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Cyclodextrins and the Biopharmaceutics Classification System of Drugs

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Abstract

Although the biopharmaceutics classification system (BCS) was originally developed for solid oral dosage forms this system can be extended to other types of drug delivery forms. According to the BCS aqueous solubility and permeability are the most important parameters affecting drug bioavailability. Cyclodextrins can enhance the aqueous solubility of lipophilic drugs without changing their intrinsic ability to permeate biological membranes. Thus, through cyclodextrin complexation it is possible to move Class II drugs, and sometimes even Class IV drugs, into Class I. However, cyclodextrins can decrease bioavailability of Class I drugs and will in most cases not improve bioavailability of Class III drugs. Through formation of drug/cyclodextrin/polymer ternary complexes it is possible to enhance the complexation efficacy of cyclodextrins and at the same time improve drug bioavailability from cyclodextrin containing drug formulations.

Introduction

In general, biomembranes, such as the mucosal membrane of the gastrointestinal tract, consist of a lipophilic membrane with an aqueous exterior. The fundamental equation describing passive drug transport through biomembranes is based on Fick's first law:

$$J = P \cdot C_{\mathrm{Aq}}, \tag{1}$$

where J is the drug flux through the biomembrane (mass/area/time), P is the permeability coefficient through the lipophilic membrane and C_{Aq} is the drug concentration in the aqueous exterior at the membrane surface. The permeability coefficient is defined as:

$$P = \frac{D \cdot K}{h}, \tag{2}$$

where D is the drug's diffusion coefficient within the membrane, K is the partition coefficient of the drug from the aqueous exterior into the membrane and h is the thickness of the membrane. Finally the diffusion coefficient can be estimated by Stokes–Einstein equation:

$$D = \frac{R \cdot T}{6\pi \cdot \eta \cdot r \cdot N}, \tag{3}$$

where R is the molar gas constant, T is the absolute temperature, η is the viscosity of the membrane, r is the radius of a spherical drug molecule permeating the membrane, and N is Avogadro's number. The equations show that for a drug molecule to be successfully delivered through a biomembrane the drug must possess some aqueous solubility (C_{Aq}) but at the same time the drug must possess some lipophilicity to be able to partition from the aqueous exterior into the lipophilic membrane (K). In addition, according to Equation (3) small drug molecules permeate membranes more easily than large molecules. Active transportation through the biomembranes, efflux, and metabolism, as well as paracellular transportation of small hydrophilic molecules, generate all some exceptions from these general equations but overall the equations are applicable for large majority of drugs. Consequently, these equations provide the basis for various computational approaches that are applied to predict drug bioavailability [1–3]. Even somewhat empirical observations are based on these equations. For example, Lipinski's 'rule of five' predicts that poor absorption or permeation is more likely when drug molecule contains more than 5 H-bond donors (expressed as the sum of OHs and NHs), more than 10 H-bond acceptors (expressed as the sum on Ns and Os), its molecular weight is greater than 500 or its calculated Log P is greater than 5 [3]. All these parameters are associated with aqueous solubility and permeability of drugs.

The biopharmaceutics classification system

Some years ago FDA introduced a Biopharmaceutics Classification System (BCS) for oral drug products. In this system drugs are classified into four groups based on the ability of a given drug substance to permeate biological membranes and its aqueous solubility, or parameters which can be found in the previously mentioned equations (Table 1) [1, 4–7]. In this system a given drug substance is considered "highly soluble" when the highest dose strength is soluble in $\leq$250 ml water over a pH range 1 to 7.5 and "highly permeable" when the extent of absorption in humans is determined to be $\geq$90% of an administered dose (in solution), based on mass-

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Table 1. The biopharmaceutics classification system (BCS)

Class I	Class II
Highly soluble Highly permeable	Poorly soluble Highly permeable
Class III	Class IV
Highly soluble Poorly permeable	Poorly soluble Poorly permeable

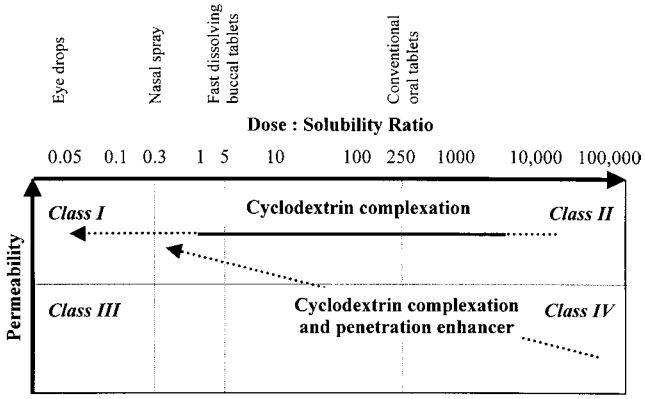

Figure 1. The effect of formulation and cyclodextrin complexation on the classification of drug substance.

balance or related to an intravenous reference dose. For a rapidly dissolving tablet ≥85% of the labeled amount of drug substance must dissolve within 30 min. Thus, for rapidly dissolving solid oral dosage forms the dose-to-solubility ratio (D:S) of the drug must be ≤250 ml over pH range of 1 to 7.5 [4, 7, 8].

Class I consists of water-soluble drugs that are well absorbed from the gastrointestinal tract and, in general, have the preferred physicochemical properties. For immediate release dosage forms the absorption rate will be controlled by the gastric emptying rate. However, to secure constant high bioavailability the dissolution rate must be relatively fast, or over 85% dissolution in 15 minutes [4].

Class II consists of water-insoluble drugs which, when dissolved, are well absorbed from the gastrointestinal tract. The dissolution rate *in vivo* is usually the rate-limiting step in drug absorption. Commonly drugs in this class have variable absorption due to the numerous formulation effects and *in vivo* variables that can affect the dissolution profile [4]. Various formulation techniques are applied to compensate for the insolubility of the drugs and the consequent slow dissolution rate. These include formulation of the amorphous solid form, nanoparticles, surfactant addition, salt formation and complexation [6, 7]. By such techniques the formulator tries to move the drugs from Class II to Class I without changing the intrinsic ability of the drug molecules to permeate biomembranes.

Class III consists of water-soluble drugs that do not readily permeate biomembranes. For these drugs the rate-limiting factor in drug absorption is their permeability. Including absorption enhancing excipients in their formulation can enhance their bioavailability.

Class IV consists of water-insoluble drugs which when solubilized do not readily penetrate biomembranes. These drugs are usually very difficult to formulate for effective oral delivery

The biopharmaceutics classification system and non-oral drug delivery

Although the BCS was originally developed for solid oral dosage forms a similar system can be applied to other types of drug formulations (Table 2). According to this system the solubility and dissolution requirements for many dosage forms are quite narrow when compared to the FDA's requirements for immediate release solid dosage forms such as conventional tablets. It can also be seen that classification of drugs according to Table 1 will depend on the formulation. A drug that is in Class I when given as an oral tablet can be in Class II when given in the form of nasal spray (Figure 1). For example, the solubility of diazepam in water (at room temperature) is 0.05 mg/ml. Diazepam and other benzodiazepines are primarily used as sedative-antianxiety drugs but they have also antiepileptic properties. Normal dose of diazepam is 5 mg. The D:S ratio is 100, which is well below the upper limit of 250 for oral delivery. The oral bioavailability of diazepam has been reported to be close to 100%. When given orally diazepam is a Class I drug. However, if diazepam is to be formulated as nasal spray for treatment of seizures the upper limit of the D:S ratio is 0.3 ml, which makes it a Class II drug. Consequently formulation of aqueous diazepam nasal spray, possessing good bioavailability, will be quite difficult. Another example is 17β-estradiol. This drug has been given as 0.3 mg dose once a day (e.g., as vaginal cream) and its aqueous solubility (at room temperature) is 0.01 mg/ml. This gives D:S ratio of 30, which makes it a Class I drug when given orally. According to Table 2 17β-estradiol is a Class II drug when given by other routes. Formulation of the drug as, for example, aqueous nasal spray (D:S $\leq$ 0.3) or as fast dissolving buccal tablet (D:S $\leq$ 10) is only possible through some solubilizing techniques.

Most new chemical entities (NCE) are water-insoluble lipophilic compounds or, in other words, Class II or even Class IV compounds. It can be quite challenging for formulation scientists to create usable pharmaceutical products of such compounds.

Cyclodextrins in drug formulations

In pharmaceutical formulations cyclodextrins are mainly used to enhance the aqueous solubility of drugs [9]. The cyclodextrin themselves have a hydrophilic outer surface and a lipophilic cavity in the center. They form hydrophilic inclusion complexes with water-insoluble lipophilic drugs. In aqueous solutions drug molecules bound within the inclusion complex are in a dynamic equilibrium with

Table 2. Approximate dose-to-solubility ratios (D:S) and dissolution requirements for some pharmaceutical formulations

Drug formulation	D:S	pH range	Dissolution requirements
Conventional oral tablets	≤250 ml	1 to 7.5	≥85% within 30 min
Fast dissolving buccal tablets	≤5 ml	2 to 7.5	∼100% within 1 min
Vaginal tablets	≤5 ml	3.5 to 4.9	–
Pulmonary drug delivery	≤0.5 ml	6 to 7.6	Solution
Aqueous nasal spray	≤0.3 ml	5 to 8.5	Solution
Aqueous eye drop solution	≤0.05 ml	6.6 to 9	Solution

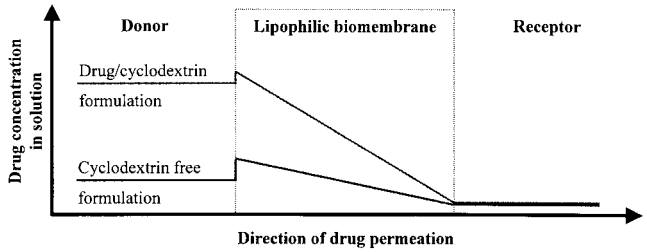

Figure 2. The effect of cyclodextrin complexation on drug permeability through biomembranes. Proper cyclodextrin solubilization of the drug increases the concentration gradient over the membrane and, consequently the flux over the membrane.

free molecules. Thus, cyclodextrins enhance the aqueous solubility of drugs without changing their intrinsic ability to permeate lipophilic membranes [10]. The natural cyclodextrins have limited aqueous solubility. For example, the solubility of β-cyclodextrin in water is only about 18.5 mg/ml at room temperature. Various water-soluble cyclodextrin derivatives have been synthesized. Cyclodextrin derivatives of current pharmaceutical interest include 2-hydroxypropyl-β-cyclodextrin, 2-hydroxypropyl-γ-cyclodextrin, sulfobutylether β-cyclodextrin, randomly methylated β-cyclodextrin, and some branched cyclodextrins such as maltosyl-β-cyclodextrin (Table 3).

Through complexation with water-soluble cyclodextrins it is possible to move Class II drugs, and sometimes even Class IV drugs, into Class I (Figure 1). Through appropriate formulation techniques it is possible to increase the value of C_{Aq} in Equation (1) without affecting the drug permeability (Figure 2). This can move drugs from Class II to Class I.

Due to their size and hydrophilicity only insignificant amounts of cyclodextrins and drug/cyclodextrin complexes are able to penetrate into lipophilic biomembranes, such as intact skin. In general cyclodextrins enhance drug delivery through biomembranes by increasing the drug availability at the membrane surface. At the surface the drug molecules partition from the cyclodextrin cavity into the lipophilic membrane [10–12]. Thus, properly designed cyclodextrin formulation will increase the drug concentration gradient over the membrane, which will increase the drug flux through the membrane (Figure 2). Since drug/cyclodextrin complexes do not readily permeate biomembranes excess cyclodextrin in pharmaceutical formulations can reduce drug bioavailability.

Including cyclodextrins in pharmaceutical formulations will, however, increase the formulation bulk of solid dosage forms. Even under best conditions, cyclodextrin complexation will result in 4- to 10-fold increase in the formulation bulk [13]. This limits the use of cyclodextrins in solid oral dosage forms to potent drugs that possess good complexing properties. Likewise, the maximum cyclodextrin concentration in isotonic solutions is between 20 and 25% meaning that for some drugs, a parenteral system containing cyclodextrin is not practical. Cyclodextrin derivatives have greater molecular weight (MW) than their parent cyclodextrins and thus result in greater increase in the formulation bulk, i.e., in the case of natural cyclodextrins the drug occupies greater fraction of the complex powder (Table 4).

Solid dosage forms

For solid dosage forms there are three requirements. First, the D:S ratio has to be below 250 ml for conventional oral tablets and below 5 ml for buccal tablets (Table 2). In other words, the aqueous solubility of the drug/cyclodextrin complex during *in vivo* dissolution has to be sufficient. In general, drugs with aqueous solubility greater than 0.1 mg/ml will seldom exhibit dissolution rate-limiting absorption after oral administration in a conventiona immediate release tablet [7]. Second, the upper limit in size is about 800 mg for a conventional oral tablet and about 250 mg for buccal tablets. Due to excipients requirements only about 700 mg of a complex (or about 70 to 175 mg of drug) can be included in a conventional tablet and only about 150 mg (or about 15 to 40 mg of drug) in a fast dissolving buccal tablet. Third, drug dissolution rate from the tablets has to be sufficient (Table 2).

The aqueous solubility of anticonvulsant drug carbamazepine is 0.1 mg/ml and its dose is commonly 100 to 200 mg two times a day. This gives a D:S ratio of 1000 to 2000 ml. Absorption from conventional tablets is slow and erratic, with bioavailability of 75–80% [14]. Peak serum carbamazepine concentration occurs 4 to 8 hours after a dose of immediate-release tablet. The minimum weight for a 100 mg carbamazepine tablet would be about 1500 mg if 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) is used but 800 mg if the natural β-cyclodextrin (β-CD) is used (Table 4). Although the carbamazepine/HP-β-CD complex is much more soluble in water (the D:S ratio is less than 6) the carbamazepine/β-CD gives sufficient solubility (the

Table 3. Natural cyclodextrins and some of their derivatives that are currently used in pharmaceutical products

Cyclodextrin	Substitution[a]	MW[b]	Solubility in water (mg/ml)[c]
α-Cyclodextrin	–	972	14.5
β-Cyclodextrin	–	1135	1.85
2-Hydroxypropyl-β-cyclodextrin	0.65	1400	>600
Randomly methylated β-cyclodextrin	1.8	1312	>500
β-Cyclodextrin sulfobutyl ether sodium salt	0.9	2163	>500
γ-Cyclodextrin	–	1297	23.3
2-Hydroxypropyl-γ-cyclodextrin	0.6	1576	>500

[a] Average number of substituents per glucopyranose repeat unit.
[b] MW given by the supplier, or the calculated value based on the average degree of substitution, for the water-free substance.
[c] Solubility in pure water at approx. 25 °C.

Table 4. The effect of cyclodextrins on the BCS. In the case of the natural β-cyclodextrin (β-CD) polymer technology was used to enhance the complexation efficiency and the aqueous solubility of the drug/β-CD complex but not in the case of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD). The complexation efficiency is expressed as mg drug in one gram of dry complex powder (mg/g compl.) and the solubility is the determined drug concentration (S) in water saturated with the drug complex at room temperature (mg/ml). Adapted from References [14, 21]

Properties	Carbamazepine	17β-Estradiol	Hydrocortisone
Dose (mg)	100	0.3	20
Solubility (mg/ml)	0.1	0.01	0.4
Abs. from GI tract	75–80	Well absorbed[a]	Well absorbed
D:S ratio	1,000	30	50
β-CD			
mg/g compl.	124	220	252
S (mg/ml)	6.5	0.24	2.5
HP-β-CD			
mg/g compl.	70	51	129
S (mg/ml)	≥17	≥20	≥20

[a] 17β-Estradiol is well absorbed but undergoes first-pass metabolism.

D:S ratio is about 15) to prevent dissolution rate limiting absorption.

The aqueous solubility of 17β-estradiol is, as previously mentioned, 0.01 mg/ml and the dose is frequently between 0.1 to 0.3 mg, which gives D:S ratio between 10 and 30 ml. 17β-Estradiol is well absorbed from the gastrointestinal tract and thus 17β-estradiol is Class I drug when given orally. However due to fist-pass effect its bioavailability after oral administration is only about 5% [14]. Delivering the drug in a fast dissolving buccal tablet can eliminate the first-pass effects. For buccal delivery the D:S ratio has to be below 5 ml, which makes 17β-estradiol a Class II drug. Cyclodextrin complexation, even with the natural β-cyclodextrin, decreases the D:S ratio to less than 1 ml, which is far below the 5 ml limit. Thus, systemic delivery of 17β-estradiol in a buccal tablet has been made possible through cyclodextrin complexation [15].

Semi-solid dosage forms

Hydrocortisone is well absorbed from the gastrointestinal tract and with an aqueous solubility of 0.4 mg/ml and common dose of 20 mg it falls into Class I when given orally (Table 4). However, in an o/w cream, where relatively small amount of an oil is dispersed in a homogeneous aqueous phase and where the total hydrocortisone concentration is 10 mg/ml, only small fraction of the drug will be in solution. Most of the drug will be in the form of suspension moving hydrocortisone into Class II (or even Class IV) when given topically to the skin. Through cyclodextrin complexation it is possible to enhance significantly hydrocortisone delivery from cream formulations to the skin [16].

Aqueous solutions

The maximum cyclodextrin concentration in pure isotonic solutions is about 25% (w/v) for the unionized water-soluble cyclodextrin derivatives. However, buffer salts and other formulation excipients, as well as the drug, will increase the tonicity of the aqueous formulation making cyclodex-

trin concentrations higher than about 20% unrealistic [13]. Through polymer stabilization of the drug/cyclodextrin complexes it is possible to both enhance the solubilizing properties of the cyclodextrins and enhance the drug bioavailability in aqueous solutions [17].

The aqueous solubility of benzodiazepines is very low. For example, midazolam is practically insoluble (<1 *mu*g/ml) at physiologic pH. In the commercial parenteral solution (Dormicum®, 5 mg/ml, from F. Hoffmann-La Roche & Ltd., Switzerland) the solubility is enhanced by lowering the pH to approx. 3.3, i.e., through ionization of the midazolam molecule. At that pH the solubility of midazolam is between 7 and 8 mg/ml. Common midazolam dosage is about 5 mg or about one ml of the acidic parenteral solution. The commercial parenteral solution has sometimes been administered nasally to needle-shy patients. However, such a large amounts of acidic solution has caused some discomfort. The D:S for nasal administration is $\leq$0.3 ml. That is, for nasal delivery 5 mg of midazolam must be dissolved in $\leq$0.3 ml of the aqueous nasal spray or, in other words, the midazolam solubility has to be increased to about 17 mg/ml. Through polymer enhanced cyclodextrin complexation of the drug it was possible obtain desired solubility at pH 4.3 [18]. Bioavailability studies in humans showed that midazolam was rapidly absorbed after nasal administration [19].

Dexamethasone is relatively well absorbed from the gastrointestinal tract and with an aqueous solubility of 0.2 mg/ml and common dose of 5 mg it falls into Class I when given orally. However, in aqueous eye drops solutions where the D:S ratio is $\leq$0.05 ml dexamethasone falls into Class II or even Class IV (Table 2). In commercial products dexamethasone is administered in aqueous solutions containing a water-soluble dexamethasone phosphate prodrug, or it is formulated as an alcoholic suspension, both of which have very limited bioavailability [20]. Through cyclodextrin solubilization of the drug it is possible to formulate up to 1.3% (w/v) dexamethasone in isotonic aqueous eye drop solutions. Human and animal studies showed that ocular absorption of dexamethasone from these solutions is many fold that seen with commercially available formulations. Cyclodextrin based dexamethasone eye drops are well tolerated in the eye and seem to provide higher bioavailability and clinical efficiency than presently available steroid eye drop formulations [20].

Conclusions

According to the BCS aqueous solubility and permeability are the most important parameters affecting drug bioavailability. Although the BCS was originally developed for solid oral dosage forms a similar system can be applied to other types of drug formulations. Cyclodextrins are ideal for Class II drugs possessing relatively high potency and good complexing capabilities.

Cyclodextrins can sometimes improve delivery of Class IV drugs. On the other hand, cyclodextrins are not suited for Class III drugs and can reduce the bioavailability of Class I drugs.

References

1. H. van de Waterbeemd: *Eur. J. Pharm. Sci.* **7**, 1 (1998).
2. F. Yoshida and J.G. Topliss: *J. Med. Chem.* **43**, 2575 (2000).
3. C.A. Lipinski, F. Lombardo, B.W. Dominy, and P.J. Feeney: *Adv. Drug Deliv. Rev.* **46**, 3 (2001).
4. G.L. Amidon, H. Lennernäs, V.P. Shah, and J.R. Crison: *Pharm. Res.* **12**, 413 (1995).
5. R. Löbenberg and G.L. Amidon: *Eur. J. Pharm. Biopharm.* **50**, 3 (2000).
6. D. Hörter and J.B. Dressman: *Adv. Drug Deliv. Rev.* **46**, 75 (2001).
7. J. Dressman, J. Butler, J. Hempenstall, and C. Reppas: *Pharm. Tech. North Am.* **25**(7), 68 (2001).
8. Center for Drug Evaluation and Research: FDA 2001, p. www.fda.gov/cder.
9. T. Loftsson and M.E. Brewster: *J. Pharm. Sci.* **85**, 1017 (1996).
10. T. Loftsson and M. Másson: *Int. J. Pharm.* **225**, 15 (2001).
11. V.J. Stella and R.A. Rajewski: *Pharm. Res.* **14**, 556 (1997).
12. K. Uekama, F. Hirayama, and T. Irie: *Chem. Rev.* **98**, 2045 (1998).
13. T. Loftsson, M. Másson, and J.F. Sigurjónsdóttir: *S.T.P. Pharma. Sci.* **9**, 237 (1999).
14. P.O. Anderson, J.E. Knoben, and W.G. Troutman: *Handbook of Clinical Drug Data*, 9th edn., Appelton & Lange, Stamford (1999).
15. H. Friðriksdóttir, T. Loftsson, J.A. Guðmundsson, G.J. Bjarnason, M. Kjeld, and T. Thorsteinsson: *Pharmazie* **51**, 39 (1996).
16. T. Loftsson: *Pharm. Technol.* **23**(12), 40 (1999).
17. T. Loftsson: *Pharmazie* **53**, 733 (1998).
18. T. Loftsson, H. Gudmundsdottir, J.F. Sigurjónsdóttir, H.H. Sigurdsson, S.D. Sigfusson, M. Másson, and E. Stefánsson: *Int. J. Pharm.* **212**, 29 (2001).
19. H. Gudmundsdottir, J.F. Sigurjónsdóttir, M. Másson, O. Fjalldal, E. Stefánsson, and T. Loftsson: *Pharmazie* **56**, 963 (2001).
20. T. Loftsson and E. Stefánsson: *Acta Ophthalmol. Scand.* **80**, 144 (2002).
21. H. Friðriksdóttir: *Faculty of Pharmacy*, University of Iceland, Reykjavik (1997).