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Nanoparticles in Protein Formulation: Challenges, Current Trends and Future Perspectives

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Abstract

Nanotechnology involves imaging, measuring, modelling and manipulating matter at dimensions ranging from 1 to 100 nanometers. They are used as a carrier for target delivery system for altering the pharmaco dynamic and pharmacokinetic properties. In Biotherapeutics applications, the proteins bio molecules whose size are at the nano scale can be used effectively in the nanoparticle system which acts as a protein delivery vehicle to increase the efficacy of proteins, reduce dose levels and improve bioavailability when compared with conventional alternatives. This paper attempts to review the different nanoparticles and state of the art technology that could be used for protein delivery while also addressing the challenges and opportunities in using these alternatives.

Keywords: Nanotechnology; Nano-emulsions; Liposomes; Polymerosomes; Hydrogel; Single protein nano capsules; Protein cages; Tunable pistons

Introduction

There's plenty of room at the bottom was the title of the lecture given by Richard Feynman to introduce the concept of Nanotechnology to the world [1]. Over the last five decades, significant progress has been made in the understanding of materials at the nano scale level. There have been many developments and improvements in formulation of drugs, however; the delivery of drugs in the required quantity at the desired target site still remains a challenge [2]. Nanoparticles are designed using methodologies that permit complete control over physicochemical attributes at the molecular scale while overcoming pharmacokinetic limitations associated with using conventional methods [2,3].

Over the last decade, number of proteins and other bio molecules that are targeted towards various cellular processes have emerged, necessitating the focus on intelligent "drug delivery carriers" that respond to various physiological stimuli [3]. These intelligent carriers at the micro and nanoscale greatly ameliorate the therapeutic efficacy of drugs because of the ability to differentiate between healthy and diseased cells thereby improving the quality of life of the patient [3]. This new class of ''intelligent therapeutics'' refers to intelligent and responsive delivery systems that are designed to perform various functions like detection, isolation and/or release of therapeutic agents for the treatment of diseased conditions. In order for these carriers to be effective, the materials of choice for nanoparticle formation either synthetic or hybrid must be designed to elicit a positive response within the biological systems at that nano scale. Materials that are responsive to physiological stimuli are also being considered for developing carriers at the nanoscale [4]. There are many challenges associated with formulation development and Figure 1 shows a schematic view of some of the barriers associated with physical, chemical and biological stability as well as activity. Nanoparticles and their use in formulation development as carriers for proteins and drugs are expected to overcome some of the challenges.

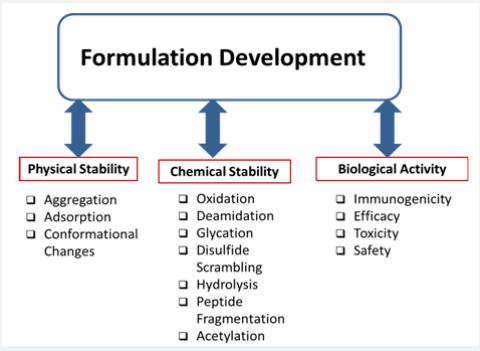

Figure 1: Schematic representation of the potential challenges encountered during Formulation Development of Biotherapeutics (Adapted from [5]).

Nanoparticles employed in protein drug delivery system

There are a number of different nanoparticle that can be used in the delivery of proteins and other bio molecules. Figure 2a shows the different nanoparticle that has been

well characterized. These include but are not limited to nanoemulsions [5-9], liposomes [10-13], polymerosomes [14-17], hydrogel nanoparticle [18-21] and single protein nanocapsules [22,23]. The methods of preparation, applications, advantages and disadvantages of these nanoparticles as carriers will be discussed in the following sections.

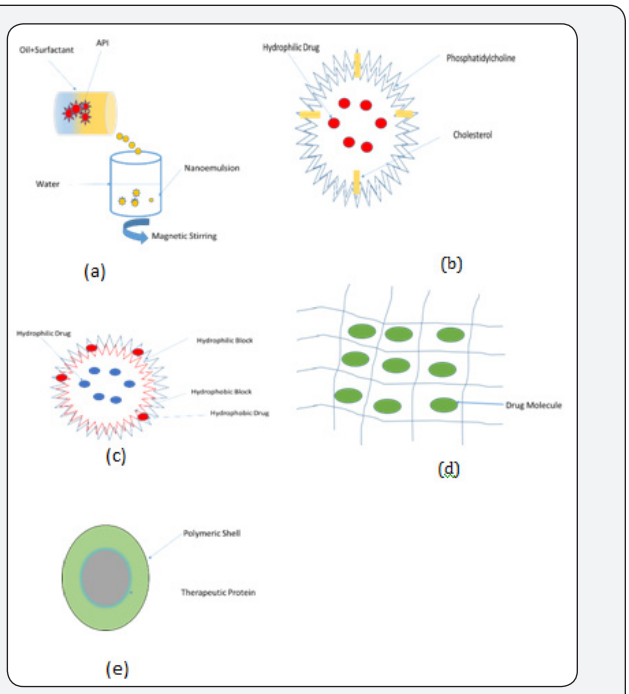

Figure 2: Nanoparticles Types. 2a: Nanoemulsion 2b: Liposomes 2c: Polymerosomes 2d: Interpenetrating hydrogel network with drug 2e: Single protein nanocapsule

Nano-emulsions

Nanoemulsions (Figure 2b) are a class of emulsions whose droplet size is between 20-500nm but typically around ~100nm. It is usually comprised of oil, water and an emulsifier. The addition of an emulsifier is crucial in reducing the size of the droplets, as it directly affects the interfacial tension [24]. The emulsifier used is generally a surfactant, but certain proteins and lipid molecules have also been effectively used in the preparation of nano emulsions [25-28].

Method of preparation: The method of preparation of nano emulsions can be classified into two broad categories; High energy and low energy methods [29-31]. High energy methods include high pressure homogenization and ultrasonication [31]. Phase Inversion temperature [32] and emulsion inversion point [33-35] are examples of low energy methods.

Applications: Nanoemulsions have applications in the food, cosmetic, pharmaceutical industries and in drug delivery. Nanoemulsions have been used in most forms of drug delivery, including topical, ocular, intravenous, internasal and oral delivery. These applications take advantage of the lipophilic nature of nano emulsions to improve the solubility of water-insoluble drugs; in addition the charge and rheology of nano emulsions to formulate aqueous solutions that allows simplified delivery of drugs [24].

Advantages and disadvantages: Advantages of nano emulsions include increased drug loading, enhanced solubility, improved bioavailability and controlled release of drug [25]. Despite these obvious advantages there are challenges associated with nano emulsions which are cost, process associated with nano emulsions preparation, and the nature of the associated interfacial chemistry is not very well understood yet [36].

Liposomes

Liposomes (Figure 2c) are spherical bilayer lipid structures whose main constituents are phospholipids [37-41]. The phospholipids are surrounded by cholesterol and other hydrophilic polymer conjugated lipids around the vesicle [37,39]. Cholesterol is an important component of the liposome because once incorporated the hydroxyl group within cholesterol is towards the aqueous phase and its tetracyclic ring is towards the membrane core [37,42]. This arrangement results in decreasing the permeability of the membrane to water-soluble molecules and improving the stability of liposomes [37,42].

Types of liposomes and their methods of preparation: Liposomes can be classified based on either their method of preparation, number of bilayer or size. However the most common classification is as multilamellar vesicles and unilamellar vesicles [37]. The method of preparation for multilamellar and unilamellar vesicles is given below.

Multilamellar vesicles (MLV): MLVs are lipid vesicles that are composed of more than two bilayer and the size of these vesicles is between 0.05 and 10μm [37]. The simplest and the most popular method for the preparation of MLVs is thin film hydration [37,43-46]. In this method, MLVs can be formed spontaneously by adding an excess volume of aqueous buffer to a thin film of dry lipids at a temperature above the phase transition temperature (PTT) of lipids [37].

Unilamellar vesicles (ULV)

ULVs can be divided into two types; large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV). LUVs are considered to be vesicles with a size >100nm [37]. The two most common methods to produce LUVs are the reverse phase evaporation technique [37,47] and the detergent removal technique [37,48]. In the reverse phase evaporation method, water in-oil emulsion composed of water and phospholipids are produced in the presence of excessive organic solvent mechanical means or by sonication. On removal of the organic solvent under vacuum, phospholipid droplets containing water are formed. These droplets coalesce to form a gel-like matrix, which is converted to a smooth paste of LUV on complete removal of organic solvent. The reported drug encapsulation efficiency for this method is 60-65%. In the detergent removal technique, micelles are formed using a combination of phospholipids and a detergent. The detergent is then removed step-wise which results in

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micelles composed mainly of phospholipids which coalesce to form single bilayer vesicles [37,48,49]. SUVs are in the size range of 25-50nm. These are produced from LUVs or multilamellar vesicles (MLV) by sonication or extrusion under high pressure [37]. Sonication can be carried out using either a probe or bath sonicator. A bath sonicator is preferred as it is easier to maintain aseptic conditions [37]. SUVs produced using sonication are usually in the size range of 25-50nm. The other method is extrusion under high pressure (20,000psi) at 4 °C. The vesicles obtained are in the size range of 15-30nm and extrusion offers better control on size compared to sonication [37].

Applications: Liposomes are primarily used in medicine and pharmacology [50]. These applications can be divided into therapeutic and diagnostic, involving the delivery of various biomarkers or drugs (therapeutic) or as a tool, model or reagent in further understanding cell-based interactions and processes [50]. The most common application of liposomes is in the delivery of anticancer drugs [37,50].

Advantages and disadvantages: Liposomes are non-toxic, biocompatible and completely biodegradable [50,51]. In addition they improve the efficacy, stability and therapeutic index of the encapsulated drug. Despite the obvious advantages there are some drawbacks associated with liposomes these include high cost, low solubility and a shorter half-life [51,52].

Polymersomes

Polymersomes Figure 2c are synthetic vesicles made of amphiphilic block copolymers [52]. In these vesicles an aqueous core is surrounded by a hydrophobic membrane [52,53]. The size of polymer somes can vary from 10nm-5µm. The thickness of the membrane can be controlled by changing the hydrophobic ratio of copolymers [52,53].

Method of preparation: The two most common methods of preparation for polymer somes are the solvent switching technique [54] and the bilayer phospholipid theory [55]. In the solvent switching technique, the organic polymer is dissolved in an organic solvent followed by the drop-wise addition of aqueous phase. The organic solvent is then removed resulting in polymer some suspensions [54]. The phospholipid bilayer theory involves the hydration of block copolymers to induce self-assembly of thin films, produced by evaporation of organic solvents which can be rehydrated using water.

Applications: Similar to liposomes, polymer somes are primarily used for therapeutic and diagnostic purposes [56]. These involve the delivery of anticancer drugs [57,58] and gene therapy from a therapeutic standpoint and intracellular tracking [56] that aids in medical diagnosis.

Advantages and disadvantages: The polymersomes are suitable for delivery of hydrophobic, hydrophilic, amphipathic drugs and multiple drug loading. They have an improved half-life, enhanced stability for encapsulated drugs and exhibit stimuli responsive release [52]. The disadvantages associated with polymer somes are high production cost and low encapsulation efficiency [59].

Hydrogel nanoparticles

Hydrogels are three dimensional polymeric networks capable of absorbing large amounts of water [60,61]. These are formed using natural polymers such as chitosan or pectin, synthetic polymers like PEG-PLGA or a combination of the two PEG-Alginate [60]. Hydrogels can be classified based on nature of side groups (neutral or ionic), mechanical and structural features method of preparation (homo- or co-polymer), physical structure and responsiveness to physiologic environment stimuli Figure 2d [61].

Methods of preparation of hydrogel and network formation: Gelation that leads to network formation can either be based on physical or chemical linkages [62]. Physical gels can further be divided into strong and weak gels. The strong gels in certain conditions may be considered as chemical gels because of the strength of the bond. Examples of strong physical gels include glassy nodules and triple helices. Weak physical gels have weak hydrogen bonds between them and are reversible Chemical gelation is a method that results in strong bonds produced using condensation, vulcanisation and polymerization [62].

Applications: Hydrogels have a variety of therapeutic applications [63]. Hydrogels have also been used in the delivery of DNA and vaccines [63].

Advantages and disadvantages: The advantages of hydrogels include safe delivery of drugs, improved transport of nutrient to cells and products from cells. It also has the advantage of being injected as a liquid that gels at body temperature. The disadvantages include that they are mechanically weak and drug-loading is difficult [63].

Single protein nano capsules

These carriers consist of a protein core with a polymeric shell attached to the core. This is a relatively new nanoparticle delivery system [64]. The choice of monomer whether neutral or cationic allows for control over surface charge of the protein. The protein core that forms the basis of the nanocapsule can be chosen from a wide variety of proteins including but not limited to enhanced green fluorescent protein (EGFP), horseradish peroxidase (HRP), bovine serum albumin (BSA), superoxide dismutase (SOD) and caspase-3 [64]. As can be seen from Figure 2e the polymeric shell surrounding the protein may be biodegradable or non-biodegradable [64].

Method of preparation: Polymerisable vinyl groups are attached to the protein through covalent linkages, further polymerization takes place when the mixture is placed in an aqueous solution containing monomers [65] and cross linkers [66]. This results in each protein core being wrapped in a polymeric shell which may be either biodegradable or non-biodegradable [64].

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Advantages and disadvantages: The single protein nanocapsule is suitable for cell internalization and provides enhanced stability for protein molecules [64]. However, it might result in the reduced protein activity.

Future trends

Apart from the nanoparticles discussed earlier there have been some new developments with regard to protein based drug delivery. Protein cages have emerged as one such example; they are hollow protein nanoparticles, such as viral capsids, virus-like particles, ferritin, heat- shock proteins and chaperonins. These nanoparticles have a defined structure and uniform size. Their protein subunits can be modified using genetic engineering [67]. Another such example is the use of si-RNA which involves the use of a hollow nano capsule, the group II chaperonin thermo some (THS) is a hollow protein nanoparticle that can encapsulate macromolecular structures.

Two large pores grant access to the protein cage. THS-Polyamidoamine (PAMAM) protects siRNA from degradation by RNase A and traffics siRNA into U87 cancer cells [68]. The use of pH as stimuli to puncture cell membranes to enable entry into the cell has also been reported [69]. The protein 'piston' consists of modified R bodies found in a bacterial endosymbiont of paramecium. These pistons go through multiple cycles of rapid extension and retraction [69].

Conclusion

The field of nanotechnology, in particular the use of nanoparticles for formulation and delivery of proteins and other bimolecular is indeed an exciting arena for biopharmaceutical companies. The recent developments in the field of drug delivery, has given the scope that one of these nanoparticles and their use as a delivery system could soon be viable option for commercialization. Two recent examples of which area PEGylated liposome for patients suffering from Kaposi's Sarcoma and a nanoemulsion of cyclosporine A used to treat dry eye syndrome have been given clinical approval in 2013 and 2015 respectively [70].

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