Journal of Pharmaceutical and Biomedical Analysis 101 (2014) 238–250

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Review

Analytical techniques for characterization of cyclodextrin complexes in aqueous solution: A review

Paola Mura*

Department of Chemistry, School of Human Health Sciences, University of Florence, Via Schiff 6, Sesto Fiorentino I-50019, Florence, Italy

ARTICLE INFO

Article history:
Received 15 February 2014
Accepted 17 February 2014
Available online 12 March 2014

Keywords:
Cyclodextrin
Inclusion complex
Spectroscopic techniques
Electroanalytical techniques
Separation techniques
Thermoanalytical techniques
Polarimetry
Analytical characterization in solution

ABSTRACT

Cyclodextrins are cyclic oligosaccharides endowed with a hydrophilic outer surface and a hydrophobic inner cavity, able to form inclusion complexes with a wide variety of guest molecules, positively affecting their physicochemical properties. In particular, in the pharmaceutical field, cyclodextrin complexation is mainly used to increase the aqueous solubility and dissolution rate of poorly soluble drugs, and to enhance their bioavailability and stability. Analytical characterization of host–guest interactions is of fundamental importance for fully exploiting the potential benefits of complexation, helping in selection of the most appropriate cyclodextrin. The assessment of the actual formation of a drug–cyclodextrin inclusion complex and its full characterization is not a simple task and often requires the use of different analytical methods, whose results have to be combined and examined together.

The purpose of the present review is to give, as much as possible, a general overview of the main analytical tools which can be employed for the characterization of drug–cyclodextrin inclusion complexes in solution, with emphasis on their respective potential merits, disadvantages and limits. Further, the applicability of each examined technique is illustrated and discussed by specific examples from literature.

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* Tel.: +39 055 4573672; fax: +39 0554573673.
E-mail address: paola.mura@unifi.it

http://dx.doi.org/10.1016/j.jpba.2014.02.022
0731-7085/

1. Introduction

Cyclodextrins (CDs) are a family of cyclic oligosaccharides, consisting of a number of α(1→4)-linked D-glucopyranose subunits, obtained by degradation of starch by the enzyme cyclodextrin glucosyltransferase [1]. The most common CDs, named α-, β- and γ-CDs, are composed, respectively, of six, seven and height glucose unites. CDs having less than six glucose units have not be found to be produced enzymatically. On the contrary, larger CDs with more than eight units, containing nine to 19, α(1→4)-linked D-glucopyranose subunits have been isolated and characterized [2,3]. However, problems of low yields, difficulty for purification, and high cost, strongly limit their practical use. Moreover, large CDs are collapsed and their cavity is even smaller than that of γCD, and therefore they present a reduced complexing ability [4]. The main chemical and physical properties of the three most common CDs are presented in Table 1.

CDs are shaped like a truncated cone, rather than a perfect cylinder, as a consequence of the chair conformation of the glucopyranose units (Fig. 1). The hydroxyl functions are oriented to the exterior of the cavity, with the secondary hydroxyl groups located on the wider edge, and the primary ones on the narrow edge. The central cavity is lined by the hydrogen atoms and the glycosidic oxigen bridges, which give it a lipophilic character. The particular three-dimensional structure of the CD molecules, characterized by a hydrophilic outer surface, and an internal relatively hydrophobic cavity, is responsible for both their water solubility and ability to partially or fully encapsulate within their cavities hydrophobic molecules of suitable size, giving rise to the inclusion complex formation [5]. The inclusion complex is present in solution in dynamic equilibrium with its constituents and is characterized by the absence of covalent bonds and by a well defined host:guest stoichiometry. Several types of forces are involved in the inclusion complex formation, and their relative contribution depends on the guest and CD type. These forces include hydrophobic interactions, reduction of conformational strain, hydrogen bonding, dipole–dipole and electrostatic interactions, van der Waals and dispersion forces; however, the main driving force is considered the replacement of the unfavoured polar–apolar interactions between both the included water molecules and the CD cavity on one hand, and water and the hydrophobic guest on the other one, by more favored apolar–apolar interactions between the guest and the cavity [4–6] (Fig. 2).

The naturally occurring CDs, α-, γ-, and particularly βCD, have limited aqueous solubility, attributed to the relatively strong intramolecular hydrogen bonds between the secondary hydroxyl groups, that diminish their ability to form hydrogen bonds with the surrounding water molecules. Therefore, several chemically-modified CD derivatives have been developed with a view to improve the physicochemical properties of parent CDs. Partial random substitution of CD hydroxyl groups, even with hydrophobic moieties (i.e. methoxy functions) results in dramatic increase of CD solubility, by transforming crystalline CDs into amorphous mixtures of isomeric derivatives, and preventing formation of intramolecular hydrogen bonds, thus making the residual free hydroxyl groups available to interact with water. Moreover, the presence of substituents can extend the CD hydrophobic cavity, improving their complexing ability [6–10].

The capacity to form inclusion complexes with a wide variety of guest molecules is one of the most interesting properties of CDs and it has been the basis for most of their applications in the pharmaceutical, agrochemical, food and cosmetic fields. In fact, such "molecular encapsulation" will positively affect many of the physicochemical properties of the entrapped molecules, thus providing a number of possible benefits. In particular, in the pharmaceutical field, CD complexation is mainly used to increase the aqueous solubility and dissolution rate of poorly soluble drugs, and to enhance their bioavailability and stability. Moreover CD complexation can also be exploited to mask unpleasant tastes or smell, reduce evaporation and stabilize volatile substances, protect molecules sensitive to light or oxygen, convert liquid substances and oils in free-flowing powders, reduce gastric, dermal or ocular irritation and prevent incompatibilities and interactions between substances. The numerous potential advantages related to their use and the increased availability of CDs at lower cost play a decisive role in the growing interest toward these molecules, particularly in the pharmaceutical field. A very relevant number of reviews, books and book chapters have been published on CDs and their applications in drug delivery, demonstrating the high interest toward these molecules in the pharmaceutical field. Tables 2 and 3 present a non comprehensive list of such publications.

However, in spite of the wide literature concerning CDs, only a limited number of reviews or books has been specifically dedicated to the analytical methods for characterization of the inclusion complexes. These studies are instead of fundamental importance for improving the applications of CD inclusion complexes. In fact, to fully exploit the potential of CD inclusion complexes, it is important to have at disposal adequate analytical techniques for their suitable and careful characterization. In particular, the determination of the stability constants of the inclusion complexes is a crucial point for the evaluation of their effectiveness, since the different possible effects related to the complex formation all rely on the stability

Table 1
Chemical–physical properties of native CDs.

	αCD	βCD	γCD
Number of glucopiranose units	6	7	8
Molecular weight	972	1135	1297
Solubility in water (% w/v) 25 °C	14.5	1.85	23.2
Inner cavity diameter (nm)	0.47–0.53	0.60–0.65	0.75–0.83
Outer cavity diameter (nm)	1.46	1.54	1.75
Cavity height (nm)	0.79	0.79	0.79
Cavity volume (nm^3)	0.174	0.262	0.472
Crystal water content (wt.%)	10.2	13.2–14.5	8.13–17.7
Water molecules in cavity	6	11	17
Melting temperature range (°C)	255–260	255–265	240–245