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PHARMACEUTICAL APPLICATION OF MICROSPHERES: AN APPROACH FOR THE TREATMENT OF VARIOUS DISEASES

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ABSTRACT: Now a day the recent development in new drug delivery systems plays a vital role in pharmaceutical industries. The drug delivery practice has been modified in the last decades and even many advanced innovations happened in recent times. Newer drug delivery systems are largely influencing the current medical practice. Alterations of a traditional or conventional drug delivery into a new drug delivery system can absolutely changing the bioavailability, safety and efficacy of the drug and also it can produce improved patient compliance. Now a day, the scope of controlled drug delivery system is tremendously influencing the pharmaceutical dosage forms because it offers a wide range of products. Out of all controlled release products, Microspheres is one among all because of the controlled release and sustained release properties. This paper focus on the various types of microspheres along with their method of preparation and basic technique to evaluate its efficiency with most important emphasizes on pharmaceutical application of microspheres by means of microspheres taken by various routes of system such as oral, trasnsdermal, parenteral *etc*. Radioactive labelled microspheres found to attain more medicinal importance for the treatment of disease with labelled isotope tagging. Beside this Fluorescent microspheres can be used for membrane based technology flow cytometry, cell biology, fluorescent linked immuno sorbent assay. Isotope of Yttrium 90 can be used for primary treatment of cancer causing diseases and also used for pre transplant management of Hepato cellular Carcinoma with promising results.

INTRODUCTION: Controlled drug delivery system over the past thirty years, because the expense and complications concerned in promoting new drug entities have magnified, with concomitant recognition of the therapeutic benefits of novel drug delivery, bigger attention has been targeted on development of novel controlled drug delivery system.

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The role of drug delivery these days is to require a therapeutically effective molecule with sub-optimal physiochemical associated / or physiological properties and develop an optimized product that may still be therapeutically effective with additional advantages. Oral route drug administration is the most preferable route for taking medications [1 - 5]. Microspheres are spherical free flowing particles consisting of polymers which are biodegradable in nature. There are two types of microspheres; microcapsules and micromatrices, which are described as, Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substance is dispersed throughout

the matrix. Microspheres are sometimes referred to as micro-particles. Micro-spheres can be manufactured from various natural and synthetic materials. Microsphere plays an important role to improve bioavailability of conventional drugs and minimizing side effects.

Ideal Characteristics of Microspheres: [5, 6]

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.

Advantages of Microspheres: [7-9]

- Size reduction leads to increase in surface area which can enhance solubility of the poorly soluble drug.
- Provide constant drug concentration in blood which can increase patent compliance,
- Decrease dose and toxicity.
- Coating of drug with polymers helps the drug from enzymatic cleavage hence found to be best for drug delivery.
- Less dosing frequency leads to better patient compliance.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Protects the GIT from irritant effects of the drug.
- Convert liquid to solid form and to mask the bitter taste.
- 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.
- Reduce the reactivity of the core in relation to the outside environment.
- Biodegradable microspheres have the advantage over large polymer implants in that they do not require surgical procedures for implantation and removal.
- Controlled release delivery biodegradable microspheres are used to control drug release rates thereby decreasing toxic side effects, and eliminating the inconvenience of repeated injections [10].

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.

Types of Microspheres:

1. Bio adhesive microspheres
2. Magnetic microspheres
3. Floating microspheres
4. Radioactive microspheres
5. Polymeric microspheres i) Biodegradable polymeric microspheres ii) Synthetic polymeric microspheres

1. Bioadhesive / Mucoadhesive Microspheres: Adhesion may be defined as sticking property of drug to the mucosal membrane by using water soluble polymers [11, 12]. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal *etc.* can be termed as bio adhesion. These kinds of microspheres exhibit a prolonged contact time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action. Or Bioadhesion may be defined as the process by which a natural or synthetic polymer can adhere to a biological membrane. When the biological membrane is a mucosal layer then it is known as mucoadhesion. Mucoadhesion is a currently used in the design of new drug delivery system.

Mucoadhesive microspheres provide a prolonged contact time at the site of application or absorption and helps in facilitating an intimate contact with the underlying surface at which absorption is suppose to be occurred and thereby improve or better to therapeutic performance of drug. Mucoadhesive polymer are used to improving drug delivery by promoting the residence time and contact time of the dosage form with the mucous membranes, it adhere the mucosal surface in the body and the drug absorption by mucosal cells may be enhanced or released at the site for an extended period of time and enhanced bio availability of the drug to high surface to volume ratio. In recent years such mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal, vaginal routes for either systemic or local effects [13].

Theories of Mucoadhesion: The phenomenon of bio adhesion occurs by a complex mechanism. Many scientists have worked over bioadhesion; till date six theories have been proposed which can improve our understanding for the phenomenon of adhesion and can also be extended to explain the mechanism of bioadhesion. The theories include

(a) The electronic theory proposes transfer of electrons amongst the surface resulting in the formation of an electrical double layer thereby giving attractive forces.

(b) The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface.

(c) The adsorption theory proposes the presence of intermolecular forces, *viz.* hydrogen bonding and Vanderwaal's forces, for the adhesive interaction amongst the substrate surfaces.

(d) The diffusion theory assumes the diffusion of the polymer chains, present on the substrate surfaces, across the adhesive interface thereby forming a networked structure.

(e) The mechanical theory explains the diffusion of the liquid adhesives in to the micro cracks and irregularities present on the substrate surface there by forming an interlocked structure which gives rise to adhesion.

(f) The cohesive theory proposes that the phenomena of bio adhesion are mainly due to the intermolecular interactions amongst like molecules [14, 15].

The term "mucoadhesion" is adhesion of the polymers with the surface of the mucosal layer. The mucosal layer is made up of mucus which is secreted by the goblet cells columnar and is a visco elastic fluid. The main components constituting the mucosa include >95% water and > 99% mucin, the other components include protein, lipids and mucopolysaccharides. The gel like structure of the mucus can be attributed to the intermolecular entanglements of the mucin glycoproteins along with the non covalent interactions which results in the formation of a hydrated gel like structure.

Magnetic Microspheres: In this larger amount of freely circulate drug can be replaced by smaller amount of magnetically targeted drug which receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc. Magnetic microspheres hold great promise for reaching the goal of controlled and site specific drug delivery. Magnetic microspheres as an alternative to traditional radiation methods which uses highly penetrating radiations that is captivated throughout the body. Its use is limited by toxicity and side effects. Now days, several embattled treatment systems including magnetic field, electric field, ultrasound, temperature, UV light and involuntary force are being used in many disease treatments (*e.g.* cancer, nerve damage, heart and artery, anti-diabetic, eye and other medical treatments). Among them, the magnetic targeted drug delivery system is one of the most attractive and promising strategy for delivering the drug to the specified site. Magnetically controlled drug targeting is one of the various possible ways of drug targeting. This technology is based on binding establish anticancer drug with ferrofluid that concentrate the drug in the area of interest (tumor site) by means of magnetic fields. There has been keen interest in the development of a magnetically target drug delivery system. These drug delivery systems aim to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the activity entity to the site of action [16 - 18].

The different types of magnetic microspheres are as follows:

a. Therapeutic magnetic microspheres used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.

b. Diagnostic microspheres, used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nanosize particles supra magnetic iron oxides.

3. Floating Microspheres: Gastro retentive drug delivery via floating types having advantages of 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, and the system is found to be floating on gastric content and increases gastric residence and increases fluctuation in plasma concentration. Moreover it also reduces chances of dose dumping. It produces prolonged therapeutic effect and therefore reduces dosing frequencies. Few drugs like Famotidine may be given in the form of floating microspheres depending upon the pharmacokinetic properties [19 - 22].

4. Radioactive Microspheres: Radio embolization therapy microspheres sized 10-30 nm are of larger than the diameter of the capillaries and gets tapped in first capillary bed when they come across [3, 21]. They are injected in the arteries that leads them to tumour of interest so all these conditions 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. Microspheres as a drug delivery system hold great promise in reaching the goal of controlled drug delivery as well as site specific delivery. In the last few decades, scientific and technological advancements have been made in the research and development of radio labeled microspheres. These are used successfully for the treatment of various types of cancers and tumors. Since response to chemotherapy and external radiotherapy is not so effective and hazardous too, so an alternative to this is internal radiation therapy. These radio labelled microspheres are very stable and have a proven efficacy in the field of primary as well as metastatic cancers. Radioactive microspheres can be selectively targeted to various tumours without undue radiation to the non tumorous tissues. The radioactive microspheres are injected to halt tumour growth *via* the blood supply, thereby enabling surgical removal once the tumour size decreases.

5. Polymeric Microspheres: The different types of polymeric microspheres can be classified as follows and they are biodegradable polymeric microspheres and Synthetic polymeric microspheres [21].

i) Biodegradable Polymeric Microspheres: Natural polymers such as starch are used with the concept that they are biodegradable, biocompatible, and also bio adhesive 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 micro-spheres is complex and is difficult to control the drug release. However they provide wide range of application in microsphere based treatment [22].

ii) Synthetic Polymeric Microspheres: 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 [4, 23].

Drug Loading and Drug Release Kinetics: [24] The drug can be loaded over the microspheres principally using two methods, *i.e*.-

1. During the preparation of the microspheres or

2. After the formation of the microspheres by incubating them with the drug / protein.

The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it affected by many other process variables such as method of preparation, presence of additives (*e.g.* cross linking agent, surfactant stabilizers, *etc.*) heat of polymerization, agitation intensity, *etc.* Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug.

The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micro-morphology of the carrier and the properties of the polymer itself. The drugs could be released through the microspheres by any of the three methods, first is the osmotically driven burst mechanism, second by pore diffusion mechanism, and third by erosion or the degradation of the polymer. In osmotically driven burst mechanism, water diffuse into the core through biodegradable or non-biodegradable coating, creating sufficient pressure that ruptures the membrane. The burst effect is mainly controlled by three factors the macromolecule / polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres.

The pore diffusion method is named so because as penetrating water front continue to diffuse towards the core. The polymer erosion, *i.e.* loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix. Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, *i.e.* whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or active ingredients.

Method of Preparation: Various techniques are adopted for the preparation of microspheres depending upon the types of drugs and polymers properties. Few examples of method of preparation are as follows.

a. Solvent Evaporation and Solvent extraction.
b. Spray Drying / Congealing Method.
c. Single / Double emulsion technique.
d. Phase separation coacervation technique.
e. Spray drying and spray congealing.

Methods of Preparation of Microsphere: [25 -27]

a. Solvent Evaporation and Solvent Extraction: This method is used for the preparation of microparticles, involves the removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvent and organic phase is removed by extraction with water. The process decreases the hardening time for the microspheres. One variation of the process involves direct addition of the drug. Solvent removal rate depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer.

b. Spray Drying and Congealing: These methods are based on the drying of the mist of the polymer and drug in the air. On the basis of the cooling of the solution and removal of the solvent, these two processes are named respectively. Atomization lead to the formation of small droplets from which the solvent evaporates leads to formation of microspheres in a size range 1-100µm. Microspheres are than separated from the hot air by means of the cyclone separator and the solvent are removed by vacuum drying [28, 29].

c. Single Emulsion / Double Emulsion Technique: Microspheres of natural polymers *e.g.* those of proteins and carbohydrates are prepared by single Emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. The cross linking can be achieve by cross linkers. This method involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is most appropriate to water soluble drugs, peptides, proteins and the vaccines.

Both the natural as well as synthetic polymers can be used. The aqueous active constituent's solution is dispersed in a lipophilic organic continuous phase. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the active constituents contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution. This consequences formation of a double emulsion [30, 31].

d. Phase Separation and Coacervation: This method is particularly designed for preparing the reservoir type of the system, *i.e.* to encapsulate water soluble drugs. However, some of the preparations are of matrix type, when the drug is hydrophobic in nature.

The principle of process is based on the decreasing the solubility of the polymer.

Evaluation of Microspheres: [3, 32 - 35]

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 [32 - 33, 36 - 39].

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 [39].

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 [40].

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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