

NATURAL PRODUCTS IN THE TREATMENT OF NEUROLOGICAL DISEASES (PART 2): HOST-GUEST COMPLEXES

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Abstract: Permeation through the blood-brain barrier is one issue that should be supplanted by the development of novel drugs to treat brain disorders. Host-guest complexes involving cyclodextrins, cucurbiturils, and calixarenes are promissory structures to tackle this problem. This paper shows the desired properties of the inclusion complexes involving natural products and how they can be used to develop new treatments for brain disease.

Keywords: Macrocycles; Host-guest; Drug properties

1. Introduction

Complexation with macrocycles can minimize side effects and improve drugs' therapeutic effects. Among the macrocycles, cyclodextrins (CDs), cucurbiturils (CBs), and calixarenes (CAs) stand out. CDs have improved several lipophilic drugs' aqueous solubility, dissolution, and bioavailability. While CBs have been used as drug delivery systems, showing low toxicity. CAs have been explored for their ability to form stable host and guest structures and deliver drugs [1–5]. All these properties are desirable for developing new drugs that will act in the central nervous system and need to transverse the blood-brain barrier.

2. Neurological diseases

Alzheimer's and Parkinson's diseases are neurodegenerative, and they cause the loss of noradrenergic neurons, the main sources of norepinephrine in the brain, affecting attention, memory, heart rate, and cognition. The hippocampus plays an important role in cognition and depression, receiving noradrenergic innervation of this type of neuron [6]. For this reason, these disorders share two symptoms: cognitive impairment and depression. Alzheimer's patients experience memory loss, language disorders, and visual-

spatial impairment. Agitation, aggression, apathy, anxiety, depression, delusions, euphoria, hallucinations, irritability, psychosis, and sleep disorders are behavioral and psychological symptoms currently observed in Alzheimer's patients [7–12]. Motor difficulties, including tremors, stiffness, and slowness of movement, characterize Parkinson's disease. The cause of these motor symptoms is the loss of dopaminergic neurons and reduced dopamine levels [12–14]. Epilepsy is not considered a neurodegenerative disease but rather a neurological disease associated with neural loss in the hippocampus, which causes seizures, cognitive impairment, and depression (one of the most common symptoms in the three diseases mentioned) [15–18].

3. Host-guest complexes

Macrocycles are excellent host candidates for the formation of inclusion complexes with drugs. CDs, CBs, and CAs (Figure 1) have been used as pharmaceutical excipients and water solubility enhancers [19]. CDs are biocompatible and have been shown to improve the aqueous solubility, dissolution rate, and bioavailability of several lipophilic drugs. They can also reduce the toxicity of anesthetic drugs [2,3,20]. The functionalization of macrocycles can improve their properties. For example, the formation of inclusion complexes between hydroxypropyl- β -cyclodextrin (HP- β -CD), THC, and CBD increased the aqueous solubility of these cannabinoids [4,21,22].

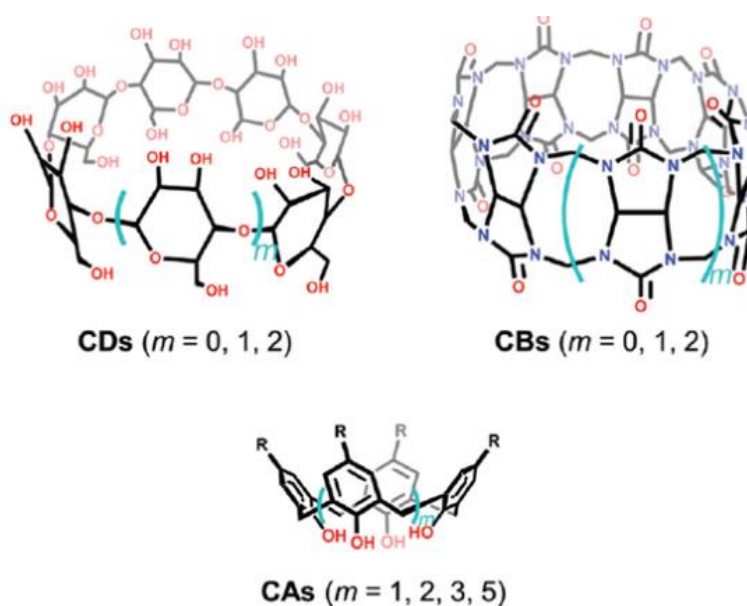


Figure 1. Molecular structures of cyclodextrins (CDs), curcubiturils (CBs), and calixarenes (CAs) [23].

CBs and CAs are potential pharmaceutical excipients and provide control of drug release [1, 24–26]. Besides, CAs have antiviral, antibacterial, anticoagulant, and anticancer activities, among others. They do not present an immunological response, hemolytic effects, or toxicity *in vivo* [27–29]. However, most CAs require functionalization to improve their aqueous solubility and complexation capacity [27, 30]. In the literature [4, 5, 31, 32], several studies explore inclusion complexes with natural products to develop improved and novel drugs. Inclusion complexes involving CDs and cannabinoids have been prepared and tested for different applications [4, 21].

4. Final remarks

Supramolecular chemistry and host-guest structures pose an excellent alternative for drug design. New macrocycles were synthesized recently and tested in different formulations. These systems are expected to be used successfully in treating brain diseases.

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