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## PREPARATION AND STUDY OF CHOLESTEROL CLATHRATE COMPLEX WITH BETA-CYCLODEXTRIN

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Currently, cholesterol (vitamin D<sub>3</sub>) deficiency is recognized as a pandemic [1]. Vitamin D<sub>3</sub> is one of the most important regulators of immunity. Recent studies have clarified the role of D<sub>3</sub> in the prevention of cancer, HIV infection [2], cardiovascular diseases, liver disorders, diabetes, cell growth, immunological and respiratory disorders [1,2]. The lipophilic molecule D<sub>3</sub> has many olefin bonds, so it is easily oxidized during processing and storage of food products under the influence of oxygen and light. For this reason, there is a need to develop water-soluble encapsulated forms of D<sub>3</sub>. In the studies available in the scientific literature, the mechanisms of encapsulation of D<sub>3</sub> are not fully disclosed. Therefore, it is important to understand the nature of the inclusion of D<sub>3</sub> in the nanostructured  $\beta$ -cyclodextrin:D<sub>3</sub> ( $\beta$ -CD:D<sub>3</sub>) complex.

In this paper, we present the results of studying the encapsulation of a lipophilic oil solution  $D_3$  with  $\beta$ -CD. The preparation of supramolecular clathrate complexes of  $\beta$ -CD: $D_3$  inclusion (1:1 and 2:1) was carried out in an aqueous-alcohol (1:1) medium using microwave activation technology. The content of vitamin  $D_3$  in these clathrate complexes corresponds from 8.7 to 10.1%. The solubility of the  $\beta$ -CD: $D_3$  complex (2:1) in distilled water was  $0.20\text{mg} \pm 0.05/100 \text{ ml}$  (20-fold increase in solubility).

In order to clarify the mechanism of encapsulation, we initially performed molecular docking of  $\beta$ -CD with the  $D_3$  molecule to determine the binding energy of their inclusion complexes in the ratio 1:1 and 1:2 ( $\beta$ -CD: $D_3$ ) (Fig.1).

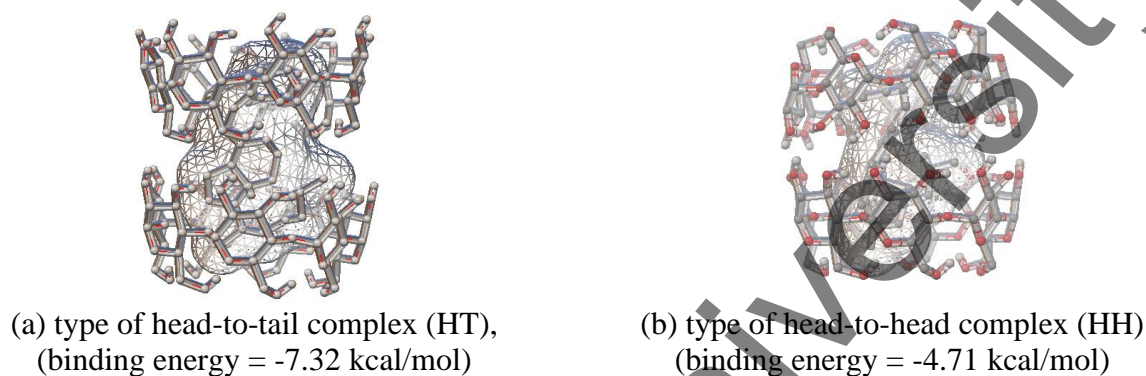


Figure 1. The two types complexes  $\beta$ -CD with  $D_3$  (2:1)

10 possible conformations of the  $D_3$  ligand with  $\beta$ -CD were considered and their binding energy was estimated. According to the calculated data, a system of 14 intramolecular hydrogen bonds between OH groups is formed in the  $\beta$ -CD molecule. At the same time, H-bonds between receptor and ligand molecules are not observed. The  $D_3$  and  $\beta$ -CD complexes were also modeled in a ratio of 1:2. We considered three types of mutual orientation between two  $\beta$ -CD molecules "head to head", head to tail and "tail to tail". It was found that the head-to-head and head-to-tail complexes demonstrate more effective binding (-4.71 and -7.32 kcal/mol, respectively) compared to the 1:1 complex (-2.7 kcal/mol).

Morphological features of the surface of vitamin  $D_3$  clathrate samples were studied using SEM. Figure 2 shows micrographs of  $\beta$ -CD, a physical mixture of  $\beta$ -CD and  $D_3$ , and a complex of inclusion of  $\beta$ -CD: $D_3$  (2:1) (U, 3 and 7 kv). The analysis of crystal morphology and shape also confirms the formation of the inclusion complex [3].

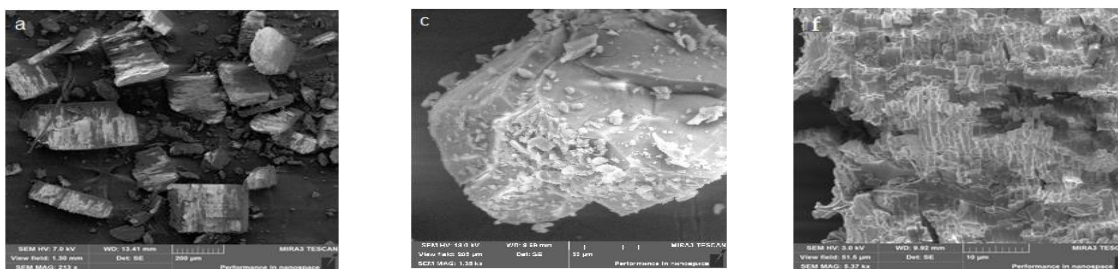


Figure 2. Scanned electronic images of  $\beta$ -CD (a), a physical mixture of  $\beta$ -CD with  $D_3$  (b) and clathrate  $\beta$ -CD: $D_3$  (2:1) (c) at various magnifications

In the IR spectra, the valence oscillations of the O-H bond are detected as a wide band with a maximum at 3398 ( $\beta$ -CD (a), 3564 ( $D_3$  (b) and 3368  $\text{cm}^{-1}$  ( $\beta$ -CD: $D_3$  (c). However, the IR spectra of the  $\beta$ -CD: $D_3$  complex lack absorption bands C=C, OH and other  $D_3$  groups. This means that these groups are masked by wide bands of  $\beta$ -CD. Analysis of the  $^1\text{H}$ - and  $^{13}\text{C}$  NMR spectra of  $\beta$ -CD: $D_3$  (2:1) clathrate has shown that all six protons of the  $\beta$ -CD complex demonstrate a pronounced chemical shift towards a strong field. The greatest difference in the values of the chemical shift  $\Delta\delta$  (ppm.) in the  $^1\text{H}$  NMR spectrum  $\beta$ -CD: $D_3$  (2:1) is characteristic of the intraspheric protons H-3 (-0.112) and H-5 (-0.108) (Table). These data indicate the formation of a clathrate (inclusive) complex [4]. Figure 3a,b shows thermograms of TG and DTG  $\beta$ -CD and  $\beta$ -CD: $D_3$  (2:1). Comparing the TG curves of  $\beta$ -CD and  $\beta$ -CD: $D_3$  clathrate, we come to the conclusion that for  $\beta$ -CD: $D_3$  in the temperature range of  $\sim 1240 \dots \sim 235^\circ\text{C}$ , there is an intense decrease in the mass of the sample ( $\sim 77.27\%$ ). This section of the TG curve corresponds to the maximum change in the rate of mass loss on the DTG curve at a temperature of  $\sim 235^\circ\text{C}$  (Fig. 3b). The loss of mass in  $\beta$ -CD: $D_3$  clathrates at lower temperatures ( $\sim 124^\circ\text{C}$ ) is associated with the removal of moisture, which is also confirmed by the data of DTG.

Table. NMR- $^1\text{H}$  and  $^{13}\text{C}$  data of  $\beta$ -CD and  $\beta$ -CD: $D_3$  complex (2:1)

Atom Number	$\beta$ -CD ( $\delta_0$ ), м.д.		$\beta$ -CD: $D_3$ ( $\delta$ ), м.д.		$\Delta\delta$ ( $\delta - \delta_0$ ), м.д.	
	$\delta$ ( $^1\text{H}$ )	$\Delta$ ( $^{13}\text{C}$ )	$\delta$ ( $^1\text{H}$ )	$\Delta$ ( $^{13}\text{C}$ )	$\delta$ ( $^1\text{H}$ )	$\Delta$ ( $^{13}\text{C}$ )
1H	4.829	102.43	4.727	102.21	-0.102	-0.22
2H	3.579	72.87	3.473	72.81	-0.106	-0.06
3H	3.516	73.54	3.404	73.39	-0.112	-0.15
4H	3.472	82.13	3.357	82.00	-0.015	-0.13
5H	3.357	72.51	3.349	72.39	-0.108	-0.12
6H	3.629	60.40	3.550	60.30	-0.079	-0.10

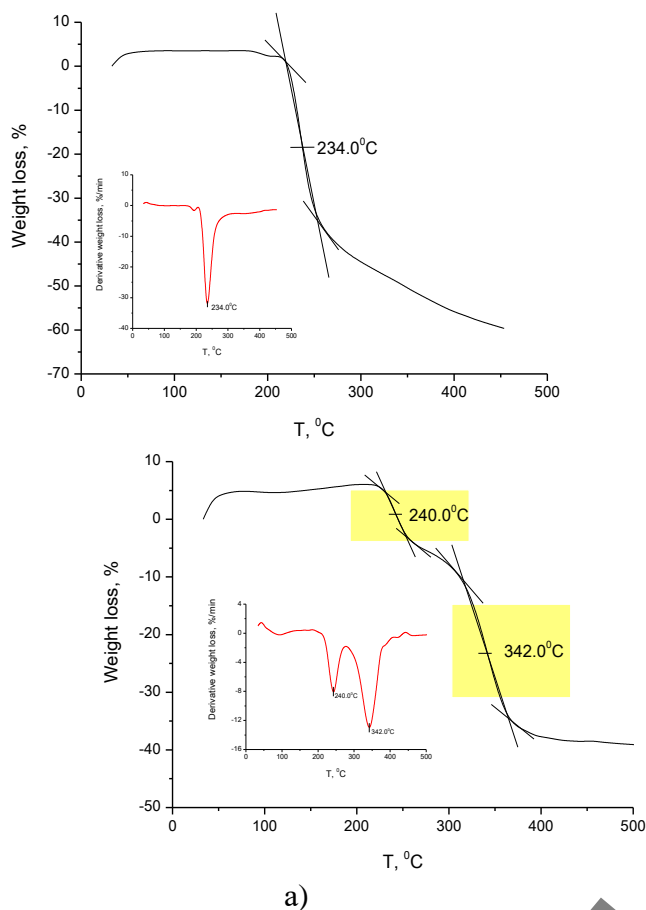


Figure 3. TG/DTG curves for  $\beta$ -CD (a) and  $\beta$ -CD:D<sub>3</sub> (2:1) (c) with a constant heating rate of 10 degrees/min

Based on the data obtained, the kinetic parameters of the thermal decomposition of  $\beta$ -CD:D<sub>3</sub> clathrate (2:1) were calculated. To compare the thermal stability, the activation energies of the decomposition reaction were determined for  $\beta$ -CD (164.58 kJ/mol) and  $\beta$ -CD:D<sub>3</sub> (103.50 kJ/mol).

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