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Improvement of clofibrate dissolution by complexation with cyclodextrin

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Abstract

Inclusion complexes of clofibrate with β-cyclodextrin (βCD) were prepared by coprecipitation, kneading and sealed heating methods and characterized by UV spectrophotometry, differential scanning calorimetry, X-ray diffractometry and infrared spectroscopy. All results were in keeping with the formation of 1:1 inclusion complex. Dissolution studies showed that clofibrate entrapped in inclusion complexes dissolved much faster than uncomplexed liquid clofibrate. The complex prepared by the sealed heating method showed the greatest improvement in dissolution rate: this complex released 50 mg of clofibrate into water within 10 min. These results show that a more easily manipulated, solid form of clofibrate may be obtained through formation of its inclusion complex with βCD, and that complex formation simultaneously enhances the solubility and dissolution rate of this drug.

Keywords: Clofibrate; Cyclodextrin; Inclusion complexation; Solubility; Solid form; Coprecipitation; Kneading; Sealed heating

1. Introduction

In recent years, extensive pharmaceutical research into cyclodextrin inclusion complexes has produced numerous publications and patents describing such complexes of a wide variety of drugs. Much of this work has been concerned with the development of preparative methods aimed at producing suitably stable inclusion complexes in high yields (Blanco et al., 1991; Fucile et al., 1992).

Clofibrate (ethyl 2-(*p*-chlorophenoxy)-2-methylpropionate) is a poorly water-soluble, bitter-tasting oily liquid that is used in treatments for some forms of hyperlipidaemia, for which it is usually formulated in soft gelatine capsules. Obtention of a solid form of clofibrate through formation of its cyclodextrin inclusion complex is of interest since it would allow easier manipulation of this drug and might also lead to enhancement of other desirable drug properties, such as solubility.

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In this work, inclusion complexes of clofibrate with β-cyclodextrin (βCD) were prepared by coprecipitation, kneading and sealed heating methods, then characterized and their dissolution properties determined.

2. Materials and methods

2.1. Materials

Clofibrate was a gift from ICI Farma España (Pontevedra, Spain); βCD (Kleptose) was purchased from Laisa (Barcelona, Spain). All other solvents and reagents were of reagent grade.

2.2. Preparation of inclusion complexes

2.2.1. Coprecipitation method

The quantities of clofibrate and βCD necessary for complex preparation were evaluated from the corresponding phase solubility curve (Anguiano-Igea et al., 1992). These components were mixed in 600 ml water and agitated at 25°C for 1 week, whereupon the precipitated product was filtered out, dried under vacuum at 30°C.

2.2.2. Kneading method

For many systems, preparation of inclusion complexes by the kneading method requires use of aqueous alcohol to make the paste; however, this is undesirable since, although present in small amounts, the alcohol may complex with the cyclodextrin. After several test runs we found that inclusion complexes of clofibrate and βCD could be prepared using deionized water alone. Thus clofibrate and βCD in 1:1 mol ratio were ground together in a mortar. A mass of water equal to that of the drug/βCD mixture was added and grinding continued until a thick paste was formed. The paste was dried under vacuum at ambient temperature until its mass was constant, and then washed with diethyl ether to remove uncomplexed clofibrate.

2.2.3. Sealed heating method

This method, first used by Nakai et al. (1987, 1989, 1990), involves heating a mixture of the drug and cyclodextrin in a sealed container. Our own studies have shown that entrapment of clofibrate by βCD using this method is strongly influenced by the conditions used (Anguiano-Igea et al., 1992). In this work, we used the conditions previously found to give optimum results: heating a 1:1 mol ratio of βCD/clofibrate and 25 μl water at 90°C for 45 min. The isolated solid was washed with diethyl ether.

Prior to analysis, each solid product from the above preparations was pulverized and sieved to give a sample with particle size between 105 and 250 μm. Complex stoichiometries were determined spectrophotometrically at 225 nm (Shimadzu UV-240 spectrophotometer).

2.3. Characterization of the inclusion complexes

2.3.1. Differential scanning calorimetry

Samples of ca. 5 mg of the product were sealed in aluminium pans, leaving a small escape for volatilized material, and heated at 10°C/min in a Perkin-Elmer DSC-4 apparatus purged with nitrogen.

2.3.2. Powder X-ray diffractometry.

Powder X-ray diffraction patterns were recorded in a Philips PW 1710 powder X-ray diffractometer using Ni-filtered, Cu-K_α radiation, a voltage of 40 kV and a current of 30 mA.

2.3.3. Infrared spectroscopy

The IR spectra of the clofibrate (as a liquid) and the solid products (in KBr disk) were recorded in a Perkin-Elmer 1330 IR spectrophotometer.

2.4. Dissolution studies

The dissolution studies were performed using USP XXII apparatus 2 (rotating paddle method; Prolabo).

Samples of each preparation equivalent to 50 mg clofibrate were spread over the dissolution medium (1000 ml deionized water, maintained at 37 ± 0.5°C and continuously stirred at 100 rev./min). At various intervals, a 5-ml aliquot of the dissolution medium was withdrawn and replaced

with an equal volume of fresh medium (a correction for the cumulative dilution was later applied). The removed sample was filtered and assayed spectrophotometrically at 225 nm.

In the case of the uncomplexed clofibrate, the pure liquid (50 mg) was added to the dissolution medium and the samples removed were centrifuged for 1 h at 30000 rev./min (Centrikon T-1075 Ultracentrifuge) before spectrophotometric determination of the dissolved clofibrate.

All experiments were carried out in quadruplicate.

Analysis of the dissolved-clofibrate/time curve used the approach proposed by Khan and Rhodes (1975), which allows evaluation of the dissolution efficiency (DE), defined as:

$$DE = \frac{\int_0^t M dt}{M_{100} t}$$

where the integral is the area under the curve up to dissolution time t and M_{100} is the 100% dissolved drug.

For each solid product, values of DE were calculated for the maximum dissolution time (DE 60 min), and the quantity of dissolved clofibrate at 10, 30 and 60 min (Q_{10}, Q_{30} and Q_{60}) was selected to evaluate the dissolution at determinate stages of the process.

3. Results and discussion

The properties of a cyclodextrin inclusion complex are determined in part by the method of preparation. In order to evaluate which method is most suitable for a given drug, initial selection of appropriate preparative methods, largely on the basis of the properties of that drug, is therefore followed by evaluation of the stoichiometric ratio and examination of the behaviour of the inclusion complex in solution.

Phase solubility studies previously carried out for mixtures of βCD and clofibrate gave a Higuchi type B_s solubility curve (Anguiano-Igea et al., 1992), thus indicating the feasibility of obtaining clofibrate/βCD inclusion complexes by the coprecipitation method. The apparent stability constant for the complex, K_s, was evaluated from this solubility curve as 1315 M^{-1}, which closely agrees with the values of 1350 and 1170 M^{-1} reported by Uekama et al. (1983) and Ben-Amor (1990), respectively.

The spectrophotometrically determined stoichiometric ratios (clofibrate/βCD) were 0.83:1 for the complex prepared by coprecipitation, 0.76:1 for the complex prepared by the kneading method, and 0.80:1 for the complex prepared by the sealed heating method. For the complexes prepared in this work, it is reasonable to assume that 1:1 complexes were formed in all cases.

3.1. Differential scanning calorimetry (DSC)

Fig. 1 shows the DSC curves obtained for the host, guest and complexes prepared by the three methods. Comparing these curves it is clear that the endotherm at ca. 270°C (1 Atm) due to vaporization of the clofibrate is absent in the thermograms of the complexes, thus confirming formation of a solid inclusion complex. This temperature does not agree with the 150°C reported

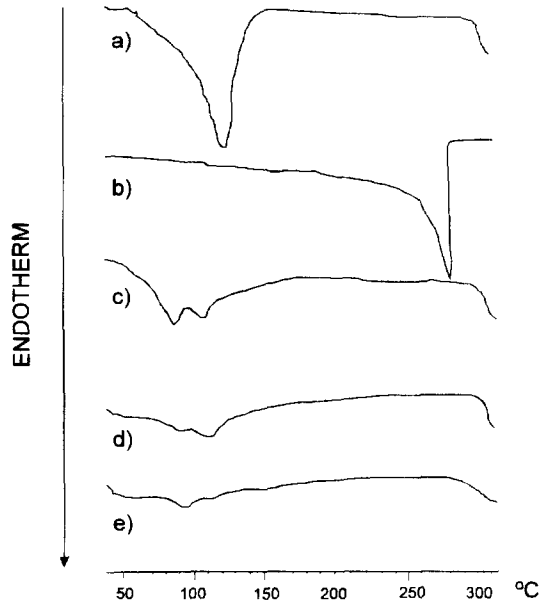

Fig. 1. DSC curves for (a) β-cyclodextrin, (b) clofibrate, and inclusion complexes of these prepared by the (c) coprecipitation, (d) sealed heating and (e) kneading methods.

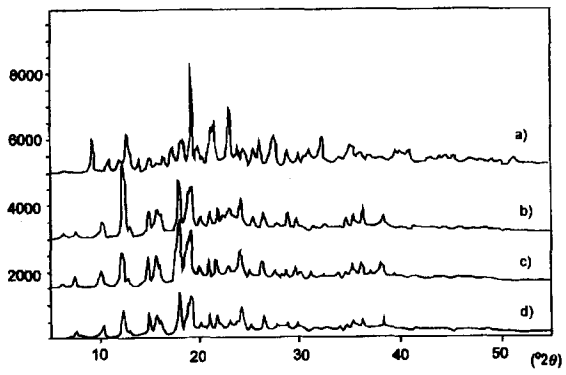

Fig. 2. X-ray diffractograms of (a) β-cyclodextrin and inclusion complexes of clofibrate with this prepared by the (b) coprecipitation, (c) kneading and (d) sealed heating methods.

by Uekama et al. (1983) who have studied complexes of clofibrate with various CDs. These authors did not explicitly state whether they used open or closed pan thermal methods, but their value roughly corresponds to the boiling point (148–150°C) reported for clofibrate at 20 mmHg (Hassan and Elazzouny, 1982; The Merck Index, 1989), and the clofibrate sample used here has a vapour pressure of ca. 20 mmHg at 165°C.

3.2. Powder X-ray diffractometry

Comparison of the powder X-ray diffraction patterns for βCD and the inclusion complexes prepared by the three methods (Fig. 2) reveals that those of the complexes are very similar, and markedly differ from that of the host alone. Notably, the peaks at $2\theta = 9.485$, 13.050, 23.240 and 32.040° 2θ in the diffractogram of the CD are not present in the diffractograms of the complexes: these peaks have been replaced by peaks at $2\theta =$ 6.260, 7.425, 10.105 and 17.850° 2θ which indicate formation of a new phase. Intensity differences between corresponding peaks in the diffractograms of the inclusion complexes suggest that the most crystalline complex is that prepared by the coprecipitation method, followed by the complexes prepared by the sealed heating and kneading methods, although the differences in signal intensity are small between the latter two methods.

3.3. Infrared spectroscopy

Fig. 3 shows the IR spectra of the βCD, clofibrate and their complexes. The spectrum of clofibrate (Fig. 3b) shows a characteristic peak at 1734 cm^{-1} due to the C=O stretching vibration. There is no displacement of the carbonyl stretching band in the spectra of the complexes suggesting that this group is not hydrogen bonded in the complexes. This is confirmed by the ^1H NMR spectrum of a mixture of clofibrate and βCD, from which it was deduced that this carbonyl group lies some distance from the secondary hydroxyls of the βCD, and thus that formation of hydrogen bonds between these groups is unlikely (Anguiano-Igea et al., 1996). The IR spectra for the three complexes obtained here are very similar, suggesting that the guest molecule is similarly accommodated.

3.4. Dissolution studies

The dissolution studies indicate that both the rate of dissolution of clofibrate and its solubility are very much enhanced by formation of its inclusion complex with βCD (Fig. 4). The complex prepared by the sealed heating method (under the conditions described) shows the greatest improve-

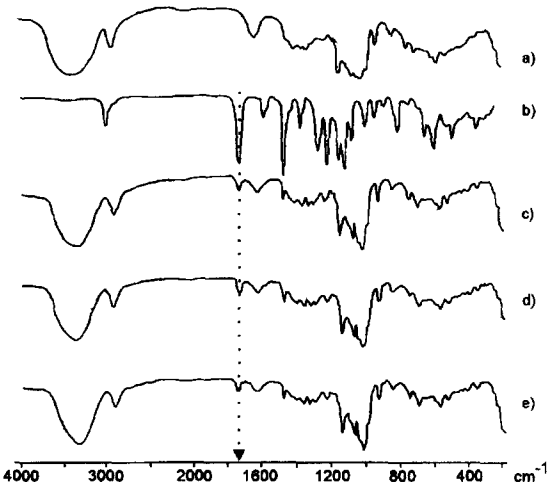

Fig. 3. Infrared spectra of (a) β-cyclodextrin, (b) clofibrate, and inclusion complexes prepared by (c) kneading, (d) sealed heating and (e) coprecipitation methods.

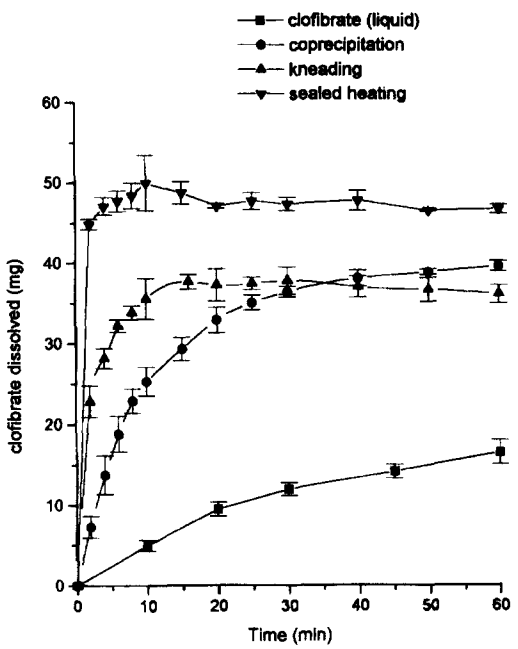

Fig. 4. Dissolution profiles of clofibrate and clofibrate/β-cyclodextrin complexes.

ment, i.e. rapid dissolution of the clofibrate that is effectively complete within 10 min. The complex prepared by coprecipitation shows the slowest rate of dissolution.

The one-way analysis of variance (ANOVA) of the DE values (Table 1) showed a significant difference between the four formulations ($\alpha < 0.01$). The complex prepared by sealed heating has the greatest DE. The slower dissolution rate observed for the complex prepared by the coprecipitation method may be partly due to its greater crystallinity.

The ANOVA of the quantities of dissolved clofibrate after 10, 30 and 60 min (Table 1) indicated that these values are significantly different ($\alpha < 0.01$), excepting Q_{30} for the coprecipitation and kneading methods.

4. Conclusions

These results show that the rate of dissolution of clofibrate is increased by formation of its inclusion complex with βCD. The complex prepared by the sealed heating method under the described conditions shows the greatest enhancement of dissolution rate, and effectively allows complete dissolution of its clofibrate component within 10 min. Additionally, this method is suitable for large-scale industrial use and does not require the use and subsequent costly elimination of large amounts of water.

The inclusion complex of clofibrate/βCD prepared by sealed heating has good flow properties (Anguiano-Igea et al., 1994), therefore it is possible to obtain a solid formulation of clofibrate that can improve some pharmaceutical and technological properties of this liquid drug.

Acknowledgements

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Table 1
DE (mean ± S.D.) and amounts of drug released (mg) after 10, 30 and 60 min, for clofibrate and inclusion complexes prepared by the indicated methods

Sample	DE_{60}	Q_{10}	Q_{30}	Q_{60}
Clofibrate	0.207 ± 0.022	5.006 ± 0.649	11.966 ± 0.827	16.550 ± 2.825
Coprecipitation	0.647 ± 0.020	25.320 ± 2.059	36.385 ± 0.766[a]	39.600 ± 0.736
Kneading	0.706 ± 0.024	35.595 ± 2.525	37.766 ± 1.701[a]	36.093 ± 1.133
Sealed heating	0.933 ± 0.098	50.145 ± 3.975	47.310 ± 0.932	46.653 ± 0.641

[a]No statistical difference ($\alpha < 0.01$).

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