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A review on microsphere for novel drug delivery system

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Abstract

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. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. 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, but also for targeting of anticancer drugs at tumor site. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe, targeted and effective *in vivo* drug delivery and supplements as miniature versions of diseased organ and tissues in the body.

Keywords: Microspheres; Controlled drug delivery system; Target site; Specificity; Therapeutic efficacy

1. Introduction

A controlled drug delivery system is used to overcome some problems associated with conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time, thereby causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion [1].

To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers, one can name soluble polymers, micro particles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g. pH-or temperature-sensitive), and even targeted by conjugating them with specific antibodies against certain characteristic components of the area of interest. One such approach is using micro spheres as carriers for drugs. Microspheres can be described as small particles (in 1-1000 micrometer size range) for use as carriers of drugs and other therapeutic agents consisting of proteins or synthetic polymers which are biodegradable in nature. The term microsphere describes a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix or as a dispersion of particles [2].

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1.1. Advantages of microspheres [3]

- Microspheres have a consistent and long-lasting therapeutic impact.
- Reduces the frequency of dosing and thereby improves patient compliance.
- Owing to their spherical form and smaller size, microspheres may be inserted into the body.
- Improved drug utilization will improve bioavailability while lowering the risk of side effects.
- The morphology of microspheres allows for controlled variability in drug release and degradation.
- Oils and other liquids are converted to solids to make them easier to handle.

1.2. Disadvantages [1]

- In case of parenteral application of microspheres, it is difficult to remove carrier completely from the body if the drug produces some adverse toxic effects.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.

1.3. Materials used [4]

Microspheres used usually are polymers. They are classified into two types:

- Synthetic Polymers and
- Natural polymers

Synthetic polymers are divided into two types:

- Non-biodegradable polymers
  - Poly methyl methacrylate (PMMA)
  - Acrolein
  - Glycidyl methacrylate
  - Epoxy polymers

- Biodegradable polymers [4, 5]
  - Lactides, Glycolides & their co polymers
  - Poly alkyl cyano Acrylates
  - Poly anhydrides

Natural polymers are obtained from different sources like Proteins, carbohydrates and chemically modified carbohydrates. [6, 7]

Proteins:

- Albumin
- Gelatin 9
- Collagen

Carbohydrates

- Agarose
- Carrageenan
- Chitosan10
- Starch

Chemically modified carbohydrates:

- Poly dextran 11
- Poly starch.

2. Types of microspheres

2.1. Bio adhesive microspheres

Adhesion is the process of attaching a drug to a membrane by using the adhesive properties of water-soluble polymers. Bio adhesion is described as the adhesion of a drug delivery system to a mucosal membrane such as the buccal, ocular, rectal, nasal, and other mucosal membranes. These microspheres have a longer residence period at the application site, resulting in close interaction with the absorption site and improved therapeutic action [8].

2.2. Magnetic microsphere

This type of delivery system is important because it allows the drug to be delivered to the exact location where it is needed. A smaller amount of magnetically targeted drug will replace a larger amount of freely circulating drug in this condition. Chitosan, dextran, and other integrated materials used in magnetic microspheres have magnetic responses to a magnetic field [9].

The different type's magnetic microspheres are:

2.3. Therapeutic magnetic microspheres

These are used to administer a chemotherapeutic agent to liver tumors. Drugs like proteins and peptides can also be targeted through this system. [8]

2.3.1. Diagnostic microspheres

They can be used for imaging liver metastases and also can be used to differentiate bowel loops from other abdominal structures by forming nano-size particles paramagnetic iron oxides [10].

2.3.2. Floating microspheres

The bulk density of floating forms is lower than that of gastric fluid, they float in the stomach and do not impact the rate of gastric emptying. If the system is floating on gastric contented, the drug is released slowly and at the desired rate, which increases gastric residence and plasma concentration variability. Strikes and dose dumping are also less likely. It also has a longer therapeutic effect, which decreases dosing frequency [11].

2.3.3. Radioactive microspheres

Therapy with Radio embolization Microspheres 10-30 nm in size are larger than capillary microspheres and are tapped in the first capillary bed as they pass through, they are inserted into the arteries that cause a tumor of interest. Thus, under all these cases, radioactive microspheres provide a high dose of radiation to the target areas without affecting normal surrounding tissues [12]. It differs from the drug delivery system, as radioactivity 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 [13].

2.4. Polymeric microspheres

The different types of polymeric microspheres can be classified as:

Biodegradable polymeric microspheres Natural polymers like starch are used because they are biodegradable, biocompatible, and bio adhesive. Due to its excellent degree of swelling in an aqueous medium, biodegradable polymer extends the residence time when in contact with mucous membranes, resulting in the formation of gels. The concentration of polymer and the release pattern in a sustained manner regulate the rate and degree of drug release. The main disadvantage is that drug loading performance of biodegradable microspheres in clinical use is complicated, making drug release difficult to manage. However, in microsphere-based therapy, they have a wide variety of applications [14].

2.5. Synthetic polymeric microspheres

Synthetic polymeric microspheres are widely used in clinical applications, as well as bulking agents, fillers, embolic particles, drug delivery vehicles, and other applications, and have been shown to be safe and biocompatible [15]. However, the main downside of these microspheres is that they have a tendency to move away from the injection site, posing a risk of embolism and further organ damage.

3. Mechanism of microspheres

The majority of drug delivery via micro particles prevents the formation of a matrix-like internal solid dispersion morphology structure. The drug may be insoluble in the polymeric matrix, and it is released by erosion. First, water diffuses into the matrix, removing the resultant close to the surface of the device. By creating a channel to the surface and releasing a specific amount of medicine during the initial drug burst, the ensuing osmotic pressure is reduced [2].

4. Method of preparation

Methods used for the preparation of microspheres are:

- Single emulsion techniques
- Double emulsion techniques
- Polymerization
- Normal polymerization
- Interfacial polymerization
- Phase separation coacervation technique
- Spray drying
- Emulsion crosslinking method
- Solvent evaporation
- Solution-enhancement dispersion method
- Ionic gelation method [16]

4.1. Single emulsion technique

This method can be used to prepare a variety of proteins and carbohydrates. The natural polymers are first dissolved in an aqueous medium, then dispersed in an oil phase, which is a non-aqueous medium. That is the initial phase in the process [17]. Two methods are used to cross-link the next step as:

4.2. Cross-linking by heat

By adding the dispersion into heated oil, but it is unsuitable for the thermolabile drugs.

4.3. Chemical cross-linking agents

By using agents i.e. Formaldehyde, di acid chloride, glutaraldehyde, etc. However, it is detrimental to the undue exposure of active ingredients to chemicals when applied at the time of preparation and then subjected to centrifugation, washing and separation. Chitosan solution (in acetic acid) by applying w/o emulsion to the liquid paraffin containing a surfactant. Microsphere is prepared using a 25 percent solution of glutaraldehyde as a cross-linking agent [18].

4.4. Double emulsion technique

It is the creation of several emulsions, i.e. W/O/W is prepared by pouring the primary w/o emulsion into an aqueous polyvinyl alcohol solution. This w/o/w emulsion shall be put at constant stirring for 30 min. slowly add some water to the emulsion for a duration of 30 min. Collection of microcapsules by filtration and dry under vacuum. It is ideally suited for water-soluble medicines, peptides, proteins and vaccines. Natural as well as synthetic polymers can be used for this process. The aqueous protein solution is distributed in a continuous organic lipophilic phase. This protein solution will contain active ingredients [19]. Disperse in oil/organic phase homogenization/vigorous i.e. the formulation of the first emulsion then the addition of the aqueous solution of PVA (Poly Vinyl Alcohol) i.e. the multiple emulsion now produced by the addition of the broad aqueous phase denaturation/hardening after this separation, the washing, drying and collection of the microspheres is prepared using the o/w/o multiple emulsion process [20].

4.5. Polymerization techniques

Two techniques are mainly used for the formulation of microspheres are as follow:

4.5.1. Normal polymerization

In bulk polymerization, a monomer or a mixture of a number of monomers along with the initiator or catalyst is usually heated to initiate polymerization. The polymer so obtained may be molded as microspheres. Drug may be done by adding the drug during the process of polymerization. It is a pure polymer formation technique but it is very difficult to

dissipate the heat of the reaction which affects the thermolabile the active ingredients. Suspension polymerization is carried out at a lower temperature and also refer to as pearl polymerization in which heating the monomer mixture with the active drug as droplets dispersion in the continuous aqueous phase [21].

4.5.2. Interfacial polymerization

The reaction of various monomers at the interface between the two immiscible liquid phases forms a film of polymer that essentially envelops the dispersed phase. In this technique two reacting monomers are employed; one is dissolved in the continuous phase while the other is dispersed in continuous phase (aqueous in nature) throughout which the second monomer is emulsified [21].

4.6. Phase separation coacervation technique

This method is based on the idea of decreasing the solubility of the polymer in the organic phase in order to influence the formation of a polymer-rich phase called coacervates. In this process, the drug particles are dispersed into a polymer solution and an incompatible polymer is added to the device, which separates the first polymer phase and engulfs the drug particles. Adding the non-solvent results to the solidification of the polymer. This process has been used to prepare polylactic acid (PLA) microspheres by using butadiene as an incompatible polymer. Process variables are very significant as the rate of achievement of the coacervates determines the distribution of the polymer film. The size of the particles and the agglomeration of the formed particles. Agglomeration must be avoided by stirring the suspension using an appropriate speed stirrer, because as the process of microsphere forming starts, the formed polymerized globules begin to adhere and form agglomerates. Process variables are therefore important as they govern the kinetics of the formed particles, since there is no given state of equilibrium attainment [21, 22].

4.7. Spray Drying

The polymer is first dissolved in a suitable volatile organic solvent, such as dichloromethane or acetone, before being spray dried. Thereafter, the compound is dispersed in a polymer solution using high-speed homogenization. This dispersion is then atomized in a hot air current. The atomization results in the formation of tiny droplets or fine mist from which the solvent evaporates instantaneously leading to the formation of microspheres in the 1-100μm range. Micro particles are separated from hot air using a cyclone separator, and the solvent residue is removed using vacuum drying. One of the main benefits of the procedure is the viability of action under aseptic conditions. This process is rapid, leading to the formation of porous micro particles [23].

4.8. Emulsion crosslinking method

This method utilizes the reactive functional group of polymers to crosslink with the aldehyde group of cross- linking agents. In this method water-in-oil (w/o) emulsion was prepared by emulsifying the polymer aqueous solution in the oily phase. Aqueous droplets were stabilized using a suitable surfactant like span 80 or dioctyl sodium sulphosuccinate. The stable emulsion was cross-linked by using an appropriate cross-linker like glutaraldehyde to harden the droplets. Microspheres were filtered and washed repeatedly with hexane or petroleum ether to remove traces of oils. They were eventually washed with water to clear the cross-linkers and then dried at room temperature for 24 hours [24].

4.9. Solvent Evaporation

Processes are carried out in a liquid production vehicle. The microcapsule is dispersed by a volatile solvent that is not mixed with the liquid stage of the method of production. The core material to be microencapsulated is dissolved or dispersed in a polymer coating solution. With agitation, the core material mixture is distributed during the liquid manufacturing process of the vehicle in order to achieve the required size of the microcapsule. The mixture is then heated, if possible, to evaporate the solvent for the polymer of the main material dispersed in the polymer solution, the polymer shrinks around the core. If the core material is dissolved in a polymer coating solution, a matrix – a form of microcapsules is formed. Core materials can be either water- soluble or water-insoluble. Core materials can be water-soluble or water-insoluble. Solvent evaporation entails aqueous (o/w) or non-aqueous formations [25].

4.10. Ionic gelation method

This technique was used to prepare the alginate/chitosan particulate system for the release of diclofenac sodium. In this step, the drug is added to an aqueous sodium alginate solution. In order to obtain a complete solution, the stirring continues and the solution containing Ca2+/Al3+ is added dropwise. The microspheres produced were held in the original solution for 24 hours for internal jellification followed by filtration for separation. The full release is obtained at pH 6.4-7.2, but the medication will not release at acidic pH [2].

5. Evaluation parameters of microspheres

5.1. Characterization

The characterization of the micro particulate carrier is a significant phenomenon that aids in the development of a suitable carrier for the delivery of proteins, drugs, or antigens. The microstructures of these microspheres vary. The release and stability of the carrier are determined by these microstructures [26].

5.2. Particle size and shape

The most well-known used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to analyze the shape and outer structure of micro particles. LM provides control over coating parameters in the case of double-walled microspheres. The microspheres structures can be seen before and after coating and the change can be measured microscopically. SEM provides a higher resolution in contrast to the LM. SEM enables the investigation of the surfaces of the microspheres, and when the particles are cross-sectioned, it can also be used for the investigation of double-walled structures [26].

5.3. Electron spectroscopy for chemical analysis

The surface chemistry of the microspheres can be determined using electron spectroscopy for chemical analysis (ESCA) [27].

5.4. Density determination

The density of the microspheres can be calculated by using a multi-volume pycnometer [28].

5.5. Isoelectric point

Micro-electrophoresis is used to calculate the electrophoretic mobility of microspheres from which the isoelectric point can be calculated [29].

5.6. Angle of contact

The contact angle is determined to determine the wetting properties of the micro particle carrier [30].

5.7. *In vitro* methods

Release studies for a specific type of microsphere are executed using a different suitable dissolution medium, often by rotating paddle apparatus (USP/BP) [2].

5.8. Drug entrapment efficiency

The entrapment efficiency of the microspheres or the percent entrapment can be determined by holding the microspheres in the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected to monograph requirements for the determination of active constituents. Drug entrapment efficiency can be calculated using the following equation,

% Entrapment = Actual content/Theoretical content x 100 [31].

5.9. Percentage yield

It is calculated as the weight of microspheres obtained from each batch divided by the total weight of drug and polymer used to prepare that batch multiplied by 100 [31].

5.10. Swelling index

The swelling index of the microsphere was determined by using the formula,

Swelling index = (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) [2].

6. Flow properties [31,32]

6.1. Bulk density

It is measured by pouring a sample of microspheres of known weight into a measuring cylinder without tapping and measuring its length, and then dividing the weight by the volume.

Bulk density = wt. of microspheres/bulk volume

6.2. Tapped density

It is determined by pouring a sample of microspheres of known weight into a measuring cylinder & thoroughly tapping it & measuring its volume, then dividing the weight by the volume.

Tapped density = wt. of the microspheres/volume after tapping

6.3. Hausner's ratio

Hausner's ratio is the ratio of the tapped density to the bulk density of microspheres & can be used to predict microspheres flow. A Low Hausner's ratio of < 1.2 indicates a free-flowing microsphere.

Hausner's ratio = bulk density – tapped density

6.4. Angle of repose

It is defined as the maximum angle to the horizontal that is attainable by a heap of microspheres. The fixed height cone and the fixed base cone are among the methods available for calculating the angle of repose.

Angle of Repose = tan−1 h/r

r = the radius of the base of the heap of microsphere h = height of the heap of microsphere

6.5. Zeta potential

The polyelectrolyte shell is set up by consolidating chitosan of various atomic load into the W2 stage and the subsequent particles are dictated by zeta potential estimation [33].

7. Applications [34]

- For Taste and odour masking
- To delay the volatilization
- For Separation of incompatible substances
- For Improvement of flow properties of powders
- To Increase the stability of the drug against the external conditions
- For Safe handling of toxic substances
- · To improve the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media
- To reduce the dose dumping potential compared to large implantable devices.
- For conversion of oils and other liquids to solids for ease of handling.

8. Novel applications of microsphere

8.1. Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against the micro-organism or its toxic product. An ideal vaccine must fulfill the requirement of efficacy, safety, convenience in application and cost. The aspect of safety and the degree of the production of antibody responses are closely related to mode of application. Biodegradable delivery systems for vaccines that are given by parenteral route may overcome the shortcoming of the conventional vaccines.

The interest in parenteral (subcutaneous, intramuscular, intradermal) carrier lies since they offer specific advantages including:

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen.

8.2. Targeting using micro particulate carriers

The concept of targeting, i.e. site specific drug delivery is a well-established dogma, which is gaining full attention. The therapeutic efficacy of the drug relies on its access and specific interaction with its candidate receptors. The ability to leave the pool in reproducible, efficient and specific manner is center to drug action mediated by use of a carrier system. Placement of the particles indiscrete anatomical compartment leads to their retention either because of the physical properties of the environment or biophysical interaction of the particles with the cellular content of the target tissue.

8.3. Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies targeting microspheres are immuno-microspheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules.

This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. The Mabs can be attached to microspheres by any of the following methods

- Non-specific adsorption
- Specific adsorption
- Direct coupling
- Coupling via reagents

8.4. Chemoembolisation

Chemoembolisation is an endovascular therapy, which involves the selective arterial embolisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent. The theoretical advantage is that such embolisations will not only provide vascular occlusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour. Chemoembolisation is an extension of traditional percutaneous embolisation techniques.

8.5. Imaging

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labeled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites. The particles injected intravenously apart from the portal vein will become entrapped in the capillary bed of the lungs. This phenomenon is exploited for the scintiographic imaging of the tumour masses in lungs using labelled human serum albumin microspheres.

8.6. Topical porous microspheres

Microsponges are porous microspheres having myriad of interconnected voids of particle size range 5-300 µm. These micro sponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils etc., are used as the topical carries system further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner.

8.7. Surface modified microspheres

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decrease their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance.

The most studied surface modifiers are:

- Antibodies and their fragments
- Proteins
- Mono-, oligo- and polysaccharides
- Chelating compounds (EDTA, DTPA or Desferroxamine)
- Synthetic soluble polymers such modifications are provided surface of microspheres in order to achieve the targeting to the discrete organs and to avoid rapid clearance from the body

9. Conclusion

Microspheres are an advanced approach to the drug delivery in an innovative way. They have better patient compliance and targeted precision compared to the other forms of drug delivery systems and are safer for medication delivery. Due to its benefits of continuous and controlled-release action, improved stability, decreased dosing frequency, dissolving rate and bioavailability, microspheres are the most popular drug delivery technology. A versatile drug delivery system, the microsphere drug delivery system can be employed for a number of purposes, including precision medication targeting, floating and vaccination delivery among others. There are many efficient ways to prepare microspheres and evaluate them after they have been prepared. In addition to distributing medications, microspheres are also utilized to diagnose bio-molecular interactions, scan tumors, and cure cancers. Owing to all the key characteristics they possess, microspheres are definitely the prospective candidates for delivering the drugs and allied substances in a novel and absolutely beneficial way, thus supposedly having a much greater impact on medicine in the future.

Compliance with ethical standards

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Disclosure of conflict of interest

There are no conflicts of interest.

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