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ADVANCES IN TARGETED DRUG DELIVERY: FOCUS ON COLON-TARGETED MICROBEADS

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ABSTRACT: The primary objective of any drug distribution system is to deliver a precise amount of medication to the infected site in the body, thereby achieving a desired therapeutic response. Targeted drug delivery has emerged as a crucial approach, ensuring that the medicament is released specifically at the desired location and pH, minimizing degradation and metabolism. This approach enables local treatment of diseases while avoiding adverse effects on other organs. Colon-targeted microbeads has gained significance for the transport of proteins and peptides, as well as for the treatment of colitis, inflammatory bowel disease, colorectal cancer, and other colon-related conditions. The colonic route offers a promising solution for drugs with poor absorption in the upper gastrointestinal tract, where longer retention times enhance bioavailability. This system aims to provide a sustained and targeted delivery of drugs to the colon, optimizing therapeutic outcomes while reducing systemic side effects. This review updated the more information about microbeads like their mechanism of drug release, drug selection criteria, different preparation methods and formulation approaches and evaluation of colon specific microbeads, etc.

KEYWORDS: Colon Targeting, Microbeads, Multi-particulate System, In-Vitro Studies ,etc.

INTRODUCTION

Any drug distribution's primary objective is to deliver the necessary dosage to the body's afflicted location in order to achieve the intended therapeutic effect. Since the medication only releases in a specific area or pH for the local treatment of sickness in the body, precisely targeting the drug at the right place is one of the most crucial strategies for any delivery method. The most of the drug reaches to its site of action without undergoing any metabolism or degradation and has no effect on other organs. The overall transport of proteins and peptides as well as the local treatment of diseases like colitis, inflammatory bowel disease, colon cancer, etc., benefit from drug administration into the colon. The colonic route has grown in importance for the distribution of medications that have a longer retention time and are broken down in the upper gastrointestinal fluid due to reduced absorption from the upper part of the stomach. By using a pH-dependent system that delivers the medication at the desired site of action after dissolving at a specific pH or a sustained release system.

pH IN THE COLON

The pH changes along the GI tract from the oral cavity to the big intestine. pH changes in the stomach, small intestine, and large intestine are caused by a number of factors, such as diet, food intake, intestinal motility, and medical disorders. Because of the volatility in the GIT pH, it is more challenging for the industry professionals to develop a delivery system that would be adequately resilient to deal with these fluctuations. This pH variation along the GIT is used to target the drug in colonic drug delivery. A pH gradient of 6.6 is seen in the proximal small intestine, a peak of around 7.5 is found in the distal small intestine, and The pH gradient in the stomach is 1.2. pH of the right, middle, and left colons is roughly 6.4, 6.6, and 7.0, respectively. The small intestine's pH can reach as high as 8 or 9.20, while the colon's pH is often lower. The presence of short chain fatty acids, which are created when bacteria ferment polysaccharides, causes a drop in pH upon passage into the colon. pH-sensitive enteric coatings must be used to target this pH drop in order to deliver the medication to the small intestine.[1]

Table-1: average pH in the GIT.

Portion of GI Tract	pH range
• Oral cavity • Oesophagus • Stomach • Small intestine • Large intestine	• 6.2-7.4 • 5.0-6.0 • Fast condition-1.5-2.0 • Fed condition-3.0-5.0 • Jejunum-5.0-6.5 • Ileum-6.0-7.5 • Right colon-6.4 • Mid colon &left colon-6.0-7.5

NEED FOR COLON TARGETING

- To directly treat local disease by delivering the drug only to the site of action, which is the colon.
- To prevent early absorption or degradation of the active compound.
- To increase systemic bioavailability and drug stability.
- To lessen the problem of bioavailability.
- To decrease the frequency of doses and extend the residence period.
- Effective for targeted delivery of proteins and peptides.
- Capable of controlled and sustained drug release.[2][3]

ADVANTAGE OF CTDDS

- By treating specific areas of the colon, such as Crohn's disease, IBD, or colitis, adverse reactions can be minimized.
- When treating colorectal cancer, anticancer drugs can be delivered to the precise spot to prevent cell death.
- NSAID-induced gastric disruption is manageable.
- It is possible to decrease the initial metabolism of steroidal medications by creating a colon-targeted delivery system.
- A decrease in the frequency of doses.
- By prolonging retention period, poorly absorbable drugs can have their bioavailability increased.
- Increased drug usage.
- Improve absorption due to longer colon transit time.[4]

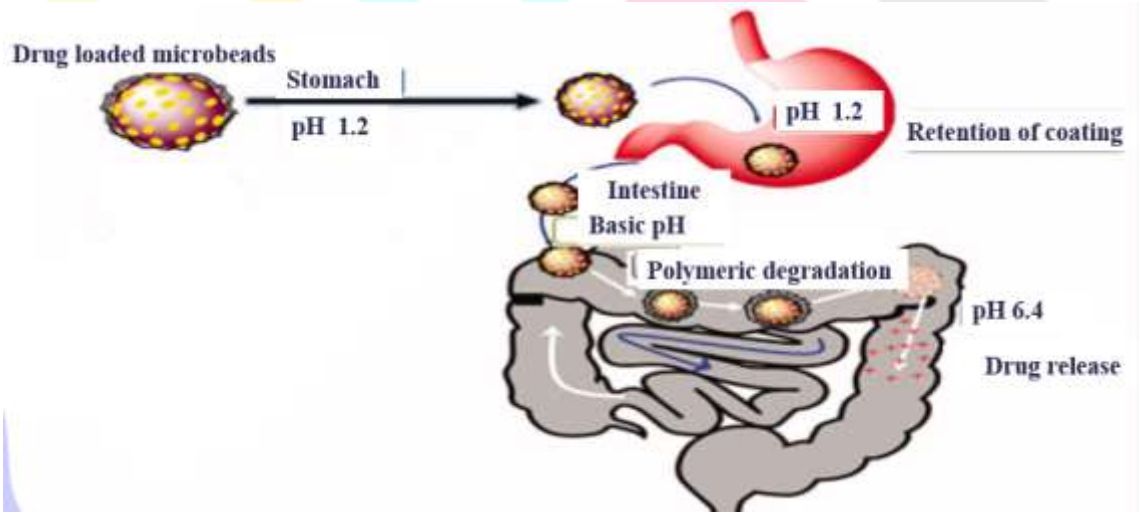

fig.1: overall colon targeting microbeads mechanism

MULTI PARTICULATE DRUG DELIVERY SYSTEM

Multi-particulate drug administration is the most widely used oral dose type. It is made up of small, discrete units with diameters varying from 0.05 to 2 mm. Each unit acts pharmacologically uniquely. Consequently, a multi-particulate drug administration is a

dosage form in which the active components are divided into several subunits or microparticles. The small particles can be crushed or put into a capsule for full drugs delivery. Multi-particle drug delivery approaches include microspheres, microbeads, micro-pellets, microemulsions, and micro-suspensions. Multi-particulate medication administration is one of the best techniques for colon-targeted drug delivery. Because of their small size and high bioavailability, pH dependent or control release polymers, which break down at the colonic pH, can be utilized to administer microbeads in the colon. A variety of pH-dependent or rate-controlling polymers, such as Eudragit S-100, ethyl cellulose, and HPMC, can be used.[5][6]

ADVANTAGES OF MICROBEADS

- Easy dispersion throughout the colon without discomfort due to their small size.
- Effective medication release and a slower transit time.
- Since drugs are specifically targeted to the intended site, their bioavailability can be enhanced.
- No dumping of doses. Increase patient adherence.
- The suitable polymer can be used to produce controlled drug release.
- The drug's stability could be enhanced.

DISADVANTAGES OF MICROBEADS

- It may be challenging to release highly molecular weight compounds due to their limited and restricted loading.
- Complexes are formed with the components of blood.
- The cost of manufacture is expensive.
- The possible environmental impact of microbeads is one of its main disadvantages.
- Synthetic polymers that are difficult for the environment to break down are frequently used to make microbeads.
- It can be difficult to achieve consistency and exact control over the microbeads' size distribution during the production process.

MECHANISM OF SUSTAINED RELEASE MICROBEADS

Drug release from microbeads is mediated by three primary processes. It depends on the kind of microbeads that are made. When the drug is exposed to the surrounding stomach juices, it either diffuses from the membrane or undergoes enzymatic lysis or hydrolysis. The complex mechanisms involved in the long-term release of drugs or other bioactive molecules from microbeads are governed by the intrinsic properties of both the encapsulated molecules and the microbeads themselves.

An outline of the general processes underlying sustained release from microbead

- **Diffusion:** Diffusion is the primary mechanism. This involves the leakage of the molecules that are encapsulated, such as drugs, into the surrounding environment after diffusing through the matrix of the microbead. The rate of diffusion is a function of the size and shape of the microbeads, the molecular weight, and the solubility of the molecules that are encapsulated. In general, smaller and more soluble molecules diffuse more readily.
- **Degradation:** Biodegradable microbeads degrade after some time, releasing the encapsulated molecules as the degradation product. This process is specifically applicable for those microbeads that consist of polymers. Which undergo hydrolysis or enzymatic degradation in biological environments. Due to this degradation of polymer matrix, the encapsulated molecules get exposed slowly which leads to sustained release for a longer period.
- **Erosion:** Besides degradation, erosion of the microbead matrix can take place due to physical or chemical processes. Mechanical forces such as shear stress or agitation can lead to surface erosion where the outer layers of the microbeads get worn away gradually and release encapsulated molecules. Chemical erosion also occurs through processes like dissolution or hydrolysis based on the composition of the microbeads.
- **Matrix Properties:** The pore size distribution, porosity, and surface area of the microbead matrix play a crucial role in the sustained release rate and mechanism.
  The more porous or the greater the surface area, the more efficient will be the diffusion and degradation processes, hence leading to faster release kinetics. In contrast, denser matrices or smaller pore sizes result in lower release rates.
- **Controlled Release Systems:** Microbeads can be engineered with specialized coatings, membranes, or multilayer structures to further control the release of encapsulated molecules. For example, coatings may act as barriers to diffusion, allowing for sustained release over a prolonged period. Alternatively, stimuli-responsive coatings can trigger release in response to specific environmental cuases such as pH, temperature, or enzymatic activity.
- **Swelling:** hydrogel system or any swellable type of microbeads would absorb surroundings water
  and thus swell and expand the microbeads; this swelling will create pores or channels that enable the escape of the encapsulated molecules within the matrix and such a system would be unable to control the rate of drug release by changing the level of cross linking or composition of the hydrogel.[7]

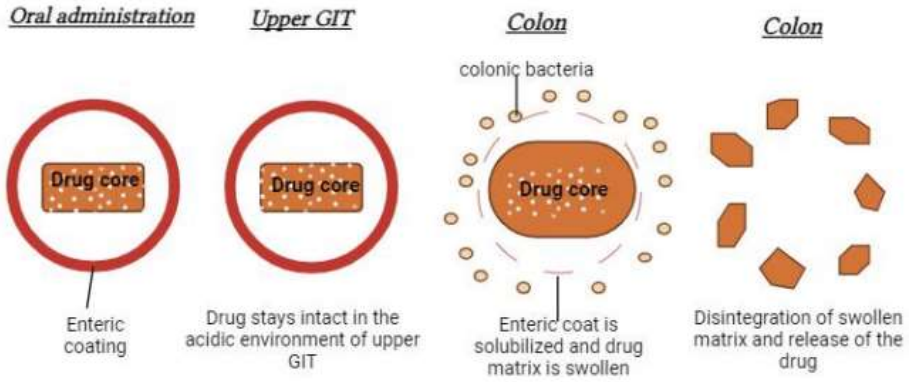

fig.2: mechanism of release of microbeads.[8]

CRITERIA FOR FORMULATION OF COLON TARGETING MICROBEADS

There are several formulation methods which have been developed to overcome the barrier seen with immediate release oral dosage forms. These processes include inert insoluble matrices, use of coatings, hydrophilic matrices, as well as the combinations of hydrophilic and hydrophobic polymers, embedding of the drug in plastic matrix, ion exchange resins, osmotic pumps and microencapsulation. The physiology of the gastrointestinal tract, the physicochemical property of the drug, the drug release pattern, the pharmacological action of the drug are the parameters that must be considered too. The physicochemical properties of the drug involve parameters like:

The physicochemical properties of the drug involve parameters like:

- Aqueous solubility,
- Stability,
- pKa, and
- Permeability values.

The Biopharmaceutical Classification System (BCS) involves placing a drug into four classifications:

- High solubility and high permeability
- Low solubility and high permeability
- High solubility and low permeability
- Low solubility and low permeability

For colon targeting BCS Class-II is considered the preferred category, while Class-IV is the less preferred category. A drug having high absorption window in the intestine are good drug candidate. drugs with low oral bioavailability and undergoes extensive first pass metabolism are good candidate. The drug permeability value must also be considered and should be more than the prescribed value. A biological half-life of a required drug is between two and six hours is the best choice of formulation because this type of criteria of the drug is avoiding the accumulation of the drug in the body.[9][10]

PREPARATION OF MICROBEADS BY USING DIFFERENT TECHNIQUES:

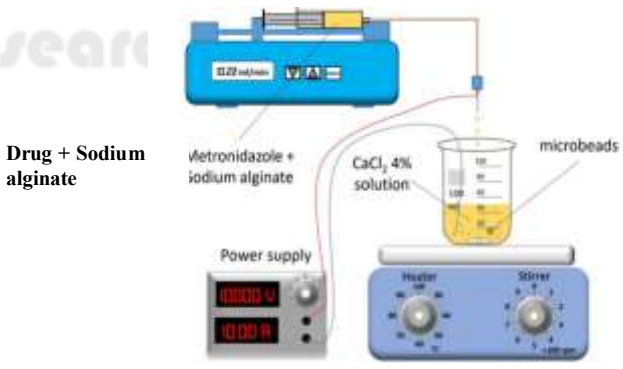

fig. 3: preparation of microbeads

METHOD OF PREPARATION

Beads can be prepared by the following method[11][12]

1. Ionotropic gelation technique
2. Cross-linking
3. Emulsification gelation technique

Ionotropic gelation technique Steps involved in the preparation of micro-beads by ionotropic gelation technique:

- Weigh accurately all the materials including the drug used, sodium alginate and calcium chloride.
- Distilled water is added to the weighed quantity of sodium alginate to make mucilage pest and allowed to heat for 5-10 minutes in a hot plate.
- After that, distilled water is also added to the weighed quantity of calcium chloride to make a solution.
- The mucilage pest of sodium alginate is then stirred in a magnetic stirrer at a suitable speed for several minutes.
- Drug is dispersed in the mucilage pest of sodium alginate and stirred at suitable speed in the magnetic stirrer.
- The micro-beads are formed by dropping the calcium chloride solution in it through a glass syringe.
- The micro-beads are filtered & washed thoroughly with distilled water. Dried at room temperature.

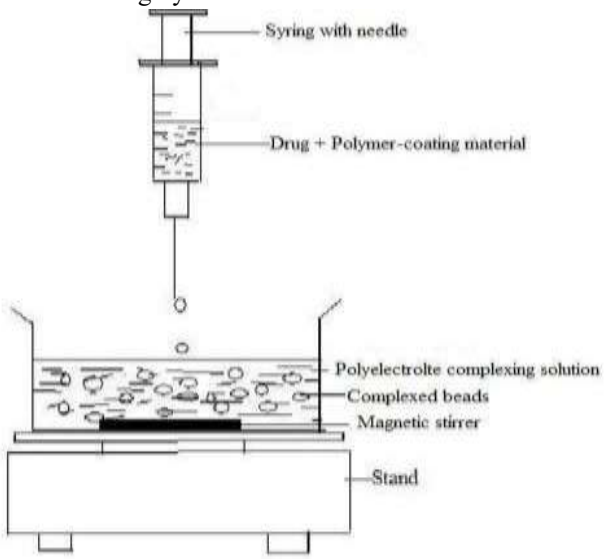

Fig.4: Ionotropic Gelation Technique

Cross-linking

Steps involved in the general preparation of beads by cross-linking:

- The cross-linking polymer solutions of different concentrations were prepared by dissolving in water under slow agitation.
- Drug was added in the polymer solution under constant stirring for 2 min for uniform distribution throughout the solution.
- Finally, drug and polymer solution were added drop wise through a 2-mm diameter needle into calcium chloride solution at room temperature under constant stirring on magnetic stirrer.
- micro-beads were formed and beads were allowed to remain in the stirred solution for 10 min.
- The micro-beads were filtered and washed with distilled water and beads are dried at room temperature for 24 hrs.

Emulsification gelation method

- Polymer and sodium alginate were dissolved in the water.
- Add drug into the polymer solution and mixed uniformly.
- The polymer solution was then added in a thin string of heavy liquid paraffin solution contained in a beaker.
- calcium chloride solution was added into the emulsion and stirring for 15 min to formed spherical micro-beads.
- The micro-beads were collected by decantation and washed with petroleum ether and air dried.

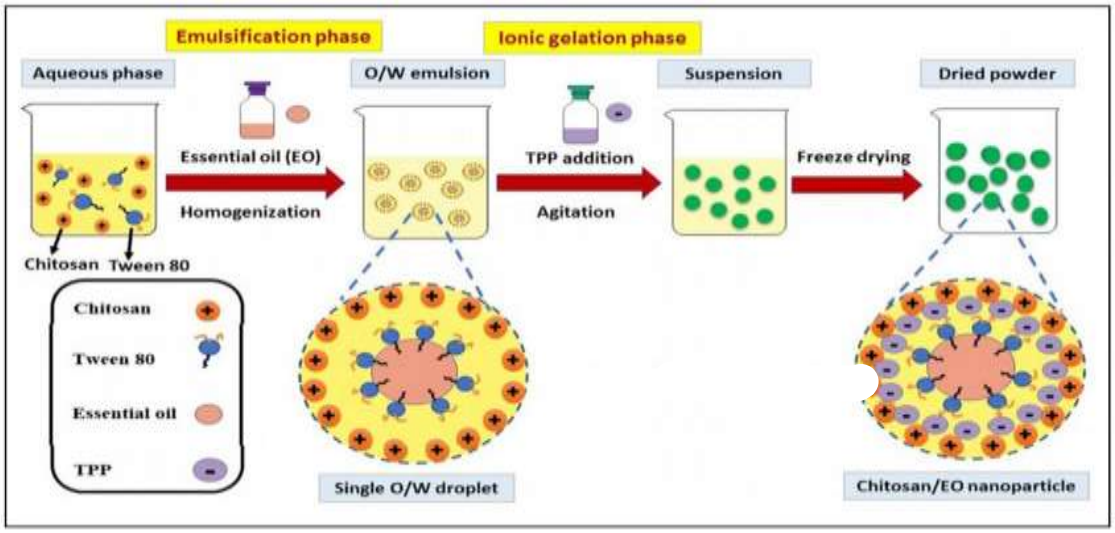

Fig.5: emulsification gelation method

Evaluation of Microbeads

Pre-formulation Studies of Drug

In addition, to formulation of any dosage form, drug and polymer characterization is very essential. In order to decide upon various properties and purity many pre formulation factors are applied, which includes melting point, calibration plot, scanning of drug and IR studies.[13]

- **Fourier Transform Infra-red Spectroscopy (FTIR) Studies**
  FTIR Spectroscopy can be carried out using potassium bromide pellets. FTIR interpret the presence of functional group in the structure that gives peak at particular wavenumber which is then compared with the standard. Pure drug is crushed with KBr pellets. The mixture is then compressed with disc and then place in an instrument. IR spectra of all samples will be recorded within a required range of wave number. FTIR spectra of drug, polymer and the mixture of drug and polymer can be recorded and interpret.[14][15]
- **UV Spectrophotometric Analysis of Drug**
  The maximum wavelength for the drug can be measured through UV analysis. The suitable solution of the drug is prepared in various media, and then it is analysed in UV spectrometry, giving the maximum wavelength of the drug in that medium, which is then compared with standard.[16]
- **Drug Excipients Compatibility Studies**
  Drug polymer compatibility studies can be conducted using FTIR and Differential scanning calorimeter (DSC). The drug and other polymer mixture should be place in a vial and store for a month in room temperature after which the samples can assay and the results can be interpretated.[17][18]

CHARACTERIZATION OF MICROBEADS

- **Percentage Yield**
  The percentage yield of total formulation can be calculated by dividing the weight of total microbeads formed by the total ingredients added multiplied by 100. It gives the total yield of dosage form.[19][20]

$$\text{Percentage yield} = \frac{\text{Amount of microbeads obtained (g)} \times 100}{\text{Theoretical amount (g)}}$$

- **Drug Entrapment Efficiency**
  Weigh Appropriate amount of dried microbeads (50mg) and crush in a mortar and pestle. The powdered microbeads were dipped in 50ml of prepared pH 7.4 phosphate buffer. Stir solution for 24 hours and filter. analyse the filtered solution in UV for drug concentration after making suitable dilution. Absorbance taken in three replica and calculate drug concentration by straight line equation in pH 7.4 phosphate buffer. The percentage drug entrapment efficiency calculated by the following formula.[21]

$$\text{Drug entrapment efficiency} = \frac{\text{Practical drug content \%}}{\text{Theoretical drug content}} \times 100$$

- **Scanning electron microscopy**
  Scanning electron microscopy is used for the analysis of magnified shape, size and surface morphology of the beads. Paste the beads on aluminium stubs with double side tape, followed by gold sputtering in order to capture the actual shape of the beads. Set the Samples in the instrument, and the shape of the beads along with its surface can be analyse through higher magnification.[22]
- **Invitro Drug Release**
  USP type I Dissolution apparatus i.e. basket type is used to assess the in-vitro drug release of formulation. accurately weigh 100mg of microbeads were and place in basket. Prepare Three different media i.e. 0.1N HCl, pH 6.8 phosphate buffer, pH 7.4 phosphate buffer and add 900ml to fill in dissolution jars. Keep dissolution temperature at 370 c and set RPM at 100. Keep the beads in 0.1N HCl for first two hours, pH 6.8 phosphate buffer for next 6 hours and then pH 7.4 phosphate buffer for 12 hours to simulated the gastrointestinal condition. Take 5ml sample after a regular time interval and analyse after suitable dilution, in the UV spectrophotometer at the λmax of the drug in various medium. After taking out the sample, add 5ml of the media to the dissolution media to keep the sink condition. Follow this process till 12hours with an estimated constant concentration and calculate the drug release.[23]

CONCLUSION

These colon-specific targeted drug delivery systems will offer much hope for therapeutic efficacy improvement, enhancement of bioavailability, and controlled release of drugs leading to better management of health problems related to the colon. This targeted delivery system has the objective of allowing drugs to be released in specific locations of the colon so as to address health problems like colitis, inflammatory bowel disease, and colorectal cancer. This targeting approach minimizes the drug degradation and metabolism, making the therapeutic response more potent .The approach of drug delivery through the colonic route overcomes the problem of poor absorption, which usually occurs at the upper gastrointestinal tract level. This method increases the bioavailability of drugs, ensuring that more drug reaches the point of action. A review of this system shows how it can give controlled and prolonged drug release to the colon. This aspect is important in order to reduce the frequency of doses and extend the residence time of the drug in the colon, thereby leading to better compliance from the patient and therapeutic outcome. The review further talks about mechanisms like pH-dependent systems, which ensure the drug is released at the desired site. This specificity is crucial for local treatment, meaning that the drug acts where it is most needed without affecting other organs.

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