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ORIGINAL ARTICLE

Self-assembled cyclodextrin nanoparticles and drug delivery

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Abstract Drug/cyclodextrin complexes self-assemble in aqueous solutions to form nanosized aggregates or nanoparticles. These complex aggregates are responsible for many of the physicochemical and biological properties of cyclodextrin complexes. Due to the aggregate formation aqueous drug/cyclodextrin solutions can behave more like dispersed nanoscale systems, such as nano-suspensions and liposomes, rather than true solutions. The aggregation can result in enhanced cyclodextrin solubilization of poorly soluble lipophilic drugs; they can serve as building blocks for ternary or higher order complexes; they can be developed into nano- and microparticulated drug carriers for targeted drug delivery to, for example, hair follicles; they can be developed into sustained drug delivery systems; and they can possible be used as mucus-penetrating drug delivery vectors. All of this can be obtained without chemical modifications of the cyclodextrin monomers.

Keywords Cyclodextrin · Complexes · Nanoparticle · Self-assemble · Aggregates · Drug delivery

Introduction

Since their discovery over 120 years ago cyclodextrins have been intensively investigated and are every year the subject of over 1,000 original research articles published in peer-reviewed journals [1, 2]. Thus, one might expect that the physicochemical properties of cyclodextrins and their aqueous solutions had already been elucidated or so it was thought. However, when you have worked with cyclodextrins for some time you start to notice some abnormalities; that the various experimental methods applied do not give consistent results or results that can be explained by the conventional thinking of guest/host complex formation [3, 4]. Frequently phase-solubility studies do, for example, suggest formation of higher order drug/cyclodextrin complexes with 1:2 or 2:1 stoichiometry although other analytical methodologies such as Job's plots and docking studies clearly show that only 1:1 drug/cyclodextrin complexes can be formed. Likewise, the numerical values of true drug-cyclodextrin formation constants (e.g. $K_{1:1}$ stability constants of 1:1 drug/cyclodextrin complexes) should be independent of both the guest and host concentrations as well as of the method applied to determine their values but frequently they are not. Lipophilic compounds that are known to have high affinity for the cyclodextrin cavity should reduce cyclodextrin solubilization of poorly soluble drugs but sometimes they actually enhance the solubilization. Polymers such as water-soluble cellulose derivatives and organic salts such as sodium acetate frequently enhance cyclodextrin solubilization of poorly soluble unionized drugs, observations that are difficult to explain if only simple drug/cyclodextrin complexes are being formed [5, 6]. These and other observations show that something more must be going on in aqueous cyclodextrin solutions than just formation of simple drug/cyclodextrin complexes.

Cyclodextrins are cyclic oligosaccharides that are known to possess some of the same physicochemical and biological properties as small linear saccharides [2]. In aqueous solutions trehalose molecules are known to interact through hydrogen bond formations to form small clusters or aggregates even at very low concentrations [7]. Trehalose is a natural alpha-linked disaccharide formed by

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two glucose units. In general the tendency of saccharides to self-assemble and form nanoparticles increases with increasing molecular weight. The natural α-, β- and γ-cyclodextrin, formed by 6, 7 and 8 glucose units respectively, are also known to form aggregates in pure aqueous solutions with diameter from approximately 60–120 nm [8–12]. However, the aggregates represent only very small fraction (much less than 1 %) of the total amount of dissolved cyclodextrin. The randomly substituted cyclodextrin derivatives, like 2-hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutyl ether β-cyclodextrin, have much less tendency to self-assemble in pure aqueous solutions. Over the years aggregates or nanoparticles were sometimes observed in aqueous cyclodextrin solutions containing lipophilic poorly water-soluble compounds [13–18] although no systematic investigation of cyclodextrin aggregates and their formation was initiated. It was simply thought that formation of such aggregates did only occur under some very special conditions. The purpose of this paper is to review what currently is known about formation of cyclodextrin complex aggregates and how the aggregates can be utilized in drug delivery.

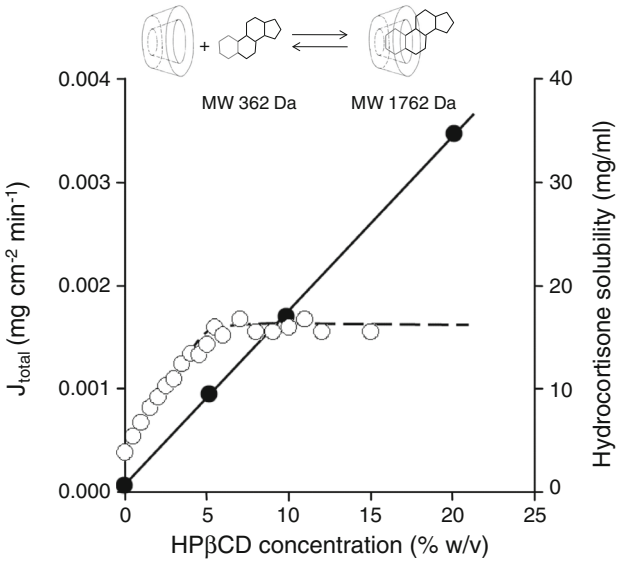

Fig. 1 The linear (i.e. A_L-type) phase-solubility profile of hydrocortisone in pure aqueous 2-hydroxypropyl-β-cyclodextrin (HPβCD) solution (*filled circle*) and the total flux (J_{total}) of hydrocortisone (i.e. both free and as drug/cyclodextrin complex) from the same hydrocortisone saturated HPβCD solutions (*open circle*) through semipermeable cellophane membrane with molecular weight cutoff (MWCO) 15,000 Da. The molecular weight of hydrocortisone is 362 Da and the mean molecular weight of HPβCD 1,400 Da. The figure is based on data from [32]

Formation of complex aggregates

During the past 25 years, or since water-soluble cyclodextrin derivatives suitable for pharmaceutical applications came available, drug-cyclodextrin interactions have been intensively investigated and how cyclodextrins can affect solubility, bioavailability and stability of drugs. One aspect of these studies was investigation of how cyclodextrins can both enhance and hamper drug permeation through biological membranes. Optimization of pharmaceutical formulations involved in vitro drug release studies from the test formulations through both synthetic and biological membranes [19–25]. One such case was formulation of aqueous mouthwash solution containing hydrocortisone [26, 27]. Hydrocortisone displays linear (A_L) phase-solubility diagram in pure aqueous solutions containing randomly substituted 2-HPβCD. The solubility increase was thought to be due to formation of one-to-one hydrocortisone/HPβCD complexes and the stability constant ($K_{1:1}$) was determined to be about 1,000 M^{-1}. The molecular weight of hydrocortisone is 362 Da and that of the 1:1 hydrocortisone/HPβCD complex approx. 1,760 Da. Thus, both individual hydrocortisone molecules and the hydrocortisone/HPβCD complex should easily permeate semipermeable cellophane membrane with molecular weight cutoff of 15 kDa. Still, when drug permeation from aqueous HPβCD solutions saturated with the drug through the membrane was studied the permeation profile showed strong negative deviation from linearity. The flux did not follow Fick's law of diffusion:

$$J = \frac{D}{h}(C_1 - C_2) \quad (1)$$

where J is the drug flux through the semipermeable membrane, D is the diffusion coefficient, h is the thickness of the membrane, C_1 is the drug concentration in the donor phase and C_2 is the drug concentration in the receptor phase. When C_1 is much greater than C_2 (called sink condition) then $(C_1 - C_2) \approx C_1$:

$$J = \frac{D}{h}C_1 \quad (2)$$

Thus under sink conditions there should be linear relationship between J and the amount of dissolved hydrocortisone in the donor phase but it is not (Fig. 1).

The flux intercept with the Y-axis represents the flux of the free hydrocortisone through the membrane and since the concentration of free hydrocortisone ($C_{hydrocortisone}$) is constant in the hydrocortisone saturated aqueous HPβCD solutions this value (i.e. $J_{free\ drug}$) will be constant throughout the study presented in Fig. 1:

$$J_{total} = J_{freedrug} + J_{drugcomplex} = \frac{D_{drug}}{h}C_{hydrocortisone} + \frac{D_{complex}}{h}C_{complex} \quad (3)$$

Based on the linear phase-solubility profile J_{total} should display a linear increase with increasing $C_{complex}$. This is what indeed happens up to about 5 % HPβCD but then the flux profiles displays a negative deviation from linearity until a plateau is reached at HPβCD concentrations above about 7 %. Similar results were obtained for different drugs and cyclodextrins, and a variety of semipermeable membranes and suggested that the negative deviation from linearity was due to formation of drug/cyclodextrin complex aggregates [3, 4, 28]. Formation of complex aggregates in the aqueous media was later confirmed by various analytical methodologies such as dynamic light scattering, osmometry and transmission electron microscopy [29–33]. Further investigation of the cyclodextrin aggregates have shown that [8, 9, 12, 18, 34, 35]:

- The natural α-, β- and γ-cyclodextrin do form aggregates by themselves in pure aqueous cyclodextrin solutions but the aggregation is very low with much less than 1 % of dissolved cyclodextrin present in aggregates.
- Aggregation of the randomly substituted cyclodextrin derivatives, such as 2-HPβCD, randomly methylated β-cyclodextrin, sulfobutyl ether β-cyclodextrin and sugammadex, is negligible in pure aqueous solutions.
- Formation of drug/cyclodextrin inclusion complexes increases the aggregation, both in the case of the parent cyclodextrins and in the case of the randomly substituted cyclodextrin derivatives.
- The diameter of the complex aggregates depends on the guest/host properties.
- The degree of aggregation depends on the availability of guest/cyclodextrin complexes in the aqueous solution, increasing with increasing complexation. Thus addition of excipients such as ethanol that decrease the complexation will reduce the aggregation. Similarly heating of the aqueous cyclodextrin solutions will result in decreased aggregation.
- Both the aggregation and the size of the aggregates formed are concentration dependent increasing with increasing drug/cyclodextrin complex concentration.
- In aqueous solutions guest/cyclodextrin complex aggregates are in dynamic equilibrium with unaggregated complexes, constantly being formed and dissembled.
- The complex aggregates are unstable and dissemble up on media dilution.
- Complexes of the natural α-, β- and γ-cyclodextrin have limited solubility in water and tend to precipitate in aqueous solutions as solid drug/cyclodextrin complex aggregates. The complexes are frequently less soluble than the cyclodextrins themselves.

Formation of nanosized drug/cyclodextrin complex aggregates in aqueous solutions appears to be rather common, even in solutions containing complexes of the randomly substituted cyclodextrin derivatives and especially if the concentration of the water-soluble cyclodextrin derivatives is higher than about 5 % (w/v). The diameter of the aggregates is most frequently less than about 1/4 of the wavelength of the visible light (i.e. 380–750 nm) and, thus, aqueous solutions containing such drug/cyclodextrin complex aggregates appear to be clear solutions to the naked eye.

Cyclodextrin aggregates in drug delivery

Due to formation of cyclodextrin complex aggregates aqueous cyclodextrin solutions tend to behave more like dispersed nanoscale systems, such as nano-suspensions, microemulsions and liposomes, rather than true solutions [36]. Formation of cyclodextrin complex aggregates allows formation of cyclodextrin-based drug delivery systems without chemical modification of the parent cyclodextrins or cyclodextrins that currently can be found in pharmaceutical products such as 2-HPβCD and sulfobutyl ether β-cyclodextrin. Following are few examples of the nanoparticulate nature of aqueous drug/cyclodextrin complex solutions and their application in drug delivery.

Solubility

Cyclodextrins are mainly used as solubilizers in pharmaceutical products [1]. Many lipophilic drugs that are poorly soluble in aqueous solutions form water-soluble complexes with hydrophilic cyclodextrins. Formation of water-soluble drug/cyclodextrin complexes allows formulation of these poorly soluble drugs as aqueous solutions for, for example, parenteral administration or topical administration to the eye [37, 38]. However, the parent cyclodextrins, especially β-cyclodextrin, and their complexes have very limited solubility in aqueous solutions. It is known that water-soluble polymers and surfactants are able to stabilize various types dispersed systems in aqueous solutions [39–41]. Similarly, water-soluble polymers and salts of organic acids have been shown to enhance the complexation efficacy of cyclodextrins and to solubilize poorly soluble drug/cyclodextrin complexes [5, 6, 42–47]. Example of such enhanced cyclodextrin solubilization is solubilization of hydrocortisone in aqueous β-cyclodextrin solutions or suspensions (Fig. 2) [6]. In pure water the phase-solubility is of B_S-type with maximum hydrocortisone solubility of about 2.2 mg/ml. When 0.25 % (w/v) hydroxypropyl methylcellulose is present in the aqueous complexation medium the maximum solubility increases to 3.6 mg/ml. When 1 % (w/v) sodium acetate is present the maximum solubility increases to 7.1 mg/ml. When both 0.25 % (w/v) hydroxypropyl

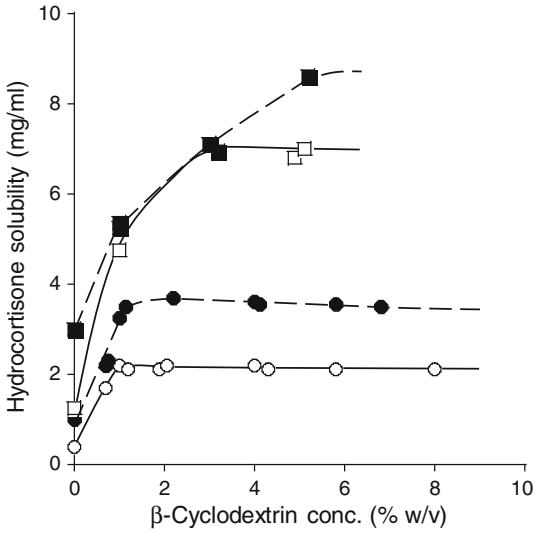

Fig. 2 Phase-solubility diagrams of hydrocortisone in aqueous β-cyclodextrin solutions or suspensions. The aqueous complexation media consisted of pure water (*open circle*), aqueous 0.25 % (w/v) hydroxypropyl methylcellulose 4,000 solution (*filled circle*), aqueous 1 % (w/v) sodium acetate solution (*open square*), and aqueous 1 % (w/v) sodium acetate solution containing 0.25 % (w/v) hydroxypropyl methylcellulose 4,000 (*filled square*). The figure is based on data from [6]

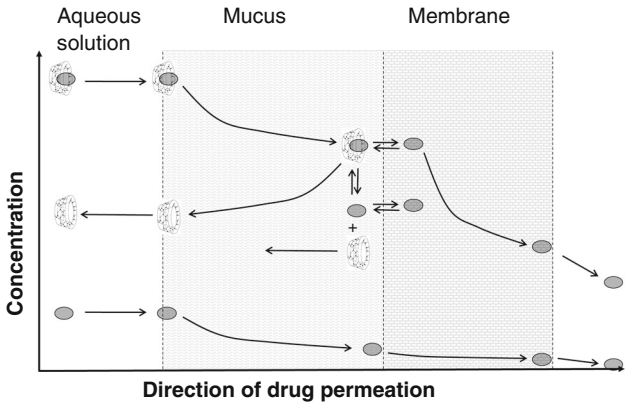

Fig. 3 Schematic drawing showing drug permeation through mucosa from an aqueous cyclodextrin solution. More detailed description is given in Refs. [51, 52]

methylcellulose and 0.1 % (w/v) sodium acetate is present the maximum hydrocortisone solubility is increased even further. The enhanced solubilization is partly due to increased solubility of β-cyclodextrin and its complex and partly due to enhanced complexation efficacy (i.e. increases in the apparent stability constant of the hydrocortisone/β-cyclodextrin complex). The aqueous solubility of hydrocortisone was determined to be 0.4 mg/ml [6]. Other water-soluble polymers, salts and surfactants were shown to have similar effects on the complexation efficiency and solubility of drug/cyclodextrin complexes and that these observations can be explained by formation of nanosized drug/cyclodextrin complex aggregates [6, 36, 48].

Permeation through biological membranes

Mucosae (or mucous membranes) are mucus-secreting membranes that line the body passages that are open to the external environment, such as the nostrils, buccal cavity, gastrointestinal tract and the respiratory tract. Mucus forms an aqueous diffusion barrier at the surface of the lipophilic membrane barrier (the epithelium) [36, 49–52]. Thus, drug permeation through mucosa encounters two types of barriers, i.e. an aqueous diffusion barrier (sometimes referred to as the unstirred water layer) and a lipophilic membrane barrier (Fig. 3). Cyclodextrins enhance drug permeation only if mucus forms a significant barrier towards drug permeation through mucosa. That is to say, when cyclodextrins enhance solubility of poorly soluble lipophilic drugs in systems where the aqueous diffusion barrier is present at the membrane surface and contributes to the barrier properties of the membrane. Under such conditions cyclodextrins enhance passive drug diffusion through mucus by increasing the drug concentration gradient over the aqueous mucus layer in accordance to Eq. 1. Some investigators have suggested that the effective thickness of the unstirred water layer in the gastrointestinal tract (i.e. the mucus layer) decreases with increasing cyclodextrin concentration leading to enhanced drug absorption [53, 54]. Still other investigators have shown that certain types of drug nanoparticles can permeate mucus faster than individual drug molecules [55, 56]. This effect has been reported to be associated with nanoparticles with hydrophilic coronas that minimize protein interaction. Thus, it is possible that cyclodextrin aggregates may act as mucus-penetrating delivery vectors that can rapidly translocate drugs from the intestinal lumen to the lipophilic membrane barrier.

Targeted drug delivery

Topical drug delivery systems that selectively target hair follicles and sweat glands are of interest to both the pharmaceutical and the cosmetic industry, not only to treat dermal complications but also for systemic drug delivery [57–59]. Possible dermal applications include treatment of acne, inflammation and hair growth disorders. Microparticulate vehicles, like liposomes [58, 60] and nanoparticles [61–63], have been shown to deliver drug molecules much deeper into the hair follicles than conventional formulations like creams and ointments. It has been shown that liposomes and nanoparticles with diameter between 300 and 750 nm penetrate preferentially into the hair follicles [64] and that titanium dioxide particles with diameter of about 100 nm penetrate into the hair follicles [65]. Studies

have indicated that, like other nanoparticles, self-assembled cyclodextrin complex nanoparticles are excellent vehicles for targeted drug delivery of lipophilic drugs to hair follicles and other microscopic openings on the skin surface [66].

Sustained drug delivery to the eye

Like in the case of drug permeation through mucosae drug permeation from the eye surface into the eye encounters two different types of barriers, i.e. an aqueous mucus (a diffusion barrier) and a membrane barrier that can either be the corneal epithelial barrier (a lipophilic membrane barrier) or sclera that mainly consists of a collagen matrix (a hydrophilic membrane barrier) [67–70]. The third barrier to topical drug delivery to the eye is the tear fluid drainage. The tear fluid is constantly produced and drained from the eye surface at a rate of a about 1.5 µl/min. The normal tear volume is only about 7 µl. Consequently, the precorneal drug half-life of dissolved drug after topical administration is less than 3 min [71]. Administration of cyclodextrin-solubilized poorly soluble lipophilic drugs in aqueous eye drop solutions increases drug delivery from the surface into the eye [52, 72]. Although drug/cyclodextrin complex self-assemble to form nanosized aggregates (nanoparticles) and although such dissolved aggregates possess some mucoadhesion they will slowly be washed from the eye surface. In other words, cyclodextrin solutions increase to some extent topical drug delivery into the eye but their efficacy is limited by their relatively short half-life on the eye surface. Increasing the size of the nanoparticles from 20–100 to 1,000–2,000 nm prevents their removal from the eye surface with the tear flow resulting in sustained high drug concentration in the tear fluid [73]. For example, aqueous eye drops containing 30 mg/ml of dexamethasone have been formulated as dexamethasone/γ-cyclodextrin complexes in nanoparticulated aqueous eye drops [74]. The eye drops consisted of relatively large nanoparticles (mean diameter 1,200 nm) containing about 85 % of the drug, smaller nanoparticles (diameter about 100 nm) containing about 13 % of the drug, free (i.e. unaggregated) dexamethasone/γ-cyclodextrin complexes (1–2 %) and uncomplexed dissolved dexamethasone molecules (<1 %). The solubility of the visible larger nanoparticles in the aqueous tear fluid is low or about 3 mg/ml but still much larger than that of free dexamethasone (about 0.1 mg/ml). Thus, sustained high concentration (duration >6 h) of dissolved dexamethasone in the tear fluid is obtained by formulating the drug/cyclodextrin complexes as mixture of large and small nanoparticles in aqueous eye drop vehicle (Fig. 4) [73]. The concentration of dissolved dexamethasone (i.e. 3 mg/ml) consists of small nanoparticles, individual drug/cyclodextrin complexes and free drug molecules all of which are able to penetrate mucus to the membrane surface. Conventional eye drops containing dexamethasone suspension (Maxidex®, Alcon Laboratories, USA) contain much less dexamethasone (1 mg/ml) and result in much less dissolved drug (approx. 0.1 mg/ml) in the aqueous tear fluid. Since drug permeation from the surface into the eye follows passive diffusion (Eq. 1) conventional dexamethasone eye drops will in theory be 30 times less effective in delivering dexamethasone into the eye. In vivo studies in rabbits have shown that the nanoparticulated eye drops deliver drugs to both the anterior and posterior segment of the eye much more efficiently than conventional eye drops [75–78]. Clinical studies in humans have confirmed their ability to deliver drug topically to the posterior segment of the eye [79].

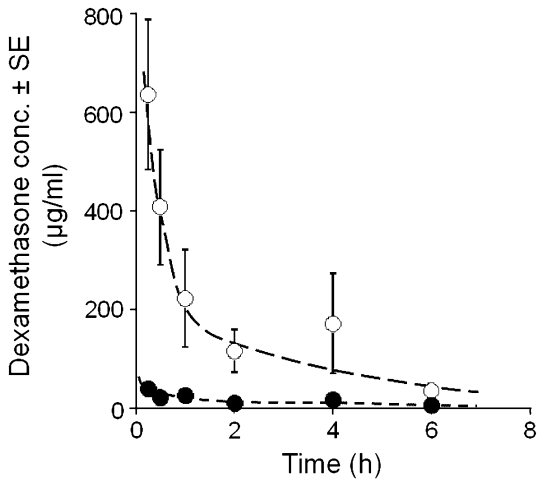

Fig. 4 Concentration of dexamethasone in the human tear film after topical application of either on drop of Maxidex® containing 1 mg/ml of dexamethasone alcoholic suspension from Alcon Laboratories, USA, (*filled circle*) or aqueous dexamethasone/γ-cyclodextrin nanosuspension (*open circle*) containing aqueous 15 mg/ml dexamethasone in a γ-cyclodextrin complex. The *error bars* represent standard error of the mean (n = 6); in some cases the bars do not extend outside the circles. The figure is based on data from [73, 80]

Conclusions

Self-assembled cyclodextrin nanoparticles are commonly formed in aqueous solutions and are responsible for many of their physicochemical and biological properties. The nanoparticles can serve as building blocks for ternary or higher order complexes leading to, for example, enhanced solubilization and mucoadhesion. They can be developed into nano- and microparticulated drug carriers (nanomedicine) for targeted drug delivery. But sometimes they form unwanted particulate matters in pharmaceutical products.

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