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Solubilization of 2-Acetoxy-Benzencarboxylic Acid Using Beta Cyclodextrins

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Abstract

2-acetoxy-benzencarboxylic acid is one of the most famous salicylate drugs today, a pharmaceutically active compound known as aspirin. It is poorly soluble in water which results in decreased bioavailability of the drug in the organism. The increase in water solubility of insoluble or poorly soluble drugs is therefore of great importance, which is the aim of this study. Inclusion of the drug in the molecule with a higher water solubility significantly increases its solubility and biological availability. Natural and hydrophilic derivatives of natural cyclodextrins are in the spotlight for their role as solubilizing excipients. Studies indicate that the use of β-cyclodextrin inclusion complexes with acetylsalicylic acid formed, increases the solubility of the drug in water. Many advantages of drug-complexation with cyclodextrins have been reported in scientific literature which includes increased solubility, enhanced bioavailability, improved stability, masking of bad test or odour, reduced side effect. Orally administered aspirin requires high and frequent dosing because it undergoes extensive pre systematic metabolism. Also chronic oral aspirin use is associated with serious gastrointestinal side-effects. Complexation with CD alleviates the side effects to some extent. The bioavailability and solubility of aspirin has to be increased to overcome the side-effects of aspirin related to stomach and gastro intestinal tract. The phase solubility study was performed according to the method of Higuchi and Connors by adding the 2-acetoxi-benzencarboxylic acid in excess to different concentrations of different beta cyclodextrins solutions. Phase solubility study records shown that the stability constant and complex stoichiometry of 2-acetoxi-benzencarboxylic acid-CD complexes gives linearly improve with the concentration of CD. Complexes were analyzed by UV-VIS spectroscopy and were characterized by infrared spectroscopy.

Keywords

2-Acetoxi-Benzencarboxylic Acid, Water Solubility, Cyclodextrin, Inclusion

Complexes

1. Introduction

2-acetoxy-benzencarboxylic acid also known as Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) orally effective in treating fever, pain, and inflammation but gastrointestinal side effects were observed (**Figure 1**). Aspirin use has been shown to reduce the incidence and mortality of human cancers, especially colon cancer. Orally administered aspirin requires high and frequent dosing because it undergoes extensive presystemic metabolism. Also, long term and chronic oral aspirin is associated with serious gastrointestinal side-effects. So, if the solubility and bioavailability of aspirin can be increased, it will reduce the gastrointestinal side-effects [1].

Solubility in different solvents is an intrinsic material characteristic for a defined molecule. To achieve a pharmacological activity, the molecules must in general exhibit certain solubility in physiological intestinal fluids to be present in the dissolved state at the site of absorption. The aqueous solubility is a major indicator for the solubility in the intestinal fluids and its potential contribution to bioavailability issues. To generally describe "solubility" the Pharmacopoeia (USP) uses seven different solubility expressions. The European Pharmacopoeia uses similar solubility definitions except the "practically insoluble" characteristic, which is not specified (European Pharmacopoeia 5.0). If a drug substance exhibits a poor aqueous solubility, the product development will have to focus on the investigation of various other drug substance characteristics like its physicochemical, biopharmaceutical properties and the targeted dose to identify the potential impact of the solubility on the further product development. Today, about 35% - 40% of the lead substances are known to have an aqueous solubility of less than 5 mg/ml [2]. Preparation of aspirin β-cyclodextrin inclusion complexes was to increase the solubility and reduce the irritation [3]. Cyclodextrins are α-1,4-linked cyclic oligosaccharides obtained from starch degraded by glucosyltransferase. The naturally CD varieties include at least six glucose units being the most common CDs those that present six (α-CD), seven (β-CD) and eight units (γ-CD). According to the literature, these compounds, cyclodextrins (α-, β- and γ-CDs), are "generally recognized as safe" by the Food and Drug Administration (FDA, USA) [4]. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but the torroidal or cone shaped (**Figure 2**) [5]. Based on this architecture the primary hydroxyl groups are located on the narrow side of the cone shape, while the secondary hydroxyl groups are located on the wider edge. Various physico-chemical properties of the organic guest molecules are altered in presence of cyclodextrins with enhanced selectivity, photo reactivity and stability. During the past two decades, cyclodextrins and their derivatives have been of considerable interest in the pharmaceutical field because of their potential to form complex formulation.

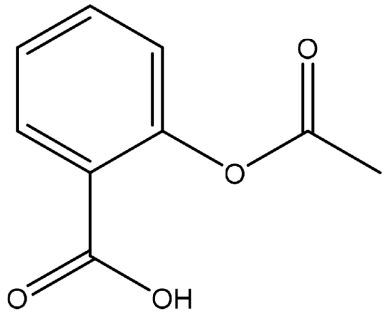

Figure 1. Stucture 2-acetoxi benzencarboxylic acid.

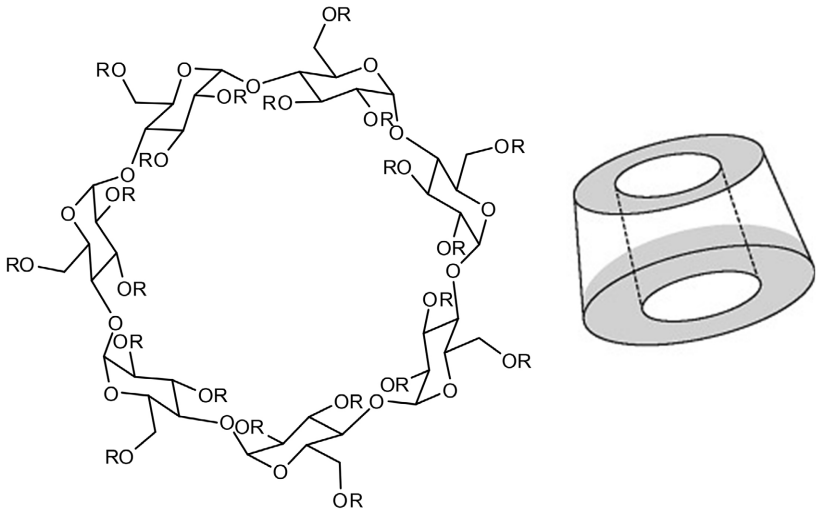

Figure 2. Structure and cone shape of cyclodextrin.

The hydrophobic cavity of cyclodextrins is capable of trapping a variety of molecules within to produce inclusion complexes [6].

Higuchi and Connors classified complexes based on solubility, into multiple phase solubility profiles which shown in **Figure 3**. Types of phase-solubility diagrams according to Higuchi and Connors [7] showing how the total drug solubility changes with increasing CD concentration. A-type diagrams are formed when the drug/CD complex is soluble in the aqueous complexation media and they are usually associated with the water-soluble CD derivatives. B-type diagrams are observed when the complex has limited solubility in the media and these are usually associated with the natural CDs that have limited solubility in aqueous media. AL: linear diagram; AP: positive deviation from linearity; AN: negative deviation from linearity; BS: the complex has some, but limited solubility; BI : the complex is insoluble. Collectively, all three curves (**Figure 3**) indicate that water-soluble complexes are being formed with solubilities higher than that of the uncomplexed substrate. If the slope is lower than unity, a 1:1 complex is formed. If the slope is greater than unity, higher order complexes are assumed to be involved in the solubilization process. Although a slope of less than unity does not exclude the possibility of higher order complexes, a 1:1 complex is often assumed to form in the absence of other information [8].

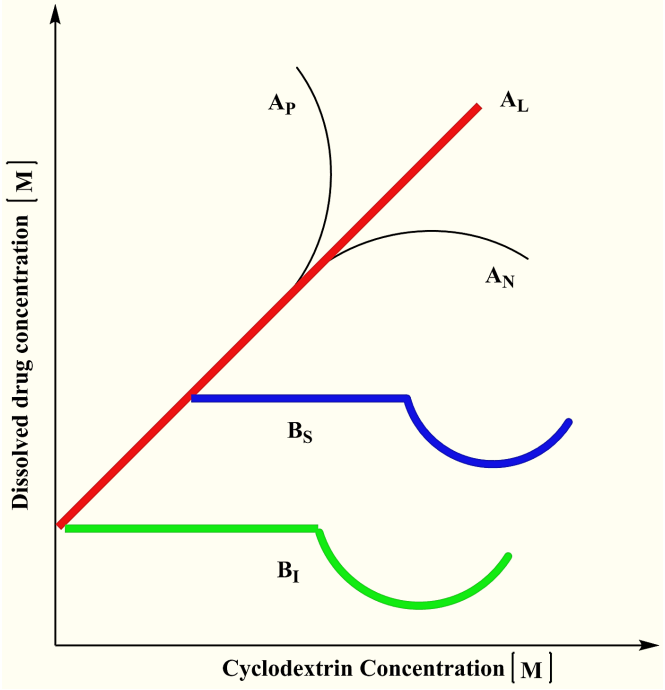

Figure 3. Higuchi and Connors solubility diagram.

2. Material and Methods

In this study, the following chemicals were used for experimental work: 2-acetoxi-benzencarboxylic acid (acetyl-salycilic acid-ASA) (Sigma Aldrich), *β*-cyclodextrin (Sigma Aldrich), 2-Hydroxypropyl-*β*-cyclodextrin (Sigma Aldrich), Methyl-*β*-cyclodextrin (Sigma Aldrich) Methanol (Merck) Ethanol (Merck).

All used chemicals are of analitical grade.

2.1. Preparation of Complex 2-Acetoxy-Benzen Carboxylic Acid-*β*-Cyclodextrin

The solubility of 2-acetoxy benzene carboxylic acid in water is about 3 mg/cm^3. According to USP solubility criteria, 2-acetoxy benzene carboxylic acid is slightly soluble in water. The samples were prepared according to the Huguchi and Connors method by adding a poorly soluble pharmaceutical active substance (ASA) in excess to aqueous cyclodextrin solutions of various concentrations. Phase solubility tests were performed in triplicate.

A constant amount of pure 2-acetoxy benzene carboxylic acid (0.15 g) was suspended in 10 mL of an aqueous solution containing successively higher concentrations of cyclodextrin (2 - 14 mmol). Well-closed vials were continuously stirred for 72 hours at room temperature (25˚C) and then the samples were filtered through 0.45 μm filter paper. Fresh samples were prepared and used to measure phase solubility on a UV-spectrophotometer with a previous dilution that corresponds to the interval of the calibration curve of 2-acetoxy benzene carboxylic acid in methanol, on the basis of which the concentration is measured (Figure 4).

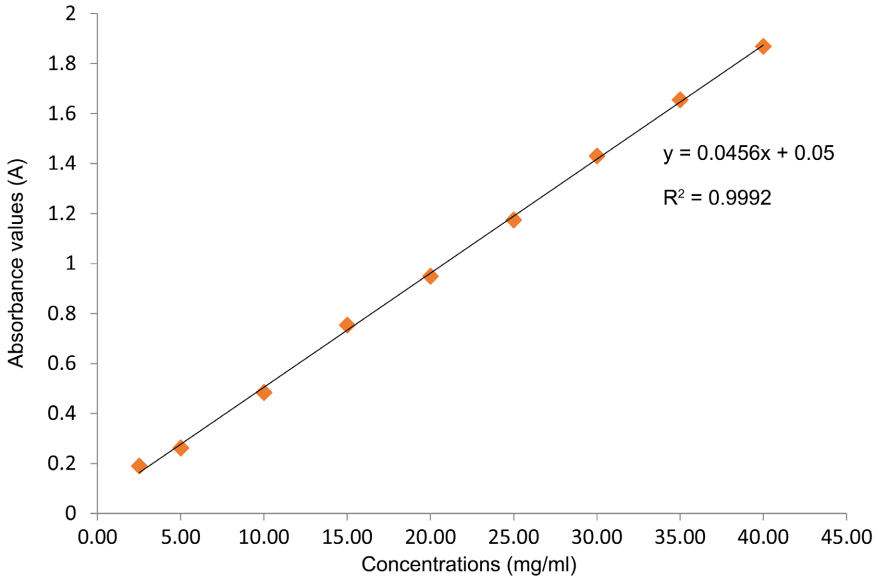

Figure 4. Calibration curve of 2-acetoxy benzene carboxylic acid in methanol.

2.2. Structural Analysis

- Phase solubility measurements were done on a UV-spectrophotometer Perkin Elmer Lambda 25 at 226 nm, on a previously constructed calibration curve. UV/VIS spectroscopy is used for analytical purposes to quantify various analytes, such as conjugated organic compounds, organic substances and biochemical macromolecules. Determination usually takes place in solutions. Organic substances, especially those with a high degree of conjugation, absorb light in the UV or visible region of the electromagnetic spectrum.

For preparation of calibration curve it is used pure 2-acetoxy benzene carboxylic acid as a standard. At the analytical balance was measured 5.00 mg of standard in volumetric flask of 10 ml and added ethanol to the mark. After dissolving, we pipetted 0.4, 0.5, 0.6, 0.7 and 0.8 ml of stock solution in volumetric flask of 10 ml and added distillated water to the mark, so we had five diluted standards with concentrations: 20, 25, 30, 35, 40 and 45 μg/ml. Groups of atoms that do not absorb radiation by themselves, but their presence in molecules causes the absorption maxima to shift to longer wavelengths is auxochromic groups. Shift of the absorption maximum (λ_{max}) towards longer wavelengths caused by the presence of auxochromes or changes in the solvent. It is a bathochromic shift or red shift. For example: introduction of groups like: -OH, -OCH_3, causes λ_{max} to shift to higher values.

- Qualitative interpretation of the complex was performed with FTIR-spectrophotometer Perkin Elmer 1000; Fourier transform spectrophotometers significantly improved the quality of the infrared spectrum, accelerated the analysis process and enabled comparison with the database. In this way, they enabled greater sensitivity and the use of minimal sample quantities. Infrared spectra of the samples were recorded on a resolution of 4 cm^{-1} and an interval of 4000 - 400 cm^{-1}.

The sample is prepared by taking 10 mg of the sample which is well powdered and homogenized, with about 90 mg of pure and well dried KBr. It is very important that KBr is dry during the preparation of the sample, because otherwise bands originating from water appear on the spectrum. The resulting mixture is filled into a metal cuvette which is placed in an FTIR spectrometer and the IR spectrum of the powder component is recorded. The spectrum can be interpreted by visual expertise of the position, intensity and shape of the absorption bands: The position of the band is determined by its peak (maximum). The intensity of the band is proportional to the absorbance, its size is the length of the absorption band in the ordinate direction. The shape of the band depends on a number of factors such as concentration, type of solvent, resolution of the apparatus, etc.

3. Results and Discussion

3.1. Complexation and Solubilization of 2-Acetoxy Benzene Carboxylic Acid with *β*-Cyclodextrin

Using *β*-CD as a natural cyclodextrin increases the solubility of 2-acetoxy benzene carboxylic acid in water. The diagram (Figure 5) shows the influence of different concentrations of *β*-cyclodextrin on the phase solubility of 2-acetoxy benzene carboxylic acid in an aqueous environment. According to the classification of phase solubility profiles according to Higuchi and Connors, this solubility belongs to the A_L type since the increase in cyclodextrin concentration results in a linear increase in the solubility of the pharmaceutical active compound. The most common type of cyclodextrin complex is the 1:1 pharmaceutical active compound/cyclodextrin (D/CD) complex, where one molecule of the pharmaceutical active compound forms a complex with one molecule of cyclodextrin.

$$C + D \underset{\text{---}}{\overset{K_{1:1}}{\rightleftharpoons}} D/CD$$

Under such conditions, the A_L type of phase solubility diagram, with a slope less than one, has a stability constant $K_{1:1}$ of the complex that can be calculated from the slope and the intrinsic solubility of the biologically active compound So in the aqueous complexation medium.

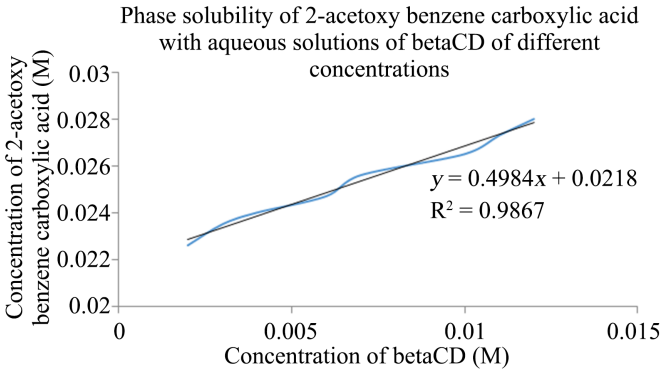

Figure 5. Phase solubility diagram of 2-acetoxy benzene carboxylic acid with aqueous solutions of *β*-CD of different concentrations.

Intrinsic solubility is the solubility of a substance when cyclodextrin is not present, *i.e.* the point where the phase solubility curve intersects the y-axis.

The stability constant of the complex was calculated from the Higuchi and Connors equation using the parameters obtained from the phase solubility diagram. The stability constant for samples of the complex 2-acetoxy benzene carboxylic acid-β-cyclodextrin is $\mathbf{K = 45.31\ M^{-1}}$ (Figure 5).

The stability of cyclodextrin complexes with organic molecules in water is most often attributed to the so-called hydrophobic hydration of the interior of the macrocycle, that is, the hydrophobic functional groups of the guest molecules. This term refers to the restructuring of water molecules around non-polar chemical compounds and in the cavity of cyclodextrin. Consequently, with the formation of a complex, the water molecules that participated in the solvation of the guest and the interior of the host can form hydrogen bonds like those in the solvent. Since it is hydrophobic interactions that form between the host and guest molecules, parts of the 2-acetoxy benzene carboxylic molecule that contain aromatic nuclei are involved. NMR studies have shown that in the complex the benzene ring of 2-acetoxy benzene carboxylic acid is located inside the cavity of the cyclodextrin molecule, while the ester and acetyl groups come out of the cone cavity [9]. The presence of hydrophilic functional groups on the edge of cyclodextrins can also significantly influence their complexation properties. 2-acetoxy benzene carboxylic acid with two carbonyl chromophores can form hydrogen bonds with the hydroxyl groups of cyclodextrin and thus enables better incorporation of the drug into the host cavity. Figure 6 shows a proposed model of the formation of a complex between one molecule of 2-acetoxy benzene carboxylic acid and one molecule of cyclodextrin by placing the aromatic benzene nucleus in the lipophilic cavity of cyclodextrin [10].

The results of research by UV spectroscopy and the analysis of UV spectra of complexed 2-acetoxy benzene carboxylic acid with different concentrations of β-cyclodextrin are shown in Figure 7. They indicate that increasing the concentration of β-cyclodextrin leads to an increase in the absorbance of 2-acetoxy benzene carboxylic acid at a wavelength of 226 nm, which indicates an increasing inclusion of the pharmaceutical active compound in the cavity of the β-cyclodextrin molecule. The spectrum shows a bathochromic and hyperchromic shift due to the presence of auxochromic groups such as hydroxyl groups derived from cyclodextrin.

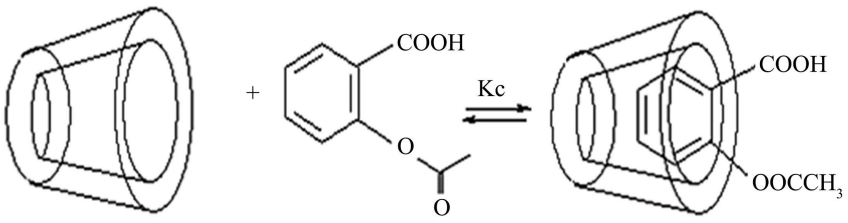

Figure 6. Proposed model of formation of 1:1 complex of 2-acetoxy benzene carboxylic acid and cyclodextrin.

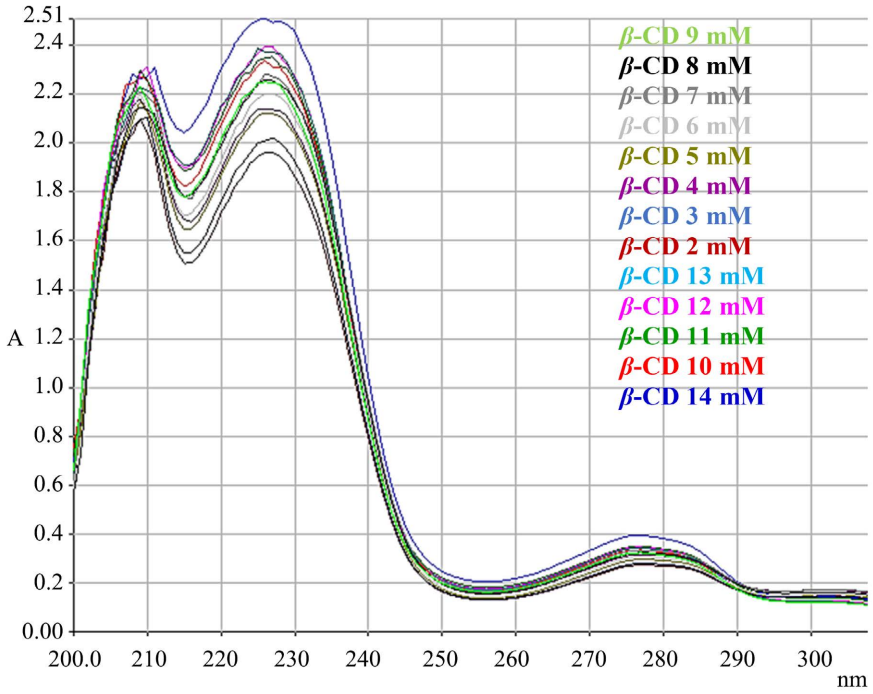

Figure 7. UV spectra of 2-acetoxy benzene carboxylic acid in aqueous *β*-cyclodextrin solutions of different concentrations (1 - 14 mM).

The formation of a complex of 2-acetoxy benzene carboxylic acid and *β*-cyclodextrin was also confirmed by FTIR characterization. The FTIR spectra of 2-acetoxy benzene carboxylic acid show two significant regions that characterize its structure. The first region refers to the existence of an intense peak at 1605 cm^{-1} which corresponds to the benzene ring. Peaks in the area of 1680 and 1750 cm^{-1} confirm the presence of two C = O groups. The second part of the IR spectrum of aspirin includes shorter and broader peaks in the region of 2500 - 3500 cm^{-1} that originate from the vibrations of O-H and C-H bonds [11].

The FTIR spectra of *β*-cyclodextrin show a broad band around 3400 cm^{-1} which is the result of valence –OH vibrations. In the region of 2900 cm^{-1} there is a band of asymmetric and symmetric valence C-H vibrations of the $-CH_2$ group, but also valence C-H vibrations from the CHOH group. If some hydrogen or Van der Waals interaction were to be established, the spectra of the inclusion complexes compared to the spectra of the starting compounds should be different in intensity, shape, position and number of bands.

The analysis of FTIR spectra (**Figure 8**) of prepared complexes 2-acetoxy benzene carboxylic acid complex and *β*-cyclodextrin shows that the broad hydroxyl band of pure *β*-cyclodextrin at 3281.2 cm^{-1} is narrowed in the FTIR spectra of the complex, which is a good indicator of the formation of an inclusion complex. This is a common phenomenon observed by many researchers in the synthesis of an inclusion complex between a *β*-cyclodextrin (host) and a guest molecule. Increasing the concentration of *β*-cyclodextrin leads to a decrease in the frequency of valence ν(OH) vibrations, which favors complexation.

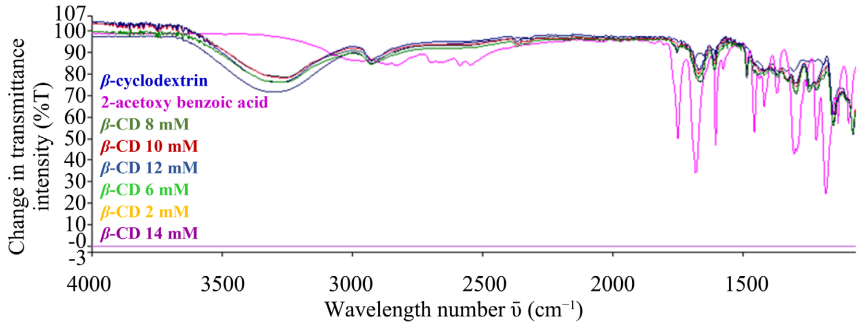

Figure 8. FTIR spectra of 2-acetoxy benzene carboxylic acid and complex of 2-acetoxy benzene carboxylic acid with *β*-cyclodextrin of different concentrations (1 - 14 mM).

3.2. Complexation and Solubilization of 2-Acetoxy Benzene Carboxylic Acid with 2-Hydroxypropyl-*β*-Cyclodextrin

2-Hydroxypropyl-*β*-cyclodextrin (HP*β*CD), a chemically modified *β*-cyclodextrin, has higher water solubility and lower parenteral toxicity compared to its parent compound *β*-cyclodextrin. Also, is a potential ingredient in pharmaceutical formulations. The phase solubility diagram for complexes of 2-acetoxy benzene carboxylic acid and aqueous solutions of 2-hydroxypropyl-*β*-cyclodextrin show that the solubility of 2-acetoxy benzene carboxylic acid increases linearly with increasing cyclodextrin concentration, so it can be classified as an A_L type diagram according to Higuchi and Connors with the possibility of forming a 1:1 complex and a 1:2 complex with cyclodextrin (**Figure 9**). The stability constant obtained from the slope of the phase solubility diagram is 53.57 M^{-1}.

UV spectra (**Figure 10**) of aqueous solutions of 2-acetoxy benzene carboxylic acid with 2-hydroxypropyl cyclodextrin show that the absorption maximum has shifted towards lower wavelengths. UV spectra show a hypsochromic shift of the absorption maximum of 2-acetoxy benzene carboxylic acid, which may be a consequence of the influence of the auxochromic group of cyclodextrin on the carbonyl group of 2-acetoxy benzene carboxylic acid. An increase in the concentration of 2-hydroxypropyl cyclodextrin is accompanied by an increase in absorbance intensity with a bathochromic shift, which is a confirmation of complexation.

The FTIR spectrum (**Figure 11**) of 2-acetoxy benzene carboxylic acid shows absorption maxima at 2696.78 cm^{-1}, which originate from the stretching vibrations of the carbonyl –OH group, at 1749.764 cm^{-1} corresponding to the carbonyl group of the ester and at 1679.79 cm^{-1} which corresponds to the acetate carbonyl group (**Table 1**). When forming a complex with 2-hydroxypropyl-*β*-cyclodextrin, the carbonyl band has a slight shift to a lower wavenumber, due to the host-guest interaction. This suggests the possibility of hydrogen bonding between the hydroxyl group of the host cavity and the carbonyl group of 2 acetoxy-benzene carboxylic acids. A slight shift of the absorption band for carbonyl groups to lower frequencies can be attributed to the breaking of hydrogen bonds between drug molecules and the formation of intermolecular hydrogen bonds of the drug with cyclodextrin.

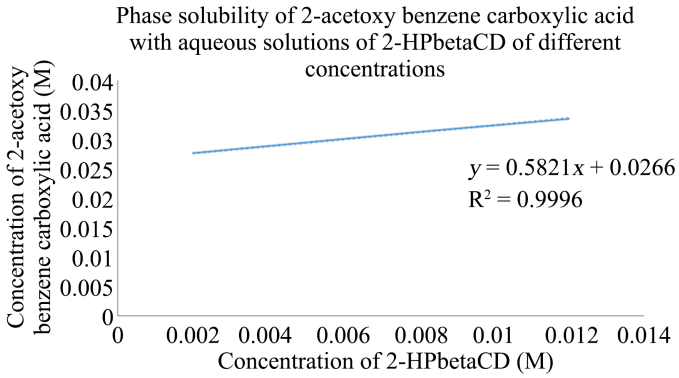

Figure 9. Phase solubility diagram of 2-acetoxy benzene carboxylic acid with aqueous solutions of 2-hydroxypropyl-β-CD of different concentrations.

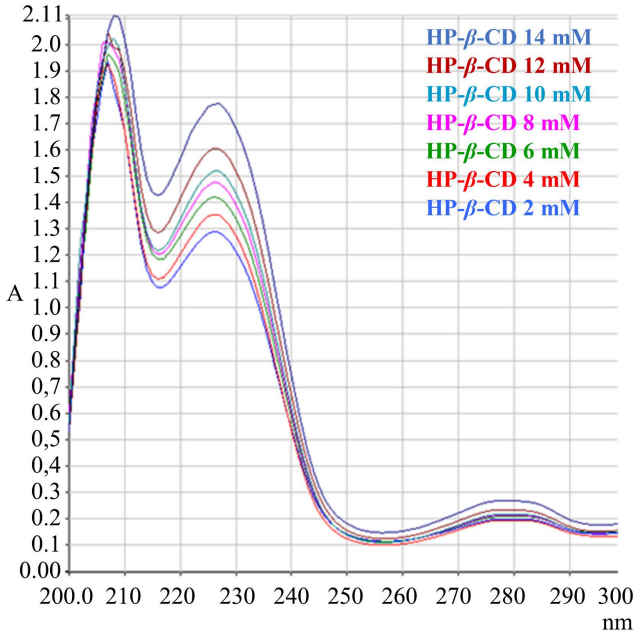

Figure 10. UV spectra of 2-acetoxy benzene carboxylic acid in aqueous solutions of 2-hydroxypropyl-β-cyclodextrin of different concentrations.

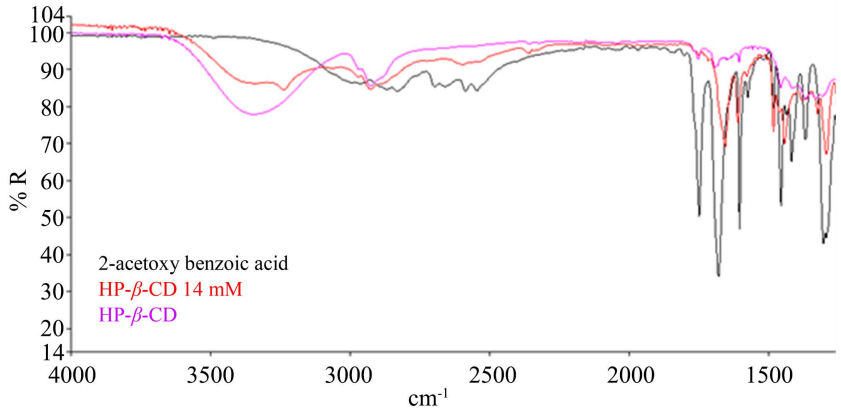

Figure 11. FTIR spectra of 2-acetoxy benzene carboxylic acid and 2-acetoxy benzene carboxylic acid complex with 2-hydroxypropyl-β-cyclodextrin (14 mM).

Table 1. Comparison of FTIR frequencies (cm^{-1}) of pure 2-acetoxy benzene carboxylic acid and complexed with 2-hydroxypropyl-*β*-cyclodextrin.

Functional group	2-acetoxy benzene carboxylic acid (cm^{-1})	Complex 2-acetoxy benzene carboxylic acid-2-HP-*β*CD (cm^{-1})
Carbonyl-OH group	2696.78	2927.38
Acetic C=O group	1749.64	1655.18
Carboxylic C=O group	1679.79	1610.20
Aromatic C=C stretches	1575.46; 1456.13; 1418.22;	1486.03; 1443.76; 1381.49
C-O (acetate ester)	1181.98	1155.30

3.3. Complexation and Solubilization of 2-Acetoxy Benzene Carboxylic Acid with Methyl-*β*-Cyclodextrin

Modified methyl-*β*-cyclodextrin (m*β*CD) offers a significant advantage as a host molecule over *β*-cyclodextrin (*β*-CD) because its solubility in aqueous solution at room temperature (>2000 mg/mL) is significantly higher. Therefore, it is expected that the higher solubility of methyl-*β*-cyclodextrin in the aqueous medium will contribute to the higher solubility of the pharmaceutically active compound when it is in the complex state.

Figure 12 shows the effect of different concentrations of methyl-*β*-cyclodextrin on the phase solubility of 2-acetoxy benzene carboxylic acid in an aqueous medium. We can see that by increasing the concentration of methyl-*β*-cyclodextrin there was an increase in the measured concentration of 2-acetoxy benzene carboxylic acid and practically doubles it. We can conclude that, according to the phase profile, it belongs to the AL type of phase solubility.

The stability constant obtained from the phase solubility diagram is 76.55 M^{-1}. Compared to the results obtained for *β*-cyclodextrin and 2-hydroxypropyl-*β* cyclodextrin, we can say that methyl-*β*-cyclodextrin binds drug molecules more strongly. The reason for this may be that the methyl group obviously increases the non-polar part of the cyclodextrin cavity, effectively increasing the depth of the cavity itself, which affects the better incorporation of the benzene ring of the "guest" molecule and thus its solubilization.

Confirmation of complexation is also shown by the UV spectra (Figure 13) of the samples, where we see that the increase in the concentration of methyl-*β*-cyclodextrin is accompanied by a higher intensity of the absorption maximum and a slight shift towards longer wavelengths.

FTIR characterization of the complex of 2-acetoxy benzene carboxylic acid and methyl-*β*-cyclodextrin confirms the formation of the complex. By comparing the spectra of pure 2-acetoxy benzene carboxylic acid and pure methyl-*β*-cyclodextrin with the spectra of the complex, we see that there are differences in the position of some bands in the complex compared to the starting compounds (Figure 14).

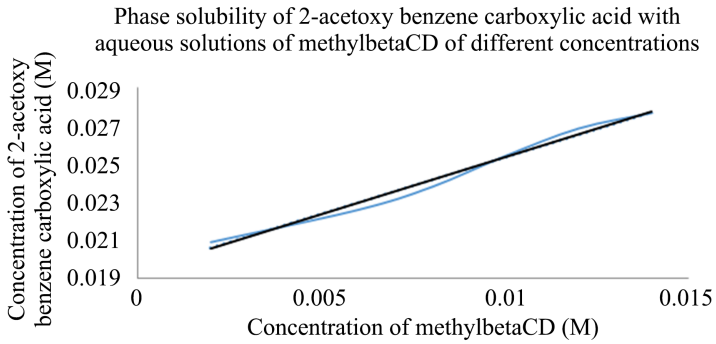

Figure 12. Phase solubility diagram of 2-acetoxy benzene carboxylic acid with aqueous solutions of methyl-β-CD of different concentrations.

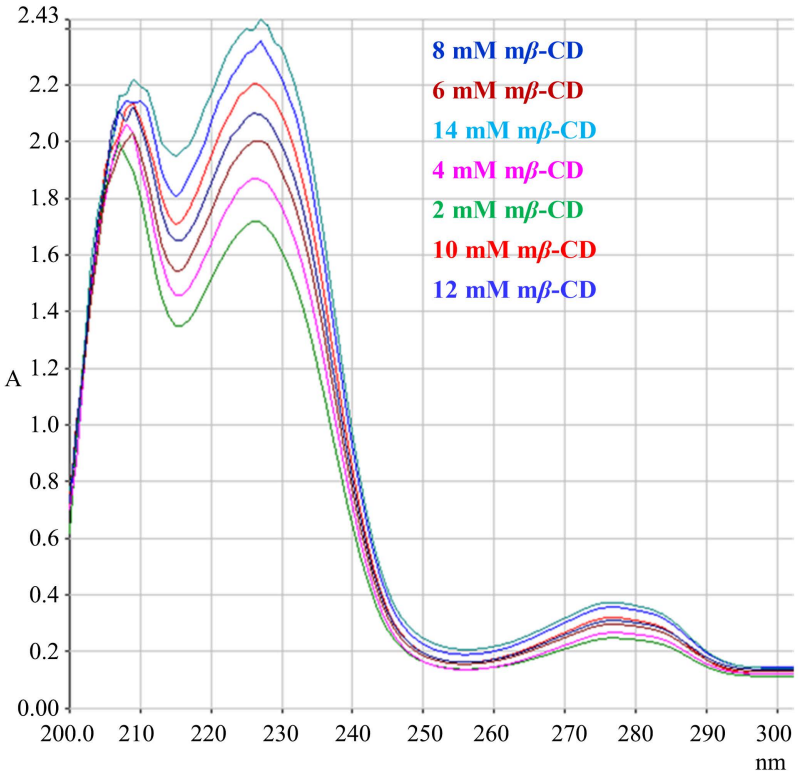

Figure 13. UV spectra of 2-acetoxy benzene carboxylic acid in aqueous solutions of methyl-β-cyclodextrin of different concentrations.

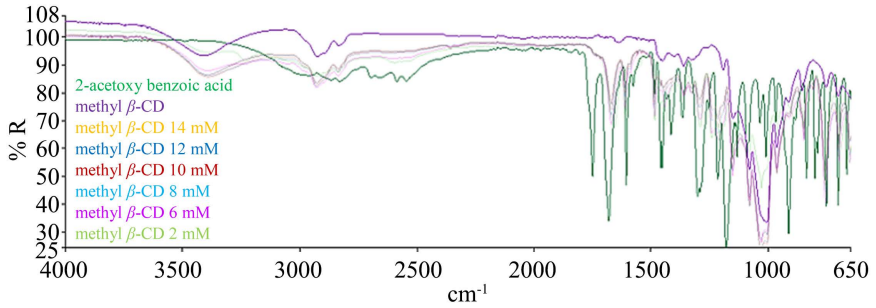

Figure 14. FTIR spectra of 2-acetoxy benzene carboxylic acid and 2-acetoxy benzene carboxylic acid complex with methyl-β-cyclodextrin of different concentrations.

4. Conclusion

Based on the obtained results, it is concluded that 2-acetoxy benzene carboxylic acid, also known as aspirin (ASA) has a low aqueous solubility of 3 mg/ml. Due to its low solubility, the bioavailability of the drug is low, and thus its effectiveness when taken into the body is reduced. For this reason, it is necessary to increase the water solubility of the drug in order for its action to be more effective. The use of cyclodextrins as solubilizing substances has proven to be very effective because they increase the water solubility of the drug and at the same time have no harmful effect because they are made of components that are naturally compatible with the body. The use of cyclodextrin leads to the formation of inclusion complexes with 2-acetoxy benzene carboxylic acid. The formed complex increases the water solubility of 2-acetoxy benzene carboxylic acid with leads to the formation of type A_L phase solubility by Higuchi and Connors which means an increase in drug concentration with increasing cyclodextin concentration. A derivative of β-cyclodextrin (2-hydroxypropyl-β-cyclodextrin and methyl-β-cyclodextrin) shows also A_L type of phase solubility of the drug. Based on the calculated value of the stability constant, it can be concluded that the best effect on solubilization is the use of methyl beta cyclodextrin with a stability constant K = **76.55 M^{-1}**. Also, the advantage of using cyclodextrins as solubilizing agents is that they simultaneously mask the bad taste of the drug and preserve the drug until the target site of action. This research can be a good basis for future research with the same topic. It is also a good basis for the application of testing different drug formulations. The formation of the complex was confirmed by UV/VIS and FTIR spectrometry where, on the basis of absorbance values, wavelengths and positions of the bands, it can be concluded that the formation of a complex has occurred.

Acknowledgements

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Conflicts of Interest

The authors declare that no conflicts of interest regarding the publication of this paper.

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