Cyclodextrin Complexation Using Sbe-B-Cd Induces the Solubility and Bioavailability of Diclofenac Sodium for Drug Delivery

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Abstract

Background: Diclofenac sodium (DS) is a poorly water-soluble drug, especially in gastric juice (15 µg/ml), which can lead to harmful effects on the gastric mucosa, including gastrointestinal bleeding after oral administration. The aim of this study was to evaluate the impact of natural and modified cyclodextrins on improving the solubility of diclofenac sodium in acidified aqueous solutions, and to confirm the formation of solid inclusion complexes between diclofenac sodium and cyclodextrins using different preparation techniques. Methods: Inclusion complexes were prepared in both solution and solid states using β-CD, HP-β-CD, Me-β-CD, HP-γ-CD, and SBE-β-CD. The solid-inclusion mixtures were obtained through dry grinding (physical mixtures), kneading, co-precipitation, and freeze-drying in a 1:1 molar ratio, and were characterized by PXRD and ATR-FTIR analyses. Results: The phase solubility isotherms revealed that the solubility of diclofenac sodium increased with higher concentrations of cyclodextrins, with the isotherms classified as AL type, indicating a 1:1 stoichiometric complexation. The stability constants (KS) ranged from 1088.8 ± 8.33 M^{-1} to 5009.57 ± 54.42 M^{-1} for all tested cyclodextrins, with SBE-β-CD showing the most significant solubility enhancement. Characterization of the binary systems by XRD and FTIR confirmed the formation of inclusion complexes, particularly in mixtures prepared by kneading, freeze-drying, and co-precipitation, as evidenced by the disappearance of drug crystallinity peaks (indicating amorphization) and alterations in the characteristic bands of the guest molecule. Conclusion: This study demonstrates that complexation with cyclodextrins is an effective strategy for enhancing the solubility of diclofenac sodium, with freeze-drying identified as the most promising method for forming stable inclusion compounds. Moreover, these strategies can be optimized for potential nanoparticale based drug delivery systems applications.

Keywords: Diclofenac sodium, Cyclodextrin complexation, Solubility enhancement, Inclusion complexes, Freeze-drying method.

Significance | This study showed the efficacy of cyclodextrin complexation, particularly using SBE-β-CD, in improving the solubility and potential bioavailability of diclofenac sodium.

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Introduction

Diclofenac [2-(2,6-dichloroanilino)phenylacetate; Fig. 1] is a well-known representative of the non-steroidal anti-inflammatory drugs (NSAID) belonging to the BCS class II drug classification system. It is a potent inhibitor of prostaglandin synthesis, and it finds application in several musculoskeletal diseases such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and sports injuries due to its analgesic and anti-inflammatory properties (Scholer et al., n.d.; Mora et al., 2010).

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Its primary mechanism of action involves cyclo-oxygenase inhibition, a decrease in arachidonic acid release, and enhanced arachidonic acid uptake. Hence, it leads to a dual inhibitory effect on the cyclo-oxygenase and lipoxygenase pathways (Carrier et al., 2007).

Diclofenac, a weak acid (pKa = 4.8), is often marketed in salt forms, the most typical being sodium, potassium, and alkyl-hydroxyl amine (Nugrahani et al., 2018). In water and at acidic pH (1-3), diclofenac sodium possesses poor solubility; at alkaline pH (5-8), it is freely soluble.

Notably, the aqueous solubility of a drug and lipophilicity for adequate permeation across biological membranes is crucial for its pharmacological activity. For orally administered drugs, dissolution poses a rate-limiting step and reduces bioavailability when the aqueous solubility is < 0.1 mg/ml (BCS Class II and IV drugs) (Mura, 2015).

Despite its wide use and applications, diclofenac sodium, being a member of the BCS class II drugs, is limited in its clinical efficacy owing to its poor solubility in gastric juice (15 μg/ml), which leads to deleterious effects on the gastric mucosa, most notably, gastrointestinal bleeding (Figure 1).

To circumvent this limitation, an improvement in the aqueous solubility of diclofenac sodium becomes of immense importance, consequently leading to improved absorption and bioavailability, reduction of doses, and associated side effects.

Over the years, many techniques have been harnessed for solubility enhancement, such as co-solvency, particle size reduction, salt formation, solid dispersions, complexation, spray drying, drug solutions in microemulsions, liposomes, and non-aqueous solvents, among other strategies.

Of the various approaches enlisted, cyclodextrin complexation has gained enormous attention and proves beneficial in enhancing solubility more linearly. Not only have cyclodextrins been utilized in the improvement of solubility and bioavailability of drugs in the BCS class II and IV, but they have been employed as strategies for the enhancement of drug performances in areas such as stabilization towards light or oxygen, odor and taste masking of unpleasant drugs, protection of volatile ingredients, conversion of free-flowing liquids and oils into powders, changes in catalytic as well as chemical activity (Brewster & Loftsson, 2007; Davis & Brewster, 2004; Kurkov & Loftsson, 2013; Mura, 2014; Mura, 2015; Pardeshi et al., 2023; Periasamy, 2020; Tian et al., 2020).

Cyclodextrins are a family of cyclic, non-reducing oligosaccharides consisting of (α-1,4)-linked α-D-glucopyranose units with a hydrophilic outer core and a lipophilic central cavity. They are derived from the enzymatic degradation of starch by glucosyltransferase enzymes and can form inclusion compounds with many drugs (guest molecules), changing their physicochemical properties. Concerning the chair conformation of their glucopyranose units, cyclodextrins assume the shape of a truncated cone rather than a perfect sphere. On the one hand, their central cavity comprises the skeletal carbon atoms and ethereal oxygen of the glycosidic bonds with polarity comparable to an aqueous ethanolic solution. On the other hand, the exterior space is formed from the hydroxyl functional groups, with the primary and secondary hydroxyl groups oriented towards the narrow and broader end of the cone, respectively (Mura, 2015; Periasamy, 2020; Brewster & Loftsson, 2007; Bouchemal & Mazzaferro, 2012; Cid-Samamed et al., 2022; Davis & Brewster, 2004; Huang et al., n.d.; Jambhekar & Breen, 2016; Loftsson et al., 2005; Pardeshi et al., 2023).

Cyclodextrins exist in both natural and modified forms (Figure 2). The natural types are α-, β- and γ- cyclodextrins, having 6, 7, and 8 glucopyranose units, respectively, while the modified cyclodextrins of pharmaceutical importance are derivatives of β- and γ-cyclodextrins, randomly methylated β-cyclodextrins, and the branched cyclodextrins, for instance, glucosyl- β-cyclodextrin.

Regarding toxicity and clinical safety, all native cyclodextrins are generally regarded as safe (GRAS) and accepted as food additives (European Medicines Agency, 2014). They behave like starches when orally administered, but their rate of metabolism decreases from γ- to β- and α-, thus preventing hydrolysis by regular starch-splitting beta amylases. Moreover, intravenous administration of β-CD is associated with more pronounced haemolysis and nephrotoxicity than the other CDs (Duchêne & Bochot, 2016). The structures of the tested cyclodextrins in this study are depicted in the diagrams below.

This study aimed to examine the influence of various natural and modified cyclodextrins on the solubility of diclofenac sodium in acidified aqueous solutions and the preparation and characterization of their solid inclusion complexes prepared by different techniques.

2. Materials and Method

2.1 Materials

Diclofenac sodium salt, HP- γ -CD and HP- β -CD was purchased from Sigma Aldrich Inc (China, Germany, & USA), respectively. β -CD from Roquette (France); SBE-β-CD from Thermo Fisher Scientific (USA); Me-β-CD from T.C.I. (Belgium). Samples were used as purchased without any further treatment, and the water content of the cyclodextrins was considered in the calculation of the solute concentrations. All other reagents used were of analytical grade purity. Distilled water was used throughout the experiment.

2.2 Phase Solubility Studies

Solubility studies were performed according to Higuchi and Connors' method (Connors & Higuchi, 1965). An excess amount of diclofenac sodium (15-20 mg) was added to a mixture of solvents in screwedcapped amber glass bottles containing 1N HCl, distilled

water and increasing concentrations of cyclodextrins (0-12mM for β-CD) and (0-20mM for HP- β-CD, Me-β-CD, SBE-β-CD, and HP-γ-CD). The mixtures were placed for 48 hours in a thermostatically controlled water bath at 25°C for equilibrium to be attained. Afterwards, adequate aliquots were withdrawn and filtered through a 0.22 µm membrane filter and diluted with 1M NaOH and water. The concentrations of diclofenac sodium in the filtrates were determined spectrophotometrically using a Shimadzu UV- Vis spectrophotometer (UV-1900i) from the absorbance at λmax= 275nm and comparing it with the calibration plot. The solubility experiments were performed in triplicates. The apparent solubility constant Ks, according to the hypothesis of a 1:1 stoichiometric ratio of the complex, was calculated from the phase solubility diagrams using the equation:

$$Ks = Slope/So(1 - Slope)$$

The slope was obtained from the initial straight-line portion of the plot of diclofenac sodium concentration against the concentration of cyclodextrins; S0 is the equilibrium solubility of diclofenac in the absence of cyclodextrins.

2.3 Preparation of Diclofenac-Cyclodextrin Inclusion Complexes

The amounts of DS/CDs used in preparing the solid-inclusion complexes by various methods were calculated in a 1:1 molar ratio. The tested cyclodextrins in this study were β-CD, HP- β - CD, Me-β-CD, SBE-β-CD, and HP- γ -CD.

2.3.1 Physical Mixtures

Physical Mixtures of diclofenac sodium/cyclodextrin binary systems were prepared by grinding appropriate amounts of the components in a mortar five times until a homogenous powder mixture was obtained.

2.3.2 Kneading Method

Physical mixtures of diclofenac sodium/CDs were first prepared by homogenous grinding of the appropriate amount of the components three times. The ethanol-water mixture (1:1 v/v) was then added drop-wisely (5-6 drops) to the physical mixture and kneaded thoroughly, then drying at room temperature for about 40 minutes. After that, more EtOH: H2O mixture was added, and kneading was repeated twice. The resultant mixture was pulverized finally into a homogenous powder mix.

2.3.3 Co-precipitation Method

In this method, known weights of diclofenac sodium and cyclodextrins were transferred into a round bottom flask and 50 ml of Methanol was added to the mixture of powders and left overnight for complete dissolution. The organic solvent was removed using a rotary evaporatorat 40°C. The precipitated samples were then recovered from the flask for further analysis.

2.3.4 Freeze-drying Method

The inclusion complexation of diclofenac and cyclodextrins were performed by accurately weighing the required stoichiometric amounts of each component into a glass bottle. To the mixture, 50 ml of distilled water was added and vortexed. The aqueous solution was covered with parafilm and frozen at -20 °C for 24 hours. Subsequently, the samples were lyophilized at -55 °C for 48 hours. The products were ground and stored in airtight containers.

2.4 Characterization of Diclofenac Sodium-Cyclodextrin Inclusion Complexes

Binary mixtures of diclofenac sodium and cyclodextrins were characterized in the solid state by Powder X-ray diffractometry and Fourier Transform Infrared Spectroscopy.

2.4.1 X-ray Powder Diffractometry (XRD)

The XRD profiles were recorded on a Bruker X-Ray diffractometer (D8 Advance) and scanned in the 5 to 40 2θ range at room temperature.

2.4.2 Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR)

The FTIR spectra of pure diclofenac sodium as well as their binary products, were obtained directly from the powders using a Shimadzu FTIR spectrophotometer (IRTracer-100) according to the ATR (Pike Miracle) method by placing powders in contact with the totally reflecting surface of the ATR crystal and pressing by a diamond piston. Analyses were performed at room temperature.

3.Results & Discussion

3.1 Phase Solubility Studies

The phase solubility plot of DS/CD inclusion complexes is illustrated in Fig 3. As seen from the graph, the aqueous solubility of DS increased linearly as a function of increased concentrations of CDs. According to Higuchi and Connors (Carrier et al., 2007), this type of plot can be classified as AL type (linear host-guest relationship). For all studied cyclodextrins, the calculated slopes were less than unity (1), suggesting a 1:1 stoichiometric complexation. The stability constants were between 1088.81 ± 8.33 M-1 to 5009.57 ± 54.42 M-1, as shown in the table above, indicating the formation of favourable inclusion compounds. These values are within the range of Ks values reported in the literature for cyclodextrins (Carrier et al., 2007). Based on association constants and factor of solubility increase, the cyclodextrins may be arranged in the following order: SBE - β -CD > Me-β-CD > HP- γ -CD > HP-β -CD > β-CD.

The solubility of DS was markedly increased by the formation of an inclusion complex with SBE - β -CD. In contrast, β-CD accounted for the least solubility compared to the other cyclodextrins studied. Pardeshi et al., and Eid et al., reported that SBE - β -CD has relatively high solubilizing effects (> 50 folds) in comparison to β -CD, improved stability, and bioavailability. The lower solubilization effect of the β-CD compared to its derivatives and the derivative of Y-CD can be attributed to its structure, which allows for forming of a ring of intramolecular hydrogen bonds, counteracting its hydration and decreasing its solubility. Replacing these hydrogen

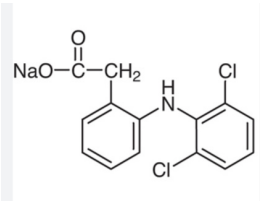

Figure 1. Structure of Diclofenac Sodium

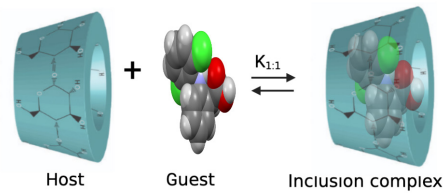

Figure 2. Schematic representation of (a) natural and some modified cyclodextrins (b) Inclusion complex of a drug in the CD cavity

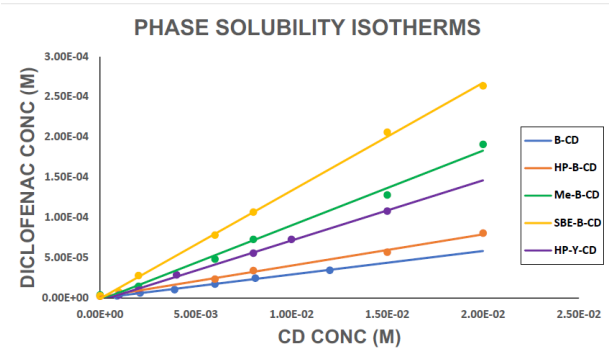

Figure 3. Phase Solubility Plot for DS/Cyclodextrins host-guest systems at 25C.

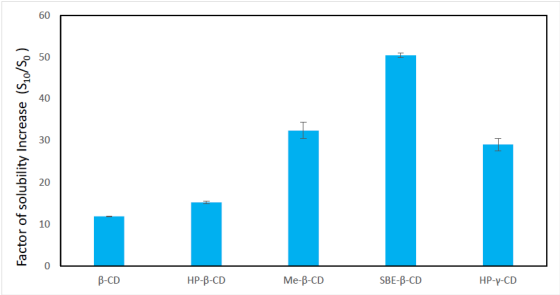

Figure 4. Plot illustrating the factor of solubility increase of diclofenac sodium by the different cyclodextrins tested.

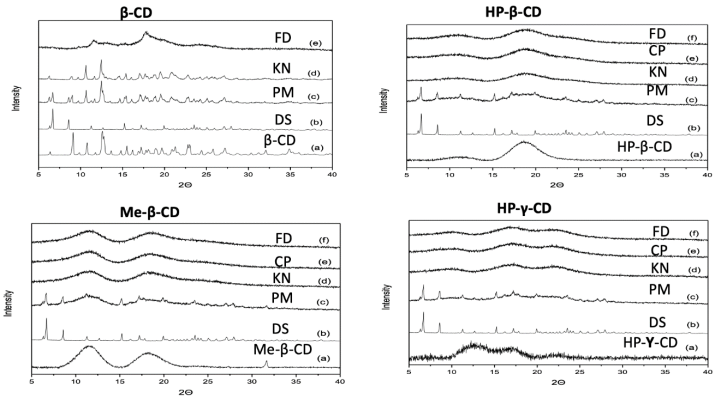

Figure 5. PXRD Diffractograms of Solid Inclusion Complexes and Pure Samples

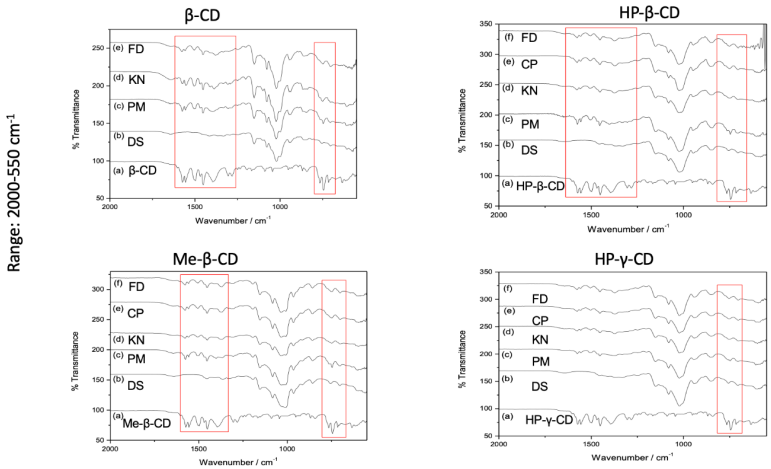

Figure 6. FTIR Spectra of Solid Inclusion Complexes and Pure Samples

bond-forming hydroxyl groups with other groups, such as the methoxy group, leads to dramatic increases in solubility (Figure 4).

3.2 Characterization of Solid Mixtures

3.2.1 X-ray Powder Diffraction

Powder X-ray diffractometry is a beneficial technique for detecting cyclodextrin complexation in powder or micro-crystalline forms. For an actual inclusion complex to be formed, the diffraction pattern of the complex is expected to differ from the mere superimposition of the pure components (Ribeiro et al., 2008). The X-ray diffraction pattern for pure diclofenac sodium shows several sharp and well-defined peaks illustrating the crystalline nature of the drug.

In the X-ray diffractogram of β-CD, the sharp peaks observed also depict the crystalline nature of the host molecule. Comparison of the diffraction patterns of the physical mixtures and wet granulation products with that of each component shows the maintenance of the crystallinity peaks, which is merely the superimposition of those of the pure components. By contrast, the diffraction pattern of the lyophilized product reveals complete amorphization and broadening of the peak suggesting the formation of an inclusion complex. Furthermore, it is evident from the figures that the diffraction patterns of pure HP- β -CD, Me-β-CD, and HP- γ -CD are characterized by amorphous and broader peaks, while that of Me-β-CD has both broad peaks and a sharp peak at around 31.50. Physical mixtures of the respective cyclodextrins illustrated features of both parent compounds. The binary mixtures of HP- β -CD and Me-β-CD, prepared by kneading, co-precipitation, and freeze-drying methods, showed complete amorphization and absence of crystallinity, while that of HP- γ -CD revealed amorphization as well as the shift in characteristic peaks of the pure cyclodextrin. It can thus be inferred that there were interactions between the drug and cyclodextrins in the solid state, leading to the formation of inclusion compounds by these three methods (Figure 5).

In terms of the preparation methods of complexes, freeze drying proves to be the most efficient method for complexation as mixtures prepared by this method resulted in the formation of inclusion compounds for all CDs used in the study. However, this technique (XRD) does not provide definitive proof of complex formation. Therefore, the samples were further characterized using FTIR.

3.2.2 ATR-FTIR Analysis

FTIR is a widely employed analytical technique in the study of complexation between active compounds and cyclodextrins by identifying vibrational modes of the guest and the host molecule disturbed during the inclusion process.

Fig 6 displays the FTIR spectra of DS/CD inclusion compounds and the spectra of the pure samples. Analyses were performed to evaluate the interaction of DS with the CDs based on the characteristics of the infrared peaks of each component. Prominent peaks around 1200 to 1000 cm-1 can be characterized for diclofenac sodium, while pure samples of β -CD showed peaks around 1625 cm-1 to 1250 cm-1 and 750 cm-1. By comparing the spectra of the pure samples to that of the physical mixtures, wet-granulation, and freeze-dried mixtures, it is apparent that there is a broadening of the bands with a decrease in the intensity of the peaks, thus, providing evidence of the formation of inclusion compounds.

Likewise, the results of the mixtures prepared with HP- β -CD, Me-β-CD show the broadening and shortening of peaks for physical mixtures, wet-granulation, co-precipitation, and freezedried mixtures with a shift in the wave number around 750 cm-1 for Me-β-CD. Findings of the HP-Y-CD also showed broadening variations in peak intensity around wavenumbers of 800 cm-1 to 700 cm-1 in comparison to the pure samples (Figure 6). All these provide evidence for the formation of inclusion compounds and can be attributed to the stretching vibrations of DS due to the inclusion into the cyclodextrin cavity. Alternatively, this may also be due to the weakening of the interatomic bonds due to the altered environment around these bonds following complex formation. The differences in the spectra produced by the different preparation techniques (physical mixtures, wet-granulation, co-precipitation, and freeze-dried mixtures) appeared indistinguishable for each tested cyclodextrin.

4. Conclusion

In conclusion, the findings reported in this study show that diclofenac sodium forms inclusion compounds with β-CD, HP- β -CD, Me-β-CD, SBE-β-CD, and HP- γ -CD in both solution and solid-state. A linear relationship in the solubility of diclofenac with these cyclodextrins with a 1:1 stoichiometry was observed, and SBE - β -CD showed the most significant solubility enhancement. Results obtained from the PXRD and FTIR show that solid inclusion complexes of DS and β- CD, HP- β -CD, Me-β-CD, SBE-β-CD, and HP- γ -CD can be prepared in a 1:1 molar ratio by wet granulation, co-precipitation, and freeze-dried methods. The freeze-drying process appears to be the gold standard for preparing these inclusion compounds. However, further studies, such as pharmacokinetic studies, need to be performed to determine the in vivo absorption and bioavailability of these complexed compounds. Moreover, these strategies can be optimized for potential nanoparticulate drug delivery systems applications.

Author contributions

I.U.K. formulated the study objectives, constructed the hypotheses, conducted the literature review, collected and analyzed the data, and revised the manuscript. The author approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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