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POTENCY OF MULTI COMPONENT DRUG DELIVERY SYSTEMS: A CRITICAL REVIEW

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ABSTRACT

Drug delivery systems have been collectively termed as smart carriers nowadays with the abundance of nanomaterials. Polymeric systems have traditionally been used in the past but the unique properties of certain nanomaterials have drastically increased the attention of the researchers around the world. Certain nanoparticles like iron oxide, silver and gold have been used in conjugation with the polymeric systems to provide more uniqueness for the delivery system like magnetism, surface Plasmon resonance and anti microbial characteristics. This work elucidates on the role of iron oxide embedded matrices to deliver drugs.

KEY WORDS: Nanoparticles, Iron oxide, Magnetite, Multi component drug delivery system.

1. INTRODUCTION

Iron Oxide nanoparticulates: Magnetite (Fe_3O_4) nanoparticles (MNPs) with their multifunctional properties such as small size, superparamagnetism, low toxicity, etc, show many potential applications in biomedicine for disease diagnosis and cancer treatment (magnetic resonance imaging, drug delivery system, hyperthermia, etc) (Kawashima, 2000) (Florence, 1995) (Takeuchi, 2001). To be applied in biomedicine, the MNPs must have long term stability in aqueous solution, particle size of less than 100 nm, and magnetization as high as possible. Apart from those properties, the MNPs have to be encapsulated to avoid the agglomeration or to make them monodisperse in suspension. Various methods have been reported for the preparation of stable dispersion of iron oxide in organic solvents including hexane and decane (Sakuma, 2001). For these solvents, the biological applications are greatly restricted because of their poor solubility in aqueous solutions. So, it is essential to modify the MNPs to increase the stability by using stabilizers such as surfactants, oxide or polymer compounds (especially biocompatible polymer) with some specific functional groups.

Chitosan: Owing to its biocompatibility and biodegradability, chitosan (CS) has been used widely in biomedicine. However, one disadvantage of chitosan is that it can only dissolve in acidic solution (pH < 6) and cannot dissolve in a physiological environment (pH = 7.4). This constrain restricts applications of CS in biomedicine. To overcome this restriction, many derivatives of CS have been manufactured. Among the variety of polymers that were used for drug-loaded nanoparticles, chitosan has received great attention in both the medical and pharmaceutical fields (Illum, 1998).

Chitosan, a biodegradable and biocompatible polymer, is a modified natural carbohydrate and the second most abundant polysaccharide in nature. It can be synthesized by the partial N-deacetylation of chitin, a natural biopolymer derived from crustacean shells such as crabs, shrimps and lobsters [6]. It consists of repeating units of glucosamine and N-acetyl-glucosamine, the proportions of which determine the degree of deacetylation of the polymer (Agnihotri, 2004). Chitosan is available in a wide range of molecular weights and deacetylation degrees. Due to its characteristics, chitosan has gained increasing attention in the pharmaceutical field. In addition, chitosan presents mucoadhesive, immunostimulating, antimicrobial and wound-healing properties (Lai, 2009) (New, 2009).

The mucoadhesive colloidal particulate system has been found to be an attractive drug delivery carrier able to improve the oral delivery of poorly absorbed drugs (Kawashima, 2000). In particular, nanoparticles are able to protect drugs from degradation, to improve permeation/penetration of the drugs across mucosal surfaces, and also to control the release of the encapsulated or adsorbed drug.(Florence, 1995) (Takeuchi, 2001). The *in-vitro* and in vivo behavior of micro- and nanoparticles tends to be greatly dominated by their physicochemical properties such as size, surface potential, hydrophilic-hydrophobic balance, and other variables (Sakuma, 2001).

One of the most widely used polysaccharides for different pharmaceutical purposes is chitosan and its derivatives. Chitosan is a biodegradable, biocompatible, and nontoxic polysaccharide that can adhere to the mucous layer by establishment of electrostatic interactions with sialic groups of mucin (Hassan, 1990). In addition, the positive charges of chitosan are probably essential for permeation enhancing effect of this polymeric excipient. These mucoadhesive and permeation-enhancing properties of chitosan were even significantly further improved by the immobilization of thiol groups on the polymer (Bernkop, 2006). These strongly improved mucoadhesive

properties are based on the formation of disulfide bonds between the thiolated polymer and cysteine-rich subdomains of the mucus gel layer (Leitner, 2004). Accordingly, thiolated chitosan nanoparticles should display comparatively stronger mucoadhesive properties than unmodified chitosan nanoparticles and should therefore be of advantage for the mucosal administration of various drugs. Stability of such particles is in most cases provided by the addition of polyanionic excipients such as tripolyphosphate, sulfate, or hyaluronic acid, leading to an ionic cross-linking of chitosan. As a result of the addition of polyanions, however, the positive charges of chitosan are neutralized, resulting in a loss of the mucoadhesive and permeation-enhancing properties of chitosan; furthermore, this may cause oxidation of free thiol groups and lack of mucoadhesion (Bernkop, 2006).

However, much attention has been focused on the natural and synthetic polymers. Chitosan is a popular type of drug carrier. It is a very important, naturally occurring polysaccharide derived from the deacetylation of chitin and has been used extensively in pharmaceutics because of its excellent biocompatibility and biodegradability (Kumar, 2004). Because it is insoluble under physiological conditions (pH = 7.4), which is one major limitation for chitosan as a drug carrier, much attention has been devoted to the application of water-soluble chitosan derivatives. These water-soluble chitosan derivatives include glycolchitosan, (Son, 2003) (Trapani, 2009) quaternized chitosan, (Wei, 2010) (Bayat, 2008) carboxymethylchitosan, (Jayakumar, 2010) (Liu, 2008) poly(ethylene glycol)(PEG)-chitosan, (Seo, 2009) (Hu, 2008) and succinyl-chitosan (Hou, 2010) (Rekha, 2009).

Carboxy methyl chitosan: In recent years, o-carboxymethyl chitosan has drawn significant attention as a surface coating agent due to its biocompatibility, biodegradability and amphiphilicity (Zhu, 2005). The active amino and carboxyl groups on the OCMC chains provide us great opportunities to intergrate OCMC stabilized magnetite nanoparticles with tailored physicochemical and biophysical properties. (Zhu, 2007). Of late the synthesis of o-carboxymethyl chitosan stabilized iron oxide nanoparticles via physical adsorption and chemical ligation was previously reported by several groups (Liang, 2007) (Zhua, 2008).

o-Carboxymethylchitosan (OCMC) has a backbone structure similar to CS, but the *o*-hydroxyl group of each monomer is substituted by a carboxymethyl group through ether bond formation. OCMC has been shown to have amphiphilic, blood compatible and effective membrane penetrable properties (Zhu, 2005a)(Zhu, 2005b). More strikingly, it can load hydrophobic anticancer drugs effectively (Zhu, 2006). Though lots of synthesized polymers (e.g., poly(vinyl alcohol) phosphate, polyethylene glycol, polyamides, polyglycidyl methacrylate, poly(acrylic acid)) were employed as a coating agent in the surface modification of iron oxide particles (Gas, 2006) (Guo, 2007) (Abu-Much, 2006) (Wan, 2007), the natural polymeric and bioactive properties of chitosan and OCMCS, preffered to explore the feasibility of synthesizing a well-dispersed aqueous dispersion of superparamagnetic Fe3O4 nanoparticles stabilized by CS or OCMC, effectively.

Covalently linked iron oxide (CLIO): Covalently linked iron oxide nanoparticles are of much interest to cancer therapy researchers around the world. The super paramagnetic behavior of iron nanoparticles enables the device to be dragged to the area of delivery and pulsed magnetic field will initiate alignment of the CLIO to the magnetic field. Reversing the poles at short intervals would create alignment in opposite directions which will cause the particles to oscillate parallel and perpendicular to the reversing poles. These oscillations will generate heat which in turn will degrade the covalently linked polymer which releases its payload of drugs. This process can be highly repeatable due to the sensitivity of the CLIO to external magnetic field.

Targeted delivery: However, there are no reports related to the cancer cell targeting and in vitro MRI applications of such OCMC-stabilized magnetite nanoparticles (OCMC-SPIONs). To fabricate a multifunctional OCMC-SPION based platforms with cancer cell specific targeting ability, targeting ligands should be attached on the surface of SPIONs to trigger active delivery to specific cancer tissues (Peng, 2008). Among the different strategies for receptor mediated delivery of nanoparticles, folic acid (FA), a high affinity ligand to folate receptors (FRs), is known as a promising targeting agent for folate receptor mediated tumor cell specific nanoparticle delivery, because FRs are overexpressed in many human cancer cells providing a distinguisable marker from normal cells. FA has received promising consideration due to its nonimmunogenicity, high stability, low cost and its faster internalization kinetics through cellular membrane (Lin, 2009) (Ke, 2010) (Stella, 2000).

The use of nanoparticles coated with mucoadhesive polysaccharides has emerged as a promising strategy to prolong the residence time and to increase the absorption of drugs through the mucosa (Liu, 2008) (Lemarchand, 2004). Polysaccharides are important natural polymers with great potential for biomedical applications, safe, nontoxic, hydrophilic and biodegradable, besides they can be obtained from several sources in nature and low cost. In particular, chitosan is a cationic polysaccharide, derived from the deacetylation of chitin, the most abundant polysaccharide in the world, after cellulose. Among mucoadhesive polymers, chitosan has been extensively

exploited due to its capacity to interact with the negatively charged mucosal surface and to enhance drug absorption by opening of the tight junctions between mucosal cells (Andrews, 2009). Some studies have demonstrated the promising use of nanoparticles coated with this polysaccharide for drug delivery. In this way, chitosan-coated nanoparticles have proven to be suitable to incorporate drugs and to be stable, under physiological conditions, to increase significantly the ocular penetration of the encapsulated drug. They also present favorable drug loading and release profiles as well as good selectivity to bladder cancer cells (Cui, 2006) (Calvo, 1997) (Bilensoy, 2009).

Curcumin is an active principle of Curcuma longa Linn, commonly known as turmeric, that displays numerous pharmacological activities such as antioxidant, antiinflammatory, antitumoral and antimicrobial (Goel, 2008). However, its clinical application has been limited due to poor aqueous solubility, rapid hydrolysis at neutral and basic pH, and fast metabolism and systemic elimination, which together are responsible for the low bioavailability exhibited by this drug (Goel, 2008) (Tonnesen, 2002) (Tomren, 2007) (Anand, 2007). Various strategies have been undertaken to overcome the limitations of the use of curcumin and to allow its therapeutic application, including the incorporation in delivery systems.

Curcumin as a cancer therapeutic agent: A great number of natural dietary compounds were investigated to look for therapeutic modalities with no or minimal side effects to normal organs in cancer treatment. Among these, curcumin, a yellow compound isolated from rhizomes of the herb *Curcuma longa*, has received considerable attention because of its putative cancer prevention and anticancer activities which are mediated through influencing multiple signaling pathways (Huong, 2008) (Sa, 2008) (Anand, 2008) (Karmakar, 2006). Curcumin is a low molecular weight phytodrug having wide range of biological activities like antioxidant, anti-inflammatory, antitumourogenic, anticoagulant, antibacterial, anticarcinogenic, anti-ischemic and wound healing (Ishita, 2004) (Phan, 2001) (Shaikh, 2009) (Shukla, 2008). Curcumin has shown to be very effective against many cancer cells like breast cancer, prostate cancer, bone cancer, head and neck cancer, lung cancer and gastrointestinal cancer (Sandur, 2007).

Although curcumin possesses these remarkable features, the extremely low solubility in aqueous solutions limits its bioavailability and chemical efficacy (Liang, 2009) (Tran, 2010). To deal with this obstacle, a variety of methods including the incorporation of curcumin into liposomes and into phospholipid vesicles are being studied (Takahashi, 2008) (Sou, 2008) (Li, 2005). More recently, the approach of biodegradable polymer nanoparticles has been developed (Anand, 2010) (Yallapu, 2010). This offers promising enhanced therapeutic performance of anticancer drugs by increasing their bioavailability, solubility, and retention time. These drug formulations are superior to traditional medicines with respect to control release, targeted delivery, and therapeutic impact. OCMCs has a structure similar to chitosan, but the o-hydroxy group of each monomer is substituted by a carboxymethyl group through ether bond formation. It is an amphiprotic ether, exhibiting nontoxicity, biodegradability, biocompatibility, and strong bioactivity and has, therefore, garnered increasing interest in biomedical applications. More strikingly, it can load hydrophobic anticancer drugs effectively (Aiping, 2006) (Anitha, 2011). Furthermore, magnetic nanoparticles with proper surface coatings have been widely developed because of their great applications. They can be used not only as magnetic resonance imaging contrast agents in medicinal diagnosis but also for therapeutic purposes such as drug delivery and hyperthermia treatment (Kumar, 2010) (Pankhurst, 2009), Koppolu, 2010) (Jain, 2009) (Park, 2005) (Lee, 2011) (Jordan, 1999) (Zhang, 2007).

CONCLUSION

Given the nature of curcumin to aggregate under aquous environment and capability of chitosan to encapsulate materials as it is being made into a nanosphere and that of the iron oxide nanoparticle to impregnate into the nansphere without disrupting the anti oxidant nature of curcumin, the trio present a unique combination for cancer therapy. With the availability of selective targeting ligands like Vascular endothelial Growth factors, mucins and over expressed folic acid receptors, the combination of chitosan, iron oxide nanoparticles and curcumin has the potency to become an effective cancer therapeutic formulation.

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