# COMPLEX FORMATION OF UNSATURATED CYCLODEXTRIN SOLUTIONS WITH VARIOUS POLYMERS

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## ABSTRACT

By using methyl orange as a competitive complexant, it was shown that solutions of poly(ethylene glycol), poly(propylene glycol) and poly(N-vinylpyrrolidone) equivalent to a concentration of 1.67 mM monomer are able to form soluble inclusion complexes with 0.20 mM solutions of α-, β- and γ-cyclodextrins. The complex formation is independent of polymer chain length. Poly(ethylene glycol) solutions complexed, on average with 40%, 45% and 75% of α-, β-, and γ-cyclodextrin, respectively. A poly(propylene glycol) solution complexed 55% α-cyclodextrin, 80% β-cyclodextrin and 90% γ-cyclodextrin. Poly(N-vinylpyrrolidone) solutions complexed on average with 90% of α-, β-, and γ-cyclodextrin.

## 1. INTRODUCTION

Insoluble inclusion complexes can be formed with saturated solutions of cyclodextrins (CD) and various synthetic polymers[1,2]. The insoluble inclusion complexes can be dissolved in water or by the addition of a stronger complexant than the polymer[1]. The polymers are selective in the formation of insoluble inclusion complexes with respect to the type of CD (α-CD, β-CD or γ-CD)[1]. Poly(ethylene glycol) (PEG) precipitates as an inclusion complex with α-CD and to a lesser extent with γ-CD[1,3]. Poly(propylene glycol) (PPG) forms insoluble inclusion complexes with β-CD and γ-CD but not with α-CD, while no insoluble inclusion complexes are formed between poly(N-vinylpyrrolidone) (PVP) and CDs[1]. By formation of insoluble inclusion complexes with PPG it is possible to purify β-CD and γ-CD[4]. Increase in the production yield of CDs by addition of PEG in enzyme synthesis reactions has been reported[5,6]. For the purpose of isolating individual types of CDs from dilute solutions, the interaction between the above mentioned polymers and unsaturated CD solutions was investigated.

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## 2. MATERIALS AND METHODS

### 2.1. Materials

PEGs with average molecular weights of 2000, 4000, 5000, 6000, 10000, 15000 and 20000 were obtained from Merck Co. PPG with an average molecular weight of 425 and PVPs with an average molecular weight of 10000, 24000 and 40000 were obtained from Fluka Co. The polymers were of technical grade. Methyl orange was obtained from Aldrich Co. CDs were purchased from Merck Co. Methyl orange and the CDs were of analytical grade.

### 2.2. Methods

2.000 g of an aqueous polymer solution equivalent to a 20 mM monomer concentration was weighed into cuvettes and 0.40 ml of a 0.3 mM methyl orange solution in 50 mM phosphate buffer (pH 6.80) containing 1.25 mM CD was added. After mixing, the absorbance was measured at 515 nm, 505 nm or 480 nm for α-CD, β-CD, γ-CD, respectively, with a lambda2 spectrometer (Perkin-Elmer Co.). Samples containing 2.000 g polymer solution and 0.40 ml of a 0.3 mM methyl orange in 50 mM phosphate buffer (pH 6.80) without CD was measured at the same wavelengths. The experiments were carried out at ambient temperature and repeated four times.

## 3. RESULTS AND DISCUSSION

### 3.1. Competitive Complexation of α-CD, β-CD, and γ-CD with Methyl Orange and Polymers

Methyl orange and CDs form inclusion complexes with 1:1 stochiometry[7]. A difference in the absorbance between the free and the complexed form of methyl orange can be found. This difference depends on the type of CD forming the inclusion complex with methyl orange. At pH 6.80, the largest difference was found at 515 nm, 505 nm and 480 nm for α-CD, β-CD, and γ-CD, respectively. Addition of a complex-forming polymer to the solution containing methyl orange and CD will change the equilibrium between methyl orange and CD. The inclusion complexes between methyl orange and CD will dissociate resulting in the release of methyl orange and a change in the absorbance of the solution. The equilibrium between methyl orange and CD will depend on the equilibrium constant and not on the amount of CD complexed by the polymer. The difference in absorbance between a solution containing methyl orange and polymer and a solution containing methyl orange, polymer and CD indicates the amount of released methyl orange due to the complexation of CD with the polymer. A standard curve was prepared by measuring the absorbance of methyl orange and CD as a function of the CD concentration. Comparing the absorbance difference of the samples with the standard curve gave the amount of CD not complexed with the polymer.

### 3.2. Soluble Inclusion Complexes

From the results in Table 1 it can be seen that all the investigated polymers formed soluble inclusion complexes with CDs. A necessary condition for complex formation to occur is the inclusion of the polymer into the CD cavity. In the case of insoluble inclusion complexes it has been reported that α-CD and γ-CD are threaded on PEG[3,8] and γ-CD can

accommodate two PEG chains[3]. Soluble inclusion complexes could be formed in a similar way. The cavity of β-CD has been regarded as too large to fit PEG since no insoluble inclusion complexes could be formed[1]. PEG can be accommodated by the CD cavity since soluble inclusion complexes could be formed between PEG and β-CD.

Insoluble inclusion complexes of α-CD with PPG have not been observed[1]. Through molecular modelling it has been shown that α-CD cannot be stringed on PPG due to steric hindrance of the methyl substituents on the polymer chain[1]. Soluble inclusion complexes can however be formed with PPG and α-CD. Binding of α-CD to the methyl substituents of the polymer could lead to a complexation without threading the polymer. PPG can be precipitated in saturated β-CD or γ-CD solutions[1]. The binding of CD has not been shown to occur by threading. Therefore it is possible that CDs could bind in more than one way to polymers with substituents which is supported by the observation that α-CD can complex with PPG.

Molecular modelling has indicated that poly(methylvinyl ether) (PMVE) is not capable of stringing α-CD or β-CD[1]. In spite of having larger substituents than PMVE, PVP was shown to form complexes with α-CD and β-CD. This could be explained by binding of the CDs to the polymers substituents as suggested above. It has not been shown that γ-CD can be stringed by PVP.

Comparing the preference of the polymers to α-CD, β-CD, and γ-CD, the highest percentage of complexation was found with γ-CD, followed by β-CD and α-CD, except for PVP that formed complexes with the CDs in equal amounts. As suggested above, inclusion complex formation is a flexible process where a large CD cavity provides a better possibility for complexing with a polymer by either threading one or more polymer chains or complexing with the substituents of the polymer.

The various polymers showed differences in their ability to form inclusion complexes with CDs. It is generally believed that the hydrophobicity of a molecule enhances the complex formation with CDs because of favourable interaction with the hydrophobic interior of the CD molecule[9]. In accordance with this, PEG, which has no hydrophobic substituents, showed the lowest ability of the investigated polymers to form complexes with CDs.

TABLE 1. Polymer complexation in 0.20 mM CD solutions

| Polymer | Complexed CD (mM) | | |
|---|---|---|---|
| | α-CD | β-CD | γ-CD |
| PEG 2000 | 0.08 ± 0.02 | 0.08 ± 0.03 | 0.13 ± 0.02 |
| PEG 4000 | 0.07 ± 0.01 | 0.09 ± 0.01 | 0.15 ± 0.01 |
| PEG 5000 | 0.06 ± 0.02 | 0.08 ± 0.02 | 0.15 ± 0.01 |
| PEG 6000 | 0.07 ± 0.01 | 0.09 ± 0.01 | 0.15 ± 0.01 |
| PEG 10000 | 0.08 ± 0.01 | 0.09 ± 0.01 | 0.15 ± 0.01 |
| PEG 15000 | 0.08 ± 0.01 | 0.09 ± 0.01 | 0.17 ± 0.02 |
| PEG 20000 | 0.08 ± 0.01 | 0.09 ± 0.01 | 0.16 ± 0.01 |
| PPG 425 | 0.11 ± 0.01 | 0.16 ± 0.01 | 0.18 ± 0.01 |
| PVP 10000 | 0.19 ± 0.01 | 0.17 ± 0.01 | 0.18 ± 0.01 |
| PVP 24000 | 0.18 ± 0.01 | 0.17 ± 0.01 | 0.18 ± 0.01 |
| PVP 40000 | 0.18 ± 0.01 | 0.16 ± 0.01 | 0.18 ± 0.01 |

Inclusion complex formation of polymers with CDs appears to be a frequently occurring event which in some cases can lead to the formation of an insoluble inclusion complex. One of the factors influencing insolubility of the complex could be the ratio between stringed CDs and the chain length of the polymer. Every stringed CD replaces a part of

the shell of ordered water molecules surrounding the polymer. At one point, most of the water shell will be displaced and the solubility will be lost. In our experiments, the polymer was present in excess so complete threading of polymer chains with CDs did not occur. CDs could therefore have interacted with the ends of the polymer chains only replacing a small fraction of their water shell resulting in the formation of soluble inclusion complexes. This could explain the observation that the various chain lengths of PEG and PVP had no effect on the complex formation.

## 4. CONCLUSION

Soluble inclusion complexes can be formed between CDs and polymers. The selectivity of the polymers for the different types of CDs in forming insoluble inclusion complexes cannot be observed in the case of soluble inclusion complexes. It is therefore not possible to separate individual types of CDs by formation of soluble inclusion complexes. The polymers have preferences with respect to the type of CD with which they are complexed. It appears that the formation of soluble inclusion complexes is independent of the molecular weight of the polymer. Polymers containing substituents (PPG and PVP) are better at forming inclusion complexes than an unsubstituted polymer (PEG).

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