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CYCLODEXTRIN-ENHANCED MICRONEEDLE SYSTEMS FOR PACLITAXEL DELIVERY: A REVIEW OF CURRENT ADVANCES AND FUTURE PROSPECTS

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Abstract
Delivering drugs safely and effectively still challenges today's medicine, especially with high-potency anticancer agents like Paclitaxel. Standard recognized formulations confront pharmacokinetic ceilings caused by Paclitaxel's low aqueous solubility and severe side effects triggered by conventional excipients, so researchers are rapidly diversifying the delivery toolbox. This review evaluates the independent advantages cyclodextrins and microneedle arrays hold as next-generation delivery platforms. Cyclodextrins are still the mainstay of polymer-based delivery systems as they encapsulate and increase the relativistic pharmacokinetics of almost any soluble and lipophilic therapeutics. In addition, solid-dissolved or fumed Powders microneedle arrays form arrays of micron-sized reservoirs that are painlessly penetrated to the skin's Visco-elastic barrier once these are applied to the skin. Both drug-loaded systems, collaborating, generate a pharmacodynamically robust subcutaneous depot that shelters Paclitaxel from excipient toxicity and dramatically narrows its tissue-accumulation zone. Research synthesizing cyclodextrins, microneedle formulations, and Paclitaxel, though at the feasibility stage, is seeding pre-clinical uses and borrowed formulations, so provisionally analogous combined studies still furnish a sound proof of concept. Credible pre-existing library and concept studies of cyclodextrin- or polymer-embedded, Paclitaxel-loaded microneedle templates validate the combined concept.

1. Introduction

1.1. Overview of Advanced Drug Delivery Systems

The field of pharmaceutical sciences has undergone development in drug delivery systems (DDS) due to the need to improve health outcomes and reduce the constraints posed by traditional methods of drug delivery.[10, 12] Conventional approaches face issues like inadequate medication solubility, quick breakdown of active drug components, low bioavailability, non-specific drug distribution leading to systemic toxic effects, and problems with patient compliance.[10] Advanced DDS Overcoming these obstacles, Advanced DDS allows for tailored delivery, controlled release, and enhanced convenience for the patient. Along these lines, the goal is to optimize the effectiveness of treatment and reduce side effects, thereby modifying the clinical effectiveness of many drugs. The pharmaceutical industry seems to be at a turning point, adopting new drug delivery systems that are safer, more effective, and centered on the needs of the patient.[10, 12] As an example, it has been said that cyclodextrins "revolutionized pharmaceutical industry" because of how they improve drug stability, solubility, and bioavailability. [10] In the same way, biomaterials, the microneedle technology's foundations, are deemed a "revolutionary paradigm shift" in drug delivery systems.[2,

3] The unfulfilled clinical needs due to conventional formulations like Cremophor EL's severe side effects profoundly motivate this collective movement.[6, 7]

1.2. Paclitaxel: A Potent Anticancer Agent with Formulatory Hurdles

Paclitaxel (PTX) is an integral part of chemotherapeutic regimens for treating complex solid tumors. This includes ovarian, breast, lung cancers, and even Kaposi's sarcoma.[20] Paclitaxel helps treat certain cancers by microtubule stabilization, which interrupts apoptosis and halts the cell cycle in tumor cells. While beneficial in some cases, the lack of multifunctional therapeutic options and poor physicochemical and pharmacokinetic properties of paclitaxel heavily limit its clinical use.[20]

A major drawback stems from Paclitaxel's very low solubility in water.[20, 28] This essential characteristic governs the formulation techniques used for its administration. The current commercially available formulation, Taxol®, utilizes a co-solvent system consisting of Cremophor EL (polyoxyethylated castor oil) and ethanol.[6, 12] Although this vehicle enables solubilization, it unfortunately gives rise to a cascade of clinically significant hypersensitivity reactions, nephrotoxicity, neurotoxicity, and other hypersensitive reactions. These reactions frequently require complex premedication regimens.[20] Cremophor EL has also been reported to have cardiovascular effects, including labored breathing, lethargy, hypotension, and even vasodilation. Moreover, it has the ability to leach plasticizers such as diethylhexylphthalate from polyvinylchloride infusion bags and sets.[6, 12] The link of the drug's characteristics, its formulation, and the resultant toxicity is indicative of the multidisciplinary challenge its clinical utility. Propylene glycol's shortcomings as an excipient, which stems from Paclitaxel's poor solubility, illustrates the urgent need for delivery systems that surpass formulation toxicity.[12, 28]

1.3. Rationale for Novel Delivery Strategies: The Promise of Cyclodextrins and Microneedles

The extensive studies into alternative delivery systems are attributed to the daunting challenges of doses and the harsh reactions to toxicity the patient experiences. The more widely known Cremophor EL based Paclitaxel has very strict release Paclitaxel infused doses. Because of the very stiff requirement to slowly infuse the drug, it has to be diluted 5-20 times.[20] This effort does not only focus on small-scale advancements; it marks a complete change in the way drugs are designed and provided. Cyclodextrins are well known as multifunctional excipients that enhance the solubility of drugs, improve their chemical stability, and increase their bioavailability.[10] At the same time, microneedle technology provides a minimally invasive option for delivering drugs through the skin. These devices, measuring in microns, allow for the painless and bloodless bypassing of the stratum corneum, the skin's toughest barrier, which enhances patient comfort and compliance greatly.[3] The combination of these two technologies seems to be of great significance as it could solve the numerous issues related to Paclitaxel delivery, providing a means for developing safer and more effective medical treatments.[12, 20]

2. Cyclodextrins in Pharmaceutical Formulations

2.1. Fundamental Properties and Mechanism of Action

Cyclodextrins (CDs) are a class of cyclic oligosaccharides generally derived from the enzymatic digestion of starch.[10] Their particular molecular architecture has a torus or cone composition with a rather hydrophobic cavity in the middle and a hydrophilic surface.[10] CDs are able to form host-guest inclusion complexes with several compounds because of their unique amphiphilic arrangement.[10]

The inclusion complex formation process involves the entrapment of lipophilic drugs into the cavity of cyclodextrin. This mechanism relies on physical forces, either the van der Waals kind, plus water molecules being physically pushed out of the cavity.[10] When the drug molecule is encapsulated, the drug is protected by cyclodextrin's hydrophilic exterior, which greatly increases the drug's aqueous solubility. Such encapsulation also prevents the guest drug from crystallization and

aggregation, thus retaining its molecular dispersion, which enhances its stability in aqueous dispersions.[10]

2.2. Types of Cyclodextrins and Their Pharmaceutical Relevance

Within pharmaceuticals, the parent cyclodextrins are α-cyclodextrin (αCD), β-cyclodextrin (βCD), and gamma cyclodextrin (γCD).[10] "αCD has 6, βCD has 7, and γCD has 8 units of differing sized cavities."[8] The use of chemically modified cyclodextrins has increased because of their greater safety as well as their better solubility. Examples include 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD).[10] There is a justified and rational reason to incorporate both native and modified β-cyclodextrins into pharmaceuticals. Their effectiveness is derived from the one-of-a-kind cavity diameter, which accommodates numerous types of drug molecules.[10]

2.3. Multifaceted Pharmaceutical Applications of Cyclodextrins

Due to their numerous properties, cyclodextrins are crucial excipients in the pharmaceutical field as their applications go beyond basic solubilization. The range of applications of healing substances boosts their effectiveness.[10]

One of the already existing applications is the improvement of the solubility and the dissolution rate of water insoluble drugs.[10] The hydrophilic coat of CD-drug complex increases the solubility of compounds in water, thus, improving dissolution in biological fluids, and consequently, its absorption.[10] Some of the drugs that come to mind are Carbamazepine, Itraconazole, and Vitamin A Palmitate that are known to increase solubility and bioavailability through cyclodextrin formulation.[10]

Apart from solubility, cyclodextrins contribute significantly to the stability and protective measures of the drug.[10] They protect fragile active ingredients from degradation caused by the light, oxidation, heat, and even enzyme or pH processes in biological systems.[10] This protective measure enables a greater proportion of the active dose to be delivered by the targeted site, which in turn, improves the efficiency of the drug. As an example, cyclodextrins induced lesser photosensitivity of indomethacin and procaine, and lesser thermal decomposition of nitroglycerin and vitamin-D.[10] While cyclodextrins are known to improve the stability of pharmaceutical compounds, some researches indicate that in some circumstances, they may boost the degradation of some particular drugs. This illustrates the need for meticulous, drug-specific tailored investigations to achieve optimum stability.[8]

Enhanced bioavailability is the result of the cyclodextrins protection from degradation as well as the improved solubility.[10] Cyclodextrins increase bioavailability by improving the rate and extent the active ingredient is absorbed into the bloodstream and by safeguarding important molecules from early degradation. The active ingredient is absorbed into the bloodstream and exerts its intended therapeutic effect to a greater extent due to cyclodextrins. This enhancement of the pharmacokinetic profile has also been shown to decrease inter-patient variability, making the therapeutic response more reliable and uniform.[10]

Moreover, cyclodextrins can help decrease side effects by stabilizing drugs and improving their systemic delivery. This is accomplished through the administration of lower drug dosages while still preserving therapeutic efficacy, thus, reducing dose-dependent toxicities.[10]

The application of cyclodextrins in pharmaceuticals demonstrates their usefulness in different routes of administration. Some of the forms include oral dosage forms like tablets and capsules and powders ophthalmic solutions parenteral preparations intramuscular and intravenous injections topical gels and creams transdermal and patch release systems as well as suppositories aerosols and patches.[10]

In advanced nanotechnological systems of drug delivery, cyclodextrins are increasingly being used. Cyclodextrins are vital in creating nanoparticles used in targeted therapies, in gene therapies, and even in antiviral therapies and oncologic drugs like Paclitaxel and Doxorubicin.[10] They are also far

more helpful in solving multifaceted problems with biopharmaceutical delivery systems, especially for drugs like Paclitaxel.[10] This is because cyclodextrins simultaneously resolve solubility, stability, and bioavailability issues.

3. Microneedle Technology for Drug Delivery

3.1. Design and Classification of Microneedles

Microneedles (MNs) are a new technology designed to enable therapeutic agent transport through biological membranes, especially the skin.[3] These devices have micron-sized sharp spikes ranging from 10 µm to 900 µm in size. They aim to polish the stratum corneum, which is the skin's outer sheath, the most superficial protective layer.[15] Most importantly, the formation of these microchannels does not invoke any peripheral nerve endings and does not reach any blood vessels. This makes the procedure relatively superficial and non-invasive in nature.[15] This is important from the standpoint of patient comfort and compliance. For microneedles, the classification of shape – conical, pyramidal, obelisk – along with materials such as metal, glass, silicon, and polymer may be most useful.[15] However, a more functional classification distinguishes them by their drug loading and delivery mechanisms:

- **Solid Microneedles:** These MNs are typically used in a "poke and patch" approach. They create transient micropores in the skin, through which a drug, subsequently applied as a solution, ointment, or transdermal patch, can permeate into deeper dermal layers.[15]
- **Coated Microneedles:** In the "coat and poke" method, the drug is pre-coated onto the surface of solid MNs. Upon insertion into the skin, the drug coating rapidly dissolves in the interstitial fluid, releasing the therapeutic agent.[15]
- **Hollow Microneedles:** Functioning as miniature syringes, hollow MNs employ a "poke and flow" approach to directly infuse liquid drug formulations into the skin layers. This method is suitable for delivering larger volumes of liquid formulations.[15]

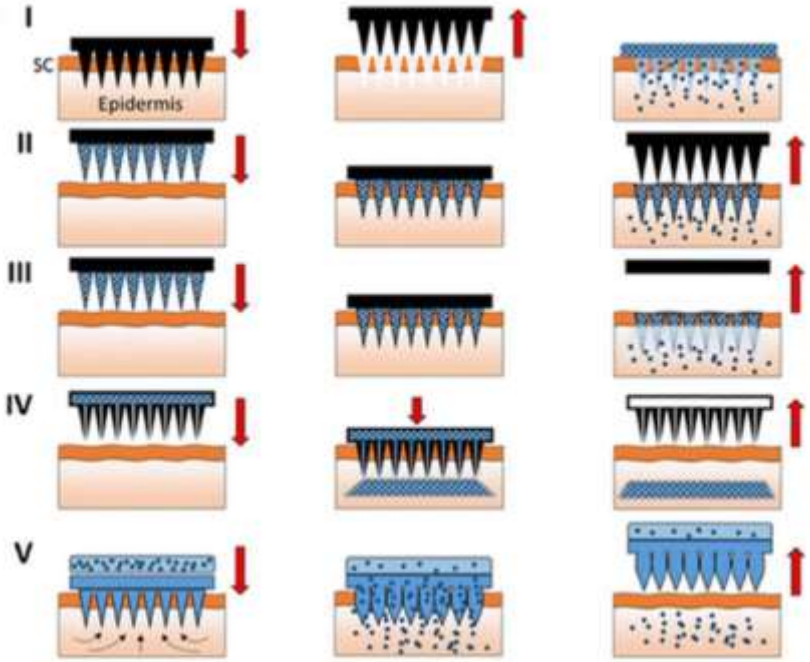

Figure 1. : Transdermal drug delivery approaches using MNs. I – ‘poke and patch’ approach; II – ‘coat and poke’ approach; III – ‘poke and release’ approach; IV – ‘poke and flow’ approach; V – ‘poke and swell’ approach. Image adapted with permission from[15]

- **Dissolving Microneedles (DMNs):** These MNs are fabricated from water-soluble polymers or sugars. Following insertion, the entire microneedle structure dissolves within the skin, releasing the encapsulated drug in a "poke and release" manner. This approach eliminates the generation of

biohazardous sharps waste and is particularly advantageous for achieving sustained drug delivery.[15]

- **Hydrogel-Forming Microneedles:** Utilizing a "poke and swell" mechanism, these MNs are made from hydrophilic polymers that absorb interstitial fluid and swell upon insertion, forming a hydrogel within the skin. This hydrogel then facilitates the controlled and sustained release of the incorporated drug.[15]

The various designs of microneedles along with their delivery methods is not simply an enumerative collection. Rather, it reflects a working continuum which affects the rate of drug release, formulary compatibility, and the clinical application. For example, the focus is on dissolving and hydrogel-forming microneedles due to their ability to offer controlled release of the drug, which is vital for hydrophobic medications that need to be maintained in therapeutic levels for extended durations.[17] Grasping these specific processes is critical for choosing the most suitable microneedle for Paclitaxel with regards to its low solubility and the need for controlled release, and for studying how cyclodextrins can be best incorporated into the microneedle matrix.

3.2. Fabrication Methods

The processes used to manufacture microneedles vary considerably and are influenced by the selected material for production.[15] The choice of materials and fabrication methods significantly influences the microneedle's mechanical strength, drug loading capacity, and performance in clinical applications.[3, 14]

Microneedles manufactured with polymers are the most common, and molding is the most widely used manufacturing method. Among these are injection molding, hot embossing, and micro molding. Other techniques are drawing lithography, and laser or X-ray micromachining.[15] For instance, photolithography provides an easy, non-molded method for making polymeric microneedles, however, this method can lead to a larger tip diameter which can adversely affect how well the needle penetrates the skin.[3]

In making silicon microneedles, lithography is the preferred technique, often accompanied by accurate wet or dry etching to create the microneedle shape.[15]

Microneedles made of metal can be produced by simpler processes such as putting together wires or hypodermic needles, or more intricate ones such as electroplating after laser metal cutting, wet etching, or 3D laser ablation.[15]

The production of glass microneedles involves pulling borosilicate glass pipettes, while the ceramic ones are made by micro molding a slurry of ceramic which is sintered at high temperatures.[15]

New innovations, especially 3D printing, are transforming the manufacturing of microneedles. This method has applications in the fabrication of male master molds using acryl butadiene styrene, as well as coatings of drugs on already prepared microneedles using inkjet printing. Furthermore, microneedles can be fully formed by direct printing using materials that polymerize upon UV exposure through stereolithography (SLA) and Digital Light Processing (DLP) or thermoplastic filaments in Fused Deposition Modeling (FDM).[15]

The construction material of microneedles affects their clinical utility, manufacturability, drug loading and stability.[15] The search for materials that can easily and robustly form microneedles suitable for penetrating biological barriers and interfacing with therapeutic molecules and living systems, illustrates the under-appreciated contribution of materials science to this technology. Hence, the successful formulation of the systems using microneedles with cyclodextrins and Paclitaxel will require the design of performance engineered polymeric materials that accommodate the cyclodextrin-drug complexes and retain mechanical strength for effective microneedle skin insertion.[10, 28]

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3.3. Advantages for Transdermal Drug Delivery

Microneedle technology has significantly advanced transdermal drug delivery, offering a compelling

alternative to conventional routes, especially for challenging therapeutic agents.[3, 2] Their distinct advantages include:

- **Overcoming the Skin Barrier:** The primary benefit of MNs is their ability to physically bypass the stratum corneum, the skin's most formidable barrier, which typically restricts the permeation of most molecules. This allows for enhanced transdermal delivery of drugs that would otherwise be poorly absorbed or require invasive parenteral administration.[15]
- **Minimally Invasive and Painless:** Unlike traditional hypodermic injections, MNs are designed to penetrate only the superficial layers of the skin, avoiding the deeper nerve endings and blood vessels. This characteristic ensures that the process is virtually painless and minimally invasive, leading to significantly improved patient comfort and compliance, which is crucial for long-term therapies.[15]
- **Delivery of Challenging Drugs:** Microneedles provide a direct pathway for macromolecules such as proteins, peptides, vaccines, and genetic material, as well as poorly permeable small molecules, which are difficult to deliver via conventional transdermal patches.[15] This includes hydrophobic drugs, for which dissolving MNs loaded with nanosuspensions have shown promising results in enhancing transdermal permeation.[17]
- **Reduced Systemic Side Effects:** By enabling localized drug delivery directly to specific skin layers, MNs can significantly reduce systemic exposure to potent drugs like Paclitaxel, thereby minimizing associated adverse effects that are common with systemic administration.[15]
- **Versatility in Drug Loading and Release:** Drugs can be incorporated directly into the MN matrix during fabrication, coated onto the surface of solid MNs, or delivered through hollow channels. This versatility allows for various drug loading capacities and enables precise control over drug release profiles.[3] Dissolving and hydrogel-forming MNs, in particular, can offer sustained drug release over periods ranging from seconds to several months, depending on the formulation and design.
- **Reduced Waste and Infection Risk:** Compared to traditional syringe injections, microneedle patches can reduce the generation of non-biodegradable sharps waste and lower the risk of needle-stick injuries and infections, contributing to safer healthcare practices.[15]

Microneedles provide a remarkable link between local and systemic drug delivery. They are frequently considered for therapeutics utilized on the surface of the skin, but their capability to administer drugs into the upper dermis permits later uptake by the abundant dermal microcirculation, thus allowing for systemic drug delivery.[17] The therapeutic flexibility for the delivery of Paclitaxel is profound; for microneedle systems designed for treating localized skin cancers, the drug can be concentrated at the site of drug delivery. On the other hand, if systemic chemotherapy is the objective, microneedle systems can be designed to allow the drug to enter circulation, dramatically increasing the systems potential therapeutic scope.

Table 2: Types of Microneedles and Their Drug Delivery Mechanisms

MN Type	Delivery Mechanism	Materials	Advantages	Disadvantages/Challenges	Representative Applications/Drugs
Solid	Pore creation for subsequent patch/solution application	Metal, Silicon, Glass	Minimally invasive, Painless, Overcomes stratum corneum	Limited drug loading, Rapid pore closure	Vaccines, Proteins, Small molecules
Coated	Drug dissolution from surface coating upon insertion	Metal, Silicon, Glass, Polymer	Minimally invasive, Painless, Direct delivery	Limited drug loading, Potential for coating loss/instability, small dose	Vaccines, Insulin, Peptides

Hollow	Liquid infusion through micro-channels	Metal, Silicon, Glass, Polymer	Controlled liquid delivery, High volume potential	Complex fabrication, Risk of clogging	Vaccines (Influenza), Insulin, Large molecules
Dissolving	Matrix dissolution in skin interstitial fluid	Polymers (e.g., PVA, PVP, PLGA), Sugars	Sustained release, No sharps waste, High drug loading potential, Patient-friendly	Mechanical strength can be a challenge for some polymers	Hydrophobic drugs (Cholecalciferol, Risperidone), Proteins, Peptides
Hydrogel-Forming	Swelling upon contact with interstitial fluid, drug diffusion from hydrogel	Hydrophilic Polymers (e.g., PVA, PVP)	Sustained release, No sharps waste, Biomarker collection	Potential for limited drug loading, Swelling kinetics control	Hydrophobic drugs (Risperidone), Insulin, Biosensing

4. Paclitaxel: Therapeutic Challenges and Novel Delivery Approaches

4.1. Therapeutic Importance of Paclitaxel

Paclitaxel (PTX) is an important chemotherapeutic agent used in the treatment of many solid tumors such as ovarian, breast, non-small cell lung, and Kaposi's sarcoma.[15] The mechanism of action includes stabilizing microtubules which disrupt cell division leading to apoptosis of rapidly proliferating cancer cells.[24, 20]

4.2. Critical Challenges of Conventional Paclitaxel Delivery

Despite its potent anticancer activity, the clinical utility of Paclitaxel is significantly hampered by several inherent physicochemical and pharmacological limitations, particularly concerning its conventional formulation:

- **Poor Aqueous Solubility:** Paclitaxel is notoriously hydrophobic, possessing extremely low aqueous solubility (less than 0.3 µg/ml).[20] This fundamental property is the primary obstacle to its formulation, necessitating the use of solubilizing agents.
- **Toxicity of Excipients:** The commercially available formulation, Taxol®, utilizes a co-solvent system of Cremophor EL (polyoxyethylated castor oil) and ethanol.[20] While effective at solubilizing Paclitaxel, Cremophor EL is associated with a spectrum of severe and dose-limiting adverse reactions. These include acute hypersensitivity reactions (necessitating extensive premedication with corticosteroids and antihistamines), nephrotoxicity, and neurotoxicity.[20] Furthermore, Cremophor EL can induce cardiovascular effects such as vasodilation, labored breathing, lethargy, and hypotension.[20] It also has the propensity to leach plasticizers, such as diethylhexylphthalate, from polyvinylchloride (PVC) infusion bags and sets, posing additional safety concerns.[20] The profound and pervasive side effects of Cremophor EL are not just a clinical inconvenience; they are the central unmet clinical need that has intensely driven significant research efforts to develop alternative Paclitaxel formulations.[20] Any successful novel Paclitaxel delivery system must, therefore, fundamentally aim to eliminate or drastically reduce reliance on this problematic excipient, placing patient safety at the forefront of its design.
- **Administration Complexities:** Due to the risk of Paclitaxel precipitation in plasma and the excipient-related toxicities, the conventional formulation requires substantial dilution (5-20 times) and a prolonged, slow intravenous infusion schedule.[20] This complicates administration, increases healthcare burden, and can impact patient comfort.
- **Non-selective Distribution and P-glycoprotein Efflux:** Free Paclitaxel exhibits non-selective biodistribution throughout the body, leading to systemic exposure and generalized toxicity to healthy tissues.[25] Additionally, many cancer cells develop multidrug resistance, often mediated by the overexpression of efflux pumps like P-glycoprotein (P-gp), which actively expels Paclitaxel from the intracellular environment, reducing its therapeutic efficacy.[1]

4.3. Overview of Novel Paclitaxel Delivery Approaches

The severe difficulties related to traditional Paclitaxel delivery systems have prompted numerous scientists to devise novel methods to increase its water solubility and decrease the toxicity associated with the excipients. These efforts have explored a wide array of advanced drug delivery platforms:

- **Liposomes:** These phospholipid-based vesicles have been investigated for encapsulating Paclitaxel, offering improved solubility, reduced toxicity, and the potential for targeted delivery to tumor sites.[1]
- **Nanoparticles (Polymeric and Lipid-based):** Nanoparticulate systems are widely considered the most promising future approach for Paclitaxel delivery.[20] Their versatility allows for the integration of multiple benefits, including enhanced solubility, controlled release, reduced systemic toxicity, and targeted delivery, while also addressing mechanisms of drug resistance.
  - **Paclitaxel-loaded nanosponges:** These cyclodextrin-based nanocarriers have demonstrated significant improvements in Paclitaxel's oral bioavailability, enhanced cytotoxicity against breast cancer cell lines (MCF-7), and exhibited prolonged *in vitro* release profiles. Crucially, these systems successfully circumvent the need for Cremophor EL, mitigating its associated toxicities.[25]
  - **Solid Lipid Nanoparticles (SLNs) with Cyclodextrins:** The modification of Paclitaxel-loaded SLNs with 2-hydroxypropyl-β-cyclodextrin (HPCD) has yielded notable advancements. These systems have shown enhanced cellular uptake, increased cytotoxicity, improved bioavailability following both oral and intravenous administration, and a reduction in nephrotoxicity.[1] A particularly significant finding is their ability to overcome P-glycoprotein efflux in multidrug-resistant breast cancer cells, thereby improving intracellular drug accumulation and therapeutic efficacy.[1]
  - **Other Nanoparticulate Systems:** Research has also explored multifunctional lipid nanoparticles for co-delivery of Paclitaxel with other agents, albumin-bound Paclitaxel formulations, and various polymeric nanocarriers, all aiming to improve drug properties and delivery.[2]
- **Cyclodextrin Complexes (non-nano):** Direct complexation of Paclitaxel with cyclodextrins has been investigated to enhance its solubility and stability, representing an earlier but still relevant strategy.
- **Prodrugs and Conjugates:** Chemical modification of Paclitaxel into prodrugs or conjugation with targeting moieties has been explored to improve its pharmacokinetic profile and enhance tumor specificity.
- **Emulsions and Gels:** Alternative liquid formulations, such as emulsions and mucoadhesive gels, have also been developed to provide different administration routes and improve drug properties.[14]

As indicated, nanoparticulate systems seem to effectively address the various complexities associated with Paclitaxel delivery. These systems stand out from others because they not only grant improved solubility for the drug, control its release, decrease systemic toxicity, amplify targeting, but also provide means to overcome some of the drug resistance mechanisms, including P-gp efflux. Therefore, they present a comprehensive, advanced, and highly attractive perspective for the future of Paclitaxel therapy.

5. Conclusion

Paclitaxel's potent anticancer activity is still limited in clinical practice because of its low water solubility and the severe toxicities associated with its conventional excipient. This review has concentrated on the unique benefits of cyclodextrins in improving the solubility, stability, and bioavailability of the drugs and the innovative microneedle technology that provides non-invasive and patent-friendly transdermal drug delivery.

As much as the direct original research that integrates microneedles, cyclodextrins, and Paclitaxel is still at its infancy, the available literature on related systems supports their combined use. The works done on cyclodextrin-based nanosponges and cyclodextrin-modified solid lipid nanoparticles have shown that Paclitaxel's solubility, cytotoxicity, bioavailability, and its ability to resist drug resistance

mechanisms were greatly enhanced. At the same time, other hydrophobic drugs have been transdermally delivered using microneedle systems, with some using cyclodextrins to improve permeation. The direct evidence of Paclitaxel incorporation into dissolving microneedle arrays supports these ideas.

Addressing the critical issues posed by Paclitaxel through these advanced drug delivery systems highlights the promise stepping toward safer and more effective and patient-centric cancer therapies. This approach could avoid the toxicities of old formulations, allow controlled and sustained release of the drug, and even allow targeted delivery. Future research directions should concentrate on the direct formulation design, full-battery in vivo assessment, and the volumetric production of these customizable systems to achieve their full therapeutic promise and to bring the next-generation Paclitaxel into clinical use.

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