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Review

Solubility of Cyclodextrins and Drug/Cyclodextrin Complexes

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Abstract: Cyclodextrins (CDs), a group of oligosaccharides formed by glucose units bound together in a ring, show a promising ability to form complexes with drug molecules and improve their physicochemical properties without molecular modifications. The stoichiometry of drug/CD complexes is most frequently 1:1. However, natural CDs have a tendency to self-assemble and form aggregates in aqueous media. CD aggregation can limit their solubility. Through derivative formation, it is possible to enhance their solubility and complexation capacity, but this depends on the type of substituent and degree of substitution. Formation of water-soluble drug/CD complexes can increase drug permeation through biological membranes. To maximize drug permeation the amount of added CD into pharmaceutical preparation has to be optimized. However, solubility of CDs, especially that of natural CDs, is affected by the complex formation. The presence of pharmaceutical excipients, such as water-soluble polymers, preservatives, and surfactants, can influence the solubilizing abilities of CDs, but this depends on the excipients' physicochemical properties. The competitive CD complexation of drugs and excipients has to be considered during formulation studies.

Keywords: cyclodextrin; complex; solubility; poorly soluble drug

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides, formed by α-1,4-linked glucose units, with a hydrophilic outer surface and a lipophilic central cavity [1–4]. α-Cyclodextrin (αCD), β-cyclodextrin (βCD), and γ-cyclodextrin (γCD) are natural products that can be found in small amounts in various fermented consumer products, such as beer. Although the unsubstituted natural αCD, βCD, and γCD, and their complexes, are hydrophilic their solubility in aqueous solutions is somewhat limited, especially that of βCD. Consequently the more soluble βCD derivatives, such as 2-hydroxypropyl-βCD (HPβCD) and sulfobutylether βCD sodium salt (SBEβCD), are preferred for use in aqueous pharmaceutical solutions, such as parenteral drug formulations, even though both αCD and γCD can be found at low concentrations in parenteral formulations [5]. Monographs for αCD, βCD, and γCD and two βCD derivatives are in the European Pharmacopoeia and the United States Pharmacopeia/National Formulary (Table 1). CDs are included in over 40 marketed pharmaceutical products worldwide, in addition to numerous food, cosmetic, and toiletry products [2,6,7].