(19) LE GOUVERNEMENT
DU GRAND-DUCHÉ DE LUXEMBOURG
Ministère de l'Économie

(11) N° de publication : **LU504397**

(12) **BREVET D'INVENTION** **B1**

(21) N° de dépôt: LU504397

(22) Date de dépôt: 01/06/2023

(51) Int. Cl.:
B01D 15/38, B01J 20/26, B01J 20/28

(30) Priorité:
05/05/2023 CN 202310496550.6

(43) Date de mise à disposition du public: 01/12/2023

(47) Date de délivrance: 01/12/2023

(73) Titulaire(s):
HEBEI CHEMICAL AND PHARMACEUTICAL VOCATIONAL AND TECHNICAL COLLEGE – 050026 Shijiazhuang, Hebei, (Chine)

(72) Inventeur(s):
FAN Jiye – Chine, ZHANG Bingzhu – Chine, ZHANG Yong – Chine, ZHENG Ligang – Chine, SUN Xing – Chine

(74) Mandataire(s):
Biopatents IP Consultancy – 5691NW Son (Pays-Bas)

(54) **Resolution system and resolution method for chiral drugs.**

(57) The invention discloses a resolution system and a resolution method for chiral drugs. an organic material with a multistage pore structure is adopted for carrying out adsorption resolution on the chiral drug to be resolved; The pore structure of the organic material with the continuous pore structure comprises interconnected base pores, and the region where the base pores are interconnected is provided with two-stage pores with a diameter smaller than that of the base pores. The invention successfully develops a novel chiral drug separation technology, realizes the high-efficiency separation and purification of chiral drugs, has lower cost and higher yield, and provides powerful support for research and development and production of chiral drugs.

Resolution system and resolution method for chiral drugs

Technical field

The invention relates to the technical field of chiral drugs, in particular to a chiral drug separation method based on a continuous porous material.

Technical background

Chiral molecule refers to the existence of enantiomers in the molecule, i.e., a left-handed and right-handed symmetrical molecular structure. Such chiral molecules widely exist in nature, including protein, sugars, nucleic acids and other biological macromolecules, as well as many small organic molecules. As the enantiomers of chiral molecules have different spatial structures and chemical properties, their roles in organisms are also different. Many compounds with chiral molecular structures containing enantiomers have physiological activity and are important raw materials for drugs, pesticides and food additives.

In general, many enantiomers have completely different physiological activities from the enantiomers of the same constituent elements in the same weight ratio. For example, levodopa and dextrodopa are enantiomers, but their physiological effects are quite different. Levodopa is a major drug for Parkinson's disease, which can promote the synthesis of dopamine in the brain and alleviate the symptoms of patients with Parkinson's disease. Dextrodopa, on the other hand, has little effect. Similarly, levoephedrine is an effective antipyretic and analgesic drug, while dextroephedrine has little effect. Due to the difference in the physiological activity of the enantiomers, the research and application of chiral molecules are particularly important in the fields of drug research and development, pesticide production and food additives.

The scientific research personnel team of the invention carries out in-depth theoretical and experimental research on the chiral medicine national platform and carries out centralized research on the porous matrix technology for chiral resolution so as to solve the defect that the chiral resolution technology in the prior art is thin and thin.

Summary of the invention

The technical problem to be solved by the invention is to overcome various defects of the prior art and provide a resolution system and a resolution method for chiral drugs, which have high physical stability, can be used under a wide separation condition and have larger adsorption capacity.

In order to solve the technical problems, the technical scheme adopted by the invention is as follows.

The invention relates to a resolution method for chiral drugs, which adopts an organic material with a multistage pore structure to carry out adsorption resolution on the chiral drug to be resolved.

As a preferred technical solution of the present invention, the organic material having a continuous pore structure has a pore structure including interconnected base pores, and a secondary pore having a diameter smaller than that of the base pores is provided in a region where the base pores are interconnected.

An organic material for chiral resolution is an organic material having a multistage continuous pore structure.

As a preferred technical solution of the present invention, the pore structure comprises interconnected base pores, and the region where the base pores are interconnected is provided with a secondary pore having a smaller pore size than the base pore.

As a preferred technical solution of the invention, the diameter of the base hole is between 0.5 μm and 200 μm.

As a preferred embodiment of the invention, the diameter of the base hole is between 10 μm and 100 μm.

As a preferred technical solution of the invention, the diameter of the secondary pores is between 0.05 μm – 50 μm and 50 μm.

As a preferred technical solution of the invention, the diameter of the secondary pores is between 0.5 μm and 10 μm.

The invention relates to a secondary modification method of a porous organic material, which is characterized in that the porous organic material is provided with a multistage continuous pore structure, the pore structure comprises base pores which are connected with each other, and secondary pores with smaller pore diameters than the base pores are arranged in the area where the base pores are connected with each other; And that chiral active group are uniformly introduced in the continuous pore structure in a chemical infiltration mode.

As a preferred technical scheme of the invention, partial active groups are subjected to secondary inactivation treatment after the active groups are uniformly introduced.

The technical scheme has the beneficial effects that the invention successfully develops a novel chiral drug separation technology. Based on the physical and chemical properties of chiral molecules, the technology realizes the efficient separation and purification of chiral drugs through accurate analysis and screening of the molecular structure of chiral molecules. The technology not only has the characteristics of high efficiency, precision and controllability, but also has lower cost and higher yield, thus providing strong support for the research and production of chiral drugs. In addition, the invention also has wide application prospect. In addition to its applications in drug development and production, the technology can also be applied to food, cosmetics, pesticides and other fields to achieve efficient separation and purification of chiral molecules. At the same time, the technology can also provide strong support for the field of environmental protection and ecological construction, such as the effective control and treatment of environmental pollution and ecological risk of hand pesticide.

Detailed description of the invention

The follow examples illustrate that invention in detail. Various raw materials and equipment used in the invention are conventional commercial products and can be directly obtained through market purchase.

It should be understood that that term "comprise ", when used in the specification and append claims, indicates the presence of described feature, integers, steps, operations, elements, and/or components, but does not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. It should also be understood that the term "and/or" as used in the specification of this application and the appended claims refers to any and all possible combinations of one or more of the associated listed items, and includes such combinations. As use in that specification of this application and the appended claim, the term "if" may be interpreted as "when" or "once" or "in response to a determination" or "in response to detection" depending on the context. Similarly, that phrase "if determine" or "if a [described condition or event] is detect" may be interpreted as mean "upon determination" or "in response to determination" or "upon detection of [described condition or event]" or "in response to detection of [described condition or event]" depending on the context. In addition, in that description of the present application and the append claims, the term "first," "second," "third," and the like are used solely to distinguish the description and are not to be construed as indicating or imply a relative importance. Reference to "one embodiment" or "some embodiment" or that like in the specification of the present application mean that a particular feature, structure, or characteristic described in connection with the embodiment is include in one or more embodiments of the present application. Thus, appearances of the phrases "in one embodiment," "in some embodiments," "in other embodiments," "in other embodiments," and the like in various places throughout this specification are not necessarily all referring to the same embodiment, but rather mean "one or more but not all embodiments," unless otherwise specifically emphasized. The terms "comprising," "comprising," "having," and variations thereof, mean "including, but not limited to," unless otherwise specifically emphasized.

Among the in-depth studies carried out by the inventor's team in the department of the national platform for chiral drugs, the most prominent scientific research finding is that an organic porous material having a specific structure can uniformly introduce optically active groups within its continuous porous structure, and thus it is possible to produce an adsorbent exhibiting excellent performance of separating optically active substances without restricting separation conditions, and the inventor has surprisingly found that a spatial recognition site is still present even after the optically active groups are eliminated from the adsorbent, thereby allowing the organic porous material to maintain an excellent ability of separating optically active substances.

Specifically, the present invention provides an organic porous material having a continuous pore structure including base pores and secondary pores which are connected to each other, secondary pores having a diameter of 0.05 μm to 50 μm are formed in the connected portions, and optically active groups uniformly introduced therein. Further, the optical separation ability obtained by removing part or all of the optically active groups from the above-mentioned organic porous material. With respect to the uniform wetting and deactivation modification of the optically active group, it is generally to prepare a mixture of an oil-soluble monomer containing an optically active group, a surfactant, and water, stir the mixture to prepare a water-in-oil emulsion, and allow the mixture to stand to polymerize the monomer. More specifically, a mixture of an oil-soluble monomer containing an optically active group, a surfactant, and water is first prepared, the mixture is stirred to prepare a water-in-oil emulsion, and the mixture is allowed to stand to polymerize the monomer, and some or all of the optically active group is eliminated.

There are a number of options for the matrix material used to form the continuous pore structure including ① styrenic polymers such as polystyrene, poly (α-methylstyrene) and poly (vinylbenzyl chloride); ② polyolefins such as polyethylene and polypropylene; ③ halogenated polyolefins such as polyvinyl chloride and polytetrafluoroethylene; ④ nitrile-containing polymer, such as polyacrylonitrile; ⑤ (meth) acrylic polymers such as poly (methyl methacrylate) and poly (ethyl acrylate); ⑥ styrene-divinylbenzene copolymer. The above polymer may be a homopolymer obtained by polymerizing one type of monomer or a copolymer obtained by polymerizing two or more types of monomers. Furthermore, mixtures of two or more polymers may be used. Among these organic polymer, styrene-divinylbenzene copolymers and vinylbenzyl chloride-divinylbenzene copolymer are preferred in view of easy introduction of optically active groups and high mechanical strength. The continuous pore structure of the organic porous material of the present invention can be easily observed using a scanning electron microscope (SEM). The pore size of the primary and secondary pores can also be observed by SEM.

The basic structure of the organic porous material of the present invention is a continuous pore structure having base pores and secondary pores, the base pores are connected to each other, and secondary pores having an average diameter of 0.05 μm to 50 μm, preferably 0.5 μm to 10 μm are formed in the connected portions. Specifically, the continuous holes generally have a structure in which base holes having a diameter of 0.5 μm to 200 μm are layered, and the layered portion has two-stage holes serving as a common opening, thereby providing an open hole structure. In the open pore structure, the pores formed by the base pores and the secondary pores become the flow path of the liquid. Overlapping base pores usually have 1 - 12 base pores, and many have 3 - 10 base pores. Two-stage pores having a diameter of less than 0.05 μm are undesirable because small-diameter two-stage pores excessively increase the pressure loss when liquid passes through. On the other hand, the secondary pore diameter

exceeding 50 μm is generally no longer applicable because the liquid does not sufficiently contact the organic porous material, resulting in a tendency of non-uniform diffusion of the liquid phase in a packed bed of the porous material, which results in degradation of resolution performance. This type of porous material is limited in minimizing the pressure of the feed liquid stream because the porous material obtained by this method has a small pore volume and insufficient secondary pore size due to the particle aggregation type structure.

In the organic porous material of the present invention, it is preferable that the value (W/R) obtained by dividing the half width (w) of the pore distribution curve at the main peak by the diameter (r) at the main peak is 0.5 or less. The pore distribution curve is determined by mercury porosimetry. For the main peak at height h from the baseline of the pore distribution curve, the half width of the pore distribution curve at the main peak represents the width at height H/2 from the baseline of the pore distribution curve. The smaller the value (W/R), the more obvious the pore distribution. In the organic porous material of the present invention, if the value (W/R) is 0.5 or less, the base pore group and the secondary pore group forming the continuous pore structure are uniformly present, resulting in a sharp secondary pore distribution, which in turn significantly increases the separation performance. Furthermore, since this structure does not contain large voids as structural defect sites, the resulting product has increased physical strength and improved resistance to swelling and shrinkage durability. The organic porous material having a value (W/R) of 0.5 or less shows significant improvement in properties and functions as compared with the organic porous material having the same composition and structure but having a value (W/R) exceeding 0.5.

On quantitative data, the organic porous material had a total pore volume of 1 - 50 ml/g. If the total pore volume is less than 1 ml/g, the amount of liquid permeation per unit area becomes small, resulting in a decrease in permeation under low pressure. Total pore volumes in excess of 50 ml/g are generally no longer acceptable because organic porous materials have very poor physical strength. The column filled with conventional packed particles has a void volume of 0.1 to 0.2 ml/ml of the packed bed volume (the volume of liquid that permeates through the packed bed) while the organic porous material of the present invention having the continuous porous structure completely different from the conventional packed particle bed described above has a total pore volume of up to 1 to 50 ml/g. Thus, the liquid can be fed at pressures as low as ½ - 1/30 of the pressure of the conventional feed fluid without compromising separation performance or reducing flow rate. When water is used as a typical liquid that penetrates through an organic porous material having a thickness of 10 mm, the permeation rate should properly fall within the range of values set in the manual. If the permeation rate and the total pore volume are within the above range, the organic porous material can exhibit excellent properties due to a large liquid contact area, smooth passage of the liquid, and robust mechanical strength. Among the organic porous materials, the material for forming the matrix of continuous pores is an organic polymer having a crosslinked structure. The polymer preferably

contains 1 mole% or more of crosslinked structural units based on the total of all structural units forming the polymer. If the content of the cross-linked structural units is less than 1% by weight, the mechanical strength is considerably insufficient.

As can be seen from the above examples, since the organic porous material of the present invention has high physical stability, can be used under a variety of separation conditions, and has an excellent ability to separate optically active substances, the material does not have the disadvantages of a conventional optical separation column, such as limited separation performance and poor stability, while exhibiting high separation performance. Therefore, organic porous materials are expected to help reduce column size or increase enantiomeric separation. Further, according to the method of manufacturing an organic porous material of the present invention, since an optically active group or a spatial recognition site can be introduced not only to the surface of the organic porous material but also to the inside of the skeletal region of the porous material, it is possible to obtain an organic porous material having a large adsorption capacity and suitable for large-scale separation and purification.

In the above-mentioned embodiments, the description of each embodiment is focused, and parts not detailed or recorded in one embodiment can be referred to the related description of other embodiments.

The above-mentioned examples are only for illustrating the technical scheme of the present invention, and not for limiting it; Although the present invention has been described in detail with reference to the foregoing embodiments, it will be understood by those of ordinary skill in the art that modifications may be made to the technical solutions described in the foregoing embodiments, or equivalent substitutions may be made to portions of the technical features thereof; And these modifications or substitutions do not depart from the spirit and scope of the corresponding technical solutions in the embodiments of the present invention, and are intended to be included within the scope of the present invention.

CLAIMS

1. A resolution method for chiral drugs, characterized in that the method adopts an organic material with a multi-stage pore structure to carry out adsorption resolution on the chiral drugs to be resolved.

2. The resolution method for chiral drugs according to claim 1, characterized in that the pore structure of the organic material with the continuous pore structure comprises interconnected base pores, and the region where the base pores are interconnected is provided with secondary pores with a diameter smaller than that of the base pores.

3. An organic material for chiral resolution, characterized in that it is an organic material having a multistage continuous pore structure.

4. The organic material for chiral resolution according to claim 3, characterized in that the pore structure comprises interconnected base pores, and the region where the base pores are interconnected is provided with two-stage pores with smaller pore diameters than the base pores.

5. The organic material for chiral resolution according to claim 4, characterized in that the diameter of the base pores is between 0.5 μm and 200 μm.

6. The organic material for chiral resolution according to claim 4, characterized in that the diameter of the base pores is between 10 μm and 100 μm.

7. The organic material for chiral resolution according to claim 4, characterized in that the diameter of the secondary pores is between 0.05 μm and 50 μm .

8. The organic material for chiral resolution according to claim 4, characterized in that: the diameter of the secondary pores is between 0.5 μm and 10 μm.

9. A secondary modification method of a porous organic material, the porous organic material having a multi-stage continuous pore structure including interconnected base pores, the two-stage pores having a smaller pore size than the base pores in a region where the base pores are interconnected, characterize in that chiral active groups are uniformly introduce in that continuous pore structure in a chemical infiltration mode.

10. The secondary modification method of a porous organic material according to claim 9, characterized in that a part of the active groups are subjected to secondary inactivation treatment after uniformly introducing the active groups.

ANSPRÜCHE

1. Auftrennungsverfahren für chirale Arzneimittel, dadurch gekennzeichnet, dass das Verfahren ein organisches Material mit einer mehrstufigen Porenstruktur verwendet, um eine Adsorptionsauflösung an den aufzutrennenden chiralen Arzneimitteln durchzuführen.

2. Auftrennungsverfahren für chirale Arzneimittel nach Anspruch 1, dadurch gekennzeichnet, dass die Porenstruktur des organischen Materials mit der kontinuierlichen Porenstruktur miteinander verbundene Grundporen umfasst und der Bereich, in dem die Grundporen miteinander verbunden sind, mit Sekundärporen versehen ist, deren Durchmesser kleiner als der der Grundporen ist.

3. Organisches Material zur chiralen Trennung, dadurch gekennzeichnet, dass es ein organisches Material mit einer mehrstufigen kontinuierlichen Porenstruktur ist.

4. Organisches Material für die chirale Trennung nach Anspruch 3, dadurch gekennzeichnet, dass die Porenstruktur miteinander verbundene Basisporen umfasst und der Bereich, in dem die Basisporen miteinander verbunden sind, mit zweistufigen Poren mit kleineren Porendurchmessern als die Basisporen versehen ist.

5. Organisches Material zur chiralen Trennung nach Anspruch 4, dadurch gekennzeichnet, dass der Durchmesser der Grundporen zwischen 0,5 µm und 200 µm liegt.

6. Organisches Material für die chirale Trennung nach Anspruch 4, dadurch gekennzeichnet, dass der Durchmesser der Grundporen zwischen 10 µm und 100 µm liegt.

7. Organisches Material für die chirale Trennung nach Anspruch 4, dadurch gekennzeichnet, dass der Durchmesser der Sekundärporen zwischen 0,05 µm und 50 µm liegt.

8. Organisches Material für die chirale Trennung nach Anspruch 4, dadurch gekennzeichnet, dass der Durchmesser der Sekundärporen zwischen 0,5 µm und 10 µm liegt.

9. Verfahren zur sekundären Modifikation eines porösen organischen Materials, wobei das poröse organische Material eine mehrstufige kontinuierliche Porenstruktur mit miteinander verbundenen Grundporen aufweist, wobei die zweistufigen Poren in einem Bereich, in dem die Grundporen miteinander verbunden sind, eine kleinere Porengröße als die Grundporen aufweisen, dadurch gekennzeichnet, dass chirale aktive Gruppen gleichmäßig in diese kontinuierliche Porenstruktur in einem chemischen Infiltrationsmodus eingeführt werden.

10. Verfahren zur sekundären Modifikation eines porösen organischen Materials nach Anspruch 9, dadurch gekennzeichnet, dass ein Teil der aktiven Gruppen nach dem gleichmäßigen Einbringen der aktiven Gruppen einer sekundären Inaktivierungsbehandlung unterzogen wird.