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Microparticles Based Drug Delivery Systems: Preparation and Application in Cancer Therapeutics

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ABSTRACT

Great leaps in the area of genetic engineering, biotechnology, combinatorial chemistry and computer aided drug design have been instrumental in creation of many active molecules. However the most frequent problems such as poor solubility, lack of bioavailability, poor diffusibility, plaque these active molecules with lack of efficacy as well as potential commercial benefits to patient and pharma industry. To overcome these critical limitations extensive research efforts are underway to develop suitable devices for drug delivery. Indeed, devices are being designed to provide maximal therapeutic effect, at right time, thereby minimizing frequency of administration and proper localization by active or passive targeting, leading to better compliance and reduced side effects. The progress in controlled drug delivery devices like formulation of polymer based pellets; disk, rod shapes and Microparticles are proving to be a boon in overcoming the difficulties associated with traditional method of administration. Microparticles consist of encapsulated or uniformly dispersed drug(s) in polymers and release it at control rate for a longer period of time. Microparticles are increasingly being explored in new anticancer therapies mainly due to their target specificity, biocompatibility and sustain drug release for long period of time. In this review, various preparative methods and application of the microparticle based drug delivery systems have been discussed.

Keywords: *Solubility, Bioavailability, Biocompatible, Anticancer, Polymers.*

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INTRODUCTION

Microparticles are generally injected either intraperitoneally, intramuscularly, subcutaneously (or) directly to the target organ. These are in the size of 1-1000 µm, and have emerged as a candidate for the sustained release vehicles for the drugs. Drug is gradually released on erosion and diffusion from the particles[1,2]. The rate of release may be increased by decreasing molecular weight of the polymer, particle size and also by controlling the nature of the polymer. Microparticles can be further categorized into 2 types namely, *microcapsules* and *microspheres*[3]. *Microcapsules* are micrometric reservoir systems. These are different from microspheres in that the drug is centrally located within the polymeric shell of finite thickness and release may be controlled by dissolution, diffusion (or) both. Quality microcapsules with thick walls generally release their medicaments at a zero order rate.[4] *Microspheres* are solid, nearly spherical micrometric matrix systems [5,6]. They are made up of biocompatable and biodegradable polymers e.g: Polylactic acid (PLA), Polylactic-co-glycolic acid(PLGA). Waxy (or) other protective materials such as starches, gums, proteins and fats. Natural polymers as gelatin and albumin are also used in preparation of microspheres. These are characteristically free flowing powders consisting of spherical particles of size ideally less than 125 µm that can be suspended in a suitable aqueous vehicle and injected by an 18 (or) 20 number needle [7]. Each particle is a matrix of drug dispersed in a polymer from which release occurs by a first order process.

Microparticles provide accurate delivery of potent drugs, reduce the concentration of drug at sites other than the target tissue and serve as effective delivery systems for insoluble (or) sparingly water soluble active agents [8].They give the products which exhibit immediate release properties and can give > 80% of active agent in less than 10 min. eg., Nimesulide. Microparticles increased the relative bioavailability of drugs and shows taste masking property [9,10]. The microparticles have great potential in reducing the dosage frequency and toxicity of various drugs. The preparative methods are simple and can be administered into the body through hypodermic needle. Microcapsules are also used as carriers for

vaccines and drugs in surgical procedures and diagnostic agents. Microparticles can be used to produce amorphous drugs with desirable physical properties. Administration of drugs using microparticles can reduce the local side effects eg. GI irritation of drugs on oral ingestion [11].

TYPES OF MICROSPHERES

***Bioadhesive microspheres*:** Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface.[12]The American society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces, which may consist of valance forces, interlocking action (or) both. Bioadhesion is defined as an ability of a material to adhere to a biological tissue such as buccal, ocular, rectal, and nasal for an extended period of time. Adhesion of bioadhesive drug delivery devices to the biological tissue gives an intimate and prolonged contact at the site of administration. This prolonged contact time can result in increased absorption and controlled release of drug. This improves the patient compliance by reducing the frequency of administration. Some of the examples include, efficient delivery of insulin into the systemic circulation via nasal route and increased nasal absorption of Gentamicin [4].

***Magnetic microspheres*:** Magnetic microspheres are supramolecular particles that are small enough to circulate through capillaries without producing embolic occlusion (<4 μm) but are sufficiently susceptible (ferromagnetic) to be captured in microvessels and dragged into the adjacent tissues by magnetic fields of 0.5-0.8 tesla. One example of site specific targeting by magnetic microspheres is in incorporation of magnatite into drug carriers.[13] In addition to polymers(eg. Chitosan, dextran), using an externally applied magnetic field is one way to physically direct these magnetic drug carriers to a desired site. In 1978, the first report on the use of magnetic albumin microspheres came, demonstrating that in the presence of a suitable magnetic field, the microspheres are taken up by the endothelial cells of target tissues in healthy as well as tumor bearing animals.

Synthetic polymeric microspheres: Synthetic polymeric microspheres are widely used in clinical applications mainly as fillers, bulking agent, drug delivery vehicles, embolic particles etc.[14] and proved to be safe and biocompatible. The main disadvantage of these kinds of microspheres is the tendency to migrate away from injection sites leading to potential risk, like in embolism (obstruction of an artery, typically by a clot of blood) and further organ damage.

***Biodegradable polymeric microspheres*:** Biodegradable polymers degrade within the body as a result of natural biological processes; avoiding the need to remove a drug delivery system after release of the active agent. [15, 16]Biodegradable polymers increases the residence time when in contact with mucous membrane due to its high degree of swelling property with aqueous medium, resulting in gel formation. The rate and extent of drug release is controlled by concentration of polymer and the release pattern in a sustained manner. In clinical settings, the main disadvantage of biodegradable microspheres is complex drug loading efficiency, drug release control, possible chances of dose dumping, stability assessment and manufacturing problem.

PREPARATION METHODS

Microparticles usually are made from polymers. These polymers are classified into two types:

1. Synthetic Polymers such as
   Non-biodegradable- PMMA (poly methyl methacrylate), Acrolein Epoxy
   Biodegradable- Lactides and Glycolides copolymers, Polyalkyl Cyanoacrylates Polyanhydrides.
2. Natural polymers such as
   Proteins- Albumins, Gelatin, Collagen.
   Carbohydrates Starch, Agarose, Carrageenan, Chitosan. Chemically modified carbohydrates: Poly (acryl) dextran, Poly(acryl)starch, DEAE (Diethylaminoethyl*)* Cellulose.[17,18]

The use of preparative technique depends upon the nature of polymer as well as nature of drug and the duration of therapy.

Ideal requirements for preparation of microspheres:

a) Biocompatibility with a controllable biodegradability
b) The ability to incorporate reasonably high concentrations of the drug.
c) Release of active reagent with a good control over a wide time scale
d) Stability of the preparation after synthesis with a clinically acceptable shelf life and susceptibility to chemical modification.

When preparing controlled release microspheres, the use of the optimal method has utmost importance for the efficient entrapment of the active substance. Various pharmaceutically acceptable techniques for the preparation of microparticles have been described. Some of the methods include:

Solvent Evaporation Method:

The solvent evaporation method involves the emulsification of an organic solvent (usually methylene chloride) containing dissolved polymer and dissolved/dispersed drug in an excess amount of aqueous continuous phase, with the aid of an agitator.

Single emulsion technique: The microparticulate carriers of natural polymers, i.e. proteins and carbohydrates are prepared by single emulsion technique.[19] In the 1st step, natural polymers are dissolved/dispersed in aqueous medium followed by dispersion in the non-aqueous medium. Ex: chloroform/oil. In the 2nd step, cross linking of the dispersed globule is carried out either by means of heat or by using chemical cross linkers. The chemical cross linking agents used are formaldehyde, butanol, gluteraldehyde, diacid chloride, terephthalate chloride, etc. Crosslinking by heat is affected by adding the dispersion to previously heated oil. However, cross linking by heat is not suitable for the thermo labile drugs. The chemical cross-linking method has an inherent disadvantage of excessive exposure of active ingredient to chemicals, if added at the time of preparation.

Double emulsion technique: Multiple-emulsion or double-emulsion technique is appropriate for the efficient incorporation of water-soluble peptides, proteins, and other macromolecules. This method can be used with both the synthetic and natural polymers. In this technique, polymers are dissolved in an organic solvent and emulsified into an aqueous drug solution to form a w/o emulsion. [20] The primary emulsion is subjected then to the homogenization before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of multiple (w/o/w) dispersions. The organic phase acts as a barrier between the two aqueous compartments, avoiding the diffusion of the active material to the external aqueous phase. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction. Finally the microspheres are collected by filtration and are washed with demineralized water.

Coacervation phase separation method: It is the simple separation of a micromolecular solution into two immiscible liquid phases. In this process, the polymer is solubilized into a solution. This process is designed for preparing the reservoir type system e.g. encapsulation of water soluble drugs i.e. peptides and proteins etc.[21] Microparticles can be prepared using the following steps with continuous agitation. The 1st step consists of formation of three immiscible chemical phases. In this method, the core material is dispersed in solution of coating polymer and further step involves deposition of coating polymer on core material, which takes place at interphase between core material and liquid vehicle phase. The final step comprise of rigidising the coating by thermal, desolvation (or) cross linking techniques to form microparticles.[22]

Spray drying and spray congealing method: Spray drying and spray congealing methods are based on the drying of the mist of the polymer and drug in the air.[23] Depending upon the cooling of the solution (or) removal of the solvent, the two processes are named spray congealing and spray drying respectively. Spray drying is used to protect sensitive substances from oxidation based on the atomization of a solution by compressed air and drying across a current of warm air. The hot air causes removal of solvent from the coating solution thus causing formation of the microcapsule in size range of 1-100 μm. Microcapsules are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying.[24] The major advantages of the process is feasibility of operation under aseptic conditions. Eg. the spray drying process is used to encapsulate various penicillins. Thiamine mononitrate and sulpha ethyl thiadizole are encapsulated in a mixture of mono and diglycerides of stearic acid and palmitic acid by using spray congealing process. On rapid solvent evaporation, it leads to the formation of porous microparticles.

Polymerization method: The polymerization techniques which are commonly used for the preparation of the microspheres are broadly classified as bulk, suspension, emulsion and interfacial polymerization. *Bulk polymerization*: In bulk, a monomer (or) a mixture of monomers along with the catalyst (or) initiator is usually heated to initiate polymerization. Polymer so obtained may be moulded / fragmented as microspheres.[25] Drug loading may occur during the process of polymerization. *Suspension polymerization*: is carried out at lower temperature and also referred as bead or pearl polymerization. Suspension polymerization is carried out by heating the monomer mixture with active drug as droplets dispersion in aqueous phase. The particle size obtained by this technique is less the 100 μm. *Emulsion polymerization* differs from *suspension polymerization* due to the presence of initiator in the aqueous phase, which afterward diffuses to the surface of micelles. *Interfacial polymerization:*[26]Interfacial

polymerization involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase. Interfacial polymerization technique is one in which two monomers, one oil-soluble and the other water-soluble, are employed and a polymer is formed on the droplet surface. The method involve the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. Whereas, in *Wax Coating and Hot Melt* technique involves dispersion of polymer in a suitable vehicle and slowly cooled to form the microspheres.[27]The polymers having low melting point formulate into microspheres by this technique easily.

APPLICATIONS

***Microspheres in vaccine delivery*:** An ideal vaccine must fulfill the requirement of safety, efficacy, convenience in application and cost. [28, 29]Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines**.** A major advantage of microspheres for vaccination is that they can be passively targeted to antigen-presenting cells (APCs) such as macrophages and dendritic cells. The ability of APCs to phagocytose particulates is dependent on the particle size. In particular, 1-10μm diameter microspheres are optimally taken up by APCs in a number of tissues and have been shown to enhance antigen-specific T-helper lymphocyte (Th) responses (thus leading to an enhancement in antigen-specific antibody responses) and elicit a cytotoxic T lymphocyte (CTL) response[30]. T-cell activation in response to antigen-encapsulating microspheres has been shown to be 100-1000 fold better than antigen alone.

Controlled-Release Vaccines have been highly successful for controlling or even eliminating many types of infectious diseases. Also new controlled release vaccines are being heavily investigated for AIDS, Hepatitis B, Anthrax, and SARS. A frequent problem is the need for repeated administrations—usually injections—to ensure permanent immunity. For example, the current anthrax vaccine requires a series of boosters at 2 and 4 weeks, and at 6, 12, and 18 months following the first inoculation; Similarly Recombivax HB vaccine for hepatitis B required for most health-care workers is administered in three injections at 0, 1, and 6 months. The need for multiple injections poses a serious problem for patients in developing countries with limited access to medical care, due to transient populations and lack of awareness.[31] Single-shot vaccine delivery system should provide the antigen(s) and adjuvant on prescribed schedule and maintain the bioactivity of the antigen, both during fabrication of the delivery device and during the often prolonged residence time of the device in the body. The table below shows the antigen dose and schedule along with the immune response data for a list of vaccines.

Mucosal and Systemic Immune Responses to Orally Delivered Microsphere Vaccines

Antigen(s)	Antigen dose and schedule	Observed immune response	Notes
Bordetella Pertussis	Single 10 μg dose of fimbriae	Serum IgM, IgG, IgA Salivary IgA, IgG Fecal IgA, IgG Vaginal IgG	>95% reduction in viable bacteria after intranasal challenge compared to unimmunized controls
Influenza vaccine	Single 70 μg dose	Salivary IgA Intestinal IgA	-
Yersinia pestis V and F1 antigens	3.0 μg V antigen 0.47 μg F1 antigen in single dose	Serum IgG Intestinal IgA Bronchial IgG	Intranasal booster significantly enhanced anti-V antigen response
Ovalbumin	Six 100 μg doses over 10 days	Systemic CTL Intestinal IgA	-
Anti-idiotype to chlamydial exoglycolipid antigen	Two 4 μg doses over 2-3 weeks	Serum neutralizing antibody	Up to 90% reduction in infectious yield after challenge compared to controls

***Microspheres in various Cancer treatments*:** Cancer is a disease caused by an uncontrolled division of abnormal cells in a part of the body. The abnormal cells are quite similar to the normal cells, with very small genetic or functional change. A main disadvantage of anticancer drugs is their deficiency of selectivity for tumor tissue separate, which causes severe side effects and results in low cure rates. Thus, it is challenging to target abnormal cells by using conventional method of the drug delivery system.

Microsphere technology is feasible method which can be used for site-specific action, without causing indicative side effects on normal cells.

Liver cancer: Microspheres are used as a bridge to surgery or transplantation or radiation therapy is used against liver cancer.[32, 33] A high energy radiation source, combined with a suitable size trans-hepatic arterial administered embolic microscopic particle, allow radiation to be delivered preferentially to the tumor. A β-emitter, such as yttrium-90, would develop a zone of high radiation exposure confined to the environment of the tumor, while managing non-tumorous hepatic parenchymal exposure to tolerable / acceptable levels. This forms the basis for radioembolization technique.[34] Millions of microspheres measuring about 30 μm in diameter, microspheres loaded with yttrium-90, are injected via a hepatic arterial catheter to the arterial supply of the tumor. Radioemobilization is a technique that provides high average doses of radiation (200 to 300 Gy) to liver tumors with minimal serious effect on the non-tumorous liver.

Breast cancer: In the breast, microspheres loaded with cytotoxin are delivered through a catheter, directly implant surgically into either a branch of the subclavian artery or into the subclavian artery itself. Usually more selective perfusion in the thyrocervical trunk can be obtained by the replacement of angiographic catheters directly into the internal mammary artery. When these microspheres administered intra-arterially, are transported by the blood flow to the capillary bed, they get embolize and release their therapeutic agent into the target organ.[35, 36] Breast cancer cells have been targeted by delivering a single pulse of adriamycin-loaded albumin microspheres through a radiologically placed internal mammary artery catheter. Adriamycin-loaded albumin microspheres can suppress tumor growth to a greater degree than free drugs in a solution as shown in animal studies [37]. The ability of intratumoral interleukin 12 (IL-12) loaded poly-lactic-acid-encapsulated microspheres (PLAM), tumor necrosis factor (TNF), and granulocyte-macrophage colony stimulating factor (GM-CSF) have generated a specific antitumor response in a murine model of breast cancer[38]. Single intratumoral injection of IL-12 and TNF-loaded PLAM into a breast tumor leads to infiltration by polymorphonuclear cells and CD8+ T-cells, with consecutive tumor regression. In addition, this local therapy increases specific antitumor T-cells in the spleen and lymph nodes, resulting in a memory-immune response.[39]

Lung cancer: In Lewis lung carcinoma cells, the paclitaxel-loaded PLGA microspheres significantly inhibited lung tumor growth *in-vivo* with no possible toxicity.[40] In the treatment of lung and pleural diseases, acid-prepared mesoporous microspheres, chemically modified with different surface molecules (lipid, a linker having a terminal amine group, a tetraethylene glycol or a thiol group), are effective vehicles for pulmonary chemotherapeutic drug delivery and are found to be nontoxic and non-immunogenic, as evaluated by differential cell counts and lactate dehydrogenase levels in pleural lavage fluids and bronchoalveolar.[41] Conjugating camptothecin onto polyethylene glycolated (PEGylated) microspheres prolongs the release of camptothecin *in-vitro* and increased the anti-cancer efficacy *in-vivo* in an orthotopic lung cancer rat model.

Brain tumor: A microsphere-based system has been developed to deliver therapeutic agents to brain tumors. The polymethylidene-malonate polymer is used to prepare 5-fluorouracil-loaded sustained release biodegradable microspheres for treatment of malignant brain tumors. That polymer exhibits degradation at slow rate, thus leading to a long-term local delivery of 5-fluorouracil.[42]

Pancreatic cancer: In patients with cancer of the pancreatic head region obstruct flow of pancreatic juice due to mechanical obstruction of the pancreatic duct, causes exocrine pancreatic deficiency with steatorrhea and creatorrhea. [43, 44] This may lead to the profound weight loss that often occurs in these patients. A trial of enteric-coated pancreatin microsphere placebo-controlled treatment in patients with unresectable cancer of the pancreatic head shows prevention of weight loss and pancreatic duct occlusion, at least for the period rapidly after insertion of a biliary endoprosthesis, by supplementation of high-dose enteric-coated pancreatin enzyme in combination with dietary counseling.

Ovarian cancer: The effects of intra-peritoneal administration of L-Lactic acid and glycolic acid copolymer microspheres containing cisplatin in rats with ovarian cancer show increased survival of rats, without increase in the systemic toxicity of cisplatin.[45]A monoclonal antibody, MJ01, recognizes human ovarian cancer antigen encapsulation of CA125 in Polylactic-co-glycolic acid (PLGA) microspheres, which is capable of increasing T3 as evidenced by the T-cell proliferation *in-vitro*, in response to the CA125. By the anti-CA125 antibody in murine rat models for ovarian cancer therapy shows promising response.[46]

Monoclonal antibodies mediated microspheres: Monoclonal antibodies targeting microspheres are immune microspheres.[47] This targeting method is used to achieve selective targeting to the specific sites. Monoclonal antibodies (mAbs) are extremely specific molecules. This extreme specificity of mAbs can be utilized to target loaded bioactive molecules in microspheres to selected sites.[48] Monoclonal antibodies

can be directly attached to the microspheres by covalent coupling. The free aldehyde groups, hydroxyl groups or amino groups on the surface of the microspheres can be linked to the antibodies.

Ophthalmic Drug Delivery: Polymers exhibits favorable biological behavior such as bioadhesion, permeability-enhancing properties, and interesting physico- chemical characteristics, which makes it single material for the design of ocular drug delivery vehicles.[49] Due to the elastic properties of polymer, polymer hydro gels offer better acceptability, with respect to semi-solid or solid formulations for ophthalmic delivery, such as ointments or suspensions, ophthalmic chitosan gels increase adhesion to the mucin, which coats the conjunctiva and corneal surface of the eye, increase drug residence time in precornea, drug elimination by the lachrymal flow decreases. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs.[50] In contrast, polymer based colloidal system were found to work as trans mucosal drug carriers, either via accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine) or via facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin). The acyclovir loaded micro spheres seems a promising means of topical administration to the eye. The duration of efficacy of the ofloxacin was increased by using high molecular weight chitosan.

Topical porous microspheres: Microsponges are polymeric delivery systems consisting of 10-25 µm porous microspheres that can entrap a wide range of active ingredients such as fragrances, emollients, sunscreens, essential oils, anti-infective, anti-fungal and anti-inflammatory agents.[51] Microsponge do not pass through the skin (capable of holding 4 times their weight in skin secretions), they collect in the tiny nooks and crannies of skin and slowly release the entrapped drug, as the skin needs it. These products are in conventional forms like gels, creams and lotions and they contain relatively high concentration of active ingredients.[52, 53] These are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to reduce side effects, enhance stability and modify drug release.

CONCLUSION

In recent years, Microparticles based formulations have shown successful applications in the therapies where the requirement of site-specific activities were of profound importance. The sustained release, biodegradability and stability are some of the desired properties of drug delivery system. In this domain, we have shown that the Microparticles do hold a firm foundation leading to maximum therapeutic efficacy with minimum undesirable adverse effects. The future work on reducing the potential toxicity of some of the microparticles based vaccines is an open area of research.

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