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Review On: Colon Targeted Microspheres

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ABSTRACT:
The microspheres are one of the novel drug delivery system in which effective therapeutic alternative to conventional or immediate release single-unit dosage forms. Microspheres can be characterized as solid, diameter having between 1–1000µm.there are different types of microsphere explained. These microspheres prepared and fill them in a hard gelatin or compress them directly. The microspheres which are prepared by using different technique that are changes their effectiveness and administration of the dosage form as compare to conventional dosage form. Microsphere will be evaluated by using different methods that analyses quality of the microsphere. The microspheres which will get central place in novel drug delivery in future .(1) In the recent year colonic drug delivery has gained importance for delivery of drug for the treatment of local diseases associated with colon and systemic delivery of therapeutic peptides and proteins. Treatment could be more effective if it is possible for drug to be directly delivered to colon. During the last decade there are new developments in site-specific formulations for targeting drug to the colon. Colon has proved to be a site for the absorption of poorly soluble drugs. Micro carriers as colon drug delivery System has gained importance for the delivery of the drug in the colon because of their increase biocompatibility, controlled release of drug and higher stability. This review is discusses in brief about introduction to colon, Micro Carrier as colon drug delivery system. Oral delivery is still the most favorable route of drug administration, especially for chronic therapies where repeated administration of drug is required. Oral administration offers less pain, good patient convenience and reduced risk of cross infection and needle stick injuries.(5)

KEYWORDS : Colon targeted drug delivery system, Microsphere

I. INTRODUCTION:

Conventional medicine in treating various diseases has been carried out for a long time. They treat local intestinal disorders, such as ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic pancreatitis, colon cancer, and intestinal fibrosis.[1] To procure maximum therapeutic efficacy, it is important to deliver API to the target tissue in the optimal amount with in right period of time which reduce the toxicity and side effects. Several approaches are available which can deliver drugs to the target site. One such approach is microspheres as carriers for drugs . Microspheres are small spherical shape particles range from 1 µm to 1000 µm in size.[2] Microsphere, as carrier for drug delivery gain popularity in recent era.[3] Inflammatory bowel diseases represent inflammatory conditions that affect the gastrointestinal tract and cause over 50,000 deaths per year.[4]

Why colon targeted drug delivery needed?

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides .[5]

TYPES OF MICROSPHERES:

1. Bioadhesive microspheres
2. Magnetic microspheres
3. Radioactive microspheres
4. Floating microspheres
5. Polymeric microspheres
6. Biodegradable polymeric microspheres
7. Synthetic polymeric microspheres

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1. **Bioadhesive microspheres**:[7-8]

Adhesion can be described as sticking of drug to membrane by using the sticking property of water soluble polymers. Adherence to the drug delivery device's mucosal membrane, such as buccal, ocular, rectal, nasal, etc. can be considered bio adherence. Such kinds of microsphere exhibit a prolonged period of residence at the application site and induce intimate interaction with the absorption site and yield better therapeutic action. Mucoadhesive microspheres provide extended contact time at the application or absorption site and help to encourage intimate contact. The underlying surface where absorption is supposed to occur, thereby enhancing or improving the therapeutic efficacy of the drug.

2. **Magnetic microspheres**:[9-10]

Microspheres are usually free moving small spherical particles consisting of proteins or synthetic polymers, of a biodegradable nature, varying in particle size from 1-1000µm. They are considered as one of the essential approaches for delivering therapeutic substance in a safe and controlled manner for release to the target site.

The different types of

a) Therapeutic magnetic microspheres Known for the application of chemotherapy to liver tumor. This device can also target medicinal products such as proteins and peptides.

b) Diagnostic Microspheres Used for visualization of liver metastases and can also be used to separate intestines loops of other abdominal structures by the production of supramagnetic iron oxides particulate nanometer.

3. **Radioactive microspheres**:[11]

Microsphere size of radio embolization therapy 10-30 nm greater than the capillary diameter and will be placed into the first capillary bed as they pass. These are placed into the arteries that lead to a tumor of interest and induce elevated radioactivity in each of these conditions. Microspheres to target areas without harming the usual tissues surrounding them. This varies from the drug delivery mechanism, as radioactivity is not emitted from microspheres but operates from within a distance typical of a radioisotope, and the different types of radioactive microspheres are α emitters, β emitters, π emitters.

4. **Floating Microspheres** :[12-13]

The bulk density of floating forms is smaller than the gastric fluid, and therefore stays buoyant in the stomach without impacting the rate of gastric emptying. The drug is released at the target rate gradually, as the body floats on gastric content and decreases gastric residence and plasma concentration fluctuation. This also reduces the risk of hitting and dose dumping. One way it creates sustained therapeutic effect and therefore reduces the frequency of dosing.

5. **Polymeric microspheres:[**11]

The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres.

6. **Biodegradable polymeric microspheres:**[14]

Natural polymers like starch are used with the idea that they are naturally biodegradable, biocompatible and even bioadhesive. Biodegradable polymers extend the duration of residence in contact with the mucous membrane due to its high swelling properties with aqueous medium. The rate and degree of drug release is sustainably regulated by polymer concentration and release pattern. The key downside is that the reliability of biodegradable microspheres in clinical use is complicated and the release of drugs is difficult to regulate. They do however offer a wide variety of applications treatment centered in a microsphere.

7. **Synthetic polymeric microspheres**:[15-16]

Synthetic polymeric microspheres are commonly used in therapeutic applications, in addition to the fact that they are often used as bulking agents, fillers, embolic particles, drug delivery vehicles etc. and have proven safe and biocompatible, but the main drawback of these microspheres is that they appear to migrate away from the injection site and lead to potential harm, embolism and further damage to organs.

ANATOMY AND PHYSIOLOGY OF COLON

- **Anatomy of colon [17]**

The whole GIT is divided into three parts Stomach, Small intestine and large intestine. The large intestine is 1.5m long and further divided into caecum (6-9 cm), appendix, colon and rectum. The colon is further dividing into the ascending, transverse and descending colon. The colon removes the water, salts and some nutrients from

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the stools. The ascending colon (20-25cm) runs through the abdominal cavity upwards towards the transverse colon.Its main function is to remove water and nutrients. The waste materials are move upward into the transverse colon by process known as peristalsisThe transverse colon (40-45cm) is the part of the colon from the hepatic flexure to the splenic flexure.The descending colon (10-15cm) is the part of the colon from the splenic flexure to the beginning of the sigmoid colon (35-40cm). The function of the descending colon is to store the food which emptied into the rectum. The human colon is shown in Figure 1. Colon is comprises of four different layers these are Mucosa, Sub mucosa, Muscularis externa, and Serosa. The Billions of bacteria coat the colon and its contents. The main function of the colon is providing the suitable environment for Colonic microflora growth and also as a storage reservoir of fecal contents and the removal of waste materials from the colon at an appropriate time. The absorption salt water and some nutrients may also take place from the colon. The absorption capacity of colon was found to be very high nearly about 2000ml.The fluid enters the colon through ileocecal valve90% of which is absorbed by the colon. The colon contains approxymately 220 gm of wet material which is equivalent to 35 g of dry matter. The majority of which is bacteria.

Fig: parts of colon

Physiology of colon [18]

a. Gastric emptying Drug delivery to the colon upon oraladministration depends mainly on gastricemptying and bowel transit time. Upon reachingthe colon the transit time of dosage formdepends in the size of the particles. Smallerparticles have more transit. time compared tolarger particles. Diarrhoea patients have shortertransit time whereas constipation patients have longer

ORGAN	TRANCIT LIMIT (HR)
Stomach	<1 (Fasting) >3 (Fed)
Small intestine	3-4
Large intestine	20-30

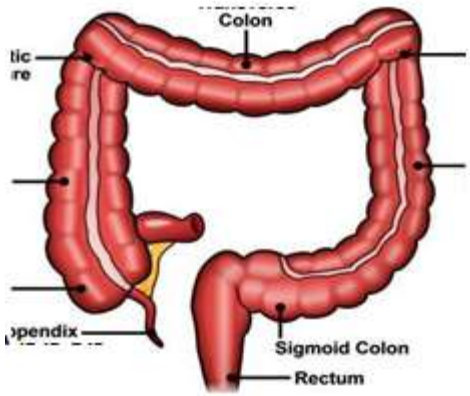

Fig : transit time of dosage form

b. pH of colon

The pH of GIT varies between differentindividuals.The food intake, diseased state, etc.influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers isdone to target the drug to the site.

c. Colonic microflora and enzymes

The GIT contains a variety ofmicroorganisms that produces many enzymes need for metabolism. The enzymes released by differentmicroorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

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CTDDS Challenged :

Colonic pH

There are significant differences in pH in healthy humans along the gastrointestinal tract. [19]

The illustration is shown in Figure 1. The food consumed and the pathological conditions in each individual can cause the pH to change slightly.[20] Consumption of carbohydrate-rich foods can cause the colonic pH to become more acidic due To the fermentation of carbohydrates by colonic bacteria. The fermentation process will produce short-chain fatty acids (SCFAs). SCFA will be absorbed and metabolized by the colonic epithelium, which causes a decrease in the pH value in the digestive tract. The fermentation process also occurs in lactulose for constipation patients, producing lactic acid. The pH condition was also noted to have decreased in patients with ulcerative colitis.[21] This is an essential consideration in manufacturing colon-targeted preparations using pHsensitive polymers .

Enzymes and colonic microflora:

Aerobic and anaerobic bacteria are found throughout the digestive tract, with the most significant number found in the colon. There are about 400 species with a concentration of about 1000 CFU/ml. These bacteria produce enzymes that can metabolize drugs and some biomolecules. The following are some enzymes involved in developing a colon-targeted drug delivery system that can be seen in These considerations regarding the specific bacteria present only in the colon are used for several approaches in manufacturing colon-targeted drug delivery systems.[22] For example, the fermentation process carried out by colonic anaerobic bacteria on polysaccharides is used as a polymer in controlled release preparations. Other techniques, such as the biotransformation of some drugs into their active forms, carried out by azoreductase enzymes against azo bonds, have been found in prodrugs approaches.[23]

Colon transit time:

Colonic transit time is essential in the bioavailability of drugs explicitly administered to the colon. The movement of substances in the colon occurs very slowly compared to the rest of the gastrointestinal tract[24]. Colonic transit time is determined mainly by drug administration, food in the gastrointestinal tract, and the type of preparation used. Some studies suggest that differences result from the different timing of drug administration in the morning and evening. This is because colonic motility occurs more slowly when the body rests. The type of preparation affects the difference in size. Smaller dosage sizes have a longer transit time than larger dosage forms.[25] Pathological conditions can also affect transit time in the colon. In UC patients, colonic transit time was approximately 24 hours faster than the average transit time in healthy humans, about 52 hour. [26]

Drug absorption in the colon:

The colon has a narrower surface area than the small intestine because there are no villi on the mucous membrane.[27] However, the substance's viscosity in the colon is higher than in other parts of the gastrointestinal tract because water absorption occurs along the colon. This affects the colonic fluid's drug dissolution process, determining the absorption process. The process of drug absorption in the colon occurs transcellular and paracellular. The transcellular process is carried out by lipophilic drugs in which drugs will pass through cells. In contrast, the paracellular process is carried out by hydrophilic drugs. Drugs will pass through tight junctions between cells. [28]

Method of preparation:

The technique choice is mainly depends upon the nature of polymer, nature of drug and the duration therapy.

Techniques for microsphere preparation

1. Single emulsion techniques
2. Double emulsion techniques
3. Phase separation coacervation technique
4. Spray drying
5. Solvent extraction
6. Solvent evaporation
7. Polymerization

a. Normal polymerization
b. Inter-facial polymerization

1. Single emulsion technique:

Single emulsion technique is used for the preparation of micro particulate carriers for drug delivery. The natural polymers are dissolved in aqueous medium and it followed by dispersion in non-aqueous medium such as oil. In the next step cross linking can be carry out either heat or by using the chemical cross linkers. Cross linking by heat: by adding the dispersion into heated oil, but it is not suitable for the thermo labile drugs. The main disadvantage of chemical cross linking is to excessive exposure of active ingredient to chemicals if added at the time of preparation and

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then subjected to centrifugation, washing, and separation.[29-30-31]

2. Double emulsion technique:

Both natural as well as synthetic polymer can be used in this method and it is more suitable for aqueous soluble drugs, peptides, proteins and vaccines. This method is involves in the preparation of double emulsions of w/o/w type. In this technique, the aqueous active constituent protein solution is dispersed in lipophilic organic continuous phase .Continuous phase is generally composed of polymer solution which encapsulates protein dispersed in water phase. After that, before addition to aqueous solution the primary emulsion is homogenized and the formation of double emulsion occurs and then solvent removal is occur either by solvent evaporation or solvent extraction method.[29-32]

3. Phase separation coacervation technique:

The coacervation term is come from latin word acervus which means ‘‘heap’’. This process was first reported to modify for the industrial production of microcapsule. In organic phase the solubility of polymer is decrease which affect the formation of the polymer rich phase called as coacervation .This process is utilize for the development of reservoir type system for example encapsulated water soluble drug like proteins, peptides. The matrix type preparations also can be developed in this process e.g. hydrophobic drug such as steroids.[29-32-33]

4. Spray drying:

The two processes spray drying and spray congealing are mainly depending on the removal of the solvent or cooling of the solution. The polymer which dissolved in a suitable volatile organic solvent. Under high-speed homogenization it dispersed in the polymer solution. Then it atomized in a stream of hot air which leads to the formation of small droplets and solvent evaporation was done which developed the formation of microspheres. By the use of cyclone separator micro particles are separated from the hot air while the trace of solvent is take out by vacuum drying. [33] In this process one of the major advantage is feasibility of operation under aseptic conditions. However this process is used to encapsulate various penicillin’s. Sulphaethylthiadizole and thiamine mononitrate are encapsulated in a mixture of monoglyceride and diglycerides of stearic acid and palmitic acid by using spray congealing.[30-31] Example- For the vaginal delivery of econazole much adhesive microsphere can be prepared by spray congealing technique [33]

5. Solvent evaporation:

Solvent evaporation method is one the most important method for the preparation of microsphere. These process are mostly use in the liquid manufacturing vehicle. In this phase organic solvent like polymer and the aqueous protein solution is added. Then sonication is done for mixing the material. After that homogenization is done for making the solution uniform. Then second aquous phase emulsifier is added. After that hardening is occur and then harvest it. After harvesting freeze drying technique is use. This is also called as lyophilization. It preserve the material by freezing it very quickly and then subjecting it to a vacuum which removes ice. And then microsphere is getting .[31-35] This technique is used for the preparation of microsphere of 5-Flurouracil by using dichloromethane and acetonitrile, however the polyvinyl alcohol is used as processing medium to solidify the microsphere. [36]

6. Solvent extraction: This method is used for the development of the micro particles, which involves in the removal of the organic phase by extraction of the organic solvent. The organic phase is eliminated by extraction with water. The hardening time of microspheres decrease in this method. The rate of solvent eliminate by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer. [37-38]

7. Polymerization technique:

Preparation of Microspheres by polymerization technique can be classified as:

a. Normal polymerization

b. Interfacial polymerization

a. Normal polymerization: The normal polymerization is done by using different techniques as bulk, suspension, precipitation, emulsion etc. In case of bulk polymerization, a monomer along with catalyst is warmed up to set up polymerization. Then the polymer is obtained and form as microspheres, as well as drug loading may be done during the process of Polymerization. Bulk polymerization is a pure polymer development procedure but it is very difficult to evaporate the heat of reaction that affects the thermo labile active ingredients. Suspension

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polymerization is also called as Pearl/Bead Polymerization which is done at low temperature. In this process heating of monomers or a mixture of monomers with active drug as droplet dispersion in continuous aqueous phase.

b. Interfacial polymerization: Interfacial polymerization involves the reaction of various monomers at the interface between two immiscible liquid phases to form a film of polymer. It broadly cover the dispersed phase. [29-31-39]

Advantages of microspheres [40]

• Microspheres provide prolonged and constant therapeutic effect.
• Microspheres reduce the dosing frequency and therefore improve the patient compliance.
• Microspheres provide controlled, sustained and targeted delivery of the drug.
• Microspheres produce more reproducible drug absorption.
• Drug discharge in stomach is hindered and that's why local unwanted effects are reduced.
• In case of microspheres, better therapeutic effect for short half-life of drugs can be Achieved.
• Microspheres provide freedom from drug and recipients incompatibilities especially with buffer.
• Microspheres reduce dose dumping.
• Microspheres provide the protection of drugs against environment.
• Microspheres also mask the taste and odor.
• Microspheres avoid the first pass metabolism.
• Microspheres can be easily injected in body because of their small and spherical size.
• Microspheres enhance the biological half-life and also improve the bioavailability.
• Microspheres also reduce the chances of G.I. irritation.(5)

LIMITATIONS OF MICROSPHERES:[42]

 Controlled release rate of microspheres may vary due to certain factors like intrinsic or extrinsic factors may be food, rate of transit through gut, mucin turnover rate etc.
 There are differences in release from one to another dosage form.
 Low drug loading is done in case of parentral microspheres.
 In case of parentral application of microspheres it is difficult to remove carrier completely from the body.
 Parental delivery of microspheres may interact or form complex with blood components.
 The release of formulation can be modified.
 Any loss of integrity in release pattern may cause potential toxicity.

Application of Microspheres:

A number of pharmaceuticalmicroencapsulated products are currently on the market.

1) Microspheres in vaccine delivery:[43]

The precondition of a vaccine is safety toward the microbes and its harmful component. An ideal vaccine should satisfy this same necessity of effectiveness, protection, affordability in application and charge. The aspect of protection and avoidance of severe effects is a complicated.The aspect of safeness and the extent of the manufacturing of antibody responses are intently linked to mode of application. Biodegradable delivery technology for vaccines which are provided by intravenous path may resolve the shortcoming of this same conventional vaccines. The involvement in parenteral (subcutaneous, intramuscular, intradermal) carrier exists even though those who offer significant benefits.

2) Microspheres in Gene delivery :[43-44]

Genotype drug delivery involves viral vectors, nonionic liposomes, polycation complexes, and microcapsules technologies. Viral vectors are beneficial for genotype delivery even though those who are extremely efficient and also have a broad variety of cell goals. Even so, if used in vivo they trigger immune responses and pathogenic effects. To resolve the restrictions of viral vectors, nonviral delivery systems have been regarded for gene therapy. Nonviral delivery system does have benefits these as simplicity of preparation, cell / tissue targeting, reduced immune system, unrestricted plasmid size, as well as large-scale replicable production. Polymer will be used as a transporter of DNA for gene delivery applications.

3) Oral drug delivery:[45]

The potential of polymer matrix usually contains diazepam like an oral drug delivery has been evaluated through rabbits. Its findings showed that even a film consisting of a 1:0.5 drug-polymer combination may have been an effectual dosage form which is comparable to commercial tablet formulations. The capacity of polymer to establish films could allow use in the formulation of film dosage forms, as an option with drug tablets. The pH sensitivity, combined with both the reactions of the main amine groups, start making polymer a

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distinctive polymer for oral drug delivery applications.

4) Transdermal drug delivery:[46]

Polymer has good film-forming characteristics. The release profile from of the devices is impacted by the membrane thickness as well as crosslinking of a film. Chitosan-alginate polyelectrolyte structure has also been prepared in-situ in beads and microspheres for potential uses in packaging, controlled release systems and surgical instruments. Polymer gel beads are an impressive highly biocompatible vehicle for chemotherapy of inflammatory cytokines for medications like prednisolone that also showed extended release action enhancing treatment effectiveness. The amount of drug discharge was found to also be depend on the characteristics of cell wall used. A mixture of chitosan membrane and chitosan hydrogel known to contain lidocaine hydrochloride, a local anaesthetic is a great comprehensive process for controlled drug release and release kinetic.

5) Targeting by Using Micro Particulate Carriers:[47]

The principle of trying to target is a well established dogma, that is trying to gain huge interest present a days. The response manufactured by drug depends itself on availability and ability to interact to binding site generally pellets technique is confirmed that can be formulated by utilising extrusion / Spheronization innovation e.g. microcrystalline cellulose (MCC) and chitosan.

6) Monoclonal Antibodies:[47-48]

Monoclonal antibodies or targeting microspheres are physiologically immunologic microspheres. One such type of trying to target is having been using to accomplish selective targeting to particular sites of an organ system. Monoclonal Antibodies are highly precise compounds that also bind to a particular portion of the body structure via which uptake occurs via.

a. Non particular adsorption and particular adsorption
b. Direct coupling
c. Coupling via reagent

7) Intratumoral and local drug delivery:[49]

In order to achieve solid lipid nanoparticles at the tumour cells in therapeutically relevant intensity, polymer films were also manufactured. Combination with medication does have promising potential to be used in controlled delivery throughout the oral cavity. Eg. Gelatin, PLGA, Chitosan and PCL.

8) Other applications:[50]

Microspheres are used for membrane technology developed for mass spectrometry, cell biology, cell biology; Fluorescent connected Immuno-Sorbent Assay. Yttrium could be used for standard treatment of hepatocellular carcinoma and even used besides pre transplant management of HCC with promising results. Applications of microencapsulation in other industry sectors are various. Carbonless copying paper, photosensitive paper, microencapsulated fragrances such as "scent-strips" (also known as "snap-n-burst") and microencapsulated aromas ("scratch-n-sniff"') are the best known microencapsulated products. These other products are usually prepared by the use of gelatin – acacia coacervation complex. Scratch-n-sniff has been used in children's literature and in the development of nutrition and cosmetics fragrance advertising. Microcapsules also are heavily included as diagnostic tests, for example, temperature-sensitive microcapsules for temperature dependent visual detection of cancer. In the biotech industry microcapsules microbial cells are used for the production of recombinant and proteins.

9) Targeting drug delivery:[51]

The concept of targeting i.e. site specific drug is a well-established conviction. It is gaining full attention. The therapeutic efficacy of drug relies on its approach and specific reaction with its receptor. In vaccine delivery- vaccine is the important delivery system for protection against the microorganism. Most of the parenteral vaccines have been compacted in biodegradable polymeric microspheres, including the diphtheria vaccine and tetanus.

10) Buccal and sublingual drug delivery:[52-53]

Buccal mucosa may have inherent for delivering peptide drugs low molecular weight, high potency and long biological half-life. mucoadhesive microspheres of venlafaxine using linseed mucilage as a muco-adhesive agent by using spray-drying technique for buccal delivery with a target to avoid hepatic first-pass metabolism, by increasing residence time in the buccal cavity. Microspheres in Cancer therapy.

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11) Nasal Drug Delivery:[54]

Polymer based drug delivery systems, like micro-spheres, liposomes and gels have been demonstrated to have good bio adhesive characteristics. It swells easily when in contact with the nasal mucosa increasing the bioavailability and residence time of the drugs to the nasal route. e.g. starch, dextran, albumin Other application- Some other applications are there. The fluorescent microspheres can be applied for membrane based technology for flow cytometer, microbiology, cell biology. Natural excipients are finding a wide application in microspheres. Many recent studies reveal that natural excipients .

- **Evaluation of microspheres**:[55-56]

The microspheres prepared by the above techniques were evaluated for

1. Percentage yield
2. Drug content
3. Entrapment efficiency
4. In-vitro drug release

1 .**Percentage yield**:

The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Product yield is calculated by using the following Equation

Product yield= Weight of the product / Weight of raw materials X 100

2. **Drug content**:

The various batches of the microspheres were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of ethyl acetate in two necked round bottomed Flask. With the help of mechanical stirrer allow it to stir for 3 hours then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 279nm.

Drug content = Practical drug content/ Theoretical drug content X 10

3.**Entrapment efficiency:**

The prepared formulations were examined for entrapment efficiency. 40mg of the prepared formulation was taken in equivalent quantity of 7.4 phosphate buffer. The suspension is ultracentrifuged at 17240rpm for 40 minutes.

EE= Total amount of drug- Amount of drug in supernatant/ Total amount of drug× 100

4.In-vitro drug release study of microsphere formulations in phosphate buffer pH 7.4: [57]

The dissolution rate testing apparatus was employed to study the release of azathioprine using phosphate buffer pH 7.4 as a dissolution medium. 50mg equivalent of azathioprine microspheres was taken and dissolution test was being carried out at 50rpm maintained at 370c + 0.50c. 5ml of sample were withdrawn at specific time interval for 12 hours. The sample volume was replaced by an equal volume of fresh medium. The concentration was determined spectrophotometric ally at 279nm.

Particle size and shape:[58-59]

The conventional scanning electron microscopy (SEM) and light microscopy (LM) are widely used for determine the shape and outer structure of micro particle. The laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the identification of size, shape and morphology of the microspheres. Light microscopies produce a control over coating parameters in case of double walled microspheres. The microspheres structures can be identified before and after coating and also change can be estimated microscopically whereas the scanning electron microscopy provides higher resolution in variation to the LM.

Determination of Density:[59]

Multi-volume pychnometer mostly using for measured the density of the microsphere. Specifically weighed sample in a cup is placed into the multi-volume pycnometer. Helium is initiated at a constant pressure in the chamber and allowed to enlarge. This development results in a decrease in pressure within the chamber. Two continuous readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume as well as the density of the microsphere carrier is determined.

Dissolution studies:[60]

The standard USP or BP dissolution apparatus have been mostly used to evaluation in vitro release profiles using rotating elements, paddle and basket. Dissolution medium used for the study which ranging from 100- 500 ml and speed of rotation from 50-100 rpm.

Stability studies:[61]

In this study placing the microspheres in screw capped glass container which is stored at following conditions:

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1. Ambient humid condition
2. Room temperature (27+/–2 º C)
3. Oven temperature (40+/–2 º C)
4. Refrigerator (5º C – 8 º C).

It was carried out of 60 days and analyzed the drug content of the microsphere.

Fourier Transform Infrared Spectroscopy:[61-62]

The drug polymer interaction and degradation of microspheres can be evaluated by FTIR.]

Drug Entrapment Efficiency[63]

Weigh amount of microsphere are taken and crushed. Then in buffer solution it is dissolved with the help of stirrer. After stirring filtered it. The filtrate is analyses by UV spectrophotometer at particular wavelength by using calibration curve. Drug Entrapment efficiency is analyses by actual weight of microspheres / the theoretical weight of drug and polymer × 100

Percentage Yield:

The percentage yield is calculated by the weight of microspheres derived from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100

Optical microscopy:[62]

The optical microscopy method is mostly used to evaluate particle size by using optical microscope. The measurement of particle size is done under 450x (10x eye piece and 45x objective) and 100 particles are measure.

Swelling Index: [63]

Swelling index is determined by measuring the extent of swelling of microspheres in a particular solvent. The equilibrium swelling degree of microspheres is determined by swelling in 5ml of buffer solution; 5mg of dried microspheres are poured in a measuring cylinder and keep it for overnight. The swelling index is calculated by given formula. Swelling index = The Mass of swollen microsphere – The mass of Dried Microspheres ×100 / the mass of dried microspheres.

Electron Spectroscopy for Chemical Analysis :[64]

The surface chemistry of the microspheres can be determined by using the electron spectroscopy for chemical analysis. It provides a means for the confirmation of the atomic composition of the surface.(8)

- **Marketed products :**

Drug	Commercial Name	Company	Technology
Risperidone	RISPERDAL® CONSTA®	Janssen®/Alkermes, Inc.	Double emulsion (oil in water)
Naltrexone	Vivitrol®	Alkermes	Double emulsion (oil in water)
Leuprolide	Lupron Depot®	TAP	Double emulsion (water in oil in water)
	Enantone Depot®	Takeda	
	Trenantone®	Takeda	
	EnantoneGyn	Takeda	
Octreotide	Sandostatin® LAR	Novartis	Phase separation
Somatropin	Nutropin® Depot®	Genentech/Alkermes	AlkermesProLease® Technology (Cryogenic spray-drying)
Triptorelin	Trelstar™ depot	Pfizer	Phase separation
	Decapeptyl® SR	Ferring	
Buserelin	Suprecur® MP	Sanofi-Aventis	N/A
Lanreotide	Somatuline® LA	Ipsen-Beafour	Phase separation
Bromocriptine	Parlodel LAR ™	Novartis	Spray dry
Minocycline	Arestin®	Orapharma	N/A

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II. CONCLUSIONS:

Microspheres are used to deliver the drug with the site specificity. A microsphere has a drug placed centrally within the particle bounded by polymers. A microsphere type of dosage form can be a novel technique in the long run for treatment of a number of diseases with better effectiveness.(10) To target colon and rectum associated with sustained drug release for 24 h, microspheres were successfully prepared and optimized with maximum drug entrapment and minimum particle size. The optimized microspheres coated with Eudragit S100, prevented drug release both in the stomach and small intestines evidenced by no drug release in 0.1 N HCl and SIF pH 6.8. The formulation with capecitabine and chitosan in the ratio of 1:10 and glutaraldehyde concentration of 1% w/v was considered optimum based on their most desirable in vitro characteristics, namely, 62.5% entrapment efficiency and 100% drug release in phosphate buffer pH 7.4 in 24 h. The results suggested the suitability of the capecitabineloaded microspheres as a colon-targeted delivery system. However, pharmacokinetic, targeting, and cytotoxicities studies are still needed to give us a better idea of the performance of the formulated microspheres in vivo.

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