Review Article

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Peptides-Incorporated Nanoparticles for Imaging and Drug Delivery Applications

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Abstract

Peptides are excellent biomolecular receptors and interactions between peptide and nanoparticle have played a major role in controlled drug delivery. Peptide-based nanoparticles (pep-NPs) are emerging as promising imaging and therapeutic agents against cancer due to their biocompatibility and tunability. This mini review dealt with development of new peptide-incorporated nanoparticles for imaging and drug delivery applications for detection and treatment of brain cancer.

Keywords: Peptides; Nanoparticles; Biodegradable; Imaging; Drug Delivery.

Introduction

Peptides are selected to use for incorporation onto nanoparticles for imaging and drug delivery applications since they are found to be excellent candidates as biomolecular receptors and interactions between nanoparticle and peptides have played a significant role in controlled drug delivery. Coating gold nanoparticle surfaces with peptide molecule will expand the applications of these nanoparticles in biomedical sciences. The peptide sequence selected to synthesize is the active site of Thioredoxin which contain Cys and Lys residues and adsorb them on nanoparticle surface. Nanoparticles can cross the blood brain barrier and can be used in drug targeting and delivery systems. Functional groups such as -SH and –NH2 present a high affinity for gold, and since amino acids contain some of these groups, they are expected to stabilize gold nanoparticles [1]. The present approach is to react a functional group (SH or -NH2) of a side chain of peptide molecules that are pre-formed via solid-phase peptide synthesis with gold particle surfaces.

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Selection of Peptide Sequence

It is proposed to synthesize the following sequence which includes the active part of Thioredoxin,

H-Ala-Glu-Trp-Cys-Gly-Pro-Cys-Lys-Met-OH (T29-37)

Thioredoxin is a naturally occurring sulfur reducing protein containing 108 amino acids.[2] It is first identified in *Escherichia coli*. Since the activity of this enzyme is essential for cell growth and survival, it is a good target for anti-tumor therapy [3]. This enzyme is up-regulated in several types of cancer, including malignant mesothelioma [4]. Motexafin gadolinium is an inhibitor of thioredoxin reductase and ribonucleotide reductase. It has been proposed as a possible chemotherapeutic agent in the treatment of brain metastases.

Thioredoxin (Trx) sequence will be synthesized by solid phase method using polystyrene crosslinked with 1, 6-hexanediol diacrylate (PS-HDODA) resin (Figure 1 & 2) [5]. With gold nanoparticles, photo thermal therapy can also be used for the destruction

of cancer cells. However gold nanoparticles are retained in a number of organs, such as liver and spleen due to their negative charge, thereby decreasing their delivery to brain. It is therefore crucial to modify the nanoparticle surface by reducing its negative charge.

The protrusion formed by 29-37 is the most striking structural feature of Thioredoxin. Since Thioredoxin is a substrate for two enzymes, thioredoxin reductase and ribonucleotide reductase, the active centre region of Thioredoxin must interact with the active centers of these two enzymes. These enzymes will have the probability of active site clefts, which are suitably adapted to fit the active site protrusion in Thioredoxin. Using the active site of Thioredoxin [Ala-Glu-Trp-Cys-Gly-Pro-Cys-Lys-Met] - a disulfide bridge can be prepared incorporating gold nanoparticle. This will stabilize the nanoparticle surface and can achieve enhanced delivery to the brain. Also the affinity of gold nanoparticles towards Lysine can be lead to the development of controlled drug delivery applications. The selected sequence which contains hydrophobic residues can stabilize the nanoparticle by promoting the formation of a stable shell around

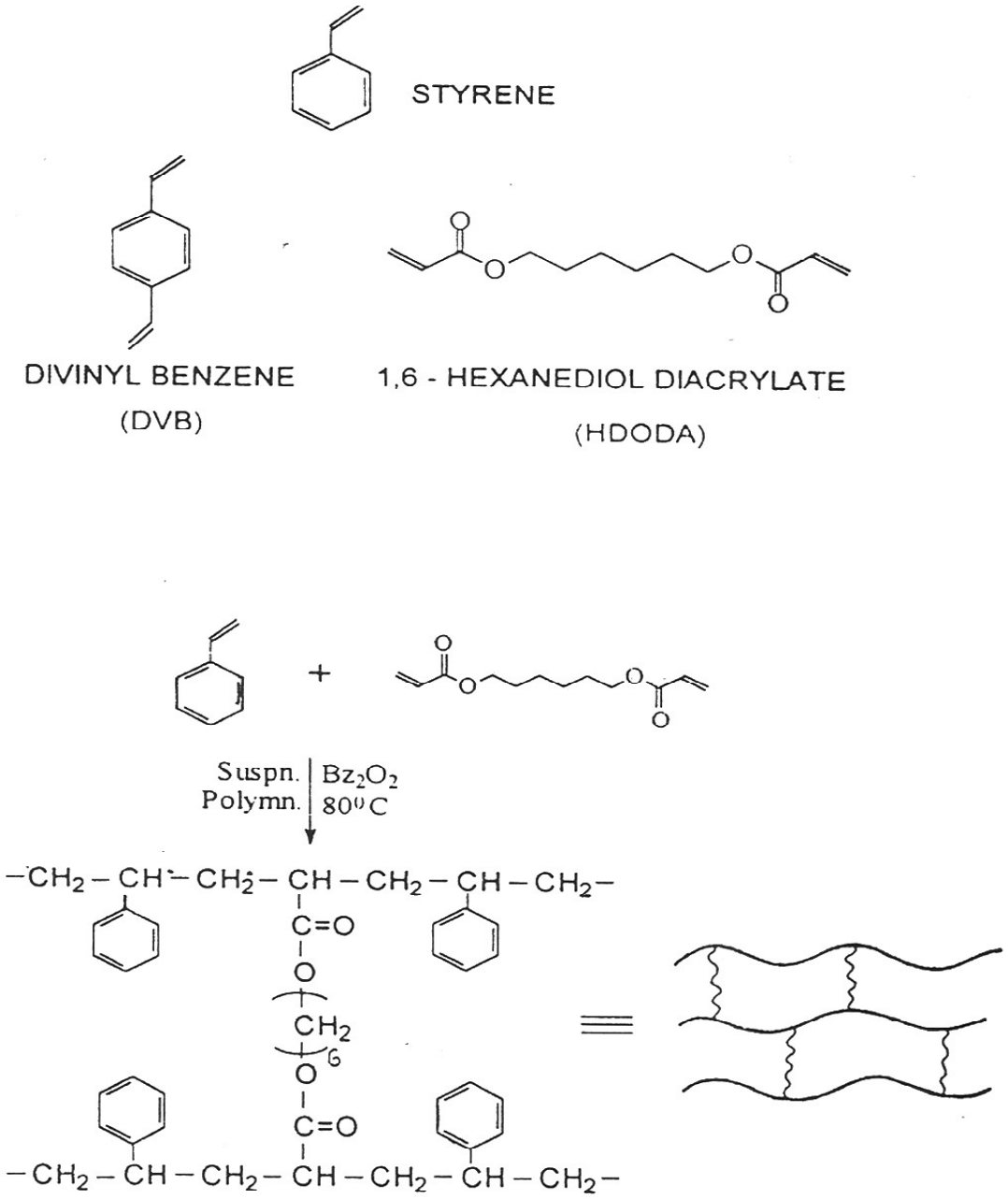

Fig. 1: Preparation of HDODA-crosslinked polystyrene by suspension polymerization

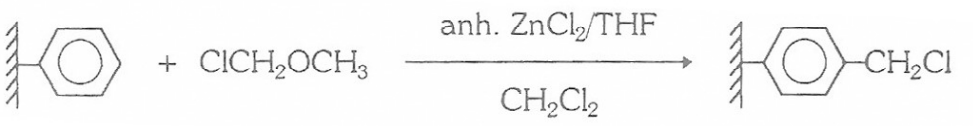

Fig. 2: Chloromethylation of HDODA-crosslinked polystyrene resin

the nanoparticle.

Synthesis of Peptides

One of the main difficulties in solid phase assembly of peptides is that of obtaining quantities of peptides and proteins in a pure state. Isolation of proteins from natural resources can be laborious and often provides only tiny quantities. Investigations dealing with the quantitative aspects of polymer-supported reactions have shown that the insoluble support does have a significant dynamic influence on the bound substrates. An efficient polymeric support for peptide synthesis should have optimum hydrophobic-hydrophilic balance compatible with the peptide being synthesized. The selected partial sequence of Thioredoxin could be synthesized by solid phase method using polystyrene cross-linked with 1, 6-hexanediol diacrylate. The flexible nature and favorable swelling and solvation characteristics of styrene-HDODA support is proved to be better than Merrifield resin and this will facilitate the effective synthesis [6].

Decorating Gold Nanoparticles with the Peptides for Imaging Applications

Gold particle bioconjugates are important constructs for cellular imaging [7]. Because of the large scattering cross section of metal particles, individual nanoparticles can be imaged under white-light illumination. This involves the covalent coupling of cysteine in the selected sequence to a particle surface via sulfur-gold bond [8]. This direct coupling affords a simple one-step procedure that produces particles with high surface coverage of peptide. One important aspect of thiol-gold chemistry is that the reaction proceeds at room temperature in aqueous solution.

Incorporation of Peptides to Plga Nanoparticles for Drug Delivery Applications

Nanoparticles made from natural polymers that are biodegradable have the ability to target specific organs and tissues in the body. In order to manufacture these polymeric nanoparticles, the drug molecules are first dissolved and then encapsulated or attached to a polymer nanoparticle matrix. One of the most important characteristics for nanoparticle delivery systems is that they must be biodegradable and the most attractive polymer material used for drug delivery studies is polylactide-co-glycolide (PLGA). PLGA has attracted considerable attention due to its attractive properties: (i) biodegradability and biocompatibility, (ii) FDA and European Medicine Agency approval in drug delivery systems for parenteral administration, (iii) protection of drug from degradation, (iv) possibility of sustained release and (v) possibility to target nanoparticles to specific organs or cells. PLGA nanoparticles loaded with drugs will be formulated using the standard emulsion method and the conjugation of peptides onto these nanoparticles would be done via carbodiimide chemistry [9,10]. In vitro studies using cell cultures and in vivo studies using animal models could be done to investigate the efficiency of these peptides conjugated nanoparticles for imaging and drug delivery applications for detection and treatment of brain cancers.

Conclusion

Cancer is a leading cause of death worldwide. Nanotechnology has great potential for early detection, accurate diagnosis and personalized treatment of cancer. But the potentialities of nanopartcles have not been exploited. Peptide coated gold nanoparticles could be used for tumor imaging and biodegradable PLGA nanoparticles for drug delivery applications.

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