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Note

The effect of 2-hydroxypropyl-β-cyclodextrin on the simultaneous dissolution and degradation of chlorambucil

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Summary

The effect of 2-hydroxypropyl-β-cyclodextrin (2-HPCD) on the simultaneous dissolution and degradation of chlorambucil from rotating compressed disks in aqueous buffer solutions was investigated. The compressed disks consisted of chlorambucil-2-HPCD complex or physical mixtures of chlorambucil and 2-HPCD, D-(+)-glucose or microcrystalline cellulose. The stabilizing and solubilizing effects of 2-HPCD on the chlorambucil molecule significantly improves the dissolution characteristics of the drug in aqueous media. The fastest rate of dissolution was obtained from disks containing chlorambucil-2-HPCD complex.

Recently, we have reported the ability of 2-hydroxypropyl-β-cyclodextrin (2-HPCD) to solubilize and stabilize chlorambucil in aqueous solutions (Loftsson et al., 1989). This drug is usually formulated into tablets and given orally, frequently for long periods of time. Oral administration of the drug is known to cause gastro-intestinal disturbances (Calabresi and Parks, 1985). Cyclodextrins have been shown to reduce the gastro-intestinal disturbances associated with oral administration of many drugs (Duchêne, 1987). The present study was undertaken to investigate the effects of 2-HPCD on simultaneous dissolution and degradation of chlorambucil in aqueous buffer solutions.

2-HPCD (degree of substitution 5.1) was supplied by the courtesy of Pharmatec, Inc. (U.S.A.). Chlorambucil was supplied by the courtesy of the Wellcome Foundation Ltd. (U.K.). Microcrystalline cellulose, type pH = 101 (Avicel®) was obtained from F.M.C. (Ireland) and anhydrous D-(+)-glucose from Merck (Germany). All other chemicals were commercially available products of special reagent grade.

A previously described HPLC method was used for quantitative determinations of chlorambucil in aqueous solutions (Loftsson et al., 1989). McIlvaine buffers were prepared at pH 2.16, 4.01 and 7.05 (Elving et al., 1956). The ionic strength of the buffer solutions was not adjusted and addition of chloride ions was avoided. The water used for the buffer preparation was distilled in all-glass apparatus.

The freeze-dried chlorambucil-2-HPCD complex was prepared by adding an excess of chlorambucil to 50% (w/w) (about 58% w/v) solution of 2-HPCD in water and sonicating the suspension for 2 h. The suspension was then filtered through 0.45

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μm membrane filter (Millex-HV from Millipore, U.S.A.), the filtrate lyophilized (Labonco Freeze Drier 5 from the Labonco Corp., U.S.A.) and the solid formed ground with a mortar and a pestle. The amount of chlorambucil incorporated into the 2-HPCD complex was determined by HPLC.

Individual disks of 250 mg chlorambucil-2-HPCD complex or physical mixtures of chlorambucil and 2-HPCD, microcrystalline cellulose (Avicel®) or D-(+)-glucose were compressed in a hydraulic press (Model 00-25 from RIIC, England) under vacuum and a force of 1×10^4 kg for 1.5 min using a 13 mm (diameter) IR potassium bromide pellet punch (RIIC). The disks had a cross-sectional area of 1.33 cm^2. Each disk contained approx. 20 mg of chlorambucil.

The dissolution study was performed at 35.3°C in apparatus similar to that described by Kuu et al. (1989). The apparatus consisted of a round bottom dissolution cell which was placed into a water bath. The dissolution medium, 250 ml McIlvaine phosphate buffer solutions pH 2.16, 4.01 or 7.05, was placed in the cell and a stainless steel disk holder containing a disk immersed into the medium. The disk holder was fixed to a shaft rotating at 100 rpm. Samples (50 μl) of the dissolution medium were removed from the cells at 2-min intervals and analyzed immediately by HPLC.

The degradation studies of chlorambucil were carried out in the dissolution cell in a 35.3°C water bath by adding stock solution (60 μl) of the drug in methanol to aqueous buffer solution (250 ml) containing 0.01% (250 mg in 250 ml) of the excipients listed under the disk preparation. The initial chlorambucil concentration was 9×10^{-3} mg/ml. All reactions were run under pseudo-first-order conditions. Samples, 50 μl, of the reaction medium were removed from the cells at various time intervals and analyzed immediately by HPLC. The pseudo-first-order rate constants (k') were determined from the disappearance of the drug by linear regression of natural logarithm of the peak height vs time plots. The correlation coefficient was calculated for each run.

The simultaneous dissolution and degradation of chlorambucil at pH 7.1, 4.0 and 2.2 is shown in Fig. 1. Generally the dissolution was much faster from the chlorambucil-2-HPCD complex than

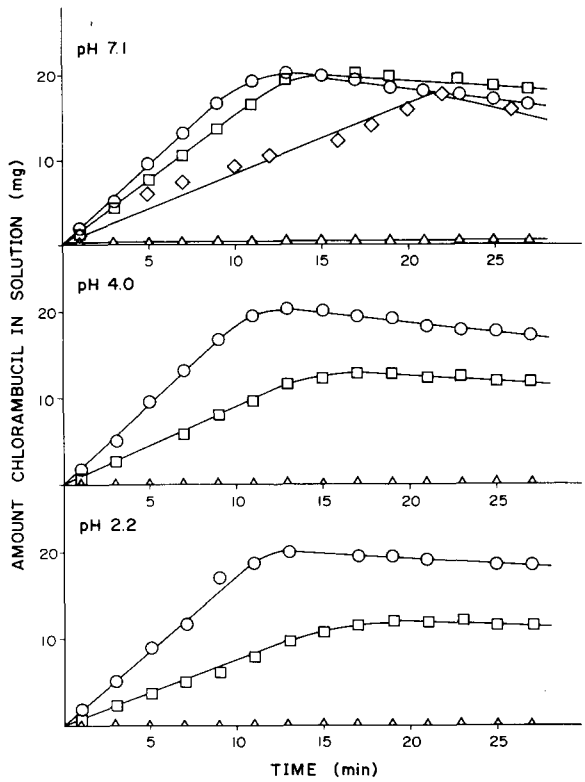

Fig. 1. Simultaneous dissolution and degradation of chlorambucil at pH 7.1, 4.0 or 2.2 and 35.3°C. 2-HPCD complex (○), 2-HPCD physical mixture (□), Avicel® physical mixture (△), D-(+)-glucose physical mixture (◊).

from the physical mixtures of chlorambucil and the excipients. The Levich equation (Levich, 1962) states that the rate of dissolution (dm_s/dt) from a rotating disk is proportional to the square root of the rotation speed of the disk:

$$dm_s/dt = 0.62\, A D^{2/3} \upsilon^{-1/6} C_s \omega^{1/2} \quad (1)$$

where A is the surface area of the disk, D is the diffusion coefficient, υ is the kinematic viscosity of the dissolution medium, C_s is the solubility of the drug (at the surface of the disk) and ω is the rotation speed of the disk. Eqn 1 assumes dissolution under sink conditions. In our experiments ω was kept constant at 100 rpm and the only significant variables in Eqn 1 were υ and Cs. Thus, Eqn 1 can be written as:

$$dm_s/dt = k \quad (2)$$

where k is equal to $0.62AD^{2/3}\upsilon^{-1/6}C_s\omega^{1/2}$.

The degradation of chlorambucil followed the well known pseudo-first-order kinetics:

$$dm_d/dt = -k'm \quad (3)$$

where m is the amount of drug dissolved in the dissolution medium and k' is the pseudo-first-order degradation rate constant. Combination of Eqns 2 and 3 gives the net change of the total amount of dissolved drug in the dissolution medium per unit time (dm/dt):

$$dm/dt = k - k'm \quad (4)$$

Integration of this equation produces Eqn 5:

$$m = \frac{k}{k'}(1 - e^{k't}) \quad (5)$$

The rate of drug dissolution is constant and continues until the amount of drug in the disk is depleted. At that time the drug is no longer available for dissolution and Eqn 5 no longer holds. The time at which this happens can be estimated by dividing k into the total amount of drug in the disk. From that time the drug in the dissolution medium will decline according to Eqn 3.

Table 1 shows the pseudo-first-order degradation rate constant (k') of chlorambucil in the various McIlvaine buffer solutions containing about 0.01% of the excipients listed under the disk preparation. The dissolution rate constants (k) listed in Table 2 were estimated from m vs $(1-e^{k't})$ plots (Eqn 5) by multiplying the slope (k/k') by the pseudo-first-order degradation rate constants (k') listed in Table 1. Chlorambucil has two ionizable groups, an amino group with pK_a of 3.0, and a carboxylic acid group with pK_a of 5.1, both at 40°C (Loftsson et al., 1989). The drug has a cation below pH about 3, is unionized between pH about 3 and 5, and has an anion at pH above about 5.

TABLE 1

The pseudo-first-order degradation rate constant (k') of chlorambucil in the various dissolution media, i.e. McIlvaine buffer solution containing 0.01% (w/v) of an excipient, at 35.3°C

Excipient	pH	k' (min^{-1})
D-(+)-Glucose	7.05	3.39×10^{-2}
Avicel®	7.05	3.37×10^{-2}
	4.01	2.67×10^{-2}
	2.16	1.18×10^{-2}
2-HPCD	7.05	2.62×10^{-2}
	4.01	2.16×10^{-2}
	2.16	1.08×10^{-2}

The initial chlorambucil concentration was 9×10^{-3} M. The correlation coefficient was in all cases equal or larger than 0.997.

TABLE 2

The initial slopes (k/k' in Eqn 5), correlation coefficients and the rate constants for dissolution (k) of chlorambucil from rotating disks containing chlorambucil-2-HPCD complex or physical mixtures of chlorambucil and 2-HPCD, microcrystalline cellulose (Avicel®) or D-(+)-glucose at 35.3°C

Excipient	pH	Slope (mg)	Corr.	k (mg/min)
2-HPCD complex	7.1	79.3	0.999	2.08
	4.0	96.8	1.000	2.09
	2.2	162.3	1.000	1.75
2-HPCD	7.1	66.9	0.998	1.75
	4.0	46.9	0.998	1.01
	2.2	74.9	0.998	0.81
Avicel®	7.1	0.6	0.999	2.0×10^{-2}
	4.0	0.2	0.990	5.4×10^{-3}
	2.2	0.4	0.992	4.5×10^{-3}
D-(+)-Glucose	7.1	28.5	0.989	0.97

Thus, the aqueous solubility of chlorambucil is lowest between pH 3 and 5 but increases at both lower and higher pH. Since the rate of dissolution is proportional to the solubility (C_s in Eqn 1) the rate should theoretically be slowest at pH between 3 and 5 but faster at both lower and higher pH. According to our results the rate of dissolution of chlorambucil is much faster at pH 7.1 (the anionic form) than at pH 4.0 or 2.2. At pH 2.2 (the cationic form) the rate was somewhat slower than at pH 4.0 (the unionized form). The reason for slower dissolution at pH 2.2 is unclear but could possibly be due to an artifact from the buffer salts. The

rate constant for the dissolution of chlorambucil was less sensitive towards changes in pH when the drug was within a 2-HPCD complex than when it was in a physical mixture with 2-HPCD or the other excipients (Table 2). The fastest rate of dissolution of chlorambucil was obtained from disks containing chlorambucil-2-HPCD complex followed by disks containing physical mixtures of chlorambucil and 2-HPCD. At pH 7.1 physical mixture of chlorambucil and D-(+)-glucose resulted in slower rate of dissolution than obtained with 2-HPCD. Very slow dissolution was obtained from disks containing physical mixtures of chlorambucil and microcrystalline cellulose.

In conclusion, our results show that the previously described stabilizing and solubilizing effects of 2-HPCD on the chlorambucil molecule significantly improves the dissolution characteristics of the drug in aqueous media.

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