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Cyclodextrin- based nanoparticles for pharmaceutical Application as an Antimicrobial Agents: A Review

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ABSTRACT: Nanotechnology is considered essential in the field of pharmaceutical applications for treating drug delivery problems as well as antimicrobial therapy and Cyclodextrin nanoparticles are noted to have an exceptional versatility playing a major role. This review will focus on these nano systems enhance drug solubility, stability and targeting (critical issues for poor bioavailable drugs or the management of problems like antimicrobial resistance) Then, possible future directions for the biocompatibility and surface modification strategies that could improve their therapeutic benefits will be discussed as well safety. Apart from pharmaceutical applications, cyclodextrin nanoparticles have been used for environmental remediation including water treatment or novel application as knowledge transfer and gas separation new area etc. Abstract This review elucidates the isolated interdisciplinary growth of PAS in health professions education and seven other domains, showcasing their potential to enhance understanding for both researchers and practitioners interested in how best to leverage their instrumentalize affordances. Hence, cyclodextrin nanoparticles might facilitate such processes to be used more routinely and predictably in the future development of health-related products and applications.

KEY WORDS: Cyclodextrin based nanoparticle, drug delivery, controlled release, Targeted therapy

INTRODUCTION: The increased applicability in areas such as pharmaceuticals and biotechnology over the last few years has made nanoscale systems more fashionable. Nanoparticles (NPs) are colloidal particles that is described as small size between 1 and less than 100 nm composed of biodegradable or non-biodegradable materials. While the diameter of nanoparticles (NPs) varies between 10 and up to ~1000 nm, there is a common adage that refers to those with sizes below 200 nm as nano-medicines (Loftsson, 1996) (Singh R, 2009). The drug is dissolved, dispersed, encapsulated or immobilized within a matrix of nanoparticulate dimensions (E F. , 2007). They may represent nano capsules (drug filled into a cavity) or nanospheres (particle improved by practical if the drug is consistently distributed in matrix); therefore, they offer different features and release patterns that allows them to be applied as vehicle for delivering various kinds of drugs (Salatin S, 2017) (Sahoo SK, 2003).

The small size of nanoparticles enables them to traverse across tissues and capillaries, offering advantages over large-sized macromolecules such as prolonged circulation half-life-time (Circulation Halftime), increased selectivity ratio, improved target organ residency time and better cell absorption (Jatariu AN, 2010). Upon contact with circulation, nanoparticles get opsonized leading to activation of macrophages. Their unique high surface area per unit mass, as well from conventional multi-particulate systems makes them not only superior but also

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interesting NPs. Its Dissolution and Bioavailability are improved by simply increasing the water solubility of drug (Gupta RB, 2006) (Wackerlig J, 2016).

Drug delivery nanoparticles include polymeric NPs, lipid NPs (solid and nanostructured), polymeric micelles, liposomes, nanotubes, nanocrystals, dendrimers, metallic NPs, quantum dots, and magnetic NPs (F., 2016) (J. Pardeike, 2009).

Nanoparticles (NPs) are used for targeted medication delivery in cancer due to the tumor's leaky design, allowing for improved penetration and retention. Drugs can be delivered through several channels, such as oral, pulmonary, nasal, parenteral, ophthalmic, brain, and dermal-transdermal (Zhou J, 2017).

The papers on cyclodextrin (CD) cover its usage in oral cancer therapy, pharmaceutical and biomedical applications, as well as medication and gene delivery. While NPs have many potential applications, there are certain limitations in their physicochemical and pharmacological properties. These issues may include reduced medication loading and trapping efficiency (Namdari P N. B., 2017).

This review addresses issues with NP drug delivery using CDs, such as poor drug loading, physical and chemical stability, target specificity, pharmacokinetics, bioavailability, and modified drug release. It also discusses the safety and efficacy of CDs in drug delivery. This review focuses on how CDs can improve nanoparticulate formulation and medicinal performance. This paper offers insights on theragnostic uses of CDs (Parveen S, 2012) (Pekamwar, 2020).

CYCLODEXTRIN-BASED NANOPARTICLES: A NOVEL APPROACH:

Types of Cyclodextrins: Cyclodextrins (CDs) are cyclic oligosaccharides composed of glucose monomers linked by α-1,4-glycosidic bonds. The most common types are:

- **Alpha-Cyclodextrin (α-CD):** Composed of six glucose units, α-CD has the smallest cavity size. It is less soluble in water compared to other CDs and is suitable for encapsulating smaller molecules (Shirodkar, 2019).
- **Beta-Cyclodextrin (β-CD):** Made up of seven glucose units, β-CD has a moderate cavity size. It is widely used due to its availability and cost-effectiveness. However, its lower aqueous solubility can be a limitation (Duddhipala, 2020).
- **Gamma-Cyclodextrin (γ-CD):** Consisting of eight glucose units, γ-CD has the largest cavity size among the common CDs. It has higher water solubility and is capable of forming inclusion complexes with larger molecules (Wong C.Y, 2018).

SNO.	CYCLODEXTRIN TYPE	NUMBER OF GLUCOSE UNIT'S	CAVITY DIAMETER (A)	WATER SOLUBILITY (g/l)	COMMON APPLICATIONS
1	Alpha- Cyclodextrin	6	4.7-5.3	14.5/100 ML	Drug Solubilization, Food Industry
2	Beta- Cyclodextrin	7	6.0-6.5	18.5/100 ML	Drug Delivery, Cosmetics
3	Gamma-Cyclodextrin	8	7.5-8.3	23.2/100 ML	Drug Stabilization, Dietary Supplements

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Table:1 Types and properties of cyclodextrins (M.E, 1996) (R.A, 1997) (G, 2014).

Methods for Preparing Cyclodextrin-Based Nanoparticles:

- **Self-Assembly:** Cyclodextrins can spontaneously form nanoparticles through non-covalent interactions, such as hydrogen bonding and hydrophobic interactions. This method often involves the use of guest molecules that can induce the assembly process (Joshi M.D, 2009) (Adeoye, 2017).
- **Solvent Evaporation:** This technique involves dissolving both the cyclodextrin and the guest molecule in a volatile organic solvent. The solution is then emulsified in an aqueous phase, and the solvent is evaporated, resulting in the formation of nanoparticles (Grimaudo M.A, 2018).
- **Co-Precipitation**: Cyclodextrin and the guest molecule are dissolved in a common solvent, which is then mixed with a non-solvent to precipitate the nanoparticles. This method is simple and can be performed under mild conditions (Pathak Y, 2007).
- **Spray Drying:** A solution containing cyclodextrin and the guest molecule is atomized into a hot drying chamber. The solvent evaporates rapidly, leaving behind cyclodextrin nanoparticles (Kanwar JR, 2011).
- **Inclusion Complexation**: Cyclodextrins form inclusion complexes with guest molecules through hydrophobic interactions. These complexes can be processed into nanoparticles using various techniques, such as freeze-drying or spray-drying (Namdari P N. B., 2017) (Ameli, 2022).

SNO.	METHOD	PRINCIPLE	ADVANTAGES	DISADVANTAGES
1	Self-assembly	Spontaneous organization of cyclodextrins into nanoparticles	Simple no need for solvents	Limited control over size
2	Solvent evaporation	Solvent removal leads to nanoparticle for motion	Good control over size and morphology	Requires organic solvents
3	Nanoprecipitation	Rapid mixing of solvent and non-solvent	Simple scalable	Limited to certain drug types
4	Spray drying	Atomization of cyclodextrin solution hot air	Scalable, continuous process	Requires specialized equipment

Table:2 Preparation methods for cyclodextrin nanoparticles (al, 2018) (Singh A, 2020) (Trotta F, 2013).

Size Range and Tailoring of Cyclodextrin Nanoparticles:

Cyclodextrin-based nanoparticles typically range in size from 50 to 500 nanometres. The size of these nanoparticles can be tailored for specific applications through various factors:

- **Choice of Cyclodextrin:** The type of cyclodextrin (α, β, or γ) can influence the size of the nanoparticles due to differences in cavity size and solubility (Li JJ, 2011).
- **Preparation Method:** Different methods of preparation can yield nanoparticles of varying sizes. For example, self-assembly may produce smaller particles compared to solvent evaporation (Ortiz Mellet C, 2011).

- **Guest Molecule:** The nature and size of the guest molecule encapsulated within the cyclodextrin can also affect the final size of the nanoparticles (Kurkov S, 2013).
- **Processing Conditions:** Parameters such as solvent type, concentration, temperature, and mixing speed during preparation can be optimized to control the size of the nanoparticles (Rogers M.A, 2016). Tailoring the size of cyclodextrin nanoparticles is crucial for their application in drug delivery, where particle size can influence bioavailability, cellular uptake, and release profiles. Smaller nanoparticles are generally preferred for intravenous administration due to better circulation and tissue penetration, while larger nanoparticles may be suitable for sustained release formulations (Loftsson T D. D., 2007) (Araujio L.H, 2020).

PHARMACEUTICAL APPLICATIONS: TAILORED DRUG DELIVERY:

Challenges with Conventional Drug Delivery Methods: Conventional drug delivery systems often face several significant challenges:

- **Poor Solubility:** Many drugs have low water solubility, which limits their bioavailability and therapeutic effectiveness (Liu Y, 2016).
- **Instability:** Drugs can degrade rapidly in biological environments due to factors like pH, enzymes, and oxidative conditions.
- **Non-specific Targeting:** Conventional methods often lack the ability to deliver drugs specifically to target tissues, leading to systemic side effects and reduced efficacy (Loftsson T B. M., 2010).
- **Short Half-Life:** Many drugs have short circulation times, requiring frequent dosing to maintain therapeutic levels.
- **Toxicity:** High doses needed to achieve effective concentrations can lead to toxicity and adverse side effects (Jambhekar SS, 2016).

Cyclodextrin Nanoparticles: Addressing Drug Delivery Challenges: Cyclodextrin-based nanoparticles offer several advantages that can address these challenges:

- **Enhanced Solubility:** Cyclodextrins can form inclusion complexes with poorly soluble drugs, significantly increasing their solubility and bioavailability.
- **Improved Stability:** Encapsulation within cyclodextrin nanoparticles protects drugs from degradation by shielding them from harsh biological environments (Laza- Knoerr .L, 2010).
- **Targeted Delivery:** Cyclodextrin nanoparticles can be functionalized with ligands that target specific tissues or cells, enhancing the precision of drug delivery and reducing systemic side effects (Challa R, 2005).
- **Extended Circulation Time:** Nanoparticles can provide sustained release of drugs, prolonging their circulation time and reducing the need for frequent dosing.
- **Reduced Toxicity:** By improving drug solubility and targeting, lower doses of the drug can be used, minimizing the risk of toxicity and adverse effects (Loftsson T J. P., 2005).

Examples of Drugs Formulated with Cyclodextrin Nanoparticles

- **Dexamethasone:** This corticosteroid has been formulated with cyclodextrin nanoparticles to enhance its solubility and stability, improving its therapeutic efficacy in inflammatory diseases (Menezer PDP, 2019).
- **Paclitaxel:** Cyclodextrin-based nanoparticles have been developed for the delivery of paclitaxel, a chemotherapeutic agent, to improve its solubility and reduce side effects associated with conventional formulations.
- **Itraconazole:** An antifungal drug that suffers from poor water solubility. Cyclodextrin nanoparticles have been used to enhance its solubility and bioavailability, leading to more effective treatment of fungal infections (Sharma N, 2016) (Chaichian S, 2020).

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- **Amphotericin B:** This antifungal drug is known for its toxicity. Formulating it with cyclodextrin nanoparticles has shown potential in reducing toxicity while maintaining therapeutic efficacy (Zhang J, 2010).
- **Curcumin:** A natural compound with poor solubility and stability. Cyclodextrin nanoparticles have been used to enhance its bioavailability and therapeutic effects, particularly in anti-inflammatory and anticancer applications. Cyclodextrin-based nanoparticles represent a promising strategy to overcome the limitations of conventional drug delivery methods, offering improved solubility, stability, targeted delivery, extended circulation time, and reduced toxicity. These benefits make them a valuable tool in the development of more effective and safer pharmaceutical formulations (Bartlett DW, 2007) (Geze A, 2002).

SNO.	DRUG	THERAPEUTIC AREA	BENEFITS OF CYCLODEXTRIN NASNOPARTICLES
1	Dexamethasone	Anti-inflammatory	Enhanced solubility and stability
2	Amphotericin B	Antifungal	Reduced Toxicity, improved solubility
3	Vancomycin	Antibiotic	Improved delivery, protection from degradation
4	Ibuprofen	Analgesic	Increased bioavailability, controlled release
5	Paclitaxel	Anticancer	Enhanced solubility and targeted delivery

Table:3 Examples of drugs formulated with cyclodextrin nanoparticles (M.E, 1996) (M.C, 2019).

ANTI-MICROBIAL AGENT DELIVERY: COMBATING RESISTANCE:

Mechanisms of Antimicrobial Resistance: Antimicrobial resistance (AMR) emerges when microorganisms adapt and become resistant to drugs that once effectively controlled them. Common mechanisms include:

- **Enzymatic Degradation:** Bacteria produce enzymes like beta-lactamases that break down antibiotics, rendering them ineffective (Wang A, 2016).
- **Efflux Pumps:** Bacteria have efflux pumps that expel antibiotics from the cell, reducing intracellular drug concentration.
- **Target Modification:** Bacteria alter the drug's target site, reducing its binding affinity and effectiveness (Ben Zirar S, 2008).
- **Reduced Permeability:** Changes in bacterial cell walls or membranes decrease antibiotic uptake.
- **Biofilm Formation:** Bacteria within biofilms are shielded from antibiotics and the immune system, contributing to chronic infections and resistance (Chen Y, 2015).

Cyclodextrin Nanoparticles in Antimicrobial Delivery: Cyclodextrin nanoparticles offer advanced solutions to combat AMR by addressing several challenges:

- **Protection from Degradation:** Encapsulation within cyclodextrin nanoparticles shields antimicrobial agents from enzymatic degradation, thereby enhancing their stability in biological environments (Popat A, 2014).
- **Enhanced Solubility and Bioavailability:** Cyclodextrins improve the solubility of poorly water-soluble antimicrobial agents, ensuring higher bioavailability and effective drug concentrations at infection sites (Erdogar N, 2018).

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- **Targeted Delivery:** Functionalizing cyclodextrin nanoparticles with ligands enables precise delivery of antimicrobial agents to bacterial cells, minimizing off-target effects and maximizing therapeutic outcomes.
- **Controlled Release:** Cyclodextrin nanoparticles can provide sustained release of antimicrobial agents, maintaining therapeutic levels over extended periods and reducing the need for frequent dosing (Ahmed A, 2012).
- **Overcoming Biofilm Resistance:** Cyclodextrin nanoparticles penetrate biofilms more effectively than free drugs, delivering antimicrobial agents directly to bacteria within biofilms and enhancing treatment efficacy (Jeganth S, 2018).

Potential Applications:

- **Hospital-Acquired Infections:** Effective against multidrug-resistant pathogens like MRSA (Methicillin-resistant Staphylococcus aureus) and VRE (Vancomycin-resistant Enterococci) prevalent in healthcare settings (Gonzalez-Gaitano G, 2017).
- **Chronic Infections:** Treats persistent infections associated with biofilm formation, such as those seen in cystic fibrosis or chronic wounds (Chen L.X, 2016).

Examples of Applications:

- **MDR Pathogens:** Cyclodextrin nanoparticles enhance the efficacy of antibiotics such as colistin and vancomycin against multidrug-resistant bacteria by protecting them from degradation and improving delivery to bacterial cells (Chen X, 2014).
- **Antifungal Delivery:** Improves the solubility and reduces the toxicity of antifungal agents like amphotericin B, enhancing their effectiveness against resistant fungal infections.
- **Combination Therapy:** Facilitates co-delivery of multiple antimicrobial agents, synergizing their effects and minimizing the emergence of resistance (S, 2019) (Larin A.O, 2020).

SNO	MECHANISM OF RESISTANCE	DESCRIPTION	CYCLODEXTRIN NANOPARTICLE SOLUTION
1	Enzymtic Degradation	Bacteria Produce Enzymes That Degrade Antibiotics	Encapsulation Protects Drugs Form Enzymes
2	Efflux Pumps	Bacteria Expel Antibiotics	Nanoparticles Bypass Efflux Pumps
3	Target Modification	Bacteria Alter Drug Targets	Targeted Delivery Enhances Binding
4	Reduced Permeability	Changes In Cell Wall/Membranes	Nanoparticles Improve Drug Penetration
5	Biofilm Formation	Bacteria In Biofilms Resist treatment	Nanoparticles Penetrate Biofilms

Table:4 Mechanisms of antimicrobial resistance and cyclodextrin nanoparticle solutions (Chaudhary, 2018)

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CHALLENGES AND FUTURE DIRECTIONS:

Challenges of Cost-Effective Large-Scale Production of Cyclodextrin Nanoparticles: Cost-effective large-scale production of cyclodextrin nanoparticles faces several challenges:

- Raw Material Costs: Cyclodextrins themselves can be expensive to produce or source in large quantities.
- Complexity of Manufacturing Processes: Processes like solvent evaporation or spray drying require precise control and may not scale easily (E D. M., 2009).
- Purification and Quality Control: Ensuring uniform particle size distribution and batch-to-batch consistency can be challenging and costly.
- Economic Viability: Balancing production costs with the need for affordable healthcare solutions poses a significant hurdle (Deng P, 2019) (Yasayan G, 2020).

Potential Issues of Immune System Responses to Cyclodextrin-Based Nanoparticles:

Potential immune responses to cyclodextrin-based nanoparticles include:

- Recognition as Foreign: Nanoparticles may be recognized as foreign by the immune system, leading to clearance or inflammatory responses (Dhul S.S, 2012).
- Hypersensitivity Reactions: Some individuals may exhibit hypersensitivity reactions to cyclodextrins or other components used in nanoparticle formulations.
- Long-term Effects: Understanding the long-term effects of repeated exposure to cyclodextrin nanoparticles on immune function is crucial (Fahmy S.A, 2022) (Zhou Y, 2019).

Ongoing Research Areas: Ongoing research focuses on:

- Surface Modification: Modifying nanoparticle surfaces with targeting ligands (e.g., antibodies, peptides) to enhance specificity for diseased tissues or cells (Fan n, 2021).

- Controlled Release Properties: Developing nanoparticles that release drugs in response to specific stimuli (e.g., pH, enzymes) for precise and sustained drug delivery (.F, 2017).

- Biocompatibility Improvements: Investigating strategies to reduce immune recognition and improve biocompatibility of cyclodextrin nanoparticles (Yokozawa T, 2016).

CONCLUSION: In summary, cyclodextrin nanoparticles represent a promising advancement in pharmaceutical science, offering solutions to critical challenges in drug delivery and antimicrobial therapy. These nanoparticles enhance drug solubility, stability, and targeted delivery while mitigating issues like antimicrobial resistance. Despite current challenges in cost-effective production and potential immune responses, ongoing research in surface modification and biocompatibility improvement shows promise. The integration of cyclodextrin nanoparticles into clinical practice holds significant potential to improve therapeutic outcomes and address global health challenges. Further interdisciplinary collaboration and innovation are essential to optimize these nanoparticles' efficacy and safety for widespread clinical use.

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