Molecularly imprinted precipitation polymerization in pharmaceutical research

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Abstract: As an emerging research technology, molecular imprinting technology exhibits promising application prospects in pharmaceutical research owing to its specific recognition performance. This paper reviews the research progress of precipitation polymerization, one of the preparation methods for molecularly imprinted polymers, in pharmaceutical research in recent years, and prospects its development trends.

Keywords: molecular imprinting technology, molecularly imprinted polymer, precipitation polymerization, pharmaceutical research, review

1. Introduction

Molecularly imprinted polymers (MIPs) possess advantages including strong molecular recognition capability, simple preparation, easy operation, stable properties, low solvent consumption, and recyclability of template molecules and MIPs [1,2]. They feature high specificity and selectivity unavailable to other separation materials, thus showing favorable application prospects in the separation and analysis of active pharmaceutical ingredients [3,5]. In recent years, molecular imprinting technology has developed rapidly in fields such as solid-phase extraction, electrochemical sensing, pharmaceutical analysis and pharmaceutical process research [6,8]. Common preparation methods for MIPs include bulk polymerization, precipitation polymerization, suspension polymerization and seed swelling polymerization. This paper mainly reviews the application status of precipitation polymerization.

2. Synthesis technology of MIPs

2.1. Precipitation polymerization

Precipitation polymerization means that the polymer produced by the reaction is insoluble in its monomers, or the monomers and initiators are soluble in the reaction medium while the resulting polymer is not. The polymer precipitates from the reaction system once formed. The polymer obtained by precipitation polymerization has uniform particle size and shape and high yield. Moreover, surfactants and stabilizers are not required in the reaction system, so the influence of these additives on the specific recognition performance of MIPs can be avoided, and clean MIPs can be obtained.

2.2. Suspension polymerization

Suspension polymerization can be divided into normal-phase suspension polymerization and inverse suspension polymerization. Normal-phase suspension polymerization uses the organic phase as the polymerization phase and the aqueous phase as the dispersion phase. Monomers are dispersed into small droplets suspended in water under stirring and the effect of dispersants, and polymerization is initiated by initiators. Inverse suspension polymerization adopts the aqueous phase as the polymerization phase and the organic phase as the dispersion phase, and it is applied to the imprinting of water-soluble monomers. Granular MIPs can be obtained by simple separation, washing and drying after suspension polymerization. However, a small number of monomers will be encapsulated in the polymer prepared by suspension polymerization and difficult to remove.

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2.3. Seed swelling polymerization

Seed swelling polymerization is a method for imprinting template molecules on the surface of seed microspheres. It can generally be classified into one-step, two-step and multi-step swelling methods according to the number of swelling steps. The general procedure involves preparing seed microspheres first, followed by adding swelling aids, template molecules, functional monomers and crosslinkers, and finally initiating polymerization. MIPs prepared by seed swelling polymerization have the advantage of uniform and controllable size [9].

2.4. Surface molecular imprinting polymerization

Surface molecular imprinting polymerization grafts functional monomers onto the surface of microsphere substrates, confining binding sites on the accessible surface, which facilitates the elution and rebinding of template molecules and solves the "embedding" phenomenon of template molecules in polymers [10,11]. Song Yaling et al. prepared silica-based surface molecularly imprinted polymers with specific adsorption capacity for pentagalloylglucose and verified the feasibility of large-scale separation and preparation of pentagalloylglucose using the polymers [12].

3. Precipitation polymerization

3.1. Application of precipitation polymerization in traditional Chinese medicine

3.1.1. Single-template natural product MIPs: prep. & adsorption

Zhang Xiao et al. [13] prepared molecularly imprinted polymers by precipitation polymerization using punicalagin as the template molecule. The MIPs exhibited good specific selective adsorption capacity within the investigated concentration range, with a maximum adsorption capacity of 32.6μmol · g^{-1}. Jiang Xuhong et al. [14] fabricated theophylline molecularly imprinted polymer microspheres and studied the effects of the template molecule to crosslinker, reaction time and solvent on the morphology, yield and properties of MIPs microspheres. Finally, the optimal conditions for morphology, yield and performance of the MIPs microspheres were determined as follows: the ratio of template molecule to crosslinker of 1:16, reaction time of 24 h and acetonitrile as solvent. Wang Song et al. [15] investigated baicalein MIPs microspheres prepared with baicalein (0.5 mmol) as the template molecule at different solvent volumes (10 mL, 30 mL, 50 mL, 70 mL). The results showed that MIPs prepared with 30 mL acetonitrile solvent possessed favorable adsorption performance, with an adsorption capacity of 250 μmol · g^{-1}. Chen Hongyan et al. [16] prepared kaempferol MIPs microspheres using kaempferol as the template molecule, 4-vinylpyridine as the functional monomer and ethylene glycol dimethacrylate (EDMA) as the crosslinker. The optimal preparation conditions were obtained by scanning electron microscopy, Fourier transform infrared spectroscopy and thermogravimetric analysis. The maximum saturated adsorption capacity of the MIPs microspheres reached 1.053mg · g^{-1}.

3.1.2. Fabrication of template-composite MIPs

Li Chao et al. [17] used soybean isoflavones with the total content of genistin and daidzin of 89.2% as template molecules to prepare MIPs microspheres with specific-like selective adsorption capacity for soybean isoflavones. The microspheres exhibit high recognition ability for substances with the typical parent ring structure of soybean isoflavones.

3.1.3. Separation & detection of natural products in TCM

Li Yun et al. [18] prepared molecularly imprinted polymer microspheres of tanshinone IIA, which were applied to the study of serum pharmacochemistry of Salvia miltiorrhiza. By combining molecularly imprinted solid-phase extraction with HPLC-MS, efficient separation, sensitive detection and comprehensive identification of multiple components in Salvia miltiorrhiza and their metabolites in rat serum were achieved. Yu et al. [19] used quercetin as the template molecule, vinylpyrrolidone and acrylic acid as functional monomers, N, N'-methylenebisacrylamide as the crosslinker, ascorbic acid and hydrogen peroxide as initiators, and ethanol-water as the porogen to prepare MIPs via precipitation polymerization. The polymer possessed specific recognition ability for quercetin in the mixture of quercetin and genistein,

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with a resolution of 6.58. Zeng et al. [20] investigated the preparation of MIPs by adopting dual functional monomers and dual crosslinkers, which were applied to separate rutin from traditional Chinese medicines. The functional monomers were acrylamide:2-vinylpyridine (3:1), and the crosslinkers were ethylene glycol dimethacrylate:divinylbenzene (3:1). The optimal molar ratio of template, functional monomer and crosslinker was 1:6:20. The prepared MIPs were used for separating rutin from Saururus chinensis and Sophora japonica, with average recoveries of 85.93% and 88.61%, respectively. Castro Lopez et al. [21] fabricated quercetin MIPs for the enrichment and purification of catechins. 4-Vinylpyridine was used as the functional monomer, EDMA as the crosslinker, and the mixed solution of acetone and acetonitrile as the porogen. The selectivity of the MIPs toward quercetin in the mixture containing quercetin, catechin, epicatechin and tocopherol with similar molecular weight was studied. The experimental results showed that the MIPs had favorable recognition ability for quercetin and its structural analogues, and the recovery of catechins from white tea could reach 90%.

3.2. Application of precipitation polymerization in chemical drugs

3.2.1. Study on preparation conditions of precipitation MIPs

Luo Mengjun et al. [22] prepared 1-deoxynojirimycin MIPs by precipitation polymerization and investigated the effects of solvent and reaction time on the yield and properties of MIPs. The results showed that when the reaction time was 24 h and acetonitrile was used as the solvent, the obtained MIPs microspheres exhibited favorable morphology and adsorption performance, with a selectivity factor of 2.26 for 1-deoxynojirimycin and N-methyl-1-deoxynojirimycin. Chen Chaonan et al. [23] prepared MIPs using sulfamethazine as the template molecule via precipitation polymerization. The study demonstrated that the MIPs possessed good selectivity and adsorption capacity toward sulfamethazine, with a maximum apparent binding capacity of 31.866 $mg \cdot g^{-1}$. Sun Yan et al. [24] fabricated norfloxacin $-Zn^{+2}$ MIPs by precipitation polymerization and compared the performances of MIPs synthesized with acidic functional monomer methacrylic acid and alkaline functional monomer 4-vinylpyridine. Norfloxacin, $Zn^{+2}$and the two functional monomers formed ternary complexes through metal imprinting, respectively. Finally, the MIPs prepared with 4-vinylpyridine showed better recognition performance.

3.2.2. Effects of solvents and initiation on adsorption of drug MIPs

Liu Jing et al. [25] prepared chloramphenicol MIPs microspheres via precipitation polymerization initiated by high-energy electron beams from an electron accelerator. UV spectroscopy, infrared spectroscopy and static nitrogen adsorption tests verified that chloramphenicol formed supramolecular complexes with the functional monomer methacrylic acid. Scanning electron microscopy and isothermal adsorption experiments demonstrated that MIPs microspheres with particle sizes of 300–500 nm could be rapidly prepared at an irradiation dose of 20 kg, and the maximum adsorption capacity was 107.65 $\mu mol \cdot g^{-1}$. Liang Bing et al. [26] synthesized chloramphenicol MIPs microspheres by precipitation polymerization in aqueous acetonitrile-water solvent. The as-prepared MIPs microspheres had an average particle size of 13.83 μm and a maximum adsorption capacity of 85 $\mu mol \cdot g^{-1}$. By contrast, MIPs microspheres prepared using neat acetonitrile without water exhibited a maximum adsorption capacity of 9.49 $\mu mol \cdot g^{-1}$, which was much lower than that of MIPs obtained with acetonitrile-water as the solvent. Kou Xing et al. [27] used erythromycin as the template molecule to obtain MIPs microspheres with particle sizes ranging from 400 to 600 nm. The optimal molar ratio of template molecule to functional monomer methacrylic acid was determined to be 1:3, and the maximum adsorption capacity reached 202.12$mg \cdot g^{-1}$. Dong Yan et al. [28] fabricated caffeine MIPs microspheres by precipitation polymerization. When the molar ratio of template caffeine: functional monomer acrylamide: crosslinker ethylene glycol dimethacrylate was 1:4:20, the resulting MIPs microspheres possessed small particle size, good morphology and adsorption performance, with a maximum apparent binding capacity of 34.407 $\mu mol \cdot g^{-1}$.

3.2.3. Fabrication of special-structured MIPs for sustained drug release

Liu Jiang et al. [29] prepared erythromycin surface MIPs via a two-step distillation-precipitation polymerization method. Firstly, microspheres were synthesized using methacrylic acid and divinylbenzene as the core. Then, core-shell structured erythromycin surface MIPs were obtained through the second step of

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distillation-precipitation polymerization, with methacrylic acid as the functional monomer and divinylbenzene as the crosslinker. After process optimization, the maximum binding capacity of the as-prepared surface MIPs was 76.8, and their recognition ability toward erythromycin was higher than that for its structural analogue roxithromycin. Su Liqiang et al. [30] fabricated MIPs microspheres with high selectivity for acetylsalicylic acid by precipitation polymerization, and their maximum apparent binding capacity was 37.97mg · g^{-1}. Ling Xia et al. [31] prepared L-methyldopa MIPs microspheres by precipitation polymerization. Studies showed that the particle size of microspheres increased with the decrease of polymerization temperature and the increase in the amount of initiator azobisisobutyronitrile. In simulated gastric fluid, the sustained drug release duration of L-methyldopa MIPs microspheres was 10 h, twice that of non-imprinted polymer microspheres, indicating that the MIPs microspheres possessed a drug sustained-release effect.

Table 1 MIPs for TCM active components by precipitation polymerization

	template molecule	Functional monomer	crosslinker	porogen	reference
1	punicalagin	acrylamide	EDMA	acetonitrile	[13]
2	theophylline	acrylamide	EDMA	acetonitrile	[14]
3	baicalein	methacrylic acid	EDMA	acetonitrile	[15]
4	kaempferol	4-vinylpyridine	EDMA	acetonitrile	[16]
5	genistin; daidzin	4-vinylpyridine	EDMA	methanol	[17]
6	tanshinone	methacrylic acid	EDMA	toluene	[18]
7	quercetin	N-Vinyl-2-pyrrolidone acrylic acid	N, N'-Methylenebisacrylamide	aqueous ethanol	[19]
8	rutin	Acrylamide 2-vinylpyridine	EDMA divinylbenzene	Tetrahydrofuran	[20]
9	quercetin	4-vinylpyridine	EDMA	Methyl ethyl ketone	[21]

Table 2 Summary of MIPs prepared by precipitation polymerization

	template molecule	Functional monomer	crosslinker	Pore-forming agent	reference
1	1-Deoxynojirimycin	methacrylic acid	EDMA	acetonitrile	[22]
2	Sulfamethazine	methacrylic acid	EDMA	acetonitrile	[23]
3	Norfloxacin	methacrylic acid 4-Vinylpyridine	EDMA	acetonitrile	[24]
4	chloramphenicol	methacrylic acid	EDMA	acetonitrile	[25]
5	chloramphenicol	methacrylic acid	EDMA	Acetonitrile-water	[26]
6	erythromycin	methacrylic acid	EDMA	Ethyl acetate	[27]
7	caffeine	Acrylamide	EDMA	acetonitrile	[28]
8	erythromycin	methacrylicacid	Divinylbenzene	acetonitrile	[29]
9	acetylsalicylic acid	Acrylamide	EDMA	acetonitrile	[30]
10	levodopa	methacrylic acid	EDMA	Methanol-acetonitrile	[31]

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4. Conclusion

Molecular imprinting technology is novel technology and has achieved rapid development in many fields after years of exploration. This paper reviews the research progress of molecularly imprinted precipitation polymerization in pharmaceutical research, which demonstrates the wide application of this technology in pharmaceutical research. MIPs possess high selectivity for specific compounds that other separation materials do not have, showing promising application prospects in the separation, enrichment and analysis of pharmaceutical components. While further researching and applying molecular imprinting technology, some existing problems remain to be solved, such as insufficient adsorption capacity for template molecules and low enrichment factors. It is necessary to better apply molecular imprinting technology in aqueous phase and improve the recognition of template molecules by molecularly imprinted polymers in aqueous environment. More types of functional monomers and crosslinkers should be developed to meet diverse molecular recognition requirements and expand the application of molecular imprinting technology.

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