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Enhancing antidepressant bioavailability and CNS targeting using cyclodextrin-enabled drug delivery systems

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Abstract
Drug delivery methods based on cyclodextrin (CD) offer a viable way to improve antidepressant medication by addressing problems including poor solubility and limited bioavailability. This review emphasizes how complexing different antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), with β-CD or derivatives enhances pharmacokinetics, decreases systemic toxicity, and improves drug solubility and stability. CD formulations improve therapeutic efficacy and allow for sustained or targeted drug release, according to analysis of *in vitro* and *in vivo* investigations. CD-based platforms are noteworthy for their cost-effectiveness, biocompatibility, and ease of formulation when compared to other delivery methods, notwithstanding difficulties with drug-loading capacity. In order to confirm the clinical benefits of CD-antidepressant complexes, particularly in treatment-resistant instances, the study calls for additional *in vivo* research. It recommends investigating hybrid solutions to address constraints and optimize advantages. In the end, including CDs into antidepressant therapies may result in more individualized depression interventions and improved therapeutic effects.

Keywords: Cyclodestrin, anti-depressants, tricyclic anti-depressants, drug delivery, targeted drug delivery

Introduction
Over 300 million people worldwide suffer from depression, a serious mental condition that causes roughly 800,000 suicides every year. Fatigue, fluctuations in weight, anhedonia, and cognitive problems are some of the symptoms of Major Depressive Disorder (MDD). It primarily affects a variety of demographics, with prevalence being higher in youngsters, the elderly, and pregnant women due to a number of causes. Recurrent seizures are linked to MDD, which is also correlated with social development and the environment. The COVID-19 pandemic has been shown to worsen MDD symptoms in infected persons [1-3].

The COVID-19 pandemic has increased the use of antidepressants, yet many of the drugs now on the market have serious adverse effects and little efficacy. Pharmacological treatments, which continue to be the standard of care in addition to therapies like psychotherapy and electroconvulsive therapy, are ineffective for a significant percentage of individuals with serious depression. TCAs, SSRIs, SNRIs, MAOIs, and atypical antidepressants are only a few of the groups of antidepressants that have distinct advantages and disadvantages, such as low bioavailability and serious side effects. Patient discontent and low adherence might result from problems including sluggish onset of action and off-target effects. This emphasizes the critical need for better delivery strategies that make use of contemporary drug delivery platforms like lipid vesicles and nanoparticles in order to increase solubility and bioavailability, boost therapeutic efficacy, and lessen adverse effects-all of which will eventually improve patient compliance [4, 5].

According to recent research, some antidepressants are susceptible to being broken down by digestive enzymes, which can reduce their efficacy. Because of their biocompatibility and capacity to create stable complexes with poorly soluble medications, cyclodextrin (CD)-based carriers are becoming more and more popular.

In addition to improving solubility, encapsulating antidepressants in β-CD or its derivatives stabilizes the medications, permits sustained release, and reduces side effects [6, 7]. This study focuses on the use of CDs in the treatment of depressive disorders, examining how they work in concert with different antidepressants and how they enhance medication transport to the central nervous system. It also analyzes pertinent research to determine the efficacy and therapeutic potential of CDs.

Cyclodextrin

Water-soluble cyclic oligosaccharides with a truncated cone form and a hydrophilic exterior and hydrophobic interior are known as cyclodextrins, or CDs. They are created when cyclodextrin glycosyltransferases break down starch, resulting in α-D-glucopyranose units connected by α-(1→4)-glycosidic linkages. Number of glusoce units classifies CDs as six (α-CD), seven (β-CD), or eight (γ-CD), as mentioned in Figure 1. The chair conformation of glucose units and restricted bond rotation give rise to the distinctive shape. Because they are amphiphilic, they can encapsulate lipophilic medications and stabilize host-guest inclusion complexes through a variety of non-covalent interactions and steric modifications. By encouraging interactions with water, the hydrophilic surface improves drug solubility, making CDs viable options for drug delivery systems [8-10].

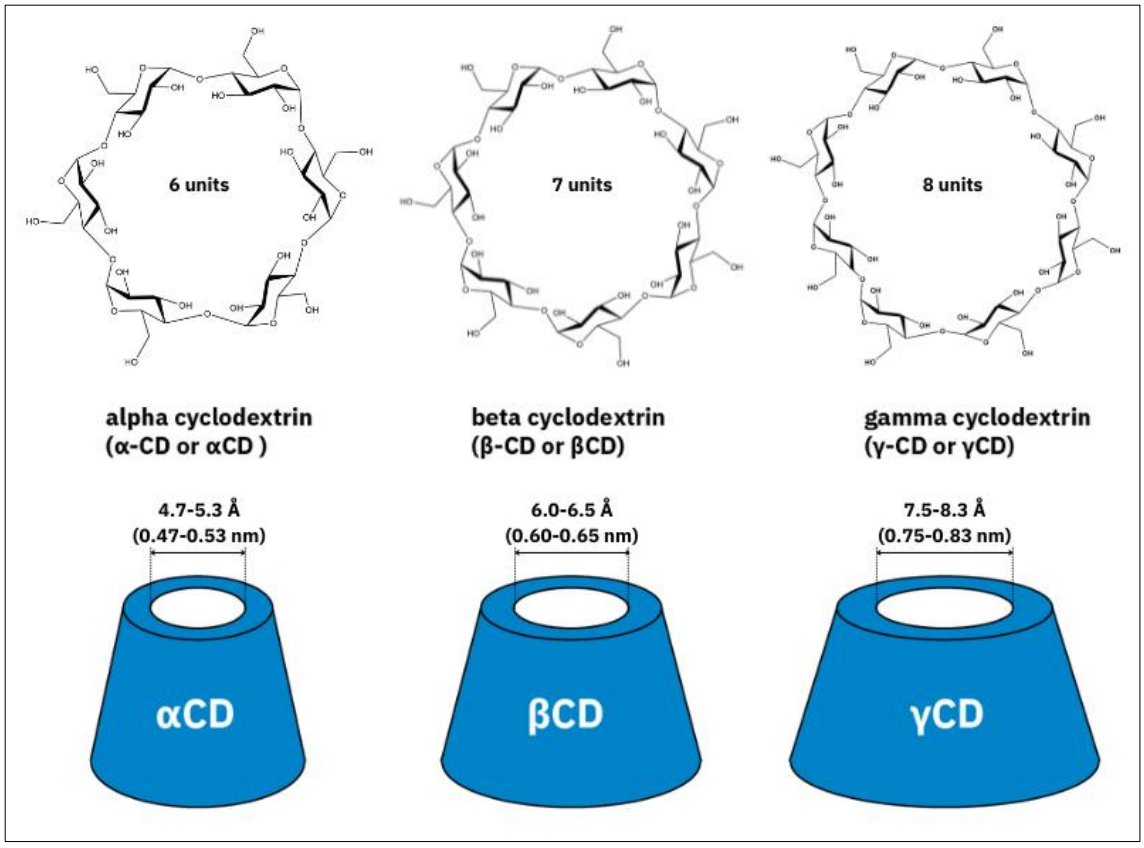

Fig 1: Chemical Structure of Cyclo-Dextrin

Cyclodextrins (CDs) have drawbacks despite improving solubility and bioavailability, such as their small cavity size-related drug-loading capability. Nevertheless, their reactive hydroxyl groups enable polymerization into cyclodextrin-based nano sponges, with β-CD being the most popular due to its affordability and non-toxicity. Cyclodextrin systems are versatile in many areas, especially medication delivery. In order to improve their applicability, recent research examines guest-host complexes with a variety of ligands, such as remdesivir and other noteworthy substances. Cyclodextrins are also used in the food sector and separation procedures. Research has increasingly concentrated on using CDs to change antidepressant medications in order to increase their solubility, stability, and toxicity due to the difficulties in their production [11, 12].

Comparision of cyclodextrin and other drug delivery systems

Table 1: Summary of CDs and few other drug delivery systems [13-15]

Drug Delivery System	Primary Mechanism/Function	Key Advantages	Key Limitations/Challenges
Cyclodextrins (CDs)	Creates inclusion complexes with hydrophobic drugs to enhance solubility and stability.	Ease of formulation, cost-effectiveness, ability to enhance solubility and bioavailability.	Limited drug-loading capacity (one drug molecule per complex), rapid renal clearance, may require modification or combination with other systems to prolong circulation.
Liposomes	Phospholipid-based vesicles that can carry both water and fat-soluble drugs.	Ability to carry both water and fat-soluble drugs, potential to pass the blood-brain barrier (BBB).	High production costs, physicochemical instability, susceptibility to structural perturbations, premature drug leakage, reduced shelf-life.

Polymeric Nanoparticles	Nanoscale particles composed of biodegradable polymers (e.g., poly lactic-co-glycolic acid).	Controlled and sustained drug release, prolong systemic drug circulation, enhance bioavailability, optimize drug delivery kinetics, enhance CNS penetration, reduce dosing frequency.	Complex fabrication techniques (limiting large-scale production), concerns regarding cytotoxicity and long-term biocompatibility with non-biodegradable polymers.
Dendrimers	Highly branched macromolecules with tunable surface chemistry and well-defined architecture.	High drug-loading capacity, can be functionalized with targeting ligands for site-specific delivery (suitable for CNS therapeutics).	Concerns regarding cytotoxicity, immunogenicity, high production costs.

Mechanism of cyclodextrin - antidepressants complexation

By creating inclusion complexes through host-guest interactions, the structural design of cyclodextrins (CDs) improves the solubility and stability of medications, thus increasing the effectiveness of drug administration for antidepressants like TCAs and SSRIs. These interactions, which are fueled by covalent forces including hydrogen bonds and van der Waals forces, aid in securing medications inside the CD cavity while preserving their water solubility. Notably, CDs help break through the blood-brain barrier (BBB) when used with antidepressants, which increases the medications' effectiveness in treating neurological disorders like depression. For example, β-CD increases the permeability and stability of dozepin, while HP-β-CD increases the stability and rate of dissolution of fluoxetine and paroxetine. Furthermore, it has been demonstrated that modified CD derivatives, such as sulfobutylether-β-cyclodextrin (SBE-β-CD), improve nortriptyline's solubility in physiological settings. Thus, controlled medication release is made possible by the clever design of CD-based systems, reducing blood level swings and enhancing therapeutic results [16, 17].

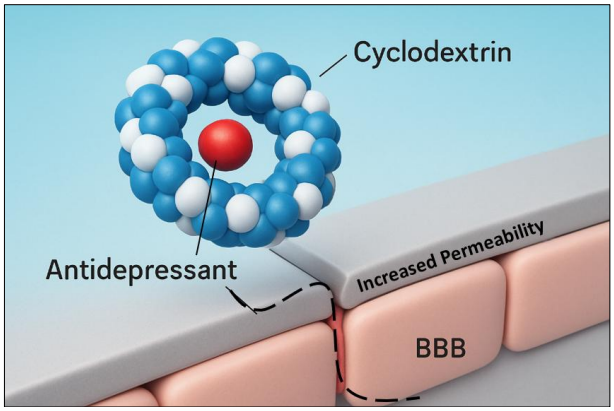

Fig 2: Schematic Representation of Mechanism of CD-Antidepressants Complexation

Different antidepressant drugs combined with cd

TCAs

According to research, clomipramine (CPM) can be used in drug delivery systems because its encapsulation with β-cyclodextrin (β-CD) improves stability through C/O-H interactions. In a similar vein, computational analyses have demonstrated that doxepin (DXP) and β-CD create stable complexes that enhance drug formulation. A comparison of transcutaneous delivery techniques in a porcine model revealed that a doxepin-HP-β-CD complex solution (CDS) produced sustained release and longer analgesic effects in rats, highlighting CDS's potential for treating chronic pain conditions like postherpetic neuralgia, whereas a pure drug solution (PDS) offers rapid release [13, 18].

When amoxapine (AXP) forms a compound with β-cyclodextrin (β -CD), its water solubility improves, suggesting the possibility of novel drug delivery formulations. Consistent with studies on nortriptyline and amitriptyline, similar outcomes were observed for imipramine (IPM), where β-cyclodextrin (β-CD) encapsulation improved drug stability through a bimodal complexation process. Additionally, protriptyline (PTR) showed stability inside the β-CD cavity, indicating that β-CD's function in drug delivery systems may improve the bioavailability and therapeutic potential of tricyclic antidepressants (TCAs) [19].

SSRIs

The efficacy of this technique was demonstrated by analyzing fluoxetine (FLX) utilizing CD-modified capillary electrophoresis for chiral separation. For the best chiral selection, a number of native and derivatized cyclodextrins (CDs) were examined. Studies on sertraline (SRT) have shown that CD incorporation increases drug solubility in particular molar ratios and improves thermodynamic stability. Sertraline-CD complexes' thermodynamic characteristics and potential for drug delivery were also investigated. By examining PXT: β-CD complexes, a study on paroxetine (PXT) demonstrated its structural flexibility and stability, observing a difference in stability between 1:1 and 2:1 ratios [20, 21].

Atypical Antidepressants

In a study, Wen *et al*. showed how to use capillary electrophoresis with acetonitrile field-amplified sample stacking for cyclodextrin-based enantioselective separation of mirtazapine and its metabolites. This method improves enantiomer resolution by taking advantage of host-guest interactions in cyclodextrins. Effective chiral discrimination and quantification of the drug's enantiomers were achieved by optimizing variables such as pH and buffer composition. This study emphasizes the value of enantioselective analysis in pharmacokinetic and pharmacodynamic studies as well as the function of cyclodextrins in improving analytical techniques for complex antidepressants [22].

In order to assess the stability and biological impacts of mianserin (MIA)-CD complexes, DFT calculations revealed thermodynamic stability. Isothermal titration calorimetry and cytotoxicity tests on Chinese hamster B14 cells showed that cell viability was over 80% when dimethyl-β-cyclodextrin (DM-β-CD) was used alone, but it dropped when mianserin was added. In contrast to the protective effect of β-CD, DM-β-CD increased the toxicity of MIA. Furthermore, a study that looked into β-CD and γ-CD as parts of a new trazodone sensing system demonstrated far higher sensitivity, precision, and repeatability than previous methods [23].

Future perspective

Cyclodextrin-based formulations may provide novel approaches to treating depression by increasing the effectiveness and absorption of pharmaceuticals. Due to genetic differences in drug-metabolizing enzymes, especially CYP enzymes, patients with the syndrome have different medication reactions. By improving pharmacokinetic profile predictability, CD-complexed formulations may be able to lessen problems brought on by these genetic variations in medication metabolism [24].

Creating dual drug-cyclodextrin complexes, which combine two complimentary antidepressants or a combination with antipsychotics, is one area of research that aims to improve medication efficacy and minimize interactions while promoting medication adherence. In order to confirm advances in solubility, bioavailability, and efficacy in human physiology, it is crucial to move from laboratory and animal research to human evaluations, with *in vivo* investigations coming before clinical trials [25].

To determine the long-term safety and therapeutic advantages of cyclodextrin-based formulations for clinical adoption, extensive clinical trials contrasting them with conventional antidepressants are crucial. Building on prior FDA and EMA approvals for specific cyclodextrin formulations, early interaction with regulatory bodies helps speed up acceptance. Thorough safety, quality, and efficacy data are essential, including evaluations of excipient effects and long-term toxicity studies. It is also necessary to show consistent production of a reliable, superior product. Additionally, by delivering medication directly to the nervous system while minimizing toxicity, innovations like customized compact discs with BBB-focused connectors could greatly improve the treatment of mental health disorders by providing safer and more individualized antidepressant options [26, 27].

Conclusion

Research shows that problems with antidepressant medication, like poor solubility and restricted bioavailability, can be successfully addressed by cyclodextrin-based drug delivery systems. Stable inclusion complexes produced by β-cyclodextrin and its derivatives improve medication solubility and controlled release. Although the research shows promise in lowering toxicity and improving pharmacokinetics, limitations still exist because of the dependence on *in vitro* models and the diversity of circumstances. In order to treat depression and CNS illnesses individually, future initiatives must standardize procedures, conduct clinical trials, and take into account hybrid systems and pharmacogenetic profiling.

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