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Nanocarriers for Controlled Drug Delivery A Convergence of Polymer and Nanochemistry

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Abstract: Nanotechnology has emerged as a leading and widely adopted technology, particularly in the improvement of healthcare strategies and other fields. In the near future, the pharmaceutical and biotechnology industries are expected to undergo significant transformations due to the integration of nanoscale technology in drug delivery systems, particularly through the use of polymeric nanoparticles. These nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields because of their potential as drug delivery systems, owing to their controlled and sustained release properties, subcellular size, and biocompatibility with tissues and cells. Several methods are employed in the preparation of polymeric nanoparticles, which are considered crucial for drug encapsulation. Materials such as PLGA, PLA, and chitosan are frequently used for encapsulating anticancer, antihormonal, and antimalarial drugs to enhance their release rates. Additionally, polymeric nanoparticles have applications in dentistry and oral health systems, particularly in the treatment of infections. The combination of polymeric nanoparticles with antibacterial drugs helps reduce infections. To achieve effective drug delivery, it is essential to understand the interactions of nanomaterials with the biological environment, including targeting cell-surface receptors, drug release, multiple drug administration, stability of therapeutic agents, and the molecular mechanisms of cell signaling involved in the pathobiology of the disease.

Keywords: Nanochemistry, Polymeric nanoparticles, Drug delivery system.

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1. INTRODUCTION

Nanochemistry is a branch of chemistry that studies chemical systems and processes at the nanoscale. The primary focus is on the properties, behavior, and manipulation of materials at the nanometer scale—typically between 1 and 100 nanometers. Due to the enhanced surface-to-volume ratio and quantum mechanical effects, nanoscale systems exhibit unique phenomena and characteristics (1). Polymeric nanoparticles, a type of nanoparticle used in drug delivery systems, are polymers prepared at the nanoscale (1-100 nm). They play a crucial role in various fields, as evidenced by numerous publications on polymeric nanoparticles, as illustrated in Figure 1. Drug delivery systems (DDSs) involve a multi-step process that includes the administration of a therapeutic product, the controlled release of active ingredients, and the transport of these active ingredients across biological membranes to reach the target site. DDSs can take various forms, such as formulations (e.g., capsules, tablets, or patches) or devices (e.g., pumps or implants) (2).

Nanochemistry is recognized as an important technique with applications across multiple fields, but it also faces limitations. To address these challenges, drug delivery systems can be integrated with nanochemistry to reduce their respective limitations. By combining these two systems, their

limitations can be minimized, making them even more significant in various applications (3).

In particular, the drug delivery system has been used to overcome some of the limitations of nanochemistry. The linkage between these two systems can reduce constraints on both sides. As a result, pharmaceuticals and other drugs can be enhanced through nanochemistry to improve their effectiveness. The use of polymeric nanoparticles with drugs enhances their efficiency, and when drugs are encapsulated with polymeric nanoparticles, the result is a highly biocompatible drug. For example, anticancer drugs encapsulated with polymeric nanoparticles become more effective and are released more rapidly at the target site (3).

This study aims to link two important systems—nanochemistry and drug delivery systems—and explain each system individually before demonstrating their combined significance. By using polymeric nanoparticles for drug encapsulation and applying them in oral and dental applications, more effective therapeutic outcomes can be achieved.

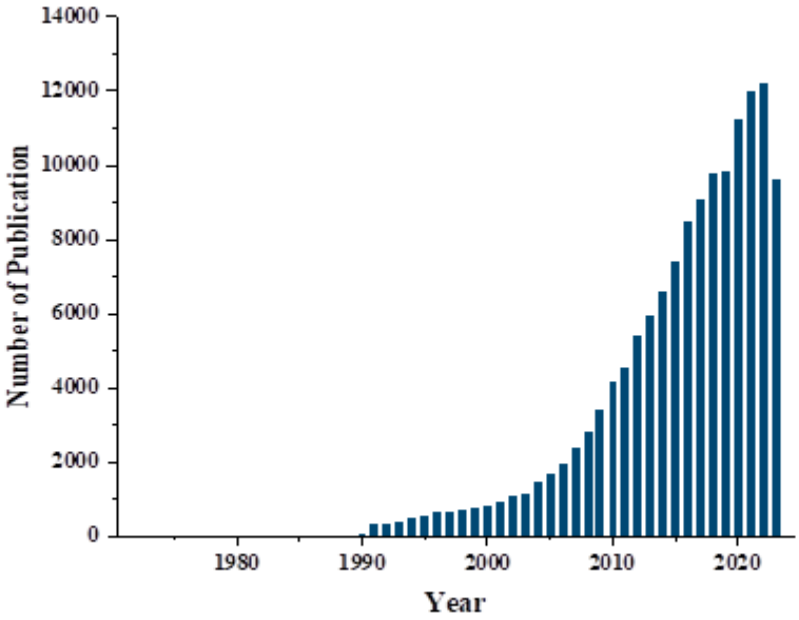

Figure 1: A visual depiction of the number of publications of polymeric particles during the period cited in Web of Science.

2. IMPORTANCE OF CONTROLLED DRUG DELIVERY

A Drug Delivery System (DDS) is defined as a system that facilitates the delivery of therapeutic drugs into the body while enhancing safety and efficiency by regulating the rate, time, and location of drug release and absorption. The DDS also refers to the interaction between the drug and the patient, determining the required dosage and administration. This process includes the use of a medicinal product, the release of active chemicals from the product, and the subsequent transport of these active compounds across biological membranes to their site of action. A substance that stimulates the development of an active therapeutic agent in vivo, such as in gene therapy, is also referred to as a therapeutic substance (2).

2.1. Drug Delivery Routes

Drugs are absorbed by the human body through several anatomical pathways. These drugs may be directed toward specific organs or intended for systemic effects. The choice of the route of administration depends on the illness, the desired outcome, and the available materials. Drug delivery routes are classified into several types. One common route is oral administration, which is preferred due to two factors: patient acceptance and ease of use. Another route is nasal drug delivery. For many years, medications have been inhaled for both topical and systemic effects. Topical treatments include medications for sinusitis, rhinitis, nasal blockages, allergies, and other long-term conditions. Examples of drugs used include corticosteroids, antihistamines, anticholinergics, and vasoconstrictors. The nasal route is appealing because it can bypass the disadvantages of oral administration, such as rapid first-pass metabolism and gastrointestinal drug breakdown.

3. POLYMERIC NANOPARTICLES

Polymeric nanoparticles (PNs) are derived from natural, semi-synthetic, or synthetic polymers. These nanoparticles are tiny, typically in the nanometer size range, often between 1 and 100 nanometers. Polymeric nanoparticles (PNs) are produced through polymerization processes involving monomer units. Under controlled conditions, these nanoparticles self-assemble into nanoscale structures (4).

3.1. Types of Polymeric Nanoparticles

Polymeric nanoparticles (PNs), based on their structural organization, are categorized into two types: nanospheres and nanocapsules. Nanocapsules differ from nanospheres in that they

have a reservoir structure, but both are important types of polymeric nanoparticles. Nanospheres, one type of polymeric nanoparticle, trap the drug within the polymer matrix. On the other hand, nanocapsules consist of a polymeric membrane encasing a liquid core of either water or oil, where the drug must dissolve within the liquid core to be effective (5). Figure 2 shows the schematics of polymeric nanoparticles.

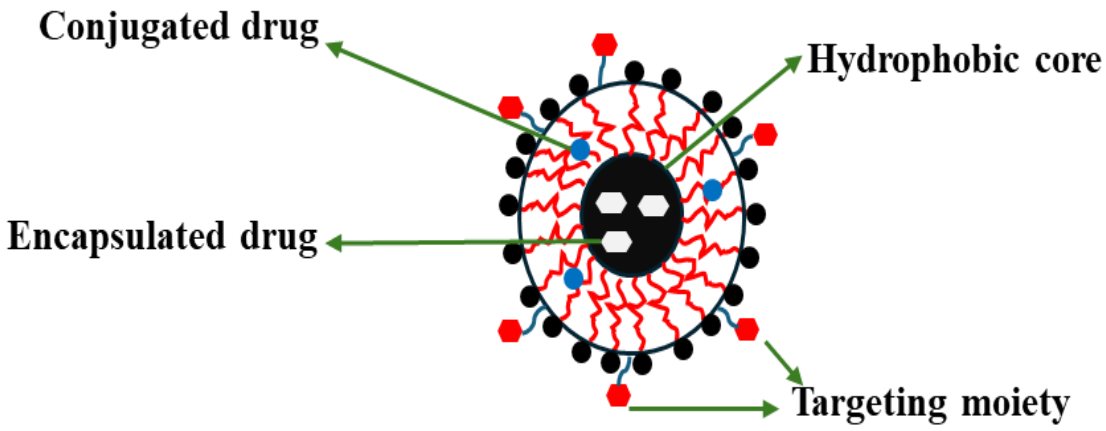

Figure 2: Schematics of polymeric nanoparticles.

3.2. Methods for Synthesizing a Polymer Nanoparticle

Polymeric nanoparticles can be prepared based on their desired application across different fields, making the preparation process crucial to their effectiveness. Two primary techniques are used for the preparation and formulation of PNs: preformed polymer dispersion and direct polymerization of monomers. The first method, preformed polymer dispersion, includes several useful approaches in polymer chemistry, such as solvent evaporation, dialysis, salting out, the use of supercritical fluid technology, and nanoprecipitation, which involves the dispersion of preformed polymers. Some preparation techniques are explained further, starting with solvent evaporation, which is the first technique under type 1 Solvent evaporation was the original method developed to produce (PNPs). The process begins by creating emulsions after preparing polymer solutions in volatile solvents. In the past, dichloromethane and chloroform were commonly used as solvents for preformed polymers, but ethyl acetate has gained popularity due to its better toxicological profile. As the solvent evaporates and the emulsion disperses into its continuous phase, it forms a suspension of nanoparticles (6). Figure 3 reveals solvent evaporation represented in schematic form.

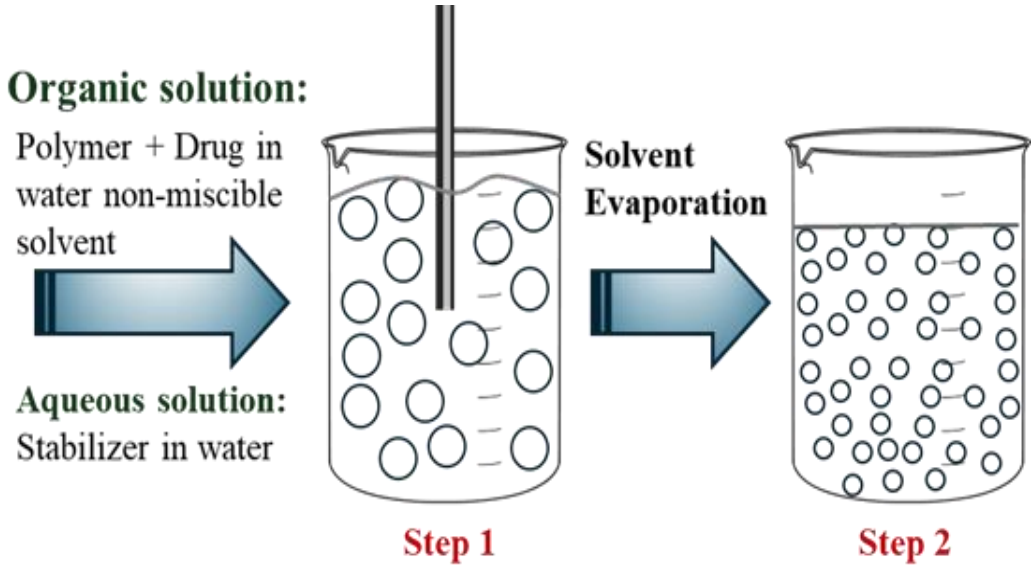

Figure 3: Solvent evaporation represented in schematic form (6).

Another technique is salting out. In this method, instead of using chlorinated solvents, a water-miscible solvent such as acetone, ethanol, or N-methyl-2-pyrrolidone is used. The aqueous phase can be saturated with electrolytes like magnesium acetate, magnesium chloride, or calcium chloride to prevent the mixing of organic and aqueous phases. To create an O/W emulsion, an organic solution containing the drug and polymer is emulsified into an aqueous phase that includes a colloidal stabilizer and salt. The emulsion is then diluted with enough water to enhance acetone penetration into the

aqueous phase, leading to polymer precipitation (7). Figure 4 The schematic representation of salting out.

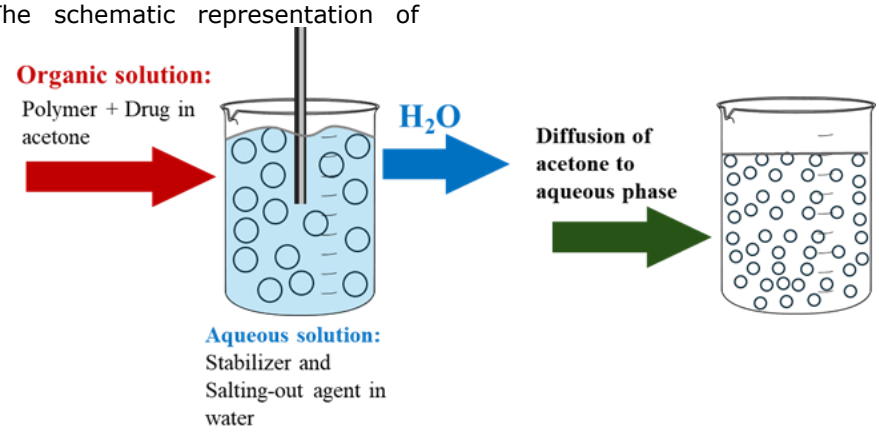

Figure 4: The schematic representation of salting out (6).

Type (2) is monomer direct polymerization, which includes several techniques such as controlled radical polymerization, microemulsion and emulsification-based polymerization, interfacial polymerization, and single-molecule direct polymerization, including mini-emulsion polymer formation (8).

Some preparation techniques are explained further. The first technique in Type 2 is emulsion polymerization, which is a highly scalable and efficient method for creating nanoparticles. This approach is divided into two categories depending on whether an aqueous or organic continuous phase is used. In the continuous organic phase method, a single molecule is distributed in an oily solution, an inverse microemulsion, or a material in which the monomer is insoluble. Several mechanisms can initiate the polymerization process. The process begins when an initiating molecule, which might be an ion or a free radical, comes into contact with a monomer molecule dissolved in the continuous phase. Alternatively, high-energy radiation, such as UV radiation or intense visible light, can convert a single substance into a starting radical. An anionic polymerization mechanism leads to the collision of monomer ions or radicals with other monomer molecules, triggering chain growth. Phase separation and the formation of solid particles can occur either before or after the polymerization process is completed (6).

Another technique is interfacial polymerization, a well-established method for creating polymer nanoparticles with a proven track record. The process involves step polymerization of two reactive monomers or agents dissolved in two separate phases: the dispersed phase and the continuous phase. The reaction occurs at the interface between these two liquids. The monomer is carried by the organic solvent, which is miscible with water, and polymerization occurs at the interface (6).

Polymers that are commonly prepared include polyprotic acid, polyglutamic acid, polycaprolactone, polylactic acid, and polyglycolic acid. On the other hand, examples of natural polymers include albumin, alginate, chitosan, collagen, and gelatin (5).

3.3. Nanotechnology-based Drug Delivery System Design

The unique properties of nanoparticles have garnered significant attention in the field of drug delivery. They enhance drug delivery in various ways, especially for poorly soluble drugs. In Figure 5, the difference between drugs that can utilize nanotubes (i.e., polymeric nanoparticles) and those that cannot is explained (9).

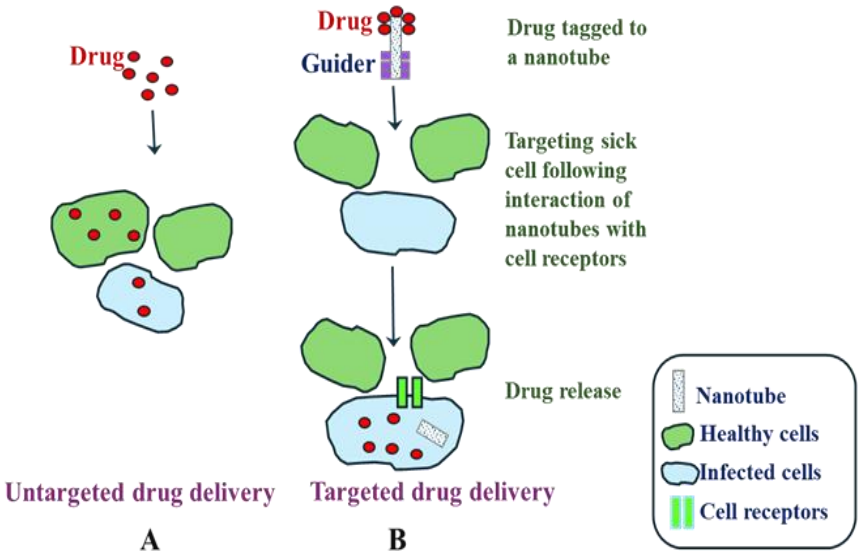

Figure 5: The distinction between targeted and untargeted delivery of drugs (9).

The following describes the role of nanoparticles in targeted drug delivery:

Better Solubility: The low solubility of many medications can limit their absorption and therapeutic effectiveness. Nanoparticles offer large surface areas and can be engineered to encapsulate or solubilize poorly soluble drugs, thereby enhancing their bioavailability. Targeted Drug Delivery: Nanoparticles can be functionalized or modified to target specific tissues or cells. This targeted delivery concentrates the drug at the site of action, reducing side effects and minimizing systemic exposure. Surface modifications, such as ligand conjugation, allow nanoparticles to recognize and bind to target cell receptors.

The Enhanced Permeability and Retention (EPR) effect is a phenomenon in which abnormal vasculature in tumors tend to accumulate nanoparticles more than in normal tissues. Nanoparticles can exploit this property, enabling passive targeting of drugs to tumor sites and thereby enhancing the effectiveness of cancer therapies.

Controlled Release: A sustained therapeutic effect can be achieved by engineering nanoparticles to release medication in a controlled manner. This is particularly useful for drugs with a narrow therapeutic window or those that need to act gradually.

Protection of Drugs: Polymeric nanoparticles can shield drugs from degradation and metabolic breakdown, which may prolong the stability and potency of certain medications.

Combination of Diagnostic and Therapeutic: Nanoparticles can be engineered to carry both therapeutic agents and diagnostic imaging agents. This enables simultaneous diagnosis and treatment, a practice known as theragnostic.

Personalized Medicine: The ability to customize nanoparticle-based drug delivery systems makes personalized medicine possible for specific patient populations.

Biocompatibility: The body can easily tolerate many materials that can be used to create biocompatible nanoparticles, reducing the likelihood of adverse reactions and immunological responses.

The use of nanoparticles in drug delivery holds great promise for enhancing the therapeutic effectiveness of medications while minimizing adverse effects. Researchers continue to explore and develop innovative nanoparticle formulations for various medical applications (10).

3.4. Drug Delivery Using Polymeric Nanoparticles

The nanoparticles of polymers known as (poly-d,l-lactide-co-glycolide, polylactic acid, poly-caprolactone, poly-alkyl-cyanoacrylates, chitosan, and gelatin) are the most widely used in drug delivery systems. The most popular polymeric nanoparticles in drug delivery systems are explained in Table 1.

Table 1: Polymeric nanoparticles that are most frequently utilized in drug delivery systems

Material	Full name	Abbreviation	Reference
Artificially created polymers	Poly(lactide) Poly(lactide-co-glycolide)	PLA PLGA	(11)
Natural polymers	Chitosan Gelatin Alginate		(11)
Copolymers	Poly(lactide)-poly (ethylene glycol)	PLA-PEG	(11)
Colloid stabilizers	Poly (vinyl alcohol)	PVA	(11)

	dextran		

Characteristics that make nanoparticles an excellent drug delivery system:

1.Non-toxic, Biodegradable, and Biocompatible:

Non-toxic: Nanoparticles used for drug delivery should not harm the body. They should not induce toxicity or cause adverse reactions.

Biodegradable: The system should be capable of breaking down into non-toxic components after delivering the drug, allowing for natural elimination from the body.

Biocompatible: The nanoparticles should interact favorably with biological systems without causing harm or triggering immune responses.

2. Improved Formulation Design:

Solubility Enhancement: Use various techniques such as micronization, nanosuspensions, or complexation to improve drug solubility.

Bioavailability Enhancement: Incorporate excipients that enhance drug absorption, such as surfactants, penetration enhancers, and lipid-based formulations.

Stability Enhancement: Develop formulations with stabilizers, antioxidants, and appropriate packaging to protect drugs from degradation.

3. Benefits of therapy:

Controlled Bioavailability: Maintaining therapeutic drug levels in the body is crucial. A drug delivery system that allows precise regulation of bioavailability ensures a predictable release of the medication.

Biodistribution and Tissue Uptake: The distribution of drugs in the body and the tissues' ability to absorb medications can significantly impact treatment outcomes. Targeted drug delivery can increase drug concentration in specific areas while reducing exposure in non-targeted cells.

Enhanced Drug Efficacy: Prolonged and controlled drug release can improve the overall efficacy of treatment, especially for medications with a narrow therapeutic window or those requiring continuous exposure for optimal effectiveness.

Improved Patient Compliance: Controlled drug delivery systems often require less frequent dosing, which can improve patient adherence to the treatment regimen.

Reduction of Side Effects: Controlled drug release can help mitigate side effects by avoiding sharp peaks and troughs in drug concentration. This results in a more stable and tolerable treatment experience for the patient (7).

4. ENCAPSULATION OF DRUGS IN POLYMERIC NANOPARTICLES

As mentioned above, polymeric nanoparticles are prepared using various methods depending on the application and the type of drug encapsulation. To demonstrate the effectiveness of nanomedicine, polymeric nanoparticles are used for the encapsulation of various drugs. The most useful polymers for this purpose are biodegradable polymeric nanoparticles. These nanoparticles offer successful drug release properties, as well as optimal subcellular size and bioactivity when interacting with cells (12). The general linkage between the encapsulation and polymeric nanoparticles is shown below in Figure 6.

5. PLGA (Poly D, L-lactide-co-glycolide)

PLGA (poly-d,l-lactide-co-glycolide) is an important nanoparticle used in nanomedicine and drug delivery systems. It is composed of biodegradable monomers, lactic acid and glycolic acid, which break down naturally in the body (4). Such as explained in Figure 7.

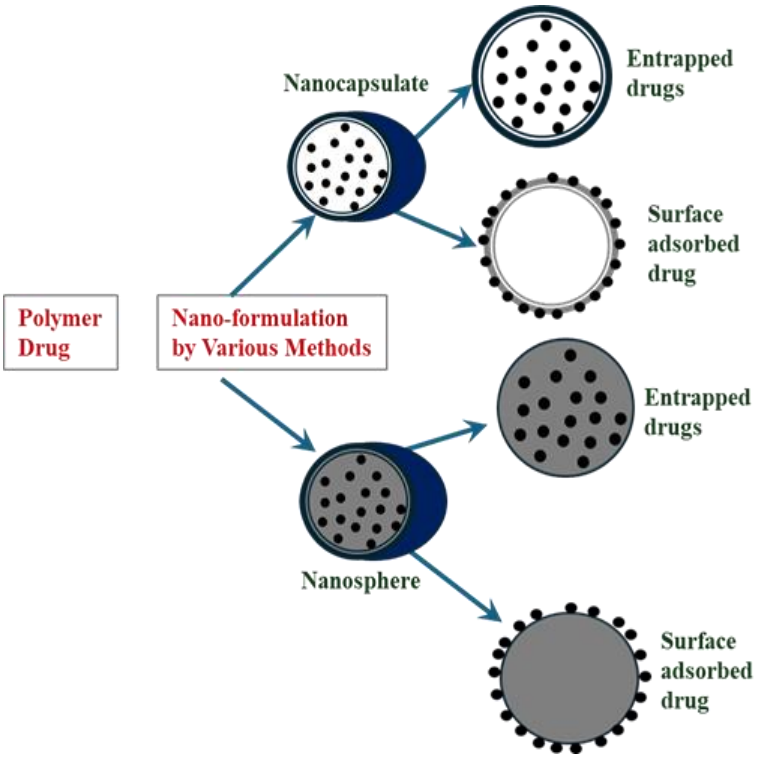

Figure 6: The encapsulation of drug and polymer nanoparticles.

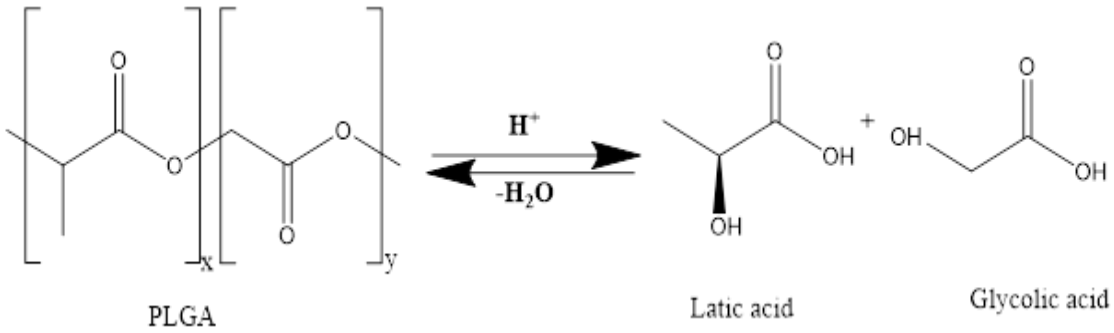

Figure 7: Hydrolysis of PLGA.

Different cancer-fighting drugs encapsulated on PLGA nanoparticles:

The FDA accepts PLGA for therapeutic use in treatment due to its beneficial properties in nanomedicine. Key characteristics of PLGA nanoparticles include:

Particle Size: The particle size of nanoparticles significantly impacts the drug delivery system. With sizes ranging from 1 to 100 nm, their small size enhances tissue penetration, cellular uptake, and provides an increased surface area for interactions.

Surface Morphology: Well-defined surface morphology improves stability, cellular uptake, and overall biocompatibility, making it an important property in nanomedicine.

Surface Charge: The stability of nanoparticles in suspension and their interaction with biological membranes are influenced by their surface charge.

9-Nitrocamptothecin (9-NC) is a potent anticancer agent, but its low water solubility and instability at physiological pH present challenges for effective delivery. Nanoprecipitation techniques can address these issues, and PLGA (poly (lactic-co-glycolic acid)) is often used to encapsulate such lipophilic drugs. By encapsulating 9-NC in PLGA nanoparticles, you can achieve high encapsulation efficiency (over 30%) while preserving the drug's biological activity and preventing degradation of the lactone ring, which is crucial for its anticancer efficacy. This approach improves the drug's stability and bioavailability, making it a promising strategy for enhancing the therapeutic potential of 9-NC (12).

Cisplatin is a widely used anticancer agent with a mechanism of action that involves forming cross-links with DNA, which inhibits DNA replication and transcription, and can affect both genomic DNA (gDNA) and mitochondrial DNA (mtDNA). This action can effectively kill cancer cells, but its clinical use is limited by side effects and the development of drug resistance (13).

To overcome these challenges, cisplatin has been encapsulated in PLGA–mPEG (poly(lactic-co-glycolic acid)–methoxy poly(ethylene glycol)) nanoparticles using a double-emulsion method. This formulation

helps improve the stability and controlled release of cisplatin at the targeted site, which can enhance its therapeutic efficacy and reduce side effects. The quick degradation of these nanoparticles and their prolonged release at the tumor site contribute to better inhibition of cancerous tumor growth, potentially improving the overall effectiveness of cisplatin-based treatments (12).

Paclitaxel is a highly effective anticancer agent used to treat various cancers, including breast, endometrial, and cervical carcinomas. However, its clinical use is often limited by its poor solubility in water, which complicates drug delivery (14). To address this issue, paclitaxel can be encapsulated using PLGA (poly(lactic-co-glycolic acid)) nanoparticles combined with vitamin E and tocopherol. The solvent evaporation/extraction methods used in this approach help trap paclitaxel within the nanoparticles, improving its solubility and stability. This method not only enhances the drug's solubility but also allows for faster and more efficient drug administration. The encapsulation in PLGA–vitamin E–tocopherol nanoparticles can improve the pharmacokinetics of paclitaxel, leading to better therapeutic outcomes and potentially reducing side effects (12).

6. POLYLACTIC ACID (PLA)

Polylactic acid (PLA) is an aliphatic polyester characterized by the presence of ester bonds connecting its monomer units. It is highly valued in the biomedical field for its biocompatibility and biodegradability, with a variety of uses for suture threads that are active, bone-fixing screws, and drug-delivery equipment (15). Figure 8 reveals the formation of polylactic acid (PLA).

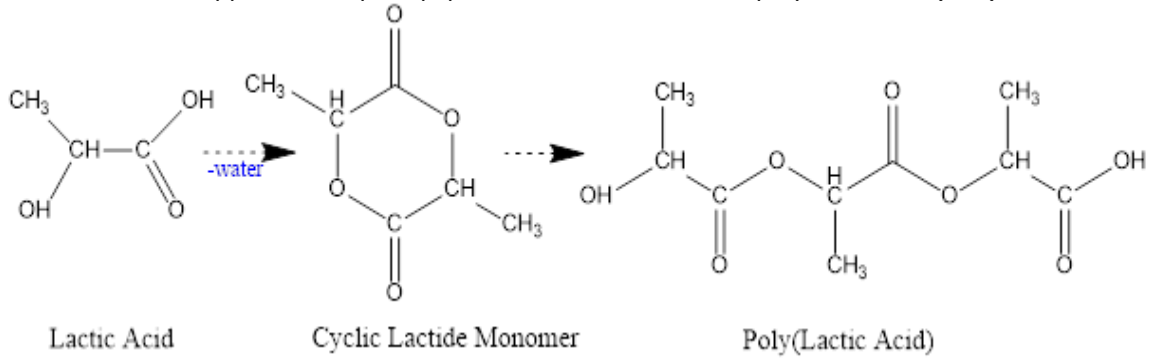

Figure 8: The formation of polylactic acid (PLA)

6.1. Encapsulation of Oridonin on PLA Nanoparticles

Oridonin ($C_{20}H_{28}O_6$) is a kaurene-type diterpenoid extracted from Rabdosia rubescens, known as "Donglingcao" in Chinese. It exhibits a range of biological activities, including anticancer, antibacterial, anti-inflammatory, and anti-fibrotic effects. However, its clinical use is limited by its low therapeutic index and poor water solubility (16). To address these limitations, oridonin can be encapsulated in poly (lactic acid) (PLA) nanoparticles using an improved spontaneous emulsion technique. This formulation helps overcome the drug's solubility issues and enhances its stability. The PLA nanoparticles facilitate a prolonged blood circulation time, which can improve the drug's therapeutic efficacy by increasing its bioavailability and allowing for sustained release at the target site (12).

6.2. Hormone (Progesterone) Encapsulation on PLA Nanoparticle

Progesterone, a C-21 steroid hormone, plays crucial roles in the female menstrual cycle, pregnancy, and embryonic development across various species. Its therapeutic applications extend beyond these physiological roles, including potential uses in cancer treatment.

To enhance the delivery and efficacy of progesterone, it can be encapsulated in PLA–PEG–PLA (poly(lactic acid)–poly(ethylene glycol)–poly(lactic acid)) nanoparticles using the solvent evaporation method (12).

7. GELATIN

Gelatin is Naturally occurring, biocompatible, and sustainable, biopolymer and contains an active group for this reason it is used in many applications and it has a low cost. Gelatin contains both anionic and cationic groups which means poly-ampholyte in nature (17).

Didanosine and chloroquine phosphate are both important medications with specific challenges in their clinical use, which can be addressed by encapsulating them in gelatin nanoparticles.

Didanosine Encapsulation

Didanosine (ddI) is an anti-HIV medication with a strong affinity for water, which facilitates its ability to cross the blood-brain barrier (BBB). However, effective delivery to the brain requires precise formulation. By encapsulating didanosine in mannan-coated gelatin nanoparticles using the desolvation method, several benefits are achieved:

Enhanced BBB Penetration: The gelatin nanoparticles, especially with mannan coating, help didanosine effectively traverse the BBB.

Improved Efficiency: Encapsulation enhances the stability and bioavailability of didanosine, ensuring

better therapeutic outcomes in the treatment of HIV.

Chloroquine Phosphate Encapsulation
Chloroquine phosphate is an antimalarial drug used to treat malaria by killing the parasite that infects red blood cells. Despite its efficacy, it is associated with side effects such as headache, drowsiness, vomiting, and nausea. Encapsulating chloroquine phosphate in gelatin nanoparticles offers several advantages:

Reduced Side Effects: The gelatin nanoparticles can help mitigate adverse reactions by controlling the release of the drug and reducing its systemic exposure.

Improved Drug Functionality: Encapsulation enhances the stability and effectiveness of chloroquine phosphate, potentially leading to better therapeutic outcomes with fewer side effects.
Both encapsulation strategies illustrate how gelatin nanoparticles can be utilized to improve the delivery, efficacy, and safety profiles of medications, addressing their inherent limitations and enhancing their therapeutic potential (12).

8. CHITOSAN

Chitosan, a biopolymer derived from chitin, is indeed a valuable material for drug delivery systems due to its unique chemical properties and biological compatibility. Three functional groups make up chitosan: hydroxyl groups both primary and secondary at places C2, C3, and C6, as well as an amino group. The hydroxyl groups in chitosan have a significant impact by chemically supplying side groups to the reactive hydroxyl groups; this process is carried out without altering the physical in natural functions of the material (18).

8.1. Encapsulation of Insulin on Chitosan Nanoparticles

Enterocytes cells lining the small intestine responsible for nutrient absorption. The absorption of insulin is facilitated by cells of intestine lining. For the purpose of enhanced intestinal absorption, The intestinal absorption of insulin was significantly improved by the insulin-loaded chitosan nanoparticles (12).

Antihormonal (glycyrrhizin) medications encapsulated on chitosan tiny particles:

Glycyrrhizin (GL) indeed a major bioactive compound found in licorice root (Glycyrrhiza glabra), and it has been recognized for diverse pharmacological and biological activities, like.

Antiviral Activity: Glycyrrhizin has proven to have antiviral properties against several viruses, such as the HIV, the influenza virus, and the herpes simplex virus.

Anti-Inflammatory Activity: According to reports, GL has anti-inflammatory qualities, which it might be helpful for inflammation-related conditions.

Antioxidant Activity: The compound exhibits antioxidant effects, which help combat oxidative stress in the body.

Anticancer Activity: Studies, both in vitro and in vivo, have suggested glycyrrhizin may have anticancer properties, with potential effects on various types of cancer cells (19).

Chitosan have demonstrated a remarkable ability to bind with ammonium glycyrrhizinate. The pattern of release of ammonium glycyrrhizinate exhibits a noticeable peak and a gradually increasing release phase; however, if the nanoparticles are employed, they may enhance the uptake of ammonium glycyrrhizinate orally (12).

9. POLY-CAPROLACTONE (PCL)

One of the rare synthetic biodegradable polymers with great potential for use in drug delivery systems is poly-caprolactone (PCL). This polymer is hydrophobic and has a crystalline structure, with its crystallinity decreasing with increasing molecular weight. This kind of polymeric nanoparticles is made using widely used methods, like the ring-opening polymerization of 2-methylene-1-3-dioxepane by free radicals. It can also be made using a different method that doesn't involve free radicals, which is ring-opening polymerization (20).

PCL nanoparticles are used to encapsulate insulin and other diabetes medications: One of the hormones made by the pancreatic beta cells that regulates our blood sugar levels and is absorbed in the intestines is insulin. Insulin administered orally via poly-caprolactone (PCL) polymeric nanoparticles is one of the most commonly used insulin carrier medications. Since the cells in the small intestine adsorb strongly to FITC-insulin-loaded nanoparticles, the cells in the intestine absorb insulin more readily when the insulin is loaded onto PCL nanoparticles (21).

Encapsulation of clonazepam drugs on PCL nanoparticles:
One medication that calms the brain and nerves is clonazepam. It is a member of the benzodiazepine drug class. The copolymer known as poly (N-isopropyl acrylamide)-b-poly(3-caprolactone) (PNPCL) is highly effective in the encapsulation of clonazepam. Additionally, poly-N-isopropyl acrylamide (PNiPAAm) is formed; the formation of these PNiPAAm hydrogel layers delayed the release of the drug because they can function as a barrier and an additional part. Consequently, the PCL copolymer has a significant impact that facilitates clonazepam's release and absorption more successfully (12).

10. BIOCOMPATIBILITY AND TOXICITY

Biocompatible Materials in Dental and Oral Systems:

To boost the effectiveness of dental and oral systems, biocompatible polymeric nanoparticles are employed. Antibiotics have been added to a range of biomaterials to target specific areas and boost the efficacy of antibiotic therapy because of this. In dentistry, where localized drug delivery can help treat infections and prevent complications, this tactic is particularly crucial. Chitosan, gelatin, and alginate, as well as Poly(lactic-co-glycolic acid), also known as PLGA and Polylactic Acid (PLA), are the two most significant polymeric nanoparticles utilized in dentistry. In addition, PLA is a biodegradable polymer nanoparticle that can be employed in dental applications, acting as a carrier and gradually releasing medication. It A naturally occurring polymeric nanoparticle that serves as an antibiotic increases the delivery of antibiotics locally, encouraging healing and lowering the risk of infections (22).

10.1. PLGA in Dentistry

PLGA is one of the most common polymer-based nanoparticles used in dentistry. They serve a variety of purposes, including screw bone fixation and periodontal pairing (23). In the form of implants, disks, and dental care films, PLGA can be used to treat periodontal disease, improve local antibiotic delivery, and lessen the systemic side effects of general antibiotic delivery (24). Direct pulp capping is used to treat exposed dental pulp, which is typically the result of trauma or caries, in order to maintain pulp vitality and promote the formation of reparative dentin. The use of PLGA composites with bioceramics in direct pulp capping is being studied, with an emphasis on different materials and techniques to increase the procedure's success. PLGA is a well-liked polymer for controlled drug delivery systems because it is biocompatible and biodegradable. On the other hand, bioceramics—a term for materials that are compatible with biological tissues—are widely used in orthopaedic and dental applications (23). The positive results of the PLGA materials indicate that more research is required, especially in the areas of material delivery to dental tissues and pulp capping ability of PLGA composites. To elaborate, the dental field employs PLGA materials for a multitude of purposes. Figure 9 illustrates the most commonly used PLGA substances and their respective applications in dentistry (25).

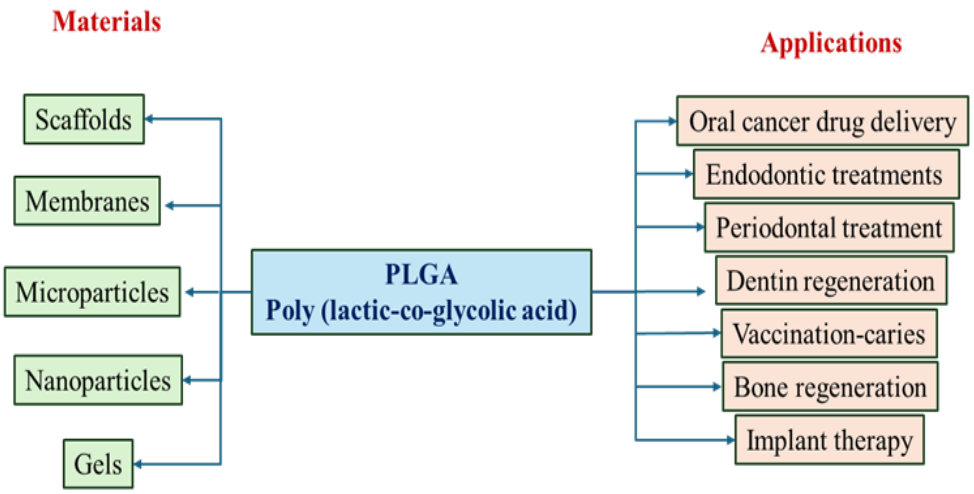

Figure 9: The most popular PLGA substances and how they are used in dentistry (25).

Dental cavity system of administration using chitosan as a natural polymeric carrier for dental disorders:

Chitosan is a natural polymer of significant functional importance, making it one of the most crucial natural polymeric nanoparticles used today due to its high biocompatibility, nontoxicity, and excellent degradability (26). Chitosan-based carriers are employed to deliver nutrients, antimicrobial agents, anti-inflammatory compounds, chemotherapy medications, and vaccines to specific cells through various forms such as films, fibers, sponges, micro/nanoparticles, and gels (26). In dental fields, chitosan-based drug delivery systems are used to treat conditions such as tooth caries and periodontitis, as well as to provide extended local anesthesia and support endodontic treatments for root canals (27).

The disadvantages of systemic antibiotic and anti-inflammatory drug administration have shifted the focus toward targeted drug delivery systems. These systems allow for the continuous release of medications in specific areas, sustaining therapeutic concentrations at the site for extended periods (28). Chitosan exhibits anti-inflammatory properties on human gingival fibroblasts (HGFs) by downregulating chemokines (such as CXCL-8) and cytokines (such as TNF-α and IL-1β). This suggests that chitosan may play a significant role in modulating the inflammatory response, which is crucial for tissue healing. The impact of chitosan on inflammation can vary depending on the substances and components involved. This underscores the importance of understanding the unique properties of chitosan formulations to maximize their beneficial effects. The potential for chitosan to support the regeneration of injured gingival tissue is supported by observed increases in cell survival and metabolic rates, as well as its anti-inflammatory effects. Thus, chitosan may be a promising option for promoting wound repair and tissue renewal in the oral cavity (29). Since gram-negative rods are the primary cause of gingivitis, metronidazole is considered an essential antibiotic for the management of gum disease. Research suggests using chitosan-based

gels and films to deliver metronidazole locally, reducing the number of applications, potential systemic side effects, and the healing time (30). A study led by Pichay Korn et al. examined chitosan nanoparticles filled with metronidazole (MTZ-MPs). The findings indicate that MTZ-MPs loaded into hydrogels exhibit a more favorable release profile compared to MTZ-MPs incorporated into films (31).

Chitosan-based drug transporters are used for the management of root canal diseases. Chitosan/gelatin nanoparticles have been applied in endodontic treatments and root canal infections, with one of the most important applications being the sustained release of calcium hydroxide. Calcium hydroxide is widely used in endodontics due to its antimicrobial properties and its ability to promote tissue repair. Nano-carriers, with their high surface area, can provide controlled release of the encapsulated drug, prolonging its therapeutic effect. This sustained release is particularly advantageous in root canal treatments, as it ensures that the therapeutic agent remains active within the root canal system for an extended period, increasing the chances of eliminating or controlling infection. Additionally, the biodegradability of chitosan is beneficial in such applications, as the nano-carriers can gradually break down and be eliminated from the body, minimizing potential long-term side effects (32). Consequently, calcium hydroxide combined with chitosan nanoparticles exhibits greater antibacterial activity compared to calcium hydroxide alone (33).

Modifications of oral hygiene products:
Porphyromonas gingivalis and Streptococcus mutans are the main pathogens that cause gingivitis and dental cavities, two common conditions in the oral cavity. Mouthwashes, dentifrices, toothpaste, and other dental products come in liquid, paste, gel, or powder form. These products contain active ingredients that work in multiple ways to maintain dental health and enhance oral hygiene. Recent advancements in dental care product development have concentrated on utilizing naturally occurring anti-plaque agents with potent anti-carious efficaciousness (34). Cytotoxicity, consistency, and biofilm-inhibiting properties have all been examined when comparing the broad spectrum prolonged anti-bacterial activity of chitosan-based toothpaste and mouthwashes to commercial ones evaluated. In the field of oral care, toothpastes containing stannous material and fluoride modified by chitosan have been the focus of much research. Chitosan-modified Fluoride Toothpaste: Fluoride is well-known for its ability to prevent tooth decay by encouraging remineralization and preventing demineralization of enamel. When combined with chitosan, this toothpaste seeks to maximize the protective effects of fluoride on tooth enamel.

The efficacy and adherence of the mixture might be enhanced by the addition of chitosan. Stannous-containing Toothpaste: Another ingredient found in toothpaste formulas is stannous fluoride. Its capacity to offer several advantages, such as antibacterial qualities and sensitivity alleviation, has been acknowledged. It is thought that stannous compounds create a layer of protection on the surface of the teeth, preventing dentin and enamel loss. In contrast to store-bought toothpaste: These altered formulations are frequently compared in studies to toothpaste products that are sold commercially. Fluoride is added to toothpaste formulations for enamel protection, along with other additives for flavor and texture, and standard cleaning ingredients. Assessing factors like bacterial inhibition, abrasion resistance, enamel hardness, and overall tissue loss reduction efficacy may be part of the comparison (34).

10.2. Antifungal Properties Substances

Numerous studies have demonstrated that chitosan coating medical devices lowers the risk of poisoning. Tissue conditioning products and denture adhesives, two of chitosan's derivatives, are expected to be effective in treating denture stomatitis and other common oral fungal infections due to their strong anti-fungal properties (36). The anti-fungal mechanism of chitosan is believed to be fungistatic as opposed to fungicidal, and it is similar to the antibacterial mechanism that was previously discussed (37). One of chitosan's well-known antimicrobial qualities is antifungal activity. By adding high-molecular-weight chitosan to the denture adhesive, wearers of dentures may benefit from improved oral health by preventing fungal growth. A low-molecular-mass chitosan solution applied for two weeks is a more effective treatment for denture stomatitis than nystatin (38). Additionally, when treating oral inflammatory and candidiasis lesions, chitosan-curcumin mouthwash without alcohol yielded better results than chlorhexidine (39).

10.3. Tissue Engineering

Periodontitis is a very serious inflammation that affects not only the bone but also the soft tissues that support the teeth, as well as dental tendons and ligaments. The phases of periodontitis are as follows: Gingivitis, the early stage of periodontal disease, is characterized by gum inflammation. Gingivitis is often brought on by plaque, a sticky bacterial film that forms on teeth. Gingivitis can lead to periodontitis if it is not properly treated. also, Periodontal Pocket Formation: As gingivitis advances, inflammation cause creation of periodontal pockets. These are openings where bacteria can grow and proliferate between teeth and gums. The pockets offer a conducive environment for growth of more harmful bacteria. bone loss: when Periodontitis is not treated the bone that shields the teeth loss results in defect the bone of the teeth. Tooth Loosening: the continued methods leads to the tooth losing bone, causing in the teeth loosening also it may be in severe cases tooth mobility becomes evident and leads to an increase in the effect of tooth loss (40). Chitosan and its derivatives are naturally occurring biomaterials that meet all of the necessary requirements and characteristics for tissue scaffolding. When the new target tissue forms, chitosan does not break down into hazardous compounds, especially when broken

down by lysosomes, nor does it trigger the immune system when it is inserted. In dentistry, bone, gums, and tooth pulp are regenerated using scaffolds made of chitosan (41).

Metallic-Based Concoction for Medicine *Administration in Dental Issues:*
Because of their unique properties, which include their high surface-to-volume ratio and importance in the study of dental issues, nanoparticles have attracted a great deal of interest in a variety of fields, including the medical sciences and dentistry. Another characteristic of nanoparticles that makes them significant is their shapes. Another type of nanoparticle used in dentistry are metallic ones. Titanium nanoparticles, for example, are used in dental implants due to their remarkable biological compatibility and durability. Gold: Used in imaging and with special optical properties for therapeutics and diagnostics. Silver: Silver nanoparticles are utilized in dental materials to prevent infections because of their well-known antimicrobial qualities (42).

11. CONCLUSION

nanotechnology has become a new revolution It is a cutting-edge method for finding and delivering drugs. Polymeric Nanoparticles that are prepared from polymers are the most types of nanoparticles used in the field of nanotechnology to improve many functions of drugs and sustain the release of the drugs in a shorter time than the drug without the use of polymeric nanoparticles, the most important polymeric nanoparticles that explained are PLGA and poly lactic acid(PLA) and chitosan also alginate, they are the most important polymeric nanoparticles and prepared by polymerization process that discussed, they are used in encapsulation of drugs such as encapsulation of anticancer and antihormonal and antimalarial also insulin most other drugs were discussed that uses polymeric nanoparticles in their encapsulation by encapsulation improve their efficiency also improve their releasing rate also can act most beneficial drugs that reduce side effects of drugs. by means polymeric nanoparticles can be used in the field of dentistry, to boost the effectiveness of dental and oral systems, biocompatible polymeric nanoparticles are employed. Antibiotics have been incorporated into a range of biomaterials to target specific regions and enhance the efficacy of antibiotic therapy due to these reasons. PLGA, PLA, and chitosan are the most important polymeric nanoparticles that are used in dental problems, chitosan used in toothpaste, has more benefits than the toothpaste used without using chitosan as a part of it, also PLGA is the most multi-functional uses in the field of dentistry such as used in endodontic treatments and oral cancer therapy, at the end of the study explained that two systems that work and link together most benefit system.

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