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STUDIES OF THE INTERACTION OF BETACYCLODEXTRIN WITH AMPICILLIN, METHICILLIN AND PHENYTOIN

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ABSTRACT

The interaction of betacyclodextrin with ampicillin, methicillin and phenytoin has been investigated. All three drugs, (in the unionized form) interact strongly with betacyclodextrin. It is suggested that the interaction of all three drugs with betacyclodextrin could perhaps be exploited to pharmaceutical advantage. For ampicillin it is possible that the complex may have an improved bioavailability and a reduction in the incidence of gastro-intestinal side effects in comparision with the uncomplexed drug. For methicillin the significant extension of the hydrolytic half life for the complex makes the oral route a possibility for this drug, which is normally given intravenously because of stability problems. The interaction of phenytoin with betacyclodextrin produces a complex with a substantially enhanced solubility likely to give greatly improved bioavailability and a reduction in intra and inter subject blood level variation.

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INTRODUCTION

Cyclodextrins were first isolated by Villiers as degradation products of starch (1). They are composed of alpha (1-4) linkage cyclic oligosaccharides containing six to twelve glucose units per ring. The main fractions, normally designated alpha-, beta-, and gamma-, contain six, seven, and eight glucose units.

Betacyclodextrin has a internal cavity with a diameter of about 6·2 A^{o} (1). Toxicity studies have shown that the compound is characterized by an impressively high degree of safety (2). A number of useful papers have been published on the interaction of betacyclodextrin and a variety of drugs (3-7).

The present paper reports studies of the interaction of betacyclodextrin with three drugs: ampicillin, methicillin and phenytoin. Ampicillin is a very widely used antibiotic. However, it is incompletely absorbed and the residue of non-absorbed drug within the lower part of the gastro-intestinal tract can alter the composition of gastro-intestinal flora and fauna which can lead to diarrhea. Methicillin is also a useful antibiotic. However, its liability to rapid hydrolysis in the gastro-intestinal tract presently precludes its administration by the conventional oral route. Phenytoin is a powerful antiepileptic drug which, unfortunately, is characterized by erratic and incomplete absorbtion. Data presented in this paper suggests that the interaction with betacyclodextrin may for all three drugs yield products for which the problems described above are reduced or even eliminated.

EXPERIMENTAL

Ampicillin and methicillin were assayed using the method described by Finholt (8). Phenytoin concentrations were determined by ultra-violet spectroscopy at 207 nm. The Beer-Lambert Law was obeyed and $E^{1\%}_{1cm}$ at 207 nm was found to be 27·5. The interaction between beta-cyclodextrin and the three drugs was investigated using the solubility method (9, 10).

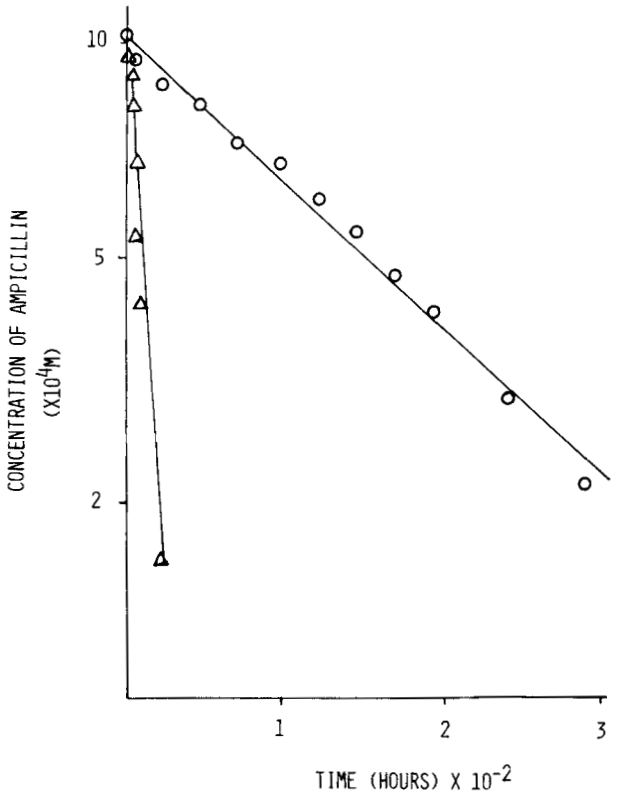

Figure 1

Hydrolysis of ampicillin with (upper curve) and without (lower curve) betacyclodextrin, pH 1·0 and 25°c

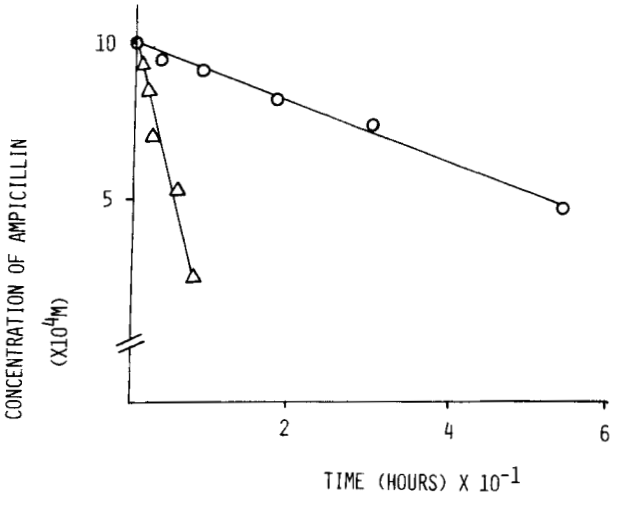

Figure 2

Hydrolysis of ampicillin with (upper curve) and without (lower curve) betacyclodextrin at pH 1·0 and 37°c

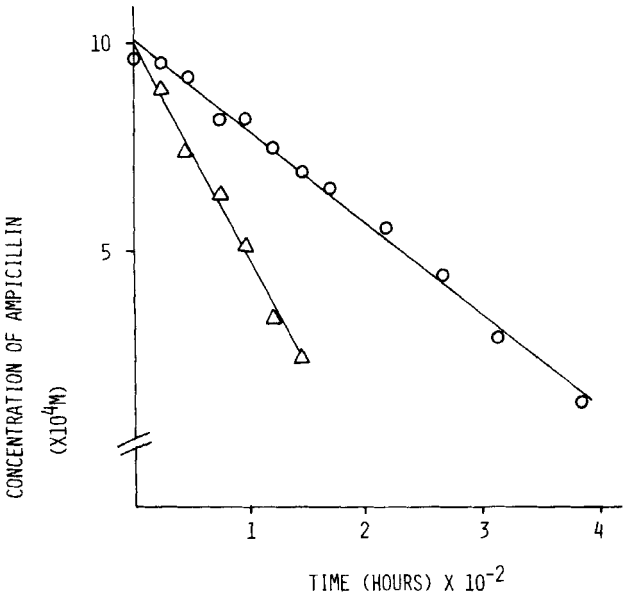

Figure 3

Hydrolysis of ampicillin with (upper curve) and without (lower curve) betacyclodextrin at pH 4·0 and 37°c

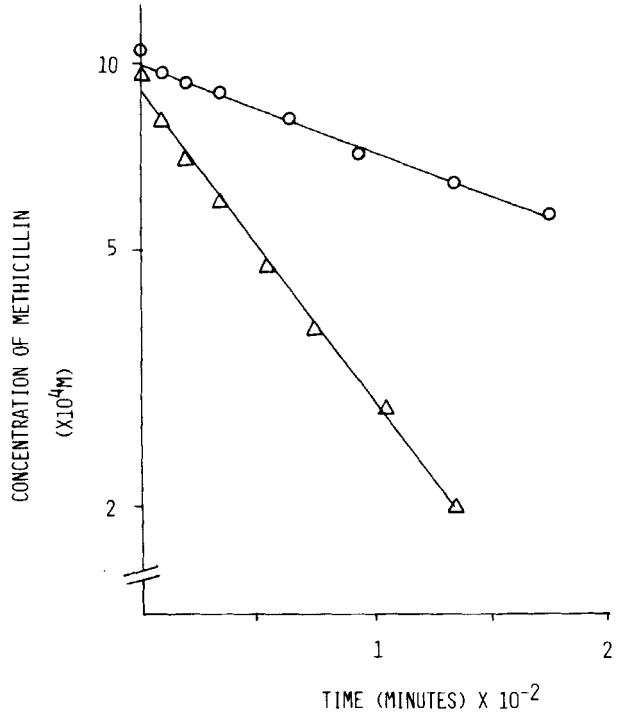

Figure 4

Hydrolysis of ampicillin with (upper curve) and without (lower curve) betacyclodextrin at pH 2·0 and 25°c

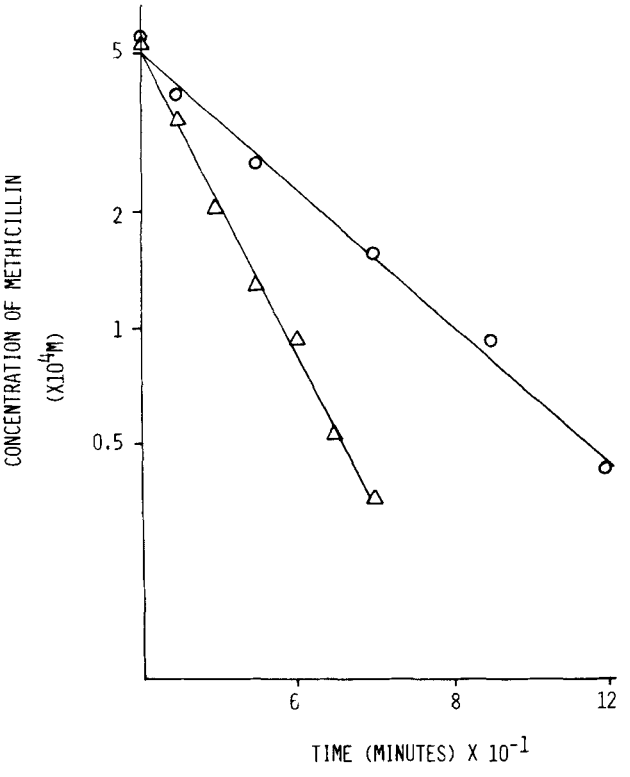

Figure 5

Hydrolysis of methicillin with (upper curve) and without (lower curve) betacyclodextrin at pH 2·0 and 37°c

RESULTS AND DISCUSSION

Fig's 1, 2, and 3 show the effect of beta-cyclodextrin on the hydrolysis of ampicillin. Fig's 4, 5, and 6 show similar data for methicillin. Data pertinent to the interaction of phenytoin with beta-cyclodextrin is shown in Fig's 7 thru 10. Tables I and II record some thermodynamic data for the interaction between phenytoin and beta-cyclodextrin.

The results reported in this preliminary paper clearly indicate that all three drugs interact quite strongly with beta-cyclo dextrins. Obviously, there is, as discussed in the Introduction,

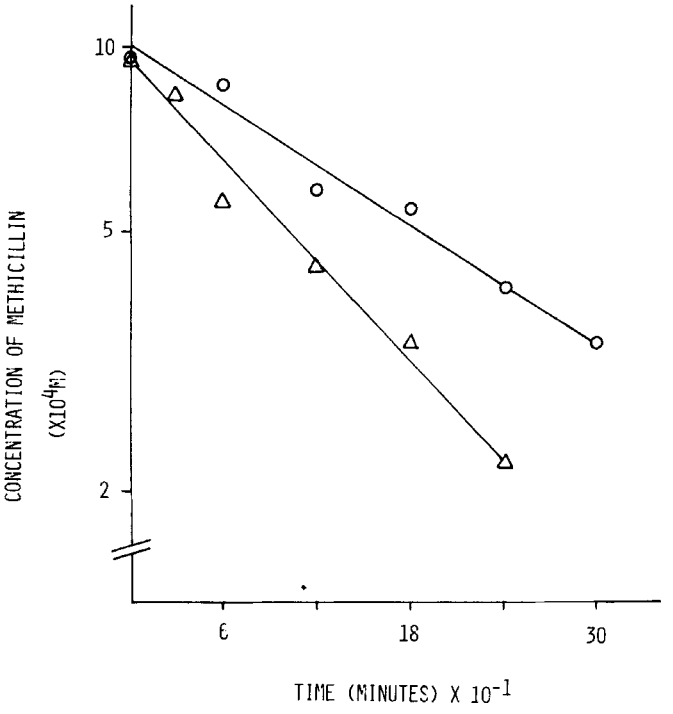

Figure 6

Hydrolysis of methicillin with (upper curve) and without (lower curve) betacyclodextrin at pH 4.0 and 37°c

TABLE I

Association constants of phenytoin-betacyclodextrin at 25°C

pH	6.0	7.0	8.0	9.0	10.0
K(M)	854	830	661	231	104

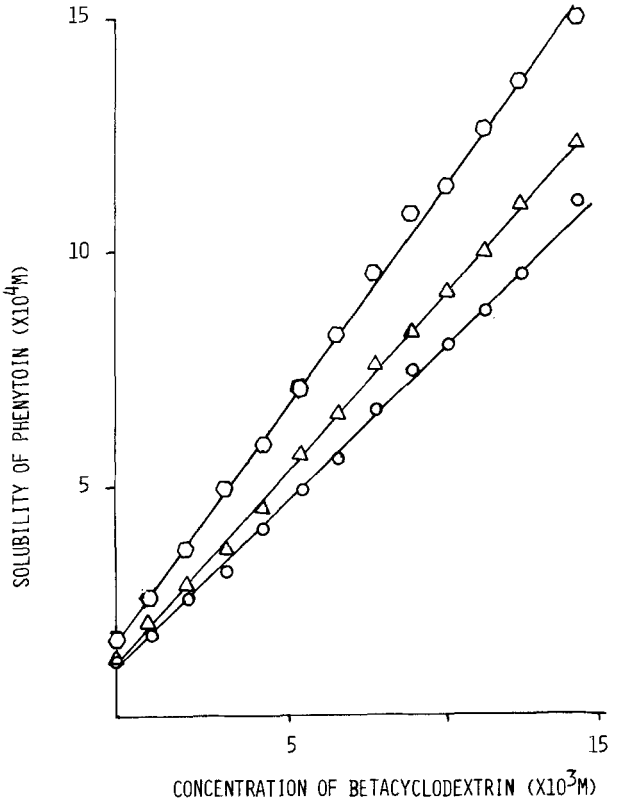

Figure 7

Solubility of phenytoin at 25°c as a function of betacyclodextrin concentration (top curve pH 8, middle curve pH 7·0, bottom curve pH 6·0)

considerable pharmaceutical potential to all three interactions. The authors are presently completing an investigation of the feasibility of preparing commercially acceptable compressed tablets, intra-muscular injections and liquid oral products containing all three drugs and beta-cyclodextrin. Results will be published shortly.

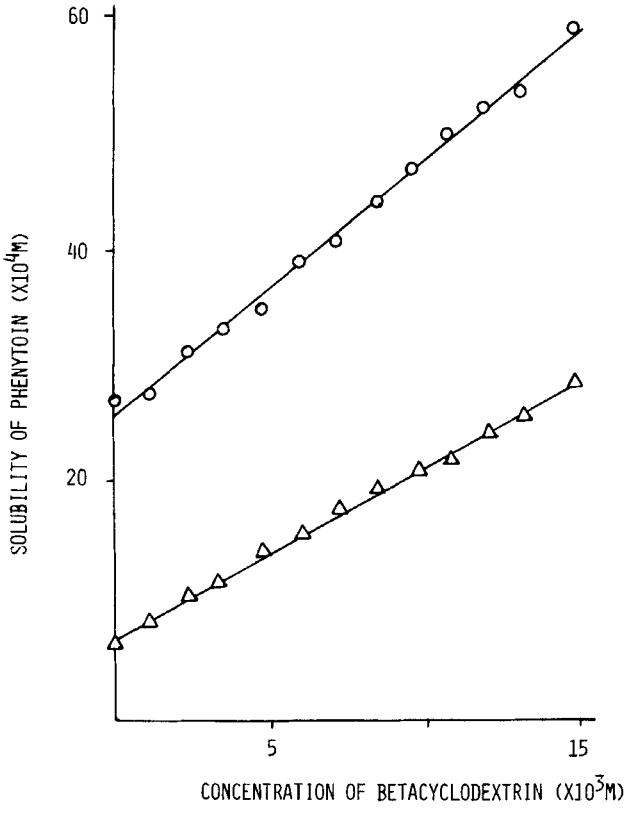

Figure 8

Solubility of phenytoin at 25°c as a function of betacyclodextrin concentration (upper curve pH 10·0, lower curve pH 9·0)

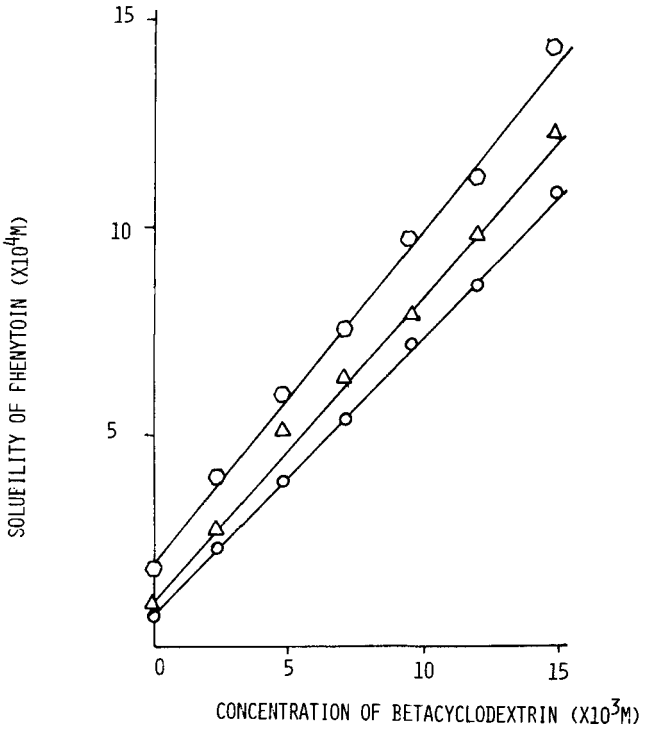

Figure 9

Solubility of phenytoin at pH 6·0 as a function of betacyclodextrin concentration (top curve 40°c, middle curve 25°c, bottom curve 10°c)

TABLE II

Association constants and free energy of phenytoin-betacyclodextrin at pH 6.0

Temp.(°C)	10.0	17.5	25.0	32.5	40.0	47.5
K(molar)	1000	936	854	719	507	453
Δ G (Kcal/mole)	-3.89	-3.95	-4.00	-3.99	-3.87	-3.90
(Kjoule/mole)	-16.3	-16.5	-16.7	-16.7	-16.1	-16.3

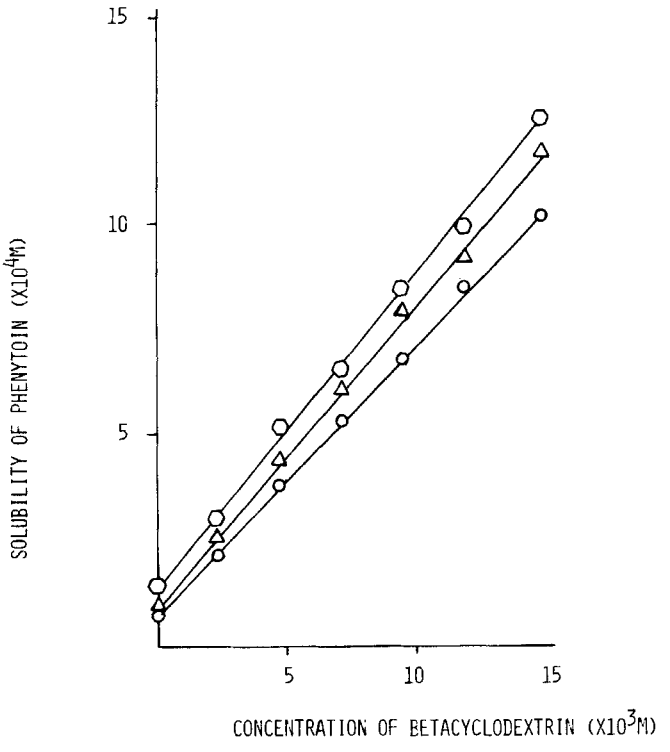

Figure 10

Solubility of phenytoin at pH 6·0 as a function of betacyclodextrin concentration (top curve 47·5°c, middle curve 32·5°c, bottom curve 17·5°c)

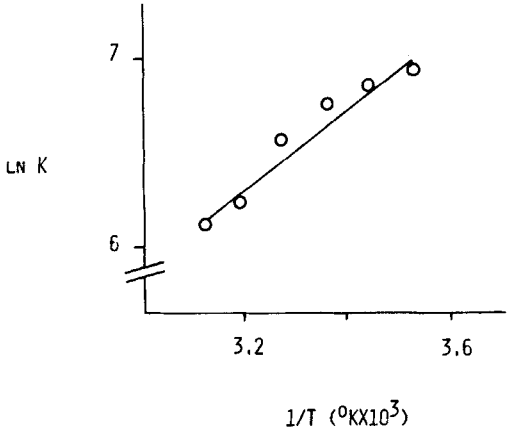

Figure 11

Van't Hoff plot for the complexation of phenytoin and betacyclodextrin

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