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Drugs–β-Cyclodextrin inclusion complex: Would be a new strategy to improve Antihypertensive Therapy?

Quiara Lovatti Alves, Samuel Barbosa Camargo, Rafael Leonne Cruz de Jesus and Darízy Flávia Silva*

Laboratory of Cardiovascular Physiology and Pharmacology, Federal University of Bahia, Salvador, Bahia, Brazil

Abstract

Taking into account the increasing use of cyclodextrins (CDs) to overcome drawbacks of drugs like antihypertensive, complex formation with of CDs seems to be a good pharmaceutical strategy to improve stability, solubility, bioavailability and reduction of side effects, thus facilitating the control of hypertension. The main objective of this short communication is to demonstrate the antihypertensive potential of complexed compounds with β-cyclodextrins and their clinical applications. This short communication identified and illustrated that β-cyclodextrin-based systems are promising sources that provide improved pharmacokinetic and formulation conditions, and important applications have been established by many research groups, optimizing β-CDs derivative systems for oral drug therapy, especially in hypertension.

Introduction

Cyclodextrins (CDs) are a family of cyclic oligosaccharides that have been largely studied and used industrially in pharmaceutical applications, due the fact they are able to form inclusion complexes with poorly water-soluble drugs and improve a variety of drug properties, such as stability, dissolution rate, solubility, bioavailability and reduction of side effects [1-3]. CDs are composed of at least 6D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds that differ in their ring size and solubility [4]. There are 3 important subtypes that naturally occur: α-CD, β-CD, and γ-CD with 6, 7 and 8 glucopyranoside units respectively [4]. They became scientifically attractive due to their application potential and important impact in hypertensive therapy. The most antihypertensive drugs are orally administered [5] and according the Biopharmaceutical Classification System (BCS) there are two important parameters that control rate and extent of drug absorption. These include drug dissolution and gastrointestinal permeability, which are considered the variables that most affecting drug bioavailability [6]. Many antihypertensive drugs are classified by BCS, in different classes, including: low solubility and high permeability characteristics after oral administration (class II), high solubility and low permeability (class III) and low solubility and permeability (class IV) [6-8]. Furthermore, controlled-release formulations of some antihypertensive drugs are unstable both *in vivo* and *in vitro* when administered orally [9], thus resulting in a lack of suitable specific antihypertensive formulations, especially for pediatric patients [10]. Taking this into account, CDs have been used to circumvent these limitations, and forming complexes with antihypertensives and CDs is a promising pharmaceutical strategy to facilitate the management of hypertension. Thus, the main objective of this short communication is to demonstrate the antihypertensive potential of compounds complexed with β-cyclodextrins and their clinical applications.

Applications of β-CD in Hypertension Treatment

For many drugs, the cavity size of α-CDs is unsatisfactory while γ-CDs is more expensive. The β-CDs has been extensively used for its immediate availability and cavity size suitable for a wide range of medications. Despite this, the use of β-CDs is limited due to low solubility in water and nephrotoxicity, especially in parenteral preparations [11]. However, when administered orally, cyclodextrins are considered safe and void of toxicity, as well as low bioavailable [12] and therefore is not sufficiently absorbed into the gastrointestinal system [13]. After the discovery of β-CD's promising properties, it was possible to study new formulations for antihypertensive drugs. Although few studies have assessed the inclusion complexes of drugs with β-CD in cardiovascular diseases, our group demonstrated that linalool, a vasodilator [14] and hypotensive monoterpene [15], complexed with β-CD promoted a significant decrease in the mean arterial pressure of spontaneously hypertensive rats (SHR) when compared to the non-complexed form, an effect that may be related to the increased stability and bioavailability afforded by β-CD [16]. Another monoterpene, β-Pinene, when complexed with β-CD significantly reduced mean arterial pressure when compared to free β-Pinene in a model of hypertension induced by L-NAME. Thus, β-Pinene complex formation with β-CD improved the pharmacological profile of this monoterpene [17].

An important derivative of β-CD is methyl-β-cyclodextrin (M-β-CD), a cholesterol binding agent. Cardiovascular studies performed in apolipoprotein E (ApoE2/2) deficient mice, where infusing angiotensin II (Ang II) promotes atherosclerosis and abdominal aortic aneurysm, and in this model, an increase in blood pressure has been reported. Isolated aortas from Ang II-infused mice were significantly less responsive to acetylcholine-induced endothelium-dependent relaxation when compared to aortas infused with vehicle control. Pre-incubation with M-β-CD in isolated aortic rings from this animals,

***Correspondence to:** Darízy Flávia Silva, PhD, Laboratory of Cardiovascular Physiology and Pharmacology, Federal University of Bahia, Avenida Reitor Miguel Calmon, Vale do Canela, 40110-902 Salvador, Bahia, Brazil, E-mail: darizy@gmail.com

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resulted in an acetylcholine-induced relaxation that was significantly greater than when compared with vehicle pre-incubation, suggesting that it partially restored the acetylcholine-induced aortic relaxation in the angiotensin II-infused mice [18]. Despite this, it has already been reported that β-CD and M-β-CD, but not α-CD, γ-CD, and HP-β-CD, are capable of inducing caspase-dependent apoptotic cell death in human keratinocytes on depletion of membrane cholesterol [19]. Therefore, more studies are needed to ensure their safety and toxicity in other cell types.

The cardiovascular effect of the complex hydroxypropyl-β-cyclodextrin (HP-β-CD), another derivative of β-CD, and Angiotensin (1-7) [(Ang-(1-7)], a cardioprotective metabolite of Angiotensine I and Angiotensine II ([20] was evaluated. The assays were performed with four experimental groups: sedentary treated with tap water, sedentary treated with oral administration of HP-β-CD/Ang-(1–7) inclusion compound, exercise-trained treated with tap water and exercise-trained treated with HP-β-CD/Ang-(1–7). Treatment was administered by gavage over the course of 10 days, concomitantly with the exercise training protocol. The complex resulted in a reduction of blood pressure, improved cardiovascular autonomic control, attenuated cardiac hypertrophy and restored left ventricular function. These results were similar to those produced by physical training in SHR, while the combined effect of both interventions potentiate the impact on blood pressure. It is important to note that the inclusion compound had no adverse effects on SHR. Additionally, chronic administration of beneficial cardiovascular responses of the HP-β-CD/Ang-(1-7) inclusion compound obtained with Ang-(1- 7) orally active also include improvement of left ventricular function and mechanical properties of cardiac muscle [21].

A relevant example of β-CD application can be found in pediatric formulations. As there is a lack of specific formulations which are suitable for pediatric treatment, individuals tend to disrupt or open capsules by breaking and/or crushing tablets, and even dilute liquid dosage in order to achieve the prescribed dosage. This effort to achieve a more easily administrable preparations for this group of patients, causes reduced precision in respect to dose and bioavailability, as well as the chemical, physical and microbiological stability of the formulation [22,23]. In children, administering in the liquid formulation tends to be preferred, due to their wider acceptability and dose flexibility [24]. The hydrochlorothiazide (HTZ) is one of the most commonly used diuretics in the treatment of hypertension, however commercial liquid formulations of HTZ are not available due to its limited solubility [25] and low stability in aqueous solution [26], leading to complications in the administration of HTZ in pediatric patients. Regardless, HTZ is the only FDA-approved diuretic for children [27]. To address this challenge, an innovative pediatric oral formulation of HTZ (2mg/mL) was developed by combining the drug-β-CD complexation with the incorporation of the complex into solid lipid nanoparticles, which demonstrated an increase in both the diuretic effect and the sustained drug release that led to an increased oral bioavailability of HTZ after complex formation [10].

Another drug commonly used for pediatric hypertension treatment is ramipril [28]. Ramipril is a highly lipophilic and poorly water-soluble drug with very low bioavailability when compared to the intravenous administration [29,30]. To prepare an oral formulation, ramipril was solubilized through complex formation with hydroxypropyl-β-cyclodextrin (HP-β-CD), a modified β-CD that offers improved solubility when compared to the β-CD. This systematic optimization of formulation parameters resulted in the development of oral liquid ramipril, a product that is stable for 12 months, offering preferential pediatric use over existing alternatives [31]. However, one of the most common side effects of ramipril use is diarrhea [32] and cyclodextrin are capable of stimulating intestinal secretion and gastrointestinal propulsion in animals, causing diarrhea. The increased gastrointestinal motility may be a result of the complex formation of bile salts with cyclodextrin, which leads to increased intestinal lipid concentrations [33]. Thus, it is possible that the combination of ramipril and CDs can intensify this adverse effect, leading to increased patients suffering from these undesirable effects. There is a dearth of clinical trial data regarding the safety and efficacy of antihypertensive drugs used in children, and many FDA-approved adult drugs are not effective in pediatric hypertension studies, thus dosage, safety and efficacy of the pediatric drug cannot be extrapolated from adult clinical trials [34].

Final Considerations

The β-cyclodextrin-based systems are currently being studied and are promising sources aimed at providing improved conditions for pharmacokinetic and formulation design efficiency. This short communication identified and illustrated important applications which have been studied by several research groups that formulate and optimize β-CDs derivates systems for oral drug therapy in hypertension.

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