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MICROSPHERES: AN APPROACH FOR THE TREATMENT OF VARIOUS DISEASES

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ABSTRACT

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. 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 are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, butnal so for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

KEYWORDS: Microspheres, controlled release, Types of microspheres, Methods of preparation, polymers used, characterisation of microspheres, applications.

INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. The ideal drug delivery system delivers drug at rate decided by the need of the body throughout the period of treatment and it provides the active entity solely to the site of action. So, carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc which modulates the release and absorption characteristics of the drug.

Types of drug delivery system are
1. Liposome
2. Niosome
3. Nanopartical
4. Microsphere

Microsphere

Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres;
1. Microcapsules.
2. Micromatrices.

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products.

Ideal Characteristics of Microspheres

a. Ability to control the release rate for a predefined period of time
b. Higher concentrations of the drug can be given serve as depot.
c. Stability of the preparation after synthesis with a clinically acceptable shelf life.
d. Controlled particle size and dispersion of the drug in aqueous solvent for parenterals.
e. Biocompatibility with a controllable biodegradability.

Types of Microspheres

Bioadhesive microspheres

Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. The term "bioadhesion" describes materials that bind to biological substrates', such as mucosal members. Adhesion of Bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.

Magnetic microspheres

This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.4 The different type are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Magnetic drug transport technique is based on the fact that the drug can be either encapsulated into a magnetic microsphere or conjugated on the surface of the microsphere. The accumulation of the carrier at the target site allow them to deliver the drug locally.

Floating microspheres

In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form.

Radioactive microspheres

Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters.

Mucoadhesive microspheres

Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, *e.g.* efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.

Polymeric microspheres

The different types of polymeric microspheres can be classified as:

Biodegradable polymeric microspheres

Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also Bioadhesive in nature. Biodegradable polymers prolongs the residence time when contact with mucous membrane due to its high degree of swelling property with aqueous medium , results gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. The main drawback is, in clinical use drug loading efficiency of biodegradable microspheres is complex and is difficult to control the drug release.

Synthetic polymeric microspheres

The interest of synthetic polymeric microspheres are widely used in clinical application, moreover that also used as bulking agent, fillers, embolic particles, drug delivery vehicles etc and proved to be safe and biocompatible. But the main disadvantage of these kind of microspheres, are tend to migrate away from injection site and lead to potential risk, embolism and further organ damage.

Classification of Polymers

Polymers based on back bone

a) Polymers with carbon chain backbone

a. Polyethylene
b. Polypropylene
c. Poly vinyl chloride
d. Poly vinyl alcohol
e. Poly acrylamide
f. Poly vinyl pyrrolidone

b) Polymers with heterochain backbone

a. Poly ethylene oxide
b. Cellulose (poly glycoside, β-1,4)
c. Amylase (polyglucose α-1,4)
d. Polydimethyl silaxone
e. Pectinic acid (polygalactouronoside)

Polymer classification based on source

a) Natural polymers

Protein based: albumin, collagen, gelatin, etc.

Polysaccharides: agarose, alginate, chitosan, cyclodextrin, hyaluronic acid, etc.

b) Synthetic polymers

Bio-degradable

Poly esters: poly lactic acid, polyglycolic acid, poly diaxanones, polyhydroxy butyrate, etc.

Polyanhydrides: polysabacic acid, polyadipic acid, polyterephthalic acid, etc.

Polyamides: polyimino carbonates, polyamino acids Phosphorous based: polyphosphates, polyphosphonates, polyphosphazenes, etc.

Synthetic polymers are divided into two types.

a) Non-biodegradable polymers

Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b) Biodegradable polymers

Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

Natural polymers obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, Collagen.

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Poly dextran**,** Poly starch.

Methods of Preperation

a. Emulsion solvent evaporation technique
b. Emulsion cross linking method
c. Coacervation method
d. Spray drying technique
e. Emulsion-solvent diffusion technique
f. Multiple emulsion method
g. Ionic gelation
h. Hydroxyl appetite (HAP) microspheres in sphere morphology

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.
5. Biocompatibility with a controllable biodegradability and
6. Susceptibility to chemical modification.

Emulsion solvent evaporation technique

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 (eudragit) 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. Aceclofenac microspheres were prepared by this technique.

Emulsion cross linking method

In this method drug was dissolved in aqueous gelation solution which was previously heated for 1 hr at 40oC. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35oC, results in w/o emulsion then further stirring is done for 10 min at 15oC. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 37oC for 10 min to block un reacted glutaraldehyde.**13** Examples for this technique is Gelatin A microspheres.

Coacervation method

Coacervation thermal change: Performed by weighed amount of ethyl cellulose was dissolved in cyclohexane with vigorous stirring at 80oC by heating. Then the drug was finely pulverized 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.

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

Spray drying technique

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 (epsilon 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 loose crystalinity due to fast drying process.

Emulsion-solvent diffusion technique

In order to improve the residence time in colon floating microparticles 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 dessicator at room temperature. The following microparticles were sieved and collected.

Multiple emulsion method

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.

Ionic gelation

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. 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 Ca2+ /Al3+ and chitosan solution in acetic acid.

Microspheres which were formed were kept in original solution for 24 hr for internal gellification followed by filteration for separation. The complete release was obtained at pH 6.4-7.2 but the drug did not release in acidic pH.

Hydroxyl appetite (HAP) microspheres in sphere morphology

This was used to prepare microspheres with peculiar spheres in sphere morphology microspheres were prepared by o/w emulsion followed by solvent evaporation. At first o/w emulsion was prepared by dispersing the organic phase (Diclofenac sodium containing 5% w/w of EVA and appropriate amount of HAP) in aqueous phase of surfactant. The organic phase was dispersed in the form of tiny droplets which were surrounded by surfactant molecules this prevented the droplets from co-solvencing and helped them to stay individual droplets While stirring the DCM was slowly evaporated and the droplets solidify individual to become microspheres.

Advantages of Microspheres

1. Size reduction leads to increase in surface area which can enhance solubility of the poorly soluble drug.
2. Provide constant drug concentration in blood which can increase patent compliance,
3. Decrease dose and toxicity.
4. Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery.
5. Less dosing frequency leads to better patient compliance.
6. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
7. Protects the GIT from irritant effects of the drug.
8. Convert liquid to solid form and to mask the bitter taste.
9. Reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects.
10. Reduce the reactivity of the core in relation to the outside environment.
11. Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
12. Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections.

Limitation

Some of the disadvantages were found to be as follows 5

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.

Evaluation of Microspheres

1. **Micromeritics Properties (Particle Size and Shape):** The most widely used procedures to visualize micro-particles are conventional light microscopy (LM), Particle size analyzers and scanning electron microscopy (SEM).
2. **Electron Spectroscopy for Chemical Analysis:** The surface chemistry of the microspheres can be

determined using the electron spectroscopy for chemical analysis (ESCA).

3. **Drug Entrapment Efficiency:** Aim is to calculate the total entrapment of drug in the microspheres. It can be calculated by calculated using following equation, Entrapment = Actual content/Theoretical content X100
4. **Density Determination:** The density of the microspheres can be measured by using a multi volume pycnometer.
5. **Isoelectric Point:** The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.
6. **Angle of Contact:** The angle of contact is measured to determine the wetting property of a micro particulate carrier.
7. ***In vitro* Methods:** Release studies for different type of microspheres are carried out by using different suitable dissolution media, by using Dissolution apparatus used in IP/USP / BP).
8. ***In vivo* Methods:** *In vivo* studies may be carried on the various subjects/cell lines to confirm the release rate and relation between *in vitro* and *in vivo* studies
9. **Swelling Index:** The swelling index of the microsphere was calculated by using the formula, Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) 100.

Application of Microspheres in Pharmaceutical Industry

Microspheres developed using polymer exhibits favourable biological behaviour such as bioadhesion, permeability-enhancing properties, and interesting physicochemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. *e.g.* Chitosan, Alginate, Gelatin

1. **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. *e.g*. Chitosan, Gelatin.
2. **Gene Delivery:** Microspheres could be a useful oral gene carrier be-cause of its adhesive and transport properties in the GI tract. *e.g.* Chitosan, Gelatin, viral vectors, cationic liposome, polycation complexes and Gene therapy with DNA plasmids and also delivery of insulin. It is also beneficial in vaccine delivery also as the prerequisite of a vaccine is protection against the microorganism or its toxic product. Biodegradable delivery system for vaccines that are given by Parenteral route may overcome the shortcoming of conventional vaccines. Several parenteral vaccines have been encapsulated in biodegradable polymeric microspheres, including the tetanus and diphtheria vaccine.
3. **Nasal Drug Delivery:** Polymer based drug delivery systems, such as micro-spheres, 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. *e.g.* Starch, Dextran, Albumin, Chitosan + Gelatin. **4. 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 *e.g.* Gelatin, PLGA, Chitosan **5.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. Chitosan, Sodium alginate. **6. 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 *e.g.* Eudragit, Ethyl cellulose + Carbopol BSA, Gelatin.
7. **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. *e.g.* Chitosan, Alginate, PLGA.
8. **Monoclonal Antibodies:** Monoclonal antibodies or targeting microspheres are biologically immune microspheres. This type of targeting is used to achieve selective targeting to specific sites of the body organ. Monoclonal Antibodies are extremely specific molecules which bind to the specific part of the body system through which absorption takes place *via*

a. Non specific adsorption and specific adsorption
b. Direct coupling
c. Coupling *via* reagents

9. **Imaging:** Diameter of microspheres plays an important role in determining the imaging of targeted sites using already labelled microspheres having radio activity. The microspheres injected *via* IV route apart from the portal vein will usually become entrapped in the area of lungs. This phenomenon is specifically used for scintigraphic imaging of tumour masses in lungs using human serum albumin microspheres.
10. **Topical Porous Microspheres:** Microsponges are porous microspheres having myriad of interconnected voids of size range 5 to 300μm. these sponges having capacity to engulf the various active ingredients such as emollients, fragrances, essential oils which is used for the topical application 40.

11. **Medical Application**

- Release of proteins, peptides and hormones over the extended period of time.

- Passive targeting of leaky tumor vessels, active targeting of tumor cells, antigens, by parenteral route.
- Magnetic Microspheres can be used for used for stem cell extraction and bone marrow purging.
- Used for Various diagnostic test for infectious disease like bacterial, viral and fungal.

12. **Radioactive Application:** It can be beneficial for the embolisation of various liver and spleen tumors which is used for radio synvectomy of local radiotherapy, arthritis, imaging of liver, bone marrow, local radiotherapy and even imaging of thrombus in deep vein thrombosis can be done.
13. **Other Applications:** Fluorescent microspheres can be used for membrane based technology flow cytometry, cell biology, fluorescent linked immunosorbent assay. Yttrium 90 can be used for primary treatment of carcinoma and also used for pre transplant management of HCC with promising results.
14. **Colonic Drug Delivery:** Polymer has been used for the specific delivery of insulin to the colon *e.g.* Chitosan.
15. **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 *e.g.* Chitosan, Gelatin, PLGA.
16. **Targeting by Using Micro Particulate Carriers:** The concept of targeting is a well established dogma, which is gaining full attention now a days. The response produced by the drug depends on its access and interaction with receptor usually pellets method is reported which can be prepared by using extrusion / Spheronization technology *e.g.* microcrystalline cellulose (MCC) and chitosan.

CONCLUSION

From this review, we could conclude that various types of preparation methods along with its pharmaceutical application are being used for Microspheres as a drug delivery system for delivering the definite amount of medications in a controlled manner. It may include oral, targeted, sustained, topical, naso-pulmonary and various biotechnology applications such as gene therapy *etc*. By developing newer delivery technologies, it can give much more therapeutic and commercial benefits by improving the safety and reducing the toxicity. Today, many pharmaceutical companies are introducing their newer products to the market which may give good therapeutic response when compared with conventional drug delivery. The development of upcoming drug delivery technologies can be applied for solving problems regarding pharmaceutical, biopharmaceutical and pharmacokinetic aspects thus, the delivery systems are growing and accepting worldwide for its better utilization.

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