International Journal of Pharmaceutics 531 (2017) 532–542

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Effects of cyclodextrins on the chemical stability of drugs

Agnieszka Popielec, Thorsteinn Loftsson*

Faculty of Pharmaceutical Sciences, University of Iceland, Hofsvallagata 53, IS-107 Reykjavik, Iceland

ARTICLE INFO

Article history:
Received 21 March 2017
Received in revised form 30 May 2017
Accepted 3 June 2017
Available online 6 June 2017

Keywords:
Aqueous solution
Catalysis
Complexation
Drug degradation
Stabilization

ABSTRACT

Cyclodextrins (CDs) are enabling pharmaceutical excipients that can enhance both solubility and stability of wide variety of drugs in aqueous solutions through formation of drug/CD inclusion complexes where apolar moieties of the drug molecules are located inside the CD cavity. In properly designed pharmaceutical formulations CDs will improve physiochemical properties of lipophilic drugs without affecting their intrinsic ability to permeate biological membranes. Here the effect of CD complexes on the chemical stability of drugs is reviewed. Numerous studies shown that in aqueous solutions CD complexation can hamper hydrolysis, oxidation, photodegradation, isomerization and enzyme catalyzed degradation of dissolved drugs. However, some drugs, such as β-lactam antibiotics, can under certain conditions undergo CD catalyzed degradation in aqueous solutions. Also, some drugs that are stabilized by CDs in aqueous solutions are destabilized by the same CDs in solid dosage forms. Thus, the effects of CDs on drug stability have to be tested and verified in the final drug formulation and under the recommended storage conditions.

1. Introduction

Cyclodextrins (CDs) can improve chemical and physical stability of drugs through formation of drug/CD complexes. In general complexes are divided into two main groups, metal ion complexes and molecular complexes. A silver ammonia complex ion ($[Ag(NH_3)_2]^+$) is an example of a metal ion complex. Molecular complexes include complexes between two small molecules as drug-caffeine complexes, complexes of small molecule and a large ligand such as drug-protein complexes (e.g., plasma protein binding) and substrate-enzyme complexes. Inclusion complexes are molecular complexes but due to their unusual structure they do not strictly adhere to the common complex classification. Calixarenes, cucurbiturils and cyclodextrins, form molecular cavities in which substrates can enter to form so called inclusion complexes or guest-host complexes where the substrates are the guest molecules and the ligands are the host molecules. Formation of a complex is a reversible process and changes the physicochemical properties of both guest and the host. In aqueous solutions dissolved inclusion complexes are generally in dynamic equilibrium with free guest and host molecules. Complexes and complex formations are very common natural phenomena which is also broadly use in pharmaceutical technology. Complexation with CDs is used to affect physical state, volatility, dissolution rate, partition coefficient, permeability, absorption and bioavailability and biological activity of many drugs. Here the effect of cyclodextrin inclusion complexes on the chemical stability of drugs is reviewed.

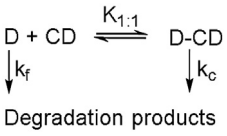
2. Cyclodextrins

Cyclodextrins (CDs) are the family of cyclic oligosaccharides consisting of α-1,4-linked glucopyranose units with a hydrophilic outer surface and a somewhat lipophilic central cavity. The most common natural CDs contain 6, 7 and 8 glucopyranose units and named αCD, βCD and γCD, respectively (Table 1). Some CD derivatives are available as pharmaceutical excipients and listed in pharmacopoeias, such as 2-hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutylether β-cyclodextrin (SBEβCD), but other derivatives have been synthesized and are commercially available as fine chemicals such as randomly methylated β-cyclodextrin (RMβCD), 2-hydroxypropyl-γ-cyclodextrin (HPγCD) and sulfobutylether γ-cyclodextrin (SBEγCD). The cyclic CD molecules are like truncated cones with the secondary hydroxy groups on the wider side and the primary hydroxy groups on the narrower side (Astakhova and Demina, 2004; Jansook et al., 2010; Szejtli, 2004). The CD cavity creates a lipophilic environment in aqueous solutions where small lipophilic molecules and lipophilic moieties of larger ones can enter to form inclusion complexes. There are no covalent bonds formed or broken during the inclusion and the interactions responsible for complex formation are relatively weak

* Corresponding author.
E-mail address: thorstlo@hi.is (T. Loftsson).

http://dx.doi.org/10.1016/j.ijpharm.2017.06.009
0378-5173/

Table 1
Characteristics of the natural α-, β- and γ-cyclodextrin (Szejtli, 1988).



Parameters	α-Cyclodextrin	β-Cyclodextrin	γ-Cyclodextrin
Number of glucose units	6	7	8
Molecular weight (g/mol)	972.86	1135.01	1297.15
Water solubility (g/L)	145	18.5	232
Cavity diameter (Å)	4.7–5.2	6.0–6.4	7.5–8.3
Outer diameter (Å)	14.6	15.4	17.5
Height of torus (Å)	7.9	7.9	7.9
Cavity volume (Å^3)	174	262	427

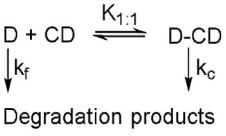
non-covalent interactions such as van der Waals forces, hydrophobic interactions and hydrogen bonds. Most frequently one drug (D) molecule forms a complex with one CD molecule in dilute aqueous solutions (i.e. m = n = 1 in Eq. (1)). The stoichiometry is then said to be 1:1 and the equilibrium constant ($K_{1:1}$) defined as

$$K_{1:1}=\frac{[D-CD]}{[D]\cdot[CD]} \quad (2)$$

where [D] is the concentration of free drug in the solution, [CD] is the concentration of free CD and [D-CD] is the concentration of the complex. Formation of drug-CD complexes can affect the physiochemical properties of drugs such as their chemical stability. In most cases an increase in chemical stability is observed upon addition of CDs to drug formulations but in some cases the stability is decreased.

4. Determination of stability and kinetic constants

In aqueous CD solutions free drug molecules are in dynamic equilibrium with drug molecules bound within CD complexes. The rates for formation and dissociation of drug-CD complexes are very close to the diffusion-controlled limits and the complexes are continuously being formed and dissociated (Stella et al., 1999). If 1:1 drug-CD complex is formed and if the drug degradation follows first-order kinetics both in the free form and within the complex then the following kinetic pathways are present:



where $K_{1:1}$ is the equilibrium constant for the complex formation (sometimes referred to as the stability constant), k_f is the observed first-order rate constant for the degradation of the free drug (D) and k_c represents the observed first-order rate constant for the drug degradation within the complex (D-CD). The observed first-order rate constant (k_{obs}) for the drug degradation in the aqueous complexation medium is the weighted average of k_f and k_c (Loftsson, 2014):

$$k_{obs}=\frac{k_f+k_c\cdot K_{1:1}\cdot[CD]_T}{1+K_{1:1}\cdot[CD]_T} \quad (4)$$

where $[CD]_T$ is the total concentration of dissolved CD in the aqueous complexation medium, assuming that the total CD concentration is much greater than the total drug concentration (i.e. $[CD]_T >> [D]_T$ and $[CD] \approx [CD]_T$). The value of k_f is determined in the complexation medium when no CD is present. $K_{1:1}$ and k_c are then obtained by determining k_{obs} at fixed drug concentration but different CD concentrations and non-linear fitting of the values thus obtained to Eq. (4). Alternatively, $K_{1:1}$ and k_c can be obtained through linear fitting such as Lineweaver-Burk plot (Loftsson, 2014):

$$\frac{1}{k_f-k_{obs}}=\frac{1}{K_{1:1}(k_f-k_c)}\cdot\frac{1}{[CD]_T}+\frac{1}{k_f-k_c} \quad (5)$$

Plot of $(k_f-k_{obs})^{-1}$ versus $([CD])^{-1}$ gives straight line from which k_c can be obtained from the intercept and $K_{1:1}$ from the slope. There are numerous reports on the effects of CDs on drug stability (Table 2). In most cases $k_c < k_f$ and the CD complexation stabilizes the drug and increases the shelf-life of the drug product but in some cases CD complexation accelerates the drug degradation and $k_c > k_f$ (Table 3).

5. Examples of how CDs affect drug degradation

5.1. Hydrolysis: β-Lactam antibiotics

β-Lactam antibiotics (e.g., penicillins, cephalosporins, carbapenems and monobactams) are a class of broad-spectrum antibacterial agents that contain a four-membered β-lactam ring in their molecular structure. In general, amides and lactams are relatively stable but due to structural strain of the four-member β-lactam ring it is readily hydrolyzed in aqueous solutions with complete loss of the antibacterial activity. Studies have shown that CDs tend to protect β-lactam ring against hydrolytic degradation under acidic conditions (Aki et al., 2004; Alsarra et al., 2007; Hidaka et al., 2010; Loftsson et al., 1994; Popielec et al., 2016), have no effect or even catalyze their decomposition at neutral pH (Alsarra et al., 2007; Aso et al., 1989; Popielec et al., 2016), and catalyze β-lactam degradation under basic conditions (Loftsson et al., 1994). This behavior can partly be explained by ionization/deionization of carboxyl group of β-lactam antibiotic (Fig. 1). The carboxyl group of β-lactam antibiotics, such as benzylpenicillin, are unionized at very acidic pH (i.e. when pH < pK_a). In their unionized form the drugs are more lipophilic and form more readily inclusion complex with CDs and within the CD cavity the molecules are somewhat protected against specific acid catalyzed hydrolysis of the β-lactam ring (Popielec et al., 2016). At pH above the pKa value the carboxyl group is ionized, the molecules become more hydrophilic and have decreased ability to enter the somewhat hydrophobic CD cavity. The catalyzing effect of CDs can be explained by the fact that CDs are oligosaccharides and like other saccharides (e.g., glucose) catalyze β-lactam degradation in aqueous solutions under neutral and basic conditions. Fig. 1 shows the effect of RMβCD on the hydrolysis of benzylpenicillin at pH 1.2 and 7.4. At pH 1.2 the pH is below the pKa value and RMβCD has stabilizing effect. The observed rate constant (k_{obs}) decreases with increasing RMβCD concentration and k_c and $K_{1:1}$ are obtained from Lineweaver-Burk plot and determined to be 1.94 h^{-1} and 450 M^{-1}, respectively (Table 3). At pH 7.4 k_{obs} increases with increasing RMβCD concentration and k_c and $K_{1:1}$ were determined to be $6.00\cdot10^{-3}$ h^{-1} and 190 M^{-1}, respectively. However, there are some exceptions from this general observation regarding CD effect on β-lactam stability. Some CDs derivatives (e.g., RMβCD, HPβCD and HPγCD) have stabilizing effect on cephalotin in neutral aqueous solution (Loftsson et al., 1994). Base catalyzed hydrolysis of benzylpenicillin can, under certain conditions, be inhibited by RMβCD while HPβCD increases the degradation under the same conditions. Positively charged derivatives of βCD, where some of hydroxyl groups have been substituted by quaternary ammonium