Review Article

A LITERATURE REVIEW OF CYCLODEXTRIN INCLUSION COMPLEXES CHARACTERIZATION - PART II: X-RAY DIFFRACTION, INFRARED SPECTROSCOPY AND NUCLEAR MAGNETIC RESONANCE

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ABSTRACT

Cyclodextrins are cyclic oligosaccharides widely used to form inclusion complexes with poor water soluble drugs, with the aim to improve their solubility. The characterization of these complexes requires several analytical techniques. In a previous review - part I, the analytical techniques used to characterize drug-cyclodextrin complex phase solubility diagram, dissolution and scanning electron microscopy were described. The aim of this review is to detail other analytical tools also used in this characterization as X-ray diffraction, infrared spectroscopy and nuclear magnetic resonance.

Keywords: Cyclodextrin, X-ray diffraction, Infrared spectroscopy, Nuclear magnetic resonance.

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

METHODS FOR IDENTIFYING AND CHARACTERIZING INCLUSION COMPLEXES

X-RAY DIFFRACTION

X-ray diffraction (XRD) determines the crystallographic structure of solids and is one of the best techniques for the characterization of inclusion complexes[1].

Depending on the crystalline form of the guest molecule, characteristic peaks are formed in difratograms. Thus, the complexation is assessed by changes in the peaks of the guest molecule and CD, compared to the complex.

When a difratogram with the characteristics of an amorphous material is obtained, i.e. without well-defined, narrow peaks, it may be indicative of the occurrence of complexation[2], as illustrated in Figure 1.

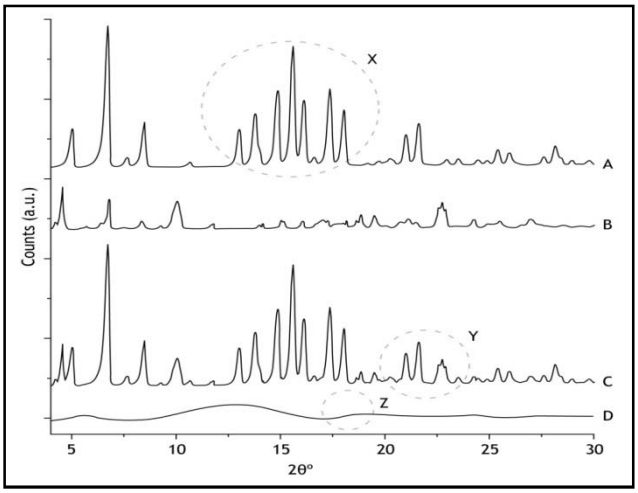

Figure 1: Hypothetical model of analysis by X-ray diffraction of the pure drug (A), CD (B), the physical mixture (C) and the complex (D). X has the well-defined, narrow peaks of a crystalline material, Y has the overlap of the patterns of the drug and CD, and Z is a region without peaks, characteristic of an amorphous material.

It is also possible to evaluate the formation of inclusion complexes by comparing the size of the characteristic peaks of the guest molecule with the size that appears in the complex. A decrease in the peaks may represent partial complexation, since non-complexed material remains in crystalline form[3].

Moreover, the diffraction pattern of the physical mixture is generally the overlap of the guest molecule and CD patterns with peaks of lower intensity; however, when compared to the pattern of the complexes, they present a higher degree of crystallinity[4].

This degree of crystallinity can be used to quantify the formation of complexes. The relative degree of crystallinity is calculated with the following equation:

$$RDC = Isam/Iref$$

Where Isam represents the height of the peak of the sample and Iref the height of the peak at the same angle in the reference sample. The guest molecule alone is often regarded as the reference sample[5].

A low RDC value indicates a lower degree of crystallinity, and, in this case, it can also be concluded that the complexation has been more efficient. However, depending on the process employed in obtaining the complexes, an amorphous material is a possibility, which leads to the disappearance of the peaks, even though the complexation of the drug has not occurred[6,7].

In addition to changes in the characteristic peaks of the guest molecule, new peaks can be observed when the formation of inclusion complexes occurs, indicating a new solid phase, corresponding to the drug-CD complex[8].

Recent studies that use XRD to evaluate the formation of inclusion complexes are presented in Table 1.

Table 1: Some examples of recent studies that use XRD characterization of inclusion complexes

Guest molecule	CD	Evidence of complexation	Reference
API[c]	HPβCD and HPGCD[d]	Peaks disappearance / amorphous material	9
Bicalutamide	βCD	RDC calculation	10
BMDBM[a]	HPβCD	Peaks disappearance	11
Budesonide	γCD	Peaks disappearance / formation of new solid phase	8
Bupivacaine hydrochloride	βCD and EPIβCD[e]	Peaks reduction	12
Camptothecin	βCDNS[b]	Peaks reduction	13
Candesartan cilexetil	βCD	Peaks disappearance	14
Carvedilol	MβCD	Peaks reduction	15
Cefdinir	βCD and HPβCD	RDC calculation	5
Celecoxib	βCD	Peaks disappearance / formation of new solid phase	16
Danazol	HPβCD	Peaks reduction or disappearance / amorphous material	17
Dipyridamole	βCD	Peaks disappearance / formation of new solid phase	18
Enalapril maleate	βCD	Peaks disappearance / amorphous material	19
Etodolac	βCD, HPβCD and γCD	Peaks disappearance / amorphous material	20
Etoricoxib	βCD	Peaks reduction or disappearance / amorphous material	3
Etoricoxib	HPβCD	RDC calculation	21
Fexofenadine	αCD, βCD, γCD and HPβCD	Peaks reduction or disappearance / amorphous material	22
Finasteride	HPβCD	Peaks disappearance	23
Fluorofenidone	βCD and HPβCD	Peaks reduction or disappearance / amorphous material	24
Glimepiride	βCD and HPβCD	RDC calculation	25
Glyburide	βCD and HPβCD	Peaks reduction or disappearance / amorphous material	26
Granisetron	HPβCD	Peaks disappearance / amorphous material	27
Halofantrine	HPβCD	RDC calculation	28
Ibuprofen	βCD	Peaks reduction / formation of new solid phase	29
Ibuproxam	βCD and derivatives	Peaks disappearance / amorphous material	30
Iprodione	βCD	Peaks disappearance / formation of new solid phase	31
Irbesartan	βCD	Peaks disappearance	32
Itraconazole	HPβCD	Peaks disappearance / amorphous material	33
Itraconazole, econazole and fluconazole	βCD	Peaks reduction / formation of new solid phase	34
Ketoprofen	HPβCD	Peaks disappearance / amorphous material	35
Lamotrigine	βCD	RDC calculation	36
Lovastatin	HPβCD	Peaks disappearance / amorphous material	3
Meloxicam	βCD	Peaks reduction or disappearance	37
Metformin	Triacetyl-βCD	Peaks disappearance / amorphous material	2
Miconazole	βCD	Peaks disappearance	38
Naproxen	HPβCD	Peaks reduction / formation of new solid phase	4
Omeprazole	MβCD	RDC calculation	39
Oridonin	HPβCD	Peaks disappearance / amorphous material	40
Oxaprozin	βCD, DMβCD and RMβCD	Amorphous material	41
Oxyphenbutazone	βCD and γCD	Peaks disappearance / formation of new solid phase	42
Piroxicam	HPβCD	Amorphous material	43
Prednisone	αCD, βCD, HPβCD and γCD	Peaks reduction or disappearance / amorphous material	44
Pyrimethamine	HPβCD	Peaks disappearance / amorphous material	45
Ropivacaine	HPβCD	Peaks reduction or disappearance / amorphous material	46
Rutin and quercetin	βCD and HPβCD	Peaks reduction or disappearance / amorphous material	47
Sericoside	βCD and γCD	Peaks disappearance / amorphous material	48
Sertaconazole	HPβCD	Peaks disappearance / amorphous material	49
Sildenafil	αCD, βCD, γCD and HPβCD	Peaks reduction or disappearance / amorphous material	50
Simvastatin	HPβCD	Peaks reduction or disappearance / amorphous material	51
Sulfadiazine	HPβCD	Peaks disappearance / amorphous material	52
Triclosan	βCD and EPIβCD[e]	Peaks reduction / peaks disappearance / amorphous material	53
Zaleplon	βCD	RDC calculation	54
Zerumbone	HPβCD	Amorphous material / formation of a new solid phase	55

[a]BMDBM: Butylmethoxydibenzoylmethane

[b]βCDNS: β-cyclodextrinnanosponges

[c]API: drug was referred by the authors as API due to reasons of Industrial Property Rights

[d]HPGCD: Hydroxypropyl-gamma cyclodextrin

[e]EPIβCD: Epichlorohydrin β-CD

Table 2: Some examples of recent studies employing IR for characterization of inclusion complexes.

Guest molecule	Cyclodextrin	Evidence of complexation	Reference
Aceclofenac	HPβCD	Disappearance and shift of the bands	61
Acetazolamide	HPβCD	Reduction of the bands	62
Atenolol	RMβCD	Reduction and shift of the bands	63
Berberine chloride	βCD	Disappearance of the bands	64
Bicalutamide	βCD	Disappearance and shift of the bands	10
Bupivacaine hydrochloride	βCD and EPIβCD	Reduction of the bands	12
Camptothecin	βCDNS[a]	Disappearance of the bands	13
Carvedilol	MβCD	Disappearance of the bands	15
Cefdinir	βCD and HPβCD	Reduction of the bands	5
Cladribine	HPβCD	Disappearance of the bands	65
Etodolac	βCD, HPβCD and γCD	Reductions and shift of the bands	20
Etoricoxib	βCD	Reduction of the bands	3
Etoricoxib	HPβCD	Disappearance and shift of the bands	21
Flavonols	βCD	Shift of the bands	66
Flurbiprofen	HPβCD	Disappearance of the bands	67
Glyburide	βCD and HPβCD	Shift of the bands	26
Granisetron	HPβCD	Disappearance and change of position of the bands	27
Ibuprofeno	βCD	Reduction of the bands	29
Ibuproxam	βCD and derivatives	Disappearance and shift of the bands	30
Irbesartan	βCD	Shift of the bands	32
Itraconazole, econazole and fluconazole	βCD	Disappearance and shift of the bands	34
Ketoprofen	EPIβCD and EPICMβCD	Shift of the bands	68
Lamotrigine	βCD	Reduction of the bands	36
Loratadine	Heptakis –DMβCD	Shift of the bands	69
Loratadine	Heptakis –DMβCD	Shift of the bands	70
Lorazepam	HPβCD	Disappearance and shift of the bands	71
Lovastatin	HPβCD	Reduction of the bands	3
Metformin	Triacetil-βCD	Disappearance and shift of the bands	2
Miconazole	βCD	Peaks disappearance	38
Naproxen	HPβCD	Disappearance and shift of the bands	4
Nimodipine	HPβCD	Reduction of the bands	56
Omeprazole	βCD and MβCD	Reduction of the bands	39
Oxaprozin	βCD, DMβCD and RMβCD	Shift of the bands	41
Piroxicam	HPβCD	Disappearance of the bands	43
Piroxicam	HPβCD	Disappearance and shift of the bands	72
Polypropylene glycol	βCD	Disappearance and reduction of the bands	73
Rutin and quercetin	βCD and HPβCD	Disappearance and shift of the bands	47
Simvastatin	HPβCD	Reduction of the bands	51
Spironolactone	HPβCD	Disappearance of the bands	74
Trazodone	HPβCD	Disappearance of the bands	75
Triclosan	βCD and EPIβCD	Reduction of the bands	53
Vinpocetin	βCD and SBEβCD	Disappearance and shift of the bands	6
Zaleplon	βCD	Disappearance and shift of the bands	54
Zerumbone	HPβCD	Shift of the bands	55

[a]βCDNS: β-CD nanosponges

Table 3: Some examples of recent studies that use NMR in the characterization of inclusion complexes

Guest molecule	Cyclodextrin	NMR type	Reference
A-007 pro-drug	αCD, βCD e γCD	HNMR, C13NMR	80
Ascorbic acid	HPβCD	C13NMR	79
Benzocain	βCD	HNMR	77
Bisphenol A	βCD	HNMR	81
Celecoxib	HPβCD	HNMR, C13NMR	82
Celecoxib	βCD	HNMR	16
Cladribine	HPβCD	HNMR	65
Clomipramine	βCD and HPβCD	HNMR, C13NMR	83
Coumestrol	βCD	HNMR	84
Di(8-hydroxyquinolon) magnesium	HPβCD	HNMR	85
Diclofenac	αCD, βCD, γCD and HPβCD	HNMR	86
Dipyridamole	βCD	HNMR	18
Doxepin	βCD	HNMR	87
Enalapril	βCD	HNMR	88
Enalapril maleate	βCD	C13NMR	19
Etoricoxib	HPβCD	HNMR	21
Finasteride	HPβCD	HNMR	23
Flavonols	βCD	HNMR, C13NMR	66
Fluoxetine	βCD	HNMR	89
Hydroxymethyl-nitrofurazone	HPβCD	HNMR	90
Ibuprofen	βCD, MβCD and HPβCD	HNMR	91
Irbesartan	βCD	HNMR	32
Losartan potassium	HPβCD	HNMR and 2D ^{1}H-^{1}H-ROESY	92
Luteolin	βCD, HPβCD and DMβCD	HNMR	93
Maleic, fumaric e L-tartaricacids	βCD	HNMR	94
Midazolam	βCD	HNMR	95
Nitroindazole	βCD e DMβCD	HNMR	96
N-octylβ-D-glucopyranoside	αCD	HNMR	97
Norfloxacin	MβCD	HNMR	98
Omeprazole	βCD e MβCD	HNMR	76
Oridonin	HPβCD	HNMR	40
Paclitaxel	6-O-CAPRO-βCD	HNMR	99
Phenothiazine	βCD	HNMR	100
Piroxicam	HPβCD	HNMR	43
Pyrimethamine	αCD	HNMR	101
Pyrimethamine	HPβCD	HNMR	45
Quinuclidine	αCD	C13NMR	102
Sildenafil	αCD, βCD, γCD e HPβCD	HNMR	50
Simvastatin	HPβCD	HNMR	103
Sulfadiazine	HPβCD	HNMR	52
Trazodone	HPβCD	HNMR, C13NMR	75
Triclosan	βCD and EPIβCD[a]	2D ^{1}H-^{1}H-ROESY	53

[a]EPIβCD: Epichlorohydrin β-CD

INFRARED SPECTROSCOPY

Infrared (IR) spectra analysis can be carried out by comparing the bands representing the guest molecule, CD and the physical mixture with the ones representing the complex. Usually the spectrum of the physical mixture is the superposition of guest molecule and CD spectra, although the bands representing the guest molecule are less evident, due to the latter's lower concentration. When complexation occurs, the peaks can change position, diminish or even disappear[2], as illustrated in Figure 2.

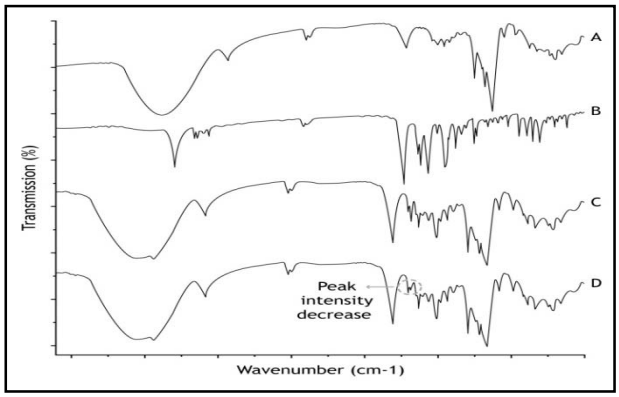

Figure 2: Hypothetical model of analysis by IR spectroscopy of the pure drug (A), CD (B), the physical mixture (C) and the complex (D).

The modification of some of the bands representing the guest molecule is indicative that only part of the molecule has been encapsulated by CD. The portion that has not been complexed is responsible for the presence of any unchanged bands[56].

However, it is important to emphasize that when complexation occurs, the bands representing CD remain unchanged, and if the guest molecule does not present a very characteristic band, the changes may be imperceptible[1]. Some authors report difficulty in interpreting results due to the lack of a band representing the guest molecule that produces noticeable changes[40,57,58]. There are still other authors who have obtained inconclusive results[59,60].

Recent studies employing IR to evaluate the formation of inclusion complexes are presented in Table 2.

NUCLEAR MAGNETIC RESONANCE

Nuclear magnetic resonance (NMR) is a technique that has been widely employed to determine the formation of inclusion complexes, because it has the advantage of being able to reveal the structure of the complex by identifying the part of the host molecule that is included in the CD cavity[1].

There are six protons in CD that can be used in the analysis of the NMR spectra of hydrogen (HNMR): three located in the outer surface (H1, H2 and H4), two in the cavity (H3 and H5), H3 near the wider exit and H5 near the narrow side. The last proton, H6, is closer to the narrow output of the cavity. The changes that occur in CD are usually in H3 and H5 and sometimes in H6, depending on the depth that the guest molecule enters the CD cavity[76,77], as illustrated in Figure 3.

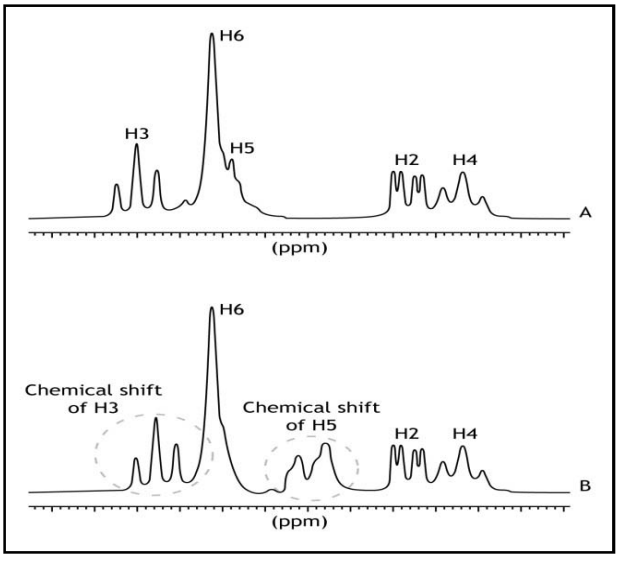

Figure 3: Hypothetical model of analysis by HNMR of CD (A) and inclusion complex (B).

Due to the formation of chemical bonds, when complexation occurs, signal changes take place in CD and guest molecule spectra[60,78].

Another technique employed in the characterization of CD complexes is carbon 13 NMR (C13NMR). The results reveal the part of the guest molecule that has been encapsulated by CD, complementing the HRMN information[79].

Recent studies that use NMR to assess the formation of inclusion complexes are presented in Table 3.

CONCLUSION

A complete characterization of drug-cyclodextrin inclusion complex can be obtained using several analytical techniques as described in a previous review - part I. The analytical tools described in this review can show important details of the molecules whose, in addition with other techniques as phase solubility diagrams, dissolution studies and scanning electron microscopy can generate a more complete characterization of the formed complexes.

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