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Smart nanocarrier based on PEGylated hyaluronic acid for deacetyl mycoepoxydience: High stability with enhanced bioavailability and efficiency

Juan Zhao, Yancai Wang*, Yingying Ma, Yangyang Liu, Beibei Yan, Lulu Wang

School of Chemistry and Pharmaceutical Engineering, Qilu University of Technology (Shandong Academy of Sciences), Jinan 250353, PR China

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1-ethyl-3(3-(dimethylamino)propyl) carbodiimide (PubChem CID: 15908)
N-hydroxysuccinimide (PubChem CID: 80170)
Polyethylene glycol (PubChem CID: 174 (Ethylene glycol))
Folic acid (PubChem CID: 6037)
Hyaluronate sodium (PubChem CID: 3084049)
Vitamin E TPGS (PubChem CID: 71406)
Ethanol (PubChem CID: 702)
Distearoyl phosphatidyl ethanolamine (PubChem CID: 102547)
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ABSTRACT

Deacetyl mycoepoxydience (DM) nanocrystals core were stabilized by the folate modified distearoylphosphatidyl ethanolamine-polyethylene glycol (DSPE-PEG_{2000}-FA) as the active-targeting stabilizer and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as the reversion of multidrug resistance stabilizer, respectively. The DM nanocrystals was acted as the core and shelled by the polyethylene glycol-hyaluronic acid (PEG-HA). The optimal core-shell system demonstrated superior stability at 4 °C for 6 weeks by the stability study and higher dissolution velocity. Cytotoxicity *in vitro* and cell proliferation inhibition was evaluated by MCF-7 cells line. Furthermore, the core-shell nanocrystals revealed a concentration- and time-dependent cytotoxicity activity and enhanced the cell proliferation inhibition. Pharmacokinetic studies in rabbits showed core-shelled DM nanocrystals significantly increased AUC and $t_{1/2}$ and reduced CL_z compared to the DM solution for intravenous delivery. Results indicated that core-shell nanocrystals nanogel was successfully established with higher stability and the bioavailability of DM with higher safety was improved.

1. Introduction

To date, many classes of the new developed drugs on the market are poorly soluble in water, which, although effective, are thus excluded from further study. Nano-particulate drug delivery system especially nanocrystals (nanosuspensions) have been provoked an important and highly concerned alternative to enhance the solubility of insoluble drugs with novel physical properties (Muller, Gohla, & Keck, 2011; Rabinow, 2004). Drugs nanosuspensions occur as a pure drug system of sub-micron colloidal which is consisted of drug and surfactants (Pawar, Singh, Meher, Gupta, & Chourasia, 2014). However, scientific clinical application of nanosuspensions still are facing many challenging problems. Nanosuspensions are used in injection delivery showing lots of common issues, such as, the physical stability is unsatisfactory and it is difficult to control the drug delivery process and the distribution *in vivo* after intravenous injection (Wang, Zheng, Zhang, Wang, & Zhang, 2013, 2018).

The presence of stabilizers in nanosuspensions is usually required to avoid aggregation deposition between drug ions (Wong et al., 2008). The nanocrystalline system has a high Gibbs free energy, which leads to the tendency of the system to gather and ripen. Therefore, understanding of the principles of stabilizers screening and using is very important. In this study, it is bright to use the distearoylphosphatidyl ethanolamine-polyethylene glycol (DSPE-PEG_{2000}) (Wang et al., 2017).

Deacetyl mycoepoxydience (DM) is secondary metabolites with a rare oxygen-bridged cyclopentadiene (CPD) skeleton, which is isolated from *Phomopsis* sp. *A123* (Wang et al., 2010). DM has been confirmed possessing complete new structure compound with antitumor activity,

* Corresponding author.
E-mail address: wangyancai1999@163.com (Y. Wang).

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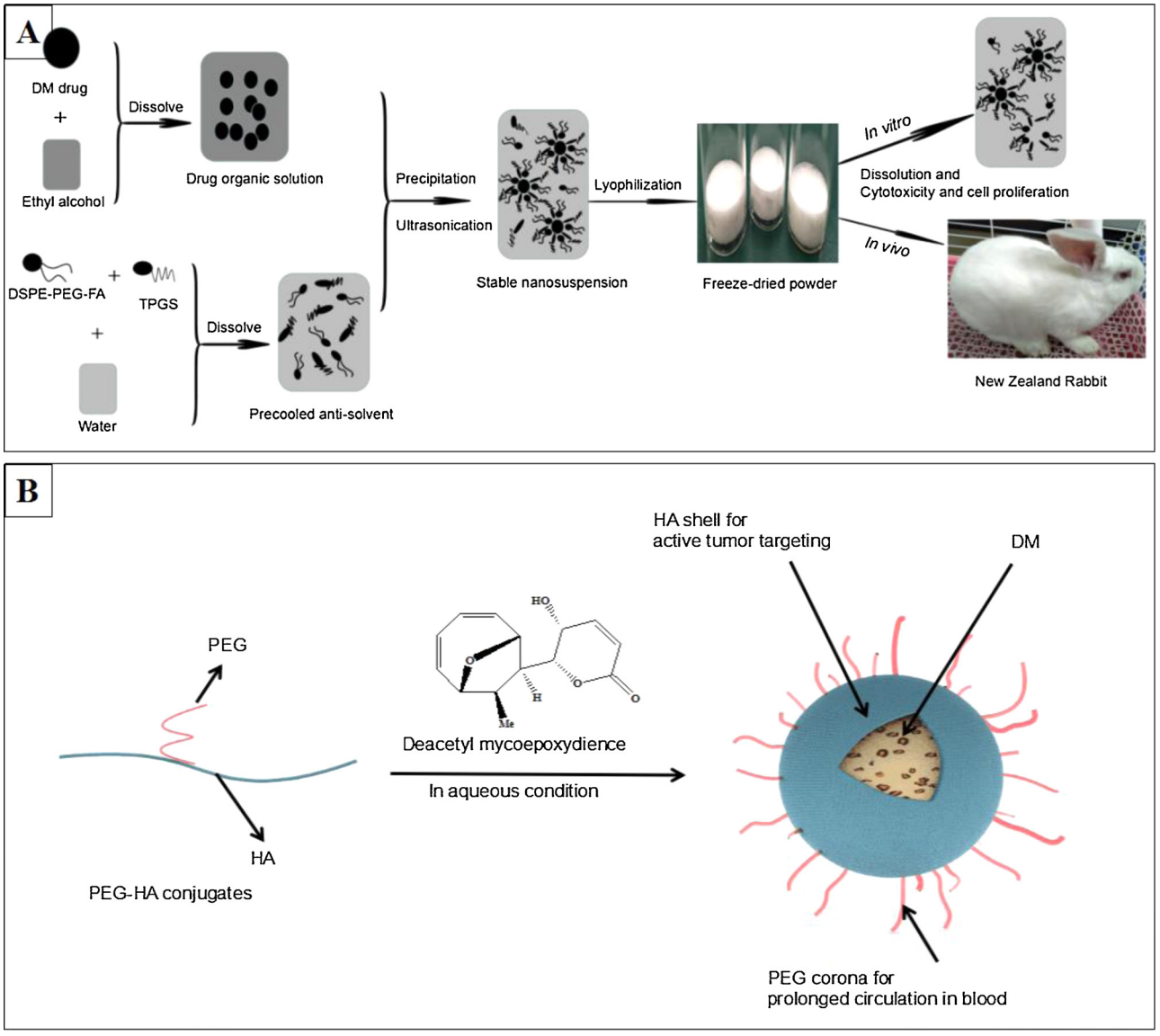

Fig. 1. Preparation of DM nanosuspensions by antisolvent precipitation (A) and the formation of drug-loaded self-assembled nanoparticles based on PEG-HA conjugate (B).

especially in the proliferation of breast cancer cells could be effectively inhibited (Zhu et al., 2015). Unfortunately, its poor water solubility brings a series of shackles like unsatisfying bioavailability and lack of long-term stability. Therefore, delivery of DM requires higher solubility and dissolution rates of drug, such as changes in particle size. Nanosuspensions of poorly soluble drug can be created by top-down and bottom-up approaches. Top-down approaches are widely used in industry. Rapamune, Emend, Avinza, Ritalin LA and Tricor have been approved by the FDA (Sun & Yeo, 2012). But these methods always require higher energy consumption and a longer operation time. Antisolvent precipitation is one of bottom-up approaches to prepared nanosuspensions, which presents lots of advantages (simple instruments, low input and energy demands) (de Azevedo Jacqueline, Fabienne, Jean-Jacques, & Inês, 2017; Yadav & Kumar, 2014), as shown in Fig. 1A.

Polyethylene glycol (PEG) is an hydrophilic polymer that is not only soluble in water but also in most organic solvents (Omar, Bardoogo, Corem-Salkmon, & Mizrahi, 2017). Many features should not be ignored, such as the physicochemical properties are stable, the side effects are small or not, and the biocompatibility is excellent, low immunogenicity, ambled to increase stability in the process of nanogel delivery. However, the hydroxyl activity of PEG is lower without modified activation, reaction with other groups will be more intense conditions, and even modified objects will be easily destroyed. PEG is used to modify protein, peptides, liposome and many small molecules such as organic materials in most cases (Min et al., 2010; Moghimi & Szebeni, 2003; Zhao et al., 2018). Therefore, the application of PEG activated into carboxyl has an important practical value (Shtenberg, Goldfeder, Schroeder, & Bianco-Peled, 2017).

As a highly bio-absorbable material with higher elasticity and plasticity, hyaluronic acid (HA) which is linear acid sticky polysaccharide, could specifically bind to a large amount of receptor CD44 on the surface of breast cancer cells with a large number of hydroxyl and carboxyl groups (Choi et al., 2009; Zhong et al., 2016). It dissolves in solution and can form numerous intra-molecular and inter-molecular hydrogen bonds which can make the HA molecular possesses rigid structure. They form a nanosized three-dimensional network structure, which has high load capacity and certain stability for nanocrystalline drugs. In addition, the nanogel shell formed by HA also has pH environment responsiveness, and is suitable as a stable carrier for small-sized nanocrystals, and can be controlled and transmitted to tumor tissues. Most of the CD44 receptors in normal cells are in silence or