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Research review paper

Nanoparticles containing insoluble drug for cancer therapy

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ABSTRACT

Nanoparticle drug formulations have been extensively researched and developed in the field of drug delivery as a means to efficiently deliver insoluble drugs to tumor cells. By mechanisms of the enhanced permeability and retention effect, nanoparticle drug formulations are capable of greatly enhancing the safety, pharmacokinetic profiles and bioavailability of the administered treatment. Here, the progress of various nanoparticle formulations in both research and clinical applications is detailed with a focus on the development of drug/gene delivery systems. Specifically, the unique advantages and disadvantages of polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanocrystals and lipid-coated nanoparticles for targeted drug delivery will be investigated in detail.

Contents

1. Introduction

Over the past two decades, nanomedicine has emerged as a catalyst for the advancement of new pharmaceutical formulations (Ferrari, 2005; Panyam and Labhasetwar, 2003; Shi et al., 2010). By permitting the dispersion of insoluble drugs in aqueous solution, many drugs previously abandoned due to their poor solubility in water can be deemed clinically applicable through encapsulation in a nanocarrier. Nanomedicine can also improve the pharmacokinetics (PK) and biodistribution of drugs that have already been approved for use by the Food and Drug Administration (FDA) (Emerich and Thanos, 2007; Sahoo and Labhasetwar, 2003). By favorably altering the PK of drugs in vivo, nanomedicine can significantly improve the safety of existing chemotherapy regimens.

Several strategies have been successfully developed to formulate nanoparticles (NPs) containing insoluble drugs. Polymers, such as poly (D,L-lactide-co-glycolide) (PLGA) (Bala et al., 2004; Cheng et al., 2007), polylactides (PLA) (Smith, 1986; Soppimath et al., 2001) and polycaprolactone (PCL) (Cai et al., 2007; Park et al., 2005), encapsulate hydrophobic drugs through hydrophobic interactions. Through these methods, efficient delivery of both paclitaxel and docetaxel has been achieved (Fonseca et al., 2002; Hrkach et al., 2012).

In addition, liposomes may also be exploited for targeted drug delivery and have been established as the most successful drug carriers marked by their biodegradability and ability to deliver drugs with a wide range of physical properties. More than ten liposomal formulations have been approved for use by the FDA and/or other regulatory authorities and several additional liposomal formulations are currently in clinical trial (Wang

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et al., 2012). Significant effort is also being made to deliver drugs using inorganic nanoparticles. The development of these nanoparticulate formulations will be reviewed and summarized in Tables 1 and 2.

2. Polymeric nanoparticles

Polymeric nanoparticles can be synthesized through various methods depending on the intended application and drug type. These methods include emulsion diffusion, nanoprecipitation and emulsion evaporation (Jain, 2000; Kumari et al., 2010; Vauthier and Bouchemal, 2009). However, the majority of polymeric nanoparticles are formulated through a self-assembly process using hydrophilic and hydrophobic block copolymers (Adams et al., 2003; Rösler et al., 2001). During the self-assembly of polymeric nanoparticles, the hydrophobic drugs are encapsulated into the core of a core–shell nano-structure via hydrophobic interactions. Typically, the final nanoparticles created from this method are 100–200 nm in diameter (Lalatsa et al., 2012; Wang and Grayson, 2012) (Fig. 1).

Polymeric nanoparticles act as drug depots characterized by controlled release of the encapsulated drug. Modification of the nanoparticles with a surface coating of polyethylene glycol (i.e. PEGylation), enables the nanoparticles' evasion of the reticuloendothelial system (RES) and prolongs circulation in the bloodstream (Esmaeili et al., 2008). This capability, along with the biocompatibility and low immunogenicity of these nanoparticles makes them an attractive delivery system, particularly for protein-based and anti-cancer drugs, as well as nucleic acids.

Among the polymers, PLA and PLGA, have been the most extensively investigated for use in drug delivery due to their biocompatibility and controlled release through the hydrolysis of the ester bonds (Li et al., 2011; Makadia and Siegel, 2011). By adjusting the composition of PLGA through alteration of the ratio between lactide and glycolide, the release rate of drugs can be adjusted from a scale of days to months (Amann et al., 2010; Faisant et al., 2002; Ramchandani and Robinson, 1998). However, there are only a few polymeric nanoparticulate formulations on the market. One of them, paclitaxel-loaded nanoparticles (Genexol-PM®) composed of an amphiphilic diblock copolymer, monomethoxy-poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA) and paclitaxel is approved for the treatment of breast and lung cancers in Asia (Lee et al., 2008b; Lim et al., 2010). The data demonstrated that Genexol-PM® showed significant antitumor activity with an increased maximum tolerated dose thus allowing the administration of higher doses of paclitaxel. Genexol-PM® has also been combined with gemcitabine and cisplatin to treat patients with advanced urothelial cancer in Phase II clinical studies (Lee et al., 2012a). Additionally, Phase I clinical trial has been completed on PEG–PLGA–PMSA-targeted polymeric NPs loaded with Docetaxel (BIND-014) (Cartwright, 2013; Prabhakar et al., 2013; Wang et al., 2012). The trial has indicated that the formulation is safe with a reasonable maximum tolerated dose and notable anti-tumor activity. A similar formulation of a docetaxel-polymeric micellar nanoparticle formulation (Docetaxel-PNP) is currently under development by Samyang Pharmaceuticals undergoing Phase I clinical trial to treat advanced solid malignancies in Korea (Miller and Wang, 2013; Svenson, 2012).

In the United States, non-biodegradable poloxamer is approved by the FDA and has been widely used to develop nanomedicines (Chang et al., 2011; Schmolka, 1991). SP1049C, composed of poloxamer and doxorubicin (Valle et al., 2011) is particularly active in treating multidrug resistant (MDR) and metastatic cancers (Danson et al., 2004; Dumortier et al., 2006); the poloxamer disrupts mitochondrial functionality in chemo-resistant cells by depleting ATP and releasing reactive oxygen species (ROS) and cytochrome C. Currently, SP1049C is advancing to an international Phase III clinical study. Likewise, similar formulations containing docetaxel (SP1012C) and cabazitaxel (SP1015C) are being evaluated in preclinical studies (Svenson, 2012).

Kataoka et al. esterified a PEG–polyaspartate block copolymer using 4-phenyl-1-butanol to enhance the hydrophobicity of copolymer and its compatibility with paclitaxel (Negishi et al., 2006). The amphiphilic

Table 1
Fabrication methods, advantages and disadvantages of different nanoparticulate fomulations.

	Fabrication techniques	Advantages	Disadvantages
Polymeric nanoparticles	Self-assembly; nanoprecipitation; emulsion-solvent evaporation	Excellent blood stability; suitability for intravenous injection; EPR dependent tumor accumulation; controlled release; multifunctional design	Limited number of polymers for clinical use; concerns over nanotoxicity; concerns over storage stability; poor PK
Polymer–drug conjugate	Covalent conjugation using stimuli-responsive linkers, such as pH-sensitive linker, disulfide and enzymatic degradable linker	Easy scale up; high drug loading; improved PK; reduced side effects; improved patient compliance; stimulated release in tumor through variable linkers	Slow hydrolysis; reduced bioactivity
Liposomal formulation	Self-assembly; remote loading from pH gradients	Biocompatible; reduction of side effects without compromising drug efficacy; suitable for delivery of drugs with diverse properties; suitable to various administration routes	Limited drug loading; poor shelf stability; high cost; complex sterilization process; slow release for hydrophobic drug
Nanocrystals	Nanoprecipitation; milling technology; high-pressure homogenization	Easy to scale up; reliable manufacturing quality; suitable for hydrophobic drugs with various properties; faster dissolution rate; improved bioavailability via oral delivery	High energy input; requires surfactant; lack of controlled release; not suitable for intravenous administration
LCP nanoparticles	Reaction based nanoprecipitation in microemulsion	Ability to encapsulate drugs with diverse properties without compromising drug efficacy; improved PK; small size; biodegradable; efficient drug encapsulation	Use of surfactant; relatively complicated manufacturing process
Inorganic nanoparticles	Covalent conjugation; nanoprecipitation; self assembly	Easily prepared with controllable size; surface functionalization; unique optical, electrical and physical properties	Concerns over nanotoxicity; few clinical applications; no FDA approved nanomedicines; not biodegradable
Solid lipid nanoparticles	High shear homogenization and ultrasound; high pressure homogenization; solvent emulsification/evaporation	No use of organic solvents; suitable to administer via various routes; established production method; controlled release; improved bioavailability; high drug payload	Particle growth; unpredictable gelation tendency; unexpected dynamics of polymeric transitions; occasional burst release observed