International Journal of Pharmaceutics 531 (2017) 276–280

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Drug solubilization by complexation

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ARTICLE INFO

Keywords:
Aqueous solution
Complex
Complexing agent
Drug
Solubility
Solubilization

ABSTRACT

Drugs must possess some solubility in water to be therapeutically effective after oral or topical administration to the eye, and drugs must be soluble to be formulated as aqueous solutions for, for example, parenteral delivery. A variety of methods can be applied to enhance aqueous solubility of poorly soluble drugs one of which is the usage of solubilizing complexing agents. There are numerous types of complexes and some are more water-soluble than others. Coordination complexes consist of drugs that act as complexing agents (i.e. ligands) and metal ions (i.e. substrates). Examples of coordination complexes are some water-soluble tetracycline-metal ion complexes. Organic molecular complexes can consist of a small substrate (i.e. the drug) and a small (e.g., caffeine) or a large (e.g., polyvinylpyrrolidone) ligand. In inclusion complexes the substrate is partly or completely enveloped by the complexing agent (e.g., cyclodextrin). Finally, pharmacosomes are drug-phospholipid complexes that can not only enhance aqueous solubility of poorly soluble drugs but also their solubility in organic solvents. This is a mini-review of solubilizing complexing agents that are or can be used in pharmaceutical products.

1. Introduction

Sufficient drug solubility in aqueous media is one of the most important prerequisites for effective drug delivery. Most biomembranes are covered with aqueous exterior layers such as mucus and only dissolved drug molecules are able to permeate the membranes. Poor aqueous solubility can hamper drug absorption after oral administration of solid dosage forms, and prevent formulation of drugs in parenteral, nasal, ocular or other types of solution dosage forms. Wide variety of methods can be applied to enhance aqueous solubility of poorly soluble drugs such as addition of organic cosolvents or surfactants, pH adjustment, salt formation, formation of amorphous solids and formation of water-soluble drug complexes (Yalkowsky, 1999). In general, pharmaceutical formulators screen several different solubilizing methods during the preformulation stage of product development in an effort to obtain sufficient drug solubility or dissolution of a solid drug, and every so often sufficient solubility can only be obtained by combining more than one solubilizing method.

Complexes are intermolecular associations of substrate and ligand molecules or ions that are kept together by somewhat strong coordinate covalent bonds or by relatively weak non-covalent forces such as hydrogen bonds, van der Waals forces, electrostatic interactions, dipole forces or hydrophobic interactions. In recent years the emphasis has been on cyclodextrins as complexing agents (i.e. ligands) and solubilizers in pharmaceutical products. Annually cyclodextrins are the topic of over 3000 research articles and over 1500 patents. However, numerous other types of complexing agents can be used as solubilizers in pharmaceutical products. Following is a mini-review on complexing agents as pharmaceutical solubilizers where complexes are classified into metal-ion coordination complexes, organic molecular complexes, inclusion complexes and pharmacosomes. The purpose is to draw the reader's attention to the wide variety of solubilizing complexing agents.

2. Coordination complexes (metal complexes)

Coordination complexes, also named metal complexes, are formed when ionic substrates (Lewis acids) such as transition metal ions (e.g., Fe^{2+}, Fe^{3+}, Co^{2+}, Co^{3+}, Cu^{2+}, Zn^{2+}, Ag^{+} and Pt^{4+}) bind via coordinate covalent bonds with ligands (Lewis bases) that are neutral molecules or anions. In a coordination complex the ligand donates both electrons forming the covalent bond with the substrate. Example of a simple coordination complex is the water-soluble silver-ammonia complex ($[Ag(NH_3)_2]^+$) where ammonia donates both electrons forming the covalent bond between Ag^+ and NH_3. The anticancer drug cisplatin is a somewhat water-soluble coordination complex (solubility about 2.5 mg/ml) containing central platinum atom surrounded by two chloride atoms and two ammonia moieties (Prestayko, 1980).

Chelate is a coordination complex where the same substrate binds with two or more sites on a ligand (a chelating agent). Chelating agents, such as citric acid and EDTA, are commonly used in pharmaceutical formulations to complex metal ions that can catalyze drug degradation but drug-metal ion chelates do exist. Sometimes formation of drug-

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http://dx.doi.org/10.1016/j.ijpharm.2017.08.087
Received 20 July 2017; Received in revised form 17 August 2017; Accepted 17 August 2017
Available online 24 August 2017

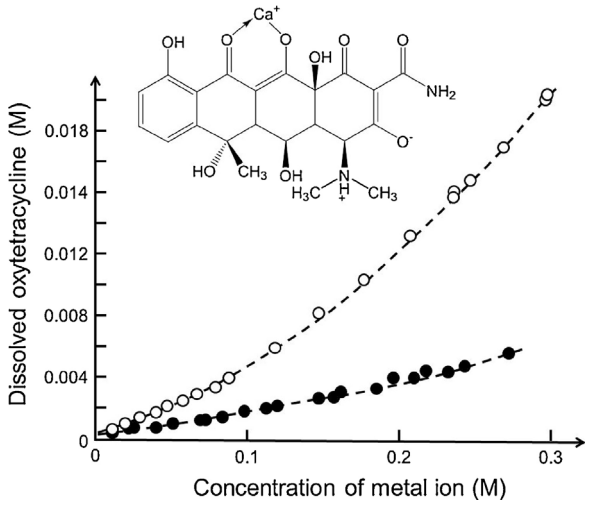


Fig. 1. The structure of 1:1 oxytetracycline-Ca^{++} coordinate complex and the phase-solubility profiles of oxytetracycline in aqueous solutions containing calcium chloride (●) or magnesium chloride (○) at pH 5 and 25 °C. From references (Higuchi and Bolton, 1959; Palm et al., 2008) with permission.

metal ion chelates reduces aqueous solubility of drugs. However, some drugs that have limited solubility in water can form water-soluble chelates where the drug is the ligand (i.e. the complexing agent) and the metal ion the substrate. Tetracyclines are known form coordination complexes (chelates) with positively charged metal ions (e.g., Al^{3+}, Ca^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Mg^{2+}, Mn^{2+}, Ni^{2+} and Pt^{2+}) (Pulicharla et al., 2017). In 1959 Higuchi and Bolton (Higuchi and Bolton, 1959) published an article on various types of oxytetracycline complexes and showed that calcium and magnesium ions increase aqueous solubility of oxytetracycline through formation of water-soluble oxytetracycline-metal ion chelates (Fig. 1). At low metal ion concentration the stoichiometry of the oxytetracycline-Ca^{++} coordinate complex is thought to be 1:1 (i.e. one drug molecules forms a complex with one Ca^{++} ion) although the positive deviation from linearity could indicate that the complex could be of higher order with regard to Ca^{++} (e.g. 1:2 or 1:3) at elevated Ca^{++} concentrations. Quinolone antibiotics are also known to form water-soluble metal complexes (Park et al., 2000; Zakelj et al., 2007). For example, Ross and Riley (Ross and Riley, 1992) studied the effects of metal ions on the solubility of lomefloxacin and showed that various metal ions form complexes with the drug. Some of the metal ions were able to enhance the aqueous solubility of lomefloxacin (Fig. 2) while other decreased its solubility. Metal ions have also been shown to enhance aqueous solubility of other drugs and nutraceuticals such as taxol (Manning et al., 2013) and curcumin (Sareen et al., 2016).

3. Organic molecular complexes

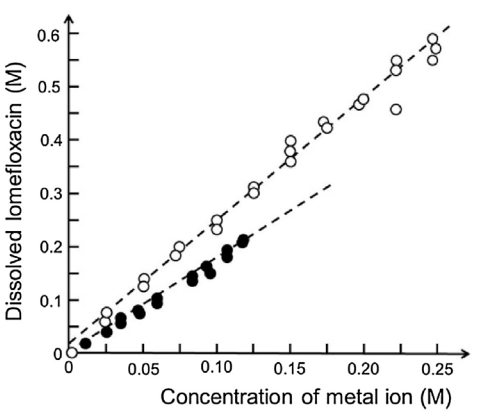
Organic molecular complexes consist of non-covalently bound substrates and ligands such as between relatively small substrates and ligands (e.g., drug–drug complexes), between small substrates and large ligands (e.g., drug-polymer complexes, and drug-protein binding) and between large substrates and small or large ligands (e.g., protein-polyalcohol complexes). Molecules forming organic molecular complexes are linked by very weak non-covalent bonds such as hydrogen bonds, hydrophobic bonds, electrostatic interactions, charge-transfer interactions and dispersion forces, and in aqueous solutions molecules bound within the complexes are frequently in dynamic equilibrium with unbound substrate and ligand molecules. Following are some examples of water-soluble organic molecular complexes of poorly soluble drugs.

3.1. Small substrate - small ligand

In the early 1950s Higuchi and coworkers published series of articles on caffeine complexes of various drugs and related substances, including sulfathiazole (Higuchi and Lach, 1954). The sulfathiazole phase-solubility diagram (Fig. 3) indicates that addition of caffeine to aqueous medium results in almost three fold increase in the sulfathiazole solubility due to formation of sulfathiazole-caffeine 1:1 molecular complex. The value of the stability constant ($K_{1:1}$) of the sulfathiazole-caffeine complex is low or only 11.3 M^{-1} at 30 °C. In comparison $K_{1:1}$ of the sulfathiazole-β-cyclodextrin complex has been determined to be 414 M^{-1} at 20 °C (Diez et al., 2007). Fig. 4 shows the phase-solubility profile of halofantrine in aqueous solution containing nicotinamide. Again relatively high concentrations of the ligand (i.e. nicotinamide) are needed to solubilize the substrate (i.e. halofantrine). The value of $K_{1:1}$ for the halofantrine-nicotinamide complex is below 10 M^{-1} while that of the halofantrine-2-hydroxypropyl-β-cyclodextrin complex has been determined to be 2500 M^{-1} (Lim and Go, 2000; Onyeji et al., 2007). Other small molecules such as monosaccharides and amino acids have been shown to increase solubility of poorly soluble drugs in water (Inada et al., 2016). In general, the stability constants of water-soluble organic molecular complexes are low and much lower than, for example, those of the water-soluble cyclodextrin inclusion complexes (Cohen and Connors, 1970; Connors, 1995).

3.2. Small substrate - large ligand

Many hydrophilic polymers form water-soluble complexes with poorly soluble drugs. The best known polymeric complexing agent is probably polyvinylpyrrolidone (PVP) that forms hydrogen bonds with wide variety of poorly soluble drugs including acetaminophen (Fig. 5) (Garekani et al., 2003), amphotericin B (Charvalos et al., 2006), diflunisal (Rodriguez-Espinosa et al., 1998), hydrocortisone (Loftsson



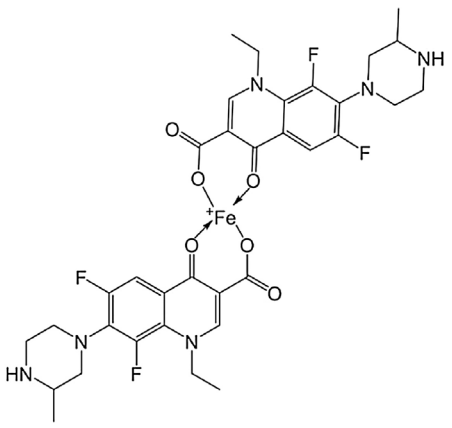


Fig. 2. The phase-solubility profiles of lomefloxacin in aqueous solutions containing Fe^{3+} at pH 1(●) or Al^{3+} (○) at pH 4.35, and 25 °C, and the structure of 2:1 lomefloxacin-Fe^{3+} coordinate complex. The stoichiometry the lomefloxacin-Al^{3+} coordinate complex is 3:1 (i.e. three drug molecules form a complex with one Al^{3+} ion). From references (Ross and Riley, 1992; Uivarosi, 2013) with permission.