Review Article

A LITERATURE REVIEW OF CYCLODEXTRIN INCLUSION COMPLEXES CHARACTERIZATION - PART III: DIFFERENTIAL SCANNING CALORIMETRY AND THERMOGRAVIMETRY

Andrea Ikeda Takahashi[1*], Francisco José Baptista Veiga[2], Humberto Gomes Ferraz[1]
[1]Department of Pharmacy, Faculty of Pharmaceutical Sciences, University of São Paulo, São Paulo, Brazil.
[2]Laboratory of Pharmaceutical Technology, University of Coimbra, Coimbra, Portugal.
*Corresponding author's E-mail: aitakahashi@usp.br

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ABSTRACT

Several analytical techniques are required to the characterization of cyclodextrins inclusion complexes. In previous reviews - part I and part II, the analytical tools phase solubility diagram, dissolution, scanning electron microscopy, X-ray diffraction, infrared spectroscopy and nuclear magnetic resonance were described. The aim of this review is to detail the thermo analytical techniques differential scanning calorimetry and thermogravimetry which complement the characterization of cyclodextrins complexes.

Keywords: Cyclodextrin, Differential scanning calorimetry, Thermogravimetry.

This article is continues part of "literature review of cyclodextrins inclusion complexes characterization – part I and part II" {Article 001 and 2, 12(1)}.

THERMAL ANALYSIS

The most commonly employed thermo analytical techniques for assessing the formation of CD inclusion complexes are differential scanning calorimetry and thermogravimetry. These techniques are usually the first to be considered when evaluating complex formations, because they are relatively simple and not time-consuming[1].

Differential Scanning Calorimetry

CD curves obtained from differential scanning calorimetry (DSC) present endothermic events that correspond to dehydration. Thus, αCD has two or three events, depending on the crystalline form, and βCD and γCD have a broad peak around 120 and 150°C, respectively[2].

Complex formation analysis can be made by comparing the DSC curve of the complex with the CD used, the guest molecule and the physical mixture (CD plus guest molecule), prepared in the same proportion as the complex. The guest molecule is in crystalline form and its curve is represented by a well-defined narrow peak, corresponding to the melting point. The curve of the physical mixture is the sum of CD dehydration and the melting peak of guest molecule. When formation of the complex occurs, the melting peak is expected to disappear, shift or broaden due to the loss of the crystalline structure caused by encapsulament (Figure 1).

When partial complexation occurs, the melting peak of the complex is expected to decrease, compared to the physical mixture, suggesting an interaction of the drug with the CD. However, the presence of the melting peak suggests that there is still a free guest molecule in the sample[3].

In some cases the physical mixture does not present the characteristic melting event of the guest molecule, because the heating of CD water can cause amorphization of the guest molecule[4]. In another situation, the peak may appear broader and shifted due to weak interactions between the guest molecule and CD[5].

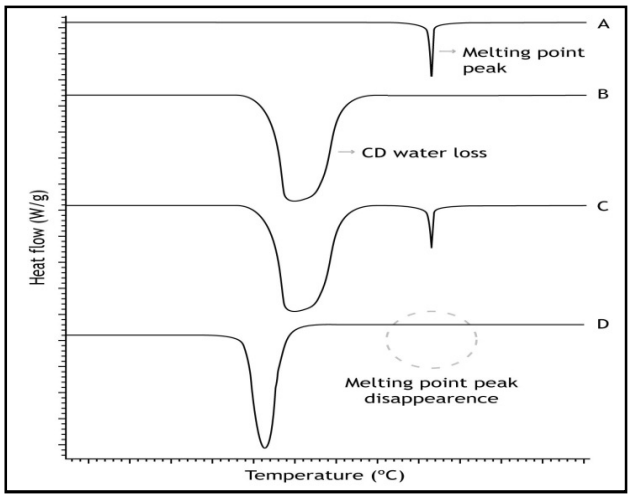

Figure 1: Hypothetical model of a DSC analysis for pure drug (A), CD (B), physical mixture (C) and complex (D).

The dehydration event of CD in the DSC curve of the complex can shift when water molecules are replaced in the cavity by guest molecules, resulting in a change in the energy state[5].

Table 1 presents some studies using DSC as a technique for the characterization of complexes.

Thermogravimetry

Natural CDs, when analyzed by thermogravimetry (TG) in a nitrogen atmosphere, show an initial weight loss due to water evaporation (adsorbed and of crystallization), and a second one from the degradation that occurs between 250 and 400°C, where they lose 70 to 80% of their weight[49].

Table 1: Some examples of recent studies that use DSC in the characterization of inclusion complexes.

Guest molecule	CD	Evidence of complexation	Reference
Aceclofenac	HPβCD	Disappearance of melting peak	6
Acyclovir	βCD	Disappearance of melting peak	7
Ascorbic acid	HPβCD	Disappearance of melting peak	8
Atenolol	RMβCD	Disappearance of melting peak	9
Benzocaine	βCD	Disappearance or reduction of melting peak	3
Benzophenone-3	HPβCD	Reduction of melting peak	10
Berberine chloride	βCD	Shift of melting peak	11
Bupivacaine hydrochloride	βCD and EPI-βCD[b]	Disappearance of dehydration peak	12
Candesartan cilexetil	βCD	Disappearance of melting peak	13
Carvedilol	MβCD	Shift of melting peak	14
Celecoxib	HPβCD	Disappearance or reduction of melting peak	15
Celecoxib	βCD	Reduction of melting peak	16
Cladribine	HPβCD	Disappearance of melting peak	17
Dipyridamole	βCD	Disappearance of melting peak	18
Efavirenz	βCD, HPβCD and RMβCD	Disappearance of melting peak	19
Etodolac	βCD, HPβCD and γCD	Disappearance of melting peak	20
Fexofenadine	αCD, βCD, γCD, HPβCD	Disappearance of melting peak	21
Finasteride	HPβCD	Disappearance of melting peak	22
Flurbiprofen	HPβCD	Disappearence of melting peak	23
Glyburide	βCD and HPβCD	Disappearance or reduction of melting peak	24
Granisetron	HPβCD	Disappearance of melting peak	25
Irbesartan	βCD	Broadening of the mealting peak	26
Itraconazole	HPβCD	Disappearance or reduction of melting peak	27
Itraconazole, econazole and fluconazole	βCD	Disappearance or reduction of melting peak	28
Loratadine	αCD, βCD, HPβCD and γCD	Disappearance of melting peak	29
Loratadine	Heptakis -DMβCD	Disappearance of melting peak	30
Loratadine	Heptakis -DMβCD	Disappearance of melting peak	31
Lorazepam	HPβCD	Disappearance of melting peak	32
Meloxicam	βCD	Disappearance of melting peak	33
Miconazole	βCD	Disappearance of melting peak	34
Naproxen	HPβCD	Disappearance or reduction of melting peak	35
Oridonin	HPβCD	Disappearance of melting peak	36
Oxaprozin	βCD, DMβCD and RMβCD	Disappearance or reduction of melting peak	37
Paclitaxel	6-O-CAPRO-β-CD[a]	Disappearance of melting peak	38
Piroxicam	HPβCD	Disappearance or reduction of melting peak	39,40
Prednisone	αCD, βCD, HPβCD and γCD	Disappearance of melting peak	41
Pyrimethamine	αCD	Disappearance of melting peak	42
Sildenafil	αCD, βCD, γCD, HPβCD	Reduction of melting peak	43
Sinvastatin	HPβCD	Reduction and disappearance of melting peak	44
Spironolactone	HPβCD	Disappearance of melting peak	45
Triclosan	βCD and EPI-βBCD[b]	Disappearance of melting peak	46
Zaleplon	βCD	Shift and reduction of melting peak	47
Zerumbone	HPβCD	Disappearance of melting peak	48

[a]6-O-CAPRO-β-CD: Amphiphilic derivative of β-CD; [b]EPI-βCD: Epichlorohydrin β-CD

Table 2: Some examples of recent studies that use TG in the characterization of inclusion complexes

Guest molecule	CD	Evidence of complexation	Reference
Astaxanthin	HPβCD	Higher degradation temperature	52
Benzophenone-3	HPβCD	Higher degradation temperature	10
Citronellol and citrnillyl acetate	αCD, βCD and γCD	Higher degradation temperature	1
Cladribine	HPβCD	Higher degradation temperature	17
Flavonols	βCD	Higher degradation temperature	53
Glimepiride	βCD, HPβCD e SBEβCD	Decrease of water loss	51
Lippiagracilis essential oil	HPβCD	Higher degradation temperature	54
Polypropylene glycol	βCD	Decrease of water loss and higher residual mass values	55
Pyrimethamine	HPβCD	Higher degradation temperature	50

Table 3: Comparative table of the methods used in the characterization of inclusion complexes

Method	Evidence of complexation	Advantages	Disadvantages
Phase solubility diagram	- Kc and CE value	- Enables prediction of the stoichiometry drug: CD. - Provides quantitative data about the complex formation	
DSC	- Disappearance or reduction of melting peak	- Simple execution - Rapid analysis	- Gives only qualitative, not quantitative, regarding the formation of inclusion complexes
TG	- Higher degradation temperature - Decrease of water loss	- Simple execution - Rapid analysis	- Gives only qualitative, not quantitative, regarding the formation of inclusion complexes
XRD	- Peaks reduction or disappearance - RDC calculation - Formation of new solid phase	- Provides information on the structure of complex	- When the process results in an amorphous materialsubstance, the technique cannot be used
IR	- Disappearance and displacement of the bands	- Provides information on the structure of complex	- The guest molecule needs to have a very characteristic band
NMR	- Signal change of H3, H5 and H6 in HRMN	- Provides information on the structure of complex	- Gives only qualitative, not quantitative, regarding the formation of inclusion complexes
Dissolution	- Comparison of percentage dissolved or efficiency of dissolution	- *In vitro* testing can predict the behavior of the drug *in vivo*	- Gives only qualitative, not quantitative, regarding the formation of inclusion complexes
Scanning electron microscopy	- Loss of original shape - Formation of a single phase	- Simple execution	- Gives only qualitative, not quantitative, regarding the formation of inclusion complexes

The most common way to detect the formation of inclusion complexes using TG is to compare the temperature at the beginning (on set) of the degradation with that of the complex (Figure 2). It is assumed that if complexation occurs, the degradation of the guest molecule takes place at higher temperatures, because the drug is protected by CD[50].

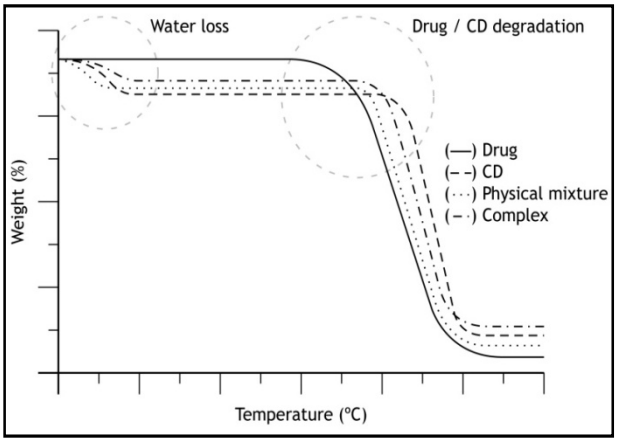

Figure 2: Hypothetical model for TG analysis of complexation of a drug with CD.

The percentage of weight loss in the complex compared to the physical mixture is also indicative of complex (drug-CD) formation (Figure 2). The loss of weight in question is the evaporation of water from the CD cavity, which occurs at temperatures of up to 150°C. Furthermore, when there is a decrease in water loss compared to the physical mixture, it is concluded that the guest molecule is taking the place of water in the cavity and that the formation of inclusion complexes has ocurred. However, when inclusion complexes do not form, water loss in the complex is equal to the physical mixture[51].

Table 2 presents recent studies that use TG to assess the formation of inclusion complexes.

Comparison between the methods employed in the characterization of drug-CD complexes

Table 3 compares the different methods used in the characterization of inclusion complexes, with the advantages and disadvantages of each, and the indicative of complexation.

CONCLUSION

The thermo analytical techniques described in this review can indicate the formation of cyclodextrin inclusion complexes by evaluating its melting peak (DSC) and degradation temperature (TG). However, these analytical tools must be used associated with those described in the reviews part I and II to obtain a complete characterization of the inclusion complexes.

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