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Historical Perspectives

Cyclodextrins and their pharmaceutical applications

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Abstract

Cyclodextrins were first described by Villiers in 1891. Schardinger laid the foundation of the cyclodextrin chemistry in 1903–1911 and identified both α- and β-cyclodextrin. In the 1930s, Freudenberg identified γ-cyclodextrin and suggested that larger cyclodextrins could exist. Freudenberg and co-workers showed that cyclodextrins were cyclic oligosaccharides formed by glucose units and somewhat later Cramer and co-workers described their ability to form inclusion complexes. By the early 1950s the basic physicochemical characteristics of cyclodextrins had been discovered, including their ability to solubilize and stabilize drugs. The first cyclodextrin-related patent was issued in 1953 to Freudenberg, Cramer and Plieninger. However, pure cyclodextrins that were suitable for pharmaceutical applications did not come available until about 25 years later and at the same time the first cyclodextrin-containing pharmaceutical product was marketed in Japan. Later cyclodextrin-containing products appeared on the European market and in 1997 also in the US. New cyclodextrin-based technologies are constantly being developed and, thus, 100 years after their discovery cyclodextrins are still regarded as novel excipients of unexplored potential.

Keywords: Complexation; Cyclodextrin; Drug delivery; Formulation; History; Regulatory; Toxicology

Contents

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1. Introduction

Carbohydrates, such as cellulose, starch and sucrose, are probably the most abundant organic substances in nature and form very ancient time they have been used for shelter, clothing and food. For thousands of years humans have processed carbohydrates through fermentation and observed their enzymatic degradation. It is now known that these processes lead to formation of mixtures of monosaccharides, disaccharides and various oligosaccharides, such as linear and branched dextrins and that, under certain conditions, small amounts of cyclic dextrins or cyclodextrins are also being formed during these degradation processes. Technological advances of the 19th century laid the foundation of carbohydrate chemistry and by the middle of the century a number of relatively pure carbohydrates such as sucrose, cellulose from cotton, starch, glucose, fructose, mannose, and lactose were known to chemists in Europe (Robyt, 1998). A short chronological summary on the development of carbohydrate chemistry, with a special emphasis on cyclodextrins, is given in Table 1. This paper describes the historical development of cyclodextrins with emphasis on their use in pharmaceutical formulations. It is not intended to be a comprehensive review of the subject nor does it give detailed historical accounts.

Every year cyclodextrins are subject of over 1000 articles in international scientific journals, 30–40 review papers and numerous patents and patent applications. In Table 2, we have listed several books and reviews on cyclodextrins that we think might be useful for further reading. Again we have selected these books and articles based on our personal perspective taken into account their historical and scientific values as well as how frequently they have been cited by the scientific literature.

2. The emerging of cyclodextrins

Professor József Szejtli (1933–2004) divided the chemical and industrial developments of cyclodextrins into three stages, the discovery period, the exploratory period, and the utilization period (Szejtli, 1998, 2004). These three development phases closely follow the technological advances that took place during the last century, first in analytical instrumentation and then in biotechnology.

2.1. The discovery period, 1891 to the mid 1930s

The first written record on cyclodextrins was published in 1891 by a French scientist A. Villiers (Fig. 1), where he described isolation of 3 g of crystalline substance from bacterial digest of 1000 g of starch (Villiers, 1891). The substance appeared to be resistant towards acid hydrolysis and, like cellulose, did not show reducing properties. His experimental results indicated

Table 1
Cyclodextrins and the development of carbohydrate chemistry

Year	Event
1808	Malus develops plane polarized light and observes optical rotation by carbohydrates.
1811	Acid-hydrolyzed starch is shown to produce sweet crystalline sugar.
1821	Production of dextrins by heating starch is discovered.
1838	The sugar from honey, grapes, starch and cellulose is found to be identical and is called glucose by Dumas.
1858	The empirical formula of glucose is determined to be $C_6H_{12}O_6$.
1870	Bayer and Fittig propose that the formula of glucose is HO-CH_2-CH(OH)-CH(OH)-CH(OH)-CH(OH)-CHO.
1888	Glucose is shown to be a six-carbon polyhydroxy aldehyde.
1888–1891	Fisher determines the structure of several carbohydrates, including glucose, fructose, mannose and arabinose.
1891	Villiers publishes his discovery of cellulosine (cyclodextrin).
1903	Schardinger publishes his first paper on α- and β-dextrins (cyclodextrins).
1920–1930	English carbohydrate research group, lead by Norman Haworth, definitely demonstrate the size of carbohydrate rings to be primary six-membered pyranoses and propose a six-membered hexagon to represent the carbohydrates.
1924	Methylation of cyclodextrins first described, later both Freudenberg and Meyer-Delius (1938) and Szejtli (1980) prepared different grades of methylated cyclodextrins.
1928–1932	The ability of cyclodextrins to form complexes with various organic compounds discovered.
1935	Freudenberg and Jacobi discover γ-cyclodextrin.
1938–1952	The chemical structure of α-, β- and γ-cyclodextrin elucidated by Freudenberg, Cramer, Borchert, French and Rundle.
1948–1951	Formation and structure of cyclodextrin inclusion complexes discovered.
1953	The first cyclodextrin patent entitled "Method for preparation of inclusion compounds of physiologically active organic compounds" was issued in Germany to Freudenberg, Cramer and Plieninger.
1954	Cramer's book on inclusion complexes (Einschlussverbindungen) published.
1957–1965	French describes the existence of large natural cyclodextrins with up to 12 glucose units.
1965	Higuchi and Connors publish their article on classification of complexes based on their phase-solubility profiles.
1976	The parent α- and β-cyclodextrin officially approved as food additives in Japan.
1976	The worlds first pharmaceutical product, prostaglandin E_2/β-cyclodextrin (Prostarmon E™ sublingual tablets), marketed in Japan by Ono Pharmaceutical Co.
1981	The first International Symposium on Cyclodextrins was organized and held in Budapest by Szejtli.
1983–1985	Brauns and Müller (Europe) and Pitha (USA) file for patents on 2-hydroxypropyl-β-cyclodextrin.
1988	Piroxicam/β-cyclodextrin tablets (Brexin®) marketed by Chiesi Farmaceutici (Italy).
1990	Stella and Rajewski file for a patent on sulfobutyl ether β-cyclodextrin.

The information listed in this table is based on the references listed at the end of this article and the following books and reviews: Cramer (1954), Bender and Komiyama (1978), Cramer (1987), Robyt (1998), Szejtli (1998), Szejtli (2004).

Table 2
Selected books, book chapters and journal reviews on cyclodextrins

Books or special journal issues[a]:
Cramer F., 1954. Einschlussverbindungen, Springer-Verlag, Berlin.
Bender M.L., Komiyama M., 1978. Cyclodextrin chemistry, Springer-Verlag, Berlin.
Duchêne D. (Ed.), 1987. Cyclodextrins and their industrial uses, Editions de Santé, Paris.
Szejtli J., 1988. Cyclodextrin technology, Kluwer Academic Publisher, Dordrecht.
Duchêne D. (Ed.), 1991. New trends in cyclodextrins and derivatives, Editions de Santé, Paris.
Frömming K.H., Szejtli J., 1994. Cyclodextrins in pharmacy, Kluwer Academic Publishers, Dordrecht.
D'Souza V.T., Lipkowitz K.B. (Eds.), 1998. Special issue on cyclodextrins, Chem. Rev. vol. 98, issue 5.
Uekama K. (Ed.), 1999. Special issue on cyclodextrins in drug delivery, Adv. Drug Deliv. Rev. Vol. 36.
Dodziuk H. (Ed.), 2006. Cyclodextrins and their complexes: chemistry, analytical methods, applications, Wiley-VCH, Weinheim.

Book chapters[b]:
Saenger W., 1984. Structural aspects of cyclodextrins and their inclusion complexes. In: Atwood J.L., Davies J.E.D., MacNicol D.D. (Eds.), Inclusion compounds, vol. 2, Academic Press, London, pp. 231–259.
Szejtli J., 1984. Industrial applications of cyclodextrins. In: Atwood J.L., Davies J.E.D., MacNicol D.D. (Eds.), Inclusion compounds, vol. 3, Academic Press, London, pp. 331–390.
Bergeron R.J., 1984. Cycloamylose-substrate binding. In: Attwood J.L., Bavies J.E.D., MacNicol D.D. (Eds.), Inclusion compounds, vol. 3, Academic Press London, pp. 391–443.
Clarke R.J., Coates J.H., Lincoln S.F., 1988. Inclusion complexes of the cyclomalto-oligosaccharides (cyclodextrins). In: Tipson R.S., Horton D. (Eds.), Advances in carbohydrate chemistry and biochemistry, vol. 46, Academic Press, New York, pp. 205–249.

Review articles:
Saenger W., 1980. Cyclodextrin inclusion compounds in research and industry. Angew. Chem. Int. Ed. Engl., 19: 344–362.
Duchêne D., Vaution C., Glomot F., 1986. Cyclodextrins, their value in pharmaceutical technology. Drug Dev. Ind. Pharm., 12: 2193–2215.
Armstrong D.W., Ward T.J., Armstrong R.D., Beesley T.E., 1986. Separation of drug stereoisomers by the formation of β-cyclodextrin inclusion complexes. Science, 232: 1132–1135.
Harada A., Li J., Kamachi M., 1992. The molecular necklace: a rotaxane containing many threaded α-cyclodextrins. Nature, 356: 325–327.
Li S., Purdy W.C., 1992. Cyclodextrins and their applications in analytical chemistry. Chem. Rev., 92: 1457–1470.
Wenz G., 1994. Cyclodextrins as building blocks for supramolecular structures and functional units. Angew. Chem. Int. Ed., 33: 803–822.
Loftsson T., Brewster M.E., 1996. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J. Pharm. Sci., 85: 1017–1025.
Rajewski R.A., Stella V.J., 1996. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. J. Pharm. Sci., 85: 1142–1168.
Irie T., Uekama K., 1997. Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. J. Pharm. Sci., 86: 147–162.
Connors K.A., 1997. The stability of cyclodextrin complexes in solution. Chem. Rev., 97: 1325–1357.
Stella V.J., Rajewski R.A., 1997. Cyclodextrins: their future in drug formulation and delivery. Pharm. Res., 14: 556–567.
Thompson D.O., 1997. Cyclodextrins-enabling excipients: their present and future use in pharmaceuticals. Crit. Rev. Therap. Drug Carrier Syst., 14: 1–104.
Ooya T., Yui N., 1999. Polyrotaxanes: synthesis, structure, and potential in drug delivery. Crit. Rev. Therap. Drug Carrier Syst., 16: 289–330.
Redenti E., Szente L., Szejtli J., 2000. Drug/cyclodextrin/hydroxy acid multicomponent systems. Properties and pharmaceutical applications. J. Pharm. Sci., 89: 1–8.
Loftsson T., Masson M., 2001. Cyclodextrins in topical drug formulations: theory and practice. Int. J. Pharm., 225: 15–30.
Liu L., Guo Q.-X., 2002. The driving forces in the inclusion complexation of cyclodextrins. J. Incl. Phenom. Macroc. Chem., 42: 1–14.
Duchêne D., Bochot A., Yu S.-C., Pépin C., Seiller M., 2003. Cyclodextrins and emulsions. Int. J. Pharm., 266: 85–90.
Szejtli J., 2004. Past, present, and future of cyclodextrin research. Pure Appl. Chem., 76: 1825–1845.
Loftsson T., Brewster M.E., Másson M., 2004. Role of cyclodextrins in improving oral drug delivery. Am. J. Drug Deliv., 2: 261–275.
Davis M.E., Brewster M.E., 2004. Cyclodextrin-based pharmaceutics: past, present and future. Nature Rev., 3: 1023–1035.
Uekama K., 2004. Design and evaluation of cyclodextrin-based drug formulation. Chem. Pharm. Bull., 52: 900–915.
Loftsson T., Másson M., Brewster M.E., 2004. Self-association of cyclodextrins and cyclodextrin complexes. J. Pharm. Sci., 93: 1091–1099.
Loftsson T., Jarho P., Másson M., Järvinen T., 2005. Cyclodextrins in drug delivery. Expert Opin. Drug Deliv., 2: 335–351.
Challa R., Ahuja A., Ali J., Khar R.K., 2005. Cyclodextrins in drug delivery: an updated review. AAPS PharmSciTechAAPS (www.aapspharmscitech.org).

[a] A number of the books listed are edited books on cyclodextrins and their complexes that contain several chapters by various authors.
[b] Book chapters in edited books that are not only on cyclodextrins or cyclodextrin related topics.

CHIMIE ORGANIQUE. — *Sur la fermentation de la fécule par l'action du ferment butyrique.* Note de M. A. Villiers.

« J'ai montré dernièrement (*Comptes rendus*, février 1891, p. 435) que la fécule de pomme de terre peut, dans des conditions déterminées, fermenter sous l'action du *Bacillus amylobacter*, les produits principaux de cette fermentation étant constitués par des dextrines.

Fig. 1. The beginning of Villiers' paper in Comptes Rendus de l'Académie des Sciences from 1891.

that the substance was a dextrin. He determined its composition to be $(C_6H_{10}O_5)_2{\cdot}3H_2O$ and named it "cellulosine". It is now thought that Villiers detected both α- and β-cyclodextrin in the digest. The Austrian microbiologist Franz Schardinger worked at an institute for food research where he studied various bacteria that caused spoilage of food products, including starch. In 1903, Schardinger published an article (Fig. 2) where he describes two crystalline compounds A and B which he had isolated from bacterial digest of potato starch. He was only able to isolate very small amounts of compound A but significantly more of compound B which he identified as Villiers'

Zeitschrift

Untersuchung der Nahrungs- und Genußmittel,

sowie der Gebrauchsgegenstände.

Heft 19. 1. Oktober 1903. 6. Jahrgang.

Über thermophile Bakterien aus verschiedenen Speisen und Milch,
sowie über einige Umsetzungsprodukte derselben in kohlenhydrathaltigen Nährlösungen, darunter krystallisierte Polysaccharide (Dextrine) aus Stärke.

Von

Franz Schardinger.

Mitteilung aus der K. K. Allgemeinen Untersuchungsanstalt für Lebensmittel in Wien.

Im vergangenen Jahre hatte die hiesige Anstalt die Frage der Zulässigkeit des Genusses längere Zeit hindurch warm aufbewahrter Speisen zu prüfen, wobei sich im Verlaufe der Untersuchung beachtenswerte mikrobiologische Funde ergaben, über die im nachstehenden eingehender berichtet werden soll. Auf Grund der Forschungsergebnisse über thermophile Bakterien konnte es keinem Zweifel unterliegen, daß bei der in Betracht kommenden Temperatur zwischen 50—60° bakterielles Leben überhaupt möglich ist, es war also zunächst festzustellen, ob in den Speisen derartige Keime vorhanden und welcher Art die von ihnen veranlassten Zersetzungen sind, soweit eine Feststellung in letzter Beziehung derzeit möglich ist.

Fig. 2. The beginning of Schardinger's paper in Zeitschrift für Untersuchung der Nahrungs- und Genußmittel from 1903.

"cellulosine" (Schardinger, 1903). In his article, Schardinger suggests that "crystalline dextrin" (Krystallisiertes Dextrin) is a better name than "cellulosine" for these compounds. Later he changed the names to α-dextrin and β-dextrin. For the next 8 years Schardinger continued his studies of these compounds and showed that they could be produced from starch of different sources such as potatoes, rice and wheat, and associated their formation to the type of bacteria digesting the starch. Although many of the physicochemical properties of cyclodextrins were still unknown in 1911, when Schardinger published his last article on cyclodextrins (Schardinger, 1911), it is generally accepted that he did lay the foundation of cyclodextrin chemistry. In the following years cyclodextrins were named Schardinger dextrins in his honor. Now these compounds are commonly called cyclodextrins (i.e. α-cyclodextrin and β-cyclodextrin) or less commonly cyclomaltodextrins (i.e. cyclomaltohexaose and cyclomaltoheptaose). In 1935, γ-cyclodextrin (cyclomaltooctaose) was discovered by Freudenberg and Jacobi (Freudenberg and Jacobi, 1935). Much later Freudenberg and Cramer suggested that larger cyclodextrins could exist (Freudenberg and Cramer, 1948) and this was later verified by French and coworkers (French et al., 1965; Larsen, 2002). However, until the mid 1980s the large-ring cyclodextrins were ignored because of difficulties in their purification and preparation of reasonable yields (Ueda, 2002).

During the discovery period the three main natural cyclodextrins were discovered and characterized. It was known that they were oligosaccharides but their molecular weight as well as their exact chemical structure and most of their physicochemical properties were still unknown.

2.2. The exploratory period, mid 1930s to 1970

In 1938, Freudenberg and co-workers showed that cyclodextrins had a ring structure of α(1 → 4)-linked glucose units with a central cavity (Freudenberg and Meyer-Delius, 1938; Freudenberg et al., 1939) and in the following years their molecular weight was determined (French and Rundle, 1942; Freudenberg and Cramer, 1948). In his book "*Einschlussverbindungen*" (Fig. 3) Cramer describes all the basic structural and physicochemical characteristics of α-, β- and γ-cyclodextrin, including their chemical structure, cavity size, solubility, reactivity, complexing abilities, and their effect on the chemical stability of guest molecules (Cramer, 1954). It was known that cyclodextrins could both have stabilizing and destabilizing effect on chemically labile compounds, that they could be used as enzyme models, and that they could solubilize lipophilic water-insoluble compounds.

During this period the enzymatic production of cyclodextrins was also being investigated. It was known that linear polysaccharides consist of α(1 → 4)-linked glucose units arranged into a left-handed screw with approximately six glucose units per turn (Freudenberg et al., 1939). It was discovered that certain type of amylase, cyclodextrin glucosyl transferase (CGTase), could detach a turn of the polysaccharide helix and link the two ends of the fragment to give a cyclic dextrin (Saenger, 1980). Many microorganism produce glucosyl transferases but only few produce CGTase. Schardinger had shown that *Bacillus macerans* formed cyclodextrin, i.e. that it produces CGTase. During the exploratory period various strains of bacteria were screened with regard to their ability to form cyclodextrins and since then several microorganisms have been shown to produce CGTase,

EINSCHLUSS-
VERBINDUNGEN

VON

FRIEDRICH CRAMER

DOZENT AM CHEMISCHEN INSTITUT
DER UNIVERSITÄT HEIDELBERG

MIT 47 TEXTABBILDUNGEN

SPRINGER-VERLAG
BERLIN · GÖTTINGEN · HEIDELBERG
1954

Fig. 3. The cover of Friedrich Cramer's book "*Einschlussverbindungen*" (inclusion compounds), published in Berlin in 1954. In this book Cramer describes various types of compounds that are able to form inclusion complexes, including cyclodextrins.

including strains of *Bacilli*, strains of the genus *Micrococcus* and strains of the genus *Klebsiella* (Sicard and Saniez, 1987). At the end of the exploratory period methods for the laboratory-scale preparation of cyclodextrins had been developed. However, only small amounts of relatively impure cyclodextrin could be produced which hampered industrial exploration of these novel oligosaccharides.

2.3. The utilization period, 1970 to present

2.3.1. Production of cyclodextrins

Treatment of starch with amylase from *Bacillus macerans* gives a crude mixture of α-cyclodextrin (∼60%), β-cyclodextrin (∼20%) and γ-cyclodextrin (∼20%) together with small amounts of cyclodextrins with more that eight glucose units (Bender and Komiyama, 1978). The mixture was difficult to purify and it frequently contained several other linear and branched dextrins together with small amounts of proteins and other impurities. The biotechnological advances that occurred in the 1970s lead to dramatic improvements in their production. Genetic engineering made different types of CGTases available that were both more active and more specific towards production of α-, β- or γ-cyclodextrin than the previously used enzymes. These enzymes together with other technological innovations made highly purified α-, β- and γ-cyclodextrin available that could be used as pharmaceutical excipients (Sicard and Saniez, 1987). In 1970, β-cyclodextrin was only available as a rare fine chemical at a price of about US$ 2000 per kg. Today the annual β-cyclodextrin production is close to 10,000 tonnes and the bulk price has lowered to about US$ 5 per kg.

2.3.2. Cyclodextrin derivatives

The aqueous solubility of α-, β- and γ-cyclodextrin is much lower than that of comparable linear dextrins, most probably due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e. relatively high crystal energy). In addition, β-cyclodextrin molecules form intramolecular hydrogen bonds that diminish their ability to form hydrogen bonds with the surrounding water molecules. Various semisynthetic water-soluble cellulose derivatives (e.g. carboxymethylcellulose and hydroxypropyl methylcellulose) had been synthesized and were used in large quantities in a variety of industrial products. Similar chemical modifications were now applied to obtain water-soluble cyclodextrin derivatives. It was discovered that substitution of any of the hydroxyl groups, even by hydrophobic moieties such as methoxy functions, resulted in dramatic increase in their aqueous solubility. With increasing degree of methylation the solubility of β-cyclodextrin (in cold water) increases until about 2/3 of all the hydroxyl groups have been methylated, and then it decreases again upon further methylation (Frömming and Szejtli, 1994). Later several new derivatives came available including the 2-hydroxypropyl derivatives of both β- and γ-cyclodextrin, the sulfobutylether derivative of β-cyclodextrin, and the branched (glucosyl- and maltosyl-) β-cyclodextrins (Hashimoto, 1991). The main reason for the solubility enhancement in the alkyl derivatives is that chemical manipulation transforms the crystalline α-, β- and γ-cyclodextrin into amorphous mixtures of isomeric derivatives (Pitha et al., 1986; Loftsson and Brewster, 1996). For example, 2-hydroxypropyl-β-cyclodextrin is obtained by treating a based-solubilized solution of β-cyclodextrin with propylene oxide, resulting in isomeric system that has solubility well in excess of 60% (w/v) (Table 3). The number of isomers generated based on random substitution is very large. Statistically there are about 130,000 possible heptakis (2-*O*-(hydroxypropyl))-β-cyclodextrin derivatives, and given that introduction of the 2-hydroxypropyl function also introduces an optical center, the total number of isomers, i.e. geometrical and optical, is even much greater (Loftsson and Brewster, 1996). Since the reactivity of the three hydroxyl groups on the cyclodextrin forming glucose units have been shown to be slightly different the substitution is usually not totally random and found to depend on, for instance, the basicity of the aqueous reaction media (Pitha et al., 1990; Rao et al., 1991). This could explain the slight differences found in the complexing abilities of identical cyclodextrin derivatives from different suppliers and sometimes from one batch to another from the same supplier. Fully substituted derivatives were shown to have lower aqueous solubility than partly

Table 3
Solubilities and pharmacopoeia monographs of some cyclodextrins that can be found in marketed pharmaceutical products

Cyclodextrin[a]	Subst.[b]	MW (Da)	Solubility in water (mg/ml)[c]	Pharmacopoeia[d]		
				Ph.Eur.	USP/NF	JPC
αCD	–	972	145	Yes	No	Yes
βCD	–	1135	18.5	Yes	Yes	Yes
HPβCD	0.65	1400	>600	Yes	Yes	No
RMβCD	1.8	1312	>500	No	No	No
SBEβCD	0.9	2163	>500	No	No	No
γCD	–	1297	232	In progress	Yes	Yes
HPγCD	0.6	1576	>500	No	No	No

[a] αCD: α-cyclodextrin; βCD: β-cyclodextrin, HPβCD: 2-hydroxypropyl-β-cyclodextrin; RMβCD: randomly methylated β-cyclodextrin; SBEβCD: sulfobutylether β-cyclodextrin; γCD: γ-cyclodextrin; HPγCD: 2-hydroxypropyl-γ-cyclodextrin.
[b] Substitution: average number of substituents per glucopyranose unit.
[c] Solubility in pure water at about 25 °C.
[d] Ph.Eur.: European Pharmacopoeia 5th Edition (2005); USP/NF: United States Pharmacopoeia 28th Edition/National Formulary 23rd Edition (2005); JPC: Japanese Pharmaceutical Codex.

substituted derivatives which could be related to the fact that the number of possible isomers decreases as the cyclodextrin molecule becomes close to fully substituted. The ability of the cyclodextrin derivatives to form water-soluble complexes is also dependent on the degree of substitution (i.e. the solubility of the cyclodextrin molecule and the access of the guest molecule to the cyclodextrin cavity). Thus, the degree of substitution is in general optimized with regard to the solubilizing abilities of the cyclodextrins. The degree of substitution of the pharmaceutical grades is about 0.65 for 2-hydroxypropyl-β-cyclodextrin (i.e. on the average 0.65 hydroxypropyl-moieties are on each glucose unit) and about 1.8 for randomly methylated β-cyclodextrin (i.e. on the average 1.8 methoxy-moiety on each glucose unit). More than 1500 different cyclodextrin derivatives have now been synthesized and described in the literature and more than 100 are available as fine chemicals (Szejtli, 1998). However, since toxicological evaluations are very costly, only very few of these derivatives are available as pharmaceutical grade excipients (Table 3). Furthermore, since new cyclodextrin derivatives are unlikely to offer broad advantages over the currently used ones availability of new cyclodextrin derivatives will most likely increase very slowly.

2.3.3. Industrial applications of cyclodextrins

Until the late 1960s almost all cyclodextrin related chemistry was carried out in Europe but the obtained technological advances did not lead to notable industrial explorations of these oligosaccharides. However, in the early 1970s a number of industrial applications were being investigated, such as within the food and cosmetic industry (Vaution et al., 1987). In the food industry, cyclodextrins were being investigated as stabilizers for flavoring agents and to reduce unpleasant odor and taste. In the cosmetic industry cyclodextrins were being tested as stabilizers of chemically labile compounds, to obtain prolonged action, to decrease local irritation and to reduce unpleasant odors. In Japan, there is a tradition for industrial usage of natural products and the Japanese regarded the parent cyclodextrins as natural materials originating from starch and thus as "non-toxic" natural products. By 1970, the Japanese were already actively studying the chemistry of cyclodextrins as well as their production and in the early 1980s cyclodextrins were introduced as industrial raw materials, mainly for the food and cosmetic industries (Hashimoto, 2003). Within the next decade Japan became the largest cyclodextrin consumer in the world with an annual consumption of about 1800 tonnes, 80% of which went into the food industry and just over 10% into the cosmetic industry. Less than 5% were used in the pharmaceutical and agricultural industries. The industrial usage of cyclodextrins progresses somewhat slower in Europe and America. In the early 1990s, Procter & Gamble, an US based company, launched cyclodextrin-based fabric softener with "longer lasting freshness" which was followed by couple of other cyclodextrin-based products and today the company is the largest single industrial user of cyclodextrins.

Introduction of new excipients to the pharmaceutical industry is much more restricted than introduction of new excipients into toiletry and food products. However, in 1976 the world first pharmaceutical product, prostaglandin E2/β-cyclodextrin (Prostarmon E^{TM} sublingual tablets), was marketed in Japan by Ono Pharmaceutical Co. It was not until about 12 years later that piroxicam/β-cyclodextrin tablets were marketed in Italy by Chiesi Farmaceutici and the first cyclodextrin-containing formulation to be introduced to the US market was itraconazole/2-hydroxypropyl-β-cyclodextrin oral solution which was approved in 1997 (Frömming and Szejtli, 1994). Worldwide 30–40 different drugs are now marketed as cyclodextrin complexes (Table 4). In pharmaceutical formulations cyclodextrins are generally used as solubilizers but sometimes as stabilizers or to reduce local drug irritation.

2.3.4. Inclusion and non-inclusion complexes

It is generally accepted that in aqueous solutions cyclodextrins form what is called "inclusion complexes" where water molecules located within the lipophilic central cavity are replaced by a lipophilic guest molecule or a lipophilic moiety on, for example, a drug molecule. However, the hydroxy groups on the outer surface of the cyclodextrin molecule are able to form hydrogen bonds with other molecules and cyclodextrins can, like non-cyclic oligosaccharides and polysaccharides, form water-soluble complexes with lipophilic water-insoluble compounds (Riley et al., 1991; Loftsson et al., 1996; Tomasik and Schilling, 1998a; Tomasik and Schilling, 1998b). Linear homologs of maltodextrins, i.e. β-1,4-linked linear glucose oligomers, have been shown to bind fluorescence probes but the binding constants are significantly smaller than those for their cyclic counterparts (Aoyama et al., 1992). It has been shown that α-cyclodextrin forms both inclusion and non-inclusion complexes with dicarboxylic acids and that the two types of complexes coexist in aqueous solutions (Gabelica et al., 2002). In saturated aqueous solutions guest/cyclodextrin complexes frequently consist of a mixture of inclusion and non-inclusion complexes (Loftsson et al., 2004b). This could explain why the value of the equilibrium constant for the complex formation is sometimes concentration dependent and why their numerical value is frequently dependant on the method applied (Loftsson et al., 2002).

2.3.5. Methods to enhance the complexation efficiency

For a variety of reasons, including toxicological considerations, formulation bulk, production cost, drug bioavailability and isotonicity, it is important to use as small amount of cyclodextrin as possible in pharmaceutical formulations (Loftsson et al., 1999, 2005a). Same applies to other industrial products such as cosmetics and food products where excess amounts of cyclodextrins can have less than optimal effects. A number of methods have been applied to enhance the complexation efficiency (or rather the solubilization efficiency) of cyclodextrins and some of them are listed in Table 5. Formation of cyclodextrin complexes is an equilibrium process where free guest molecules are in equilibrium with molecules in the complex. Increasing the solubility of the guest through ionization, salt formation, formation of metal complexes and addition of organic cosolvents to the aqueous complexation media will, if the conditions are right, lead to enhanced complexation effi-

Table 4
Cyclodextrin-containing pharmaceutical products

Drug/cyclodextrin	Trade name	Formulation	Country
α-Cyclodextrin			
Alprostadil (PGE_1)	Prostavastin, Rigidur	I.V. solution	Japan, Europe, USA
OP-1206	Opalmon	Tablet	Japan
Cefotiam hexetil HCl	Pansporin T	Tablet	Japan
β-Cyclodextrin			
Benexate HCl	Ulgut, Lonmiel	Capsule	Japan
Cephalosporin (ME 1207)	Meiact	Tablet	Japan
Chlordiazepoxide	Transillium	Tablet	Argentina
Dexamethasone	Glymesason	Ointment	Japan
Diphenhydramin HCl, Chlortheophyllin	Stada-Travel	Chewing tablet	Europe
Iodine	Mena-Gargle	Solution	Japan
Nicotine	Nicorette, Nicogum	Sublingual tablet, chewing gum	Europe
Nimesulide	Nimedex	Tablet	Europe
Nitroglycerin	Nitropen	Sublingual tablet	Japan
Omeprazol	Omebeta	Tablet	Europe
PGE_2	Prostarmon E	Sublingual tablet	Japan
Piroxicam	Brexin, Flogene, Cicladon	Tablet, Suppository, Liquid	Europe, Brazil
Tiaprofenic acid	Surgamyl	Tablet	Europe
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Propulsid	Suppository	Europe
Itraconazole	Sporanox	Oral and I.V. solutions	Europe, USA
Mitomycin	Mitozytrex	I.V. infusion	Europe, USA
Methylated β-cyclodextrin			
Chloramphenicol	Clorocil	Eye drop solution	Europe
17β-Estradiol	Aerodiol	Nasal spray	Europe
Sulfobutylether β-cyclodextrin			
Voriconazole	Vfend	I.V. solution	Europe, USA
Ziprasidone mesylate	Geodon, Zeldox	IM solution	Europe, USA
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Voltaren	Eye drop solution	Europe
Tc-99 Teoboroxime	Cardiotec	I.V. solution	USA

The information listed in this table is partly based on the following references: Loftsson et al. (2004a), Szejtli (2004) and Loftsson et al. (2005b).

ciency (e.g. enhanced solubilization) in aqueous cyclodextrin solutions saturated with the guest (Loftsson et al., 1999). Application of supercritical fluids to prepare complexes is also partly based on enhancement of the intrinsic solubility (Van Hees et al., 1999).

2.3.6. Cyclodextrin aggregates

The effects of various excipients in Table 5, e.g. water-soluble polymers and certain organic acids and bases, can be explained by the fact that both cyclodextrins and cyclodextrin complexes self-associate to form nano-scale aggregates that interact with these excipients (Faucci et al., 2000; Loftsson et al., 2004b, 2005c; Duan et al., 2005). Formation of such structures is not easily detected and they have for the most part been ignored until relatively recently. They can, however, be made visible by Cryo-TEM micrographs. The size and shape of β-cyclodextrin aggregates in water have, for example, been shown to depend on the cyclodextrin concentration and other external factors and to have a minimum hydrodynamic radius of about 90 nm (Bonini et al., 2006). Other investigations have indicated that the aggregate diameter is much smaller or from 3 to 5 nm (Duan et al., 2005). Discovery of these aggregates, as well as the ability of cyclodextrins to form non-inclusion complexes, is likely to have profound influence on future cyclodextrin research.

2.3.7. Drug availability from cyclodextrin-containing products

It has been widely believed that drug availability in cyclodextrin-containing formulations will be hampered by the slow release of drug molecules from the cyclodextrin cavities. However, it has been shown that the rates for formation and dissociation of drug/cyclodextrin complexes are very close to diffusion controlled limits with complexes being continually formed and broken down (Stella and Rajewski, 1997). Consequently, presence of water-soluble drug/cyclodextrin complexes right at the hydrated epithelial surface will frequently increase the availability of dissolved drug molecules, especially of lipophilic drugs with poor aqueous solubility (Loftsson et al., 2006). Studies have shown that cyclodextrin enhance oral bioavailability of FDA's Class II (poor aqueous solubility, high permeability) drugs but they can hamper bioavailability of Class I (high solubility, high permeability) and Class III (high solubility, poor permeability) drugs (Loftsson et al., 2004a).

Table 5
Examples of methods that have been applied to enhance the complexation efficiency (or rather the solubilization efficiency) of cyclodextrins in pharmaceutical formulations

Effect	Consequences	References
Dug ionization	Unionized drugs do usually form more stable complexes than their ionic counterparts. However, ionization of a drug increases its apparent intrinsic solubility resulting in enhanced complexation.	Loftsson and Bodor (1989), Hussain et al. (1993), Krishnamoorthy and Mitra (1996), Li et al. (1998)
Salt formation	It is sometimes possible to enhance the apparent intrinsic solubility of a drug through salt formation, i.e. forming a more water-soluble salt of the drug without significantly reducing its ability to form cyclodextrin complexes.	Piel et al. (1998), Redenti et al. (2001), Granero et al. (2003), Loftsson et al. (2004c)
The acid/base ternary complexes	It has been shown that certain organic hydroxy acids (such as citric acid) and certain organic bases are able to enhance the complexation efficiency by formation of ternary drug/cyclodextrin/acid or base complexes.	Tinwalla et al. (1993), Selva et al. (1998), Fenyvesi et al. (1999), Redenti et al. (2000), Mura et al. (2003)
Polymer complexes	Water-soluble polymers form a ternary complex with drug/cyclodextrin complexes increasing the observed stability constant of the drug/cyclodextrin complex. This observed increase in the value of the constant increases the complexation efficiency.	Loftsson and Másson (2004)
Metal complexes	Many drugs are able to form somewhat water-soluble metal complexes without decreasing the drugs ability to form complexes with cyclodextrins. Thus, the complexation efficiency can be enhanced by formation of drug: metal ion: cyclodextrin complexes.	Yamakawa and Nishimura (2003)
Cosolvents	Addition of cosolvents to the complexation media can increase the apparent intrinsic solubility of the drug that can lead to enhanced complexation efficiency.	Furuta et al. (1993), Li et al. (1999)
Ion pairing	Ion pairing of positively charged compounds with negatively charged cyclodextrins enhances the complexation efficiency.	Zia et al. (2001)
Combination of two or more methods	Frequently the complexation efficiency can be enhanced even further my combining two or more of the above mentioned methods. For example drug ionization and the polymer method, or solubilization of the cyclodextrin aggregates by adding both polymers and cations or anions to the aqueous complexation medium.	Granero et al. (2003), Loftsson et al. (2003), Loftsson and Másson (2004)

2.3.8. Cyclodextrins in dispersed systems

Both the parent cyclodextrins and their derivatives have been used in dispersed vehicle systems such as emulsions, microcapsules, microspheres, nanospheres, nanocapsules, liposomes and niosomes (Duchêne et al., 2005; Trichard et al., 2006). Inclusion complexes of glycerides, fatty acids or fatty alcohols do possess surface activity and this property together with their ability to form aggregates frequently result in formation of dispersed systems. In other cases cyclodextrins have been uses to increase drug loading of polymeric microspheres or to increase drug availability from dispersed systems. Novel surface active cyclodextrin derivatives have also been synthesized and used as drug delivery systems (Hıncal, 2005; Memişoğlu-Bilensoy et al., 2005).

3. Toxicological considerations and regulatory status

Most of the currently used pharmaceutical excipients were developed several decades ago when regulatory issues, especially regarding toxicological evaluations, were much more relaxed. When highly pure cyclodextrins became available the requirements of toxicological evaluations had become much stricter. The industrial explorations of cyclodextrins have been hampered by toxicological evaluations, not because cyclodextrins are toxic but rather due to the high cost of proofing that they are not. Review article, published in 1957, refers to unpublished data reporting that rats died within a week from oral feeding of β-cyclodextrin (French, 1957). Several years later it was shown that oral feeding of α- or β-cyclodextrin to rats did not cause any toxic reactions (Andersen et al., 1963; Szejtli and Sebestyen, 1979) and that the previously observed toxicity was most likely due to impurities (Szejtli, 1988). However, the first erroneous toxicological report did for many years hamper pharmaceutical applications of cyclodextrins and their acceptance by the regulatory authorities.

3.1. Toxicological evaluations

The chemical structure of cyclodextrins (i.e., the large number of hydrogen donors and acceptors), their molecular weight (i.e., >972 Da) and their very low octanol/water partition coefficient (approximately $\log P_{o/w}$ between less than −3 and 0) are all characteristics of compounds that do not readily permeate biological membranes (Lipinski et al., 2001; Loftsson et

al., 2005b). Studies have shown that only negligible amounts of hydrophilic cyclodextrins and drug/cyclodextrin complexes are able to permeate lipophilic membranes such as gastrointestinal mucosa and skin (Irie and Uekama, 1997; Matsuda and Arima, 1999). All toxicity studies have demonstrated that when administered orally cyclodextrins are practically non-toxic due to lack of absorption from the gastrointestinal tract (Irie and Uekama, 1997). However, the lipophilic methylated β-cyclodextrins are surface active and they are to some extent (∼10%) absorbed from the gastrointestinal tract and consequently only limited amounts of these lipophilic cyclodextrin derivatives can be included in oral formulations, and they are unsuited for parenteral formulations. Due to toxicological considerations β-cyclodextrin cannot be used in parenteral formulations and the usage of α-cyclodextrin in parenteral formulations is severely limited although it can already be found in one marketed formulation (Table 4) (Irie and Uekama, 1997). In animal studies, γ-cyclodextrin has been found to be virtually non-toxic when given intravenously (Munro et al., 2004). Extensive toxicological studies have been completed for 2-hydroxypropyl-β-cyclodextrin (Gould and Scott, 2005) as well as for sulfobutylether β-cyclodextrin (Rajewski et al., 1995), both of which can be found in marketed parenteral formulations at relatively high concentrations (Table 4).

3.2. Regulatory status

The regulatory status of CDs is continuously evolving. The natural β-cyclodextrin can be found in a number of pharmaceutical formulations in numerous countries throughout the world (Table 4). Under certain conditions it is generally recognized as safe (GRAS) by the FDA and is listed in both the European Pharmacopoeia (Ph.Eur.) and US Pharmacopoeia (USP/NF) as well as in the Japanese Pharmaceutical Codex (JPC). In fact, all three natural cyclodextrins (i.e. α-, β- and γ-cyclodextrin) are listed in JPC and in Japan all three have been approved as food additives. α-Cyclodextrin is listed in Ph.Eur. and 2-hydroxypropyl-β-cyclodextrin is listed in both Ph.Eur. and USP/NF. 2-Hydroxypropyl-β-cyclodextrin is cited in the FDA's list of Inactive Pharmaceutical Ingredients. Consensus appears to be building among regulators that cyclodextrins are excipients and not part of the drug substance, which is logical based on their physicochemical properties as drug solubilizers and stabilizers.

4. Patents

The first cyclodextrin-related patent entitled "Verfahren zur Herstellung von Einschluβverbindungen physiologisch wirksamer organischer Verbindungen" (Fig. 4) was issued in Germany in 1953 (Freudenberg et al., 1953). This patent describes the basic properties of α-, β- and γ-cyclodextrin complexes, their precipitation in aqueous solutions and how the complexation enhances the chemical stability of biologically active compounds, increases their duration of activity and improves their taste. It contains four claims on preparation of cyclodextrin complexes with emphasis on what now is generally referred to as the precipitation method. However, this patent never found any industrial application (Cramer, 1987).

Erteilt auf Grund des Ersten Überleitungsgesetzes vom 8. Juli 1949
(WiGBl. S. 175)

BUNDESREPUBLIK DEUTSCHLAND

AUSGEGEBEN AM
5. NOVEMBER 1953

DEUTSCHES PATENTAMT

PATENTSCHRIFT

№ 895 769

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Dr. Karl Freudenberg, Heidelberg,
Dr. Friedrich Cramer, Heidelberg-Schlierbach und
Dr. Hans Plieninger, Heidelberg
sind als Erfinder genannt worden

Knoll A.-G. Chemische Fabriken, Ludwigshafen/Rhein

Verfahren zur Herstellung von Einschlußverbindungen physiologisch wirksamer organischer Verbindungen

Patentiert im Gebiet der Bundesrepublik Deutschland vom 26. August 1951 an
Patentanmeldung bekanntgemacht am 5. März 1953
Patenterteilung bekanntgemacht am 24. September 1953

Es ist bereits bekannt, Additionsverbindungen von organischen Stoffen herzustellen, die die zweite Komponente in den Hohlräumen ihres Moleküls oder Kristallgitters einschließen. So sind z. B. Additionsverbindungen von Desoxycholsäure, Harnstoff und von den Schardinger-Dextrinen bekannt, die die verschiedensten Stoffe eingeschlossen enthalten. Diese Additionsverbindungen, die treffender als Einschlußverbindungen bezeichnet werden, weil sie die eingeschlossenen Komponenten in getarnter Form enthalten, haben die Eigenschaft der Schwerlöslichkeit.

Während bisher bei den Schardinger-Dextrinen Addukte nur mit sauerstofffreien, physiologisch indifferenten, halogenhaltigen Kohlenwasserstoffen, insbesondere der aromatischen Reihe, und mit höheren Alkoholen bekannt waren, wurde nunmehr gefunden, daß diese Dextrine auch mit beliebigen, insbesondere mit physiologisch wirksamen Stoffen Einschlußverbindungen bilden. Diese neuen Addukte zeichnen sich ebenfalls durch Schwerlöslichkeit und meist damit verbundene protrahierte Wirkung, durch Beständigkeit gegen Körpersäfte, durch Geschmacksverbesserung und durch Lagerungsbeständigkeit aus.

Die neuen Addukte werden dadurch hergestellt, daß man konzentrierte wäßrige Lösungen der Schardinger-Dextrine mit den Einschlußkomponenten vereinigt. Zu diesem Zweck wird die heiß gesättigte, wäßrige Dextrinlösung mit der Einschlußkomponente versetzt und darauf allmählich erkalten gelassen. Nach einer anderen Ausführungsform des Verfahrens wird die gesättigte wäßrige Dextrinlösung mit der suspendierten Einschlußkomponente durchgeschüttelt. Man kann auch so vorgehen, daß man die wäßrige Dextrinlösung mit einer Lösung der Einschlußkomponente in einem mit

Fig. 4. The first page of two of the first cyclodextrin patent entitled "Method for preparation of inclusion compounds of physiologically active organic compounds". The patent was issued 5 November 1953 in Germany to Karl Freudenberg, Friedrich Cramer and Hans Plieninger.

Current cyclodextrin patents fall into four categories. First, certain methods for production of cyclodextrins are patent protected. For example, the cyclodextrin producing companies have patents on certain production techniques for producing α-, β- and γ-cyclodextrin and some of their derivatives. Second, there are patents on pharmaceutical applications of certain cyclodextrin derivatives. For example, Johnson & Johnson has patent on pharmaceutical applications of 2-hydroxypropyl-β-cyclodextrin in the US and CyDex has a patent on sulfobutylether β-cyclodextrin. Third, there are patents on methods to improve the performance of cyclodextrins. For example, certain formulation techniques for improving the solubilizing effects of cyclodextrins through addition of hydroxyacids or water-soluble polymers. Finally, there are patents on specific drug/cyclodextrin combinations. More than third of all cyclodextrin-related patents fall into this last category.

5. Conclusions

It took cyclodextrins 100 years to evolve from interesting chemical oddities to enabling pharmaceutical excipients. They were discovered in 1891, characterized in the first half of the last century but only came available as highly purified excipi-

ents during the past thirty years. Cyclodextrin-containing drug formulations have been approved for marketing in Japan and Europe and, within the last ten years, also in the US. In the beginning cyclodextrins were used to enhance aqueous solubility and chemical stability of drugs and these functionalities were related to their ability to form drug/cyclodextrin inclusion complexes. However, in recent years cyclodextrin have been shown to participate in various types of non-inclusion complexes with, for example, organic salts and water-soluble polymers. They have also been shown to form aggregates, either alone or in combinations with other excipients. These aggregates can form dispersed drug delivery systems such as micro- and nanoparticles. Thus, one hundred years after their discovery cyclodextrins are still regarded as novel excipients of unexplored possibilities.

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