Journal of Pharmaceutical and Biomedical Analysis 113 (2015) 226–238

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 the solid state: 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 29 January 2015
Accepted 30 January 2015
Available online 9 February 2015

Keywords:
Cyclodextrin
Inclusion complex
Thermo-analytical techniques
X-ray diffraction
Spectroscopic techniques

ABSTRACT

Cyclodextrins are cyclic oligosaccharides able to form inclusion complexes with a variety of hydrophobic guest molecules, positively modifying their physicochemical properties. A thorough analytical characterization of cyclodextrin complexes is of fundamental importance to provide an adequate support in selection of the most suitable cyclodextrin for each guest molecule, and also in view of possible future patenting and marketing of drug–cyclodextrin formulations. The demonstration of the actual formation of a drug–cyclodextrin inclusion complex in solution does not guarantee its existence also in the solid state. Moreover, the technique used to prepare the solid complex can strongly influence the properties of the final product. Therefore, an appropriate characterization of the drug–cyclodextrin solid systems obtained has also a key role in driving in the choice of the most effective preparation method, able to maximize host–guest interactions. The analytical characterization of drug–cyclodextrin solid systems and the assessment of the actual inclusion complex formation is not a simple task and involves the combined use of several analytical techniques, whose results have to be evaluated together.

The objective of the present review is to present a general prospect of the principal analytical techniques which can be employed for a suitable characterization of drug–cyclodextrin systems in the solid state, evidencing their respective potential advantages and limits. The applications of each examined technique are described and discussed by pertinent examples from literature.

Contents

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

http://dx.doi.org/10.1016/j.jpba.2015.01.058
0731-7085/

1. Introduction

Cyclodextrins (CDs) are a group of cyclic oligosaccharides composed by α-D-glucopyranose units linked together with α-1,4 glycosidic bonds. The chair conformation of the glucopyranose units makes CD molecules have the shape of a truncated cone with a central cavity. The hydroxyl functions of the glucopyranose units are oriented toward the exterior of the cavity, with the secondary and primary hydroxyl groups located, respectively, on the wider and narrow edge, conferring a hydrophilic character to the outer surface and providing water solubility. On the contrary, the inner cavity of the macrocycle is lined by hydrogen atoms and glycosidic oxygen bridges, presenting a relatively hydrophobic character [1]. CDs are widely used as "molecular cages" in pharmaceutical, cosmetic, food and chemistry industrial sectors, owing to their capacity to entrap in their cavity a variety of hydrophobic guest molecules of suitable size, leading to the formation of inclusion complexes [2]. The three most frequently used native CDs, i.e. α-, β and γ-CD, containing 6,7, and 8 glucopyranose units, respectively, exhibit a limited water solubility, due to the presence of strong intramolecular hydrogen bonds between the secondary hydroxyl groups, that reduce their capacity to interact with the surrounding water molecules. Natural CDs can be differently functionalized in order to conveniently modify their solubility and complexing properties and extend the range of pharmaceutical applications of the parent molecules [3–7].

CD complexation is mainly utilized in pharmaceutical field to enhance water solubility and dissolution rate of poorly soluble drugs, and improve their stability and bioavailability [8–10]. Furthermore CD molecular encapsulation can also be used to mask unpleasant taste or odor, lessen volatile substances evaporation, protect sensitive molecules from light or oxygen, convert liquids and oils in free-flowing powders, reduce drug topical irritation phenomena, overcome incompatibility problems between substances. Finally, hydrophobic CD derivatives, such as the peracylated ones, have been proposed as sustained-release carriers for highly soluble drugs, in virtue of their ability to form poorly water-soluble complexes [11–13].

A prudential estimate of publications regarding CDs gives figures of over 1000 articles in international scientific journals and about 30–40 review papers, books and book chapters every year in the last years, showing the importance of such molecules in the pharmaceutical sector. A non-comprehensive list of reviews about the main applications of CD complexation in the pharmaceutical field is presented in Table 1.

Nevertheless, in spite of the wide literature about the uses and benefits of CDs, only a very limited number of reviews or books has been specifically devoted to the methods for analytical characterization of the CD inclusion complexes (Table 2). A thorough physico-chemical characterization of such compounds is instead of critical importance, representing an essential step, at the preformulation stage, in order to exploit at the best the potential advantages of CD complexation, by driving in the right selection of the most appropriate CD for a given guest molecule, as well as to increase the industrial applications of CD inclusion complexes, considering the possible implications for their patenting and marketing.

The full analytical characterization of CD inclusion complexes both in solution and in the solid state is not a simple task and involves the use of several analytical techniques, whose results have to be combined and evaluated together. The CD inclusion complexes are present in solution in dynamic equilibrium with their constituents and are characterized by a well determined host:guest stoichiometry and the absence of covalent bounds [1]. A review about the main analytical tools which can be used for the characterization of drug–CD inclusion complexes in solution, with their

Table 1
A non-comprehensive list of reviews on cyclodextrin applications in the pharmaceutical field.

Topics	References
Pharmaceutical applications	R.A. Rajewski, V.J. Stella, 1996, J. Pharm. Sci. 85: 1017–1025 T. Irie, K. Uekama, 1997, J. Pharm. Sci. 86: 147–162 E. Redenti, L. Szente, J. Szejtli, 2000, J. Pharm. Sci. 89: 1–8 K. Uekama, 2002, J. Incl. Phenom. Macroc. Chem. 44: 3–14 M.E. Davis, M.E. Brewster, 2004, Nature Rev. 3: 1023–1035 S. Shimpi, B. Chauhan, P. Shimpi, 2005, Acta Pharm. 55: 139–156 T. Loftsson, D. Duchêne, 2007, Int. J. Pharm. 329: 1–11 T. Loftsson, M.E. Brewster, 2010, J. Pharm. Pharmacol. 62: 1607–1621
Drug and gene delivery	V.J. Stella, R.A. Rajewski, 1997, Pharm. Res., 14: 556–567 T. Loftsson, P. Jarho, M. Masson, T. Jarvinen, 2005, Exp. Opin. Drug Deliv. 2: 335–351 R. Challa, A. Ahuja, J. Ali, R.K. Khar, 2005, AAPS PharmSciTechAAPS 6: 329–357 A. Vyas, S. Saraf, S. Saraf, 2008. J. Incl. Phenom. Macrocycl. Chem. 62: 23–42 J. Li, X.J. Loh, 2008, Adv. Drug Deliv. Rev. 60: 1000–1017 G. Tiwari, R. Tiwari, A.K. Rai, 2010, J. Pharm. Bioallied Sci. 2: 72–79 J. Otero-Espinar, J.J. Torres-Labandeira, C. Alvarez-Lorenzo, J. Blanco-Méndez, 2010, J. Drug Del. Sci. Tech. 20: 289–301 A.L. Laza-Knoerr, R. Gref, P. Couvreur, 2010, J. Drug Target. 18: 645–656 M.J. O'Neill, A.M. O'Mahony, C. Byrne, R. Darcy, C.M. O'Driscoll, 2013, Int. J. Pharm. 456: 390–399 W.F. Lai, 2014, Biomaterials 35: 401–411 F.J. Otero-Espinar, J. Blanco-Méndez, 2014, Curr. Top. Med. Chem. 14: 463–4
Oral, topical, transdermal, ocular, rectal targeted delivery	F.W. Merkus, J.C. Verhoef, E. Marttin, S.G. Romeijn, P.H. Van der Kuy, W.A. Hermens, N.G. Shipper, 1999, Adv Drug Deliv Rev. 36: 41–57 T. Loftsson, T. Jarvinen, 1999, Adv. Drug Deliv. Rev. 36: 59–79 H. Matsuda, H. Arima, 1999, Adv. Drug Deliv. Rev. 36: 81–99 F. Hirayama, K. Uekama, 1999, Adv. Drug Deliv. Rev. 36: 125–141 T. Loftsson, M. Masson, 2001, Int. J. Pharm. 225: 15–30 K. Cal, K. Centkowska, 2008, Eur. J. Pharm. Biopharm. 68: 467–478
Excipients	D.O. Thompson, 1997, Crit. Rev. Therap. Drug Carrier Syst., 14: 1–104 F.J. Otero Espinar, A. Luzardo Alvarez, A. Blanco-Méndez, 2010, Med. Chem. 10: 715–725 T. Loftsson, M.E. Brewster, 2012, J. Pharm. Sci. 101: 3019–3032
Drug carrier	K. Uekama, F. Hyrayama, T. Irie, 1998, Chem. Rev. 98: 2045–2076 T. Irie, K. Uekama, 1999, Adv. Drug Deliv Rev. 36: 101–123 E. Redenti, C. Pietra, A. Gerloczy, L. Szente, 2001, Adv. Drug Deliv Rev. 53: 235–244 K. Uekama, 2004, Yakugaku Zasshi 124: 909–935
Solubilization and bioavailability improvement	T. Loftsson, M.E. Brewster, 1996, J. Pharm. Sci., 85: 1017–1025 V.M. Rao, V.J. Stella, 2003, J. Pharm. Sci. 92: 927–932 T. Loftsson, M.E. Brewster, M. Masson, 2004, Am. J. Drug Deliv., 2: 261–275 C.H. Dubin, 2006, Drug Deliv. Technol. 6: 34–38 M.E. Brewster, T. Loftsson, 2007, Adv. Drug Deliv. Rev. 59: 645–666 R.L. Carrier, L.A. Miller, I. Ahmed, 2007, J. Control. Release 123: 78–99 K.K. Saravana, M. Sushma, R.Y. Prasanna, 2013, J. Pharm. Sci & Res. 5: 120–124