Review Article

NANOSPHERES: A NOVEL APPROACH FOR TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Nanospheres are the particles having the size range between 10-200 nm in diameter. Nanospheres can be amorphous or crystalline in nature and also they have the ability to protect the drug from enzymatic and chemical degradation. It has been shown that the hydrophobic surfaces of these particles are highly susceptible to opsonization and clearance by the reticulo endothelial system. The tiny capsule of drug store house is called vesicles and the solid skeleton structure is called Nanospheres. Biodegradable Nanospheres include albumin Nanospheres, modified starch Nanospheres, gelatin Nanospheres, polypropylene dextran Nanospheres and polylactic acid Nanospheres. In addition there are two more types of Nanospheres, immune Nanospheres and magnetic Nanospheres. Immuno-magnetic nanospheres can be prepared by combining the above two kinds of nanospheres, which could significantly improve its targeting. There are various ways of targeting nanospheres on the tumor, as long circulation purpose and also for the drug delivery in the brain. Nanospheres can be prepared by various methods but the solvent displacement technique is the best method. Now a days Nanotechnology is widely used for targeting the cancerous cells.

Keywords: Nanospheres, Opsonization, RES, Drug targeting, Drug delivery.

INTRODUCTION

Nanoparticles can be divided into two main families: nanospheres, which have a homogeneous structure in the whole particle, and nanocapsules, which exhibit a typical core-shell structure. Nanospheres are the spherical particles which have the size between 10-200 nm in diameter and that exhibit some new enhanced size dependent properties in comparison of larger spheres of the same material. Basically the drug is dissolved, entrapped, encapsulated or attached to the matrix of polymer. In the matrix system of polymer the drug is physically and uniformly dispersed. Nanospheres can be amorphous or crystalline in nature and also they have the ability to protect the drug from enzymatic and chemical degradation[1-5]. Even though elimination may be slowed by the submicron particle size of nanospheres, clearance is still unavoidable due to capture by the reticulo endothelial system (RES), isolating particles within organs such as the liver and spleen[6]. It has been shown that the hydrophobic surfaces of these particles are highly susceptible to opsonization and clearance by the RES. Hence, it became clear that in order to prolong the circulation of nanoparticles, the surfaces must be modified to ''look like water'' so that they appear to be invisible to the RES[7]. Attempts have been made to alter the surface of nanoparticles by adsorbing various surfactants to the particle surface including poloxamine, poloxamer and Brij[8-10]. Although surfactant coating reduced the total uptake by the RES organs over short periods of time, no difference between uncoated and coated particles was found over longer periods likely due to desorption of the surfactan[6,11]. Characteristics of Nanospheres formed in frozen state, phase separated solid matrix core, crystalline and amorphous in nature, uniform in size. A main challenge of the formulation of nanospheres is adapting the choice of their own structure to the final aims of drug delivery, Biocompatibility of the polymer, physicochemical properties of the drug, and therapeutic goals.

Particulate agents with usual size of 10–200 nm are a tiny spherical entity, in which drugs are wrapped by polymer materials or dispersed in polymer materials. The tiny capsule of drug store house is called vesicles and the solid skeleton structure is called nanospheres. Administration of medication via such systems is advantageous because nanospheres can be ingested or injected and they can be tailored for desired release profiles and used site-specific delivery of drugs and in some cases can even provide organ-targeted release. According to biodegradability, it can be divided into biodegradable nanospheres and non-biodegradable nanospheres. Biodegradable nanospheres include albumin nanospheres, modified starch nanospheres, gelatine nanospheres, polypropylene dextran nanospheres and polylactic acid nanospheres, etc. According to the current literature reports on non-biodegradable nanospheres, polylactic acid is the only polymer approved to be used by people and used as a controlled-release agent In addition; reports on immune nanospheres and magnetic nanospheres are also common in recent years. Immune nanospheres possess the immune competence as a result of the antibody and antigen was coated or adsorbed on the polymer nanospheres. Magnetic nanospheres possess a unique magnetic feature, namely their reaction to a magnetic force. These are generally coated with protective shells as magnetic polymer nanoparticles. Immuno magnetic

nanospheres can be prepared by combining two kinds of nanospheres, which could significantly improve its targeting. The popularity of these systems is due in part to the several advantages they provide for delivering their drug payload. The nano-size range of these delivery systems allows them to be injected directly into the systemic circulation without the risk of blocking blood vessels. It has been shown that the size of the nanoparticle is a major factor determining the in vivo fate of the particles.

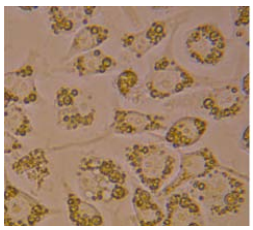

Figure 1: Raw cells engulfing PLGA Nanospheres

Researchers have demonstrated that opsonization and subsequent recognition and Phagocytosis by macrophages are strongly correlated with the size of the particle. It has been found that particles under 200 nm in diameter display a decreased rate of clearance and thus an extended circulation time as compared to those with a larger diameter. This phenomenon may be explained by the fact that smaller particles display a surface with a high radius of curvature preventing the efficient binding of opsonins. The major goal of designing the Nanospheres as a target delivery system are:-

- Control the particle size.
- Release of pharmacologically active agents to achieve the site specific action of the drug at the therapeutically optimal rate and dose regimen[12-13]

Benefits of Nanospheres drug delivery system:

- Nanospheres can easily pass through the smallest capillary vessels due to their ultra tiny volume[14-15].
- They can avoid the rapid clearance by phagocytes so that duration in bloodstream can be prolonged.
- Nanospheres can easily penetrate the cells and tissue gap to arrive at target organs eg. Liver, spleen, lungs, spinal cord, and lymph's.
- It shows the controlled release property.
- Site specific targeting by attaching the ligands to the surface of the spheres.
- They can be easily administered by various routes including oral, nasal, parenteral, etc[16].
- Reduction of toxicity is also an important advantage of Nanospheres.

Drawback of Nanospheres drug delivery system:

- Physical handling of Nanospheres is difficult in liquids and in dry form.
- Due to the smaller size and larger surface area of Nanospheres, chances of particle aggregation increases.
- Drug loading and burst release is limited due to the smaller size and larger surface area[17].

Method of preparation of Nanospheres:

There are various types of method by which Nanospheres are prepared.

- Polymerization (Emulsification polymerization)
- Solvent Evaporation.
- Solvent displacement technique.
- Phase inversion temperature methods.

Polymerization (Emulsification polymerization): In polymerization, polymeric compounds such as polymethylmethacrylate and polyethylcyanoacrylate are emulsified for emulsification polymerization and another polymerization is interfacial polymerization of polyalkylcyanoacrylate.

In the polymerization monomers are polymerized to form the Nanospheres in an aqueous solution. Basically in this technique drug is incorporated by dissolving it in the polymerization medium or by adsorption onto the Nanospheres after that polymerization is completed. After that Nanospheres are purified for removal of stabilizers and for the polymerization by centrifugation or resuspension surfactant is added in an isotonic surfactant free medium[18-19].

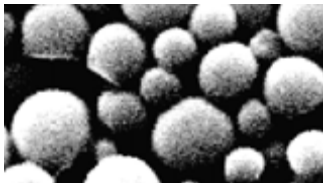

Figure 2: Magnetic PLGA Nanospheres prepared by Emulsification method

Solvent evaporation: This method is used in the formulations of nanospheres, in which the macromolecules are dissolved in the phase to be dispersed (mainly organic solvent). This process involves the removal of the organic (and volatile) solvent from the formulation and therefore polymer precipitation within the organic phase template. Removing the solvent can be performed by evaporation or diffusion shock. The main difference from the previous process appears to be the fact that not only are synthetic polymers used, but also natural macromolecules, such as chitosan, polysaccharides, alginate, gelatine etc, hence increasing their biocompatibility with the potential therapeutic objectives.

Solvent displacement technique: This method is differing from the previous section is the number of examples in the literature proposing the formulation of nanospheres by low-energy method, especially the solvent

displacement method. If the polymers such as biodegradable polyesters and their copolymers are used in the preparation of Nanospheres with the help of PEG then Nanospheres can be achieved by solvent displacement technique[20-21].

In solvent displacement technique polymer is dissolved in an organic, water miscible solvent. After that, adding it into the aqueous phase in the presence or absence of a surfactant. Addition of organic solvent from the oil phase to aqueous phase can diffuse immediately by which precipitation of polymer occurs and Nanospheres are formed.

Most nanospheres engineering using preformed polymers described in the literature, is shown to be performed by low-energy spontaneous nano-emulsification, the so-called solvent displacement method described above. The general idea is to consider the macromolecules dissolved in organic solvent (plus possibly hydrophobes, like oil), as neutral for the spontaneous nano-emulsification process. Thus, the solvent diffusion towards the aqueous phase, generating nano-emulsions causes the polymer to precipitate uniformly within the nano-emulsion template. Classical examples are the works of Fessi et al, or Leroux et al. Many different polymers and organic solvents are commonly used.

Phase inversion temperature method: In this process, desolubilization of the polymer occurs with the help of nano-emulsion droplets to formulate nanospheres. In fact, a non-volatile dispersed phase is generally used, and avoiding it does not appear physically possible. However, by substituting oil with a volatile solvent, into which the polymer has been introduced before hand, the authors established nano-emulsion followed by solvent evaporation below the PIT to generate nanospheres. To date, the literature does not provide other formulations of polymeric nanospheres using the PIT method. Likewise, in that using dissolved polymers involves the use of harmful organic solvents. The main advantage of PIT methods, that of being organic solvent is lost. There appears to be no further interest to change the phase inversion temperature method in such a way.

Nanospheres as targeted drug delivery:

There are various ways to using of Nanospheres as targeted drug delivery system.

1. Targeting on the tumor: Basically Nanospheres are able to deliver the concentrate dose of the drug to the tumor targets through permeability enhancing and retention effect or active targeting by ligands on the surface of Nanospheres. Its can reduce the toxicity by reducing the drug exposure of health tissue by limiting drug distribution to the target organ. Nanospheres have higher concentration manifested in liver, spleen, lungs than in other parts of body.

By this study Bibby, we can say that there is no doubt that Nanospheres have an effective role in the treatment of cancer. But they have a drawback which was reported that during biodistribution of drug which is incorporated into the Nanospheres mainly accumulated in liver. 56% of drug accumulated in the liver and only 1.6% of drug reaches to the tumour. Thus we can say that Nanospheres have a great tendency to be captured by liver. So it is a great challenge to avoid particles uptake by mononuclear Phagocytic system (MPS) in spleen and liver for using Nanospheres for tumour targeting. It has been proved that using doxorubicin with Nanospheres have a great effect against hepatic metastasis than free drug used[22].

2. Long circulation of Nanospheres: Basically Nanospheres are able to target tumors which are localized outside MPS (Mononuclear Phagocytic system). For long circulation of Nanospheres a major break came in the field when hydrophilic polymer (PEG, Poloxamine) is coated to the surface of Nanospheres by which opposite effect is produced to the uptake by the MPS[23-24].

The coating provides a cloud of hydrophilic and neutral chain at the particle surface which repels plasma proteins. As a result coated Nanospheres become invisible to MPS and remain for a longer duration during circulation[25-27].

3. Nanospheres for oral delivery: It is very difficult to use the bioactive molecules (peptides and proteins) with suitable carriers. These suitable carriers remain a challenge due to the fact that bioavailability of these molecules is limited and they get degraded by enzymatic action. So the polymeric Nanospheres allow encapsulation of bioactive molecules and protecting them against enzymatic degradation[28].

4. Nanospheres for drug delivery in the brain: In central nervous system the most important factor is Blood brain barrier (BBB) for the development of new drugs and it is characterized by impermeable endothelial cells with tight junction, enzyme activity and active transport systems[32]. Basically the BBB only permits selective transport of molecules. So if we use Nanospheres as targeted drug delivery it will interact with specific receptor-mediated transport system in BBB. E.g. Polysorbate 80/LDL is capable for delivery. So the drugs which cannot easily cross the BBB, can pass easily with the help of nanospheres[29-33].

There are also other drug delivery systems present for this purpose.

- Nanospheres for gene delivery
- Nanospheres targeting to epithelial cells etc.

Future prospects

Presently Nanospheres have been widely used for drug delivery, polypeptides, proteins, nucleic acid, genes etc. And now researchers focused on various parameters for the development of Nanospheres drug delivery system:

- Selection and combination of carrier materials to obtain a suitable **Drug release speed.**

- Another parameter is the **surface modification** of the Nanospheres.
- **Drug delivery capability increment** is the important parameter on which researchers are focusing**.**
- Polymeric materials is also used for the preparation of Nanospheres for drug delivery and it should be biocompatible and biodegradable.eg. Polyglycolic acid, polylactic acid etc.

CONCLUSION

By this study we can conclude that Nanospheres have great potential and they have the ability to convert poorly soluble, poorly absorbed drugs into the better deliverable drugs. Nanospheres are site specific and also protect the drug from various body fluids (enzyme action) which can degrade the drug during targeting.

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