

Thermal behaviour of a modified encapsulation agent

Heptakis-6-iodo-6-deoxy-beta-cyclodextrin

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Abstract Thermal behaviour of heptakis-6-iodo-6-deoxy-beta-cyclodextrin (HIDBCD) under inert and oxidative conditions was investigated by TG/DTG/DTA, FTIR, and using the hyphenate technique TG–FTIR. Due to the fact that thermal behaviour of HIDBCD was not studied before, we set our goal in the investigation of thermal degradation process in a dynamic air atmosphere vs. nitrogen atmosphere at a heating rate of 10 °C min⁻¹, up to 500 °C, respectively, 600 °C. It was found that the degradation process in air occurs in a single step, with a total mass loss of 99.9 %. The results of TG/DTG/DTA–FTIR indicated that the thermal behaviour of this cyclodextrin can be divided into three stages and more information was provided about the reaction sequences and the relevant products of reaction.

Keywords Modified cyclodextrin · Thermal behavior · EGA study · Encapsulation agent · Iodine

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Introduction

Beta-cyclodextrin (BCD) is considered a ‘key molecule’ in the field of supramolecular chemistry. Beyond the limit of supramolecular chemistry, cyclodextrins are nowadays used in pharmaceutical field as excipients [1] or complexation agent in order to increase solubility of poor-soluble drugs [2]. Modified BCD is used in preclinical and clinical experimental treatments for Niemann–Pick type C disease [3].

According to their toroid molecular structure and disposition of functional groups, cyclodextrins are less hydrophilic inside than outside, so they can form inclusion complexes with hydrophobic compounds enhancing their bioavailability [4]. Combined with their insignificant cytotoxicity, cyclodextrins are considered very appropriate to be used as vehicles for nano-delivery systems [5]. Recent studies have even revealed that exposing cells or model membranes to BCD results in removal of cellular cholesterol, and a molecular mechanism of cyclodextrin mediated cholesterol extraction was proposed [6].

In the domain of food and drinks, cyclodextrins are used in the stabilization of volatile or unstable compounds, as well for the decreasing or elimination of unwanted tastes and odours [7]. BCD inclusion complexes with food colourants such as carotenoids have been shown to produce an intensification of colour, increase water solubility, and improve light stability [8].

Functionalization of naturally occurring cyclodextrins is the main route in obtaining new modified encapsulation agents, which can dramatically change their binding abilities depending on the pH value of the medium [9].

Heptakis-6-iodo-6-deoxy-beta-cyclodextrin (HIDBCD) is a semi-synthetic derivative (see Fig. 1) currently used as a precursor in the synthesis of functionalised BCD that could act as inhibitors for Anthrax toxins [10]. HIDBCD is

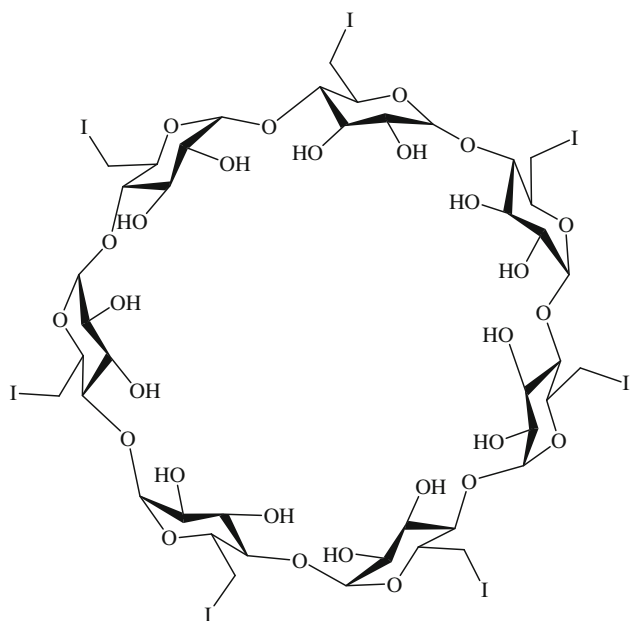


Fig. 1 Molecular structure of heptakis-6-iodo-6-deoxy-beta-cyclodextrin (HIDBCD)

now considered an important building-block in the synthesis of new modified cyclodextrins by nucleophilic substitution of iodide with different moieties [11].

Thermal analysis is among the frequently used techniques for problems solving in pharmaceutical technology areas [12, 13]. The use of thermoanalytical methods in pharmaceutical industry is necessary for the quality control and for the development of new pharmaceutical formulations [14, 15]. TG/DTA curves provide important information regarding the physico-chemical properties of active substance (stability, compatibility, kinetic analysis, and polymorphism) [16–18]. The stability of a formulation can be defined with the time in which this keeps its stability and biological activity which is different of the chemical stability of the active substance when it is alone [19]. The obtained information can be completed with the results of hyphenate techniques which became essential in modern methodologies of formulation development [20–23].

Due to the fact that thermal behaviour of HIDBCD was not studied before, we set our goal in the investigation of thermal degradation process in a dynamic air atmosphere and in nitrogen atmosphere, at a heating rate of $10\text{ }^{\circ}\text{C min}^{-1}$, up to $500\text{ }^{\circ}\text{C}$, respectively, $600\text{ }^{\circ}\text{C}$.

Experimental

The HIDBCD is a commercial product and used as received without further purification. It was obtained from Acros Organics, Geel, Belgium and has a purity of 99.6 %.

TG/DTA measurements were performed on a Perkin-Elmer DIAMOND instrument. The experiments were carried out using about 7 mg of sample which was weighted into an open aluminium crucible. The furnace temperature was programmed to rise under non-isothermal conditions from ambient temperature to $500\text{ }^{\circ}\text{C}$ linearly at a heating rate of $10\text{ }^{\circ}\text{C min}^{-1}$. The experiments were completed in an air atmosphere at a flow rate of 100 mL min^{-1} and nitrogen gas of high purity ($\geq 99.999\%$) with a flow rate of 50 mL min^{-1} .

The FTIR spectra of both pure HIDBCD and of the remaining char after heated were carried out using a Perkin Elmer SPECTRUM 100 device. The data was collected in the range of $4,000\text{--}600\text{ cm}^{-1}$ on an UATR device, with 16 acquisitions for each spectrum at a resolution of 4 cm^{-1} .

The evolved gas analysis (EGA) was carried out by a coupled TG/FTIR technique, using a Perkin Elmer SPECTRUM 100 device with an IR gas chamber connected by a transfer line to the exit of the DIAMOND furnace which is a 1-m-long stainless steel tube with an internal diameter of 2 mm. For TG–FTIR measurements, about 10 mg sample was weighted into an open aluminium crucible. In order to assure a sufficient concentration of evolved gas mixture so FTIR spectra can be recorded, a heating rate of $20\text{ }^{\circ}\text{C min}^{-1}$ was used, with a synthetic air/nitrogen flow of 100 mL min^{-1} . Nitrogen gas of high purity ($\geq 99.999\%$) was used as carried gas. The FTIR spectra have been identified based on the FTIR reference spectra available in the Sadtler Gas Vapor Library.

Results and discussion

TG/DTG/DTA curves corresponding to the thermal behaviour of HIDBCD at the heating rates $10\text{ }^{\circ}\text{C min}^{-1}$ in air atmosphere are shown in Fig. 2. The TG curve indicated that the thermal behaviour of HIDBCD was characterized by two stages with a total mass loss of almost 100 % in $25\text{--}500\text{ }^{\circ}\text{C}$ temperature range. The first peak had an endothermic nature and was assigned to the loss of water molecules from the analysed cyclodextrin. The first mass loss process ($\Delta m = 5.40\%$) which occurs in $25\text{--}204\text{ }^{\circ}\text{C}$ temperature range can be associated with the release of six molecules of water from cyclodextrin ($\text{DTA}_{\text{peak}} = 99\text{ }^{\circ}\text{C}$).

Above $99\text{ }^{\circ}\text{C}$, DTA curve exhibits three processes with the peak temperatures 217.1 , 222.7 , and $334.2\text{ }^{\circ}\text{C}$, respectively. The first peak ($217.1\text{ }^{\circ}\text{C}$) corresponds to an endothermic event, namely, the phase transition (melting) of the anhydrous cyclodextrin. The second and third events present exothermic peaks and correspond to the degradation process of the polysaccharide structure (see Fig. 2a).

The analysis of TG/DTG/DTA curves obtained in nitrogen atmosphere reveals a similar thermal behaviour in solid state for HIDBCD, namely in the temperature range

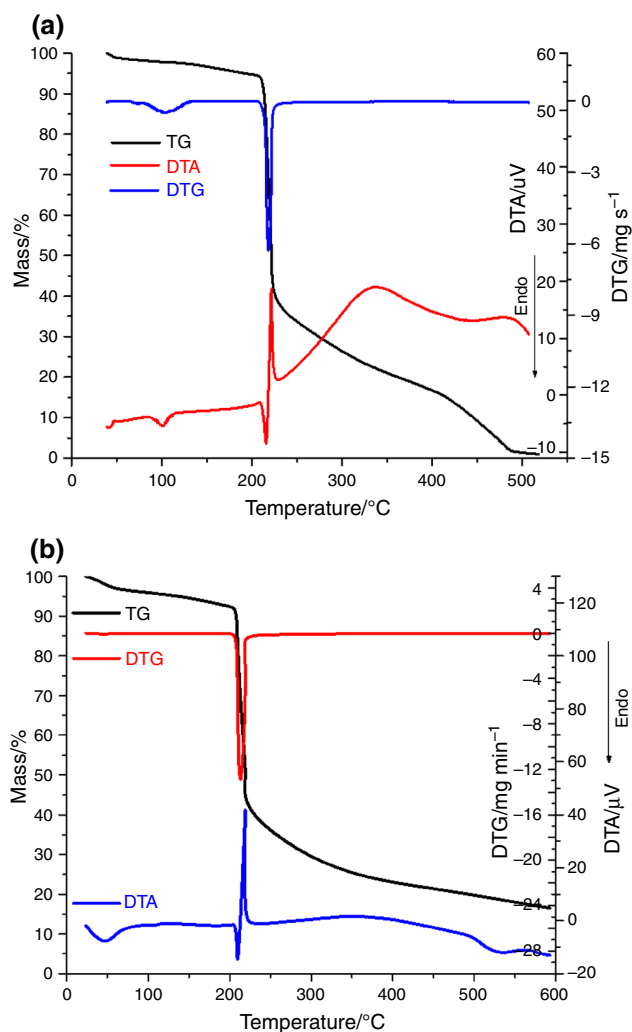


Fig. 2 The TG, DTG, and DTA curves of HIDBCD in **a** air atmosphere; **b** nitrogen atmosphere

25–204 °C, six molecules of water from cyclodextrin are released, but at a considerable lower temperature ($DTA_{\text{peak}} = 46$ °C). This similar behaviour was expected, due to the fact that formation of anhydrous cyclodextrin is not influenced by the nature of the surrounding gas (air or nitrogen). The degradation of HIDBCD in nitrogen is similar with the one that occurs in air atmosphere, but only up to 230 °C. DTA curve exhibits two processes with the peak temperatures 210 and 219.5 °C, respectively. The peak at 210 °C corresponds to an endothermic event, namely, the melting of the anhydrous cyclodextrin. The peak at 219.5 °C presents an exothermic effect and corresponds to the degradation process of the HIDBCD (see Fig. 2b).

At temperature higher than 230 °C, thermal behaviour of HIDBCD is different in air atmosphere vs. nitrogen atmosphere. Due to the fact that in nitrogen atmosphere,

thermo-oxidations cannot occur, the mass loss process has a slower tendency. Total mass loss in this case is 82 % at 600 °C, which is considerable lower than the one obtained in air atmosphere at 500 °C. The difference can be explained by the fact that degradation of HIDBCD up to 230 °C does not require the presence of oxygen and can be associated with the molecular structure of the cyclodextrin. After internal degradation of HIDBCD, the lack of oxidative medium from nitrogen atmosphere restrains the advanced degradation of cyclodextrin skeleton and obstructs the formation of CO_2 (see Fig. 2).

The EGA was carried out at a heating rate $\beta = 20$ °C min^{-1} in both nitrogen and air atmosphere. The temperature of the EGA-FTIR device and transfer line is similar with the one inside the furnace.

Gram–Schmidt profiles for the case in which the nitrogen was used as carrier gas (Fig. 3a) indicated that the gaseous products began to evolve at ≈ 230 °C and reached their maximum releasing rate at 248 °C ($t \approx 10$ min) which coincided with the DTG_{peak} (244 °C). At this point, the EGA spectrum was recorded for the analysed cyclodextrin.

The FTIR spectra of the evolved gas from degradation of HIDBCD drawn up in air/nitrogen atmosphere were compared (Fig. 4a, b).

Similarity of the EGA spectra recorded in nitrogen at different temperature values is observed throughout the analysed process; the wavenumbers are identical and they characterize the existence of the same compounds which result from total breakdown of the initial cyclodextrin.

The main difference consists in the fact that in air atmosphere, the mechanism of decomposition is different than the one in nitrogen, fact sustained by the differences of the absorption bands which appear in the spectra: in the case of air thermo-oxidation, the presence of a sharp and strong band at $\nu = 2,293$ cm^{-1} , characteristic for the asymmetrical stretching vibration of CO_2 molecules and at $\nu = 800$ cm^{-1} , characteristic for the bending suggest its formation by the destruction of the hydrocarbonated chain. These products identified in the EGA spectra are in accordance with the molecular skeleton of HIDBCD and demonstrate a significant destruction of the structure.

Regarding the degradation in inert atmosphere, it can be noticed that the formation of CO_2 molecules does not occur. Another important bands that can be identified are the ones corresponding to CH_3I (2,955 cm^{-1} , intense and 2,984 cm^{-1} , intense), as well the ones corresponding to degradation products of 6-deoxy-D-glucose: $\nu_{(\text{O}-\text{H})}$ bands are observed in the 3,500–3,200 cm^{-1} spectral region. Further, the resolution of this band is poor due to the overlap of $\nu_{(\text{O}-\text{H})}$ of water molecule. The vibrational frequencies of the ring for the bending modes of $\delta_{(\text{OCH}, \text{CH}_2 \text{ and } \text{CCH})}$ are observed at 1,460–1,340 cm^{-1} .

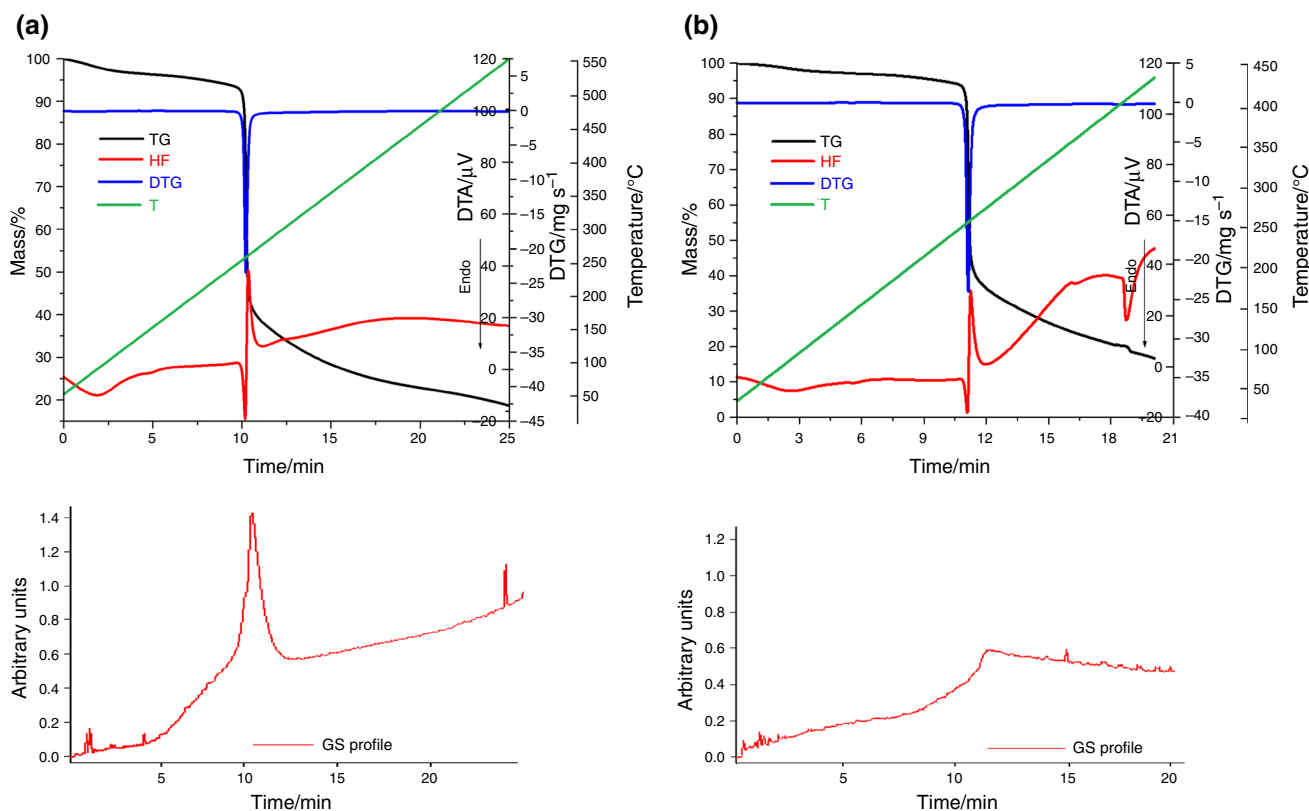


Fig. 3 Gram–Schmidt profile and thermoanalytical curves for HIDBCD ($\beta = 20\text{ }^{\circ}\text{C min}^{-1}$); **a** nitrogen atmosphere; **b** air atmosphere

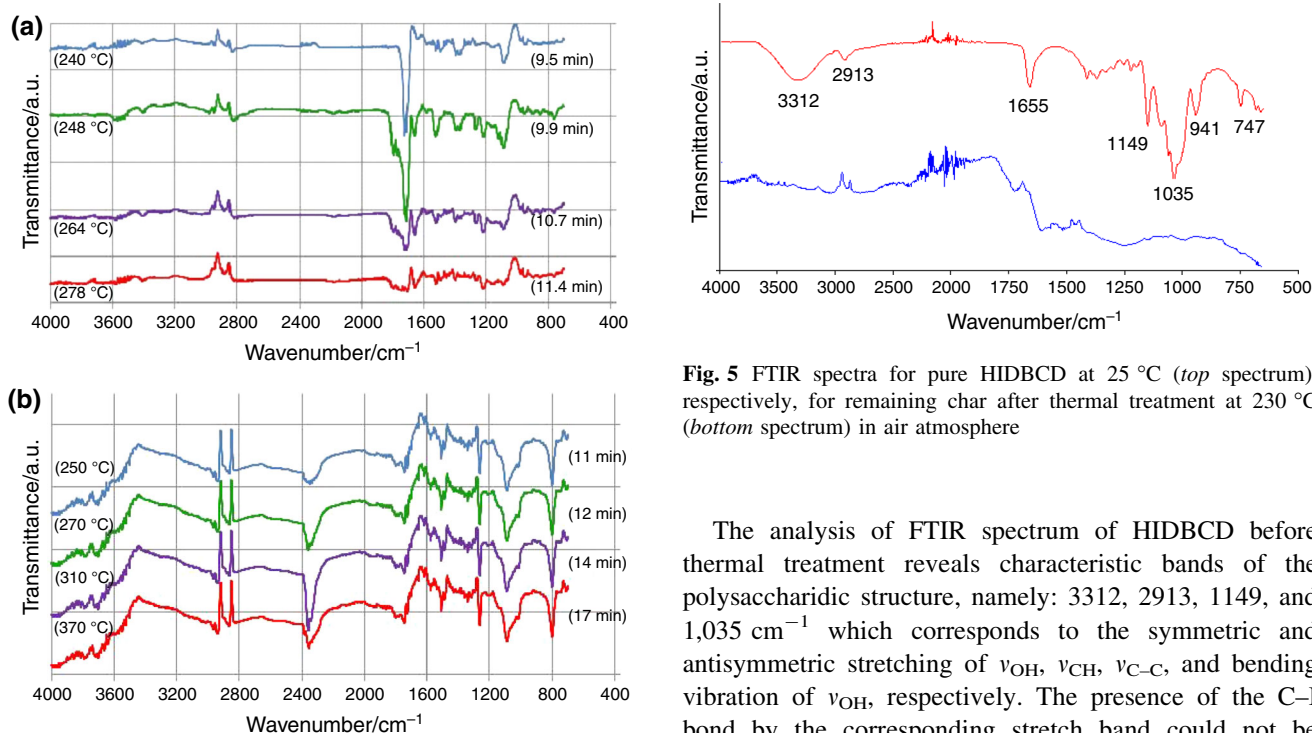


Fig. 4 FTIR spectra of gaseous mixtures observed for HIDBCD in nitrogen (**a**) and air (**b**) measured by the online TG–FTIR system (initial sample mass: 6.879 mg, heating rate: $20\text{ }^{\circ}\text{C min}^{-1}$)

Fig. 5 FTIR spectra for pure HIDBCD at $25\text{ }^{\circ}\text{C}$ (top spectrum), respectively, for remaining char after thermal treatment at $230\text{ }^{\circ}\text{C}$ (bottom spectrum) in air atmosphere

The analysis of FTIR spectrum of HIDBCD before thermal treatment reveals characteristic bands of the polysaccharidic structure, namely: 3312, 2913, 1149, and $1,035\text{ cm}^{-1}$ which corresponds to the symmetric and antisymmetric stretching of ν_{OH} , ν_{CH} , $\nu_{\text{C-C}}$, and bending vibration of ν_{OH} , respectively. The presence of the C–I bond by the corresponding stretch band could not be revealed by FTIR spectra, due to the fact that occurs at wavenumbers between 200 and 500 cm^{-1} [24]. Even if the supplier does not mention the presence of water molecules

in the cyclodextrin cavity, the FTIR spectra, corroborated with thermal analysis, reveal its presence in the molecular structure with the characteristic bending for H–O–H at $1,655\text{ cm}^{-1}$ [25] (see Fig. 5).

By the analysis of the FTIR spectra of the cyclodextrin after heating at $230\text{ }^{\circ}\text{C}$, it can be observed that the characteristic vibrational bands disappear, suggesting an advanced destruction of the polysaccharide moieties. The lack of bands obtained for this char suggests that it mainly consist in carbon residues, which decompose with the increasing of temperature, so at $500\text{ }^{\circ}\text{C}$, no remaining char is observed. Corroborating these data with the ones obtained by EGA technique, it is clearly that in the $230\text{--}500\text{ }^{\circ}\text{C}$ temperature range, carbon residues suffer oxidation to CO_2 in air atmosphere (see Fig. 4b).

Conclusions

A comparative thermal behaviour of HIDBCD in both air and nitrogen atmosphere was realized. It was proved by FTIR spectroscopy and thermal analysis that commercial HIDBCD contains up to six molecules of water which are released under heating with the formation of anhydrous cyclodextrin. The degradation of HIDBCD in inert atmosphere is similar with the one that occurs in air atmosphere, but only up to $230\text{ }^{\circ}\text{C}$. Due to the fact that the inert atmosphere prevents thermo-oxidations, the mass loss process is considerably slower.

Even if in nitrogen atmosphere the thermal behaviour was studied up to $600\text{ }^{\circ}\text{C}$, a complete degradation of molecular skeleton was not achieved; while in air atmosphere, a mass loss of 99.9 % was reached at $500\text{ }^{\circ}\text{C}$. All the data obtained from thermal curves were corroborated with the ones obtained by FTIR spectroscopy and the ones from TG–FTIR-hyphenated technique.

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References

1. Wesolowski, M., Rojek, B.: Thermogravimetric detection of incompatibilities between atenolol and excipients using multivariate techniques. *J Therm Anal Calorim.* 2013. doi: [10.1007/s10973-013-3070-y](https://doi.org/10.1007/s10973-013-3070-y).
2. Ambrus R, Aigner Z, Catenacci L, Bettinetti G, Szabó-Révész P, Sorrenti M. Physico-chemical characterization and dissolution properties of niflumonic acid–cyclodextrin–PVP ternary systems. *J Therm Anal Calorim.* 2011;104:291–7.
3. Liu B, Turley SD, Burns DK, Miller AM, Repa JJ, Dietschy JM. Reversal of defective lysosomal transport in NPC disease ameliorates liver dysfunction and neurodegeneration in the npc1^{−/−} mouse. *Proc Natl Acad Sci USA.* 2009;106:2377–82.

4. Becket G, Schep LJ, Tan MY. Improvement of the in vitro dissolution of praziquantel by complexation with α -, β - and γ -cyclodextrins. *Int J Pharm.* 1999;179(1):65–71.
5. Valle ED. Cyclodextrins and their uses: a review. *Process Biochem.* 2004;39:1033–46.
6. López CA, de Vries AH, Marrink SJ. Molecular mechanism of cyclodextrin mediated cholesterol extraction. *PLoS Comput Biol.* 2011;7(3):e1002020.
7. Menezes, P.P., Serafini, M.R., Quintans-Junior, L.J., Silva, G.F., Oliveira, J.F., Carvalho, F.M.S., Souza, J.C.C., Matos, J.R., Alves, P.B., Matos, I.L., Hădăruță, D.I., Araujo, A.A.S.: Inclusion complex of (–)-linalool and beta-cyclodextrin. *J Therm Anal Calorim.* 2013. doi: [10.1007/s10973-013-3367-x](https://doi.org/10.1007/s10973-013-3367-x).
8. De Oliveira VE, Almeida EWC, Castro HV, Edwards HGM, Dos Santos HF, De Oliveira LFC. Carotenoids and β -cyclodextrin inclusion complexes: Raman spectroscopy and theoretical investigation. *J Phys Chem A.* 2011;115(30):8511–9.
9. Meo PL, D’Anna F, Gruttadauria M, RIELA S, Noto R. Synthesis and characterization of new polyamino-cyclodextrin materials. *Carbohydr Res.* 2012;347(1):32–9.
10. Moayeri M, Robinson TM, Leppla SH, Karginov VA. In vivo efficacy of β -cyclodextrin derivatives against anthrax lethal toxin. *Antimicrob Agents Chemother.* 2008;52(6):2239–41.
11. André S, Kaltner H, Furuike T, Nishimura S, Gabius HJ. Per-substituted cyclodextrin-based glycoclusters as inhibitors of protein–carbohydrate recognition using purified plant and mammalian lectins and wild-type and lectin-gene-transfected tumor cells as targets. *Bioconjug Chem.* 2004;15(1):87–98.
12. Fulias A, Vlase T, Vlase G, Doca N. Thermal behaviour of cephalixin in different mixtures. *J Therm Anal Cal.* 2010;99: 987–92.
13. Anghel M, Vlase G, Bilanin M, Vlase T, Albu P, Fulias A, Tolan I, Doca N. Comparative study on the thermal behavior of two similar triterpenes from birch. *J Therm Anal Calorim.* 2013;113(3): 1379–85.
14. Fulias A, Ledeti I, Vlase G, Vlase T. Physico-chemical solid-state characterization of pharmaceutical pyrazolones: an unexpected thermal behaviour. *J Pharm Biomed Anal.* 2013;81–82:44–9.
15. Fulias A, Vlase G, Grigorie C, Ledeti I, Albu P, Bilanin M, Vlase T. Thermal behaviour studies of procaine and benzocaine. *J Therm Anal Calorim.* 2013;113(1):265–71.
16. Fulias A, Ledeti I, Vlase G, Popoiu C, Hegheș A, Bilanin M, Vlase T, Gheorgheosu D, Craina M, Ardelean S, Ferechide D, Mărginean O, Moș L. Thermal behaviour of procaine and benzocaine Part II: compatibility study with some pharmaceutical excipients used in solid dosage forms. *Chem Cent J.* 2013;7:140.
17. Ledeti I, Simu G, Vlase G, Săvoiu G, Vlase T, Șuta L-M, Popoiu C, Fulias A. Synthesis and solid-state characterization of Zn(II) metal complex with acetaminophen. *Rev Chim Bucharest.* 2013;64(10):1127–30.
18. Fulias A, Vlase G, Vlase T, Soica C, Hegheș A, Craina M, Ledeti I. Comparative kinetic analysis on thermal degradation of some cephalosporins using TG and DSC data. *Chem Cent J.* 2013;7:70.
19. Fulias A, Bobric A, Vlase G, Vlase T, Doca N. Thermal stability and biological interactions of some cephalosporins. *Rev Roum Chim.* 2011;56(10–11):959–66.
20. Ledeti I, Fulias A, Vlase G, Vlase T, Bercean V, Doca N. Thermal behaviour and kinetic study of some triazoles as potential anti-inflammatory agents. *J Therm Anal Calorim.* 2013. doi: [10.1007/s10973-013-3123-2](https://doi.org/10.1007/s10973-013-3123-2).
21. Vlase T, Vlase G, Doca N, Iliu G, Fulias A. Coupled thermogravimetric-IR techniques and kinetic analysis by non-isothermal decomposition of Cd^{2+} and Co^{2+} vinyl-phosphonates. *J Therm Anal Calorim* 2009;97:467–72.

22. Fuliş A, Popoiu C, Vlase G, Vlase T, Onetiu D, Săvoiu G, Simu G, Pătruţescu C, Iliă G, Ledeti I. Thermoanalytical and spectroscopic study on methotrexate: active substance and tablet. *Dig J Nanomater Bios.* 2014;9(1):93–8.
23. Ledeti IV, Bercean VN, Badea V, Bălan M, Csunderlik C. New heterocyclic tioether derived from 3-substituted-4H-4-amino-5-mercapto-1,2,4-triazole and succinic acid. *Rev Chim Bucharest.* 2010;61(11):1028–30.
24. Stuart BH. *IR spectroscopy: fundamentals and applications—analytical techniques in the sciences.* New York: Wiley; 2004.
25. George SJ, Vasudevan DT. Studies on the preparation, characterization, and solubility of 2-HP- β -cyclodextrin–meclizine HCl inclusion complexes. *J Young Pharm.* 2012;4(4): 220–7.