Synthesis of new polymer for controlled drug release system
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Abstract —β-cyclodextrins (β-CD) are cyclic oligosaccharides which have been widely employed for pharmaceutical applications. Matrices of insoluble polymers were synthesized by crosslinking β-CD with the reagent citric acid (CA), sodium dihydrogen phosphate as a catalyst and polyvinylalcohol as a modifier in proceeding of in an environment. In this work, the possibility of employing a polymer containing β-CD for drug delivery of an anti-inflammatory (Diclofenac sodium) has been investigated. The interaction of Diclofenac sodium with the polymers was evidenced by X-ray diffractometry and Differential scanning calorimetry. Drug release kinetics was carried out at physiological conditions of pH and temperature. The kinetic and the regression constants (R²) were calculated. The drug release followed a simple Fickian diffusion mechanism for all the model drugs. This study suggests that these matrices are potentially suitable as controlled release systems.

Keywords: β-cyclodextrin, Diclofenac sodium, Release profiles, Drug delivery.

I. Introduction

β-cyclodextrin (β-CD), a natural molecule derived from starch, is a torus-shaped cyclic oligosaccharide with a relatively hydrophobic cavity [1]. It is well known that this structure gives rise to a remarkable capacity to form inclusion complexes with organic molecules, through host-guest interactions [2]. A great variety of applications for CDs has been described: water purification, analytical separations, food and pharmaceutical industry uses [3-5].

Numerous studies have revealed that CDs are capable of improving the solubility and bioavailability of poorly soluble drugs [6]. The efficiency and applicability of cyclodextrins can be increased if they are incorporated into a polymeric structure (i.e. an insoluble three-dimensional network). In the last 20 years, the pharmaceutical research studies have been focused on obtaining new compounds useful for drug controlled release [7].

β-cyclodextrin insoluble polymers using citric acid as a crosslinking agent with PVA can be obtained as reported in Figure 1. The high capacity of retaining water for these polymers suggests the possibility of using them as carriers of drugs for controlled release. The controlled release allows keeping dosage of drugs within the therapeutic level. This fact reduces the administration frequency, toxicity and potential side effects. Once the polymers have been obtained it is important to know the predominant mechanism of drug release. Incorporation of CDs into polymeric systems can influence these mechanisms [8]. The quantitative analysis of the physical, chemical and potentially biological phenomena, which are involved in the control of drug release, offers another fundamental advantage: the underlying drug release mechanisms can be elucidated [9]. Mechanistic mathematical theories are based on real phenomena, such as diffusion, dissolution, swelling, erosion, precipitation and/or degradation. This type of models allows for the determination of system specific parameters that can offer a deeper insight into the underlying drug release behaviour. For instance, the relative importance of several processes that are involved (e.g. drug diffusion
and polymer swelling) can be estimated. The aim of this work is the synthesis and characterization of novel β-cyclodextrin polymers (β-CDP) as well as to study their applicability as drug carriers for drug release. The mechanisms involved in the process have been studied using a model drugs (diclofenac sodium: DFCNa; Figure 2). Water-insoluble β-CDP was synthesized using citric acid (AC) as crosslinking agent, sodium dihydrogen phosphate (DHPNa) as catalyst and polyvinylalcohol (PVA). The structure of β-CDP was characterized by Fourier-transform infrared spectroscopy (FTIR). The resulting matrix of this method was used for preparing co-precipitated mixtures DFCNa/β-CD and DFCNa/β-CDP with DFCNa according to the molar ratio 1/2. These complexes were characterized by XRD and DSC. The release study of the active ingredient from gelatin capsules containing the complex DFCNa/β-CD and DFCNa/crosslinked β-CD was performed at simulated gastric pH (pH=1.2). A comparison of the release profiles was made between native and cross-linked matrices. The drug release followed a simple Fickian diffusion mechanism which is described by the equation of the first order.

II. Experimental

II.1. Material

β-Cyclodextrin is purchased from Sigma-Aldrich. Citric acid (CA), sodium dihydrogen phosphate (DHPNa) and polyvinylalcohol (PVA) are analytical pure reagents purchased from Fluka–Guaranter and Pprolabo. Potassium bromide (KBr) used for FTIR is a spectrum pure reagent purchased from Riedel-deHaën. Diclofenac sodium (DFCNa) was obtained from Aldrich.

II.2. Polymer synthesis

β-CD, citric acid, sodium dihydrogen phosphate, PVA and some distilled water were mixed in a round bottom flask. The mixture was stirred and heated to 160°C in a boiling water bath for 30min. After cooling, the mixture is transferred to a petri dish and then dried in an oven at 50 °C. At the end of the powder is sifted in a mortar.

II.3. Samples preparation

The co-precipitate mixtures DFCNa/β-CD and DFCNa/β-CDP was prepared in the molar ratio (1/2) by placing 2g of excipient and 0.28g of DFCNa with a small amount of distilled water in a flask and stirring for 10 min at 60°C.

II.4. Characterization

Methods used are: XRD analysis and Thermal analysis (DSC).

II.5. Release studies in vitro (pH=1.2)

The drug release from capsules is done according to Pharmacopoeia European. We used a paddle apparatus type Heidolph RZR 2041 and a 900ml beaker containing the buffer solution. The temperature was maintained at 37±0.5°C. The stirring speed of pallets is set at 100 rev/ min. Harvest volumes vary from 1 to 4 ml [10].
II.6. Mathematic modeling

Four kinetic models explain the release of different mixtures of β-CD and β-CDP were used: First order equation, Elovich, power function, and Higuchi [11].

- First order:
  \[ \log C = \log C_0 + k_p \times t \]

- Elovich:
  \[ C = a + k_E \times \ln t \]

- Function power:
  \[ \ln C = \ln a + k_F \times \ln t \]

- Higuchi:
  \[ C = R t^{1/2} + \text{constant} \]

Where

- \( C \): is the total amount of DFCNa released at time \( t \).
- \( C_0 \): is the total amount of DFCNa released at time \( t_0 \).
- \( k_p \), \( k_E \), and \( k_f \) are coefficients of the release rate.

The model gives the regression coefficient higher (but lower values 1) was considered the most appropriate model to describe the release of DFCNa from capsules. In this case, a good linearity of the experimental points is observed.

III. Results and discussion

III.1. FTIR characterization of β-CDP

![Figure 3: FTIR spectra of native β-cyclodextrin.](image)

![Figure 4: FTIR spectra of crosslinked cyclodextrin.](image)

Analysis of FTIR spectra for the native and crosslinked β-CD clearly shows that the crosslinking of the β-CD is well produced with citric acid. This is indicated by the new absorption band at 1733 cm\(^{-1}\) which corresponds to the stretching vibration of carbonyl of the ester thus formed.

III.2. Structural characterization

From this result of X-ray diffraction, the reflectivity is measured in the range of angles \( \theta \) from 0 to 20°. The XRD of native β-cyclodextrin, when compared with that of diclofenac sodium showed a higher number of reflections of a higher intensity. The interplanar distances correspond to high intensities are 6.951, 5.732, 4.185 and 3.909 Å. The XRD of DFCNa said other reflections of high intensity, and they correspond to the following distances: 15.595, 13.137, 5.791, and 3.771 Å. The XRD of the mixture co-precipitate (DFCNa/β-CD) indicated the characteristic peaks of inclusion complex and their appearance indicated the formation of a new crystal inclusion complex (DFCNa/β-CD). Indeed, for these systems, the diffractogram exhibit a considerable decrease of the peaks suggest that leaving the mixture is less crystalline. For the co-precipitate mixture of DFCNa/β-CD, there is a divergence in the diffraction pattern of β-CD and the β-CDP. There is an increase in crystallinity for the crosslinked. The XRD of DFCNa, the β-CDP and their mixture showed that diclofenac sodium formed a new crystal. This is evidenced by the peaks appeared in the co-precipitate mixture. This peaks which are not included in either the XRD of β-CD or in the DFCNa confirm the formation of an inclusion complex. The DSC thermogram of pure DFCNa shows a characteristic peak at 289°C, which represents its melting point. The DSC thermogram of pure β-CD shows no peak in the region of the melting point of pure DFCNa, a peak is observed at 106°C. The appearance of a new peak near 128°C which is attributed to the melting point of the complex formed (the disappearance of the characteristic peaks of starting materials and the appearance of a new peak confirm the true inclusion in the DFCNa of the β-CD in the product obtained).
Figure 5: XRD of native β-cyclodextrin.

Figure 6: XRD of diclofenac sodium.

Figure 7: RX diffraction pattern of the mixture DFCNa/β-CD co-precipitate.

Figure 8: XRD of crosslinked β-cyclodextrin.

Figure 9: RX diffraction pattern of the mixture DFCNa/β-CDP co-precipitate.

Figure 10: Thermogram (DSC) of diclofenac sodium.

Figure 11: Thermogram (DSC) of diclofenac sodium.

Figure 12: Thermogram (DSC) of the mixture DFCNa/β-CD co-precipitate.

Figure 13: Thermogram (DSC) of cross-linked β-cyclodextrin.

Figure 14: Thermogram (DSC) of the mixture DFCNa/β-CDP co-precipitate.
DSC thermogram of the binary system shows the presence of a new peak at 118 °C with the disappearance of the characteristic peaks of starting materials (peak characterizing the β-CDP at 95°C and that of the drug is 289°C). This confirms the formation of an inclusion complex between these two molecules.

3.3. Release kinetics studies
After analyzing the curves, we note first that in each case the rate of release of DFCNa from different capsules excipient, which is the β-CDP, is lower compared to the vehicle which is the β-CD.

The curves of the kinetics of dissolution samples of co-precipitated mixtures have a similar shape: the dissolution is initially very fast, after, the curves are inflected in plateau because most of the entire active ingredient is dissolved. Delays to the dissolution statements to trials may be due, to one side, to the gelatin shell, but on the other hand, the slowdown of dissolution can be attributed to a factor inherent in the powder in the capsule, the amount and quality of the excipients. So, the co-precipitation is better for sustained release of active ingredient.

a. Data analysis

Mathematical modeling of release profiles showed that the best model for the controlled release of DFCNa from different systems is that of Power function whose regression coefficient is closer to one.

Several investigations have reported that the release from capsules containing different mixtures is governed by a diffusion mechanism, which is described by the first order equation.

IV. Conclusion
Diclofenac sodium (DFCNa) release from polymers obtained by treatment of natural β-cyclodextrin with citric acid and PVA was studied. Release of DFCNa from DFCNa/β-CD.
CDP matrix was compared with the release of DFCNa from DFCNa/β-CD matrix. Results showed that controlled release of DFCNa from all DFCNa/β-CD and DFCNa/β-CDP was achieved. The presented results together with previously demonstrated drug uptake may encourage further research on modified natural cyclodextrin as prospective excipients for pharmaceutical applications.

References