

## Application Progress of Porous Materials in Modern Pharmaceutical

Yi Sun<sup>2</sup>, Wen Liu<sup>1\*</sup>

<sup>1</sup> Chemistry Experiment Teaching Center, School of Basic Science, Tianjin Agricultural University, Tianjin, China.

<sup>2</sup> Traditional Chinese Medicine Department, Tianjin Hexi District Youyi Street Community Health Service Center, Tianjin, China.

\***Correspondence to:** Wen Liu, School of Basic Science, Tianjin Agricultural University, Tianjin, China. E-mail: 4386468@qq.com.

### Highlights

In order to solve the problems of difficult separation and purification of drugs and poor sustained release performance, researchers began to pay attention to porous materials with regular micro-porous structure. Because of their excellent performance, safety, non-toxicity, low cost and easy production, the common porous materials such as molecular sieves, macroporous adsorption resins and activated carbon are not only widely applied to industry, but also widely studied in the field of medicine. This paper summarizes the progress of the above porous materials in the field of medicine. It is found that these porous materials can be used to extract natural drugs and remove heavy metal impurities in drugs when promoting drug separation and purification, and they can reduce toxicity of raw materials, control drug release time and improve drug targeting when improving drug sustained release performance.

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## Abstract

Porous materials have regular three-dimensional pore structure, which has unique advantages in the field of modern pharmaceutical. At present, porous materials commonly used in the pharmaceutical field are mainly molecular sieves, macroporous adsorbent resins, activated carbon, etc. In this paper, the application status of these porous materials in the pharmaceutical field is reviewed, and the future development is prospected.

**Keywords:** Porous materials, Molecular sieves, Macroporous adsorbent resins, Activated carbon

## 摘要

**目的:** 多孔材料具有规则的三维孔道结构, 将其应用于制药领域具备独特的优势。目前在制药领域常用的多孔材料主要有分子筛、大孔吸附树脂、活性炭等, 本文综述了上述多孔材料在制药领域的应用现状, 并对未来的发展进行了展望。

**关键词:** 多孔材料; 分子筛; 大孔吸附树脂; 活性炭

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## Background

Porous materials have a regular three-dimensional pore structure and have unique advantages in the pharmaceutical industry. At present, the porous materials commonly used in the pharmaceutical field mainly include molecular sieves, macroporous adsorption resins, activated carbon, etc. This paper reviews the application status of the above porous materials in the pharmaceutical field, and prospects for future development.

Porous materials generally have physical properties such as low density, large specific surface area, and good permeability due to their large number of multi-dimensional pore structures. And also display unique mechanical properties, adsorption properties, photoelectric properties and chemical properties. It gradually being used in Chemical adsorption, chemical synthesis, drug separation, drug release and many other fields. Porous materials can be classified into three types according to their pore size: microporous (<2nm), mesoporous (2-50nm) and macroporous (>50nm) materials.

Natural porous materials mainly include sponges, cork, corals, natural zeolites, *et al.* Under normal circumstances, the pores of natural porous materials are relatively disordered, and it is difficult to directly realize industrial applications. Synthetic porous materials, such as molecular sieves, activated carbon, and resins, have regular pores. The structure shows unique biological and chemical functions, and many of them have already achieved industrial application. For example, molecular sieve materials are widely used in coal-to-olefin and nylon synthesis industries, and resin materials are widely used in industries such as ion exchange and adsorption separation.

In recent years, some researchers have begun to apply porous materials, especially mesoporous and macroporous materials, in the direction of drug preparation, such as the use of molecular sieve materials for drug sustained release, the use of macroporous resins for drug separation and purification, and achieved good results.

## Molecular sieve material

Molecular sieves are generally composed of aluminosilicates, which are chemically stable, non-toxic, with regular pore structure and numerous micropores and mesopores. They have the advantages of high selectivity, easy regeneration and good slow release performance adsorption, encapsulation and separation of different chemical substances, and have good development prospects.

### Preparation of molecular sieve drug complexes

In 2001, Vallet Regi, *et al* [1] made the first attempt to use MCM-41 as a carrier for Ibuprofen, pioneering the application and research of mesoporous silica in the medical field.

Ren Jungang, *et al* [2] first synthesized mesoporous molecular sieve McM-41 with ethyl orthosilicate as the silicon source and cetyl trimethylammonium bromide as the template by the traditional method, and then successfully assembled puerarin in the molecular sieve pore channel by dipping method, with the drug load up to 17.2%. After compound with molecular sieve, the dissolution rate of puerarin was increased, the retention time of puerarin in rats was prolonged, and the bioavailability of puerarin was improved.

According to the research of Xu wujun, *et al.* [3], the adsorption capacity of Ibuprofen on monodisperse spherical mesoporous molecular sieve with different particle sizes increases with the increase of molecular sieve ratio surface, and the larger the molecular sieve particle size, the more severe the agglomeration, the slower the drug release rate. In the carboxyl functionalized sba-15 mesoporous molecular sieve, the release rate of famotidine decreases with the decrease of mesoporous pore size. In the carboxyl/trimethyl-silicon dual-functionalized sba-15 mesoporous molecular sieve, the release rate of famotidine decreases significantly with the increase of trimethyl-silicon group content. On this basis, a ph-sensitive enteric sustained-release drug can be obtained by further coating hydroxypropyl methyl cellulose phthalate polymer film.

Li na, *et al.* [4] loaded curcumin into mesoporous silica molecular sieve channels by dipping method, which can significantly improve the dissolution rate and dissolution degree of curcumin, providing a new idea for improving the bioavailability of water-insoluble drugs.

For cancer treatment, on the one hand, particles with a size of 100-130 nm have a passive targeting effect on the tumor site. It is difficult to pass through normal blood vessels, but they can pass through tumor capillaries with high permeability. Therefore, we can make full use of this feature for cancer treatment. Xu, *et al.* [5] prepared gel coated mesoporous silica molecular sieve particles, and then synthesized doxorubicin into particle pores as an anticancer drug, which can significantly reduce the toxicity of API when used for cancer treatment, and has a good therapeutic effect. On the other hand, mesoporous silica particles can be modified to form special interactions with tumor cells by modifying the targeted molecules to transport drugs to the target area for treatment. Cui, *et al* [6] made a composite carrier of transferrin, PLGA and magnetic mesoporous silica molecular sieve particles, loaded adriamycin and taxol onto the composite carrier for the treatment of glioma, and proved that the composite carrier could significantly improve the tumor inhibition effect. Researchers have also explored more physicochemical conditions-responsive silica molecular sieve composite drugs, such as ph-sensitive targeted drug delivery system triggered by the pH response, REDOX response targeted drug delivery system [10], photosensitive tumor targeted drug delivery system and so on [11-12].

## Molecular sieve for separation and purification of traditional Chinese medicine

Due to its unique structure of ordered channels, molecular sieves can not only be used to compound with drugs for sustained release, but also to separate and purify drugs.

Zhang Chunxiu, *et al* [13] prepared a continuous 13X molecular sieve coating with good crystallinity on the surface of the alumina ceramic pavilion by pre-coating method. The coating of 0.12g was used to remove lead and cadmium from salvia miltiorrhiza with the initial concentration of 2mg/L, and the removal rates reached 86.7% and 44.2%, respectively. Meanwhile, the retention rates of salvia miltiorrhiza, salvianolic acid B and rosemary acid reached 99.6%, 96.8% and 99.3%, respectively. Wang Pengfei *et al* [14] prepared Ca-X molecular sieves by using Na-X molecular sieve raw powder, which was used to remove harmful heavy metals such as copper, cadmium, lead, mercury, arsenic and other harmful heavy metals in traditional Chinese medicine, and found that the removal efficiency of heavy metals was high, the loss of effective components of traditional Chinese medicine was small, and it could be recycled. In addition, they further prepared molecular sieve membranes on porous alumina ceramic materials, which can also be effectively used for the effective removal of heavy metal ions in traditional Chinese medicine extracts [15].

### Macroporous adsorption resin material

Macroporous adsorption resin, as a kind of porous compound polymerized with styrene and acrylate, has a unique three-dimensional pore structure and can selectively adsorb and separate metal ions and organic compounds in solution, which is widely used in the fields of environmental treatment, chemical production and drug separation. The common macroporous adsorbents can be divided into three categories: polar, medium and non-polar. The types and models of macroporous resins should be selected according to the specific properties of the separated target, resin adsorption capacity and separation effect. The application process of macroporous adsorbent resin generally includes resin pretreatment, adsorption, elution and resin regeneration steps, which are characterized by simple operation and low cost. However, a certain amount of wastewater needs to be treated in the pretreatment and regeneration steps of resin.

Macroporous resins are widely used in drug separation and purification because of their properties. The particle size of resin is generally in the millimeter level, adsorption separation is usually carried out at room temperature, compared with distillation and other thermal separation methods can maximize the retention of the active ingredients of the separated drugs, compared with extraction and can avoid organic solvent residue, and the cost is low, in drug separation and purification has a unique advantage.

### Macroporous adsorption resin is used to remove heavy metals in traditional Chinese medicine

Liu yan *et al.* [16] first extracted traditional Chinese medicinal materials such as salvia miltiorrhiza and liuwei

dihuang pill through solvent to obtain aqueous solution of traditional Chinese medicine extract, and then mixed chelate resin and ion exchange resin to obtain mixed resin, and removed heavy metals such as copper, arsenic, cadmium, mercury and lead by adsorption of the mixed resin in aqueous solution of traditional Chinese medicine extract. Wu Jianxiang, *et al* [17] with alkaline ethanol solution such as pretreatment of four different polar styrene type macroporous adsorption resin, and then by water, 95% ethanol, steps of elution resin to remove the heavy metal residues in the resin, selection of refined cassia twig tuckahoe capsule of radix paeoniae alba and cortex moutan in common composition, 3 batch production purification with resin, and the result has not been the organic residue and heavy metal detection. This study not only proves that macroporous adsorbent resin can be used for important separation and purification, but also provides an idea for how to recycle the resin after it adsorbs heavy metals in traditional Chinese medicine.

### Macroporous adsorption resin for purification of traditional Chinese medicine

Fu Huaqiang, *et al* [18] selected the seven different macroporous resin and total flavonoids in different process conditions research hovenia dulcis adsorption performance, to find the most suitable for type AB 8 macroporous resin purification of total flavonoids in hovenia dulcis, and obtained the optimum process conditions of separation and purification, including mass concentration, the higher the sample fluid rate, pH, elution rate, etc., under the condition of the flavonoids from 14.03% to 42.54% purity. Yao Haiyan, *et al* [19] selected X-5 resin with good adsorption and desorption performance and purified ginsenosides from ginseng extract with macroporous adsorption resin, and optimized the process. The results showed that the purity of total ginsenosides could reach more than 60% under the optimum technological parameters, such as the mass concentration, adsorption velocity, elution velocity and so on, which was suitable for industrial application. Yang, *et al* [20] compared the 17 kinds of macroporous resin for lilacs glycosides, acanthopanax glycosides E, adsorption and separation effect of different oxazine skin organism, according to whether the macroporous adsorption resin with high adsorption capacity and adsorption rate index model for HPD100C, select the best resin also studied the best conditions of use at the same time, in the process under the condition of the above three kinds of drug recovery rate reached 80.93%, 93.97% and 93.79% respectively.

The research on the application of macroporous adsorbent resin materials in drugs is relatively mature and has a good prospect of industrialization. At present, there are mainly such problems as residual unpolymerized monomer, solvent residue in the synthesis process and large amount of waste water generated in the regeneration process of macroporous resin, which need to be studied and solved continuously.

### Activated carbon materials

Activated carbon material is an important porous material with mature preparation process, low cost and wide use. It can be selectively adsorbed to target components through surface adsorption and internal pore structure, and is widely used in wastewater treatment, VOCs exhaust gas adsorption and other fields. Activated carbon has the advantages of large specific surface area, uniform pore size distribution, good biocompatibility, non-toxicity and easy regeneration. It is of great significance to study its application in traditional Chinese medicine.

Spherical activated carbon was prepared by han yongping [21] carbonized activated polymer resin, which was used in the adsorption and desorption experiments of traditional Chinese medicine. The apparent adsorption capacity of activated spherical carbon to berberine hydrochloride, diosgenin and rutin was dried. Alkali content was 35.46 mg/g, 47.12 mg/g and 40.88 mg/g, respectively. The static elution rates of the three components were 83.71%, 91.45% and 87.69%, respectively, which could be further promoted in the separation and purification of traditional Chinese medicine. P. Iovino, *et al.* used activated carbon nanoparticles as adsorbent to adsorb ibuprofen and studied its adsorption mechanism. He applied Langmuir adsorption theory to the adsorption of activated carbon in ibuprofen solution. When ibuprofen was adsorbed in solution, the adsorption amount was related to the physical morphology of ibuprofen in solution, which was consistent with Langmuir's adsorption theory. Nano-activated carbon is used as a sustained-release agent for compounding with active pharmaceutical components. Currently, there are mainly 5-fluorouracil, mitomycin C, and docetaxel, and activated carbon plays a very good role. Wu yaqin *et al.* used activated carbon and drugs [23] for clinical treatment of patients, and used activated carbon tablets and traditional Chinese medicine plus mannitol enema to treat patients with chronic renal failure, which can significantly improve the efficacy compared with the use of activated carbon.

The application of activated carbon in industry is relatively mature. As a result, when applied to pharmaceuticals, it has few problems with industrial scaling up. However, before activated carbon can be used in the medical field, it is necessary to carefully select the appropriate drug type and study its application scope.

## Conclusion

Porous materials have been used in other industries for decades, such as molecular sieves for chemical product synthesis, resin materials for water purification and chemical separation, activated carbon materials for the removal of pollutants from waste gas, *et al.* It is still in its infancy in the pharmaceutical industry. Nevertheless, However, due to the porous materials with regular channel itself unique properties such as the structure, can avoid the currently existing in drug preparation method such as distillation, extraction, crystallization of relievers - use it for drugs, drug in heavy metal ions removal and

purification of drugs has great potential and a clear advantage.

In the future research, more attention should be paid to solving the existing problems, such as the separation of molecular sieve and drug extract, monomer and solvent residues in the preparation of macroporous adsorption resin materials, and the mechanical strength of activated carbon is not enough. Only in this way can the industrial application of porous materials in pharmaceutical field be promoted continuously and the continuous progress of modern pharmaceutical technology be realized.

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