PHARMACEUTICAL DEVELOPMENT AND TECHNOLOGY, 2016
http://dx.doi.org/10.1080/10837450.2016.1180394

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Evaluation of γ-cyclodextrin effect on permeation of lipophilic drugs: application of cellophane/fused octanol membrane

Chutimon Muankaew[a,b], Phatsawee Jansook[c] and Thorsteinn Loftsson[a]

[a]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland; [b]Faculty of Pharmacy, Siam University, Bangkok, Thailand; [c]Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

ABSTRACT

According to the Biopharmaceutics Classification System, oral bioavailability of drugs is determined by their aqueous solubility and the ability of the dissolved drug molecules to permeate lipophilic biological membranes. Similarly topical bioavailability of ophthalmic drugs is determined by their solubility in the aqueous tear fluid and their ability to permeate the lipophilic cornea. Enabling pharmaceutical excipients such as cyclodextrins can have profound effect on the drug bioavailability. However, to fully appreciate such enabling excipients, the relationship between their effects and the physicochemical properties of the permeating drug needs to be known. In this study, the permeation enhancing effect of γ-cyclodextrin (γCD) on saturated drug solutions containing hydrocortisone (HC), irbesartan (IBS), or telmisartan (TEL) was evaluated using cellophane and fused cellulose-octanol membranes in a conventional Franz diffusion cell system. The flux (J), the flux ratio (J_R) and the apparent permeability coefficients (P_{app}) demonstrate that γCD increases drug permeability. However, its efficacy depends on the drug properties. Addition of γCD increased P_{app} of HC (unionized) and IBS (partially ionized) through the dual membrane but decreased the P_{app} of TEL (fully ionized) that displays low complexation efficacy. The dual cellophane-octanol membrane system was simple to use and gave reproducible results.

ARTICLE HISTORY
Received 18 December 2015
Revised 2 March 2016
Accepted 7 March 2016
Published online 4 May 2016

KEYWORDS
Franz diffusion cell; γ-cyclodextrins; lipophilic drugs; octanol membrane; permeation enhancer

Introduction

According to the Biopharmaceutics Classification System (BCS) and the Lipinski's rule-of-five oral bioavailability of drugs are affected by their physicochemical properties, mainly by their aqueous solubility and lipophilicity although other properties such as the ability of the permeating molecule to form hydrogen bonds and its size are also important[1,2]. In general, most low-molecular weight lipophilic drugs display relatively high permeability through biological membranes but their limited solubility in water can hamper their bioavailability[3–6]. *In vitro* permeation studies have shown that the two main factors affecting transportation of lipophilic drug molecules across a given biomembrane are (1) drug solubility in the aqueous membrane exterior and the consequent passive drug permeation across the aqueous diffusion barrier (i.e. the unstirred water layer (UWL)), and (2) drug permeation through the lipophilic membrane barrier which is determined by drug partition from the aqueous exterior into the lipophilic membrane and diffusion of the drug molecules across this lipophilic membrane barrier. For example, in topical drug delivery to the eye, the drug molecules should dissolve in the aqueous tear fluid (i.e. the UWL) in order to reach the surface of the lipophilic cornea[7,8]. Furthermore, dissolved drug molecules have maximum tendency to partition from the aqueous exterior into the lipophilic membrane when the aqueous exterior is saturated with the drug. One approach that is often used to overcome the poor aqueous solubility is to include solubilizers such as surfactants and complexing agents in an aqueous formulation to increase the availability of dissolved drug molecules at the membrane barrier. However, solubilizers can hamper drug permeation by reducing the ability of dissolved drug molecules to partition from the exterior into the membrane.

For many years, natural cyclodextrins (CDs) (i.e. αCD, βCD and γCD) and their derivatives have been used to improve aqueous solubility of drugs through formation of water-soluble inclusion complexes leading to enhanced drug bioavailability[9,10]. CDs are commonly employed as absorption enhancers in topical and oral drug formulation[11–13]. The hypothesis of how CDs enhance drug permeation through biomembranes is that when an UWL is the main permeation barrier incorporation of CDs in formulation increases drug permeation through the UWL by enhancing the drug concentration gradient across the UWL[14–16]. However, it is known that addition of excess CD, more than is needed to solubilize all drug in the aqueous exterior, can decrease drug permeation through biomembranes due to drug/CD complex aggregation and decreased drug partition from the aqueous exterior into the lipophilic membrane[17,18]. Novel permeation models are needed to further elucidate the effects of CDs on drug permeation through biomembranes. Various models have been developed to assess and predict transportation and absorption of drug molecules in biological systems, and of these commercial artificial lipid membranes such as the parallel artificial membrane permeability assay (PAMPA) and silicone polymer membranes are widely used in laboratory to estimate drug permeability[19,20]. Also, Caco-2 cell permeability assays are frequently used to obtain additional information on drug absorption via transporters. However, the Caco-2 assays are somewhat complex and time-consuming and, thus, may not be suitable for routine work during formulation development[21–23].

The primary aim of this study is to understand the effect and contribution of the natural γCD to permeation of three model drugs; hydrocortisone (HC), irbesartan (IBS), and telmisartan (TEL). Permeability assessments were conducted using Franz diffusion

CONTACT Thorsteinn Loftsson thorstlo@hi.is Faculty of Pharmaceutical Sciences, University of Iceland, Hofsvallagata 53, IS-107 Reykjavik, Iceland