COMMUNICATION

The Bioavailability Difference Between Genuine Cyclodextrin Inclusion Complexes and Freeze-Dried or Ground Drug Cyclodextrin Samples May Be Due to Supersaturation Differences

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ABSTRACT

Better than expected oral bioavailability or biological response of genuine or true cyclodextrin inclusion complexes are often observed from in vitro dissolution rate results. On the contrary, worse biological results than expected are often the case for cyclodextrin inclusion complexes prepared by, e.g., freeze-drying or grinding. A theoretical based discussion showed that the discrepancies between in vivo and in vitro results may be caused by an incorrect interpretation of the drug supersaturation phenomena that cyclodextrin inclusion complexes can give rise to. A new interpretation of the supersaturation, taking into consideration the solubility diagram for the drug cyclodextrin system, was presented. The new interpretation may explain why genuine or true cyclodextrin inclusion complexes perform better in vivo than do, e.g., freeze-dried or ground cyclodextrin inclusion complexes.

INTRODUCTION

Cyclodextrins are oligosaccharides which have received attention in the pharmaceutical field. Cyclodextrins are able to complex lipophilic drugs, thus changing the physicochemical and biopharmaceutical properties of the drugs.

Solid cyclodextrin inclusion complexes of lipophilic drugs usually increase the oral bioavailability and the biological response of the drug (1).

The increased bioavailability and biological response of cyclodextrin inclusion complexes are considered to be caused by two mechanisms:

- Increased dissolution rate of cyclodextrin inclusion complexes compared with the dissolution rate of the pure drug
- Drug supersaturation phenomena caused by cyclodextrin inclusion complexes

Solid cyclodextrin inclusion complexes are either isolated by crystallization from an aqueous solution or manufactured by freeze-drying a drug–cyclodextrin solution or by grinding a paste of cyclodextrin and drug. When inclusion complexes are isolated by crystallization the isolated products are probably genuine or true inclusion complexes, whereas products manufactured by freeze-drying or grinding often are physical mixtures of drug and cyclodextrin. Often the drug is amorphous in the freeze-dried or ground products. The cyclodextrin part of the mixture can be amorphous, too.

According to Szejtli (2), there is a clear tendency for genuine or true inclusion complexes to show better bioavailability performance than complexes manufactured by freeze-drying or grinding. Often the difference in bioavailability is not reflected in the in vitro dissolution tests carried out to characterize the complexes (2).

The aim of the present paper is to discuss the in vitro dissolution rate test of cyclodextrin inclusion complexes and to put forward a new interpretation of the supersaturation phenomena caused by cyclodextrin inclusion complexes. The new interpretation may explain the often seen difference in the bioavailability data for genuine/true cyclodextrin inclusion complexes and complexes manufactured by other processes such as freeze-drying or grinding.

DISCUSSION

The traditional ways to carry out dissolution rate and supersaturation testing are (i) by adding a powdery form of the cyclodextrin inclusion complex, the pure drug, and a physical mixture of drug and cyclodextrin to an aqueous medium or (ii) by applying a rotating disk method. The rotating disk method ensures that the same surface area is present for the various samples. Dissolution rate curves such as the ones depicted in Fig. 1 (3) are often seen for cyclodextrin inclusion complexes, physical mixtures of cyclodextrin and drug, and the pure drug.

Usually an excessive amount of drug is added during the test, ensuring drug saturation of the dissolution medium will take place. Cyclodextrins usually increase

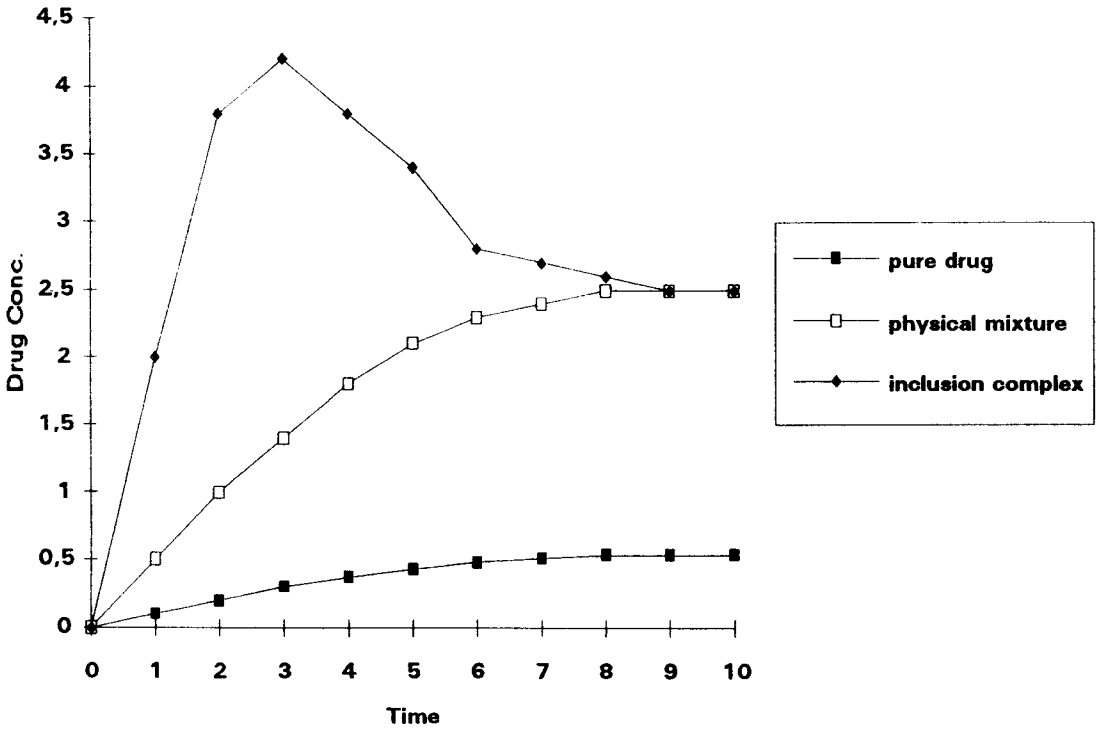

Figure 1. Dissolution rate curves.

the apparent solubility of drugs poorly soluble in water. Therefore the dissolution rate curves for the cyclodextrin inclusion complex and the physical mixture of cyclodextrin and drug end at a higher drug concentration level than does the dissolution rate curve for the pure drug.

Supersaturation of the aqueous medium normally is present within the first minutes after initiating the test (4). The dissolution rate curves are employed to disclose supersaturation phenomena (4). If the drug concentration at any moment exceeds the equilibrium solubility at the end of the dissolution rate test, a drug supersaturation was present, according to Frömming and Szejtli (4). This procedure has been used in numerous cyclodextrin studies in the last 20 years.

According to this procedure the dissolution rate curve for the cyclodextrin inclusion complex depicted in Fig. 1 indicates, that a supersaturation phenomenon was present initially; afterwards the drug concentration dropped back to the equilibrium solubility.

As mentioned above, it is often seen that genuine or true cyclodextrin inclusion complexes perform better in oral bioavailability tests than expected considering the complexes' in vitro dissolution rate and their ability to cause supersaturation. If for some reason the employed in vitro method does not disclose all supersaturation episodes, that may explain the lacking correlation between in vitro and in vivo results. Instead of measuring or disclosing cyclodextrin inclusion complex caused supersaturation phenomena by drug dissolution rate curves, Fig. 1, a better starting point may be the drug–cyclodextrin solubility diagram.

A solubility diagram of the AL type is depicted in Fig. 2 (5). Further details about solubility diagrams are provided by Higuchi and Connors (5).

The curve on the solubility diagram corresponds to pairs of cyclodextrin and drug concentrations, where the drug concentration equals the drug saturation concentration at the actual cyclodextrin concentration.

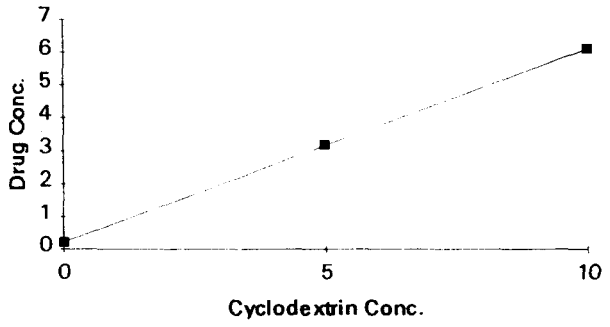

Figure 2. Solubility diagram for a drug–cyclodextrin system.

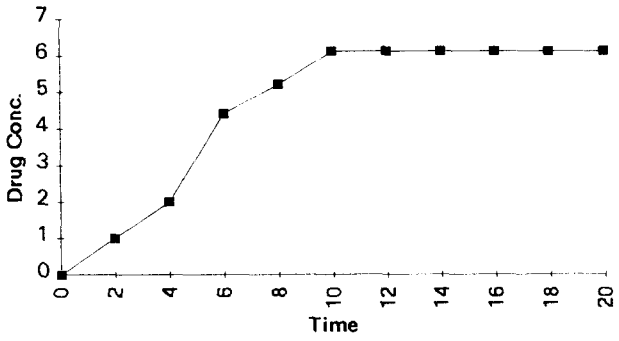

Figure 3. Superimposed drug dissolution rate curves for a genuine or true cyclodextrin inclusion complex and for a complex prepared by freeze-drying or grinding.

Theoretical dissolution rate curves for a genuine or true cyclodextrin inclusion complex and for a cyclodextrin inclusion complex manufactured by freeze-drying or grinding of a drug–cyclodextrin paste is depicted in Fig. 3. The two dissolution rate curves are superimposed. According to the traditional way to disclose cyclodextrin inclusion supersaturation phenomena, the dissolution rate curves do not indicate supersaturation, Fig. 1 and 3. Because the dissolution rate curves

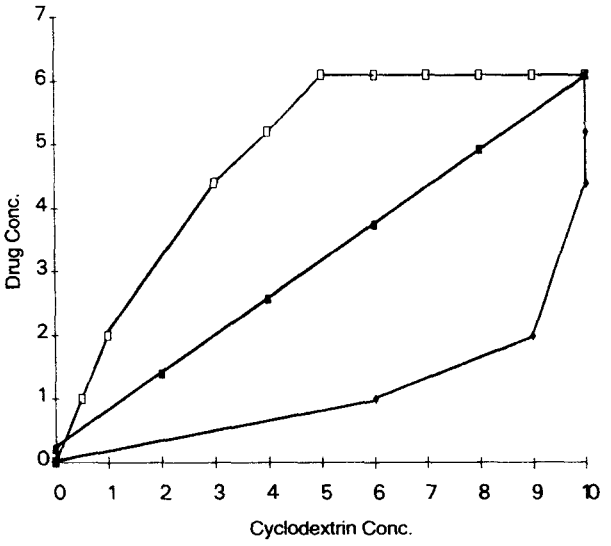

Figure 4. Solubility diagram and paired cyclodextrin–drug concentrations obtained during dissolution rate tests: ■, solubility diagram; □, genuine or true complex; ◆, freeze-dried or ground complex.

Table 1

Theoretical Dissolution Test Results for a Cyclodextrin Inclusion Complex Prepared by Freeze-Drying or Grinding (I) and for a Genuine or True Cyclodextrin Inclusion Complex (II)

Time (arbitrary units)	I		II	
	Cyclodextrin (mg/ml)	Drug (μg/ml)	Cyclodextrin (mg/ml)	Drug (μg/ml)
0	0	0	0	0
2	6.0	1.0	0.5	1.0
4	9.0	2.0	1.0	2.0
6	10.0	4.4	3.0	4.4
8	10.0	5.2	4.0	5.2
10	10.0	6.1	5.0	6.1
12	10.0	6.1	6.0	6.1
14	10.0	6.1	7.0	6.1
16	10.0	6.1	8.0	6.1
18	10.0	6.1	9.0	6.1
20	10.0	6.1	10.0	6.1

for the two cyclodextrin inclusion complexes are superimposed, a difference is not expected in their bioavailability or their biological response.

If both the drug and the cyclodextrin concentration were measured during the dissolution rate testing, the results might be as tabulated in Table 1.

The paired cyclodextrin and drug concentrations from Table 1 are depicted together with the solubility diagram for the drug–cyclodextrin system in Fig. 4. While some of the paired concentration points for the genuine or true cyclodextrin inclusion complex are placed above the solubility diagram curve, all the paired concentration points for the complex prepared by freeze-drying or grinding are situated at or below the curve.

That is, although the traditionally used dissolution rate curves, Fig. 3, did not reveal either supersaturation or any difference between the two inclusion complexes' dissolution rates, a difference regarding presence of supersaturation did exist. The genuine or true cyclodextrin inclusion complex showed supersaturation while the freeze-dried or ground product did not.

The disclosed supersaturation—which the hitherto applied method, Fig. 3, does not catch—may explain why genuine or true cyclodextrin inclusion complexes perform better in biological tests, such as oral bioavailability or biological response studies, than cyclodextrin inclusion products prepared by freeze-drying or grinding.

As shown in Table 1, the reason why the genuine or true complex in this theoretical case caused supersaturation was that the cyclodextrin part was dissolved slowly. That is, only a small concentration of drug in the solution was needed to cause supersaturation according to the solubility diagram, Fig. 4. On the contrary, the cyclodextrin dissolution rate from the freeze-dried or ground sample was high, meaning that a high drug concentration was needed to obtain a drug supersaturation phenomenon in the dissolution medium. That is, the high cyclodextrin dissolution rate prevented the occurrence of a drug supersaturation episode.

It is believed that the above-mentioned mechanism often will be operating because in the genuine or true inclusion complex the cyclodextrin will be a part of a drug–cyclodextrin crystal with a quite low water solubility, whereas in the freeze-dried or ground sample the cyclodextrin molecules often will be present either in an amorphous state or as cyclodextrin crystals. While a low cyclodextrin dissolution rate is expected for genuine or

true cyclodextrin inclusion complexes, a high cyclodextrin dissolution rate is expected for freeze-dried or ground samples, simply due to the different solid state of cyclodextrin in the two types of cyclodextrin inclusion complexes.

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