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Research Progress on Trimethoprim Cyclodextrin Inclusion Complexes

Jiedan Liao†*, Jiawei Weng†, Zhuoran Deng, Lanyi Zhang

School of Animal Science and Technology, Foshan University, Foshan 528225, Guangdong, China.
†These authors contributed equally to this work and share the first authorship.

**Corresponding author: Jiedan Liao, liaojiedan@fosu.edu.cn*

Abstract: Trimethoprim (TMP), as a broad-spectrum bacteriostatic antibiotic, is widely used in clinical anti-infection therapy and livestock breeding. However, its low water solubility leads to insufficient bioavailability, which has become a key problem restricting its development. Cyclodextrins and their derivatives, with their unique cyclic structures, can form inclusion complexes with TMP to improve its properties. This article reviews the pharmacological characteristics of TMP, the types and properties of common cyclodextrins, focusing on introducing various preparation methods of trimethoprim cyclodextrin inclusion complexes and multiple characterization methods for identifying the inclusion complexes, aiming to provide a reference for further research and development of trimethoprim cyclodextrin inclusion complexes.

Keywords: Trimethoprim; Cyclodextrin; Inclusion technology; Characterization method; Research progress

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1. Introduction

Trimethoprim (TMP), as a broad-spectrum antibacterial synergist, selectively inhibits bacterial dihydrofolate reductase, blocks bacterial nucleic acid and protein synthesis, and is widely used in the treatment of bacterial infections in clinical and veterinary fields. However, TMP has extremely poor water solubility, only 0.4 mg/mL, and a bitter taste, which seriously limits its bioavailability and clinical efficacy. Although trimethoprim lactate has good water solubility, it has strong hygroscopicity and poor stability, and faces many formulation problems when compatible with alkaline drugs such as sulfonamides [1]. To improve the physicochemical properties and biological activity of TMP, researchers have turned their attention to cyclodextrins and their derivatives.

Cyclodextrins (CDs) are a class of cyclic oligosaccharides produced by the action of glucosyltransferases from *Bacillus* on amylose [2, 3]. Under the action of cyclodextrin glucosyltransferase, a series of cyclic oligosaccharides with 6-12 glucose units and molecules with 6, 7, and 8 glucose units of different degrees of polymerization are obtained, which are named α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, respectively [4].

Their solubilities in water are 145 mg/mL, 18.5 mg/mL, and 232 mg/mL [5]. Specifically, α-cyclodextrin has a small inner cavity and can only include small molecules, which has certain limitations [6]. It can regulate gastrointestinal reactions, improve constipation, reduce blood glucose concentration, help in weight loss, and can also be used as a pharmaceutical excipient [7]. β-cyclodextrin has an inner cavity diameter of 0.7–0.8 nm, low water solubility, low production cost, and can be used as an antioxidant [8, 9]. γ-cyclodextrin has a larger cavity and can include more substances, which can increase the water solubility, reactivity, stability, and volatility of drugs, but its production cost is high, and it cannot be produced in large quantities [10, 11]. Among them, β-CD is the most widely used, with a suitable cavity size, easy availability, reasonable price, and a retention rate higher than that of α and γ-CD [12]. In recent years, to solve the problems of formulation design and safety and effectiveness caused by drugs' insufficient solubility, stability, and bioavailability, researchers at home and abroad have prepared drug delivery systems such as inclusion complexes, solid dispersions, and nanoparticles with cyclodextrins, which have expanded the application of cyclodextrins and their derivatives in pharmaceutics [3].

In recent years, significant progress has been made in the research on trimethoprim cyclodextrin inclusion complexes in terms of solubilization mechanisms and preparation technologies. This article systematically reviews the preparation methods and structural characterization of TMP cyclodextrin inclusion complexes, aiming to provide a reference for the research and development of new trimethoprim preparations and their clinical applications.

2. Preparation technologies of trimethoprim cyclodextrin inclusion complexes

Common preparation technologies for trimethoprim cyclodextrin inclusion complexes include saturated aqueous solution method, ultrasonic method, freeze-drying method, grinding method, etc. Different methods have different effects on the formation efficiency and physicochemical properties of inclusion complexes.

2.1. Saturated aqueous solution method

The saturated aqueous solution method has a simple process and does not require expensive equipment, making it one of the most commonly used methods for preparing inclusion complexes [13]. It is also one of the commonly used methods for preparing trimethoprim-cyclodextrin inclusion complexes [14]. In this method, the guest drug trimethoprim is added to an aqueous solution in which cyclodextrin is dissolved, and under appropriate conditions, such as temperature, molar ratio, rotation speed, and time, sufficient mixing and stirring are carried out to allow the inclusion of trimethoprim with cyclodextrin. After the reaction, the undissolved drug is removed by cooling crystallization and suction filtration, and the product is obtained after drying. Zou *et al*. used the saturated aqueous solution method with a host-guest molar ratio of 3:1, a reaction system pH of 7.5, an inclusion time of 4 hours, a rotation speed of 800 r/min, and vacuum drying and grinding at 60°C [15]. The solubility of the obtained inclusion complex was 26 times higher than that of the original drug. Li *et al*. adopted the solvent method (a derivative process of the saturated aqueous solution method), dissolving TMP in an aqueous solution containing 2% acetic acid, and reacting with β-cyclodextrin at a molar ratio of 1:1, which significantly improved the water solubility of TMP [16]. In addition, Hu prepared inclusion complexes of TMP with β-cyclodextrin and its derivatives by the aqueous solution method (with a molar ratio of 1:1 for all), and found that the hydrophobic cavity of β-cyclodextrin is more conducive to the embedding of TMP molecules, providing a reference for the process optimization of this method [17].

2.2. Ultrasonic method

The ultrasonic method first prepares a mixed saturated solution of the guest substance and cyclodextrin, sets the ultrasonic power, ultrasonic time, and the on and off time of each pulse, then uses ultrasonic equipment to synthesize the inclusion complex, and finally obtains the powdery inclusion complex by drying methods (such as spray drying or freeze-drying) [18]. The ultrasonic method is suitable for the preparation of most inclusion complexes, resulting in a high inclusion rate, and the inclusion complex is not easy to disintegrate during the preparation process [19]. The cavitation effect, mechanical effect, and thermal effect of ultrasound are used to promote the inclusion reaction between trimethoprim and cyclodextrin. Sun *et al.* prepared inclusion complexes by the ultrasonic-microwave freeze-drying method, and optimized ultrasound was used in the preparation of TMP-sulfobutyl ether-β-CD inclusion complexes [20].

2.3. Freeze-drying method

Freeze-drying is the most widely used technology to improve the stability of compounds [21]. The freeze-drying method is suitable for the preparation of temperature-sensitive TMP-cyclodextrin inclusion complexes, which can avoid the impact of high temperature on drug activity. Macedo OFL prepared inclusion complex samples by the suspension method, adding TMP to HP-γ-CD aqueous solution at a molar ratio of 1:1, stirring the suspension at a dark temperature for 8 hours. After the drug was included, the water was removed by vacuum drying and freeze-drying to obtain a loose powdery inclusion complex. This method is suitable for temperature-sensitive drugs [22].

2.4. Grinding method

Cyclodextrin is dissolved in water to prepare a saturated solution, and a solvent containing an appropriate amount of the drug to be included is added. The mixture is ground into a paste under suitable conditions, such as grinding temperature, time, and type of solvent. After suction filtration, washing, and filtration, the filtrate is concentrated and dried to obtain the product. In the industry, colloid mills are mostly used for including drugs. The kneading method is a simplified process of the grinding method. Cyclodextrin and a small amount of pure water are mixed in a mortar at a specific molar ratio to form a paste. TMP is added and fully kneaded, and the product is obtained after solvent washing and drying. This method is simple, efficient, and scalable [23]. Figueiras A added β-CD to a ceramic mortar with deionized water until a paste was obtained, slowly added TMP, kneaded the slurry, and allowed the final product to equilibrate in the dark at room temperature and humidity for 72 hours to obtain the inclusion complex. This method has difficulties in controlling the grinding time and operation degree, resulting in poor drug inclusion rate and repeatability [24].

3. Screening of cyclodextrin derivatives

Cyclodextrins themselves have the ability to recognize molecules and selectively include guest molecules [25]. Cyclodextrins are not easily decomposed in environments such as heat, acid, and alkali, and can improve the solubility, stability, safety, and bioavailability of drugs or achieve other purposes [26, 27]. Natural cyclodextrins have disadvantages such as low water solubility and difficulty in perfectly including drugs. To improve these problems, scientists have introduced groups such as sulfobutyl, hydroxypropyl, and methyl to form new cyclodextrin derivatives, thereby changing their own properties and expanding their application range [28]. Cyclodextrins

and their derivatives, with their unique cavity structures, physical and chemical properties, can form host-guest inclusion complexes with a variety of drugs. Cyclodextrin derivatives, with their unique cylindrical structure, moderately sized molecular weight, and hydrophilic exterior and hydrophobic interior characteristics, have become carriers for various drugs, and form inclusion complexes with many small molecule drugs to improve the solubility of poorly soluble drugs [29]. CD derivatives obtained by introducing substituent groups on CD have stronger solubility and solubilizing ability than the parent, and can improve water solubility when forming inclusion complexes with water-insoluble functional components [30]. The use of sulfobutyl ether, hydroxypropyl, and carboxymethyl β-CD can obtain better CD-guest complex performance [31].

Drugs carried by cyclodextrins or their derivatives can significantly prolong the retention time of drugs in the body, enhance the targeting of drugs, improve bioavailability, and improve drug properties [32]. Among various cyclodextrins, β-cyclodextrin (β-CD) has become a new type of pharmaceutical excipient due to its special cavity structure, non-toxicity, safety, and easy formation of stable hydrates. It is mainly used to mask the irritating odor of drugs, increase drug stability, improve solubility and bioavailability, and also can play a sustained-release role [33]. Based on the advantages of β-cyclodextrin, the research on its derivatives has attracted much attention. At present, three ideal pharmaceutical excipients with good water solubility are considered: hydroxypropyl-β-cyclodextrin (HP-β-CD), methyl-β-cyclodextrin (Me-β-CD), and 2,6-dimethyl-β-cyclodextrin (DM-β-CD) [34]. Among them, methyl-β-cyclodextrin (M-β-CD), as the most effective solubilizer for insoluble substances among β-CD alkylated derivatives, can be used in oral preparations, suppositories, transdermal absorbents, nasal sprays, and other dosage forms at very low doses for poorly soluble and highly active drugs [35, 36]. In the research on trimethoprim (TMP), β-cyclodextrin and its derivatives, such as hydroxypropyl-β-cyclodextrin and sulfobutyl ether-β-cyclodextrin have become research hotspots due to the high matching degree between their cavity size and TMP molecules, and different cyclodextrin derivatives have significant differences in the solubilizing effect on TMP.

4. Characterization methods of trimethoprim cyclodextrin inclusion complexes

In modern preparations, inclusion complexes are mainly used to increase the dissolution rate of drugs and improve drug stability. During their formation, several physicochemical property changes occur, such as optical properties, thermodynamics, electrochemistry, and solubility, which are used to evaluate whether cyclodextrins and guest molecules form inclusion complexes. Sometimes the difference in a certain property is not obvious, so multiple methods need to be comprehensively used for determination [17]. For example, Li *et al.* studied the inclusion complex of TMP with β-cyclodextrin, used ultraviolet spectrophotometry and phase solubility method to determine the properties of the inclusion complex in aqueous solution to prove that TMP was included, and characterized the formation of solid inclusion complexes by differential scanning calorimetry (DSC) and powder X-ray diffraction (X-RD) [16, 17].

4.1. Phase solubility method

The apparent inclusion constant (Kc) of the inclusion complex is an important parameter determining the inclusion properties of cyclodextrins. The magnitude of Kc reflects the strength of the binding force when cyclodextrins and drug molecules form inclusion complexes, and the main determination method is the phase solubility method. The phase solubility method is an important method to study the formation and stability of inclusion complexes. By determining the solubility of TMP in cyclodextrin solutions of different concentrations and drawing a phase

solubility diagram, the formation and stability constant of the inclusion complex can be judged. The solubility of TMP increases with the increase of HP-β-CD concentration, and also increases with the increase of temperature [37]. Zou *et al*. conducted a phase solubility study, and the phase solubility curve was a typical AL type, indicating that TMP and HP-β-CD formed an inclusion complex within this concentration range [15].

4.2. Differential scanning calorimetry

To accurately investigate the effect of temperature on volatile substances in the inclusion complex and verify the formation of the inclusion complex, auxiliary evidence can be obtained from the thermogravimetric analysis chart. The formation of the inclusion complex can be judged by studying the change of properties of different substances with temperature [38]. Differential scanning calorimetry (DSC) characterizes inclusion complexes by measuring the heat flow change of samples under programmed temperature control, which is a commonly used method for the characterization and analysis of cyclodextrin inclusion complexes. Lu *et al.* used Chem3D Ultra 8.0 and SYBYL software for molecular simulation and phase solubility method to explore the possibility of inclusion of trimethoprim by hydroxypropyl-β-cyclodextrin, and both thin-layer chromatography and differential scanning calorimetry verified the formation of the inclusion complex [39]. The DSC spectra of TMP, Me-β-CD, and their inclusion complexes show obvious differences [40]. The melting point of TMP is 199–203°C, and it has been reported in the literature that TMP has a sharp melting endothermic peak near 199°C, and Me-β-CD has a dehydration endothermic peak at 80–120°C [41]. After the formation of the inclusion complex, the melting peak of TMP disappears or is significantly weakened, indicating that TMP molecules have entered the cavity of Me-β-CD [42].

4.3. Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy studies the inclusion effect by analyzing the changes in molecular vibration frequencies, and obtains information by observing the absorption peaks of substances in the infrared region [43]. FTIR can reveal the transition of intramolecular vibrational energy levels and judge whether the inclusion complex is formed by comparing the changes in infrared absorption of specific functional groups between physical mixtures and inclusion complexes [44]. The functional group bands related to the inclusion of drugs with cyclodextrins are studied by infrared spectroscopy to obtain more evidence for the formation of inclusion complexes [45].

The interaction between CD and TMP molecules in solids can be evaluated by infrared spectroscopy. The shift of TMP absorption spectrum indicates the change in the hydrogen bond mode of polymorphic substances [46]. In the characterization of TMP-cyclodextrin inclusion complexes, by comparing the infrared spectra of TMP, cyclodextrin, physical mixtures, and inclusion complexes, it can be judged whether the inclusion complex is formed. If an inclusion complex is formed, the characteristic absorption peak of TMP may shift, change in intensity, or even disappear, and new absorption peaks may appear. When preparing TMP-sodium butyl ether-β-cyclodextrin complexes, Sun *et al.* found a new peak at 1162.34 cm^{-1} in the TMP-SDS-β-cyclodextrin complexes. It was speculated that this peak might be caused by the C-O-C stretching vibration of the TMP being included, which preliminarily indicated that the complexes had been formed [20].

4.4. Nuclear magnetic resonance spectroscopy

Proton nuclear magnetic resonance spectroscopy is used to record the hydrogen spectra of inclusion complexes

formed by TMP with different CDs. TMP interacts with protons on CD inside the cavity due to van der Waals forces. By comparing the chemical shift changes of specific hydrogen atoms after physical mixing and inclusion reaction, it can be judged from the spectrum whether TMP has entered the hydrophobic cavity of CD. If the drug accumulates in the cavity of the inclusion material, the hydrogen atoms in the cavity will be shielded by the drug molecules, resulting in a change in the chemical shift value, while the hydrogen atoms outside the cavity will not change [38]. Ma *et al.* judged the occurrence of the inclusion reaction based on the chemical shift of H in TMP in the region of 5.0–8.0 [47]. In the physical mixture, the chemical shift of H in TMP molecules almost did not shift, while in the inclusion complex, they all changed, indicating that each CD cavity contained TMP molecules.

4.5. Scanning electron microscope

Scanning electron microscope (SEM) excites various physical information through the interaction between the light beam and the substance, and collects, amplifies, and images this physical information, to achieve the purpose of characterizing the micro-morphology of the substance. By analyzing the signals generated by the interaction between the light beam and the sample, SEM can characterize the micro-morphological structure of the substance [48]. When the drug is included by cyclodextrin, its lattice arrangement will change, which can be observed under the electron microscope. The formation of the inclusion complex can be judged by comparing the three-dimensional structure differences between the inclusion complex and the original drug molecules [49]. Li *et al.* conducted spray gold coating experiments on TMP raw materials, β-cyclodextrin, and TMP-β-cyclodextrin complexes, respectively [14]. Scanning electron microscopy observations revealed that the TMP-β-cyclodextrin complex contained no crystalline form of TMP but instead formed dense polymer aggregates. This suggests that TMP molecules are dispersed within the β-cyclodextrin matrix, creating irregular agglomerates that enhance both solubility and dissolution profiles through increased specific surface area.

Cyclodextrins have unique molecular structures and can interact with guest molecules, but it is impossible to intuitively study the formation process of inclusion complexes only by experiments, so molecular simulation is widely used to explore cyclodextrin inclusion complexes [50]. Molecular simulation is a computer simulation method for simulating the properties of molecules or molecular systems, used to study the properties and three-dimensional structures of molecules. Molecular simulation methods such as molecular docking and molecular dynamics simulation can show the details of intermolecular interactions that cannot be captured by experiments, and better understand the structure and inclusion mechanism of cyclodextrin inclusion complexes [51]. However, the flexibility and asymmetric shape of cyclodextrins lead to a rather complex conformational space of the formed inclusion complexes. There seem to be multiple binding modes, but usually only one of them is dominant, and this main conformation can often be determined by molecular simulation [52].

5. Summary

In conclusion, the research on the inclusion of trimethoprim with cyclodextrins provides an effective way to improve the physicochemical properties of TMP and enhance its bioavailability. This article systematically combs the preparation methods, experimental characterization methods of trimethoprim cyclodextrin inclusion complexes, and the synergistic role of molecular simulation technology in the structural verification and mechanism analysis of inclusion complexes. These studies not only deepen the understanding of the laws of host-guest interactions but also lay a theoretical and experimental foundation for the subsequent development of

trimethoprim and cyclodextrin inclusion complexes.

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References

[1] Zou Y, 2011, Preparation of Trimethoprim Hydroxypropyl-β-cyclodextrin Inclusion Complex and Its Pharmacokinetic Study in Rabbits, thesis, Sichuan Agricultural University.

[2] Kinart Z, Tomaš R, 2022, Studies of the Formation of Inclusion Complexes Derivatives of Cinnamon Acid With α-Cyclodextrin in a Wide Range of Temperatures Using Conductometric Methods. Molecules, 27(14): 4420.

[3] Xiao S, Ji S, Jiang X, et al., 2021, Application of Cyclodextrins and Their Derivatives in Pharmaceutical Preparations. Journal of Liaocheng University (Natural Science Edition), 34(6): 77–83, 91.

[4] Zheng T, 2012, Research Progress on the Antibacterial Synergistic Effect of Trimethoprim on Traditional Chinese Medicine. Chinese Journal of Veterinary Medicine, 48(5): 68–69.

[5] Sarabia-Vallejo A, Caja M, Olives A, et al., 2023, Cyclodextrin Inclusion Complexes for Improved Drug Bioavailability and Activity: Synthetic and Analytical Aspects. Pharmaceutics, 15(9): 2345.

[6] Yang L, Li D, Luan H, et al., 2019, Theoretical Study on the Inclusion and Stability of Gabapentin With α- and β-Cyclodextrins. Journal of Atomic and Molecular Physics, 36(3): 361–372.

[7] Zhang H, Li Y, Zhang Y, et al., 2019, Preparation of α-Cyclodextrin Immobilized Starch and Effect of Its Physicochemical Properties on Sizing Performance. Applied Chemical Industry, 48(6): 1259–1264.

[8] Iannazzo D, Mazzaglia A, Scala A, et al., 2014, β-Cyclodextrin-Grafted on Multiwalled Carbon Nanotubes as Versatile Nanoplatform for Entrapment of Guanine-Based Drugs. Colloids and Surfaces B: Biointerfaces, 123: 264–270.

[9] Bai Z, 2022, Preparation and Application of β-Cyclodextrin-Based Antibacterial Materials, thesis, Nanjing University of Posts and Telecommunications.

[10] Bai Y, Wu H, 2021, Research Progress in Industrial Production of γ-Cyclodextrin. Food and Fermentation Industries, 47(22): 279–287.

[11] Tao Z, Yang J, Wang Q, et al., 2022, Enzymatic Properties and Product Specificity of γ-Cyclodextrin Glucosyltransferase. Food and Fermentation Industries, 48(13): 25–32.

[12] Lu N, Liu Y, 2020, Structural, Physicochemical, and Functional (Antioxidant-Antimicrobial) Properties of 2-O-Methyl-Beta-Cyclodextrin Inclusion With Hexahydro-Beta-Acids in Chitosan Films. Colloids Surf B Biointerfaces, 191: 111002.

[13] Ji X, Wei X, Lian T, et al., 2024, Preparation, Characterization and Pharmacokinetic Study in Rats of Florfenicol-β-Cyclodextrin Inclusion Complex. Journal of Agricultural Science of Yanbian University, 46(2): 45–52.

[14] Li X, 2013, Preparation and Properties of Trimethoprim Solid Dispersions and Inclusion Complexes, thesis, Xihua University.

[15] Zou Y, Fu H, Zhang W, et al., 2010, Preparation of Trimethoprim Hydroxypropyl-β-cyclodextrin Inclusion Complex and Its Pharmacokinetic Study in Rabbits. Chinese Veterinary Science, 40(12): 1285–1290.

[16] Li N, Zhang Y, Wu Y, et al., 2005, Inclusion Complex of Trimethoprim With Beta-Cyclodextrin. Journal of Pharmaceutical and Biomedical Analysis, 39(3–4): 824–829.

[17] Hu S, 2011, Preparation, Structural Analysis and Molecular Simulation of Drug-β-cyclodextrin Inclusion Complexes, thesis, Hebei University of Science and Technology.

[18] Cui H, Siva S, Lin L, 2019, Ultrasound Processed Cuminaldehyde/2-Hydroxypropyl-Beta-Cyclodextrin Inclusion Complex: Preparation, Characterization and Antibacterial Activity. Ultrason Sonochem, 56: 84–93.

[19] Zhang Z, 2024, Preparation of Albendazole-Methyl-β-cyclodextrin Inclusion Complex and Its Pharmacokinetic Study in Dogs, thesis, Foshan University.

[20] Sun H, Wang J, 2017, Preparation, Characterization and Molecular Simulation of Trimethoprim-Sulfobutyl Ether-β-Cyclodextrin Inclusion Complex. Chinese Pharmaceutical Journal, 52(13): 1159–1166.

[21] Lin Y, 2021, Preparation, Characterization of p-Anisaldehyde/β-cyclodextrin Inclusion Complex and Its Application in Strawberry Preservation, thesis, Jilin University.

[22] Macedo O, Andrade G, Conegero L, et al., 2012, Physicochemical Study and Characterization of the Trimethoprim/2-Hydroxypropyl-Gamma-Cyclodextrin Inclusion Complex. Spectrochimica Acta A Molecular and Biomolecular Spectroscopy, 86: 101–106.

[23] Zhao J, Wang Y, Sun K, et al., 2025, Research Progress on Sustained-Release Antibacterial Properties of Cyclodextrin Inclusion Complexes. Journal of Functional Materials, 56(2): 2050–2057.

[24] Santos P, Souza L, Araujo T, et al., 2017, Methyl-Beta-Cyclodextrin Inclusion Complex With Beta-Caryophyllene: Preparation, Characterization, and Improvement of Pharmacological Activities. ACS Omega, 2(12): 9080–9094.

[25] Qi Y, 2022, Application and Research Progress of Cyclodextrins in Water Treatment. Guangdong Chemical Industry, 49(7): 101–103.

[26] Saokham P, Muankaew C, Jansook P, et al., 2018, Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes. Molecules, 23(5): 1161.

[27] Zhou Y, Li Q, Liu H, et al., 2022, Preparation and Characterization of β-Cyclodextrin and Polylactic Acid Inclusion Complex. Guangdong Chemical Industry, 49(3): 69–71.

[28] Zhang Y, Huang L, Xu Z, 2008, Research Progress in Modification and Application of Cyclodextrins. Modern Food Science and Technology, 24(9): 947–951.

[29] Yang Y, Li Z, Jin T, et al., 2021, Preparation and Characterization of Allylgestrenol-β-cyclodextrin Water-Soluble Derivative Inclusion Complex. China Animal Husbandry & Veterinary Medicine, 48(11): 4094–4104.

[30] Xu D, Liu J, Liu Y, 2021, Research Progress on β-Cyclodextrin and Its Derivatives in Increasing Water Solubility of Guest Molecules. Science and Technology of Food Industry, 42(16): 404–411.

[31] Liu J, Zhang X, Tian B, 2020, Selective Modifications at the Different Positions of Cyclodextrins: A Review of Strategies. Turkish Journal of Chemistry, 44(2): 261–278.

[32] Li Q, Lou L, Long X, et al., 2020, Research Progress of β-Cyclodextrin and Its Derivatives as Drug Carriers. Modern Salt and Chemical Industry, 47(4): 1–2.

[33] Xu Y, Yao Y, Sheng J, et al., 2023, Preparation, Characterization and Properties of Torreya Grandis Essential Oil/β-Cyclodextrin Inclusion Complex. Packaging Engineering, 44(7): 76–84.

[34] Kose K, Tuysuz M, Aksut D, et al., 2022, Modification of Cyclodextrin and Use in Environmental Applications. Environmental Science and Pollution Research International, 29(1): 182–209.

[35] Calcagnile M, Bettini S, Damiano F, et al., 2018, Stimulatory Effects of Methyl-Beta-Cyclodextrin on Spiramycin Production and Physical-Chemical Characterization of Nonhost@Guest Complexes. ACS Omega, 3(3): 2470–2478.

[36] Chen J, Su W, Wang E, 2016, Determination of Optical Purity of Ibuprofen Using Hepta-(2,6-di-O-methyl)-β-cyclodextrin as NMR Chiral Solvating Agent. Chemical Research and Application, 28(4): 508–511.

[37] Zhang W, Fu H, Chen J, et al., 2011, Study on Inclusion of Trimethoprim by Hydroxypropyl-β-cyclodextrin. China Animal Husbandry & Veterinary Medicine, 38(11): 66–69.

[38] Cai J, Qian H, Ma Y, 2021, Research Progress on Characterization of Inclusion Complexes and Their Application in Modern Preparations. Northwest Pharmaceutical Journal, 36(5): 849–852.

[39] Lu C, Fu H, Zou Y, et al., 2014, Study on Inclusion Process of Trimethoprim by Hydroxypropyl-β-cyclodextrin. Computers and Applied Chemistry, 31(2): 175–180.

[40] Mura P, 2014, Analytical Techniques for Characterization of Cyclodextrin Complexes in Aqueous Solution: A Review. Journal of Pharmaceutical and Biomedical Analysis, 101: 238–250.

[41] Li N, Zhang Y, Xiong X, et al., 2005, Study of the Physicochemical Properties of Trimethoprim With Beta-Cyclodextrin in Solution. Journal of Pharmaceutical and Biomedical Analysis, 38(2): 370–374.

[42] Jansook P, Kurkov S, Loftsson T, 2010, Cyclodextrins as Solubilizers: Formation of Complex Aggregates. Journal of Pharmaceutical Sciences, 99(2): 719–742.

[43] Sun L, Zhang L, Sun X, 2023, Study on Identification of Cowhide and Polyurethane Leather by Fourier Transform Infrared Spectroscopy. Synthetic Materials Aging and Application, 52(4): 34–35.

[44] Wang Y, Zhang L, Sun H, et al., 2019, Preparation and Thermal Decomposition Kinetics of Menthol and β-Cyclodextrin Inclusion Complex. China Food Additives, 30(7): 98–103.

[45] Xu S, 2024, Preparation of Ketoconazole-Methyl-β-cyclodextrin Inclusion Complex and Its Pharmacokinetic Study in Dogs, thesis, Foshan University.

[46] Hao B, Ren L, Huang B, et al., 2021, 2-Hydroxypropyl-Beta-Cyclodextrin Encapsulates Dimethyl Disulfide Producing a Controlled Release Formulation. Science of the Total Environment, 773: 145293.

[47] Ma Y, 2024, Preparation of Trimethoprim Cyclodextrin Inclusion Complex and Its Pharmacokinetic Study in Dogs, thesis, Foshan University.

[48] Zheng X, You J, Zhu Y, et al., 2022, Application of Scanning Electron Microscopy in Polymer Characterization. Acta Polymerica Sinica, 53(5): 539–560.

[49] Nie J, 2024, Preparation of Ivermectin-Hydroxypropyl-γ-cyclodextrin Inclusion Complex and Its Pharmacokinetic Study in Dogs, thesis, Foshan University.

[50] Wang W, Ye Z, Gao H, et al., 2021, Computational Pharmaceutics – A New Paradigm of Drug Delivery. Journal of Controlled Release, 338: 119–136.

[51] Dong L, Cheng Y, Sun C, et al., 2025, Application of Molecular Simulation in the Study of Cyclodextrin Inclusion Complexes. Chinese Pharmaceutical Journal, 60(11): 1110–1117.

[52] Bao X, Liu X, Dou R, et al., 2023, How Are N-Methylcarbamates Encapsulated by Beta-Cyclodextrin: Insight Into the Binding Mechanism. Physical Chemistry Chemical Physics, 25(20): 13923–13932.