



The extraction, separation and purification of alkaloids in the natural medicine

JI Yubin^{1,2*}, Yu Miao^{1,2}, Wang Bing³ and Zhang Yao¹

¹Center of Life Science and Environmental Science, Harbin University of Commerce, Harbin China

²Engineering Research Center of Natural Anti-tumor Drugs, Ministry of Education, Harbin China

³School of Food Engineering, Harbin University of Commerce, Harbin, China

ABSTRACT

In this paper, I will have natural medicine alkaloids extraction, separation and purification methods for a talk, the presence of alkaloids of natural medicine are in the form of free or salt alkaloids, so inorganic acidic water can be used to extract in order to have alkaloids organic acids replaced with inorganic acid salt and increase its solubility; The free alkaloids or salt both can be dissolved in methanol, ethanol, we can use heated alcohol under reflux extraction or ultrasonic alcohol extraction; and most of the free alkaloid is lipophilic, also can use heated alcohol under reflux to extract free alkaloids with the organic solvent such as chloroform, benzene, ether and so on. Most obtained alkaloids by extracting are mixture, according to the alkaloids class, basicity, solubility differences and the special functional group of alkaloids to separate the alkaloid mixture. Then the separated monomer detectable.

Keywords: Extraction, Separation, Purification, Alkaloids

INTRODUCTION

Alkaloids is from the biological world, mainly refers a class of nitrogen-containing organic compounds in the Plantae, most of them have more complex cyclic structure, the nitrogen atom is combined with inside the loop, mostly appears alkaline, and combines with acid to be salt; many of them have significant physiological activity. In plants, a few of very weak alkaline alkaloids present in free form, such as an amide alkaloids. Alkaloids which have an alkaline mostly exist in organic salts form, such as citrate, oxalate, tartrate, succinate and so on. Few exists in inorganic salt form, such as berberine, such as morphine sulfate. There are still other forms of N-oxide alkaloid glycosides. Most plants containing alkaloids are a variety of alkaloids coexist and alkaloid biosynthesis pathway are often similar in the same plant, so chemical structure is also similar, belong to the same family of plants often have the same parent nucleus, or the same structure as the compound.

EXPERIMENTAL SECTION

Extraction of water or acidic water

Having alkaline alkaloids is present in salt form in the plant, so choose water or acidic water to extract them. Usually inorganic acidic extraction is used, so that the organic acid of alkaloids salt is replaced inorganic acid salt, and increasing its solubility. Acid extraction method usually use 0.1% to 1% sulfuric acid, hydrochloric acid or acetic acid, tartaric acid solution as a solvent, by dipping method or percolation extraction, the individual who has less starchy use boiling method. For example, Zhang-Can use 0.5% sulfuric acid to extract crude alkaloids of *Menispermum dauricum*, followed reusing alkaline water sedimental method got crude alkaloids [1]. The advantage of that acidic extraction is changing alkaloids molecules into small molecule organic acid salts of inorganic acids, increasing the solubility in water, and the extraction method is relatively simple. However, the main drawback of this method is need more extraction solution, difficulty concentrating, and has more water-soluble impurities. So with the acidic extraction, generally the purification and enrichment of alkaloids as following methods:

Cationic exchange resin method

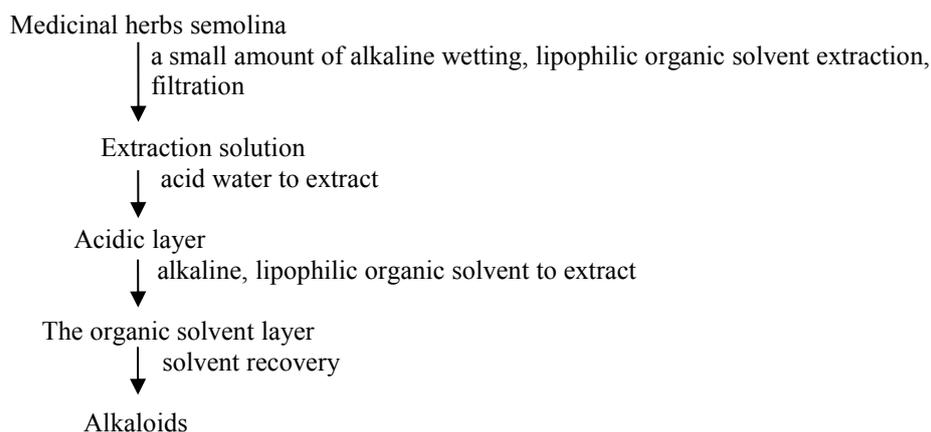
Alkaloids salts can dissociate alkaloid cations in water, alkaloid cations and cation exchange resins occurs ion exchange reaction, which is switched to the resin. Operation will alkaloids acidic liquid through a strong acid cation exchange resin column, so that the alkaloids acidic cation exchange resin, precipitation reactions with alkaloids checks whether the exchange altogether. After completion of the exchange, with neutral water or ethanol, washed the column impurities. During operation acidic liquid of alkaloids through a strong acid cation exchange resin column, so that the alkaloids of acidic liquid and resin be exchanged, and then using alkaloids precipitation reactions check whether the exchange altogether or not. After completion of the exchange, with neutral water or ethanol washing the column impurities. $BH^+ Cl^- \rightarrow BH^+ + Cl^-$ (Cation alkaloid \rightarrow alkaloid hydrochloride) $R^+ H^+ + BH \rightarrow R^+ BH^+ + H^+$ (Note: R represents cation exchange resin, B represents free of alkaloids.) After completion of the above process, alkaloids can be eluted from the resin alkaloids as the following methods. Alkaloids is basified with chloroform or ether extract the alkaloids have the exchange resin poured from the chromatogram, basified with aqueous ammonia to a PH value of about 10, and then an organic solvent such as chloroform or ether refluxed concentrated Extracts were relatively pure alkaloids obtained. An alkaline elution ethanol elution with ethanol containing ammonia, and in the eluent, ethanol recovery that is more pure alkaloids. $R^+ BH^+ + NH_3 \cdot H_2O \rightarrow R^+ NH_4 + B$ (free base) + H_2O Acidic or acidic ethanol elution alkaloid exchange cations to the resin, eluted with acidic or acidic ethanol, the acid of the cation to the replaced, are adsorbed on the resin surface, to continue with the acidic or acidic ethanol elution can be more pure alkaloids salts $R^+ BH^+ + H^+ + R^+ BH^+ + Cl^-$ Have the extracts of acidic water basified, after the alkaloid is free, if it is precipitated, filter it and obtain it; if not precipitated, have an appropriate lipophilic organic solvent extracting, then recovery solvent, and total alkaloids has obtained.

Extraction of alcohol solvent

Both free and salt alkaloids can be dissolved in methanol, ethanol, alcohol reflux, percolation or immersed can be used to extract them. The advantage of alcohol extraction is that different alkaloids or alkaline salts can be suit, in addition to the water-soluble impurities such as polysaccharides, proteins are less extracted. But its drawback is more fat-soluble impurities is extracted. So we can use acidic water- alkaline - extraction methods to remove fat-soluble impurities. The specific method is that recover alcohol from alcohol extracts and add dilute acid water and stir, place, filter, after basifying solution, use an appropriate lipophilic organic solvent to extract, recover solvent and total alkaloids are obtained.

Extraction of lipophilic organic solvent

Most of the free alkaloid are lipophilic, so chloroform, benzene, ether and methylene chloride can be used to extract free alkaloid. Impregnated, reflux or continuous reflux extraction can be used to extract. But generally use a small amount of alkaline water wetting medicine and then extracting so that make the alkaloid free, also may increase the solvent penetrating the plant cell. The general process with the lipophilic organic solvent extracting is as follows:



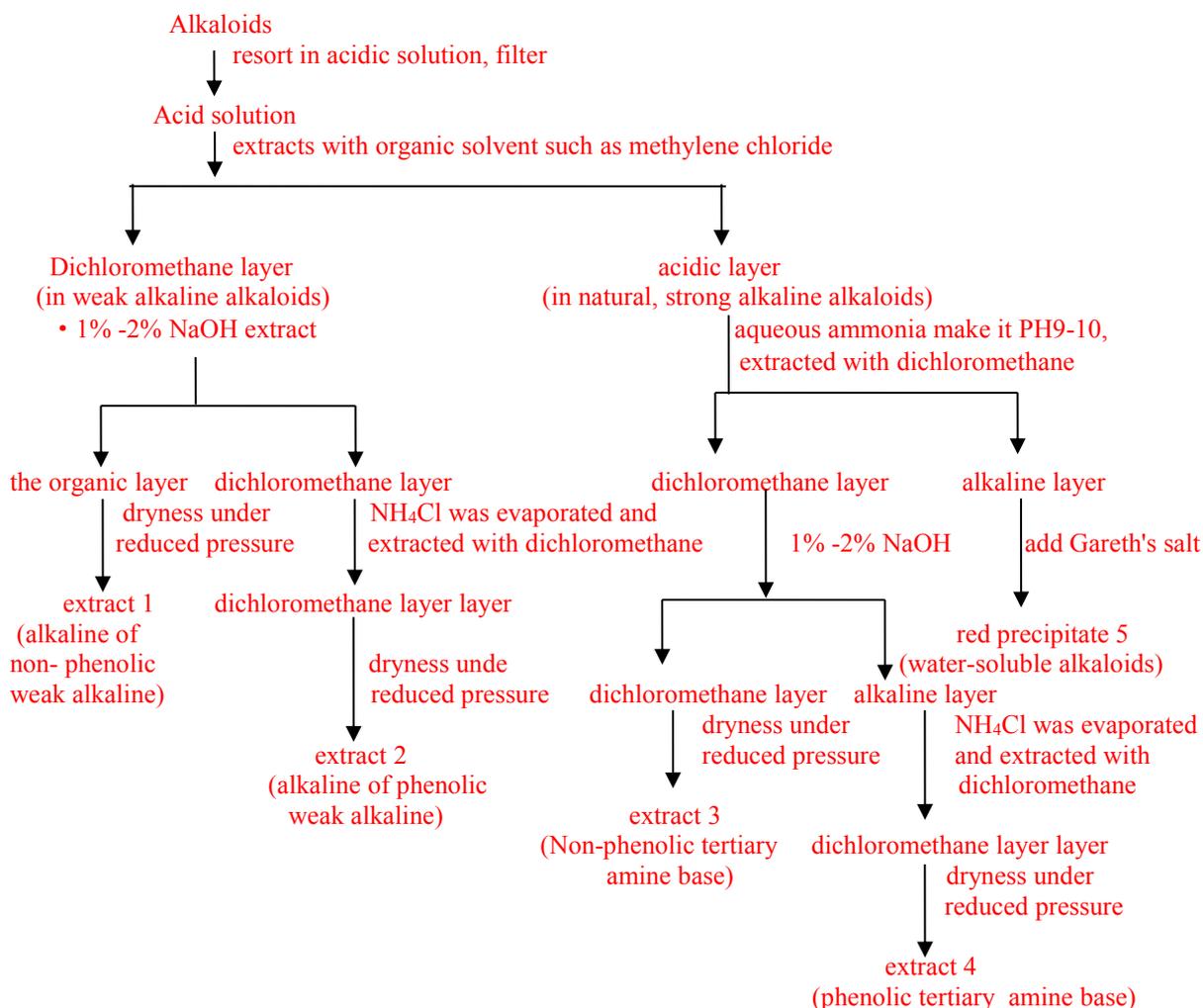
The main advantage of this method is the extraction of water soluble impurities are less, according to the process of fat-soluble impurities can be removed by acidic extraction. The main disadvantage is that the high price of the solvent, poor security, but also for high demanding equipment to prevent solvent leakage. In addition, volatile alkaloids such as ephedrine be available to steam distillation. Sublimated alkaloids such as caffeine can use sublimation method to extract.

Separation of alkaloids

Generally, a medical plants often contain a variety of alkaloids, mostly obtained by extracting are a mixture of alkaloids. According to needs, need to be further separated into the desired monomer alkaloids.

Separation of different classes of alkaloids

Have total alkaloids as basicity, and whether water-soluble phenolic and preliminary or not divided into five categories, such as the separation of Amaryllidaceae plants lycoris longituba bulb Alkaloids [2]. The separation process is as follows:

*According to the basic difference of alkaloids to separate*

Each monomer of alkaloids often has different alkaline, we can use the PH gradient extraction to separate. There are two specific methods. One method is have total alkaloids dissolved in the lipophilic organic solvents such as chloroform, then with different acid buffers to extract in descending order by PH, alkaloids according to its alkaline from strong to weak formed salt and sequentially to be extracted, Respectively is basified and extracted with organic solvent. Another method is that have the total alkaloids dissolved in acidic water, gradually adding alkaline water to make PH value from low to high, whenever adjusting PH value, must be extracted with other organic solvents such as chloroform, each monomer alkaloids according to its alkaline from strong to weak formed salt sequentially to be extracted and then separated. For two alkaloids have different alkaline f, after adjusting correct PH, choosing traditional simple extraction method to separate. For example, separating hyoscyamine and scopolamine from Flos Daturae's ethanol leaching solution, which is using their different alkaline, have the concentrated ethanol solution basified to leach in PH9-10, extracted with chloroform, then have chloroform extracts extracted with dilute acid water, this dilute acidic solution was basified with solid NaHCO_3 and extracted with chloroform, because of its low alkaline, scopolamine was extracted. Aqueous layer was basified by Ammonia to PH10, using chloroform to extract hyoscyamine whose PH is higher than scopolamine.

According to the solubility difference of alkaloids or its salt to separate

Each monomer of total alkaloids has different polarity, their solubility vary in an organic solvent, we can use this difference to separate the alkaloids [3]. For example 1, the separation of matrine and oxymatrine in Flavescent, we can use oxymatrine's polar slightly stronger than matrine, and it is insoluble in ether and matrine is soluble in ether, have

Matrine dissolved in chloroform, add ether for more than 10 times, oxymatrine can precipitate. For example 2, the separation of harringtonine and homoharringtonine from China *Cephalotaxus sinensis*'s leaves and branches by countercurrent distribution method, also use different mineral polar of two to separate. Separation conditions as follows: stationary phase, disodium hydrogen phosphate and citric acid buffer solution whose PH is about 4, the mobile phase is chloroform, have the two mutually saturated. make the total alkaloids samples dissolved in the mobile phase, extracting with countercurrent fractional step, harringtonine mainly distributed in the stationary phase, Homoharringtonine mainly distributed in the mobile phase. And then use Al_2O_3 chromatography column to purify respectively, two pure is obtained [4]. Different alkaloid and acid formed salts may have different solubility, this difference also can be used to separate the alkaloids or alkaloids salt. For example, using the solvent method to extract and separate ephedrine, pseudoephedrine from ephedra, namely using the water-soluble of their two Oxalate, after extraction and treatment obtaining a toluene solution, use oxalic acid solution extracting and then concentrated, because of its lower solubility, oxalic acid ephedrine precipitate crystals, and oxalic acid pseudoephedrine solubility stay in the mother liquor as its higher solubility [5].

According to alkaloids special functional group to separate

Some alkaloids' molecule containing phenolic hydroxyl or carboxyl group, there are Lactone or lactam structure, these groups or structure can occur reversible chemical reaction, so it can be used for separation. Phenolic alkaloids form a salt and soluble in water in alkaline conditions, so they can be separated from the general alkaloids. For example, in the opium alkaloids, morphine have phenolic hydroxyl and codeine having no phenolic hydroxyl, with sodium hydroxide solution treating opium alkaloids solution, morphine form salt and dissolve, codeine precipitate, so the two has separated. Lactone or lactam structure alkaloids can be saponified by heating in an alkaline aqueous solution to generate open-loop and form carboxylic acid salt which is water-soluble, so can separate from other alkaloids, they can synthesis primary alkaloids and precipitate in acid conditions. For example, the culminate has a lactone ring in Camptothecin. Using this property extracting and separating camptothecin in the processes.

According to chromatographic to separate

Alkaloids are often complex in medicine, and the structure is similar. The separation methods often cannot be completely separated as above, so column chromatography is needed, now alkaloids separation by column chromatography method described below.

Adsorption column chromatography

Al_2O_3 or Silicone use as the commonly adsorbent, sometimes with cellulose, polyamide and etc. Using benzene, chloroform, ethyl and other lipophilic organic solvent or the mixture of them as the eluent system. Such as four steroidal alkaloids' separation in *Fritillaria* [6].

Partition column chromatography

Although most alkaloids can separate with desorption chromatography, some of alkaloids' structure is similar especially, the separation is not satisfactory, and so partition chromatography can be used. For example, the separation of harringtonine and Homoharringtonine which is used as anti-cancer alkaloids in *Cephalotaxus*, both of them only has a difference of methylene group in structure, the results of adsorption chromatography are poor, allocated chromatography separation is ok. The specific method is based on Silicone as a support agent, and PH5.0 buffer as the stationary phase, uses the chloroform solution which is saturated with PH5.0 buffer to eluent. The first to eluent is Homoharringtonine, the middle part is a mixture of both, and the last part is the harringtonine.

High Performance Liquid Chromatography (HPLC)

HPLC separation method has good performance, high sensitivity, fast analysis of advantages, enabling many other chromatographies difficult to separate mixed alkaloids be separated. HPLC separation of alkaloids, the available silica gel adsorption column, and C18 reversed-phase column can also be used. In addition, preparative thin layer chromatography, dry column chromatography, medium-pressure or low-pressure column chromatography is also used for the separation of alkaloids. The introduction of several alkaloid separation methods, for certain species of plant alkaloids are more similar to those structures, one of the methods alone is difficult to separate the pure alkaloid, generally require a variety of separation methods with the application.

The separation of Water-soluble alkaloids

Water-soluble alkaloids mainly refer quarter ammonium, the general separation method by the following.

Precipitation method

We can use precipitation reagent precipitate Water-soluble alkaloids from the aqueous solution, and separate water-soluble impurities which is remaining in the filtrate, in order to obtain higher purity water-soluble alkaloids or salts. Commonly use Reye ammonium salt precipitation reagent in the laboratory, because of higher prices and not

commonly used in the industrial production. the general steps for Reye ammonium salt purified quaternary ammonium bases are as follows.

Precipitate quarter ammonium bases

Have quaternary ammonium base solution with dilute mineral acid solution to adjust PH 2-3, add freshly prepared alkaloids Reye salt saturated aqueous solution, the alkaloids Reye salt precipitate, filtration after complete precipitation, precipitation was washed with a little water to the washing liquid is not red so far.

Evolution of column chromatography

Alkaloids Reye salt was dissolved in acetone, the insoluble were filtered off. Make the filtrate pass through a short alumina column, eluting with acetone and collect the elution. Alkaloid Reye salts are eluted by acetone, and some polar impurities are adsorbed by alumina column so that to be eliminated. Don't add a saturated aqueous solution of silver sulfate in the eluate until Reye silver salts generate precipitate, filter the precipitation, the alkaloids are converted to sulfate salts and remain in primary solution. Add an equal number of moles of barium chloride solution (toxic) in solution to sulfate silver in the solution, generates sulfate barium precipitation and chloride silver precipitate, then filtered off above precipitation, alkaloids are converted to hydrochloride salt and remain in the solution, the filtrate was concentrated to obtain purer quaternary ammonium bases crystals.

Solvent method

Using the water-soluble polar alkaloids which can be dissolved in the more polar in organic solvent and stratified with water, have these solvents and alkaline liquid of water-soluble alkaloid extracted repeatedly so that the water-soluble alkaloids and alkali hydrophilic impurities can be separated.

Purification of alkaloids

Alkaloids are extracted in natural medicine mostly are mixture, thus still needed to be isolated and purified, the common separation methods base on the following principle: according to the difference of substance's solubility to separate, such as according to the difference of a substance's solubility at different temperatures to recrystallize or in different solvents to precipitate successively; according to the difference of a substance's solubility in a two-phase solvent to separate, such as liquid - liquid extraction and liquid-liquid counter current distribution and so on; according to the difference of substance's adsorption to separate, such as the traditional active carbon or solid phase extraction; What's more, according to the size of molecular of the substance and the difference of its dissociation level, this thesis will describe the classical separation method .

The extraction method of two-phase solvent

The extraction method is according to the ingredients of the mixture in the two immiscible solvents, because of the difference of the distribution coefficient and then achieve to separate. Have the two immiscible solvents placed after shaking, they can be divided into upper and lower layers, the concentration ratio of the solute in the two phases namely distribution coefficient K at a certain temperature and pressure is a constant, that is: $K = C_U / C_L$. K is the partition coefficient, C_U represents the solute concentration of solvent in the upper phase, C_L represents the solute concentration of solvent in the lower phase. During the extraction if each ingredients have the greater difference partition coefficient in the two-phase solvent, the separation efficiency the more higher. separation factors β represents the degree of difficulty separation. β is the ratio of distribution coefficient of two solutes in the same solvent system, namely: $\beta = K_A / K_B$ ($K_A > K_B$) Normally, when $\beta \geq 100$, the extraction can be achieved to basic separation only once; when $100 > \beta \geq 10$, the extraction need several times (about 10 times); when $\beta < 2$, the extraction can be achieved to basic separation by more than 100 times; when $\beta \cong 1$, it indicates that there is little difference in two substances partition coefficient, using the solvent system is difficult to achieve separate, you should consider choosing another solvent system.

Simple extraction method

If the desired ingredients are fat-soluble, we can use an organic solvent such as benzene, chloroform or ether with water conducting liquid-liquid extraction to remove water-soluble ingredients such as sugars, inorganic salts. If the desired ingredients are hydrophilic substance, the water solution can be extracted with the weak lipophilic solvents such as ethyl acetate, butanol, pentanol acetate. Sometimes we can add a small amount of methanol or ethanol in chloroform or methylene chloride to extract. We often use PH gradient extraction method in the separation of alkaloids, so that making strong alkaline alkaloids and weak alkaline alkaloids to achieve initial separation. Because of the ingredients of plants are complex, usually use several solvent which polarity is from low to high to extract sequentially by liquid - liquid extraction, each part of the resulting is used for anti-tumor screening. The extraction and separation of herbal to achieve active ingredients by liquid - liquid extraction method, often according to the differences of the nature of active ingredients or in coexistence of impurities, have one or a certain type of component distribution coefficient changed significantly with some methods. Such as alkaloids' purification, according to

changing the PH value of alkaloids' solution to make the alkaloids free in alkaline conditions, then extracting with an organic solvent and separating from the hydrophilic impurities; or treated with the acid solution to remove hydrophilic or lipophilic impurities so that improving alkaloids' purity. PH gradient extraction method is also based on a component can form salt or be free under a certain PH, changed the distribution coefficient of the composition in a solvent system and separate from the other component. In addition, with polar solvent water "wash" the extraction of lipophilic solvent to remove mixed polar impurities, or with a lipophilic solvent "wash" the lipophilic impurities of water extraction. These can be used repeatedly extraction method to complete.

Continuous extraction method

Use a continuous extractor to overcome the problems of using a separatory funnel to extract many times. This instrument uses the different specific gravities of two solvents stratify naturally and dispersed droplets pass through the continuous phase solvent to occur mass transfer. During Selecting the continuous extraction method, depending on the specific gravity of the needed solvent is greater than or less than the situation of the extracted aqueous solution, and to use different type of instrument. The specific methods of operation is adding herbal aqueous solvent in the tube after solvent extraction, it can automatically flow into the heater, evaporation into the gas, after met the condenser to condense into the liquid, then extracted, and so endless cycle. This method is simple and can avoid the emulsifying, because the two-phases are flowing conditions to meet countercurrent and always maintain a large density difference, the extraction process can be carried out continuously, so the amount of solvent is lesser and the extraction efficiency is much higher.

Solid Phase Extraction method

SPE is according to the different strength of the interaction of extracted components and the other components of the sample at a fixed filler to make them separate from each other. SPE uses a solid -phase extraction column, usually is polypropylene column, also are glass or stainless steel column, add the extractant into the column Commonly used octadecylsilane chemically bonded silica or phenyl alkyl bonded silica, Now there are a cyano group, an amino or other special group filler to supply, upper and lower ends are covered with glass sand core or other porous filter. add the sample into the column, make it flow through the solid phase extraction agent, the extracted sample was retained into the extraction agent, the solvent and other substances which are retained difficultly to outflows from the column, and then further using appropriate detergents to elute these unwanted components. Finally, using the eluent to elute the sample which is in the extraction column to obtain the desired compounds. For example, using SPE to measure the determination of caffeine content in coffee: make the coffee solution passing the extraction column which is filled C₁₈ bonded silica, after the sample flowing through the column bed, with a certain volume of water to rinse firstly, and then dried under reduced pressure, finally with chloroform eluting the adsorbed caffeine for content determination. The advantage of this method is simple equipment, easy operation, fast speed, and can avoid emulsification that the simple extraction could cause, and the resulted extraction is no need to dry, it is suitable for the separation of trace components. SPE depend on the different separation purposes selecting different solid adsorbents and elution solvent.

Droplet countercurrent distribution method

Droplet countercurrent distribution method is using each component of the mixture has different distribution coefficient between the two liquid; the mobile phase formed into droplets and be used as the liquid column of the stationary phase to achieve the purpose of separation and purification. The apparatus of the current application consists of three parts; the first part is the infusion part, constituted by micro-pumps, mobile phase solvent storage tank and the sample liquid injector. The second part is extraction tubes, the amount of extraction tubes are between 300 and 500. The third part is constituted with detection and automatic fraction collector. Because the mobile phase form into the droplets, it can contact effectively and first constantly with the stationary phase to form a new surface in the narrow extraction tube, to promote the solute distribute in the two phases, the separation affection is higher, and no emulsification. Driving the mobile phase with nitrogen, the separated substance is not oxidized by the oxygen which is existing in atmosphere. Droplet-flow method was applied satisfactorily to separate and purify many ingredients, except alkaloids but saponin, proteins, peptides, amino acids, sugars and so on. For example, Bupleurum contains a variety of saponin, these Saikosaponin has little difference in the structure, using the general approach is more difficult to separate and purify, especially is Bupleurum a and d, the only difference is the configuration of the hydroxyl group vary in C₁₆ position, and the R_f values are very close in the TLC, using the countercurrent distribution method can be successfully separated them.

Fractionation method

For the separation of the system of immiscible liquids, different boiling points can be used for fractionation, and then refining and purification, this method is often used in the volatile oils and purification of liquid alkaloids. For example, after freezing the menthol crystals can precipitate from peppermint oil, the remaining oil distilled atmospheric, a

fraction which is less than 150 °C mainly exists in acetaldehyde, acetone, iso-valeric acid and iso-amyl alcohol, which is between 150 and 200 °C mainly exists in monoterpene compounds, which is between 200 and 220 °C mainly exists in menthol, which is greater than 250 °C exists in sesquiterpene compounds. To prevent some of the ingredients in the volatile oil destroyed when boiling, often using vacuum distillation. In general, the boiling point of the liquid mixture is above 100 °C, the solution can be fractionated repeatedly several times to achieve the purpose of separation. If the difference of the boiling point is below 25°C, you need to use a fractionating column, the difference of the boiling point is more smaller, the more finer fractionation unit is needed. Each fraction of the resulting of the fractionation often overlapping cross therefore, to be further re-purified by crystallization or other methods is needed.

Precipitation method

Precipitation method is using the nature of the components of certain plants which can precipitate with certain reagent and then to be separated or removed impurity. But in terms of the required components, this precipitation reaction is reversible. The commonly method is Lead Salts method; it can be used to remove impurities, but also can be used for precipitation of an active ingredient. The neutral or alkaline lead acetate can generate insoluble lead salt or complex salt precipitation with many substances in water or dilute alcoholic solution, so we can take advantage of this nature to separate impurity from the desired composition. Passing into hydrogen sulfide gas often as a deleading method, make it decompose and convert into an insoluble precipitate of lead sulfide and then to be removed. However, the excess hydrogen sulfide may present in the solution, we can pass into the air or carbon dioxide so that let air bubbles take the excess hydrogen sulfide gas away. For the thermal stability compounds, have the solution placed in an evaporating dish, heated in a water bath and then concentrated to remove. Lead sulfide is generated during deleading, which is adsorption, we can use the organic solvent to extract and then recover the substances which have been adsorbed, but in general, it is not be recycled. The deleading method can also be use sulfuric acid, phosphoric acid, sulfate, phosphate and so on, but the resulting of lead sulfate and lead phosphate has a easy solubility in water, so the removal of lead is not complete, because this method is simple, it is still using in the lab now. Although the cation exchange resin can be used as deleading, the ionic compound in plants is also be exchanged to loss, and promote the ion exchange resin aging, so it is not commonly used.

Salting out method

Salting-out method is often adding the soluble inorganic salts to the water extraction of the herb to a certain concentration, or saturated, so that some components' solubility is lower in water and precipitate or extract with the organic solvent, and thus separating with the water-soluble impurities. Inorganic salts which commonly used is sodium chloride, ammonium chloride, ammonium sulfate, sodium sulfate, magnesium sulfate. For example, the powder of barberry's root soaked with dilute acid, add sodium chloride in the dilute acid solution nearly it is saturated until berberine hydrochloride precipitated; Another example is obtaining Notoginsenoside A from Yunnan's Panax notoginseng powder with amyl alcohol, the residue is extracted with ethanol, alcohol extraction is dissolved in water, insoluble materials were filtered and added magnesium sulfate saturated so that precipitated notoginsenoside b. Some components such as protoanemonin, ephedrine and matrine has a larger water-soluble, add a certain amount of salt in the aqueous solution when extracting, and then extracted with an organic solvent.

CONCLUSION

Isolation and purification of alkaloids is the difficulty and key of new Chinese medicine research and development, some of the traditional separation and purification technology problem is low yield, high cost of purification. This article describes a method for the extraction of alkaloids in traditional, as opposed to traditional methods, new extraction methods such as membrane separation technology, molecular distillation technology, high-speed countercurrent chromatography, molecular imprinting technology has unparalleled advantages, in improving the alkaloid preparations quality, increasing productivity and quality, reducing environmental pollution, saving time and energy has a positive role in promoting. How these new technologies can be used into production, many problems need to be solved. With the development of technology, alkaloids extraction and purification technology will also be more in-depth research and development, we believe that more efficient, convenient and fast method will continue to emerge.

Acknowledgements

This work is supported by National Natural Science Foundation of China (81274067); Natural Science Foundation of Heilongjiang Province (D201126); Technology Projects of Department of Education of Heilongjiang Province (1211135); Key Technology Project of Department of Education of Heilongjiang Province (12511z011); Harbin Special Foundation for Young Technological Innovative Talented Person (2013RFQXJ150).

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