymer network containing the hydrogel Microspheres by mixing Xanthan gum with a superabsorbent polymer and poly(vinyl alcohol) in a water-in-oil emulsion. They produced a range of different microspheres by varying the ratio of the superabsorbent polymer to poly(vinyl alcohol). Sophisticated electron microscopy revealed that the microspheres had loose and rigid surfaces. After loading the

microspheres with the antibiotic, the researchers tested their ability to release the antibiotic in both acidic and alkaline media. All the produced microspheres released the antibiotic successfully. The drug-loaded polymer-based microspheres changed from a rubbery state to a dry state on releasing the drug through an unusual diffusion process.[18]

1.4 Factors to be considered in designing Colonic Drug Delivery

1.4.1 Anatomy of colon

The large intestine, also known as the colon, is part of the digestive tract. The entire colon is about 5 feet (150 cm) long and is divided into 5 major segments. The GI tract is divided into stomach, small intestine and large intestine. Large intestine extending from the ileocecal junction to the anus and it is divided into 3 main parts. **(Figure-1.2)** i.e colon, rectum and canal. Perinatal folds are called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon and hepatic flexure. The left colon consists of descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus .The colon tissue contains the villi, lymph, muscle, nerves and vessels. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which 90% of fluid is absorbed. The adult colon is line by atleast 8 distinct epithelial cell types, viz columnar or absorptive cells, deep crypt secretary cells, vacuolated cells, microfold or M cells, undifferentiated crypt cells, multivesicular or caveolated cells, goblet cells and variety of endocrine cells. The colon removes water, salt, and some nutrients forming stool.

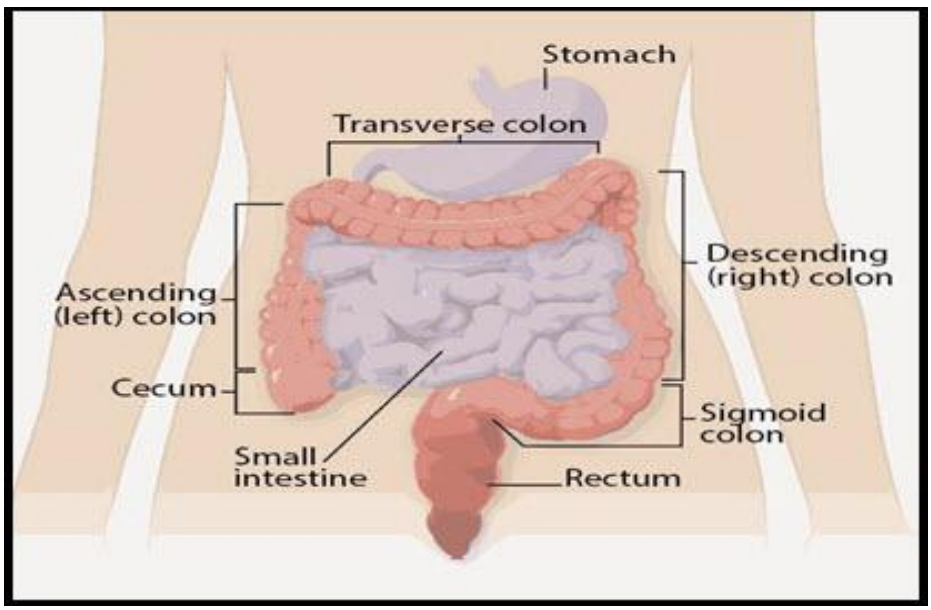

Figure1.2: Anatomy of.

1.4.2 Physiology of colon[19]

The colon formally acts as a storage reservoir of faecal contents and expulse the colon contents at an appropriate time. Apart from this, it serves major role in water and sodium ion absorption from gut lumen along with secretion and excretion of potassium and bicarbonate. It also creates suitable environment for the growth of colonic microorganisms by offering friendly environment which pay a key role in digestion of proteins, carbohydrates, into their simpler form, by secreting various enzymes. The physiology of proximal and distal colon differs in many aspects related to their function and may affect drug absorption at each site.

Table 1.1: Differences between proximal colon and distal colon.

	Proximal	**Distal**
Function	Fermentation chamber, absorption	Absorption, Storage
Innervation	Vagal/Pelvic lumbar muscle more distensible	Pelvic, Lumbar, greater sensitivity to neutral stimulation
Blood supply	Superior mesenteric Artery and vein, greater blood flow	Inferior mesenteric Artery and vein
Absorption	92% chloride dependent transport is electro neutral greater overall capacity	Chloride-dependent transport mainly, Amiloride sensitive
Luminal contents	Liquid, lower pH (4.6-7.8), Active microbial metabolism	Semisolid, neutral pH, lower bacterial activity

Table 1.2: Summary of anatomical and physiological features of small intestine and colon.

Region of Gastrointestinal tract			**Characteristics**
Length (cm)	Entire Gastrointestinal tract		600-700
	Small intestine	Duodenum	25-30
		Jejunum	160-200
		Ileum	250-350
	Large intestine	Cecum	6-7
		Ascending colon	45
		Transverse colon	40
		Descending colon	30
		Sigmoid colon	40
		Rectum	12
		Anal canal	3
Internal diameter (cm)	Small intestine		3-4
	Large intestine		6
pH	Stomach	Fasted	1.5-3
		Fed	2-5
	Small intestine	Duodenum(fasted)	~ 6.5
		Duodenum(fed)	~ 5.4
		Ileum	~ 7
	Large intestine	Cecum and Colon	~ 5.5-7
		Rectum	7

1.4.3 Absorption in colon

Surface area of the colon is much less as compared to the small intestine and it is compensated by absence of endogenous digestive enzymes and it has a long residence time of colon (10-24 hours).There are different factors which affect the colonic absorption.

• It passes through colonocytes (Trans cellular transport).

• It passes between adjacent colonocytes (Para cellular transport).

Mostly the absorption of lipophilic drugs occurs through the transcellular route. On the other hand absorption through paracellular routes involves the transfer of hydrophilic drugs through tight junction between the cells. The oral absorption of protein and peptide drugs is limited because of degradation in acidic environment of stomach, enzymatic degradation in small and large intestine, rapid transit from small intestine, low mucosal permeability and extensive first pass metabolism by absorbing membrane and the liver.

1.5 Development of colonic formulation: Common Deliberations[20,21]

a. Colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.
b. For the avoidance of hepatic first pass metabolism of drugs.
c. Greater responsiveness to absorption enhancers.
d. For fundamental understanding of anatomic and physiological characteristics of human gastrointestinal tract.
e. Oral delivery of vaccines as it is rich in lymphoid tissue.
f. Targeting opportunities offered by colonic bacterial enzymes.
g. Site for delivery of delicate drugs (proteins and peptides).
h. Treatment of local pathologies.

1.5.1 Factors affecting colon drug delivery[22,23,24]

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolite products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus disease state.
- Transit through GIT.
- Lower surface area and relative tightness of the tight junctions in the colon can restrict drug transport across the mucosa in to the systemic circulation.

- Various factors such as formulation factors, retention time, retrograde spreading etc. Influence absorption.
- Physicochemical and biopharmaceutical properties of drug like solubility, permeability, stability at the intended site of administration.
- Successful delivery requires the drug to be in solution before it arrives in the colon,but the fluid content in the colon is lower and more viscous than in upper GIT, which is the limiting factor for poorly soluble drugs.

1.6 General consideration for design of colonic formulation[25,26]

The design of a colonic formulation is to provide a burst release or to sustain/ prolong release once they reach colon. The appropriate selection of a formulation approach is based upon the various another important parameters are:

1. The dissolution and release rate from colonic formulations is slow because of the less fluid present in the colon then it causes to lead the lower systemic availability of the drugs.
2. The design of delayed release colonic formulation due to the pH gradient of the gastrointestinal tract.
3. Physicochemical and biopharmaceutical properties of the drug are solubility, stability and permeability at the intended site of delivery.
4. It has adequate release profile of the active ingredients.

1.6.1 Advantages of colon targeted drug delivery[27,28,29,30,31]

a. Particle size reduction for enhancing solubility of the poorly soluble drug.
b. It provides constant and prolonged therapeutic effect.
c. Provide constant drug concentration in blood by increasing patient compliance.
d. Decrease dose and toxicity.
e. Protect the drug from enzymatic and photolytic cleavage hence found to be best for drug delivery of protein.
f. Reduce the dosing frequency and thereby improve the patient compliance.
g. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
h. It required smaller quantity of the drug for local treatment.
i. Convert liquid to solid form & to mask the bitter taste.
j. Protects the GIT from irritant effects of the drug.

k. Drugs which are destroyed by the stomach acid and/or metabolized by pancreatic enzymes are slightly affected in the colon.
l. No distribution throughout the body. (no dilution effect) Controlled release for longer period of time (like 1-3 months).
m. Frequency is reduced and hence patient compliance is increased.
n. Improved antigenicity by adjuvant action.
o. Modulation of antigen release.
p. It reduces the gastric irritation which is caused by many drugs e.g. NSAIDS.
q. It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.

1.6.2 Drawbacks of colon targeted drug delivery[20,32]

1. The costs of the materials and processing of the controlled release preparation are substantially higher than those of standard formulations.
2. The fate of polymer matrix and its effect on the environment.
3. The fate of polymer additives such as plasticizers, stabilizers, antioxidants and fillers.
4. Reproducibility is less.
5. Process conditions like change in temperature, pH, solvent addition, and evaporation/agitation may influence the stability of core particles to be encapsulated.
6. The environmental impact of the degradation products of the polymer matrix produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents.
7. Intended mainly for parenteral route which causes pain.
8. Forms a depot in tissue or muscle for longer period and hence may produce pain when muscle activities are done.
9. Once administered, it is difficult to take back the dose.
10. Polymer may produce toxic effects.

1.7 Potential use of microspheres in the pharmaceutical industry

- Taste and odour masking.
- Conversion of oils and other liquids to solids for the ease of handling.
- Protect the drugs from the environment (moisture, light etc.).
- Separation of incompatible materials (other drugs or excipients).
- Improve the flow of powders.

- Aid in dispersion of water-insoluble substances in aqueous media, and Production of SR, CR, and targeted medications.

1.8 Polymers used in the Microsphere preparation

Polymers used for the preparation of microsphere are classified into two types.

1. Synthetic Polymers: Synthetic polymers are divided into two types.

(a) Non-biodegradable polymers

- Poly methyl methacrylate (PMMA)
- Acrolein
- Glycidyl methacrylate
- Epoxy polymer

(b) Biodegradable polymers

- Lactides, Glycolides & their co polymers
- Poly alkyl cyano Acrylates
- Polyanhydrides

2. Natural polymers

They are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

A. Proteins: Albumin, Gelatin, Collagen

B. Carbohydrates: Agarose, Carrageenan, Chitosan Starch

1.9 Approaches in colon targeting

There are many formulations which have been developed for the conventional colon targeting approaches such as pH dependent system, microbial triggered system and time controlled system etc. Several innovative approaches have been designed for effective colonic delivery.

1.9.1 Primary approaches[33,34,35,36,37]

1.9.1.1 pH sensitive system

In the G.I.T, there is presence of pH gradient which approximately ranges from 1.2 in stomach, 6.6 in proximal small intestine, 7.5 in distal intestine & pH of colon is about 6.4. Generally Eudragit L100 is used for the colon delivery it dissolves at pH greater than 7.0, which results in premature drug release from the system. It is concluded that pH of G.I.T. was not a reliable criteria for colonic targeting. Problem of premature drug release can be overcomed by the use of Eudragit L100 which is shown in **Figure-1.3**.

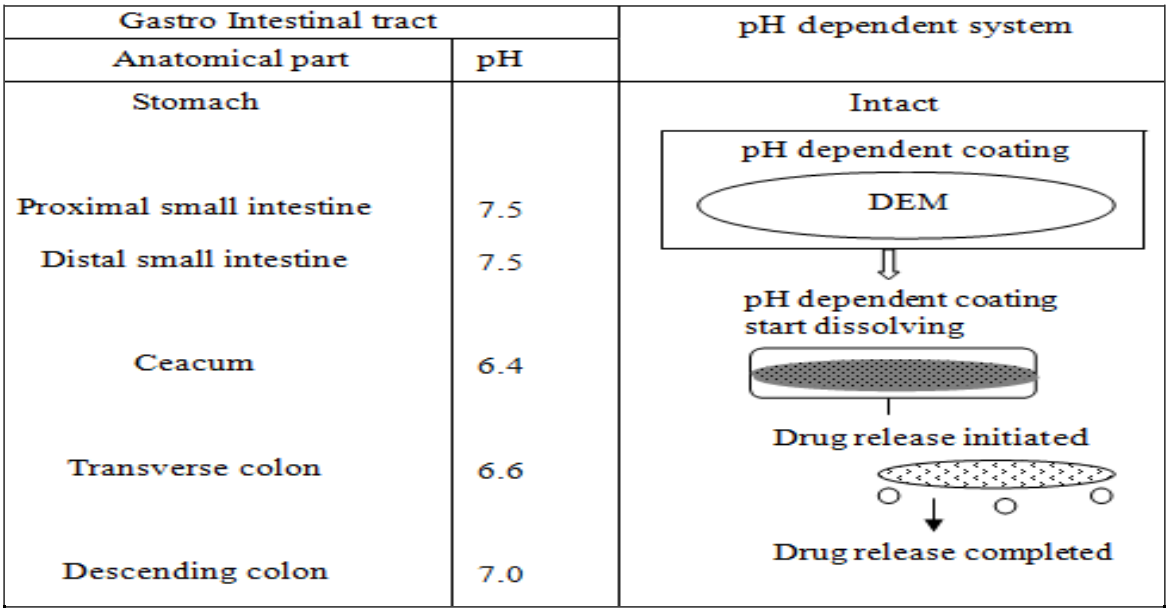

Figure1.3: Presentation of pH dependant release.

Table 1.3: pH of different grade of polymers.

S.No	Polymers	Threshold pH
1	Eudragit L 100	6.0
2	Eudragit S 100	7.0
3	Eudragit L-30D	5.6
4	Eudragit FS 30D	6.8
5	Eudragit L 100-55	5.5
6	Polyvinyl Acetate Phthalate	5
7	Hydroxypropyl Methylcellulose Phthalate	4.5-4.8
8	Hydroxypropyl Methylcellulose Phthalate 50	5.2
9	Hydroxypropyl Methylcellulose Phthalate 55	5.4
10	Cellulose Acetate Phthalate	4.8
11	Cellulose Acetate trimellate	5.0

Table 1.4: Utilization of pH dependent polymers along with drugs in different dosage forms.

Drug used	Polymer used	Formulation
Ornidazole	Acrycoat L-100	Microspheres
Mesalazine	Eudragit S 100	Microspheres
Theophylline	Eudragit S100 &L 100	Microspheres
Diltiazem Hydrochloride	Eudragit S100	Microspheres
5-Fluorouracil	Eudragit S100	Enteric coated capsules
Theophylline	Eudragit S100	Microbeads

1.9.1.2 Delayed (Time controlled release system) release drug delivery to colon[38,39,40,41]

Time dependent/controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability.

Time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve the site specificity of drug delivery to the colon. Since the transit time of dosage forms in the small intestine is less variable i.e. about 3±1 hr. On the other hand, in the stomach, the drug release should be suppressed by a pH sensing function (acid resistance) in the dosage form, which would reduce variation in gastric residence time. Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function).

1.9.1.3 Microbially triggered drug delivery to colon[42,43]

Colon is rich in microflora and variety of microbes were found in colon, that obtained there basic requirement or fulfil their energy needs from the undigested foods present in small intestine such as di-trisaccharidesvia fermentation process. Bacterial count in colon is much higher around 1011-1012 CFU/ml with some 400 different species which are.

A. Fundamentally aerobic, predominant species such as bacteroides, Bifidobacterium, and eubacterium etc., whose major metabolic process occurring in colon are hydrolysis and reduction. The enzymes present in the colon are.

B. Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, hydrogenase etc.

a) Prodrug approach

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation in vivo to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine which is shown in **Figure-1.4**. The type of linkage that is formed between the drug and carrier would decide the

triggering mechanism for the release of the drug in the colon. In this method the prodrugs are designed to undergo minimum absorption and hydrolysis in the upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the carrier. Different types of conjugates were used to prepare 5-ASA prodrugs, which are succeed in releasing the 5-ASA in colonic region.

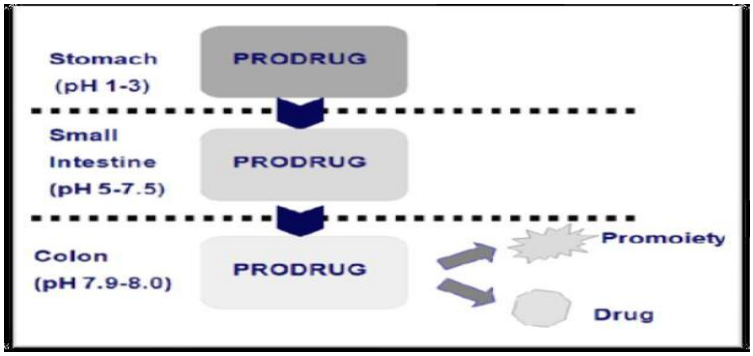

Figure 1.4: Design of Prodrug Approach.

b) Azo-Polymeric Prodrugs

Sub-synthetic polymers form a polymeric prodrug with azo linkage between the polymer and drug moiety. Azo polymers have been found to be susceptible to cleavage by the azo reductase in the large bowel as shown in **Figure1.5**.

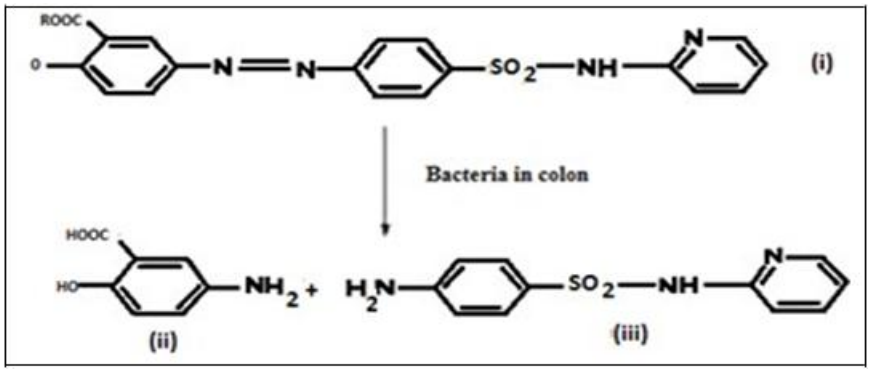

Figure1.5: (I) hydrolysis of sulphasalazine (ii) 5-aminosalicylic acid (iii) sulfapyridine.

c) Combination of pH and Polysaccharides[44]

The polysaccharide delivery vehicles may be layered with an enteric blocking agent. The purpose of such a coating is to protect the delivery vehicle from degradation by stomach acids and proximal intestinal enzymes. David and Sergio (1997) patented controlled release vehicles like nonporous microspheres, microcapsules and liposomes for delivery of drugs to colon. Budesonide delivery system and pectin admixture was compressed into tablets. These

matrices were coated with Eudragit L-100 yielded enteric release characteristics. In another research, the concentration of 14C hydrocortisone was measured in both urine and ileal effluents for 3-5 days after ingestion of porous microscopic beads loaded capsule. It was observed in all the subjects that 14C was excreted mostly by ileal route. It was also observed that almost all excretion occurred within 24 hr of ingestion of the capsule. Therefore, the results indicated that the active ingredient was released primarily in the colon. The detection of 14C hydrocortisone in considerable concentration in faeces within 24 hr of ingestion suggests that pectin matrices loaded in Eudragit L-100 coated capsules could also be used to deliver in sufficient quantity of drugs in the colon for treatment of IBD.

Table 1.5: List of various polysaccharides used in microbially triggered colonic delivery.

Polysaccharides		**Bacteria**	**Enzymes**
Plants origin	Guar gum	Bacteroides, Ruminococcus	Galactomannase
	Inulin	Bacteroides, Bifidobacterium and Eubacterium	Inulinase
	Pectin	Bacteroides	Pectinase
Animal origin	Chitosan	Bacteroides, Eubacterium	Chitinase
Microbial origin	Dextran	Bacteroides	Dextranse

1.9.2 Novel approaches for colon

1.9.2.1 Pressure controlled drug delivery system (PCDDS)[45,46,47,48]

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for the disintegration of the formulation. The system also appeared to depend on capsule size and density. Because of re-absorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethyl cellulose single unit capsules the drug is in a liquid. CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

1.9.2.2 PORT system

This system based on the principle of delayed drug release. This system consists of.

- Gelatin capsule coated with semi-permeable membrane (e.g., cellulose acetate) housing.
- An insoluble plug (e.g., lipidic).
- An osmotically active agents along with the drugs formulation.

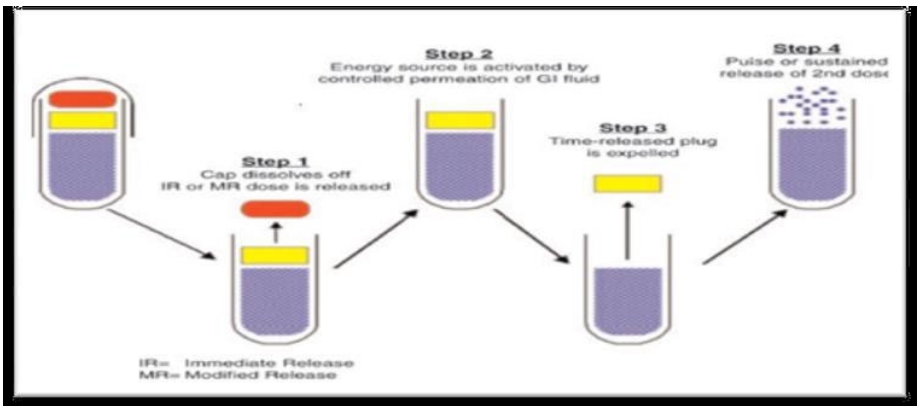

Figure 1.6: Design of Port system.

1.9.2.3 Osmotic controlled drug delivery (OROS-CT) (49,50)

The concept of osmotic controlled drug delivery has been around for several years, the applications of this technology in the design of colon-specific oral dosage forms have gained popularity only in the 10–15 years. The OROS-CT is an example of a system regulated by osmotic pressure. It consists of a hard gelatin capsule which dissolves in the pH of the small intestine and allows water to enter the unit. This then causes it to swell and the drug is forced out. Within each capsule therecanbeasmanyas5–6 units, and each unit is surrounded by a drug impermeable enteric coating which prevents water from entering in the acidic environment of the stomach **(Figure 1.7).** However, this coating dissolves and the water enters once the capsule enters the higher pH of the small intestine. Within the enteric coating there is a semi permeable membrane which encompasses an osmotic push compartment as well as a drug compartment. The water causes the push compartment to swell and forms a gel in the drug compartment that is forced out of an orifice through the membrane next to the drug compartment. The rate at which the drug flows out depends on the rate at which water enters. To prevent drug release in the small intestine, these systems can also be designed such that there is a lag time between when the enteric coating dissolves and the drug is released.

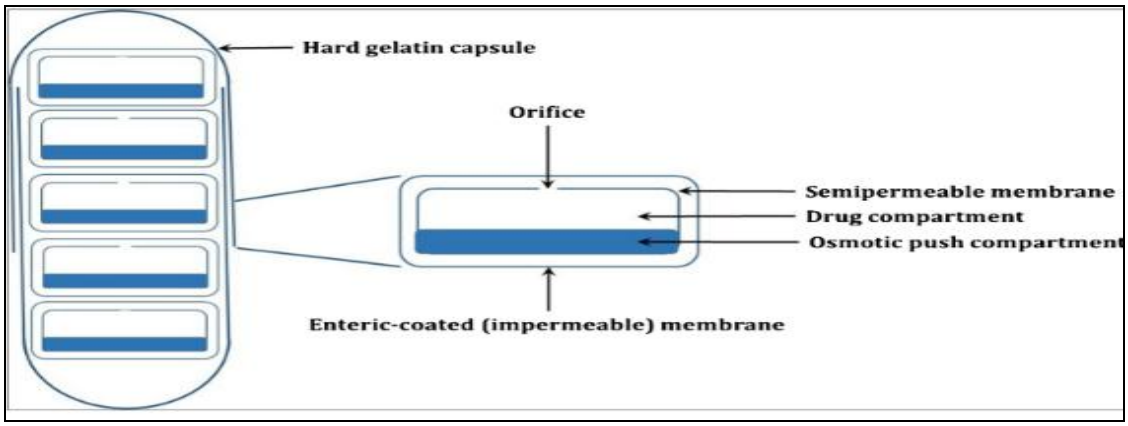

Figure 1.7: Schematic representation of the cross-section of the OROS-CT.

1.9.2.4 PULSINCAP approach[51]

These (single-unit) systems are mostly developed in a capsule form. The drug is released as a "Pulse" from the insoluble capsule body by swelling or erosion of plug (control lag time). A swellable hydrogel plug was used to seal the drug contents into the capsule body, and when in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The length of the plug and its point of insertion into the capsule controls the lag time.

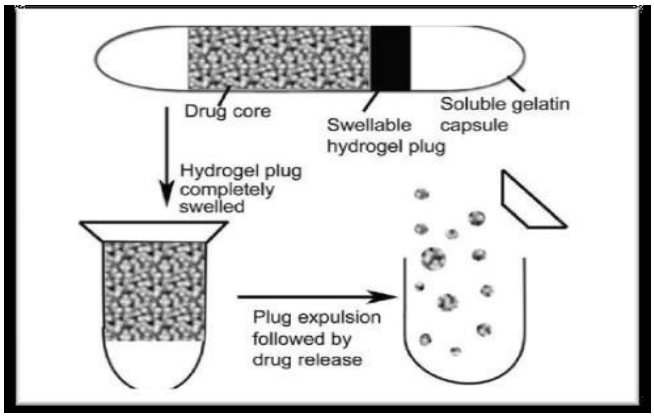

Figure1.8: Design of Pulsincap system.

1.9.2.5 Novel colon target drug delivery system (CODES™)[52,53,54,55]

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon **(Figure1.9).** The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated

with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine. Once the tablet arrives in the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release.

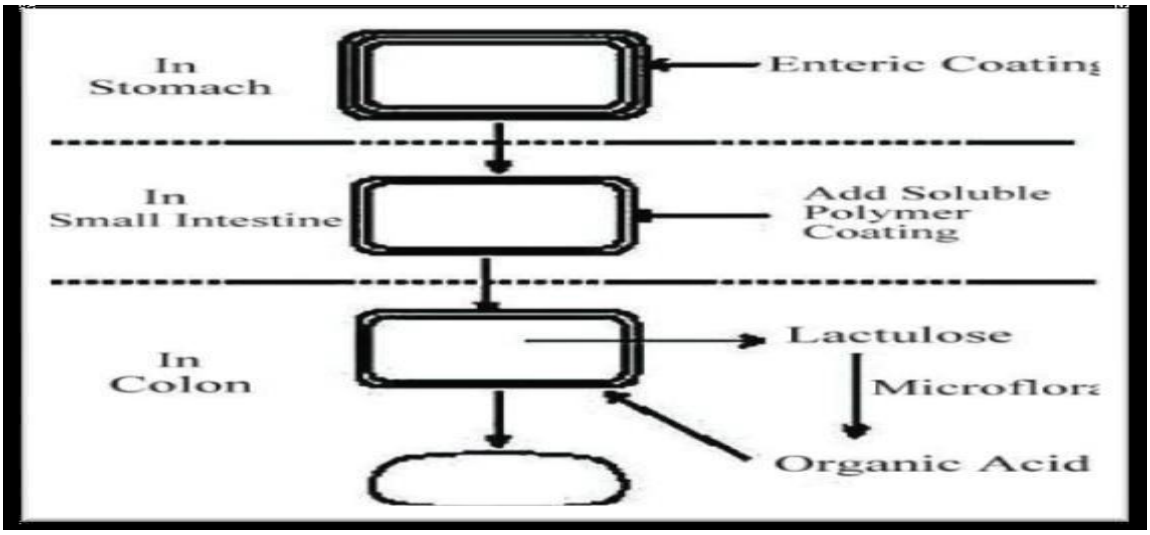

Figure1.9: Design of CODES.

1.10 Microencapsulation techniques in drug delivery[56,57,58,59]

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded and enclosed, by an intact shell. The concept of microencapsulation was initially utilized in carbonless copy paper. In 1931 Bungenburg de Jong co-workers conducted research work on the development of microencapsulation procedures used for the manufacturing of pharmaceuticals and include in the manufacture of small spheres by coating the hot gelatin solution around the spheres by coacervation technique.

In the present days the various pharmaceutical industries and researchers are involved to develop newer drug delivery systems by using several coating materials for the microencapsulation of oral products. In the microencapsulation process the aqueous polymeric dispersion of drug converted into small solid spheres by altering surface properties of polymeric material, induces to form a protective layer and sustaining the release characteristics of drug candidate. The microparticles are small discrete particles with a diameter of 1–1000μm, irrespective of the precise interior or exterior structure are generally

formulated by encapsulation process whereby a drug candidate included in a colloidal polymeric dispersion which forms a protective gel layer or forms thick membrane or polymeric protective shell. In other words, microparticles are formulated by adding active core either solid, liquid or gas into homogenous mixture polymer and converted into micron size particles.

Research to find new or to improve microencapsulation techniques to fabricate certain newly discovered active medicaments by using nontoxic, inert polymeric materials and solvents is much important progress because of the limitations of the current pharmacopeia. Besides of this, the regulatory authorities, such as the U.S. Food and Drug Administration (FDA), are restricting to greater degrees the amounts of additional components allowed such as organic solvents or tensioactive molecules.

The development of new microencapsulation techniques to produce reproducible product and quality of dosage regimen, one must take into considered several manufacturing requirements; the physical and chemical stability of the drug should not be affected during the microencapsulation process, the formulated spheres or beads with high yield and drug encapsulation efficiency, good mechanical strength and should not exhibit aggregation or adherence. The drug release from the formulation is a reproducible manner with specified time limit and the process should be usable at an industrial scale and the residual level of organic solvent should be lower than the limit value. There are several techniques for microencapsulation which is shown in **Table-1.5.**

Table 1.5: Various processes of microencapsulation technique.

Chemical process	**Mechanical process**
Coacervation and phase separation	Spray drying
Interfacial polymerization	Spray coating
Ionotropic gelation technique	Fluidized bed coating
Emulsion polymerization	Electrostatic deposition
Single emulsion technique	Centrifugal extrusion
Double emulsion technique	Vibrational nozzle process
Emulsion cross-linking technique	Rotational suspension separation
Solvent evaporation	Polymerization at liquid gas
Melt solidification	Air suspension process
Layer by layer adsorption process	Co-axial ultrasonic technique

1.11 Ionotropic gelation technique[60,61]

Microencapsulation by ionotropic gelation is one of the widely used technique for developing the oral solid microparticles to control the drug release, reduce the dose related adverse effects especially drug with small therapeutic range and improve the bioavailability of poor water soluble drugs. Ionic-gelation may be defined as a physicochemical process of micro-droplet hardening by chelation of polyelectrolyte with polyvalent ions. Such a chelation results in cross-linking of the polyelectrolyte molecules while forming a shell in the form of a polymeric gel. The most widely used system is based on gelation of aqueous sodium alginate, gellan, carrageenan, pectin and chitosan solutions by the addition of divalent cations such as calcium chloride, tripolyphosphate, aluminum chloride, barium chloride; potassium chloride induces the cross-linking of the polymers, and instantaneously the formation of discrete solid microparticles.

By this method strong spherical shape and narrow particle size with high yield microparticles are formed. The ionic gelation mechanism of alginates with divalent calcium ion has widely used for the preparation of calcium alginate microbeads which are recently used as a vehicle for oral controlled drug delivery system of many therapeutic agents such as NSAIDs, hypertensive, antibiotics, anticancer drugs, antihistamines, cardiovascular agents, vitamins, tranquilizers.

1.12 Inflammatory Bowel Disease (IBD)[62]

Inflammatory bowel disease, or IBD, is a collective term encompassing related, but distinct, chronic inflammatory disorders of the gastrointestinal tract, such as Crohn's disease, ulcerative colitis (UC), indeterminate colitis, microscopic colitis and collagenous colitis. Crohn's disease and ulcerative colitis are the most common diseases. Another chronic disorder of the gastrointestinal tract is irritable bowel syndrome (IBS). For most patients, IBD and IBS are chronic conditions with symptoms lasting for months to years. Inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease are serious intestinal diseases that can ultimately lead to the surgical removal of the colon. It is most common in young adults, but can occur at any age. It is found worldwide, but it is most common in industrialized countries such as the United States, England, and Northern Europe. For example, IBD affects an estimated two million people in the United States alone.

1.13 Ulcerative Colitis

Ulcerative colitis is a chronic inflammation of the large intestine (colon).It is a disease that causes inflammation and sores, called ulcers, in the lining of the rectum and colon. Ulcers form at sites where inflammation has killed the cells that usually line the colon, then bleed and produce push. Ulcerative colitis is closely related to another condition of inflammation of the intestines called Crohn's disease. Together, they are frequently referred to as inflammatory bowel disease (IBD). Ulcerative colitis can occur in people of any age, but it usually starts between the ages of 15 and 30, and less frequently between 50 and 70 years of age. It affects men and women equally and appears to run in families, with reports of up to 20 percent of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease. A higher incidence of ulcerative colitis is seen in Whites and people of Jewish descent.

1.13.1 Symptoms of ulcerative colitis

The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Patients also may experience.

- Anemia
- Fatigue
- Weight loss
- Loss of appetite
- Rectal bleeding
- Loss of body fluids and nutrients
- Skin lesions
- Joint pain
- Growth failure (specifically in children)

1.14 Application of microspheres in Pharmaceutical industry

1. Ophthalmic Drug Delivery
2. Oral drug delivery
3. Gene delivery
4. Nasal drug delivery
5. Intratumoral and local drug delivery
6. Buccal drug delivery
7. Gastrointestinal drug delivery

8. Transdermal drug delivery
9. Colonic drug delivery
10. Vaginal drug delivery
11. Targeting by using microparticulate carriers

1. Ophthalmic Drug Delivery

Microspheres developed using polymer exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Example: Chitosan, Alginate, Gelatin.

2. Oral drug delivery

The ability of microspheres containing polymer to form films permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications. Example: Chitosan, Gelatin.

3. Gene delivery

Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Example: Chitosan, Gelatin, viral vectors, cationic liposomes, polycation complexes.

4. Nasal drug delivery

Polymer based drug delivery systems, such as microspheres, liposomes and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. Example: Starch, Dextran, Albumin, Chitosan+Gelatin.

5. Intratumoral and local drug delivery

In order to deliver paclitaxel at the tumor site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity. Example: Gelatin, PLGA, Chitosan and PCL.

6. Buccal drug delivery

Polymer is an excellent polymer to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Example: Chitosan, Sodium alginate.

7. Gastrointestinal drug delivery

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of the drug .Example: Eudragit, Ethyl cellulose+Carbopol BSA, Gelatin.

8. Transdermal drug delivery

Polymer has good film-forming properties. The drug release from the devices is affected by the membrane thickness and cross-linking of the film. Example: Chitosan, Alginate, PLGA.

9. Colonic drug delivery

Polymer has been used for the specific delivery of insulin to the colon. Example: Chitosan.

10. Vaginal drug delivery

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycotic infections of the genitourinary tract. Example: Chitosan, Gelatin, PLGA.

11. Targeting by using microparticulate carriers

Pellets are prepared with polymer by using the extrusion/spheronization technology.

CONCLUSION

Microspheres are better choice of drug delivery system than many other types of drug delivery system. In future by combining various other strategies, microspheres will find the central and significant place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, Colon targeted, specific and effective *in-vitro* delivery and supplements as miniature version of diseased organ and tissues in the body.

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