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Review Article

Microspheres Review: As a Carrier in Novel Drug Delivery

SARIPILLI RAJESWARI*, SATYAJITH PANDA, RANJITH PRASAD SWAIN, VINUSHA GOKA, TELLA PRASANTHI

Department of Pharmaceutical Technology, Maharajah's College of Pharmacy. Phoolbaugh, Vizianagaram, AP, India

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ABSTRACT

Colon specific drug delivery has gained increased importance not just for delivery of drug for the treatment of local diseases, associated with the colon but also potential site for systemic delivery of therapeutic drug. Treatment could be more effective if it is possible for drug to be directly delivered to colon. This article gives an overview on anatomy and physiology of the colon and approaches utilized for colon specific drug delivery. This article also discusses advantages and limitations of the different approaches and also deals with the microsphere, various methods used for preparations of microspheres and advantages and disadvantages of microspheres.

INTRODUCTION

Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea and colon cancer. In addition, the colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs[2].

Colon which is rich in lymphoid tissue can be exploited for the uptake of antigen into mast cells of colonic mucosa that produces rapid local production of antibodies and this helps in efficient vaccine delivery. Region of colon is recognised as having somewhat less hostile environment with less diversity and intensity of activity than stomach and small intestine. The colon is a site where both local and systemic drugs can be delivered. Local delivery allows topical treatment of inflammatory bowel disease[2-3].

However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. The colon has high water absorption capacity. Since the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. Drugs, which are destroyed by the stomach acid or metabolized by pancreatic enzymes, are slightly affected in the colon and sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina and arthritis.

Controlled release dosage forms are designed to achieve a prolonged therapeutic action by releasing the medication over an extended period of time by administration of single dose. Controlled drug delivery technology is concerned with systemic release of a pharmaceutical agent to maintain a therapeutic level of the drug in the body for a sustained period of time. Various different approaches are used to develop controlled drug delivery systems. One such approach is using microspheres as carriers for drugs. Due to its small size they are widely distributed throughout the GIT which improves drug absorption and reduces side effects due to localized buildup of irritating drugs against the gastro intestinal mucosa. Microencapsulation is one of the methods used to prepare controlled release dosage form. The capsule shells can be designed to release their ingredients at specific rate and/or under specific set of conditions. Microencapsulation is perhaps the most widely accepted technique for oral and parenteral controlled release[3-4].

Author for Correspondence:
Email: rajeswarimalli@gmail.com

Following techniques are used for the preparation of microspheres

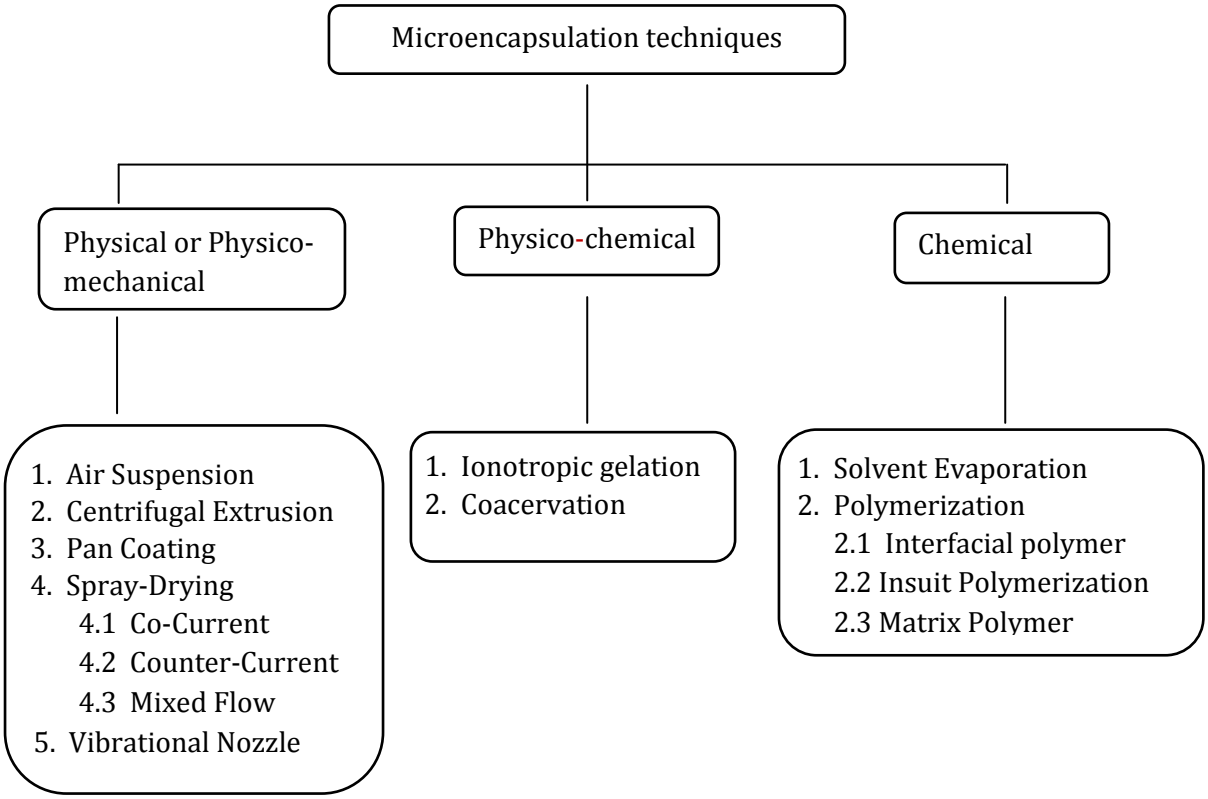

Figure 1: Different techniques used for the preparation of microspheres

Prerequisite for ideal micro particulate carriers

The materials utilized for the preparation of micro particulates should ideally fulfill the following prerequisite:

- Longer duration of action
- Increase of therapeutics efficiency
- Reduction of toxicity
- Control of content release
- Relative stability
- Biocompatibility

Advantages of microspheres[6-8]

- Microspheres are used because they provide constant and prolonged therapeutic effect
- Reduces the dosing frequency and there by patient compliance are improve
- Microspheres are smaller in size and having spherical shape so that they can be injected into the body
- Microspheres morphology allows a controllable variability in degradation and drug release

Disadvantages of microspheres[6-8]

- The release rate of the controlled release dosage form may vary from a variety of factors like food
- Different in release rate from one dose to another
- Dosage forms of this kinds should not be crushed or chewed
- Controlled release formulations generally contain higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity

General methods of preparation

The microspheres can be prepared by using many techniques, but the choice of technique mainly depends on the nature of polymer used, the nature of the drug, the intended use and the duration of therapy. The method of preparation and its choice are equally determined by some formulation and technology related factor as mentioned below.

1. The particle size requirement
2. The drug or protein should not adversely affected by the process
3. Reproducibility of the release profiles and the methods
4. No stability problem

There should be no toxic products associated with the final product. Various microencapsulation processes can be divided into chemical, physiochemical and electrostatic and mechanical processes.

Types of microspheres[8,9]

1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Mucoadhesive microspheres
6. Polymeric microspheres
7. Biodegradable polymeric microspheres
8. Synthetic polymeric polymers

Methods of preparation of microspheres[14]

1. Emulsion solvent evaporation technique
2. Emulsion cross linking method
3. Coacervation method
4. Spray drying technique
5. Emulsion-solvent diffusion technique
6. Multiple emulsion method
7. Ionic gelation

Preparation of microspheres should satisfy certain criteria

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersibility in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.

Methods of preparation of microspheres

1. Emulsion solvent evaporation technique [16,18]

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0.2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.

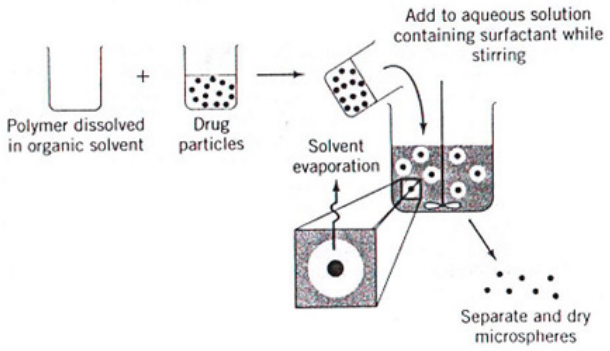

Figure 2: Emulsion solvent evaporation technique[26

2. Emulsion cross linking method [16,18,&21]

In this method drug was dissolved in aqueous gelation solution which was previously heated for 1 hr at 40 °C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 °C, results in w/o emulsion then further stirring is done for 10 min at 15 °C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5 mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100 mL of 10 mm glycine solution containing 0.1%w/v of tween 80 at 37 °C for 10 min to block un reacted glutaraldehyde.

3. Coacervation method[16,18,21&26]

3.1. Coacervation thermal change:

Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80 °C by heating. Then the drug was finely pulverised and added with vigorous stirring on the above solution and phase separation was done by reducing temperature and using ice bath. Then above product was washed twice with cyclohexane and air dried then passed through Sieve (Sieve No. 40) to obtain individual microcapsule.

3.2. Coacervation non solvent addition:

Developed by weighed amount of ethyl cellulose was dissolved in toluene containing propyl isobutylene in closed beaker with magnetic stirring for 6 hrs at 500 rpm and the drug is dispersed in it and stirring is continued for 15 mins. Then phase separation is done by petroleum benzoin with 14 times continuous stirring. After that the microcapsules were washed with n-hexane and air dried for 2 hrs and then in oven at 50 °C for 4 hrs.

4. Spray drying technique [21-26]

This was used to prepare polymeric blended microsphere loaded with ketoprofen drug. It involves dispersing the core material into liquefied coating material and then spraying the mixture in the environment for solidification of coating followed by rapid evaporation of solvent. Organic solution of poly (psilon caprolactone) (PCL) and cellulose acetate butyrate (CAB), in different weight ratios and ketoprofen were prepared and sprayed in different experimental condition achieving drug loaded microspheres. This is rapid but may lose crystallinity due to fast drying process.

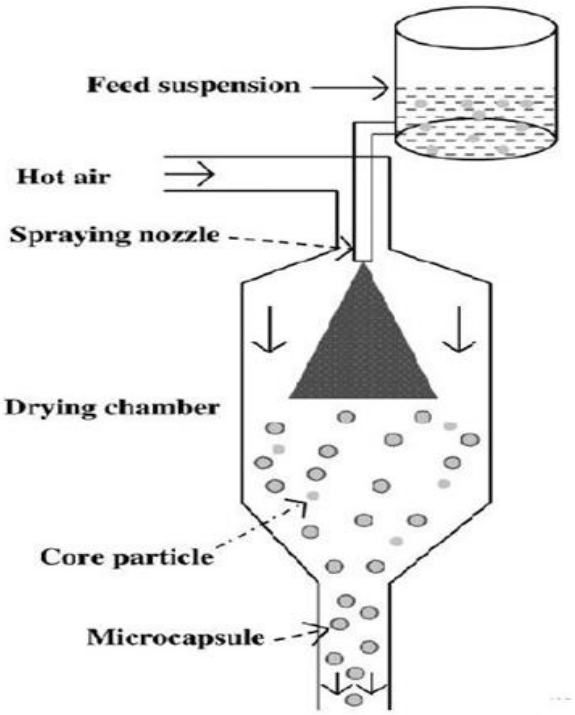

Figure 3: Spray drying technique[26]

5. Emulsion-solvent diffusion technique [21,22]

In order to improve the residence time in colon floating micro particles of ketoprofen were prepared using emulsion solvent diffusion technique. The drug polymer mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and then the mixture was added drop wise to sodium lauryl sulphate (SLS) solution. The solution was stirred with propeller type agitator at room temperature at 150 rpm for 1 hr. Thus the formed floating microspheres were washed and dried in a desiccator at room temperature. The following micro particles were sieved and collected.

6. Multiple emulsion method [20-22]

Oral controlled release drug delivery of indomethacin was prepared by this technique. In the beginning powder drug was dispersed in solution (methyl cellulose) followed by emulsification in ethyl cellulose solution in ethyl acetate. The primary emulsion was then re emulsified in aqueous medium. Under optimized condition discrete microspheres were formed during this phase.

7. Ionic gelation [20,22&26]

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. About 25% (w/v) of diclofenac sodium was added to 1.2% (w/v) aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it was added drop wise to a solution containing Ca_2^+/Al_3^+ and chitosan solution in acetic acid. Microspheres which were formed were kept in original solution for 24 hrs for internal gellification followed by filtration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.15.

Applications of microspheres[25]

1. Microspheres in vaccine delivery

An ideal vaccine must fulfil the requirement of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines. The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

1. Improved antigenicity by adjuvant action
2. Modulation of antigen release
3. Stabilization of antigen

2. Targeting using micro particulate carriers

The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is centre to drug action mediated by use of a carrier system.

3. Chemoembolization

Chemoembolization is an endovascular therapy, which involves the selective arterial embolization of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent.

4. Imaging

The particle size range of microspheres is an important factor in determining the imaging of particular sites using radio labelled microspheres. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintigraphy imaging of the tumour masses in lungs using labelled human serum albumin microspheres

Anatomy and Physiology of Colon[27-29]

- The GI track is divided into stomach, small intestine and large intestine
- Large intestine is divided into three parts they are the colon, rectum and anal canal
- The colon itself is made up of the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon
- The entire colon is about 1.5 m long
- The wall of the colon is composed of four layers:serosa, muscularies-externa, sub mucosa and mucosa

Functions of the colon[29,31&33]

- Creation of suitable environment for growth of colonic microbes
- Storage reservoir of faecal contents
- Expulsion of the contents of the colon at an appropriate time
- Absorption of potassium and water from the lumen, concentrating the faecal content

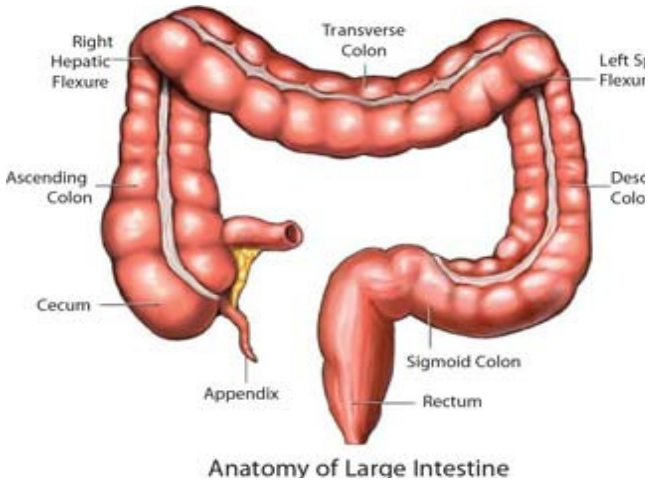

Figure 4: Structure of Colon.[27]

Advantages of colon specific drug delivery system[27]

1. Drugs are directly available at the target site.
2. Comparatively lesser amount of required dose.
3. Decreased side effects.
4. Improved drug utilization.
5. Improved patient convenience and compliance.
6. Reduction in fluctuation in steady state level.
7. Increased safety margin.
8. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.
9. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability

Limitations of colon targeting drug delivery system[27,31&33]

1. Multiple manufacturing steps.
2. The resident microflora could also affect colonic performance via metabolic degradation of the drug.
3. Incomplete release of drug.
4. Bioavailability of drug may be low due to potentially binding of drug to intestinal content.

Approaches for colon targeted drug delivery[31-45]

1. Drug carrier molecule conjugates
   - Azobond prodrugs
   - Glycoside conjugated prodrugs
   - Glucuronide conjugated prodrugs
   - Dextran conjugated prodrugs
   - Amino acid conjugates
   - Cyclodextrin conjugates
   - Azo polymeric prodrug
2. Surface modified novel drug delivery systems
   - Coating with pH sensitive polymer
   - Embedded in biodegradable polymer matrix system
   - Bio adhesive system
   - CODE system
   - Osmotically controlled system
   - Time released system

Approaches for colon targeted drug delivery:

1) **Approaches to drug carrier molecule conjugates- Prodrug approaches**

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires

enzymatic transformation in the biological environment 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 and after reaching the colon, enzymatic cleavage regenerate the drug.

i. *Azo bond conjugate*[31-33]

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. In the latter approach the drug is attached via an azo bond to a carrier. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora. Sulphasalazine, used for the treatment has an azo bond between 5-amino salicylic acid (ASA) and sulpha pyridine. In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier sulphasalazine.

***ii. Glycoside conjugation*[34]**

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone and is linked to the sugar part, which forms the glycone part of the glycoside. Because they are bulky and hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidase, releasing the drug part from the sugar. The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glyosidic bond, these conjugates can be expected to be good colon specific drug carriers

Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone.

iii. *Glucuronide conjugates*[34&37]

Bacteria of the lower GIT secrete glucuronide and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. Example: Opiates, whentaken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon.

iv. *Cyclodextrin conjugate*[37,38]

Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through 1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability. Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed.

v. Dextran conjugate

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolysed by moulds, bacteria, and mammalian cells. The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, whereas high dextranase activity is shown by anaerobic gram-negative bacteria, especially the bacteria, which are present in a concentration as high in colon. This led to the use of dextran as carriers for drug molecules to the colon.

E.g. glucocorticoid-dextran conjugates.

vi. *Amino acid conjugation*[37-39]

Due to the hydrophilic nature of polar groups like $-NH_2$ and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme

vii. *Polymeric prodrugs*

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose. Sub

synthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety.

2. Approaches to surface modified novel drug delivery systems

i. *pH dependent approach*[41-44]

This approach utilizes the existence of pH gradient in the git that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0). By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of acrylic acid and cellulose.

ii. *Coating with pH sensitive polymers*[41,42]

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon. The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter and intra individual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas eudragit S is used for the colon delivery it dissolves at pH greater than 7.0 (attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system

iii. *Embedding in pH-sensitive matrices*[43]

The drug molecules are embedded in the polymer matrix. Extrusion spheronization technique can be used to prepare uniform sizepellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness citric acid promoted the palletisation process resulting in a narrower area distribution. However, eudragit S100 could not cause statistically significant delay in the drug release at lower pH.

iv. *Time dependent delivery*

It is also known as pulsatile release or sigmoidal release system. This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the acidic environment of the stomach and to undergo a lag time of predetermined span of time, after which release of drug take place. The lag time in this case is the time requires to transit from the mouth to colon. A lag-time of 5 hrs is usually considered sufficient since small intestine transit is about 3-4 hrs, which is relatively constant and hardly affected by the nature of formulation administered. Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a preselected site of the GI tract.

v. *Colon-Targeted Delivery capsule based on pH sensitivity and time-release principles*[44]

The system contains an organic acid that is filled in a hard gelatine capsule as a pH adjusting agent together with the drug substance. This capsule is then coated with a three-layered film consisting of an acid soluble layer, a hydrophilic layer, and an enteric layer. After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer

vi. *Bio adhesive systems*[41-44]

Oral administration of some drugs requires high local concentration in the large intestine for optimum therapeutic effects. Bio adhesion is a process by which a dosage form remains in contact with particular organ for an augmented period of time. This longer residence time of drug would have high local concentration or improved absorption characteristics in case of poorly absorbable drugs. This strategy can be applied for the formulation of colonic drug delivery systems. Various polymers including polycarbophils, polyurethanes and polyethylene oxide-polypropylene oxide copolymers have

been investigated as materials for Bio adhesive systems .Bio adhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.

vii. *Osmotic controlled drug delivery* (43,44&47)

The OROS-CT system can be single osmotic unit or may incorporate as many as 5-6 push-pull units. Each 4mm in diameter, encapsulated within a hard gelatine capsule. Each push-pull units bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle semipermeable membrane is permeable to the inward entry of water and aqueous GI fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by eudragitS100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤7. As a result water enters the unit causing the osmotic push compartment to swell forcing the drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hrs post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hrs in the colon.

CONCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Drug targeting to the diseased colon is advantageous in reducing the systemic side effects, lowering dose of a drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. All the approaches of colon drug delivery provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. The wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, makes the reliability, delivery efficiency of formulation and targeting to colon complicated.

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