Review

Phytosomes: an effective approach to enhance the oral bioavailability of active constituents extracted from plants

Haijun Hao*, Youzhi Jia, Ru Han

Instrumental Analysis & Research Center, Shanghai Institute of Pharmaceutical Industry, Shanghai 200437, China

Abstract: Many active constituents from herbal plants have well-established pharmacological effects in vitro. But they demonstrate less or no activities in vivo due to various problems of themselves, which severely restricts their clinical applications. After forming phytosomes with phospholipids in aprotic solvent, the active constituents exhibit different physicochemical properties from the free form. In particular, the bioavailability of the active constituent-phytosomes is enhanced greatly due to the improved capacity to cross the biomembrane and reach circulation. Therefore, increasing attention has been attracted to the use of phytosomes in recent years. Based on the published reports, we reviewed the recent progress in the research of phytosomes including preparation, characterization, structure verification and clinical applications.

Keywords: Phospholipids; Phytosomes; Active constituents; Bioavailability

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Contents

1. Introduction

Many active constituents extracted from herbal plants show limited efficacy in vivo, because they are poorly absorbed due to poor solubility and other undesirable properties[1]. The lack of in vivo activity represents one of the greatest challenges in modern pharmaceutical research. The effectiveness of many herbal medication is dependent on delivering an effective level of the active constituents[1,2]. Therefore, increasing the absorption of these active constituents is very important for improving the pharmacological effects. In recent years, many approaches have been developed to improve the oral bioavailability. Among the possible strategies, the preparation of phytosomes (or named as phospholipid complex) from natural resources[3,4] represents an exciting approach. Phytosomes are an advanced form of formulation produced by binding

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*Corresponding author. Tel.: 86-21-55514600-222;
E-mail: haohj2007@126.com

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active constituents of herbal extract to phospholipids through charge transfer in aprotic solvent, resulting in a product that is better absorbed and produces higher bioavailability compared to free active constituents. The term “phyto” means plant while “somes” means cell-like. The mainly used phospholipids to make phytosomes is phosphatidylcholine. Some active constituents can form complex with phospholipids under certain conditions. After forming phytosomes with phospholipids, the cell membrane permeability of active constituents is improved greatly, which increases the bioavailability. Moreover, phospholipids is an important component of cell membrane, which has low toxicity and good biocompatibility. It also plays a significant role in maintaining the normal structure of liver, and people who lack of phospholipids are vulnerable to diseases such as hepatitis fatty liver and hepatocirrhosis[5]. The formulation of active constituents with phospholipids could produce lipid compatible complexes (Fig. 1), exhibiting better pharmacokinetic and pharmacodynamic profile than free herbal extracts. The active constituents carried by phytosomes are well protected from destruction by digestive enzymes and gut bacteria, leading to higher bioavailability and activity than their non-complexed active constituents[6–13].

The phytosomal formulations have gained importance in various fields like pharmaceuticals, cosmeceuticals and nutraceuticals in preparing different formulations such as solutions, emulsion, creams, lotions, gels, etc. This article reviews the progress in phytosome research and highlights the recent advances in their therapeutic applications.

2. Properties of phytosomes

Phytosome is a complex formed by active constituent and phosphatidylcholine. Based on their physicochemical and spectroscopic properties, it has been shown that the main interaction of active constituent-phytosomes is the hydrogen bonds between the polar head of phosphatidylcholine and the polar groups of the substrate[14–16]. Phytosomes can form agglomerates when treated with water, resembling a small cell in appearance likes liposomes, but the formation mechanisms of liposome and phytosome exhibit fundamental differences. The difference between liposomes and phytosomes is shown in Figure 2. The liposomes are closed vesicles formed by lipid bilayers, encapsulating drugs in an aqueous compartment or multiple lipid bilayers, but not mixing with drugs. There may be hundreds or even thousands of lipid molecules surrounding water-soluble compound. However, phytosomes are formed by the combination of drugs with the polar end of phosphatidylcholine, becoming an integral part of the membrane[17–19] and the ratio is from 1:1 to 1:2 depending on the drug substance(s)[20]. Phytosomes look like liposomes, but not a drug delivery system. These differences result in phytosomes being much better absorbed than liposomes. Phytosomes have also been found superior to liposomes in topical and skin care applications[15,16].

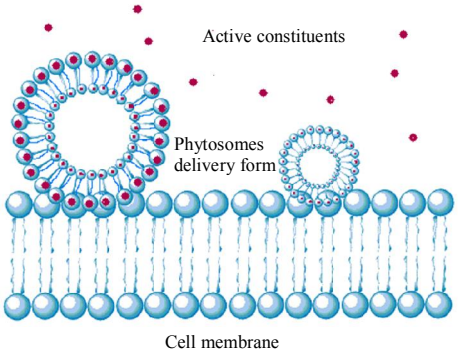

Figure 1. Active constituent-phytosomes produce a lipid compatible molecular complex.

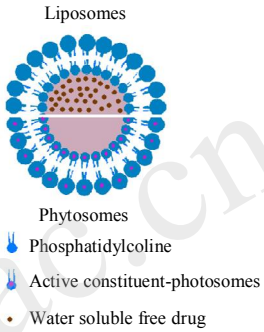

Figure 2. Difference between liposomes and phytosomes.

Active constituents with high polarity can not overcome the lipid barrier of the skin or gastro-intestinal system, leading to poor absorption. The phytosomes can help to reduce the polarity of active constituents, making them more easily absorbable. So the phytosomes formulation can be used to improve the absorption of active constituents.

3. Preparation of phytosomes

Natural or synthetic phospholipids (such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine) are used to prepare phytosomes. Solvent evaporation method is the most common technique for the preparation of phytosomes. The aprotic solvent is usually needed to avoid the interfering interactions between active constituents and phosphatidylcholine. The common candidate solvents are acetone, dichloride methylene, tetrahydrofunan, ethyl acetate and so on[11,16–23]. The complexes become extremely soluble in these solvents after forming phytosomes comparing to active constituent alone. The change of solubility is due to the formation of true stable complexes[24]. Recently, a newer method for the preparation of phytosomes was developed using hydroethanolic solvents, because products made in this way are in compliance with the regulation of health and food products[25,26].

The appropriate ratios of active constituents and phospholipid are placed in round-bottom flask and dissolved in appropriate reaction medium. Then the complex can be isolated by vacuum drying, lyophilization or spray

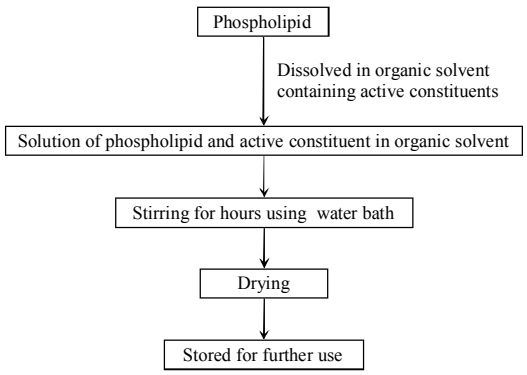

Figure 3. Common stages for preparation of phytosomes.

drying[27,28]. The dried residues are filtered to obtain pure active constituent-phytosomes. The common steps for preparation of phytosomes are shown in Figure 3. In addition, it is important to make sure that the reaction medium is as completely removed as possible.

The yield (%) of active constituent in complex with phospholipid is a very important index for the preparation. The free active constituents are precipitated and separated. The yield (%) of active constituent in complex with phospholipids is determined using the following formula equation: The yield (%) = [(a – b)/a] × 100%. Where 'a' is the content of active constituents in complex with phospholipids, 'b' is the content of free active constituents in the complex.

Because the reaction temperature, phospholipid-to-active constituent ratio, reaction time and drug concentration highly influence the yield (%), a central composite design approach[22,29] and a spherical symmetric design-response surface methodology[30,31] are used for process optimization.

4. Characterization of phytosomes

4.1. Differential scanning calorimetry

Differential scanning calorimetry (DSC) is a thermoanalytical technique used to measure a number of properties of a sample. It is possible to observe the transition temperature, the elimination of endothermic peaks, appearance of new peaks, changes of relative peaks area and so on[21,24,32–34].

4.2. Dynamic light scattering and photon correlation spectroscopy

The particle size and zeta potential can be determined by dynamic light scattering (DLS), using a computerized inspection system. Photon correlation spectroscopy (PCS) can also be used to determine the particle size of phytosomes[35].

4.3. Scanning electron microscopy and transmission electron microscopy

The surface morphology of the complex can be observed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). In the complex, active constituents are combined with the polar part of phospholipids. When stirred in distilled water, lots of complexes form a structure of vesicles by themselves. Therefore, there are many particles suspended in water, like liposomes but not liposomes essentially[21,24,32,33,36,37].

4.4. X-ray diffractometry

X-ray diffractometry (XRD) is used to identify specific crystalline compounds based on their crystal structure. The results of related researches[19,21,24,29,32,38,39] show that the powder X-ray diffraction pattern of active constituents usually consists of partial sharp crystalline peaks, which is the characteristic of an organic molecule with some crystallinity. In contrast, phospholipids generally show an amorphous structure lacking crystalline peaks. The crystalline peaks usually disappear in the phytosomes compared with that of the physical mixture.

4.5. UV-spectra

Appropriate amounts of the test samples (active constituents, phospholipids, their physical mixture and the complex) are used to obtain the UV-spectra. Some results[30,40] show that the UV absorption characteristics of active constituents before and after complexation usually have no difference, which is a strong indication that the bonding of the drug with phospholipids does not affect the conjugation system of drug and the chromophores are not altered.

4.6. Solubility studies

The determination of solubility of active constituent, active constituent-phytosomes and physical mixture of active constituent and phospholipids in *n*-octanol/water, or known as *n*-octanol/water partition coefficient (*P*), are necessary for solubility studies. Due to the strong dispersibility or/and amorphous form of active constituent-phytosomes, which can significantly increase the lipophilicity and hydrophilicity of active constituents. The solubility of phytosomes could be much higher than that of active constituents[19,21,24,33,38].

5. Structure verification of phytosomes

In order to confirm the formation of phytosomes as well as to study the corresponding interaction between active constituent and phospholipids, the following methods usually employed.

5.1. Nuclear magnetic resonance

The nuclear magnetic resonance (NMR) spectrum of the silybin-phospholipid complex has been studied[40]. The ^{1}H NMR spectrum showed that the signals of the protons in silybin and phospholipids had remarkable distinction,

some of the phospholipids protons have weakened so remarkably that they can not be observed, indicating that these protons were involved in the formation of the complex, whereas the proton signals of the fatty acid chains in phospholipids were still clear with no change, indicating that they were not involved in complexation.

In the study of the silybin-phospholipid complex by ^{13}C NMR[40], the results showed that the relaxation time of the drug's carbon cores has decreased significantly, making the corresponding signals of the carbon spectrum decreased or disappeared. Meanwhile, the signals of $-N(CH_3)_3^+$ in phospholipids have broadened, whereas conjugant signals of fatty acid chains retain their original sharp peaks.

These NMR studies demonstrate that information obtained from ^{13}C NMR and ^{1}H NMR spectrum can help us to confirm the formation of active constituent-phytosomes or to study reciprocal interaction between the active constituents and the phospholipids.

5.2. FTIR spectroscopy

The structure of the complex also can be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their physical mixtures. It has been reported that[41] the physical mixture of matrine and phospholipids and the matrine-phospholipid complex showed distinct IR spectra. Compared with the complex, the peaks at 1737 cm^{-1} and 1630 cm^{-1} were clearly found in the spectrum of physical mixture. However, in the spectrum of their complex, the characteristic absorption peak of matrine was almost completely masked by that of phospholipid at 1644 cm^{-1}. The FTIR method can also be considered as a valuable tool in confirming the stability of active constituent-phytosomes by comparing its spectrum in solid form with that of the spectrum of micro-dispersion in water after lyophhilization at different times[42].

6. Advantages of phytosomes

Compared to conventional formulations, phytosomes have many advantages[43]. The yield (%) of active constituent in complex with phospholipids is relative high. Related researches[14,18–24,27,29,31] showed that the yields of prepared phytosomes were all above 92%. Because of the strong interactions between phosphatidylcholine and active constituents, phytosomes have relatively stable profile. It is reported[44] that phytosomes are stable under the freezing condition (–20 °C) for months, which confirms the physicochemical stability. Phytosomes can form small cells in gastrointestinal tract, which can protect active constituents from destruction by digestive enzymes and gut bacteria[21,24,32,33,36,37]. Phytosomes can be transported from a hydrophilic environment to the lipid-friendly environment of the enterocyte cell membrane and continue into the cells and finally reaching the blood. Therefore, phytosomes can enhance the bioavailability of active constituents greatly. The dose required is also reduced [14,22,32,33,37]. Dmello et al[45] evaluated hepatoprotective activity of the ethanolic extract of *P. guajava* (200, 400 mg/kg) and its phospholipids complex (100 mg/kg), the results showed that the complex exhibited better protective effect against hepatotoxicity than the plain extract at lower does. Using phospholipids as material for the preparation of active constituent-phytosomes, the resulting phytosomes not only have low toxicity and good biocompatibility but also can show synergistic action when hepatoprotective drugs are administrated[37]. In liposomes, the active constituent is dissolved in the medium contained in the cavity or in the layers of the membrane, whereas in the phytosomes it is an integral part of the membrane. Therefore, phytosomes are superior to liposomes in skin care products[15].

7. Effect of phytosomes on cellular permeability

In order to understand whether the active constituent-phytosomes enhance the cellular permeability compared to free drug, intestinal perfusion model and Caco-2 cell culture model can be employed.

7.1. Intestinal perfusion model

Intestinal perfusion models include Sing Pass Intestinal Perfusion (SPIP) and Cycle Intestinal Perfusion (CIP). Zhou et al reported[47] that apparent permeability coefficients (*Papp*) of the zedoary turmeric oil phospholipid complex was enhanced by about 5 times compared to free drugs using SPIP model. Tang et al[48] employed the CIP to investigate the *Papp* of breviscapine phytosomes. The results showed that the intestinal permeability of breviscapine was enhanced by 73.13%. These results indicated that the phospholipid complex can increase the hydrophilicity of the free active constituents, which improves the absorption in intestine of rats significantly.

7.2. Caco-2 cell culture model

In order to predict the bioavailability of prepared phospholipid complex, Caco-2 cell model can be employed. Chen et al reported[49] that the *Papp* of baicalin-phospholipid complex was significantly greater than that of free drug ($P<0.05$), which closely correlated with phytosomes produce a lipid compatible molecular complex.

8. Applications in medicine

Many drugs have obvious pharmacological effects but limited clinical applications. They can be made into phytosomes to improve the absorption and bioavailability of the active constituents. In order to examine the various

advantages of phytosomes, especially their ability to enhance the bioavailability of active constituents as compared with the conventional means, various therapeutic applications in medicine of phytosomes have been explored. The earliest class of drugs used to prepare phytosomes was the flavoniods, and most of the phytosomal studies were focused on silybum marianum[33,40,44,50,51]. It was discovered later that other class of drugs could also been prepared into phytosomes. Moreover, the phytosome formulation can also be applied on cosmetics, when topically applied on the skin it can increase the absorption of active ingredients[42,52–55].

Silybin, similar to other flavonoids, is not well-absorbed. When combining with phospholipids, water-soluble flavonoid molecules can be converted into lipid-soluble complexes. Xiao et al[33] prepared silybin-phospholipid complex to increase oral bioavailability of silybin. After a series of steps silybin-phospholipid complex was formed. Due to an impressive improvement of the lipophilic property of the complex, the solubility of complex in water and in *n*-octanol was greatly enhanced and the bioavailability in rats was also increased remarkably after oral administration of the silybin-phospholipid complex.

Tedesco et al[56] reported that when silymarin was made into silymarin phospholipid complex (silymarin phytosome), it showed better anti-hepatotoxic activity than silymarin alone and could provide protection against the negative effects of aflatoxin B_1 (AFB_1) in broiler chicks. Bombardelli et al[57] reported that when silymarin was combined with phospholipids, the complex showed higher specific activity and a longer lasting action than non-complexed constituents. Barzaghi et al[58] conducted a human study to assess the absorption and pharmacokinetic profile of silybin when combined with phopholipids. In his study plasma levels were determined after oral administration of silybin-phytosomes and a similar amount of silybin in healthy volunteers. The result indicated that the complexation with phospholipids greatly increases the oral bioavailability of silybin compared to the absorption of silybin, probably by facilitating its passage across the gastrointestinal mucosa.

Qin et al[30] prepared a bergenin-phospholipid complex to increase oral bioavailability of bergenin. After investigated the influence of reaction temperature, drug concentration and the drug to phospholipid ratio, they found that these factors highly influenced the combination percentage. A statistical model incorporating interactive and polynomial terms was used to evaluate the response, and they finally found the optimum condition for the preparation of bergenin-phospholipid complex. Their results indicated that bergenin-phospholipid complex could enhance solubility and improve oral bioavailability.

Maiti et al[37] prepared curcumin-phospholipid complex to overcome the limitation of absorption and to investigate the protective effect of curcumin-phospholipid complex on acute liver damage in rats. The results indicated that curcumin-phospholipid complex could significantly protect the damaged liver comparing with free curcumin at the same doses. In their animal experiment, they found that serum concentration of curcumin obtained from the complex was higher than from pure curcumin and that the complex maintained effective concentration of curcumin for a longer period of time in rat serum.

Quercetin is a typical flavonoid with diverse biological effects, such as apoptosis induction, antimutagenesis, protein kinase C inhibition, lipoxygenase inhibition and so on. Due to bacterial degradation of the molecule, its absorption is very poor when administered orally or by topical application. In order to enhance the therapeutic efficacy of quercetin, the quercetin-phospholipid complex was prepared[59], and the results showed that the complex had higher efficacy in animal study when comparing to the molecule itself.

Hyaluronic acid (HA) is an acidic linear mucopolysaccharide, possessing an important function of water keeping[60]. However, several limitations exist and influence the gastrointestinal absorption of exogenous HA when it is administered orally, such as high relative molecular mass (Mr) and poor liposolubility of HA. Huang et al[61] reported that the physicochemical properties of HA-phospholipid complex were different from free HA. After the complex was administered to rats orally, the serum concentration of HA was increased when compared with the physical mixture or HA control groups ($P<0.05$). The $AUC_{0-12\,h}$ of HA-phospholipid complex was also greater than that of the other groups ($P<0.05$).

Naringenin (4′,5,7-trihydroxyflavanone) is a naturally occurring flavanone, possessing a variety of biological activity. Due to its rapid elimination, naringenin needs frequent administration to maintain an effective plasma concentration. Maiti et al[62] reported that the naringenin-phospholipid complex could enhance the antioxidant activity of the molecule and reduce the fast elimination of the molecule from human body. The complex also protected the liver significantly for a longer time as compared with naringenin itself at the same dose level.

Ursodeoxycholic acid (3α,7β-dihydroxy-5β-cholanoicacid, UDCA) can be used for the dissolution of cholesterol-rich gallstones in patients with functioning gallbladders and in the treatment of primary biliary cirrhosis. UDCA has also shown some promise in the treatment of non-alcoholic steatohepatitis and refractory graft-versus-host disease of the liver in transplant patients. However, the absorption is very poor when administered orally or by topical application. Yue et al[27] employed the UDCA-PLC to improve the bioavailability of ursodeoxycholic acid, and the results showed that the relative bioavailability of UDCA-PLC was increased by 241% compared with the ursodeoxycholic acid tablet.

Daidzein is one of the main abundant isoflavones in soybean and pueraria, and it shows various biological activities such as estrogenic activity, antidipsotropic, antiatherogenic and antiosteoporotic activity. However, daidzein has poor hydrophilicity and lipophilicity, which

Table 1. Commercially available phytosome preparations

Phytosomes	Active constituents	Indications
Ginkgoselect phytosomes	Ginkgo flavono glycosides	Antiskin ageing
Hawthorne phytosomes	Flavonoids	Strengthen cardiovascular system
Ginselect	Saponins	Good choice for anti-aging
Mirtoselect phytosomes	Antcinocide	Antioxidant
Leucoselect phytosomes	Procyanidolic oligomers (PCOs)	Protects against heart disease
Silybin phytosomes	Silybin	Food Product, antioxidant
Panax	Ginsenosides	Food Product
Green tea phytosomes	Epigallocatechin3-*O*-gallate	Protection against cancer, food product
Olive oil phytosomes	Polyphenols	Anti-inflammatoryactivity
Ginseng phytosomes	Ginsenosides	Nutraceutical, immunomodulator
Echinacea phytosomes	Echinacosides	Nutraceutical, immunomodulator
Glycyrrhiza phytosomes	18-Beta glycyrrhetinic acid	Anti-inflammatory activity
Grapeseed phytosomes	Procyanidins	Nutraceutical, systemic antioxidant
PA_2 phytosome	Proanthocyanidin A_2	U.V. protectant
Escin β-sitosterol phytosome	Escin β- sitosterol	Antioedema
Crataegus phytosome	Vitexin-2-*O*-rhamnoside	Antioxidant
Centella phytosomes	Terpenes	Vein and skin disorders

limits its intestinal absorption. Zhang et al[63] provided an effective strategy to formulate daidzein into daidzein-phospholipid complex and then lipid nanocarriers (DLNs) to improve its intestinal absorption after oral administration. The results showed that the areas under the concentration-time curve (AUC_{0-t}) of DPC and DLNs were enhanced by 3.62-fold and 6.87-fold compared with that of free drug, which suggested that the phospholipid complex improved the oral absorption of active constituent.

These described experimental results demonstrated that phytosomes as a novel drug delivery system could improve the property of active constituents and increase their bioavailability and enhance their therapeutic efficacy due to their complexation with phospholipids[64]. The details of the type of phytosomes, active constituents, and indications are listed in Table 1.

9. Discussion and conclusion

Phytosomal products showed their great potential in cosmetics[15,16,49–51,54] and were firstly investigated in this field, but mounting evidence of potential for herbal drug delivery also has been accumulated in recent years[65]. The poor absorption of some constituents, particularly polyphenolics, is due to two main factors. First, these are multiple-ring molecules not quite small enough to be absorbed from the intestine into the blood. Second, they typically have lipophilicity with oils and other lipids. Phytosomes can improve the lipophilicity of active constituents significantly, which could be advantageous for permeating cell membranes and entering into systemic circulating or the interior of tissue cells to exert pharmacological effects. The increased bioavailability of the phytosomes over the free herbal active constituents has been demonstrated by pharmacokinetics research or by pharmacodynamic studies in animals[11,12,25–27,29–31,33]. Recently, a number of drug delivery systems are emerging and the delivery systems based on phospholipids show great potentials.

The formation mechanism of active constituent-phytosomes has also been studied. Several types of interactions, like ionic interaction, hydrogen bonding, and Van der Waals forces, are involved in the formation of phytosomes. However, it cannot explain why some active constituents are unable to form phytosomes with phospholipids. With the advance of research of phytosomes, more suitable explanation will emerge[44].

The active constituent-phytosomes can also be used to prepare solid dispersions[34], microemulsion[66], nanoparticles[38,63,67–70], mixed micelles[71,72], self-emulsifying drug delivery systems (SEDDS)[41,73], polymer gel[24,74], and so on to enhance bioavailability in further. Therefore, it is essential to continue the research of phytosomes to improve the therapeutic efficacy of the active constituents.

Acknowledgements

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磷脂复合物: 一种能够提高中药活性成分口服生物利用度的有效方法

郝海军*, 贾幼智, 韩茹

上海医药工业研究院 分析测试中心, 上海 200437

摘要: 很多中药活性成分在体外具有确切的药效, 但是由于自身的各种缺陷导致药物在体内有很小甚至没有药效, 限制了在临床上的应用。中药活性成分与磷脂在非质子溶剂中形成磷脂复合物后, 显示出与原料药不同的理化性质, 尤其是由于药物磷脂复合物透膜能力的改善, 使活性成分很容易进入体循环, 其生物利用度得到很大的提高。因此, 近几年来药物磷脂复合物受到了越来越多的关注。本文根据文献报道, 分别从磷脂复合物的制备、表征、鉴定以及在药学方面的应用进行了综述。

关键词: 磷脂; 磷脂复合物; 活性成分; 生物利用度

Master Hao graduted from school of Pharmaceutical Sciences, Henan University in 2007 with the Bachelor degree. Then he entered the workforce at Hualan Bio in Henan from 2007 to 2009. He obtained his Master of Pharmacy from Shanghai Fudan University in 2012. And then went to work in Instrumental Analysis & Research Center, Shanghai Institute of Pharmaceutical Industry. His research area is new drug-delivery system of Traditional Chinese medicine and pharmaceutical analysis.

郝海军硕士, 2007年7月毕业于河南大学药学院并获得学士学位; 2007年8月–2009年9月在河南新乡华兰生物工作; 2012年7月获上海复旦大学药学院药剂学硕士学位; 同年进入上海医药工业研究院分析测试中心工作。研究方向: 中药新型给药系统及药物分析。