Review Article

IJCRR
Section: General Science
Sci. Journal Impact Factor 4.016
ICV: 71.54

Multi-Functional Silver Nanoparticles for Drug Delivery: A Review

Prashob Peter K J

Department of Chemical Oceanography, Cochin University of Science and Technology, Kochi 682016, India.

ABSTRACT

An operative management of complex physiochemical properties of drugs is vital for their effective cellular uptake and action. During the last decade, the complexity of drugs addressed in the state-of-the-art therapeutics has increased along with the computational capability to generate more and more detailed information from the structure activity relationships. With the development of drug delivery carrier, particularly polymer carriers, targeted release of drugs have reached new levels. Whilst slower than other architectures - like hydrogels - at the beginning of the new generation cargo molecules, silver nanoparticle (AgNPs) incorporated drug carriers have now reached new levels in both amelioration of toxicity and in enhancing stability and solubility of drugs. These progresses allow AgNPs integrated systems to generate output which are competent with the ones obtained from the cutting-edge polymer carriers, while keeping the benefits of conserved action at varying physiological conditions.

Key Words: Drug delivery, Silver nanoparticles, Photothermal therapy

INTRODUCTION

The need for drug delivery systems with novel mode of action to improve the solubility and stability and to minimize the toxicity of potent drugs is a major impetus for research in drug transport systems[1-6]. This paper highlights the recent developments in drug delivery units using AgNPs, to enhance the therapeutical index and its successful *in vivo* applications. Hybrid molecular units containing AgNPs are used in the designing of drug-delivery systems responsive to optical, thermal and pH modulations to target malignance, inflammatory and infectious ailments, as these nanoscale metals posses exceptional biocompatibility viable for therapeutic settings [7-8]. AgNPs (Fig. 1) are extensively used in the state-of-the-art drug delivery carriers in recent years, because of their facial synthesis methods to functionalize surface and tune optical features[7-12]. Colloidal silver with superior quality, high yield and responsive to changing environment and external stimuli can be rapidly synthesized [12]. Synthetic progress in the last decade stimulates AgNPs of different shapes and structure including silver nanoplates, Fe/Ag nanoshells, AgNP prisms and Ag Nanowiers, which all show surface plasmon absorbance which can be effectively utilized in photothermal therapy to supress malignant cells [12-15]. In this mini review, highlight will be on the photo thermal features of AgNPs in different morphologies and their biomedical applications along with synthetic methods opted to functionalize the carrier molecule and impart biocompatibility to the structure.

SILVER NANOPARTICLES FOR DELIVERY

AgNPs can be tailored to incorporate nucleic acid making them ideal delivery agents for RNAi based therapy [7]. Lee and co-workers developed conjugates suitable for spherical nucleic acid colloids using AgNPs functionalized with oligonucleotide[8]. These tri cyclic disulphide moieties in the oligonucleotide enhance the particle stability and effectively tolerate heat, aging and oxidative degradation. Exceptionally high cooperative binding properties were shown by these AgNPs functionalized with oligonucleotide. Due to sharp melting transitions shown by these colloids, hybridization and dehybridization can easily be achieved by varying sodium chloride concentration, making them an apt choice for gene delivery[8].

Biocompatibilty and potential of nano-silver molecular unitsto detect pathophysiological faults in maligant cells and cargo therapeutic genestargeting tumour was significantly improved, when integrated with graphene oxide. For example, uptake of GO@Ag-DOX-NGR by tumour cells were 8.4 times efficient than normal cells [9]. These grapheme oxide-nanosilver loaded with DOX not only selectively released the drugs but also assisted in the photothermal ablation

Corresponding Author:
Prashob Peter K J, Department of Chemical Oceanography, Cochin University of Science and Technology, Kochi 682016, India.
E-mail: prashobpeter@cusat.ac.in

Received: 03.03.2017 **Revised:** 23.03.2017 **Accepted:** 12.04.2017

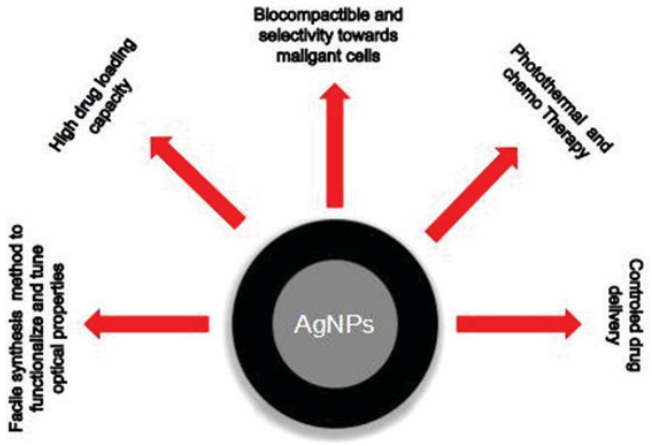

Figure 1: Major highlights of drug delivery using multi functional silver nanoparticles.

of tumor when stimulated with Near-infrared (NIR)[9]. As precise response of these composites to external stimuli along withan enhanced affinity for malignant cells, compared to normal cells, apparently reduce the toxic side effects and enhance the chemo-photothermal potential of therapeutic agents [9]. Fe_3O_4@C@Ag hybrid nanoparticles developed by Chen and co-workers is another example for NIR light-responsive drug delivery templates with high drug loading capacity. These templates were effectively used to deliver doxorubicin near cell nucleus to enhance apoptosis[16]. Photothermal transducing property of colloidal silver can be effectively used in activating localized hyperthermia of tumours[10]. For example, silver nanotriangles synthesized using chitosan showcased a strong surface plasmon resonance in near-infrared, to function as photothermal mediators against human non-small lung cancer cells[10]. These chitosin functionalized AgNPs demonstrated excellent biocompatibility as inferred from the cellular uptake studies performed on healthy human embryonic cells. This result along with high selectivity towards malignant cells enhances their potential in *in vivo* applications. Further, number of viable cells exponentially decreased in presence of silver nanotriangles coated with chitosan, when compared to gold nanorods stabalized using thiolated poly(ethylene) glycol, a commonly used hyperthermia agent [10].

Photoactivated gene silencing can be achieved through drug delivery system made of silver, moulded to nanoscale-antisense platforms[11]. Their usefulness in photo activated drugs has been attributed to the unique optical properties. In order to enhance the photo activations, Brown and associates functionalized the AgNPs surface with thiol-terminated photolabile DNA oligonucleotides[11]. Compared to commercially available transfection vectors, these engineered nanosilver templates showcased increased stability to nucleases, enhanced hybridization activity upon photo-release and effective cellular uptake[11]. Modulation of Intracellular Adhesion Molecule-1 silencing by these functionalized AgNPs demonstrate their potential as effective agents for the delivery of oligonucleotide based therapeutics.

AgNPs can be engineered to deliver drug molecules in response to electromagnetic and pH stimuli. A multifunctional drug carrier responsive to photo and pH stimuli has been developed by Fang and co-workers by uniformly coating mesoporous silica on the surface of Pd@Ag nanoplates. Pd@Ag nanoplates function as transducers that convert NIR to thermal energy. Presence of mesoporus silica with pores of approximately 10 nm on the surface of nanocomposite increase the drug loading capacity. pH sensitive coordination bonds formed between mesoporus silica and drugs are responsible for the specific release of drugs inside the cells[12].

Silver incoperated multi-metal nano-cage can be used in designing drug-carriers without surface functionalization[13]. Liu and co-workers developed gold-silver alloyed triangular nano-cages and investigated their potential as drug delivery carriers for anti-cancer drug. This carrier molecule showcased strong absorbance in the NIR and was susceptible to laser induced near-field ablation[13]. Hollow nano-cage structure of nano-template encapsulated the drug, which was effectively delivered on ablation[13].

AgNPs can be hybridized with carbon nanotubes(CNT)for the in situ production of NO from RSNO [17]. These CNT@Ag hybrids can be used in the slow delivery of NO from external aromatic nitrosothiols when compared to CNT@AuAg [18]. And this slow release is extremely important in the prevention of infections arising from colonization of bacteria and formation of biofilim [19].

Silver nano-carriers to target folate receptor expressing tumour were developed by functionalizing the surface of AgNPs with folic acid. This folic acid functionalized AgNPs delivered exceptional receptor-mediated cellular uptake along with electrostatic binding to drugs. Receptor-mediated cellular uptake has been verified by surface enhanced raman scattering imaging and fluorescent lifetime imaging. Electrostatically bound drug (DOX) were slowly released into the cytoplasm of cells and induced apoptosis [20]. AgNPs integrated hydrogel demonstrated excellent potential to deliver antibacterial drugs[21]. These cross linked nano-hydrogel composites loaded with curcumin showcased high swelling rate and thermal stability. These hydrogel nano-composites were particularly useful in the slow release of loaded curcumin, emphasising their vital role in preventing infections while wound and burn healing treatments [21].

A biocompatible triplex Ag@SiO_2@mTiO_2 core–shell nanocolloids developed by wang and co-workers in 2012 is an excellent example for the utilization the endocytosis mechanism of nanoparticles to enhance the cellular uptake and consequent delivery of anti-cancerous drugs. Cytotoxicity

studies carried out using these nano-colloids against human breast adenocarcinoma cell line studies established their biocompatibility. And mesoporus silica siginificantly increased the drug loading capacity of the carrier[22]. The successful *in vitro* internalisation and potential to induce apoptosis in lung adenocarcinoma cells and lung normal fibroblasts using nano silver wire along with their biocompatible nature highlight the prospects as novel drug delivery carriers to suppress lung cancer [15].

PREPARATION OF SILVER NANOPARTICLES

The synthesis of target specific and biocompatible nano silver in cooperated drug carriers is one of the most challenging task in drug carrier research. This section comprehends the synthesis of AgNPs that are responsive to photo, thermal and pH stimuli. Drug delivery platform responsive to NIR light was realised by integrating AgNPs on the surface of Fe_3O_4@C nanospheres. A 200 nm superparamagnetic Fe_3O_4@C nanospheres, functionalized with carboxyl and negative charge were dispersed in dimethyl formamide prior to hybridization of silver nanoparticles on their surface. These carbon encapsulated Fe_3O_4 nanospheres was synthesised using the one step solvo-thermal process of ferrocene [23]. AgNPs used for surface hybridization were synthesised by reducing silver ions in DMF solution using glucose at 70 °C. Purified Fe_3O_4@C@Ag nanospheres were dried and encapsulated with drug [16]. GO@Ag is an another example for drug carriers that are responsive to NIR[9]. They have been rapidly synthesised by facile method in which AgNPs are deposited uniformly on the surface of graphene oxide by hydrothermal reaction. These GO@Ag incorporate drugs (DOX) via ester bonds and showcased high drug loading capacity[9]. In order to impart tumour targeting potential and stability in physiological conditions, these doxorubicin loaded GO@Ag was again functionalized by DSPE-PEG2000-NGR [9].

AgNPs incorporated polymer composites sensitive to photo-stimuli has been synthesised by Park and co-workers in 2011 by using epoxy resin and photo acid generator [14]. Composites synthesised in this method consist of uniformly dispersed AgNPs. In an another attempt to develop photosensitive drug delivery carriers, Anandhakumar and coworkers in 2011 effectively utalized polyol reduction method [24]. Drug loading in these composites are modulated by the electrostatic interaction between drug and carriers. Drug can be easily loaded to silver incorporated nano composites by thermal encapsulation method. Encapsulated drug are effectively delivered by applying laser pulses[24].

Drug loading capacity of mesoporus nano silica and their response to NIR have been effectively increased by incorporating AgNPs. Fang and co-workers effectively utilized the potential of silver nanoplates to absorb and convert NIR light into thermal energy, to enhance the delivery of drugs from mesoporus silica [12]. In this case, seeding method used for the preparation of core shell architecture [25] developed by Huang and associates was opted. Initially, Pd@Ag nanoplate core of mean diameter 41 nm was synthesised, to impart photothermal stability to the carrier molecule. Prior to functionalizing the Pd@Ag nanoplates with mesoporous silica, a thick layer of silica was developed on the nanoplates as per Stöber method to function as template to electrostatically adsorb CTAC micelles[26]. The oblate spheroids with an average diameter of 110 nm and a thickness of 60 nm Pd@Ag@sSiO2 particles obtained were then functionalized with mesoporous silica as reported by Yokoi et al. [26]. In a mild basic reaction media, mesostructure of co-assembled silica and CTCA are obtained. Rate of reaction in this process was regulated by L-Arginine. In order to enhance the pore surface trimethylbenzene was used as a swelling agent. Stability of co-ordination bonds formed by these carrier molecules is highly sensitive towards pH and thermal energy. High porous area and electrostatic interactions along with pH and thermal responsive nature enhance the drug loading capacity and delivering capacity of Pd@Ag@sSiO_2@mSiO_2[26].

Unique pH responsive AgNP-hydrogel composite can be synthesised using silver ions, poly(2-hydroxyethyl methacrylate, poly(ethylene glycol) methyl ether methacrylate and methacrylic acid[27]. Deprotonized polar carboxylic acid present in the reaction media assist in the synthesis of AgNPs from silver ions anchored in the hydrogel. Morphology and size of the nanoparticle synthesized can be effectively tuned by altering the silver ion concentration in the hydrogel. Along with pH switchable electrical properties these hydrogel composite also have higher swelling ratio and faster deswelling rate compared to pure poly(HEMA–PEGMA–MAA) hydrogel [27].

DISCUSSION

The preparative methods used for developing silver incorporated nano-carriers are facile and cheap. Even though these synthesis methods developed carriers that are highly selective and biocompatible, much emphasis is necessary in this field to overcome the challenges faced in this area of application. In this regard polymers from marine compounds are useful prospects for developing drug delivery units using AgNPs. Recently silver-nanoplates were synthesised using biocompactible humic acids, isolated from mangrove ecosystem, with potential against Dalton lymphoma ashites [28]. Biocompactible nature of humic acid along with polar functional groups are useful in designing self-assembled AgNPs[29]. Another extensively available biocompactible marine resource is fucoidan, a sulphated polysachride, capable of synthesising stable spherical AgNPsfor suppressing both human and marine pathogens [30].

CONCLUSION

Common challenges in drug delivery workflow can be addressed by hyphenating silver nanoparticles with carrier molecules. The desired biocompactibility throughput vital for in vivo applications can be achieved by functionalizing the surface of AgNPs with apt agents and synthetic methods. Since NIR photo activation can be easily achieved by stimulating the surface plasmons on the surface of AgNPs, nano silver in cooperated carrier matrix is a perfect choice for photo dynamic therapy. The high selectivity and target specific response to photo, thermal and pH stimuli enable both bio-compatibility and enhancement of theraputical efficiency. Due to the dynamic range of functionalization provided by facile synthetic methods, both high and low molecular weight drugs can be delivered with same efficiency. Even though topical and systemic side effects have been associated with long-term exposure to silver incorporated products, intake of nano-silver in small concentrations is often considered safe to humans. Considering the fact that, results concerning the side effects of colloidal silver and its composites are inconclusive, much in vitro and animal studies are required prior to their extensive use as drug carriers.

ACKNOWLEGMENT

Author is thankful to the facilities provided by dept. of Chemical Oceanography and Inter University Center for Development of Marine Biotechnology, Cochin University of Science and Technology, to prepare this article. Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed. In addition, author thanks Miss Ektha Martin for grammatical correction.

Conflit of Intrest: Author declare no conflict of interest.

ABBREVIATIONS

AgNPs	:	Silver nanoparticle
CNT	:	Carbon nanotubes
CTAC	:	Critical micelle concentrations of cetyltrimethylammonium chloride
DOX	:	Doxorubicin
DSPE-PEG2000	:	1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)- 2000]
GO	:	Graphene Oxide
HEMA	:	2-hydroxyethyl methacrylate
MAA	:	Methacrylic acid
NGR	:	Asparagine-glycine-arginine
NIR	:	Near-infrared
NO	:	Nitric oxide
PEGMA	:	Poly(ethylene glycol) methyl ether methacrylate
RSNO	:	S-nitrosothiols

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