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# RECENT APPLICATIONS OF CYCLODEXTRIN-BASED ADSORBENTS IN SOLID AND LIQUID PHASE EXTRACTION FOR THE DETERMINATION OF ANTIBIOTICS: A MINI REVIEW

## (Aplikasi Baharu bagi Penjerap Berasaskan Siklodekstrin dalam Pengekstrakan Fasa Pepejal dan Cecair bagi Penentuan Antibiotik: Suatu Tinjauan Mini)

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### Abstract

Antibiotic residues are being continuously detected in the environmental and food matrices. Though the level of antibiotic residues is typically in minute concentration, adverse effects of these antibiotics on the environment and human health have been observed. Hence, there is a demand for simple, rapid, accurate, reliable, inexpensive, and selective sample preparation with high sensitivity and throughput analysis for antibiotic compounds. Conventional extraction techniques such as liquid-liquid extraction (LLE) and solid phase extraction (SPE) are commonly used for sample preparation. However, most of the LLE and SPE techniques suffer from several major drawbacks such as consuming a large amount of toxic organic solvents, being relatively expensive, involving multi-step, time-consuming, and tedious operation. Thus, to overcome these shortcomings, a number of new-generation materials have been developed for the purification and separation of analytes. Over the past few decades, cyclodextrin-based adsorbents have drawn worldwide attention as new-generation adsorbents for sample preparation and extraction due to their extraordinary physicochemical properties. Cyclodextrin is a family of cyclic oligosaccharides built by the hydrophilic outer wall and hydrophobic cavity. These unique properties are modified with chemical functionalization to enhance their extraction capability. This review outlined the recent application of the cyclodextrin-based adsorbent in the sample preparation techniques of a variety of matrices. These methods represent fast, modern, sensitive, and efficient approaches to detecting antibiotic compounds. In this review, several new sample preparation techniques incorporated with cyclodextrin-based adsorbent developed from 2015 – 2022 is discussed in terms of their analytical performance which includes their sensitivity and efficiency toward the extraction, preconcentration, and isolation of antibiotic compounds from various type of matrices.

**Keywords**: cyclodextrin adsorbent, sample preparation, antibiotics, microextraction

## Abstrak

Sisa antibiotik telah dikenal pasti di matriks sekitaran dan makanan. Walaupun paras sisa antibiotik ini kebiasaannya dalam kepekatan yang sangat kecil, kesan buruk daripada antibiotik ini terhadap sekitaran dan kesihatan manusia telah dicerap. Justeru, terdapat permintaan terhadap penyediaan sampel yang ringkas, cepat, tepat, boleh diguna pakai, tidak mahal, dan selektif dengan kepekaan dan hasil yang tinggi bagi sebatian antibiotik. Setelah beberapa dekad, penjerap berasaskan siklodekstrin telah mendapat perhatian global sebagai penjerap generasi baharu bagi penyediaan sampel dan pengekstrakan disebabkan sifat fizikokimianya yang luar biasa. Tinjauan ini menggaris kasar aplikasi baharu bagi penjerap berasaskan siklodekstrin dalam teknik penyediaan sampel di dalam pelbagai jenis matriks. Teknik pengekstrakan konvensional seperti pengekstrakan larutan (LLE) dan pengekstrakan fasa pepejal (SPE) selalunya digunakan untuk penyediaan sampel. Walaubagaimanapun, kebanyakan teknik LLE dan SPE ini mempunyai beberapa kelemahan seperti menggunakan jumlah pelarut organik toksik yang banyak, agak mahal, melibatkan banyak kaedah dan mengambil masa yang panjang dan berlarutan. Justeru, bagi mengatasi kelemahan ini, beberapa jenis bahan generasi baharu telah dibangunkan bagi penulenan dan pemisahan analit. Setelah beberapa dekad yang yang lalu, bahan penjerap berasaskan siklodekstrin telah mencetuskan perhatian sebagai penjerap generasi baharu bagi penyediaan sampel dan pengekstrakan oleh kerana sifat-sifat fizikokimia yang luar biasa. Siklodekstrin adalah kumpulan bagi oligosakarida siklik terhasil dengan dinding luar yang hidrofilik dan kaviti yang hidrofobik. Sifat-sifat unik ini telah diubahsui dengan berfungsikan kimia bagi meningkatkan keupayaan pengekstrakan. Tinjauan ini menggaris kasar aplikasi baharu bagi penjerap berasaskan siklodekstrin dalam teknik penyediaan sampel di dalam pelbagai jenis matriks. Teknik-teknik ini menggunakan pendekatan yang cepat, moden, sensitif, dan efisien untuk mengesan sebatian antibiotik. Di dalam tinjauan ini, beberapa teknik penyediaan sampel baharu yang digabungkan bersama penjerap berasaskan siklodekstrin yang dibangunkan dari 2015 – 2022 dibincangkan dari segi prestasi analitikal termasuk kepekaan dan kecekapan terhadap pengekstrakan, prakepekatan, dan pengasingan bagi sebatian antibiotik daripada pelbagai jenis matriks.

**Kata kunci:** penjerap siklodekstrin, penyediaan sampel, antibiotik, pengekstrakan mikro

## Introduction

Since their discovery, antibiotics have been widely used for the growth and function disruption of bacteria by targeting certain parts within them [1]. Antibiotics have helped to increase the average life expectancy of men because they are utilized to prevent and treat bacterial infections or as dietary supplements, bringing to heels numerous life-threatening infectious diseases [2,3]. Tetracyclines, amphenicols, macrolides, beta-lactam antibiotics, etc. are natural or semi-synthetic classes of antibiotics that are employed extensively to treat livestock against the activities of the wide variety of gram-positive and gram-negative bacteria, thus promoting healthy living and rapid growth in animal husbandry [4,5]. Antibiotics have been administered to prevent the spread of diseases, antibiotics limit or kill harmful bacteria in order to protect a flock or herd from illnesses. Their use promotes good animal health and helps with food safety, disease prevention, and the livelihood of farmers. In addition, these drugs were commonly used as non-prescription feed additives for the development and growth of farm animals [6].

However, the emergence of human antimicrobial resistance from the misuse and overuse of these antibiotics can leave residues in human and dairy products like milk, egg, and meat [3,7]. These sub-therapeutic residues in foods can lead to the occurrence of antibiotic resistance bacteria and cause liver and tissue damage, gastrointestinal and neurological disorders, teratogenesis, carcinogenesis, and allergic reactions in hypersensitive humans [3,8,9]. Hence, the existence of these minute concentrations of antibiotic residue in animal-based food products is a major risk to human health and the ecological environment, thus a public concern. Different groups of antibiotics discussed in this review are presented in Table 1.

In a bid to curtail the potential threats, and sustain food quality and safety, regulatory bodies like the US Food and Drug Administration and European Commission have introduced and adopted the maximum residue limits (MRLs) for antibiotics and veterinary drugs in human and dairy products like milk, egg, and meat [7,10]. The MRLs are legally documented acceptable residue limits in different food matrices without toxicological effects on man. The tolerance levels adopted by China, Brazil, Canada, Codex and European Union ranged from 100 to 600 µg/kg for individual antibiotics and their combinations in dairy products (poultry, cattle, swine, fish, meat, eggs, liver, and muscle) [11–14]. MRLs for selected antibiotics in poultry and milk matrices are listed in Table 2.

Table 1. Different groups of antibiotics are discussed in this review

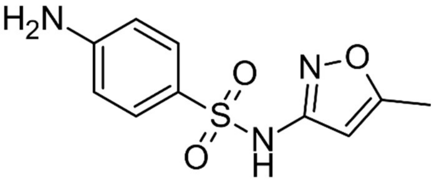
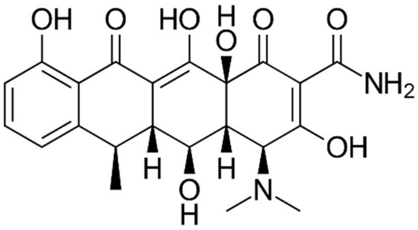
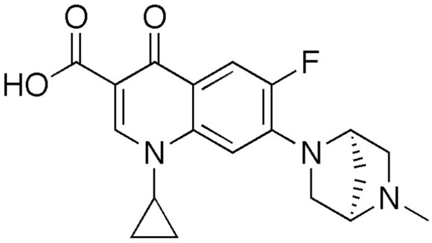
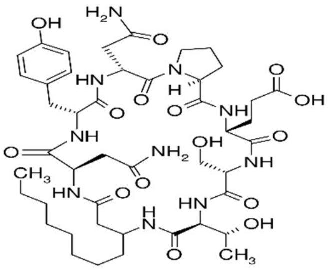
| Antibiotic Groups | Name of Antibiotics | Structure |
|---|---|---|
| **Sulfonamide** | Sulfamethazine, sulfadiazine, sulfamethoxazole, sulfamerazine |  |
| **Tetracycline** | Oxytetracycline, doxycycline, chlortetracycline, minocycline |  |
| **Fluoroquinolone** | Danofloxacin, ciprofloxacin, ofloxacin, enrofloxacin |  |
| **Lipopeptide** | Bacillomycin, daptomycin, surfactin, mycosubtilin |  |

Table 2. Information on MRL of antibiotics [7,10]

| **Analyte** | **MRL (µg/kg)** | |
|---|---|---|
| | **Poultry** | **Milk** |
| Danofloxacin | 300 | 30 |
| Enrofloxacin | 100 | 100 |
| Ciprofloxacin | 30 | 100 |
| Sulfadimethoxine | 100 | 100 |
| Sulfamethazine | 100 | 100 |
| Sulfonamide | 100 | 100 |
| Oxytetracycline | 300 | 100 |
| Tetracycline | 600 | 100 |
| Chlortetracycline | 100 | 100 |

The regulatory bodies have devised the means of regularizing the requirements for analytical methodology and result interpretations. Because of this, there is a need to develop an effective, selective, and sensitive analytical method that can detect, preconcentrate, and degrade several antibiotic residues and their derivatives at low concentrations levels from a variety of matrices. The newly developed sample pre-treatment methodology in conjunction with advanced analytical instrumentation must be able to monitor, assess, and quantify low concentrations of antibiotics in complex environmental and food matrices despite the existence of major interferences. These interfering compounds must be removed via the sample pretreatment process before analytical instrumental analysis. The methodology applied for the detection and determination of antibiotic residue falls into two categories. The first category comprises screening steps that are easy to use, cheap, and have high sample through-put, although are considered low in selectivity and sensitivity. They include surface plasmon resonance technology biosensors, magnetic immunoassays (MIAs), rapid test-kit, and enzyme-linked immunosorbent assays (ELISA). The second category includes the confirmatory methods which are specific and provide structural elucidation in conjunction with other detectors when assessing and quantifying target antibiotics [15].

Different analytical instrumentation techniques have been employed for the detection of antibiotics, including high-performance liquid chromatography (HPLC) [16], ELISA, thin-layer chromatography (TLC), gas chromatography [17], and capillary electrophoresis (CE) in conjunction with mass spectrometry, ultraviolet, fluorescence, or tandem mass spectrometry [18]. Despite the advances in technology, especially in instrument development, most analytical instruments cannot handle the samples directly due to high matrix interferences and the conditions of the complex samples. Hence, there is demand for the development of powerful and inexpensive sample preparation techniques that are simple, rapid, reliable, and accurate. Sample preparation step is required in any chemical analysis procedure. It is used to (a) convert the analyte into the instrument-compatible form, (b) eliminate major interferences and reduce matrix effects, (c) enrich the analytes and improve the sensitivity of the method, and (d) improve the precision of the methods. The ideal sample preparation requirements include exhibiting reliable analytical performance in terms of high extraction efficiency and sample clean-up, minimum toxic solvent consumption, being inexpensive, high sensitivity, reusability, high accuracy, and being environmentally friendly.

The conventional sample preparation method, solid phase extraction (SPE) is the most frequently applied method owing to its high enrichment factor, especially with the emergence and use of automated online SPE with direct injection. However, it is a time and solvent-consuming approach, with a potential loss of volatile compounds during the concentration step. Also, the clogging and plugging of the cartridges can affect consistency in the flow of the automated SPE. These drawbacks can be ameliorated by employing different adsorbents for the preconcentration of antibiotics [19]. To overcome these shortcomings, nanomaterials were usually applied as an adsorbent in sample preparation steps. The advantages of using nanomaterials in various analytical procedures are due to their large surface areas. These can be used to improve the sensitivity and miniaturization of devices by removing interferences species and enhancing analyte concentration. Furthermore, they can be incorporated with different functional groups to improve their affinity for compounds, which makes them particularly useful in the selective extraction of target analytes from complex matrices [21].

One of the best sorption materials ever discovered is cyclodextrin (CD), a series of cyclic oligosaccharides with 6-12 d-glucopyranose units characterized by toroidal (doughnut-shaped) structure. It was first developed in 1881 by Villier from the digestion of starch with *Bacillus amylobacter*; subsequently, Schardinger established its cyclic structure in 1903 [20]. The CDs are natural, eco-friendly, non-reducing, water-soluble, macrocyclic malto-oligosaccharides comprising glucans linked together by α-(1,4) glycosidic bonding. They are produced from the degradation of starch through intramolecular transglycosylation reaction using CD glucanotransferase (CGTase enzyme). Parent CDs are of three types: α-, β- and γ- CD having six, seven, and eight α-(1,4) linked glycosyl units respectively. Moreover, the exterior surface of the CD is hydrophilic while its interior is hydrophobic; these properties entrap biological, organic, and inorganic guest compounds moderately or entirely without covalent bonding to create reversible and noncovalent inclusive complexes.

The CD-based materials has garnered a lot of attention from researchers in recent times because it is nontoxic, economical, readily available, and can be grafted on nanoparticles forming an adsorbent that creates a favorable adsorption site for small organic compounds owing to its unique hydrophobic cavities, high adsorption capacities, and fast adsorption [22]. The supramolecular host-guest interactions exist between the β-CD (host) and organic molecules (guest) which can also be reversed to allow the desorption of the organic molecules from the β-CD (Figure 1). This makes the β-CD sorption material to be reusable, recyclable, efficient, and selective [23]. Also, the outer surface of the β-CD contains hydroxide functionalities which allow metal ions to covalently bond to it; in addition, dehydration, and condensation of β-CD with carboxyl groups will yield complex structure polymers. The tunability properties of the novel β-CD adsorbents allow the efficient and simultaneous removal of different pollutants. In addition, the chemical functionalization of CDs enhances their solubility and stability towards oxygen or light, and also regulates the reactivity of guest molecules [24].

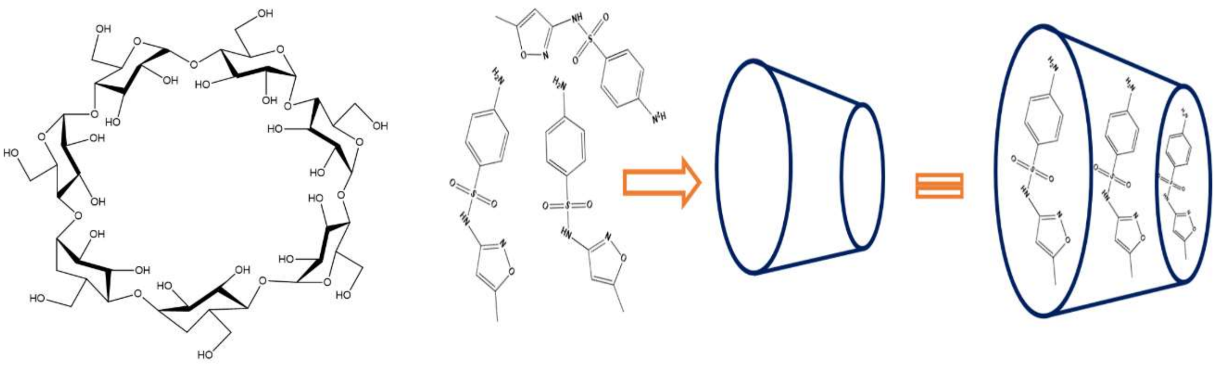


Figure 1. Structure of cyclodextrin (CD) and formation of inclusion complex with antibiotic molecules

This review paper aims to report an overview of sample preparation techniques for the determination of antibiotic compounds using CD-based adsorbents. The review highlights the analytical performances, advantages, limitations, and applications of the adsorbent in extraction techniques to extract antibiotics. Advances from 2015 to 2022 in the sample preparation of antibiotics in variety of matrices are reviewed here. Furthermore, future research of CD-based adsorbents is also elaborated. To the best of our knowledge, the application of CD-based adsorbent in sample preparation of antibiotic compounds has not been reported in an individual review.

## Preparation of cyclodextrin-based adsorbents

β-cyclodextrin (β-CD) and their derivatized β-CD-based adsorbent materials have been configured with active sites using various configurations of functional groups to establish unique features which fit for adsorption and extraction performance, touted to be efficient, selective, and reusable adsorbent. As cyclic oligosaccharides makeup of the glucopyranose monomer units interconnected by α(1→4) glycosidic linkages, the presence of hydrophilic exteriors rich hydroxyl (-OH) groups and hydrophobic internal cavity in β-CD has expedited the modification or functionalization strategies with various functional groups [25]. To date, β-CD and its derivatized β-CD have been utilized as adsorbents for lipopeptide antibiotics [26], metronidazole antibiotics [27], tetracycline antibiotics [25,28–32], fluoroquinolone antibiotics [33–36], and sulfonamide antibiotics [37]. Modified CD-based adsorbents for the extraction of antibiotics can be prepared using various strategies. These include chemically modifying cyclodextrins to attach reactive groups, immobilizing them onto solid supports or nanoparticles, and employing techniques like molecular imprinting and supramolecular assembly. These strategies customize the adsorbents, allowing selective capture and extraction of antibiotics from complex samples, thereby enhancing the efficiency and reliability of the sample preparation process.

In order to achieve desired adsorbent properties and evolve as a class of multifunctional adsorbent materials, different chemical modification techniques have been employed to overcome some of the limits experienced by the β-CD, for instance strong inter/intramolecular hydrogen bonding among molecules which result in poor solubility, difficulty to separate, and maximum steric hindrance due to presence of secondary OH groups in the structure [38,39]. Yakout et al. described the formation of Cu-nanoparticles immobilized β-CD functionalized reduced graphene oxide (Cu/β-CD/rGO) via chemical reduction procedures using graphene oxide (GO) and copper nitrate trihydrate ($Cu(NO_3)_2{\cdot}3H_2O$) with sodium borohydride ($NaBH_4$) as an oxidizing agent. The Cu/β-CD/rGO nanocomposite was applied as an adsorbent for efficient extractors of tetracycline antibiotics residues. The morphological analysis revealed that the nanocomposite appeared as a random three-dimensional porous structure with uneven surfaces and the diameter determined by the dynamic light scattering (DLS) technique was found to be in the range of 17.6 to 18.8 nm. Moreover, the successful immobilization of Cu-nanoparticles and β-CD onto rGO was observed at a peak 26.3° for rGO while three peaks at 43.2°, 50.3°, and 74.0° were attributed to Cu nanoparticles which were in good agreement with standard Cu. Four types of interactions were identified which are π-π stacking interactions, cation-π-bonding, inclusion of tetracycline structure in the hydrophobic central cavity of β-CD, and cation-π bonding bridge/and cation-n bonding bridge [25]. Zhao et al. fabricated a microporous structure of monolithic polymer via radical polymerization using allyl-β-CD and methyl methacrylate as co-monomers, triallyl isocyanurate and ethylene glycol dimethacrylate as co-crosslinkers, and azobisisobutyronitrile (AIBN) as an initiator. The microporous structure in the monolithic polymer material was more than 50 nm with a specific surface area of 31.89 $m^2\ g^{-1}$. The lipopeptide antibiotics occupied molecular recognition with the allyl β-CD polymer monolithic column through multiple interactions such as hydrogen bonding, hydrophobic interaction, π-π interaction, and dipole-dipole interaction. The resulting allyl β-CD polymer monolithic column also showed good precision, excellent recovery, good repeatability, and cost-saving which provide advantages for the multi-action separation mechanisms [26].

Ying Zhang et al. reported magnetic mesoporous core-shell structured silicas containing covalently bound CDs ($Fe_3O_4@SiO_2@mSiO_2$-CD) using facile route by introducing β-CD-silica with core-shell structured mesoporous $Fe_3O_4@SiO_2@mSiO_2$ microspheres. The presented adsorbent established multiple interactions with doxycycline antibiotic such as inclusion interactions, hydrophobic interactions, electrostatic attractions, and π-π interactions. Moreover, based on the adsorption kinetic study, the maximum adsorption capacity of the adsorbent (83.33 mg $g^{-1}$) fitted with pseudo-second order with coefficient determination ($r^2$) and the adsorption process was via chemisorption procedure. The synergistic mechanism in the mesoporous structure and cavity of β-CD has provided good adsorption performance with multiple interactions with the doxycycline antibiotic, as well as the process was spontaneous and exothermic [29]. Similarly, study by Y. Li et al. (2018) found that the prepared CD metal-organic framework (CD-MOF) using γ-CDs and alkali metal cations exhibited excelled selectivity and adsorption capacity against sulfonamide antibiotics with the main force of interaction was due to the hydrogen bonding formed between the antibiotics and OH groups in the CD-MOF adsorbents. The kinetic experiments data showed that the equilibrium adsorption capacity was achieved and fitted pseudo-second-order model with $r^2 > 0.99$ and the process were facilitated by chemisorption [37].

In a study conducted by Sereshti et al., they noted that the addition of β-CD to the hydrophilic/hydrophobic deep eutectic solvent (DES) system improved the extraction efficiency for the tetracycline antibiotics as a result of selective supramolecular host-guest inclusion between the adsorbent and analytes. This was supported by the notorious feature of DES as a disperser and extraction solvent which facilitates and retains the host-guest complexation ability. Moreover, the molecular structure of β-CD which consist of hydrophobic cavity and hydrophilic external surface has made the dissolution in the DES undemanding yet at the same time retaining its ability to establish host-guest complexation [31]. Belenguer-Sapiňa et al. in their study reported that a new adsorbent based on type UMV-7 mesoporous-silica modified with γ-CD has been successfully synthesized for extraction protocol of fluoroquinolones-based veterinary antibiotics. The prepared material exhibited interparticle porosity (0.71 $cm^3 g^{-1}$) and intraparticle porosity (0.14 $cm^3 g^{-1}$) with the size of internal cavity of about 0.98 nm enabling more efficient extraction performance as well as more selective towards the targeted veterinary antibiotics [34].

## Comparison of sample preparation methods

Numerous sample preparation strategies incorporated with CD-based adsorbents have been developed for the extraction and preconcentration of antibiotic molecules in a variety of matrices. The applications of CD-based adsorbents in sample preparation for the determination of antibiotics in various matrices from recent years are summarized in Table 3. Modified CD-based adsorbents offer several advantages in sample preparation for analytical purposes. They provide selectivity by specifically capturing target compounds, improving isolation from complex samples. These versatile adsorbents can be tailored to capture a wide range of analytes, making them applicable in various fields. By concentrating target analytes, the CD-based adsorbents enhance sensitivity, allowing for the detection of trace-level compounds.

## Applications of cyclodextrin-based adsorbents in sample preparation

CD based adsorbents that are applied in extraction as sample treatment involved more than one interaction besides the hydrophobic guest-host inclusion complexes with the target analytes. The interior of CD is hydrophobic while the outer part is hydrophilic and it rarely occurs that the degree of the extraction capacity is much higher, indicating the synergistic interaction based on both structural components [40,41]. Owing to CD's unique structure which include reactive OH groups, it is feasible to chemically modify them to alter their solubility, increase their capacity for inclusion, or produce desirable qualities applied as adsorbent in sample treatment [35,36].

The optimization on extraction parameters in consideration of hydrophobic/hydrophilic structure of CDs as adsorbent involves improving the enrichment factor of target analytes extracted from diverse types of samples matrices [42,43]. Different types of extraction techniques have been reported which employed CDs in quantification of antibiotics from varied type sample matrices, which include biological fluids, environmental water, and food matrices. Regardless of how simple or complex the sample matrices are, sample preparation is still essential to guarantee that the analytes are successfully isolated, cleaned up, and enriched in the final extract and are in a state that is compatible with the desired analytical technique. Natural CDs has certain solubility in aqueous solution, which limits its application in the field of adsorption due to the steric hindrance and hydrophobicity between CDs and target analytes [44,45]. So, improvement of solubility become the crucial point for CD-based adsorbent/solvent in sample preparation field to improve the target analyte (antibiotic)'s isolation and enrichment factor. The extraction from these sample matrices can be solid phase extraction (SPE) [34,37,46], solid phase microextraction (SPME) [35,47], magnetic solid phase extraction (MSPE) [37,48–51], dispersive solid phase extraction (DSPE) [36,52], and dispersive liquid-liquid microextraction (DLLME) [31,49] which are further discussed on their related CDs adsorbents as well as their application for the selective extraction/clean-up of antibiotic.

## Online solid phase extraction and offline solid phase extraction

Since its inception in the early 1990s, solid phase extraction (SPE) has been a common approach for sample preparation. In comparison to the traditional liquid-liquid extraction (LLE), SPE offers simplicity, rapidity, excellent selectivity, and low cost, which have led to its widespread use especially in separation and extraction of antibiotics [53]. In addition, its use in sample preparation is beneficial for extraction, concentration, and sample cleanliness in a short amount of time due to the automation of the extraction procedure and ability to combine with different detection techniques in both on-line and off-line modes [37,53]. To date, various types of SPE adsorbents have been formulated by researchers to obtain high extraction recoveries in different complex traces. In 2018, cyclodextrin metal organic framework (CD-MOF) was developed to preconcentrate sulfonamide (SA) antibiotics and overcome prior SPE adsorbents with poor extraction performance and low hydrophobicity of SA that must be separated and preconcentrated [37]. ɣ-CD with cetyltrimethylammonium bromide (CTAB) were exploited to form a uniform cubic crystal with an average size of 200 – 500 nm and then used as SPE adsorbent for extraction of five selected SA. Elution solvent of acetonitrile/methanol (2:1, v/v) was chosen as it gave the highest recoveries of all SA about 90 – 101.2%. To validate its effectiveness in real samples, four different meats (chicken, pork, fish, and liver) with specific sample preparation were selected and good linear calibration ($R^2$ = more than 0.9907) were achieved with limit of detections (LODs) varied from 0.32 to 1.7 ng/mL. The prepared CD-MOF was also compared to previous SPE adsorbents [54–57] and successfully applied in SPE for SA preconcentration with high adsorption capacity in less than 10 minutes, high extraction efficiency, and satisfactory recoveries comparable with other methods.

Other than that, the man-made fluoroquinolones (FQs) antibiotic with a functional piperazine group in its structure against Gram-negative and Gram-positive bacteria were also of interest [58]. The widespread use in agricultural and veterinary sectors marked them as an emergent class of pollutant in water [59], and excessive use can cause serious safety and health problems due to their carcinogenicity and antibiotic resistance [60]. Thus, an efficient adsorbent development based on CD in SPE was invented to improve selectivity of targeted FQs. Belenguer-Sepina et al. designed the adsorbent based on porous glycidyl methacrylate (GMA) and ethylene dimethacrylate polymeric material (EDMA) with ɣ-CD as a surface modifier to extract FQs from ground water [46]. The final product of GMA-S-ɣ-CD adsorbent undergone two-step process: functionalization of CD and polymerization of GMA-co-EDMA. Raman spectrometry was used to verify the binding between functionalized CD with GMA-co-EDMA; it revealed the disappearance of thiols stretching (around 2500 $cm^{-1}$) indicating a good assembling between them, and presence of small peak in GMA-S-ɣ-CD indicating that the presence of small proportion -SH group did not react with modified CD.

The developed GMA-S-ɣ-CD adsorbent was then optimized and compared to previously reported β-CD polymeric material [61]. A significant improvement on recoveries was observed when ɣ-CD was used due to the similar size of targeted analytes with internal cavity of ɣ-CD. The selected optimum conditions for SPE were pH 1 of sample solution, 3 M of NaCl, 1 mL/min flow rate of sample through cartridge, 5:1 (m/v) of adsorbent with respect to sample volume, and 6 mL of methanol as elution solvent. The experimental procedure together with UPLC-MS/MS showed lower LODs between 0.2 – 0.5 µg/L with overall recoveries for five FQs more than 76%, and reusability of adsorbent was tested up to five times according to its constant recoveries. Although the enrichment and selectivity of targeted FQs were improved, the two-step process may be the limitation of this procedure.

A year later, the same group introduced a novel UVM-7 mesoporous silica modified with ɣ-CD as adsorbent for SPE for the isolation of ofloxacin, norfloxacin, and ciprofloxacin in milk samples [34]. UVM-7 material is the nanometric version of MCM-41 that has a macro and meso-pores on its structure. With the addition of CD into the structure, it will produce a truncated cone shape with hydrophilic part in the outside, and hydrophobic in the central part, making it capable to trap the host guest molecules. In this experiment, 10 mL of sample solution at pH 7 and addition of 2 M NaCl into the sample solution was used as the optimum condition for SPE. 100% of water as an efficient washing solvent was applied to remove any impurities clogging in the solid phase and 2 mL of acetonitrile as an elution solvent. Although the recoveries of extraction method were decreased between 60 – 70% due to the analytes losses during the treatment of sample, the result has a good precision to determine analyte under study in milk samples with high degree of confidence. The prepared adsorbent also showed that it is possible to reuse up to six times when dealing with real matrices.

### Solid phase micro-extraction

Liu et al. 2019 successfully developed a series of β-CD with varied substituents and applied as supramolecular functional monomers for supramolecularly imprinted polymeric (SMIP) solid phase microextraction (SPME) coatings [47]. Their study showed supramolecular monomer β-CD as the promising adsorbents for the SPME of both nitrophenols and bisphenol A from water samples. The morphology of the prepared SMIP SPME coatings have been characterized by X-ray diffraction analysis (XRD), infrared analysis (IR), scanning electron microscopy (SEM), field emission SEM (FESEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM) demonstrating that the ideal adsorbent has a greater number of pores (0.02 $cm^3/g$), enhanced intercommunity, and inclusion interaction from β-CD cavities, which boost molecular selectivity recognition. The relative accuracy for the extraction of target analyte from environmental water samples reported was from 88.2 to 90.2% with reusability of SMIP up to 100 cycles. The combination of SMIP technology with inclusion interactions contributed by β-CD cavities such as the hydrogen-bonding interactions, were the main contributions that enhance the extraction efficiency with reported LODs from 1.5 to 3 µg/L.

Another work by Celia-Ruiz et al. reported on β-CD modified nanocellulose (CD-NC) as an adsorbent material where β-CD was covalently bonded to amine-modified nanocellulose through amidation-reaction [35]. Supramolecular self-assembly of CD-modified NC by danofloxacin as guest molecule or target analyte showed excellent extraction efficiency and reusability with improved molecular recognition over its metabolite. These nanocavities with β-CD at its surface has greatly enhanced the SPME selectivity with recovery from 80 to 90% and LOD in milk samples was 2.5 µg/L. The combination of various molecular interactions, including H-bonding, dipolar interactions, and steric interactions between the hydroxyl groups of the CD and the analyte, contributes to the selective recognition of SPME packed mini column. The SPME was carried out using phosphate buffer solution with 12% acetonitrile as the eluent where all encapsulated target analyte was entirely stripped from CD-NC by electrophoretic analysis. The combination of H-bonding and dipolar interactions enabled the analyte to be further separated with higher extraction selectivity and CD-NC reusability, which has been reported to last up to 40 cycles.

## Magnetic solid phase extraction and dispersive solid phase extraction

Since its first invention by Anastassiades et al. in 2003, the dispersive solid phase extraction (DSPE) technique has received tremendous attention among researchers due to its improvement on contact surfaces, enhanced adsorbent-analytes interactions, high extraction performance, low organic solvent consumption, and fast approach for extraction [62]. Native CDs such as α-, β- and γ-CD and their modified version have been notably applied in the separation analysis of various analyte compounds due to their explicit features which comprised of hydrophobic cavities and hydrophilic external surfaces as well as readily undergoing modifications. Cui et al. introduced a novel DSPE composite adsorbent prepared from ATP coupled with β-CD using glycidoxypropyltrimethoxysilane as a silane coupling agent for the quantitative determination of (fluoro)quinolones in real honey sample. The adsorption behavior is performed under acidic conditions to enable ion-exchange interactions since the quinolone antibiotic possesses cationic formation as a result of the protonation of carboxylic and amino groups in the quinolone heterocyclic ring. The recoveries of all targeted analytes improved when the ratio of ammonia in methanol increased up to 40%. Moreover, the utilization of β-CD/ATP composite-DSPE under optimum conditions achieved low LODs between the range of 0.30 to 3.95 mg $L^{-1}$ with good recoveries between 83.6 – 88.6% and relative standard deviations (RSDs) less than 7.4%. Next, the applicability of the DSPE technique in real honey samples has successfully quantified the presence of four (fluoro)quinolones antibiotics which are ciprofloxacin, ofloxacin, gatifloxacin, and norfloxacin. The established sample preparation methodology using β-CD/ATP composite demonstrated excellent extraction efficiency due to its mesoporous feature as well as the contribution from the affinity of the hydrophobic cavity and hydrophilic external surfaces [36]. Zhang et al. synthesized porous β-CD polymer derived from CD and rigid aromatic groups tetrafluoroacetonitrile for the determination of quinolones using DSPE method. Several factors were optimized during the execution of the DSPE, including the amount of adsorbent, eluent and adsorption mount, and desorption time. The LODs of four quinolones antibiotics were obtained between 2.67 to 5.50 ng $mL^{-1}$ with relative recoveries ranging from 96.43 to 103.3% and RSDs less than 4.5%. In addition, the robustness of the porous β-CD polymer-DSPE expressed its reliability of the method during normal usage with RSD less than 6.7%. Additionally, the established method offers low-cost extraction with good recoveries, comparable LOD with the commercialized adsorbent, and relatively wider linear range between 25 to 5000 ng $mL^{-1}$ [52].

Magnetic solid phase extraction (MSPE) was first introduced by Šafaříková and Šafařik in 1999. It involves the use of a copper-coloured dye with an adsorbent containing a silanized iron magnetite. After the adsorbent has been absorbed, a magnetic field is then used to separate it from the sample solution. The extracted analytes are then eluted using a solvent that is suitable for the process. The eluent is then isolated from the adsorbent using a magnet. Over time, the use of the micro magnetic adsorbents that were originally developed for use with the MSPE (Figure 2) has since been replaced by more diverse nanosized adsorbents that are composed of hybrid or advanced materials [63]. Recent works showed that β-CD is usually functionalized with iron (II, III) oxide or magnetic nanoparticles with other material such as graphene oxide [49], chitosan [50], and silica [51] to enhance its selectivity in capturing those antibiotics compounds. Since MSPE has shown a great affinity towards analyte, with easy preparation steps, and be less messy and non-toxic, several works have been published to study the interaction between β-CD and antibiotics molecule. Two studies [37,48] functionalized β-CD with metal organic framework (MOF) to achieve the magnetic field capability. Both studies were on sulfonamide antibiotic using HPLC for analysis. Yang et al. [48] showed a good calibration curve ranging from 2 to 100 ng/mL with $r^2$ value more than 0.993. This method has a good sensitivity with LOD of 0.8 – 1.6 ng/mL. The satisfactory repeatability and reproducibility (RSD < 8%) and acceptable relative recoveries in the range of 78 – 112% were produced in chicken sample. A similar work was produced by Li et al. [37] to determine sulfonamide in meat sample. MSPE was performed on the meat sample using CD-MOF. The developed method showed a good linearity in acceptable concentration with low detection limit of 0.32 ng/mL. The reproducibility gives a good value of RSD < 7% and acceptable recoveries (76 – 102%). Another work by Al-Afy et al. used combination of β-CD with magnetic graphene oxide coated using silica composite to extract tetracycline antibiotic from milk sample. The method showed a good LOD at 1.8 – 2.9 µg/L. This might be due to the preconcentration factor of 667. The high enrichment is from two extraction techniques applied in this work: DLLME followed by MSPE. The reproducibility and repeatability of method is within acceptable range (RSD < 8.8%) and recoveries (70.6 – 121.5%) [49]. In two previous studies [50,51], magnetic nanocomposites of CD were synthesized for the determination of fluoroquinolones in wastewater samples. Li et al. [51] determined the residue of fluoroquinolones using HPLC-MS/MS. They grafted the CD to magnetic silica composite to form $Fe_3O_4@SiO_2@CD$ nanocomposite. Due to its core-shell sandwich structure, the analytes adsorb better on the adsorbent surface making a good detection limit at 0.0014 – 0.023 µg/L. A set of very good linearity was established ranging from 0.5 to 500 µg/L ($r^2 > 09981$). The method also noted a high precision (RSD < 4%) and analytes recoveries of 93.2 – 105%. Mashile et al. [50] used magnetic mesoporous carbon/β-CD-chitosan. The selective and sensitive method was based on affinity of CD enhanced by chitosan giving a low detection limit of 0.45 – 1.1 ng/L. Under optimized parameter, the used method showed a good linearity (0 – 300 µg/L, $r^2 > 0.9979$), robustness, accuracy, and precision (RSD < 4.4%) of fluoroquinolones in wastewater sample.

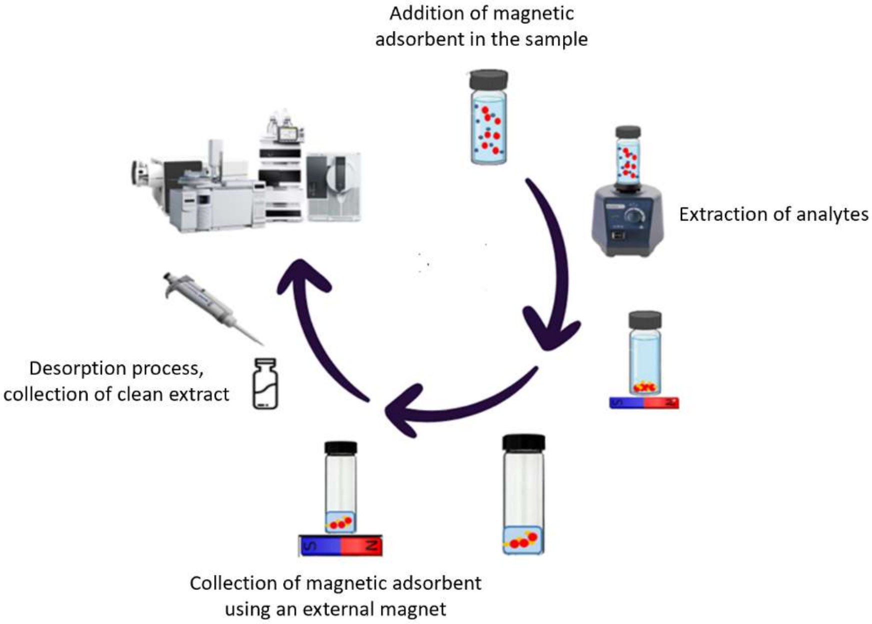


Figure 2. Schematic of MSPE process

### Dispersive liquid-liquid microextraction

Dispersive liquid-liquid microextraction (DLLME) (Figure 3) is one of the liquid-based extraction techniques that involves dispersing tiny droplets of the extraction solvent throughout an aqueous sample. The exceedingly large collective surface area of the droplets allows for instant partitioning of analytes into the extraction phase. Compared to conventional liquid or solid phase extraction procedures, DLLME gives higher enrichment factors and minimal solvent consumption.

Hassan et al. developed a green method that utilizes deep eutectic solvent (DES) as a disperser/extraction co-solvent in the extraction of tetracyclines antibiotics (TCs) in water samples [31]. Hydrophobic DES octanoic acid/thymol and hydrophilic DES choline chloride/ethylene glycol was synthesized and applied as extractant and disperser solvent respectively. The addition of β-CD in the extraction medium was to enhance its capability in higher extraction selectivity towards TCs. The dispersive effect of the extraction solvent and the stability of the murky solution were extremely higher with the addition of β-CD to DES. Furthermore, it has doubled the DLLME performance with higher recovery (74 – 113%) as compared to extraction solvent that only applied DES octanoic acid/thymol. The structure of β-CD that possesses a hydrophobic cavity and a hydrophilic external surface can interact with both hydrophobic/ hydrophilic DES. Through its hydrophobic cavity and hydrophilic surface, DES was dissolved during guest-host complexes formation and breaking into more fine droplets that maximized the contact surface of the analyte from aqueous into extraction medium. β-CD also acted as both co-extractants and co-disperser during the formation of supramolecular inclusion complexes (β-CD/TCs) and increased the selectivity during TCs migration from the sample solution. The extraction was analyzed with HPLC-DAD in environmental samples with reported LODs from 1.37 to 3.48 µg/L.

Another work by Nour Al-Afy et al. applied two types of sample preparation in combination: magnetic-SPE and DLLME in quantitation of tetracyclines (TCs) antibiotic in bovine milk samples [49]. The β-CD ($Fe_3O_4$@$SiO_2$@GO-β-CD) as the adsorbent material with the hydrophobic TC’s aromatic ring can freely fit into the cavity of the β-CD and formed a strong and stable host-guest combination. The hydrophobic-hydrophobic interaction was the main factor in the inclusion complex within the inner side of the β-CD cavity instead of the amine and amide groups from TCs that was unfavorable to the formation. The hydrophilic adsorbent's structure had polar groups that made it faster to dissolve in a polar solvent, with methanol working as the best desorption solvent toward the extraction of TCs in milk samples. DLLME was utilized as the subsequent sample extraction, and it was discovered that n-hexane was the best dispersant since it was water-insoluble (low density) and offered a high enrichment factor for 667 with a cleaner baseline in the chromatogram. Fe3O4@SiO2@GO-β-CD is a favorable adsorbent due to its great ability to extract TCs from milk samples with recovery rates ranging from 70.6 to 121.5% in milk samples and from 78.5 to 109.3% in water samples. This proposed method offered high precision (RSD < 8.8%), satisfactory recovery and improved preconcentration factor with reported LODs ranged from1.8 to 2.9 µg/L.

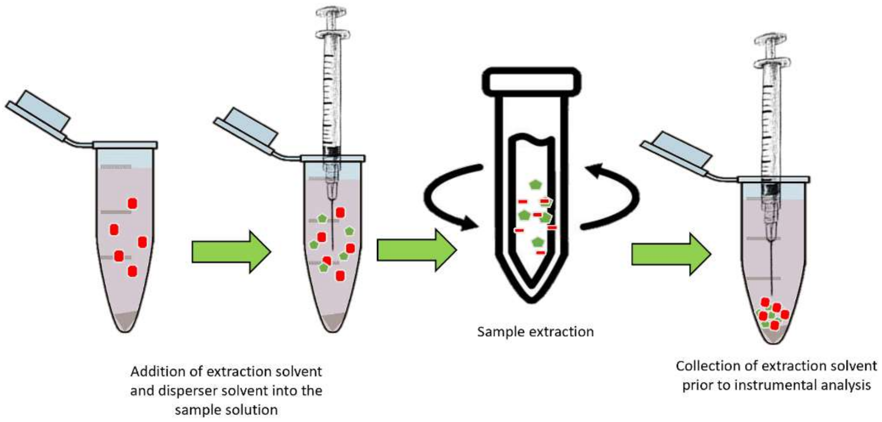


Figure 3. Schematic of DLLME process.

Table 3. The recent applications of CD-based adsorbents in sample preparation for the determination of antibiotics in various matrices.

| **Adsorbent** | **Extraction techniques** | **Quantitation instrument** | **Analytes** | **Sample matrix** | **Linearity** | **LOD** | **RSD (%)** | **Relative Recovery / Recovery (%)** | **Pre-Con factor** | **Reusability** | **Ref** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| β-Cyclodextrin-functionalized magnetic covalent organic framework ($Fe_3O_4$@COF@Au-β-CD) | MSPE | HPLC-MS/MS | Sulfonamides | Chicken | 2-100 µg/kg, $R^2 = 0.9936$ | 0.8-1.6 µg/kg | 2.4 – 8.6 | 78- 112 | 20 | - | [48] |
| β-cyclodextrin functionalized silica-coated magnetic graphene oxide ($Fe_3O_4$@$SiO_2$@GO-β-CD) | MSPE | HPLC-DAD | Tetracycline | Bovine milk | 10-200 µg/L, $R^2 = 0.9929$ | 1.8-2.9 µg/L | < 8.8 | 70.6 – 121.5 | 667 | 15 | [49] |
| Magnetic mesoporous carbon/β-cyclodextrin–chitosan | DMSPE | HPLC-DAD | Fluoroquinolone | Wastewater | 3.7-1000 ng /L, $R^2 = 0.9979$-0.9990 | 0.45-1.1 ng/L | < 4.4 | 93.5 – 98.8 | 90 – 150 | - | [50] |
| cyclodextrin-derivatized hybrid magnetic nanocomposite (Fe3O4@SiO2@CD) | MSPE | HPLC-MS/MS | Fluoroquinolone | Water | 0.5-500, µg/L, $R^2 = 0.9981$ - 0.9998 | 0.0014-0.023 µg/L | <4 | 93.2 – 105 |  | 5 | [51] |
| CD-MOF | MSPE | HPLC-DAD | Sulfonamide | Meat | 10-1000 ng/mL, $R^2 \geq 0.9907$ | 0.32-2.0 ng/mL | < 7 | 76 – 102 | - | - | [37] |
| UVM-7 mesoporous silica with ɣ-cyclodextrin | SPE | LC-FLD | Fluoroquinolone | Milk | 1.8-250 µg/L | 30-39 ng/L | 4 – 13 | 83 – 92 (water)<br>60 – 70 (milk) | - | 6 | [34] |
| ɣ- cyclodextrin (glycidyl co-ethylene dimethacrylate | SPE | UPLC-MS/MS | Fluoroquinolone | Water | 0.2-500 mg/L | 0.2-0.5 µg/L | - | 76 – 89 | - | 5 | [61] |
| β-cyclodextrin-modified nanocellulose (CD-NC) | SPME | Electrophoretic | Danofloxacin | Milk | 8-800 µg/L | 2.5 µg/L | - | 80 – 90 | - | 40 | [35] |
| Deep eutectic solvent doped β-cyclodextrin (DES-CD) | DLLME | HPLC-DAD | Tetracycline | Water | 4.58-500 µg/L $R^2 = 0.993$-0.996 | 1.37-3.48 µg/L | < 4.7 | 74 – 113 | - | - | [31] |
| β-CD/ATP composite | DSPE | HPLC-DAD | Fluoroquinolone | Honey | 10-1500 µg/L, $R^2 > 0.9991$ | 0.3-3.95 µg/L | < 7.4 | 83.6 – 88.6 | - | - | [36] |
| Porous β-CD polymer | DSPE | HPLC-DAD | Fluoroquinolones | Wastewater | 25-5000 ng/mL, $R^2 > 0.9994$ | 2.67-5.50 ng/mL | < 4.5 | 96.43 – 103.3 | - | - | [52] |

**Abbreviations: MSPE – magnetic solid phase extraction, SPME – solid phase microextraction, DLLME – dispersive liquid-liquid microextraction, DSPE – dispersive solid phase extraction, SPE – solid phase extraction, HPLC-MS/MS – high performance liquid chromatography tandem mass spectrometry, HPLC-DAD – high performance liquid chromatography diode array detector, LC-FLD – liquid chromatography fluorescence detector, UPLC-MS/MS – ultra performance liquid chromatography tandem mass spectrometry*

## Conclusion

The present review discussed the development of sample preparation techniques of antibiotic molecules using CD-based adsorbents. Overall, in most of the synthesis methods, the CD is attached to the adsorbent via a linker. It was noted that β-CD has been commonly used and prepared as an adsorbent in the sample preparation of antibiotic molecules, compared to other types of CDs. CD is at advantages in terms of green adsorbent as it is easy to prepare, flexible to functionalize, and improve selectivity and efficiency of extraction. Antibiotic molecules that are of the right size to enter CD cavity will exhibit higher extraction efficiency. The CD-based adsorbents offer advantages such as selectivity, versatility, efficient extraction, reduced matrix interference, compatibility with various techniques, and enhanced sensitivity. These factors make them promising adsorbents for sample preparation in the determination of targeted compounds, enabling more accurate and reliable analytical results. Future research would likely be towards the improvement of functionalities of the developed adsorbents through (a) the preparation of amphiphilic adsorbents towards variety polarity of targeted molecules, (b) use of a mixture of CDs in the preparation of adsorbents that can expand their use and efficiency, (c) production of new generation of selective CD materials with molecularly imprinted technology, and (d) combination of CD with other nanomaterials to improve their properties such as surface area, stability, and selectivity. It can be summarized that there has been a rapid development in the extraction and enrichment techniques for antibiotic molecules using CD-based materials, which were useful for monitoring antibiotics and have the potential to reduce the environmental pollution and eliminate food-chain contaminations. In the following years, an increase in the number of advanced greener sorbents and green sample preparation methods designed for monitoring antibiotics can be expected with the ultimate goal to prevent the development of antibiotic resistance phenomenon.

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