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APPLICATION OF NANOTECHNOLOGY IN DRUG DELIVERY SYSTEMS FOR SILYBIN

Yixin Ding*, Chuyi Liu, Hongzhi Yu, Xiaochang Xu and Shuguang Jiang*

College of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China.

***Corresponding Author**: **Shuguang Jiang**
College of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China.

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ABSTRACT
Silybin, a water insoluble flavonolignan compound, which with low toxicity and high performance of protecting hepatic function, is the major active constituent of Silybum marianum Gaertn. However, the clinical application of silybin has been severely limited by the weakness of poor aqueous solubility and low oral bioavailability. Fortunately, nanotechnology has displayed a great potential since last two decades. Compared to traditional preparations, nanotechnology-based drug delivery system can improve the water solubility and bioavailability of insoluble drugs, prevent chemical degradation, and enhance pharmacological activity. Here we review several promising approaches to nanotechnology-based drug delivery for silybin. Although these efforts are still in early stages, nanotechnology has opened new ways to delivery water-insoluble drugs.

KEYWORDS: SILYBIN, SILIBININ, NANOTECHNOLOGY, APPLICATION.

INTRODUCTION
Silybin, synonymous with silibinin, is the main component of silymarin and is a polyphenolic bioactive natural product extracted from the seeds and fruits of the milk thistle plant *Silybum marianum*. The extract is a mixture of four isomeric flavonolignans, i.e., silybin, isosilybinin, silydianin and silychristin.[1] Besides, silybin is also a mixture of two diastereomers A and B in approximately 1:1 proportion (Fig. 1). Among the extract, silybin is the major biologically active component and largely responsible for the antihepatotoxic activity.[2] Also currently, silybin and its preparations are advocated for the treatment of cirrhosis, chronic hepatitis and liver diseases associated with alcohol consumption and environmental toxin exposure. Recently, silybin received attention due to its beneficial activities that are not directly bound to its hepatoprotective or antioxidant effects. These include mostly anticancer and chemopreventive actions, as well as hypocholesterolemic, cardioprotective, neuroactive and neuroprotective activities.

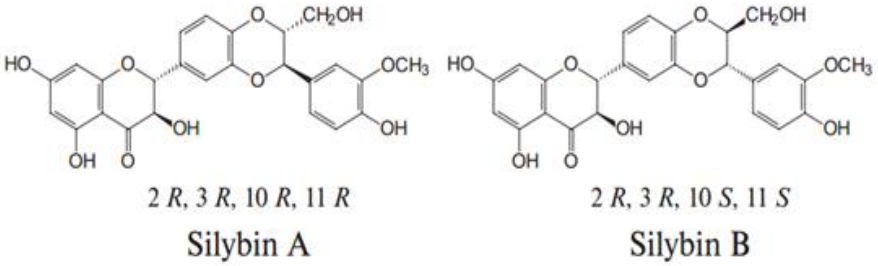

Fig. 1 structure of silybin A and silybin B

Silybin is considered safe and there are only a few reports on the adverse effects.[3][4] Gastrointestinal symptoms were the most common adverse effects reported, with a frequency ranging from 2% to 10% in controlled trials, which was indistinguishable from that of placebo.[3] Furthermore, Silybin displayed inhibition of the catalytic activities of cytochrome P450 (CYP) isoenzymes *in vitro* in concentrations greatly exceeding

physiologically reachable ones.[5][6] It was also shown that silybin does not interfere with the expression of CYP1A2 and CYP3A4.[7] These findings imply that no adverse effects of silybin in terms of drug-drug interactions would be expected. However, further study of mechanisms of action and well-designed clinical trials with detailed reporting of adverse effects are needed.

However, several factors such as low aqueous solubility, low oral bioavailability, short half-life and poor intestinal absorption limit its direct clinical use. Pharmacokinetic studies have shown that only 23%-47% of silybin is absorbed from the gastrointestinal tract upon oral administration.[8] Therefore, it is very necessary to develop new drug delivery systems to overcome shortcomings above. Fortunately, nanotechnology-based drug delivery system (NDDS) has displayed a great potential since last two decades. Compared to traditional preparations, NDDS can improve the water solubility and bioavailability of insoluble drugs, prevent physical and chemical degradation, enhance stability and pharmacological activity. Besides, it is a promising approach to reduce side effects and realize targeting or sustained drug delivery system. In regard to Solid lipid nanoparticles, liposomes, microemulsion and self-emulsifying drug delivery system, Chen[1] et al and Wang[2] et al have reviewed before, here we enumerated several new cases. Also, we reviewed some other new nanotechnology such as nanocrystal and carbon nanotubes.

Silybin-phytosome

Silybin-phytosome is one of the most widely applied silybin preparations, and preparation procedure is relatively mature. Silybin-phytosome preparation has been on the market now. Phytosome not only improves the biocompatibility of insoluble drugs, but also has therapeutic effects on a variety of diseases itself. But researchers are still trying to optimize the formulation. Loguercio et al[11] evaluate the effects of this new pharmaceutical complex of silybin-vitamin E-phospholipids in patients with nonalcoholic fatty liver disease. Data suggest that it can improve bioavailability, antioxidant and antifibrotic activity. The complex could be used as a complementary approach to the treatment of patients with chronic liver damage.

Emulsion

Self-emulsifying drug delivery system (SEDDS)[12] is a condensed mixture which is composed of the drug, oil phase, nonionic surfactants and cosurfactants. Through the gastrointestinal peristalsis or gentle stirring, it can be emulsified spontaneously as the size of less than 5μm in the gastrointestinal tract or 37°C environment. Ding et al[13] evaluated the silybin-SEDDS both in vitro and in vivo. Besides, the silybin-SEDDS was filled in a capsule to improve stability. The result in vivo showed that the relative bioavailability of silybin-SEDDS to free silybin reached to 1265.22% in the rat. With simple composition and process, the self-emulsifying drug delivery system is an excellent new dosage form.

Zhou et al[14] developed silybin emulsomes and evaluated their physicochemical properties and the in vivo pharmacokinetics of silybin delivered by emulsomes in rats. silybin emulsomes were prepared using the thin film dispersion method. The entrapment efficiency was above 80%. The average particle size and zeta potential were 364.1±20nm and -34±8mV, respectively. Compared to silybin solution, emulsomes produced sustained release for up to 48h after an initial burst release in vitro. The pharmacokinetics of silybin emulsomes in rats were evaluated after intravenous injection and the AUC was 2.2-fold higher and the mean residence time was 2.5-fold higher than the corresponding values recorded using silybin solution. Hence, emulsomes might represent a promising system for improving the bioavailability of lipophilic drugs.

Nanoparticles

Velmurugan et al[15] preparaed silybin nanoparticles and evaluated the effect for Hepatocellular carcinoma in-vitro and in-vivo. With the polymer of poly-ε-caprolactone, the silybin nanoparticles were prepared by Emulsion (o/w) solvent evaporation method. Results show that the number of neoplastic nodules was significantly reduced but no obvious decrease was observed in mean body weight. While the number of liver nodules was found reduced by more than 93%. It indicated that silybin nanoparticles were more effective and safe in the treatment of hepatocarcinoma in rats than that of silybin.

Gohulkumar et al[16] prepared silybin-loaded nanoparticles (SILNPs) with Eudragit® E (EE) and stabilizer of polyvinylalcohol (PVA) by the nanoprecipitation technique. The anticancer efficacy in oral carcinoma (KB) cells was evaluated. MTT assay showed that the cytotoxic efficacy of SILNPs was higher than that of free SIL. Contemporary, reactive oxygen species (ROS) determination revealed significantly higher intracellular ROS levels in SILNPs treated cells compared to free SIL treated cells. Thus, the difference in cytotoxicity between SILNPs and SIL may be due to the discrepancy of intracellular ROS levels. Moreover, the induction of apoptosis with nanoparticle treatment was confirmed and extent of DNA damage inSILNPs was significantly increased. These results suggest that silybin-loaded nanoparticles can be used as an effective drug delivery system to produce a better chemopreventive response for the treatment of cancer.

Nano-liposomes

The liposomes consist of an aqueous core entrapped by one or more bilayers composed of natural or synthetic lipids. The size of nano-liposomes is usually less than 100nm. Ochi et al[17] evaluated a co-encapsulated pegylated nano-liposome system based on two herbal anti-tumor drugs, silybin and glycyrrhizic acid, for

delivery to hepatocellular carcinoma (HCC) cell line (HepG2). The average size of nano-liposomes was 46.3nm with a narrow distribution, and the encapsulation efficiency (EE) for silybin was 24.37%. Results of in vitro study showed that the nano-liposome encapsulation of silibinin and glycyrrhizic acid increased the biological activity, stability and synergistic effect.

Ripoli et al[18] prepared phytoliposome-based silybin delivery system and evaluated the cellular delivery and antiviral activity. With reverse phase evaporation (RPE), the preparations use soybean lecithin (SL) as common phospholipid matrix. The data clearly demonstrated that the efficiency of cell absorption of phytoliposome-encapsulated silybin is 2.4 fold more than free silybin, and 300 fold more potent pharmacological activity. Furthermore, they observed that the phytoliposomes themselves could inhibit the virus entry by reducing the infectivity of viral particles. Results above suggested that the phytoliposomes used in this study may be a promising drug delivery system in the future.

Nanocrystal

A new silybin nanocrystal self-stabilized Pickering emulsion (SN-SSPE)[19] was developed using a high-pressure homogenization method to improve the oral bioavailability of silybin. The emulsion droplet of SN-SSPE with the size of 27.3± 3.1 μm showed a core–shell structure consisting of a core of oil and a shell of SN-NC. SN-SSPE has shown high stability over 40 days. The in vitro release rate of SN-SSPE was faster than silybin coarse powder and similar to silybin nanocrystalline suspension (SN-NCS). The peak concentration of silybin of SN-SSPE following intragastric administration in rats was increased by 2.5-fold and 3.6-fold compared with SN-NCS and silybin coarse powder, respectively. The AUC of SN-SSPE was increased by 1.6-fold and 4.0-fold compared with SN-NCS and silybin coarse powder, respectively. All these results showed that the Pickering emulsion of silybin could be stabilized by nanocrystals of silybin itself and increased the oral bioavailability of silybin. The drug nanocrystalline self-stabilized Pickering emulsion was a promising oral drug delivery system for poorly soluble drugs.

Carbon Nanotubes

Carbon nanotubes (CNTs) are carbon-based nanoparticles, with rolled-up graphene sheets held together by strong interactions of van der Waals to form large aggregates.[20] Due to unique electrical, optical, thermal, physical, and chemical properties, it has been a promising nanodrug delivery system in therapeutic applications. Tan et al[21] developed a silybin delivery system with commercially available carboxylated multiwalled carbon nanotubes (COOH-MWCNTs) and evaluated its in vitro sustained release and cytotoxicity action. It was found that the release of silybin from the COOH-MWCNTs nanocarrier was sustained and pH-dependent. The maximum dissolution was 96.6% and 43.1% within 1000 minutes when exposed to pH 7.4 and pH 4.8 solutions, respectively. The releasing curve fits pseudo-second order kinetic model well. MTT result showed that the silybin-MWCNTs exhibited enhanced cytotoxicity to human cancer cell lines in comparison with free silybin at lower concentrations. Therefore, the silybin-MWCNTs nanohybrid may be a promising nanodrug delivery system with sustained release property for the treatment of cancers.

Certainly, there are still many other interesting approaches. Since the extent of paper is limited, next we just enumerate briefly. Such as silybin β-cyclodextrin inclusion complexes[22], silybin-nanodispersion[23], porous silica nanoparticles[24], solid lipid nanoparticles[25][26], micelle-templated porous calcium phosphate microparticles[27], PEGylated-PLGA gold nanocomposite.[28]

CONCLUSION

All the nanotechnology-based drug delivery systems of silybin referred above can effectively improve dissolution in vitro and bioavailability in vivo. Some of them have proved the enhanced cytotoxicity to cancer cells. However, nanotechnology preparations also have much weakness. For example, the preparing process is usually very complex and lack of reproducibility, which is difficult to translate to industrial production. Besides, the drug loading capacity usually is very low and the preparations are unstable during storage. There is still a long way before they come to market.

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