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Method Development for Analysis of Cyclodextrin Inclusion Complexes with HPLC

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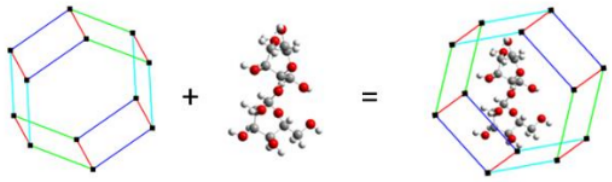
ABSTRACT *:Background: Cyclodextrin inclusion complexes have been widely used in the pharmaceutical industry to improve drug solubility and bioavailability. Analysis of these complexes using HPLC requires the development of appropriate and validated methods. Objectives: To analyze and compare various HPLC methods used for the analysis of cyclodextrin inclusion complexes, and to identify challenges and trends in method development. Methods: A literature review was conducted of articles published in the last 10 years, focusing on HPLC methods for the analysis of cyclodextrin inclusion complexes. Parameters compared included column type, mobile phase composition, flow rate, and detection method. Results: The majority of studies used C18 columns with varying lengths and particle sizes. The composition of the mobile phase varied, reflecting the diversity of properties of the complexes analyzed. The flow rate was generally 1.0 mL/min, with the exception of the HPLC/MS method. Detection methods included UV-Vis, PDA, fluorescence, and mass spectrometry. The main challenges included the dynamic equilibrium of the complexes and stability during analysis Conclusions: HPLC method development for the analysis of cyclodextrin inclusion complexes requires optimization of various parameters to overcome specific challenges. Future trends are towards the use of advanced technologies such as UHPLC and high-resolution mass detection.*

Keywords:*Cyclodextrin inclusion complexes, HPLC, method development, validation, pharmaceuticals*

1. INTRODUCTION

Cyclodextrin (CD) is a type of cyclic α-1,4-linked oligosaccharide formed from D-glucopyranose units, the result of starch degradation by the enzyme glucosyltransferase which is currently widely used by the pharmaceutical industry. The most abundant CDs are the α-, β-, and γ-CD types which consist of 6, 7, and 8 D-Glucopyranose units respectively. It has hydrophilic properties on the external surface and hydrophobic properties in its internal cavity (Nguyen, 2019). Because of this property, cyclodextrin compounds can bind guest molecules to form inclusion complexes. Hydrophobic interactions between the walls of the cyclodextrin cavity and guest molecules can cause the formation of cyclodextrin inclusion complexes with hydrophobic compounds. In addition to hydrophobic interactions, other interactions such as dipole-dipole and van der walls interactions are also involved (Kang, 2019). In addition to hydrophobic compounds, cyclodextrin can also form encapsulation with non-polar compounds. This encapsulation characteristic is very useful for use in various industries, especially the pharmaceutical industry, because of its benefits in increasing the solubility of the hydrophobic and non-polar compounds it binds (Bosînceanu et al., 2013)



Host Guest Inclusion Complex

Figure 1. Schematic illustration of the formation complex between a cyclodextrin (host) and a guest. This illustration was created inspired by the work of Kfoury, et all. (5).

The use of CD in the pharmaceutical industry to increase the solubility of a compound has been widely used, for example, the Cefixime compound in the research of Jadhav, et all, the Rutin compound which is one of the flavonoid compounds in the research of Chang, et all, the α-Mangostin compound in the research of Muchtaridi, et all, the Cilostazol compound in the research of Desai and Prabhakar, , the Efavirenz compound in the research of Braga et all, , the Naringenin compound in the research of Papaioannou et all, the Amiodarone compound in the research of Creteanu et all, and there are still many studies using other compounds that are being developed. The many developments of inclusion complexes that have been carried out encourage researchers to develop new analytical methodologies to assess the physicochemical properties and stability of drugs to provide information on the effectiveness of the drug.

High-Performance Liquid Chromatography (HPLC) is the most widely used method because it can provide data in large quantities during the analytical process, sometimes several critical parameters must be considered because of the many variables used that need to be adjusted correctly before each process is run. Some critical parameters used include interphase polarity, flow rate, pH, composition, and several properties of the sample matrix as well as other environmental factors such as temperature and detector type (13). Because of the many variables that affect the analysis process of cyclodextrin inclusion complex compounds, and the still very rare analytical methods of compounds in inclusion complexes with cyclodextrin that have been published, this analysis and study are needed for consideration in determining the development of cyclodextrin complex compound analysis methods.

2. METHOD

The method used in this study is a literature review method. The literature used was taken from several international journals, published on but not limited to: Pubmed, ScienceDirect, and Google Scholar in the last ten years (2013-2023). The keywords in searching for articles used were 'Cyclodextrin', 'Analysis Method', 'HPLC', 'Chromatography', and 'Inclusion Complex'. There were 40 articles that met the search criteria. Then a more specific selection of criteria was carried out so that 5 articles provided information on the HPLC analysis method used on compounds with cyclodextrin inclusion complexes.

3. ANALYSIS OF CYCLODEXTRIN INCLUSION COMPLEXES WITH HPLC

High Performance Liquid Chromatography (HPLC) has been widely used in the determination of qualification and quantitative, stability studies and solubility of drugs and matrices. The basic principle of HPLC separates a compound based on its polarity (14). The cyclodextrin complex that has been made is dissolved using water or other polar solvents, then testing and development of appropriate analysis methods are carried out.

Table 1. Comparison of Analysis Methods with HPLC for Cyclodextrin Inclusion Complexes

Title	Column	Mobile Phase	Flowrate	Detector	Wavelength
Establishment of a stability indicating HPLC method for Dronedarone Hydrochloride in tablets and in cyclodextrin inclusion complexes: application to degradation kinetic studies. (Method 1 : HPLC Method)	Waters XBridgeTM C18 column (250 mm x 4.6 mm, 5μm; Milford, MA, USA) – maintained at temperature 25±1°C	Buffer Solution pH 4.9 : Acetonitrile (35:65, v/v) Buffer solution pH 4.9 are solution 0.3% glacial acetic acid adjusted with ammonium hydroxide)	1.0 mL/min	PDA	289 nm
Establishment of a stability indicating HPLC method for Dronedarone Hydrochloride in	Poroshell 120 EC-C18 column (3.0 x 100 mm; 2.7μm) operated at	Methanol : 0.1% Glacial acetic acid (75:25,v/v)	0.3 mL/min	Triple quadrupole mass detector	

Title	Column	Mobile Phase	Flowrate	Detector	Wavelength
tablets and in cyclodextrin inclusion complexes: application to degradation kinetic studies. (Method 2 : HPLC/APCI-MS Method)	temperature 25±1°C				
Validation of a new HPLC method used for determination of Amiodarone from the complex with hydroxypropyl-beta-cycodextrin and from commercial tablets	C18 (Hypersil Betasil C18, 150 mm x 4.6mm; 5 µm)	A mixture of formic acid 0.5% in phosphate buffer solution pH 7.6 : Methanol (25:75, v/v)	0.7 mL/min	DAD-UV VIS	254 nm
Quantitative analysis of Norfloxacin in β-Cyclodextrin Inclusion Complexes-Development and Validation of a Stability-indicating HPLC Method	Phenomenex, C18 column (150 mm x 4.6 mm; 4 µm) at temperature 40 °C	Buffer phosphate 25mM pH 3.0 : Acetonitrile (87:13, v/v) Buffer phosphate pH 3.0 adjusted with phosphoric acid.	1.0 mL/min	Fluorescence	λ excitation = 278 nm λ emission = 445 nm
Improved pharmacokinetics of aceclofenac immediate release tablets incorporating its inclusion complex with hydroxypropyl-β-Cyclodextrin	RP C-18 column (Hypersil BDS C18; 250 mm x 4.6 mm; 5 µm)	Methanol : 0.3% TEA pH 5.0 (60:40, v/v)	1.0 mL/min	UV-Vis	275 nm
Formation of inclusion	C-18 column (250 mm x	0.025 mol/L	1.0 mL/min	UV-Vis	278 nm

Title	Column	Mobile Phase	Flowrate	Detector	Wavelength
complex of enrofloxacin with 2-hydroxypropyl-β-Cyclodextrin	4.6 mm, 5 μm)	aqueous phosphoric acid: acetonitrile (83:17)			

4. DISCUSSION

4.1 Comparison of Chromatography Column Methods

The selection of chromatography columns is a crucial aspect in the development of HPLC methods for the analysis of cyclodextrin inclusion complexes. From the data presented in Table 1, it can be seen that the majority of studies use C18 columns with various specifications. The widespread use of C18 columns can be explained by their versatile nature and ability to separate various types of compounds (Moldoveanu & David, 2016).

Marcolino et al. (2019) used a Waters XBridgeTM C18 column (250 mm x 4.6 mm, 5μm) for the analysis of Dronedarone Hydrochloride. This column has a relatively large length (250 mm) which can provide high resolution, but also has the potential to increase analysis time and system pressure. On the other hand, in the second method they used a Poroshell 120 EC-C18 column (3.0 x 100 mm; 2.7μm) which is shorter and has a smaller particle size. The use of columns with smaller particles can increase separation efficiency and allow faster analysis (Fekete et al., 2017).

Bosînceanu et al. (2013) chose a C18 column (Hypersil Betasil C18, 150 mm x 4.6 mm; 5 μm) for Amiodarone analysis. The 150 mm column length offers a balance between resolution and analysis time. Meanwhile, Mendes et al. (2015) used a Phenomenex C18 column (150 mm x 4.6 mm; 4 μm) for Norfloxacin analysis. The use of a particle size of 4 μm can provide good efficiency without a significant increase in back pressure as might occur with sub-2 μm particles (Kazakevich & LoBrutto, 2018).

Dahiya et al. (2015) and Ding et al. (2020) both used a 250 mm long C18 column, but with different brands (Hypersil BDS C18 and a common C-18 column). The use of these longer columns may improve resolution, which may be necessary for the separation of more challenging inclusion complexes. This comparison shows that although all studies used C18 columns, there was variation in the column length, particle size, and brand selected. This

selection is likely based on the specific nature of the analyte, the complexity of the sample matrix, and the need for resolution or speed of analysis (Sahu et al., 2018).

4.2 Mobile Phase Analysis and Its Composition

The mobile phase composition plays an important role in chromatographic separation and can greatly affect the retention and selectivity of the analysis. From the data presented, significant variations in the composition of the mobile phases used are seen, reflecting the diversity of the physicochemical properties of the inclusion complexes analyzed.

Marcolino et al. (2019) used two different mobile phase compositions in their two methods. The first method used a mixture of pH 4.9 buffer and acetonitrile (35:65, v/v), while the second method used methanol and 0.1% glacial acetic acid (75:25, v/v). The use of buffer in the first method can help control the ionization of the analytes and improve the reproducibility of the separation (Schellinger & Carr, 2016). Meanwhile, the use of methanol in the second method can provide different selectivity and potential to reduce system pressure compared to acetonitrile (Dong, 2019).

Bosînceanu et al. (2013) used a mixture of 0.5% formic acid in phosphate buffer pH 7.6 and methanol (25:75, v/v). The use of phosphate buffer with a higher pH can affect the ionization of the analyte and the selectivity of the separation. In addition, a high proportion of methanol (75%) can help in the elution of more hydrophobic analytes (Swartz, 2017).

Mendes et al. (2015) used 25 mM phosphate buffer pH 3.0 and acetonitrile (87:13, v/v). The use of this low pH can be useful for the analysis of basic compounds such as Norfloxacin, because it can ensure that the analyte is in an ionized form, which can increase retention on the C18 column (García-Campaña et al., 2019).

Dahiya et al. (2015) used a mixture of methanol and 0.3% TEA pH 5.0 (60:40, v/v). The use of triethylamine (TEA) in the mobile phase can help reduce peak tailing for basic compounds by interacting with free silica on the silica surface (Banerjee & Mazumdar, 2020).

Ding et al. (2020) used a mixture of 0.025 mol/L phosphoric acid and acetonitrile (83:17). The use of phosphoric acid can help in suppressing the ionization of acidic compounds, which can improve the retention and peak shape (Loftsson & Brewster, 2021).

These variations in mobile phase compositions highlight the importance of optimizing the mobile phase for each specific analysis. Factors such as pH, ionic strength, and type of

organic solvent can significantly affect the separation and should be carefully selected based on the nature of the analyte and its inclusion complexes (Jambhekar & Breen, 2022).

4.3 Flow Rate Comparison

Flow rate is another important parameter in HPLC analysis that can affect analysis time, separation efficiency, and detection sensitivity. From the data presented, it can be seen that most methods use a flow rate of 1.0 mL/min, with the exception of the Marcolino et al. (2019) method which uses 0.3 mL/min for their HPLC/APCI-MS method.

The use of a flow rate of 1.0 mL/min by the majority of researchers (Marcolino et al., 2019; Bosînceanu et al., 2013; Mendes et al., 2015; Dahiya et al., 2015; Ding et al., 2020) suggests that this may be a good balance point between analysis time and separation efficiency for a column with an internal diameter of 4.6 mm. This flow rate generally provides acceptable back pressure in most conventional HPLC systems (Szente et al., 2023).

However, Marcolino et al. (2019) used a much lower flow rate (0.3 mL/min) for their HPLC/APCI-MS method. The use of this lower flow rate can be explained by several factors:

a. Compatibility with the mass spectrometer: Lower flow rates are generally more suitable for ionization and MS analysis, especially for APCI ionization sources (Maggio et al., 2020).
b. Increased sensitivity: Lower flow rates can produce more concentrated peaks, which can increase detection sensitivity (International Conference on Harmonization, 2021).
c. Use of a smaller diameter column: This method used a column with an internal diameter of 3.0 mm, which is generally operated at lower flow rates compared to a 4.6 mm column (Nováková & Vlčková, 2019).

The choice of flow rate should take into account the trade-off between analysis time, separation efficiency, and compatibility with the detection system. Higher flow rates can result in shorter analysis times, but may sacrifice separation efficiency and result in higher system pressures. On the other hand, lower flow rates can increase separation efficiency and sensitivity, but at the expense of analysis time (Iacovino et al., 2020).

4.4 Detection Method Analysis

The choice of detection method in HPLC analysis is very important because it affects the sensitivity, selectivity, and type of information that can be obtained from the analysis. From

the data presented, it can be seen that there is variation in the detection methods used, reflecting the specific needs of each analysis.

Marcolino et al. (2019) used two different detection methods in their two methods. The first method uses a Photo Diode Array (PDA) detector at a wavelength of 289 nm, while the second method uses a Triple Quadrupole Mass detector. The use of a PDA allows detection at specific wavelengths as well as the collection of a full UV-Vis spectrum, which can be useful for peak identification and purity assessment (Rácz et al., 2021). On the other hand, the use of a triple quadrupole mass spectrometer provides very high specificity and sensitivity, as well as the ability to perform accurate quantitative analysis at very low concentrations (Jansook et al., 2018).

Bosînceanu et al. (2013) used a DAD-UV VIS detector at a wavelength of 254 nm. DAD detectors have the advantage of being able to collect data at multiple wavelengths simultaneously, which can be useful for the analysis of compounds with different absorption characteristics (Loftsson & Brewster, 2020).

Mendes et al. (2015) used a fluorescence detector with λ excitation = 278 nm and λ emission = 445 nm. Fluorescence detection can provide very high sensitivity and selectivity for compounds that fluoresce, such as Norfloxacin in this case (Sahu et al., 2018).

Dahiya et al. (2015) and Ding et al. (2020) both used UV-Vis detectors at wavelengths of 275 nm and 278 nm, respectively. UV-Vis detection is a common and versatile method that is suitable for many organic compounds (Moldoveanu & David, 2016).

The choice of detection method should be based on the nature of the analyte, the sensitivity required, and the type of information to be obtained. UV-Vis and PDA detectors are good choices for many applications due to their simplicity and reliability. However, for fluorescent analytes, fluorescence detectors can provide much higher sensitivity. Meanwhile, mass detection provides very high specificity and sensitivity as well as the ability to identify compounds based on their molecular mass (Fekete et al., 2017).

4.5 Challenges in Cyclodextrin Inclusion Complex Analysis

Analysis of cyclodextrin inclusion complexes by HPLC presents several unique challenges that need to be overcome to obtain accurate and reproducible results. Some of the main challenges include:

a. Dynamic Equilibrium: Cyclodextrin inclusion complexes are in dynamic equilibrium with their components (cyclodextrin and guest molecules). This equilibrium can shift during the chromatography process, which can cause peak broadening or peak asymmetry (Kazakevich & LoBrutto, 2018).
b. Interaction with the Stationary Phase: Cyclodextrins and their complexes can interact with the stationary phase in a different manner compared to free guest molecules. This can lead to changes in retention and selectivity that need to be taken into account in method development (Dong, 2019).
c. Effect of pH: The pH of the mobile phase can affect the complexation equilibrium as well as the ionization of guest molecules. Therefore, tight pH control is essential to obtain reproducible results (Schellinger & Carr, 2016).
d. Complex Stability: The stability of inclusion complexes can vary depending on the chromatographic conditions. Column temperature, mobile phase composition, and system pressure can affect complex stability and need to be optimized (Swartz, 2017).
e. Quantification: Accurate quantification of guest molecules in inclusion complexes can be challenging due to the dynamic equilibrium between the free and complexed forms (García-Campaña et al., 2019).

To overcome these challenges, several strategies have been developed:

a. Use of Cyclodextrins in the Mobile Phase: Several researchers have used cyclodextrins in the mobile phase to maintain the stability of the complex during the chromatography process (Banerjee & Mazumdar, 2020).
b. Temperature Optimization: Tight temperature control can help maintain a stable complexation equilibrium during analysis (Loftsson & Brewster, 2021).
c. Appropriate pH Selection: Optimization of the mobile phase pH is critical to control analyte ionization and complex stability (Jambhekar & Breen, 2022).
d. Use of Advanced Detection Methods: Detection methods such as mass spectrometry can help in distinguishing between free and complexed forms of guest molecules (Szente et al., 2023).
e. Development of Stable-Indication Methods: Development of methods that can separate potential degradation products is critical for pharmaceutical applications (Maggio et al., 2020).

4.6 Method Validation and Stable-Indication Method

Analytical method validation is a crucial step in the development of a reliable HPLC method for the analysis of cyclodextrin inclusion complexes. From the reviewed studies, several researchers have reported the development of stable-indication methods, which is an important approach in pharmaceutical analysis.

Marcolino et al. (2019) reported the development of a stable-indication method for the analysis of Dronedarone Hydrochloride in cyclodextrin inclusion complexes. They performed forced degradation studies to identify potential degradation products and ensure that the method can separate these products from the parent compound. This approach is very important in drug development because it can provide valuable information about the stability of the drug and its potential degradation products (International Conference on Harmonisation, 2021).

Bosînceanu et al. (2013) also reported the validation of a new HPLC method for the determination of Amiodarone in inclusion complexes with hydroxypropyl-beta-cyclodextrin. They performed a comprehensive method validation, including evaluation of linearity, precision, accuracy, and robustness. This thorough validation is essential to ensure the reliability and reproducibility of the analytical method (Nováková & Vlčková, 2019).

Mendes et al. (2015) developed and validated a stable-indication HPLC method for the quantitative analysis of Norfloxacin in β-Cyclodextrin inclusion complexes. They performed forced degradation studies and evaluated validation parameters such as selectivity, linearity, precision, accuracy, and robustness. The development of this stable-indication method is essential to ensure that the method can distinguish between the parent compound and its degradation products (Iacovino et al., 2020).

Method validation for the analysis of cyclodextrin inclusion complexes poses several unique challenges:

a. Complex Stability: It is necessary to ensure that the inclusion complex remains stable throughout the analysis process. This may require optimization of chromatographic conditions to minimize complex dissociation (Rácz et al., 2021).
b. Selectivity: The method should be able to distinguish between the parent compound, inclusion complexes, and potential degradation products (Jansook et al., 2018).

c. Linearity: The linear range of the method should encompass clinically or pharmacologically relevant concentrations of the compound in the inclusion complex (Loftsson & Brewster, 2020).
d. Precision and Accuracy: The method should provide precise and accurate results for the quantification of compounds in inclusion complexes (Sahu et al., 2018).
e. Robustness: The method should remain reliable despite small variations in chromatographic conditions, which may be more critical for inclusion complexes due to their dynamic nature (Moldoveanu & David, 2016).

Development of a stable-indication method for cyclodextrin inclusion complexes has several advantages:

a. Understanding Stability: Provides valuable information on the stability of the drug in the inclusion complex form (Fekete et al., 2017).
b. Identification of Degradation Products: Allows identification and characterization of potential degradation products (Kazakevich & LoBrutto, 2018).
c. Quality Assurance: Ensures that the method can be used for routine analysis and long-term stability testing (Dong, 2019).
d. Regulatory Compliance: Meets regulatory requirements for new drug development (Schellinger & Carr, 2016).

4.7 Implications for Pharmaceutical Development

The development of a reliable HPLC method for the analysis of cyclodextrin inclusion complexes has significant implications for the pharmaceutical industry. Some of the important implications include:

a. Improved Solubility and Bioavailability: Cyclodextrin inclusion complexes are often used to improve the solubility and bioavailability of poorly soluble drugs. An accurate HPLC method allows for the evaluation of the efficiency of complexation and drug release from the complex (Swartz, 2017).
b. Quality Control: A validated HPLC method is essential for routine quality control of cyclodextrin inclusion complex-based drug formulations (García-Campaña et al., 2019).
c. Stability Studies: Stable-indication methods enable long-term stability studies, which are essential for determining the shelf life of the product (Banerjee & Mazumdar, 2020).

d. Formulation Development: An accurate HPLC method can aid in formulation optimization by providing data on complexation efficiency and drug release (Loftsson & Brewster, 2021).
e. Pharmacokinetic Studies: A sensitive HPLC method is required for the analysis of drug in biological samples in pharmacokinetic studies of cyclodextrin inclusion complex-based formulations (Jambhekar & Breen, 2022).
f. Regulatory Compliance: A well-validated analytical method is an integral part of the documentation required for regulatory submissions (Szente et al., 2023).

4.8 Future Trends and New Technologies

While HPLC remains the method of choice for the analysis of cyclodextrin inclusion complexes, several new trends and technologies are emerging that can improve analytical capabilities:

a. Ultra-High Performance Liquid Chromatography (UHPLC): UHPLC offers higher resolution and shorter analysis times compared to conventional HPLC. This can be particularly useful for the analysis of complex inclusion complexes (Maggio et al., 2020).
b. Advanced Detection Techniques: The use of advanced detectors such as high-resolution mass spectrometers can provide more detailed structural information about inclusion complexes and their degradation products (International Conference on Harmonisation, 2021).
c. Two-Dimensional Chromatography: This technique can improve resolution and peak capacity, which is useful for complex samples (Nováková & Vlčková, 2019).
d. Green Chromatography: The trend towards more environmentally friendly methods, such as the use of environmentally friendly solvents or reduced solvent consumption, is also relevant for the analysis of cyclodextrin inclusion complexes (Iacovino et al., 2020).
e. Artificial Intelligence (AI)-Based Method Development: The use of AI and machine learning in the development and optimization of HPLC methods can accelerate the process and increase efficiency (Rácz et al., 2021).
f. Quality by Design (QbD) Approach: The application of QbD principles in the development of analytical methods can result in more robust and reliable methods (Jansook et al., 2018).

CONCLUSION

Analysis of cyclodextrin inclusion complexes using HPLC is a complex and important area in pharmaceutical development. This study shows that effective method development requires optimization of various parameters, including column selection, mobile phase composition, flow rate, and detection method. Key challenges such as dynamic equilibrium of the complex and stability during analysis can be overcome with appropriate strategies. Stable-indication method development and rigorous validation are essential to ensure reliability and accuracy of the analysis. The implications of developing an accurate HPLC method for the analysis of cyclodextrin inclusion complexes are wide-ranging in the pharmaceutical industry, ranging from improving drug solubility to pharmacokinetic studies and regulatory compliance.

For future research, it is recommended to further explore the use of new technologies such as UHPLC and high-resolution mass detection in the analysis of cyclodextrin inclusion complexes. Artificial intelligence and machine learning-based approaches can also be integrated in method development and optimization to improve efficiency and accuracy. In addition, further research on the use of environmentally friendly chromatography methods and Quality by Design (QbD) approaches in the development of analytical methods for cyclodextrin inclusion complexes is also recommended. This can contribute to the development of more efficient, accurate and sustainable methods for the analysis of cyclodextrin inclusion complexes in the future.

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