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Article *in* Powder and particle · January 2018

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Published online 30 September 2017
KONA Powder and Particle Journal /Doi:10.14356/kona.2018015 Review Paper

Nanoparticles Carrying Biological Molecules: Recent Advances and Applications †

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Abstract

In the past few decades, enormous advances have been achieved in the field of particle technology and the trend has been shifted from macro to micro and recently to the nanoscale. Integration of nanotechnology and biotechnology has paved the way to the development of biological nanoparticles, derived from biomolecules, and biomolecule-nanoparticle conjugates for numerous applications. This review provides an overview of various types of biological nanoparticles and the methods of their fabrication with primary emphasis on the drying methods, particularly on the newly emerging technique, the electrospraying. Recent advances in the integration of biomolecules with nanoparticles in the past five years to present are also discussed. Finally, the application of the biomolecule-nanoparticle conjugates in various fields including medicals and pharmaceuticals, biosensors and bioelectronics, foods, and agricultures are also highlighted.

Keywords: powder, particle, electrospray, biomaterial, enzyme

1. Introduction

Nanotechnology is a rapidly growing field that deals with the processing of materials with size less than 1000 nm, from the production to its applications (Jaworek A. and Sobczyk A.T., 2008). Owing to its large surface area to volume ratio, the reduction of particle size to nanoscale offers remarkable improvement in the physical, mechanical, electrical, and optical properties, that is not seen in the bulk materials (Yurteri C.U. et al., 2010). Breakthroughs in nanomaterial synthesis increased diverse nanomaterials production and subsequently their applications.

Nature had provided various types of biomolecules such as proteins, nucleic acids, lipids, and polysaccharides, which have their own unique properties that can be utilised for the development of nanoparticles (Sperling R.A. and Parak W.J., 2010). These organic based nanoparticles received little attention in the past; in comparison with inorganic based such as metals, metal oxides, ceramics and quantum dots where enormous researches and technological advancements have been made (Kumar R. and Lal S., 2014). However, in recent years, considerable interest has been shown in the utilisation of biological nanoparticles, derived from biomolecules as an alternative to the chemically synthesised nanoparticles. This is due to the need for developing biocompatible and biodegradable nanoparticles in addition to the other advantages offered including ease of availability and non-immunogenic (Sundar S. et al., 2010).

Biomolecules can also be engineered to possess unique compositions and functionalities and can be conjugated with various types of nanoparticles such as metals and metal oxides, to complement the unique properties of nanoparticles with intrinsic features of biomolecules, to yield novel biomolecule-nanoparticle hybrid. To date, many review papers are available in the literature that highlights the development and application of nanoparticles in various sectors (De M. et al., 2008, Salata O.V., 2004, Wang E.C. and Wang A.Z., 2014). However, limited reviews are available for biological nanoparticles and the integration of nanoparticles with biomolecules. Therefore, up to date information on the technology and current trend in the field is required. The present review details the types of biological nanoparticles, their methods of synthesis, the recent advances in the integration of biomolecules with nanoparticles, and the application of biomolecule-nanoparticle conjugates in medicals and

† Received 12 April 2017; Accepted 4 August 2017
J-STAGE Advance published online 30 September 2017
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pharmaceuticals, biosensors and bioelectronics, foods, and agricultures. For the context of this review, only nanoparticles derived or conjugated with biomolecules were discussed.

2. Types of biological nanoparticles

Biological nanoparticles are particles with size ranging from 10 nm to 1 μm, derived from biomolecules or organic compounds. They can be divided into four major categories which are proteins, nucleic acids, lipids and polysaccharides based (Kumar R. and Lal S., 2014).

Protein is the predecessor of the naturally occurring material used for the preparation of nanoparticle, attributed to their unique functionalities and defined primary structure. These features enable various possibilities for surface modifications and attachment of other compounds such as drugs and therapeutics (Bhunchu S. and Rojsitthisak P., 2014; Jahanshahi M. and Babaei Z., 2008). Additionally, they can be processed in the form of gels, emulsions and dried particles, have greater stability in vivo and during storage, and relatively easy to synthesise with controllable size distribution (Sundar S. et al., 2010), which allows them to be an ideal material for nanoparticles preparations. To date, wide varieties of proteins have been used for nanoparticle formulations including albumin, gelatine, elastin, collagen, gliadin, zein, ferritin (Nitta S.K. and Numata K., 2013) and silk proteins such as sericin and fibroin (Hazeri N. et al., 2012; Zhao Z. et al., 2015).

Nanoparticles can also be formulated from nucleic acids strands of DNA and RNA. These biomolecules can be engineered to form 3-dimensional nano-scaffolds due to the simplicity of their primary structure. Furthermore, nucleic acids have a unique ability to self-assemble into compact and stable structures with precise control over the nanoparticle size, geometry, and composition (Panigaj M. and Reiser J., 2016). The current research in the development of bio-based nanoparticles have shown that the DNA and RNA nanoparticles can be utilised as scaffolds and can be tagged with various types of biological and therapeutic compounds such as aptamers, fluorophores, and oligonucleotides to carry its desired function (Friedman A.D. et al., 2013; Panigaj M. and Reiser J., 2016).

Lipid based nanoparticles which include liposomes, nanoemulsions, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have emerged as a potential nanoparticulate system and have been recognised among the most promising encapsulant in the nanobiotechnology field (Tamjidi F. et al., 2013). In addition to their high encapsulation efficiency, lipid nanoparticles demonstrated longer shelf life and storage stability, hassle-free scaling up from lab to industrial scale, and ability to target and entrap compound with different solubility (Weiss J. et al., 2008).

Polysaccharides are naturally occurring carbohydrate polymers that are linked together by glycosidic bonds. They can be obtained from plants (e.g. pectin, insulin), animals (e.g. chitosan), and algae (alginates) and also from a microorganism such as a dextran. Among various types of polysaccharides, chitosan is one of the most valued polysaccharides probably due to its permeability enhancing properties. Chitosan, a cationic polyaminosaccharide, have high-density amino groups and mucoadhesive properties, allowing facile chemical modification and complexation with negatively charged molecules (Sahdev P. et al., 2014). By exploiting the charge mediated ionic interactions, a wide variety of biomolecules such as proteins (Mattu C. et al., 2013), plasmid DNA and antigens as well as bioflavonoids (Ha H.-K. et al., 2013; Hosseini S.F. et al., 2013) have been successfully incorporated into chitosan nanoparticles. The nanoparticles are commonly fabricated through ionotropic gelation and self-assembly of polyelectrolytes, a relatively simple procedure that does not require the use of organic solvents and operated in mild temperature and pressure condition (Rampino A. et al., 2013; Sahdev P. et al., 2014).

3. Methods to synthesise biological nanoparticles

Synthesis of nanoparticles derived from inorganic compounds such as metal, metal oxides and polymeric materials have been discussed deeply in a number of review papers. However, only a few reviews are available for the synthesis of biological nanoparticles. Design and synthesis of biological nanoparticles with desired properties is an important field of research in nanotechnology to allow applications of such materials in various fields which consequently give a positive impact to nature and human being. Recently, different strategies for production of nanosized materials exist and new techniques are constantly developed (**Table 1**). In biotechnology context, several criteria have to be taken into account for the selection of techniques to produce particles with controlled characteristics such as uniform size distribution, morphology, high purity, and composition. Additionally, the method should be simple, inexpensive, and have high throughput (Peltonen L. et al., 2010). In this section, general overviews of the methods to synthesise biological nanoparticles which include two steps procedures based on emulsification, a one-step procedure involving nanoprecipitation, desolvation, and gelation, and through drying methods are presented, with primary emphasis on the preparation by drying process.

Table 1 Summary of various types and methods to synthesise biological nanoparticles.

Material	Fabrication method	Particle size and characteristics	Application	Reference
BSA	Dynamic aggregation, radiation-induced cross-linking	20–40 nm	Drug carrier	Achilli E. et al. (2015)
Cruciferin	Cold gelation	~200 nm spherical, polydispersity index (PDI) of 0.2–0.3	Delivery of bioactive food components	Akbari A. and Wu J. (2016)
Chimeric polypeptide	Genetically encoded synthesis in E. Coli	60 nm, nearly monodisperse	Treatment of cancer Conjugated drug: paclitaxel	Bhattacharyya J. et al. (2015)
Fibronectin	Electrospraying	28.2–31.52 nm	Functionally active protein for tissue engineering	Fornari E. et al. (2015)
Zein	Electrospraying	175–900 nm	Encapsulant for food coloring and ingredients	Gomez-Estaca J. et al. (2012)
Fluorescent proteins	Liquid nanodispensing (NADIS)	50 nm–microns	Nanodevice (Scanning probe lithography)	Fabie L. et al. (2015)
Fibroin	Electrospraying	80 nm	Wound dressing and tissue engineering	Gholami A. et al. (2010)
Whey protein isolate (WPI)	Homogenisation-evaporation	90 nm	Delivery vehicle for beta-carotene to intestine	Yi J. et al. (2015)
Soybean protein isolate (SPI)	Homogenisation-evaporation	370 nm	Delivery vehicle for beta-carotene to intestine	Yi J. et al. (2015)
Chitosan oligosaccharide/ β-lactoglobulin	Ionic gelation	150–30 nm, Spherical	Delivery of hydrophobic bioactive compounds into aqueous foods	Ha H.-K. et al. (2013)
Bioactive peptides/chitosan	Ionic gelation	150 ± 4.3 nm, PDI = 0.05 to 0.14	Encapsulant of epigallocatechin-3-gallate (EGCG) for nanochemoprevention	Hu B. et al. (2012)
Chitosan	Ionic gelation	550–850 nm, spherical with some irregular shape particles	Protein carriers in tissue engineering	Mattu C. et al. (2013)

3.1 Two steps procedure based on emulsifications

Methods for the preparation of biological nanoparticles based on emulsification strategies have been evolved in the past decades due to the advancement in the technology and emulsification devices (Kumar R. and Lal S., 2014). The emulsion system can be in the form of oil in water (o/w), water in oil (w/o) and oil in oil (o/o), depending on the type of the dispersed phase and dispersion medium. A more complex system based on a combination of multiple emulsions has also been synthesised such as water in oil in water (w/o/w), oil in water in oil (o/w/o) and water in oil in oil (w/o/o). After generation of the emulsion nanodroplets, nanoparticles can be produced through precipitation induced by various solvent extractions mechanisms such as solvent evaporation, solvent diffusion or salting-out. Other techniques such as gelation and polymerisation can also be used for converting the emulsions to nanoparticles (Bilati U. et al., 2005; Kumar R. and Lal S., 2014).

Emulsification method offers high encapsulation efficiency and high batch-to-batch reproducibility. Furthermore, nanoparticles obtained through this method usually have narrow size distribution (Chaturvedi S.P. and Kumar V., 2012; Pal S.L. et al., 2011). The avoidance of heat treatment during the preparation step has made this method as a useful strategy for encapsulation of highly thermolabile compounds. However, the presence of residual solvent in the final dispersion is undesirable due to regulatory concern. Therefore, intensive washing procedures are required to eliminate the solvent residue (Chaturvedi S.P. and Kumar V., 2012). Moreover, the application of this method is mainly limited to lipophilic molecules. Compounds which have limited solubility in organic solvent require a subsequent addition of excess water, resulted in dilute dispersion that needs to be concentrated by means of another operation such as filtration and evaporation (Das S. and Chaudhury A., 2011). The

particles generation through emulsification have been reviewed extensively by Anton and co-workers (2008) and will not be discussed in details.

3.2 One step procedures

Nano-precipitation is a method to synthesise nanoparticles based on the interfacial deposition of polymer after displacement of a semi polar solvent (miscible with water) from a lipophilic solution. Therefore, nano-precipitation is also termed as interfacial deposition or solvent displacement methods. This method was developed by Fessi et al. in the late 1980s (Kumar R. and Lal S., 2014). Nanoparticles are formed through a quick diffusion of the polymer solvent such as acetone in the non-solvent or aqueous phase. The reduction in the interfacial tension between the two phases resulted in the increase of the surface area and momentary precipitation of nanoparticles. The process can occur in the absence or presence of mechanical stirring. This method provides a simple and rapid route for the fabrication of biological nanoparticles from natural polymers and peptides with high reproducibility, even at low concentration. However, the use of nanoprecipitation approach is often hampered by the low nanoparticle recovery yields due to the low concentration of polymer required and low entrapment efficiency for water-soluble molecules such as drugs (Bilati U. et al., 2005; Kumar R. and Lal S., 2014).

Desolvation or also known as coacervation, a technique designed by Marty et al. in 1978 is a thermodynamically driven self-assembly of proteins that occur based on the addition of desolvating agents such as salts, alcohol or solvents (e.g. acetone) in a solution of biomolecules, which separates and coacervates the molecules in the aqueous phase. In this process, electrostatic interaction plays a vital role to promote self-assembly of protein (Sundar S. et al., 2010). Variety types of proteins such as albumins (human serum albumin and bovine serum albumin), gliadin and gelatine, polysaccharide particles such as chitosan, DNA and oligonucleotides have been fabricated through this method (Allouche J., 2013). To improve the stability of the nanoparticles and prevent dissolution in water, crosslinking reaction with glutaraldehyde and carbodiimide was usually performed (Sundar S. et al., 2010).

Many proteins have gel forming properties at particular conditions of pH and temperature. These properties enable the proteins to form heat-induced gels through thermal gelation process, attributed to the protein structures (primary, secondary, tertiary and quaternary) and the surrounding conditions. Under suitable conditions, the protein molecules will denature and unfold followed by the rearrangement and aggregation into a 3-dimensional structure that finds numerous applications in food industry. For charged biomolecules such as chitosan and alginate, gelation can occur through interactions with small ions of opposite charges to form nanoclusters that can be stabilised further with the addition of oppositely charged polyelectrolytes (Allouche J., 2013; Nitta S.K. and Numata K., 2013).

3.3 Preparation by drying process

Environmental considerations have motivated researchers to find alternative methods for synthesis of nanoparticles with the elimination of the use of organic solvents (Allouche J., 2013). To achieve this goal, preparation of biological nanoparticles through drying method has been seen as a promising alternative to the conventional methods discussed above. Furthermore, dry formulation of biological nanoparticles offers further stabilisation against degradation, improves shelf life and ease of handling that often difficult to achieve in liquid formulation due to the complexity of the biological molecules (Haggag Y.A. and Faheem A.M., 2015).

Besides, nanosuspensions often need to be dried for further processing and formulation for example in the form of tablets or capsules. In this regard, drying based techniques provide a convenient and straightforward method, as dried nanoparticles can be produced directly in a single step without the need for further drying steps, and the dried particles still preserved the unique properties of the original suspension (Peltonen L. et al., 2010). There are three main strategies to produce biological nanoparticles through drying methods which are supercritical drying, spray drying and the newly emerging technique, the electrospraying method which will be discussed in details.

3.3.1 Supercritical drying

Supercritical drying involves utilisation of supercritical fluid (SCF) as a drying medium (antisolvent) which offers unique property of having the density and solvating power of a liquid but with gas-like transport properties (with respect to its viscosity and diffusivity). In most supercritical fluid processing, carbon dioxide (CO_2) is used, attributed to its low critical temperature and pressure, nontoxic, non-flammable and environmentally friendly characteristics as well as availability at low prices (Sellers S.P. et al., 2001). A number of supercritical techniques are currently available for production of submicrometer-sized and nano-sized particles.

The rapid expansion of a supercritical solution (RESS) typically uses supercritical CO_2 to form finely divided dry thermolabile drugs and pharmaceutical powders. In this technique, biological constituents are solubilised in supercritical CO_2 which subsequently decompress through a nozzle into an ambient air. This process created high supersaturation conditions that promote homogeneous

nucleation and precipitation of the biological solutes into well-dispersed particles. Despite the ability to generate nano-sized particles, the coalescence mechanism involved in the free jet promotes particle aggregation into micro-sized. Besides that, although the process can be conducted in a solvent free environment, the solubility of many pharmaceutical constituents in supercritical CO_2 is very low (Allouche J., 2013). Therefore, another supercritical technology such as solution enhanced dispersion by supercritical solution (SEDS) has been developed. In this system, co-solvents have been used to improve the solubility of the pharmaceutical compounds in CO_2 (Zhao Z. et al., 2015). This method has been used for precipitation of protein nanoparticles such as lysozyme, insulin, and rhDNase from their aqueous solution with the use of ethanol as co-solvent, yielding nanoparticles with size ranging from 100–500 nm (Chan H.K. and Kwok P.C.L., 2011; Sellers S.P. et al., 2001). Alternatively, supercritical fluid antisolvent (SAS) strategy can be applied to exploit the low solubilities of the solute compounds in supercritical CO_2 by mixing the solution with compressed CO_2 to promote crystallisation or by spraying into the compressed CO_2. Organic non-aqueous solvents such as dimethylsulfoxide that have been normally used in the SAS technique to enhance miscibility of solute with CO_2 at its recrystallisation temperature and pressure, however, compromised the environmental friendly nature of the CO_2. Thus, this method may not be favourable for biomolecules processing as it may cause conformational changes to their native structure (Tabernero A. et al., 2012; Zhao Z. et al., 2015).

3.3.2 Spray drying

Spray drying has been used since the 1980s as an alternative means of fine particles or powders production. The utilisation of this method for drying of biological compounds was started in the early 1990s when the potential of therapeutic proteins or drugs delivery through pulmonary route was discovered (Chan H.K. and Kwok P.C.L., 2011). In spray drying, a solution containing biomolecules is atomised into a plume of fine droplets which subsequently dry in a hot air to form solid particles. The dried particles finally collected via a cyclone. The spray drying technology has been evolved in the past years and many types of biological solution have been processed into nanoparticles or nanopowder through this technology particularly for food and pharmaceutical application. However, the collection yield of particles generated through the conventional spray drying method is very low, resulted from the very small size of the nanoparticles. Recently, a nano-spray dryer has been developed by BÜCHI Labortechnik AG to increase the particle recovery. In this system, tiny droplets with size much smaller than the conventional spray dryer were generated by using piezoelectric actuator. The actuator is driven at an ultrasonic frequency to provide vibrating energy to a membrane, which causes ejection of millions of nanodroplets per second. The size of the particles collected depends on various factors such as the solution properties (e.g. concentration), operating conditions (e.g. feed rate, drying temperature) and the presence or absence of surfactant (Haggag Y.A. and Faheem A.M., 2015; Lee S.H. et al., 2011). By using this innovative approach, spherical shape BSA nanoparticles with smooth surface have been successfully produced by Lee S.H. et al. (2011) from BSA solution in the presence of surfactant (Tween-80). Despite the technological advancement in the spray drying system, the applicability of such system to produce biologically active particles remain a hot debate. This is mainly due to the fragile nature of biomolecules when subjected to hot drying air during the process which may lead to aggregation and loss of biological activity (Mehta P. et al., 2016). The inclusion of surfactant or disaccharide to the heat-sensitive materials such as proteins, peptides and enzymes can help to minimise these effects (Lee S.H. et al., 2011).

3.3.3 Electrospraying

Electrospraying is an electrohydrodynamic atomisation of liquid into uniform sized droplets under the influenced of electrical forces. The phenomenon of the interaction of liquid with electric field was first reported by William Gilbert in the sixteenth century who discovered that a water droplet transformed into conical shape when a piece of amber was held close to it (Yurteri C.U. et al., 2010). The first attempt to use electrospraying for the production of protein nanoparticles was demonstrated by Gomez A. et al. (1998). Insulin was used as a model protein to study the feasibility of electrospraying to produce monodispersed protein particles with preserved biological activity. In their work, the electrospraying was conducted in Taylor cone jet mode with controlled current and flowrate of 64–100 nA and 0.17–0.38 µL/min, respectively. The size of the produced insulin particles was in the range of 98–117 nm with a doughnut shape. The analysis of receptor binding properties of the electrosprayed insulin and the control insulin showed identical results, which proved that biological activity of insulin is preserved upon electrospraying. With these findings, researches involving the generation of active particles of biomolecules using the electrospraying method have emerged rapidly, especially for drug delivery application.

Besides the ability to preserve the bioactive properties of the biomolecules, the emerging utilisation of the electrospraying method is also attributed to the other unique advantages offered; the production of monodisperse particles in cone-jet mode which is often difficult to be achieved by the other particle synthesis methods, a reduction in the number of molecular aggregates due to the co-

alescences of droplets with the same polarity, a reduction in the risk of product contamination, can be operated in ambient conditions, cost effectiveness and simple operation. In view of these advantages, a few types of biologically active substances including DNA (Lee Y.-H. et al., 2011), proteins such as sericin (Hazeri N. et al., 2012), fibroin (Gholami A. et al., 2010), cytochrome c (Mortensen D.N. and Williams E.R., 2015), and α-lactalbumin (α-LA) (Uematsu I. et al., 2004), enzymes such as alkaline phosphatase (ALP) (Avseenko N.V. et al., 2001) and peptide such as α-cyano-4-hydroxycinnamic acid (Wei H. et al., 2004) have been successfully electrosprayed with preserved biological activity.

Basic electrospraying setup, which consists of a high voltage supply, metal capillary, and grounded collector, and the mechanism of particle generation, is shown in **Fig. 1**. The four major processes involved in electrospraying are; 1) generation of charged droplets, 2) shrinkage of the droplets due to removal or evaporation of solvent, 3) continual disintegration of the droplets to form dry particles, and finally, 4) collection or deposition of the particles (Lenggoro I.W. et al., 2002; Naim M.N. et al., 2010).

In electrospraying, the particle size and shape can be controlled by controlling the solution properties such as conductivity and surface tension and also the electrospraying parameters which include spraying voltage, flowrate and distance of the needle tip to the collector. In our group, the electrospraying technique was used to produce cyclodextrin glucanotransferase (CGTase) nanoparticles from its aqueous suspension. It was found that by conducting the electrospraying in cone jet mode and changing the needle tip to collector distance from 10 to 25 cm, nanoparticles with narrow size distribution can be obtained and the average particle size was reduced significantly from 201 to 75 nm. The reduction in the particle size has been shown to improve the CGTase catalytic performance (Saallah S. et al., 2014).

4. Integrated biomolecule-nanoparticle systems

Biomolecules exhibit nanoscale dimensions comparable to the dimensions of nanoparticles (**Fig. 2**). Revolutionary of nanotechnology and biotechnology have paved the way to complement these size similarities and intrinsic features of biomolecules with unique properties of nanoparticles to yield novel biomolecule-nanoparticle hybrid of synergistic characteristics and functions (Sperling R.A. and Parak W.J., 2010). Biomolecules also display several fundamental features that can be utilised as future building blocks for nanoparticle architecture. For example, the nature-evolved multiple binding sites of biomolecules in addition with its catalytic properties could facilitate the development of multifunctional nanoparticles (Katz E. and Willner I., 2004). Recently, substantial research efforts were directed towards developing and extending the applications of biomolecules by integrating the biomolecules with biological nanoparticles such as polysaccharides and lipids (Liao W. et al., 2016; Rassu G. et al., 2015) and other types of nanoparticles including metals (Chinen A.B. et al., 2015; Politi J. et al., 2015), metal oxides (Cao Y. et al., 2016; Shahrestani H. et al., 2016) and polymers (Cavalli R. et al., 2011; Lin T.-T. et al., 2016) through various conjugation strategies (**Table 2**).

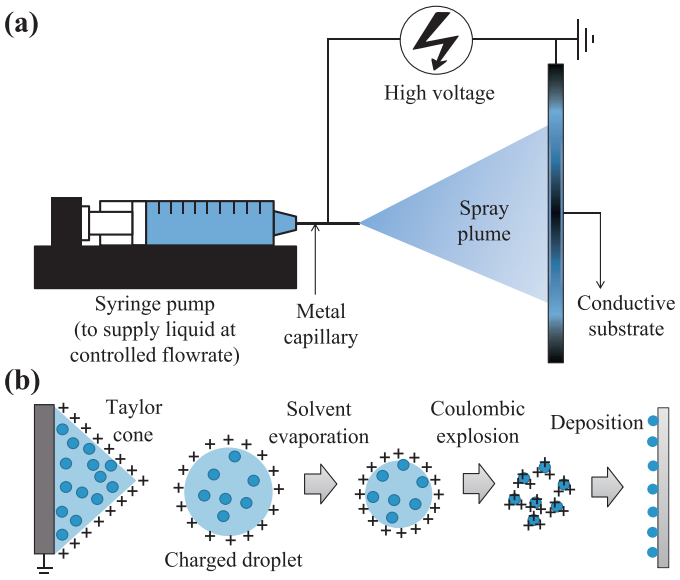

Fig. 1 (**a**) Basic electrospraying setup and (**b**) Electrospraying mechanism.

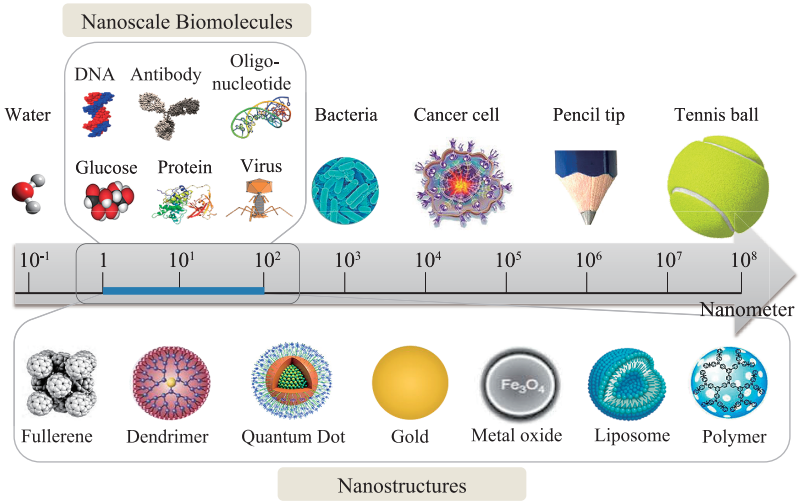

Fig. 2 Nanoscale integration of nanoparticles and biomolecules.

4.1 Strategies for the development of biomolecule-nanoparticle conjugates

4.1.1 Functionalisation of nanoparticles with biomolecules through non-covalent interactions

Non-covalent biofunctionalisation is a physical conjugation strategy that can be realised through electrostatic, hydrophobic and affinity interactions (**Fig. 3**) (Yu M.K. et al., 2012). Electrostatic adsorption is useful for the assembly of biomolecules to nanoparticles that are stabilised by anionic ligands such as lipoic acid and citrate in which the interaction of nanoparticles and the biomolecules rely on the opposite charged of both materials (Niemeyer C.M., 2001). Biological nanoparticles can be engineered to have a specific charge to enable interaction with biomolecules. The recent example is the utilisation of cationic lipid nanoparticles modified with a supercharged coiled-coil protein having positively charged arginine residues to facilitate interaction with the negatively charged SiRNA (Rabbani P.S. et al., 2017). Another example is the development of a self-assembled nanocomplex based on fucoidan, a sulphated marine polysaccharide and protamine, a strongly basic protein by utilising the electrostatic interaction between the oppositely charged polysaccharide and protein (Lu K.Y. et al., 2017). The non-covalent electrostatic complexes between proteins and polysaccharides can potentially enhance the functional properties by the synergistic combination of functional properties of both materials, compared to the single biological nanoparticle system (Hosseini S.M.H. et al., 2015).

In some cases, the strong electrostatic interaction between the charged biomolecules and its host is not always preferred. As observed by Lebre F. et al. (2016), the strong binding between positively charged chitosan and negatively charged DNA resulted in low transfection efficiency in vivo. To encounter this issue, the electrostatic interactions between the cationic chitosan nanoparticles with the anionic DNA were modified by attaching anionic human serum albumin onto the chitosan nanoparticles surface. This system enabled the intracellular release of DNA, thus enhancing the transfection efficiency.

The role of electrostatic interactions in adsorption of protein onto inorganic nanoparticles such as silica and metal oxides has been well described in many studies (Meissner J. et al., 2015). For instance, immobilisation of lysozyme and β-lactoglobulin, a globular protein onto negatively charged silica nanoparticles and binding of bovine serum albumin and β-lactoglobulin to cationic gold nanoparticle functionalised with 3,6,9,12-tetraoxatricosan1-1-aminium, 23-mercapto-*N*,*N*,*N*-trimethyl, under different pH and ionic conditions (Chen K. et al., 2011; Meissner J. et al., 2015). Generally, the maximum adsorption occurs at the protein isoelectric point. This is due to the minimum repulsion between the adsorbed protein molecules at its isoelectric point which allow them to make a closer packing at the particle surface.

Although extensive investigation on the interactions of biomolecules such as amino acids, proteins, and peptides with silica nanoparticles have shown that binding of biomolecules to silica nanoparticle is mainly driven by electrostatic interaction, Puddu V. and Perry C.C. (2012) found that hydrophobic interactions were responsible for the recognition and adsorption of peptide sequence of different charge on silica at various pH conditions. They also showed that it is possible to modulate the uptake of biomolecules on nanoparticles by tuning the surface properties and binding environments such as the biomolecules bulk concentration and pH. Bioconjugation of silica with peptide sequence having hydrophobic character is favoured when the surface charge of silica is close to its point of zero charge (more hydrophobic) (Puddu V. and Perry C.C.,

Table 2 Summary of integrated biomolecule-nanoparticle systems.

Biomolecule	Nanoparticle	Fabrication method	Conjugation strategy	Application	References
(i) Organic-organic nanoparticle conjugates					
BSA	Tripolyphosphate-crosslinked chitosan	Ionic gelation	Electrostatic interaction, encapsulation	Sustained release of protein	Mattu C. et al. (2013)
Propolis	Lipid	High shear homogenisation	Entrapment	Nasal drug delivery	Rassu G. et al. (2015)
D. indusiata polysaccharide	Selenium	Redox reaction	Encapsulation	Anticancer treatment	Liao W. et al. (2016)
Curcumin	O-carboxymethyl chitosan/fucoidan	Ionic gelation	Crosslinking	Oral delivery system	Huang Y.C. and Kuo T.H. (2014)
Quercetin	Chitosan oligosaccharide/ β-lactoglobulin	Ionic gelation	Covalent	Encapsulation of bioactives	Ha H.-K. et al. (2013)
Curcumin	Zein–pectin/ alginate	Electrostatic deposition	Electrostatic interaction, encapsulation	Functional foods and beverages	Hu K. et al. (2015)
Beta-carotene	Whey protein concentrate	Electrospraying	Encapsulation	Encapsulation of bioactives	López-Rubio A. and Lagaron J.M. (2012)
Anthocyanin-rich extract	Whey protein isolate/beet pectin	Thermal processing	Electrostatic complexation	Encapsulation of natural colorants and food nutraceuticals	Arroyo-Maya I.J. and McClements D.J. (2015)
(–)-epigallocatechin-3-gallate	Peptide/chitosan	Ionic interaction, hydrophobic association	Encapsulation	Nano-chemoprevention	Hu B. et al. (2012)
(ii) Biomolecule-polymeric nanoparticle conjugates					
BSA	PLGA	Co-axial electrospraying	Encaspulation	Drug delivery	Zamani M. et al. (2014)
BSA	HPMA/Ac-DAP-Boc	One-pot synthesis	Encaspulation	Delivery of platinum drugs into cancerous cells	Dag A. et al. (2015)
Cholestrol	Polyamidoamines	Electrospraying	Covalent	Tamoxifen delivery	Cavalli R. et al. (2011)
Chitosan	Polylactic acid/ nifedipine	Emulsion	Encapsulation	Treatment of angina pectorice and hypertension	Chinh N.T. et al. (2016)
Serum albumin	PCL/PLGA	Electrospraying	Encapsulation	Delivery of therapeutics	Bock N. et al. (2014)
Sorafenib	PEG-PLGA/PLGA co-polymer	O/W emulsion	Encapsulation	Systemic treatment of liver fibrosis	Huang X. et al. (2016)
Cisplatin	PCL-block-PEG-diblock copolymer	Dialysis, lyophilisation	Encapsulation	Treatment of glutathione over-expressed breast cancer cells	Surnar B. et al. (2015)
(iii) Organic-inorganic nanoparticle conjugates					
Lysozyme and β-lactoglobulin	Silica	—	Electrostatic interaction	Not specifically mentioned	Meissner J. et al. (2015)
Hydrophobin Vmh2	AuNP	One pot synthesis	Covalent	Biomedical	Politi J. et al. (2015)

Chitosan/Collagen	Bioactive glass	Sol-gel/freeze drying	Non-covalent	Injectable scaffolds in bone and cartilage repair	Moreira C.D.F. et al. (2016)
Spherical nucleic acid	AuNP	—	Covalent	Cellular uptake	Chinen A.B. et al. (2015)
DNA	Magnesium phosphate	Water-in-oil emulsion	Entrapment	DNA vaccine formulation	Bhakta G. et al. (2014)
Mussel adhesive proteins	Iron(III)–3,4-dihydroxyphenylalanine (DOPA)	Electrospraying	Crosslinking	pH-responsive drug delivery Model drug: Doxorubicin	Kim B.J. et al. (2015)
Plasmid DNA	Calcium phosphate	Precipitation	Encapsulation	Stem cell uptake and gene transfer	Cao X. et al. (2011)
Pepsin	AuNP	Chemical reduction	Covalent-amide coupling	Analytical sample preparation	Höldrich M. et al. (2016)
α-amylase, pectinase, cellulose	Fe_3O_4	Co-precipitation	GA crosslinking	Clarification of fruit juices	Sojitra U.V. et al. (2016)
(iv) Biomolecule-hybrid nanoparticle conjugates					
BSA	Ampiphilic polymer coated hydrophobic silver nanoparticle	Chemical precipitation	Physisorption	To study protein-nanoparticle interaction	Guo J. et al. (2015)
Lipase	Hydroxyapatite-encapsulated-c-Fe_2O_3	Chemical precipitation	EncapsulationCovalent	Interesterification of soybean oil	Xie W. and Zang X. (2016)
Curcumin	Albumin–polycaprolactone	Ring opening polymerisation	Covalent	Drug delivery system for prostate carcinoma therapeutics	Jiang Y. et al. (2016)
Xylanase	Fe_3O_4/SiO_2	Co-precipitation	Covalent	Enzymatic clarification of fruit juices	Shahrestani H. et al. (2016)
Organic fluorescent dye	$PVP/SiO_2/Fe_3O_4$	Co-precipitation, polymerization, sol–gel	Encapsulation Electrostatic interaction	Biomedical, analytical and catalytic application	Viswanathan K. (2011)
Glucose oxidase	Fe_3O_4/Polypyrrol	Co-precipitation	Encapsulation	Potentiomeric glucose biosensor	Yang Z. et al. (2014)
Trypsin	$AuNP/Fe_3O_4$	Solvothermal reaction	Covalent	Enzymatic digestion of proteins to peptides	Cao Y. et al. (2016)
Aptamers	$AgNP/Fe_3O_4$	Redox reaction	Streptavidin-biotin affinity binding	Detection of *Staphylococcus aureus*	Abbaspour A. et al. (2015)
v) Self-assembled biomolecule-nanoparticle hybrid					
BSA	Copper(II) phosphate	Self-assembly	—	Decomposition of organic dyes in wastewater treatment	Huang Y. et al. (2015)
α-lactalbumin, laccase, carbonic anhydrase and lipase	Copper(II) phosphate	Self-assembly	—	Bionsensors	Ge J. et al. (2012)
Sericin	Copper(II) phosphate	Self-assembly	—	Adsorption of heavy metal ions	Koley P. et al. (2016)

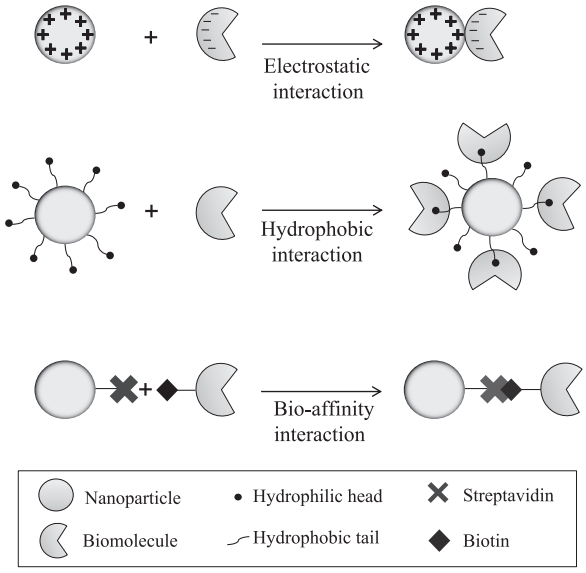

Fig. 3 Non-covalent functionalisation of nanoparticles with biomolecules.

2012). Hydrophobic interaction can also be utilised to allow binding of biomolecules with protein nanoparticles having hydrophobic properties such as gliadin as reported by Joye I.J. et al. (2015). Through fluorescence quenching and thermodynamic analysis, they found that binding of gliadin nanoparticles and resveratrol, a polyphenol extracted from a grape skin is predominantly mediated by hydrophobic interactions rather than hydrogen bonding.

Both of the electrostatic and hydrophobic interactions requires fewer modification steps, thus provide a simple and rapid route for Biofuntionalisation of nanoparticles. However, molecular orientations of the physically bound biomolecules are difficult to control. By introducing specific functional groups on the nanoparticles such as avidin, biomolecules can bound onto the nanoparticles more effectively through affinity interactions (Zhang Y. et al., 2012). Avidin is a glycoprotein composed of four identical subunits which have high specificity and affinity towards biotin, resulted in a strong affinity interaction. Despite these advantages, avidin possesses several drawbacks including a high degree of non-specific binding in vivo attributed to its basic isoelectric point and glycosylation, and the high possibility of immunogenicity. Moreover, the strong avidin-biotin interaction might hinder the release of tagged biomolecules from the biotin or avidin. To overcome these issues, extensive research effort has been devoted to develop new variants of avidin from different sources or through genetic modification (Jain A. and Cheng K., 2017).

Streptavidin, a non-glycosylated tetrameric protein, is the most widely used avidin analogue. Biotinylated proteins such as immunoglobulins and bovine serum albumin, oligonucleotides and single strand DNA have been bound onto streptavidin functionalised nanoparticles such as silver and gold (Tauran Y. et al., 2013). By utilising an electric-field-directed self-assembly method, Hsiao A.P. and Heller M.J. (2012) have successfully developed a multilayer structures glucose sensor composed of glucose oxidase, horseradish peroxidase and alkaline phosphatase enzymes conjugated with streptavidin/avidin-biotin nanoparticles through affinity interaction. The catalytic activity of the enzymes was preserved after the assembly, suggesting that the process employed did not have an adverse effect on the enzyme. Affinity interactions can also be achieved through antibody-antigen binding to allow assembly of NP-antibody conjugate with its respective antigen which is beneficial to increase the NP-antibody-antigen association constant, with respect to the free antibody (Katz E. and Willner I., 2004).

4.1.2 Functionalisation of nanoparticles with biomolecules through covalent interactions

Conjugation of biomolecules with nanoparticles via covalent interactions can be achieved by means of chemisorption of the biomolecules on the particle surface or through the use of a bifunctional linker (De M. et al., 2008). Chemisorption is a simple chemical reaction that occurs between thiol group of biomolecules and the nanoparticles through cysteine residues that are present on the surface of the biomolecules (**Fig. 4a**). If no thiolated residues available in the native biomolecules, the thiol group can be introduced chemically onto the outer part of biomolecules using Traut`s reagent (2-aminothiolane) to allow biomolecules-NP interaction (**Fig. 4b**) (De M. et al., 2008; Zhang Y. et al., 2012). The noble metal nanoparticle, particularly gold (Au) nanoparticle is highly reactive toward thiol group, thus forming a superior Au-S bond. The strong binding affinity of Au towards thiols has been exploited for conjugation of biomolecules such as DNA, peptides, antibodies, and proteins onto the nanoparticle surface (Katz E. and Willner I., 2004; Spampinato V. et al., 2016; Yu M.K. et al., 2012). Conjugation of maltose binding protein (MBP) to gold nanoparticles funtionalised with thiol-modified glucose (TG) self-assembled monolayers has been studied by Spampinato V. et al. (2016).

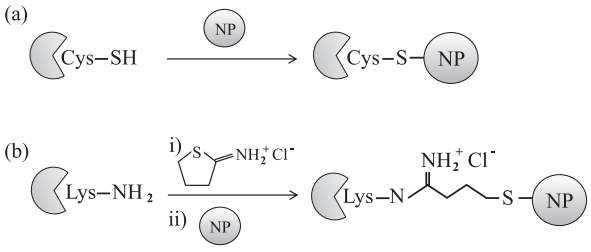

Fig. 4 Covalent functionalisation of nanoparticles through **a)** Cysteine residue; **b)** Addition of Traut's reagent.

Surface chemistry analysis of the gold nanoparticles before and after functionalisation and interaction with TG and MBP revealed that the reaction of the thiolated gold nanoparticles with MBP occurred with specific amino acid residues exist in the protein binding pocket. In another study, Mejias S.H. et al. (2016) have demonstrated the successful assembly of an idealised protein building block, the consensus tetratricopeptide repeat (CTPR) into the nanoparticle surface through thiol chemisorption of the protein cysteine residues. As a comparison, adsorption of CTPR without cysteine residues on the gold surface was also carried out. They found that direct adsorption of CTPR having cysteine residues occurs through a single-point interaction of the thiol-derivative protein on the gold surface while the adsorption of CTPR with no cysteine residues proceeds through unspecific multipoint attachment of the protein.

Covalent binding through bifunctional linkers provide a versatile means for biomolecules conjugation. Low molecular weight bifunctional linkers which have anchor groups such as thiols, disulfides and phosphine ligands containing terminal carboxy, amino or maleimide groups are commonly used to bind biomolecules to the nanoparticles such as Au, CdS, ZnS, CdSe/ZnS and Ag. These anchor groups can be utilised to replace weakly adsorbed molecules for the nanoparticles stabilisation. Besides, during the synthesis stage of the nanoparticles, the anchor groups can be introduced to functionalise the nanoparticles surface for further reactions. Coupling of biological components to the ligands occur via carbodiimide- mediated amidation and esterification, or through reaction with thiol groups (De M. et al., 2008; Niemeyer C.M., 2001). For the oxide nanoparticles such as SiO_2, alkoxy- or halosilane groups are commonly used to covalently bind the linkers to the nanoparticles (Katz E. and Willner I., 2004). In other research done by Mejias S.H. et al. (2016), gold nanoparticles were attached to the immobilised CTPR having cysteine residues via the formation of a covalent amide linkage between the terminal amine of the protein and the carboxylate groups of the gold nanoparticles, resulting in the formation of an ordered monolayer of CTRP that can be applied in the controlled patterning of gold nanoparticles.

4.1.3 Encapsulation of biomolecules in polymeric materials

Polymeric nanoparticles are solid particles that have been used extensively as carriers for biomolecules attributed to their unique properties such as can be copolymerised, easy to synthesise and the polymer surface can be modified for biomolecules conjugation (Menon J.U. et al., 2014).. They can be fabricated in the form of nanospheres and nanocapsules (**Fig. 5**). The entire mass of the nanospheres composed of a solid polymer and the biomolecules can be attached to the surface or encapsulated within the particle while the nanocapsules are designed in such a way that the biomolecules are confined inside a core-shell structure (Rao J.P. and Geckeler K.E., 2011; Wang E.C. and Wang A.Z., 2014). In some cases, the bioactive substances can also be adsorbed on the surface of the capsule (Jawahar N. and Meyyanathan S., 2012).

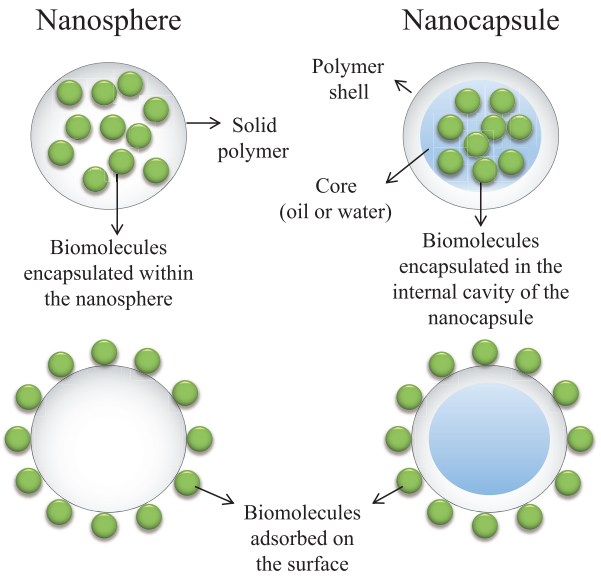

Fig. 5 Different modes of interaction of biomolecules with polymeric nanosphere and nanocapsule.

Encapsulation is a rapidly growing technology with diverse potential applications particularly in pharmaceutical and food industries. The major advantage of the encapsulation strategy is the protection of biomolecules against denaturing environment which might cause undesirable conformational changes to the biomolecules native structure and function. Moreover, encapsulation allows controlled release of biomolecules at the targeted sites. Techniques for nanoencapsulation of food and bioactive compounds have been reviewed comprehensively by Ezhilarasi P.N. et al. (2013).

4.2 Recent advances in the integration of biomolecules with nanoparticles

4.2.1 Organic-organic nanoparticle conjugates

Biological nanoparticles form part of many industrial products, particularly in food, pharmaceutical, and cosmetic industries. One of the most important features of biological nanoparticles is that they offer relatively simple means for encapsulation of biomolecules, resulting in the formation of organic-organic nanoparticle complexes. For instance, encapsulation of β-carotene into whey protein concentrate (WPC) was achieved by means of electrospraying from aqueous solutions of β-carotene/WPC mixture at various pH conditions, resulting in a formation

of nanocapsule with high encapsulation efficiency and stability against photo-oxidation (López-Rubio A. and Lagaron J.M., 2012).

Biological nanoparticles derived from a single component of biomolecule have been widely used as cancer chemo-preventive and therapeutic agents. However, the single component biological nanoparticle system might possess a lack of stability and potential toxicity in a cellular system. These challenges can be potentially solved by conjugation of biomolecules with biological nanoparticle through strategic functionalisation. Liao W. et al. (2016) reported that selenium nanoparticles functionalised with a *Dictyophora indusiata* polysaccharide formed monodispersed nanoparticles with high stability attributed to the high electrostatic repulsion between hydrophilic moieties on the surface of the polysaccharide in comparison with the bare selenium. Moreover, the nanoparticle conjugate exhibited enhanced selectivity and antiproliferative activity by inducing cell apoptosis.

Strategies of mixing of two or more biological components to yield hybrid biological nanoparticles have also been reported by several researchers for encapsulation of biomolecules and bioactives such as curcumin (Huang Y.C. and Kuo T.H., 2014), quercetin (Ha H.-K. et al., 2013) and (–)-epigallocatechin-3-gallate (Hu B. et al., 2012) into chitosan based nanoparticles. This is due to the fact that nanoparticles formulated from bare chitosan is unstable and can be easily dissociated at low pH which potentially leads to the release of the encapsulated biomolecules. By mixing the chitosan with other biological compounds such as fucoidan, β-lactoglobulin, and peptide, hybrid nanoparticles with remarkable improvement in stability, encapsulation efficiency and functional properties were obtained (Ha H.-K. et al., 2013; Hu B. et al., 2012; Huang Y.C. and Kuo T.H., 2014).

Recently, considerable interests have been shown to utilise hydrophobic protein nanoparticles such as zein for encapsulation of lipophilic compounds such as curcumin. However, zein nanoparticles have poor stability against the changes in environmental conditions such as pH and temperature. Coating the protein nanoparticle with polysaccharide molecules allow the modulation of an electrostatic interaction and steric repulsion between the particles, thus improving the nanoparticle stability. The recent example is the development of zein-pectin/alginate nanoparticle for encapsulation of curcumin as reported by Huang X. et al. (2016). The curcumin loaded core-shell nanoparticles show enhanced water dispersibility and antioxidant activity.

4.2.2 Biomolecule-polymer nanoparticle conjugates

A great deal of effort has now been focused on designing biomolecule-polymer nanoparticle conjugates with unprecedented properties, driven by the vast development of novel bio-conjugation and polymerisation techniques. Various type of polymeric materials have been investigated either as support or carrier matrix for biological compounds which include poly (ethylene glycol) (PEG), poly (lactic acid) (PLA), polyglycolides (PGA), poly (lactide-co-glycolides) (PLGA), polycaprolactone (PCL) and poly(hydroxy butyrate) (PHB) (Panta P. et al., 2014; Sapsford K.E. et al., 2013). These polymers are mostly biocompatible and biodegradable and may have other useful properties such as stimulus-responsive function and good mechanical strength that can be utilised for fabrication of various types of biomolecule-polymer conjugates (Wang E.C. and Wang A.Z., 2014).

Conjugation of polymer with protein such as albumin has been widely explored for drug delivery applications. The resulting nanoparticles usually have a biocompatible and bioactive albumin shell while the core is rich in a hydrophobic polymer that can entrap drugs. This strategy can aid the delivery of drugs and targeting the cancer cells. Protein-polymer nanoparticles conjugate consisted of FDA approved thermoplastic hydrophobic polymer of poly-methyl methacrylate (PMMA) and bovine serum albumin (BSA) have been successfully synthesised by Ge J. et al. (2011) for application in drug delivery. This hybrid nanoparticle with spherical structure and an average size of 100 nm were fabricated by using nanoprecipitation method. The size and surface charge can be tuned by controlling the weight ratio and concentration of both the BSA and PMMA. Encapsulation of hydrophobic drug, a camptothecin in the BSA-PMMA nanoparticles showed efficient cell uptake and enhanced antitumor activity. Since PMMA is a nondegradable polymer, Jiang Y. et al. (2016) prepared a curcumin loaded albumin-polymer nanoparticle from a biodegradable polymer of polycaprolactone (PCL) and the performance of this nanoparticle was compared with PMMA for prostate carcinoma therapy. The fully degradable PCL-based nanoparticles can deliver the drug more efficiently in comparison with the PMMA-based nanoparticles and effectively limits the tumor growth.

Other work on the synthesis of a protein-polymer hybrid was done by (Dag A. et al., 2015) to enhance the delivery of macromolecular platinum drugs into cancer cells. The polymer was prepared by copolymerization of N-(2-hydroxypropyl) methacrylamide (HPMA) and Boc protected 1,3-diaminopropan-2-yl acrylate (Ac-DAP-Boc), yielded a P(HPMA 14-co-(Ac-DAP-Boc), which was used as a macromolecular ligand for the conjugation of the platinum drug. After activation, the polymer-drug was further conjugated with albumin by exploiting the Cys34 functionality. This albumin-coated nanoparticle shows superior toxicity to the cancer cell in comparison with the polymer nanoparticles without protein coating.

A special form of polymeric nanomaterial, a dendrimer,

is a cationic polymer with well-defined molecular shape and unique architecture. This type of polymer has high water solubility and a large number of surface groups which make them as a versatile nanostructure. Conjugation of protein to dendrimer has been reported by Chanphai P. et al. (2016). Polyamidoamines (PAMAM) dendrimers were conjugated with trypsin from bovine pancreas and trypsin inhibitor from glycine. Stable bindings of the PAMAM dendrimers with both proteins occur through hydrophilic and hydrogen bonding as well as Van der Waals interaction, suggesting that this hybrid system could be used further enzymatic catalysis study. Besides that, the PAMAM dendrimers have been studied previously by Menjoge A.R. et al. (2011) for the delivery of drug to pregnant women, without affecting the fetus by intercepting the drug so that it cannot pass through the fetal membrane.

4.2.3 Organic-inorganic nanoparticle conjugates

Considering the versatile physicochemical properties of inorganic nanoparticles including wide availability and rich functionality, in combination with their unique optical, electronic, and catalytic properties, conjugation of biological molecules and inorganic nanoparticles have opened a new route in the development of advanced functional materials with significantly enhanced features and broad applications. Various inorganic nanoparticles including metals, metal oxides, and quantum dots have been prepared by various synthetic procedures and hybridised or immobilised with biomolecules such as DNA, enzymes, and antibodies either through covalent or non-covalent interactions that have been discussed previously.

Gold nanoparticles (AuNPs) represent one type of metal nanoparticles that found numerous applications in imaging, sensing, and nanomedicine. The utilisation of biomolecules to tune the surface chemistry and the assembly of AuNPs is a very attractive approach for the development of next generation nanometric complexes. Politi J. et al. (2015) have shown that hybridisation of a fungal protein, namely hyrophobin (HFB) Vmh2 with AuNPs can be achieved via a simple one step chemical reduction process, yielding a highly stable HFB-AuNPs that can interact well with a model protein of BSA and immunoglobulins. The addition of dicarboxylic acid-terminated polyethylene-glycol (PEG) during the synthesis process produced hybrid complexes with outer surface rich in functional chemical groups that can be tailored for attachments of various compounds.

Integration of enzymes with inorganic nanoparticles has shown to have a remarkable effect on the enzyme catalytic performance. This is attributed to the extremely small size of the nano scale material and their unique surface chemistry (Ding S. et al., 2015). For example, covalently bound pepsin on gold nanoparticles via amide coupling has produced efficient biocatalyst with sufficiently high stability for application in analysis of therapeutic proteins and peptides (Höldrich M. et al., 2016).

Recently, multi-enzyme catalysis was developed by Sojitra U.V. et al. (2016) by covalently bind three types of enzymes (alpha-amylase, pectinase and cellulase) on amino functionalised magnetic nanoparticles for clarification of fruit juices. The tri-enzyme magnetic nanobiocatalyst allows rapid reduction of the fruit juices turbidity, in comparison with the individual enzyme system. Another multienzyme-nanoparticle complex was constructed by Honda T. et al. (2015) by using magnetosome display system to prepare a system that can mimick natural cellulosomes on magnetic nanoparticle. As a proof of concept, two types of fluorescent proteins which are the green fluorescent and mCherry were initially immobilised on the MNPs. These proteins showed a close proximity on the magnetic nanoparticles. Later, endoglucanase (EG) and β-glucosidase (BG) were immobilised on the magnetic nanoparticles to promote rapid hydrolysis of carboxymethyl cellulose.

4.2.4 Biomolecule-hybrid nanoparticle conjugates

Hybrid nanocarrier can be prepared by mixing two or more components such as magnetic and metal nanoparticles. By using this strategy, properties of both materials can be merged and enhanced. As recently being reported by Cao Y. et al. (2016), a magnetic iron oxide nanoparticles were coated with a layer of gold nanoparticles and used for trypsin immobilisation. This system provides a robust carrier for the enzyme. Moreover, the magnetic feature facilitated separation from the reaction media and enabled repeated usage of the enzyme. Magnetic nanoparticles can also be designed in a form of core-shell structure by conjugation with other materials such as hydroxyapatite (Xie W. and Zang X., 2016), silica (Shahrestani H. et al., 2016) and polypyrrol (Yang Z. et al., 2014) for the development of novel composites support for enzyme immobilisation.

A sandwich hybrid nanoparticle has been designed by Abbaspour A. et al. (2015) by immobilising a biotinylated primary aptamer on capture probe of a streptavidin coated magnetic nanoparticle. A secondary aptamer was coupled to a silver nanoparticle (AgNP) for the target detection. In the presence of target bacterium (*S. aureus*), a sandwich complex of Apt/*S.aureus*/Apt-AgNP is formed on the magnetic nanoparticle surface, giving an electrochemical signal. This sandwich system combined the unique features of magnetic nanoparticles as a carrier of affinity ligands for solution-phase recognition, a hassle free magnetic separation and highly sensitive signal amplification by AgNP.

Hybrid nanoparticles based on polymeric materials conjugated with protein have also been reported. In the

study done by Jiang Y. et al. (2016), bovine serum albumin (BSA) was utilised as a hydrophilic moiety of the hydrophobic maleimide-terminated polycaprolactone nanoparticles to improve the biodegradability and biocompatibility of the polymer nanoparticle for encapsulation of curcumin.

4.2.5 Self-assembled biomolecule-nanoparticle conjugates

Self-assembly is an advanced technology that is capable of integrating different components together spontaneously for the fabrication of the desired hybrid materials. Proteins can be incorporated into nanostructures during the growth phase of the inorganic material and a unique flower-like structure was obtained as shown in the study done by Ge J. et al. (2012). The formation of hybrid nanoflowers is believed due to the protein-induced nucleation of copper phosphate crystal during the self-assembly process, which binds the nanocrystal petals together. Incorporation of laccase into the protein-inorganic nanoflowers resulted in enhanced laccase activity and stability, in comparison with the free enzyme.

Huang Y. et al. (2015) extended this work to explore the potential applications of the inorganic copper-phosphate framework of the hybrid nanoflowers by introducing BSA as the model protein. This copper-phosphate framework has an intrinsic peroxidise-like activity that promotes the development of a hybrid material with superior durability and stability. Moreover, the nanostructure morphology can be preserved during catalytic reaction, even at high temperature. The system also has been tested by using glucose oxidase (GOx) to replace BSA as the protein component to study the communication between artificial and natural enzyme. Interestingly, they found that a self-activated cascade reaction could be achieved through in one integrated system whereby the artificial enzymatic cascade could mimic the natural ones. Through this newly developed technology, deep understanding of the complex enzymatic reactions could be achieved. They also proposed that this hybrid nanoflowers have potential to be applied in the decomposition of organic dyes and waste water treatment.

Most recently, the fabrication of hybrid nanoflowers with abundant surface porosity has been reported by Koley P. et al. (2016). Sericin, a silk protein was used as the organic component and copper-phosphate as the inorganic counterpart. By tuning the protein concentration, various morphological structures of the nanoflowers were observed. Similar with the BSA-copper phosphate nanoflowers synthesized by Huang Y. et al. (2015), this sericin hybrid nanoflowers exhibited excellent thermal stability even after calcination. The calcination process resulted in the complete evaporation of the sericin molecules which eventually increases the nanoflowers porosity, thus significantly increased its surface area for adsorption of heavy metal ions from wastewater.

5. Applications of biomolecule-nanoparticle conjugates

5.1 Medical and pharmaceutical

The recent development in the field of nanomedicine particularly in the drug delivery application has led to the discovery of nanoparticle-based therapeutics for diagnosis and treatment of diseases such as cancer, diabetes, and allergy. The fundamental characteristics of nanoscale materials such as greater solubility and diffusivity have been shown to improve drug release characteristic and blood circulation half-life (Valo H., 2012). Furthermore, the nanoparticle-based drug delivery system allows better control of drug release to the targeted area which consequently lowers the administration frequency and minimises the possibilities of systemic side effects (Mahapatro A. and Singh D.K., 2011).

Several studies have been attempted to develop biomolecule-nanoparticle conjugates for cancer therapies. By mimicking the ability of *Salmonella enterica* serotype Typhimurium pathogen to reverse multidrug resistance, a semi-synthetic 'Salmonella nanoparticle mimic' based on gold nanoparticle packaged with effector protein (SipA) has been constructed by Mercado-Lubo R. et al. (2016). The system could suppressed the growth of tumour by reducing the P-glycoprotein, a multidrug resistance transporter, at a SipA dose significantly lower than the free SipA and increases tumour sensitivity to conventional chemotherapeutics. In another study, conjugation of prostate-specific antigen (PSA) to gold nanoparticles has enhanced the efficacy and sensitivity of the PSA for diagnosis of prostate cancer based on localised surface plasmon resonance (Jazayeri M.H. et al., 2016). Enzyme prodrug therapy based on horseradish peroxidase (HRP) immobilised onto mesoporous silica nanoparticles converts a prodrug (indole-3-acetic acid (IAA)) into cytotoxic radicals, which caused apoptotic tumor cell death in human colon carcinoma cells as reported by Hung B.-Y. et al. (2015).

Integration of nanoparticle with biomolecule also allows the development of three-dimensional scaffolds based on gelatin-hydroxyapatite hybrid nanoparticles with uniformly distributed nano-topologies for application in osteogenesis (Yang G. et al., 2017). Interestingly, the particle morphology has shown to have a remarkable effect on bone formation in which the spherical nanoparticles show the strongest bone formation capacity in comparison to the nanoparticles with a different shape.

For minimising carrier-induced undesirable cytotoxicity,

nanoparticle which are derived from proteins and polysaccharides are promising vehicles in nanoparticle-mediated delivery systems (Gan Q. et al., 2005; Hu B. et al., 2012; Nitta S.K. and Numata K., 2013). Encapsulation of dietary phytochemicals, (–) epigallocatechin-3-gallate (EGCG) with highly biocompatible nanoparticles derived from bioactive peptide/chitosan is able to enhance bioavailability of the EGCG (Hu B. et al., 2012). The EGCG loaded-peptide/chitosan nanoparticle could serve as an effective nanochemoprevention in cancer management and prevention.The use of protein nanoparticles as a carrier for various types of drugs allows the drugs to be transported across the blood-brain barrier (Sundar S. et al., 2010). Binding of drugs to polysaccharide nanoparticles such as albumin and gelatine could enhance the antitumour function of the drugs (Huang Y.C. and Kuo T.H., 2014; Jiang Y. et al., 2016; Kobayashi K. et al., 2014). In an advanced drug delivery system, more types of drugs could be delivered simultaneously to generate synergistic therapies of diseases.

One of the major challenges in the intracellular delivery of anti-cancer drugs to a cancer cell is the rapid changes in pH due to the acidification that occurs in the endosomal compartments. In this viewpoint, a novel strategy has been designed by Kim B.J. et al. (2015) for the synthesis of pH-responsive drug delivery system by using mussel adhesive proteins (MAPs)-based iron(III)–3,4-dihydroxyphenylalanine (DOPA) nanoparticles. The pH-responsive release of drugs was achieved by exploiting the pH-dependent changes in the coordination stoichiometry of the DOPA complexes. This newly developed system has shown effective cytotoxicity towards cancer cells and therefore, can be applied further for the diverse controlled-drug delivery application.

With the significant advantages of the nanoscale materials and the advancement made in the drug delivery, several types of the drug-bound biological nanoparticles are currently under clinical trial and a few are already commercialised such as albumin-bound paclitaxel, which is marketed as Abraxane, for use in metatstatic breast cancer treatment. Most recently, Bhattacharyya J. et al. (2015) have successfully designed a new drug delivery system for paclitaxel that outperforms the readily commercialised Abraxane with 2 times greater systemic exposure and tumor uptake. The system was prepared with a chimeric polypeptide that could self-assemble spontaneously, producing monodispersed nanoparticle of 60 nm in size. The chimeric polypeptide-paclitaxel conjugate has shown near complete tumor regression in breast and prostate cancer tumor models after single dose injection. These outstanding performances are attributed to the improvement of the aqueous solubility, plasma-half life, tumor uptake and therapeutic potential of the self-assembled chimeric polypeptide nanoparticle.

5.2 Biosensors and bioelectronics

Nanotechnology has broadened the opportunities and added a new dimension in designing powerful biosensor and bioelectronic devices for diagnostic of diseases and detection of contaminants in medical, food and agricultural sector. Substantial research efforts are currently being directed towards the utilisation of biological molecules hybridised with nanoparticles for the development of novel biosensor and bioelectronic system (Willner I. et al., 2007).

Ulltrasensitive biosensor for detection of epithelial tumor marker has been developed by Hu R. et al. (2014) through the immobilisation of hairpin oligonucleotide (HO) and horseradish peroxidase (HRP) on AuNPs. The HO-AuNP-HRP conjugate provides multiple signal amplification strategy that could enable rapid detection and enhanced the detection sensitivity in a wide linear range. This strategy was achieved by modification of the biosensor surface by carbon nanotubes for accelerating the electron transfer while the HO-AuNPs-HRP enzyme acts as a tracing tag for the electrochemical detection. This newly developed electrochemical method can be applied for diagnostic and detection of diseases.

Besides for cancer detection, a biosensor based on immobilised enzyme-nanoparticles has also been applied for neurobiology for detection of glutamate, important excitatory signaling molecules that are responsible for carrying out various brain functions. Özel R.E. et al. (2014) used nanocomposite based on ceria and titania nanoparticles, dispersed in a semi-permeable membrane made up from chitosan, that was co-immobilised with glutamate oxidase (GmOX) on the platinum electrode for fabrication of glutamate biosensor. Conjugation of the ceria and titania nanoparticles provide ‘oxygen rich’ environment for the biosensor to detect glutamate in hypoxic conditions while the immobilisation of this nanoparticle conjugate in a biocompatible chitosan membrane facilitate the enzyme stabilisation.

Enzymes-based biosensors are now gaining more popularity for a rapid detection and on-line and *in situ* monitoring of specific compounds in medical, environmental and food industries. For example, a novel potentiometric glucose biosensor has been fabricated by Yang Z. et al. (2014) by immobilising core-shell hybrid nanoparticles of iron oxide, glucose oxidase (GOx) and polypyrrole to the surface of magnetic glassy carbon electrode. This biosensor enabled fast detection and highly-selective glucose monitoring with low detection limit and wider linear range. Enzymes-based biosensors have also been used for detection of phenolic compounds by using various types of enzymes such as tyrosinase, horseradish peroxidise and laccase (Rodríguez-Delgado M.M. et al., 2015).

Recently, many researchers discovered the unique and

programmable molecular recognition of DNA for the development of artificial, machine-like devices. DNAzymes, an important functional nucleotide acid have been recognised as important building blocks for the construction of nanodevices. The development of a walking system based on DNAzymes that are moving along a DNA track has been reported. The motion is driven by the chemical energy that has been supplied by the DNAzyme substrate. This concept was used by Liu and co-workers (2013) to design DNA hemin-G-quadruplex-DNAzyme-based walkers which allow the chemiluminescence, chemiluminescence resonance energy transfer (CRET), electrochemical, or photoelectrochemical transduction of the switchable states of the different DNA machines. Besides that, the DNA exhibited a unique feature of being easy to code which enables them to be used in the computational operation and logic gates (Gong L. et al., 2015).

Development of nanoscale memory devices is another interesting application of biomolecule-nanoparticle conjugates. Hybrid nanoparticle composed of recombinant azurin, a well-characterised redox protein and a quantum dot (CdSe-ZnS) have been developed by Yagati A.K. et al. (2017). By introducing a site specific amino acid sequences in azurin, the CdSe-ZnS nanoparticle can bind with the protein, thus forming resistive random access memory (ReRAM) device with reversible voltage driven-switching function and repeatable writing-reading processes.

5.3 Foods

Despite the explosion of nanotechnology in diverse fields, particularly in medical and pharmaceutical, the application of nanotechnology in the food sector is considered still in infancy stage due to the public perception and preference on the so called 'natural' food products, which limit the development of new food technologies (Duncan T.V., 2011). However, as the nanotechnology has been revolutionised in the past few years, the potential uses of nanotechnology in food industries have already been recognised in every chain of food products development, ranging from the processing to packaging and storage (Berekaa M.M., 2015).

Nanoparticles have been used as nanocarrier which is known as 'nutrition delivery system'. The nanoscale delivery system plays an important role in improving food or nutrients absorption in the human body, particularly for those who suffer from the gastroinstestinal disease. Nanoparticles are also useful for enhancing bioavailability of poorly soluble bioactive compounds and improving food properties such as stability and texture.

The main criterion for the application of nanoparticles in food products is the particles which must be developed from food grade materials. In this regard, nanoparticles from biomolecules origin are the most suited for that purpose (Ha H.-K. et al., 2013). Chitosan and whey protein have been widely used as encapsulant of neutraceuticals, food ingredients, probiotics and enzymes due to their ease of availability in large quantity in combination with their good physical and mechanical properties. Ha and co-workers (2013) used linoleic acid modified chitosan/β-lactoglobulin for encapsulation of quercetin, a hydrophobic bioactive compound with good anticancer, antiviral and antioxidant properties. Findings by Yi J. et al. (2015) has shown that whey protein isolate was more effective for encapsulating beta-carotene than other type of protein such as soybean protein with great improvement in radical scavenging and cellular antioxidant activities. Recently, calcium induced cruciferin nanoparticles from canola protein prepared by cold gelation method have been utilised as a protecting agent for β-carotene to increase its bioavailability (Akbari A. and Wu J., 2016). The main driving forces for the formation of the nanoparticles were hydrophobic interaction and electrostatic forces. Another study done by Marelli B. et al. (2016) shows that coating of food ingredients with protein nanoparticles such as silk fibroin has a positive effect on improving food shelf-life.

Besides used in the development of food products, nanotechnology also plays a crucial role in food packaging sector. Incorporation of nanoparticles in food packaging materials could provide efficient food preservation system by improving barrier protection by scavenging oxygen and other spoilage causing constituents and improve antimicrobial properties. For example, packaging film made up from whey protein-montmorillonite nanoparticle activated with lycopene could improve the film barrier property against water vapour and at the same time provide antioxidant activity and UV-light protection (Pereira R.C. et al., 2016).

5.4 Agricultures

The role of nanotechnology in agricultural sectors covers the conversion of agricultural waste into energy or other useful byproducts, detection and prevention of crops diseases, treatment of plants using various types of nanocides and delivery of agrochemicals such as pesticides, fertilizers, genetic materials and growth hormone (Nair R. et al., 2010; Nuruzzaman M. et al., 2016). With respects to the delivery of agrochemicals, nanoscale materials have novel characteristics that can improve bioactivity and agrochemicals efficiency through the development of a smart delivery system. In the smart delivery system, nanoscale carriers are utilised with the aim to enhance controlled-release properties of the agrochemicals, increase the active ingredients solubility, and improve the stability of pesticides as well as for preventing premature degrada-

tion of crops.

Silica nanoparticles have been explored as a control agent for agricultural pesticides. Conjugation of terpenes (α-pinene and linalool) onto the silica nanoparticles surface resulted in enhanced bioavailability of the compounds and improved the antifeedant potential of the individual terpenes against insects which consequently prolonged shelf-life of the terpenes (Usha Rani P. et al., 2014).

Nowadays, growing interest has been shown in the utilisation of biodegradable and biocompatible materials derived from natural materials particularly chitosan-based for the development of the agriculture nanocarriers. Chitosan is a versatile polymer which is well known to serve two major functions in agriculture; preventing the spread of pathogens with its wide-spectrum of antimicrobial properties and enhancing immunity defenses of the plant (Xing K. et al., 2016).

The presence of phytopathogenic fungi and viruses has resulted in severe damages to many crops around the globe. The control of diseases caused by these microorganisms is a problem that remains unsolved (Cota-Arriola O. et al., 2013). To protect crops from fungal pathogens, the growth of the fungi can be inhibited by using protein-chitosan nanoparticle conjugate as demonstrated by Sathiyabama M. and Parthasarathy R. (2016). The chitosan nanoparticle was prepared through the biological method by the addition of anionic proteins to the chitosan solution. They found that this protein-chitosan nanoparticle conjugate has high antifungal activities which inhibit the growth of the phytopathogenic fungi tested. Additionally, treatment of the chitosan nanoparticle with chickpea seeds allows the nanoparticle to be used as a growth promoter. Chitosan-based nanoparticles have also been prepared by Xing K. et al. (2016) for controlling pathogenic fungi in agriculture. The antifungal nanoparticle was prepared by grafting oleoyl onto the chitosan molecules, yielding an oleoyl-chitosan nanoparticle hybrid with size around 297 nm. Improvement in the antifungal index was observed as the concentration of the nanoparticle increased.

6. Conclusions and future prospects

In this review, various types of biological nanoparticles and the synthesis methods have been discussed. Fabrication of biological nanoparticles through drying methods, particularly electrospraying is highlighted mainly due to the ability of the method to generate nanoparticles with a narrow size distribution that often could not be achieved by the other nanoparticulate fabrication techniques. In order to broaden the application of biological nanoparticles, integration of biomolecules with other types of nanoparticles such as inorganic and polymeric through numerous biofunctionalisation strategies have been established. However, much remains to be discovered in this newly emerging field. With the recent technological advancements and innovations, next generation of biological nanoparticles that has multiple functionalities will be developed which could improve the characteristics of the biological nanoparticles and extend its application to diverse fields.

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