Review

Advances in the nanoparticle drug delivery systems of silymarin

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Abstract: The recent advances in nanoscience and nanotechnology have greatly facilitated the development of nanoparticle drug delivery system. A nanoparticle drug delivery system of silymarin will improve its poor solubility in water and oil, thus enhancing its bioavailability. A variety of nanoparticle formulations of silymarin such as solid lipid nanoparticles, microemulsion and self-emulsifying drug delivery system, and liposomes have been extensively investigated. This paper reviews the advances of these formulations on their preparation and characterization, absorption and bioavailability, as well as in vivo and in vitro studies, in order to provide an assessment of current research for further pharmaceutical studies of silymarin.

Keywords: Nanoparticle drug delivery system; Silymarin; Research advances

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Contents

1. Introduction

Silymarins, a group of naturally occurring pentacyclic triterpenoids from milk thistle (*Silybum marianum*), are used in China, Germany, Japan, and other countries for the treatment of liver diseases. It has significant anti-neoplastic effect on prostate, colon, bladder and lung cancers[1]. Silymarin is a low solubility drug with high permeability, composed of three isomeric compounds, silibinin, silidianin and silicristin. Its main biological active component is silibinin, which is largely responsible for the anti-hepatotoxic activity[2]. Silibinin and its derivative, dehydrosilybin, inhibit glucose uptake by directly interacting with GLUT4 in 3T3-L1 adipocytes[3]. It also could form dimers regioselectively through bond formation and tautomerisation[4]. Various clinical and pharmacological effects of silymarin have been reported, such as targeting cancer cell metastasis[1,5], inducing activation of death receptor and mitochondrial apoptotic pathways in human breast cancer MCF-7 cells[6]. Unfortunately, silymarin's poor solubility in water and oil has resulted in permeation through the intestinal epithelial membrane and low absorption in rats' gastrointestinal tracts[7]. Therefore, there is a strong need to develop new drug

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delivery systems to improve the solubility and bioavailability of silymarin[8].

In the past decades, increasing attention has been paid to the development of nanoparticle drug delivery systems[9]. The emergence of nanoscience and nanotechnology allows the creation and utilization of materials and tools at the nanometer scale, which has had a particularly strong impact on the pharmaceutical industry[10]. The nanoparticle dosage forms include polymeric nanoparticles and nanocapsules, liposomes, solid lipid nanoparticles (SLNs), and nanoemulsion. Compared to conventional dosage forms, nanoparticle drug delivery system could enhance the solubility, stability, bioavailability, and pharmacological activity, improve tissue macrophages distribution, protect from physical and chemical degradation, and decrease toxicity[10,11].

In this review, nanoparticle systems were discussed with respect to SLNs, microemulsion, and a self-emulsifying drug delivery system. Recent investigations have shown that nanoparticle drug deliver systems would be more appropriate dosage forms to meet the clinical application requirement for silymarin.

2. Solid lipid nanoparticles

2.1. Preparation and characterization

Silymarin-loaded solid lipid nanoparticles (Sly-SLNs) can be prepared by the cold homogenization technique, and characterized using mean diameter, entrapment efficiency and drug loading[12]. The influencing factors, such as ratios between drug to Compritol 888 ATO, amount of emulsifier, and poloxamer 188 in the emulsifier and homogenization pressure were investigated[13]. Under the optimal conditions, the prepared Sly-SLNs have a mean diameter of 190.9 nm, entrapment efficiency of 95.9%, and drug loading of 8.6%[13].

It was reported that the mixture of 2% lactose and 2% glucose could prevent nanoparticles from aggregating followed by the optimal lyophilization process: precooled at –45 ºC for 10 h; primary drying at –25 ºC for 5 h; secondary drying at 10 ºC for 3 h; finally drying at 30 ºC for 6 h[14]. The wide particle size distribution during lyophilization could be minimized by optimizing the parameters of the lyophilization process and adding a supporting agent[14].

Further study found that SLNs composed of stearic acid and surfactant Brij 78 (polyoxyethylene 20 stearyl ether) can incorporate fairly large amounts of silibinin (up to 7.55%) as colloidal carriers. Silibinin-loaded nanoparticles in nanometer range were dispersed in an amorphous state and can be used for their parenteral administration[15].

2.2. Oral absorption and bioavailability

SLNs of various sizes (150, 500 and 1000 nm) parpared by Compritol 888 ATO as the material and silymarin as a model drug were investigated to determine the effects of particle size on their oral absorption. The author reported that the *AUC* of 150 nm SLNs was 2.08-fold higher than that of 500 nm SLNs and 2.54-fold higher than that of 1000 nm SLNs administered orally to rats ($P<0.05$). The oral bioavailability of 150 nm SLNs was remarkably higher than the other two sizes[16].

For in vivo study, the oral bioavailability of Sly-SLNs in beagle dogs was studied; it was confirmed that SLN was a good carrier for improving the oral bioavailability of poorly soluble drugs[17]. Sly-SLNs had better bioavailability than the reference preparation (Yiganling Pian as reference). The pharmacokinetics of tested preparation and Yiganling Pian can be fitted with one compartment model, and the relative bioavailability of Sly-SLNs was 258%[17].

3. Microemulsion and self-emulsifying drug delivery system

3.1. Preparation and formulation

Self-emulsifying drug delivery systems (SEDDS) are consisting of oils and surfactants, ideally isotropic, and co-solvents to form a fine oil-in-water emulsion in order to improve the drug's bioavailability[18]. Micronized silybin particles were prepared by emulsion solvent diffusion and uniform spherical and rod-shaped particles were formed with a mean size of 2.48 μm and 0.89 μm using 0.1% sodium dodecyl sulfate at 30 ºC and 15 ºC, respectively[19].

Compared to the commercial silybin powder, both the spherical and rod-shaped silybin particles exhibited a significantly enhanced dissolution rate. Long et al. investigated the formulation of SEDDS by orthogonal design and evaluated its emulsifying rate, light transmittance, and dissolution[20]. They concluded that when the silymarin SEDDS was composed of Tween-85, olive oil, glycerin, and silymarin, its dissolution in simulated gastric fluid and intestinal fluid was the same as silymarin capsules (Legalon) from Germany.

3.2. Experiment design method

Pseudo-ternary phase diagrams are widely used to design SEDDS. Oil, surfactant and co-solvent were selected by determining the solubility of silymarin and drawing pseudo-ternary phase diagrams. Subsequently, silymarin self-emulsifying microemulsion was prepared using particle size, emulsification time and color of emulsion as the evaluation indexes[21]. When the formulation contained 5% silymarin and the glycerin octanoate, decanoate, Cremophor RH40 and 1,2-propylene glycol ratio was 0.5:5:3.6:0.9, a satisfactory self-microemulsifying effect could be achieved. The emulsion particles were 68.6 nm in average diameter, micro-emulsified within 3 min, and dissolved completely in 0.1 mol/L HCl within 10–15 min.

It has recently been reported that silymarin self-microemulsifying capsules were developed by investigating the solubility of silymarin in different media by constructing a pseudo-ternary phase diagram. By studying the pharmacokinetics after oral administration of silymarin self-microemulsifying capsules and raw material in rats, it was shown that the formulation of silymarin self-microemulsifying drug capsules could significantly increase drug dissolution in vitro and absorption in vivo[22].

3.3. In vivo and in vitro studies

The difference in bioavailability between silymarin self-microemulsion and commercial silymarin capsule was determined in dogs by oral administration. Firstly, dynamic light scattering, transmission electron microscope, accelerated tests, and dialysis methods were used to evaluate the physical properties[23]. After silymarin self-microemulsion was confirmed to have good stability, oral administration to dogs was carried out to determine bioavailability. The author concluded that the self-microemulsion formulation of silymarin was obtained easily and the bioavailiablity of silymarin was increased significantly. In addition, Xiao et al. surveyed the morphology and size distribution of silymarin microemulsion to investigate absorption in rat intestine as well as the absorption of silymarin micelle in rat jejunum[24]. The result showed that silymarin microemulsion was well absorbed at the middle and lower segments of intestine in rats and the absorption was a first-order process with a passive diffusion mechanism.

4. Liposomes

El-Samaligy et al. introduced silymarin hybrid liposomes for buccal administration to improve the poor bioavailability of oral products, after investigating the stability and in vivo hepatoprotective efficiency[2]. Silymarin-loaded hybrid liposomes were prepared by lecithin, cholesterol, stearyl amine and Tween 20 in a molar ratio of 9:1:1:0.5[2]. The prepared silymarin hybrid liposomes produced a significant decrease in transaminase levels when challenged with CCl_4 (intraperitonially) in comparison with orally administered silymarin suspension, which was also confirmed histopathologically.

The protective effect of silymarin liposomes (L-SIL) on the CCl_4 induced acute liver injury in mice was investigated. L-SIL could inhibit the increase of serum ALT, AST levels induced by CCl_4 in a dose-dependent manner (P<0.05–0.01), decrease MDA content (P<0.01) and prevent the SOD and GSH-PX reduction in the liver homogenate (P<0.05–0.01)[25]. The protective effect of L-SIL on CCl_4-induced acute liver injury in mice was more effective than that of silymarin tablets (T-SIL) at the same dosage. The same authors also investigated the protective effect of L-SIL on the BCG+LPS-induced liver injury in mice in comparison with T-SIL[26]. The result showed that L-SIL could inhibit the increase of serum ALT, AST activities induced by BCG+LPS, decrease MDA, NO contents, reduce the coefficient of liver and prevent the reduction of SOD, GSH-PX activities in the liver homogenate.

The protective effect of L-SIL on the BCG+LPS-induced liver injury in mice was more effective than that of the same dose of T-SIL.

5. Other nanoparticle formulation

Silymarin proliposome was prepared using the film-deposition on carriers and the pharmacokinetic characteristics and bioavailability after oral administration of silymarin proliposome and silymarin in beagle dogs were compared, in order to find a method to increase oral bioavailability of silymarin[27]. Silymarin proliposome was stable and the gastrointestinal absorption of silymarin was enhanced. The silymarin liposome suspensions formed automatically after the proliposome was contacted with water. The high bioavailability of silymarin proliposome could be obtained by oral administration[27]. Furthermore, nanosuspensions of silybin with smaller particle size revealed a higher potential to increase their oral bioavailability due to the increased surface area. For intravenous infusion, the lower pressure produced silybin nanosuspensions appeared to maintain a more sustained drug release profile compared to the coarse powder[28].

6. Conclusions

Silymarin, which is a member of triterpenoids, is widely used for the treatment of liver disease and cancer. Nanoparticle drug delivery system is developed for the clinical application to enhance the aqueous solubility. However, more studies are needed to investigate the mechanisms of the nanoparticle drug delivery system of silymarin.

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水飞蓟素纳米传递系统的研究进展

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摘要: 纳米科学和纳米技术在纳米药物传递系统中具有很大的潜力。水飞蓟素纳米药物传递系统的研究和开发将改善其水溶性和脂溶性, 并提高生物利用度。固体脂质纳米粒、微乳、自微乳和脂质体等一系列水飞蓟素纳米处方的研究已越来越受到关注。本文综述了水飞蓟素纳米制剂的制备表征, 性能评价, 吸收、生物利用度等体内外研究, 为其制剂的进一步研究提供科学基础。

关键词: 纳米传递系统; 水飞蓟素; 研究进展