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MiniReview

Cyclodextrin-Based Formulations: A Non-Invasive Platform for Targeted Drug Delivery

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Abstract: Cyclodextrins (CDs) are recognized as promising pharmaceutical excipients due to their unique ability to form water-soluble inclusion complexes with various poorly soluble compounds. The numerous investigations on CDs and their use in nanomedicine have received considerable attention in the last three decades, leading to the rapid development of new CD-containing formulations that significantly facilitate targeted drug delivery and controlled drug release, with consequent improvements in drug bioavailability. This MiniReview highlights the efficacy and recent uses of CDs for non-invasive drug delivery. Using ophthalmic and nasal drug delivery as examples, an overview of chemical properties, mechanisms of CDs on drug solubilization, stabilization and permeation, along with their toxicological profiles relevant to nasal and ocular administration, are provided and discussed. The recent development and application of CD-based nanocarrier systems for targeted drug delivery are summarized.

Cyclodextrins (CDs) are natural cyclic oligosaccharides that are produced by enzymatic degradation of starch. There are three native CDs designated αCD, βCD and γCD, which are composed of 6, 7 and 8 D-glucopyranose units linked by α-(1, 4) glycosidic, respectively [1]. The molecules are commonly described as truncated cone, bucket-like or donut-shaped, with a hydrophilic outer surface and a relatively hydrophobic inner cavity that allows entrapment of small hydrophobic drug molecules or hydrophobic moieties of larger molecules [2], thereby providing drugs with new physicochemical characteristics without altering their intrinsic properties. Table 1 summarizes the characteristics of different CDs. Natural CDs are preferred for complexation; however, their usability is limited by the small cavity size of αCD, poor aqueous solubility of βCD and low productivity of γCD [3]. Derivatized CDs can be obtained by substituting their hydroxyl groups with desired functional moieties. Methyl-(MeβCD and MeγCD) [4,5], hydroxypropyl-(HPαCD, HPβCD and HPγCD) [6–8] and sulphobutylether (SEBβCD) derivatives [9] are frequently found in pharmaceutical products and have improved solubility and inclusion capacity over natural CDs. Pharmaceutical applications of both natural CDs and their derivatives are common when drug/CD complexes are used to increase drug solubility, improve organoleptic properties [10], enhance drug permeation [11] and increase drug stability, resulting in increased product shelf-life and drug bioavailability [12]. In addition, spontaneous self-assembly of drug/CD complexes into aggregates can lead to innovative drug delivery systems, such as CD-containing liposomes and microspheres as well as micro- and nanoparticles [13]. Polymerized CDs (e.g. Epi-αCD and Epi-βCD) have also been synthesized to enhance the self-assembly ability of CDs, and to strengthen their interactions with drugs and biological membranes [14]. Compared with other pharmaceutical excipients, CDs have been shown to reduce the toxicity of several drugs and are biocompatible [15–17]. As a result, they are appealing for use in the development of pharmaceutical formulations, including the reformulation of existing drug products.

Non-invasive drug delivery routes, such as topical and transmucosal administration, achieve painless systemic and local therapeutic effects, and are an attractive alternative to oral and injectable routes of drug delivery. The unique advantages of topical and transmucosal delivery approaches are their ease of use, avoidance of first-pass metabolism that subsequently reduces fluctuations in drug levels and elimination of systemic effects [18]. Recently, there has been growing interest in non-invasive ocular drug delivery and intranasal drug delivery research. However, the complexity of biological membranes is an enormous challenge for effective drug delivery systems, for instance, the presence of microvilli, and double layer of mucus on the nasal epithelium that can clear drugs from the nasal cavity [19]. The eye cornea is covered with an aqueous tear film that is highly impermeable to hydrophobic drugs. The nasal and ocular routes of delivery are also hampered by the volume that can be delivered, which is approximately 25–250 μl to the nasal cavity and 30 μl to the eye [20].

The ocular drug bioavailability in conventional eyedrops is very poor, being less than 5–10% of drug administered.

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