ENHANCED BIOAVAILABILITY OF DIGOXIN BY γ -CYCLODEXTRIN COMPLEXATION¹⁾

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Inclusion complex of digoxin with γ -cyclodextrin (γ -CyD) in 1:4 molar ratio was prepared, and its dissolution and absorption behaviors were compared with those of digoxin alone. The dissolution rate of digoxin in water was found to be markedly increased by γ -CyD complexation. Bioavailability of digoxin following the oral administration of γ -CyD complex to dogs was 5.4 times as much as that of digoxin alone. The present data did indicate the improvement of dissolution and absorption characteristics of digoxin by inclusion complexation, suggesting the decrease in dose in oral digoxin therapy.

Keywords — digoxin; γ -cyclodextrin; inclusion complex; bioavailability; dissolution rate; plasma level; oral administration to dogs

Digoxin is a widely prescribed digitalis glycoside used in the maintenance therapy of cardiac patients. However, considerable variations in oral bioavailability were noted in commercial tablets.²⁻⁴⁾ The main cause of this variability seems to be related to the unsatisfactory factors of the drug such as extremely low water solubility and chemical instability in acidic medium.⁵⁾ Cyclodextrins (CyDs) have been extensively applied to improve the physicochemical properties of various drug molecules.⁶⁻⁹⁾ In this preliminary communication, we report the development of rapidly dissolving form of digoxin by means of CyD complexation, anticipating an enhanced bioavailability.

According to the solubility study,¹⁰⁾ we have isolated a soluble complex of digoxin- γ -CyD in 1:4 molar ratio to give a molecular weight of 5960. The inclusion complex formation of digoxin with γ -CyD in solid phase was ascertained by infrared spectroscopy, X-ray diffractometry, and thermal analysis. In sharp contrast, α - and β -CyDs did not yield any solid complex, the smaller

cavity size apparently allowing little penetration of the bulky guest molecule. Then, the pure digoxin- γ -CyD complex was subjected to the following studies.

FIG. 1. *Dissolution Behaviors of Digoxin (O) and Its γ -CyD Complex (●) in Water at 25°C by Rotating Disk Method*

Each point represents the means of three determinations.

Figure 1 shows the dissolution behaviors of digoxin and its γ -CyD complex in water from the rotating disk with constant surface area.¹¹⁾ It is apparent that the complexed form of digoxin dissolved much more rapidly (about 30-fold) than digoxin itself. The improved dissolution characteristic of digoxin may be due to the increase in solubility and/or the decrease in particle size through inclusion complexation.¹²⁾ Our preliminary study also revealed that γ -CyD significantly retarded the hydrolysis of digoxin in an acidic medium. These improved physicochemical properties of the drug suggested that the complexed form of digoxin may have a good bioavailability. For the absorption studies *in vivo*, the fine powder of digoxin or its γ -CyD complex was compressed to tablets in an average weight of 50 mg to give the final digoxin content of 0.1%.*

Figure 2 shows the mean plasma levels of digoxin following the oral administrations of the tablet to dogs, where the concentration of digoxin

FIG. 2. Plasma Levels of Digoxin following the Oral Administration of Digoxin (○) and Its γ -CyD Complex (●) Tablets Containing 100 μ g Digoxin to Dogs

Each point represents the means $\pm$ S.E. of six dogs.

* $p < 0.01$ in (○) versus (●).

in plasma samples was determined by enzymeimmunoassay.¹³⁾ The maximum plasma level of 0.90 ± 0.14 mg/l was attained at 45 min after oral administration of the complex, which was about 3 times higher than that of digoxin alone. The area under plasma concentration time curve of the complex up to 24 h post-administration was found to be 5.4 times as much as that of digoxin alone.

Thus, the enhanced bioavailability of digoxin by γ -CyD complexation apparently suggests the possibility of smaller doses and fewer side effects in oral digoxin therapy. Furthermore, the 1:4 complexation of digoxin with γ -CyD results in a 7.6-fold increase in molecular weight of the drug, which should facilitate the pharmaceutical formulation of the tablets, particularly from the viewpoint of content uniformity.

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* The formulations of the tablets were as follows: 98–99% (w/w) lactose as diluent, 1.0% (w/w) magnesium stearate as a lubricant, and 0.1% (w/w) digoxin or 0.76% (w/w) digoxin- γ -CyD complex.

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