Role of Nanotechnology in the Management of Brain Disorders

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***Abstract*—Brain disorders such as Alzheimer's disease, Parkinson's disease, and brain tumors remain difficult to treat due to the complex structure of the central nervous system and the restrictive blood–brain barrier (BBB). Nanotechnology offers innovative strategies to overcome these challenges by enabling targeted and controlled drug delivery to the brain. Nanocarriers like liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles improve drug stability, enhance BBB permeability, and minimize systemic toxicity. Surface modification of nanoparticles with ligands or antibodies allows site-specific delivery and sustained therapeutic action. In addition to therapy, nanotechnology contributes to early diagnosis through nanosensors and imaging agents, enabling real-time monitoring of disease progression. Thus, nanotechnology holds immense potential in advancing both the diagnosis and treatment of brain disorders, providing new avenues for effective and personalized neurotherapeutic interventions.**

***Index Terms*—Alzheimer's disease, Parkinson's disease, liposomes, polymeric nanoparticles**

I. INTRODUCTION

Brain disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), glioblastoma, epilepsy, stroke, and multiple sclerosis (MS) pose significant treatment challenges due to the complexity of the central nervous system (CNS) and the presence of the blood-brain barrier (BBB). The BBB, a highly selective physiological barrier, restricts the passage of most therapeutic agents from the bloodstream into the brain parenchyma, drastically limiting the effectiveness of conventional pharmacotherapy [125,130]. In recent years, nanotechnology has emerged as a promising strategy to overcome these challenges by enhancing drug delivery, improving targeting, and reducing systemic toxicity.

II. ROLE OF NANOTECHNOLOGY IN THE MANAGEMENT OF BRAIN DISORDERS

1. Overcoming the Blood-Brain Barrier

Nanoparticles, defined as materials with dimensions in the nanometer range (1–100 nm), possess unique physicochemical properties, including high surface-to-volume ratios, tunable surface chemistry, and the ability to encapsulate both hydrophilic and hydrophobic drugs. Nanocarriers such as liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, dendrimers, and micelles can be engineered to cross the BBB through various mechanisms, including transcytosis, receptor-mediated transport, or by temporarily opening tight junctions. Surface modification of nanoparticles with ligands (e.g., transferrin, lactoferrin, or antibodies) enables receptor-mediated targeting, enhancing brain-specific delivery while minimizing off-target effects.

2. Application in Neurodegenerative Diseases

In Alzheimer's disease, nanocarriers have been designed to deliver anti-amyloid and anti-tau therapies, antioxidants, and neuroprotective agents directly to affected brain regions. For example, curcumin-loaded nanoparticles show improved BBB penetration and reduced amyloid aggregation compared to free curcumin. Similarly, in Parkinson's disease, dopamine-loaded nanoparticles or gene delivery systems targeting α-synuclein aggregation are under investigation to provide sustained drug release and neurorestoration.

3. Application in Brain Tumors

Glioblastoma, the most aggressive primary brain tumor, remains resistant to conventional chemotherapy due to poor drug penetration and

tumor heterogeneity. Nanotechnology-based delivery systems, such as temozolomide-loaded nanoparticles, gold nanoparticles for photothermal therapy, and nanocarrier-mediated immunotherapy, are being developed to enhance drug accumulation within tumors and overcome multidrug resistance. Additionally, nanoparticle-mediated co-delivery of chemotherapeutic agents and gene therapies holds promise for synergistic anti-tumor effects.

4. Application in Stroke and Neuroinflammation

In ischemic stroke, nanocarriers are explored to deliver thrombolytic agents (e.g., tissue plasminogen activator) with targeted release at the clot site, reducing systemic bleeding risk. Anti-inflammatory nanoparticles and antioxidant-loaded nanocarriers are also being developed to mitigate secondary neuroinflammation and oxidative stress following stroke or traumatic brain injury [179].

5. Advantages and Challenges

Nanotechnology offers several advantages in CNS drug delivery, including enhanced bioavailability, controlled and sustained release, and the potential for multi-functional "theranostic" platforms combining therapy and diagnostics. However, challenges remain, including nanoparticle toxicity, immunogenicity, large-scale manufacturing, and the need for regulatory approval. Comprehensive preclinical and clinical studies are essential to establish the safety, efficacy, and long-term effects of these advanced delivery systems.

Nanotechnology represents a transformative approach in the management of brain disorders, offering solutions to longstanding barriers in CNS drug delivery and therapy. While several nano-based systems are still under investigation, early evidence suggests their potential to revolutionize treatment paradigms for neurodegenerative diseases, brain tumors, stroke, and neuroinflammatory conditions. Continued interdisciplinary research and translation into clinical applications hold promise for improving patient outcomes in the near future.

III. CLASSIFICATION OF NANOPARTICLES

Nanoparticles (NPs) are particulate substances with dimensions typically between 1 and 100 nanometers. Their small size, large surface area-to-volume ratio, and tunable surface properties make them ideal for various applications in medicine, electronics, energy, and environmental remediation. The classification of nanoparticles is given below:

i. Polymeric Nanoparticles

Nanoparticle is colliodial dispersions in which the drug is enclosed, entrapped, encapsulated or attached. Dependent upon the process of provision of nanoparticles, nanospheres or nanocapsules can be attained. Nano capsules are vesicular arrangements containing drugs in polymeric openings. Nanospheres are matrix systems containing the drug are physically and equally dispersed.

ii. Solid lipid Nanoparticles

Solid lipid Nanoparticles are particles of nanometer dimensions with a solid lipid matrix. The oily droplets made from lipids which are solid at room temperature and stabilized by using surfactants. The benefit of SLNs is that there is no need of organic solvents in the preparation, they deliver protection from water and can be used for controlled release. SLN particulate systems for parental medication with mean atom diameters ranging from 50-1000 nm. They also have application in cosmetics.

iii. Nanosuspensions /Nanocrystals

Disperse system of solid-in-liquid or solid-in-semisolid, the dispersed phase comprising pure active compound or an active compound mixture. The average diameter of the dispersed phase is between 10 nm and 1000 nm. The nanosuspension can be surfactant free, but can also consist of surfactants or stabilizers or both. Nanosuspension can also be lyophilized or spray dried, and the nanoparticles of a nanosuspension can also be combined into a solid carrier matrix.

IV. EXCIPIENTS USED IN THE PREPARATION OF NANOPARTICLES:

- Cross linking agent: Glutaraldehyde
- Desolvating agents: Sodium sulphate, Ethanol, Isopropyl alcohol
- Counter ions: Tripolyphosphate Surfactant: Pluronic F-68, tween 80, Span 80 etc.
- Stabilizer: Polyvinyl alcohol Solvent: Acetone, methanol, chloroform, dichloromethane, water, Isopropyl Alcohol etc.

3. Nanocapsules

Nanocapsules, as characteristic class of nanoparticles, are made up of one or more active materials (core) and a protective matrix (shell)

[181] in which the therapeutic substance may be confined. The nanocapsules have attracted great interest because of their protective coating, which is usually pyrophoric and easily oxidized. Nanoparticles have also been extensively investigated as drug carriers and for the past five decades, many of such carriers in the nanometer range have been in development. Most of them are used in cancer therapy and diagnosis. Anticancer drugs are embedded in or conjugated with inert nanocarriers and are referred as nanomedicines. They are therapeutically more advantageous over free drugs; however, the inert carrier materials acting as major component (generally more than 90%) possess low drug loading contents and thus, necessitate excessive use of parenteral excipient [182]. Their main advantages are namely sustained release, incremental drug selectivity and effectiveness, improvement of drug bioavailability and alleviation of drug toxicity. Nanocapsules, which are submicron in size, when administered intravenously, reach to the target and release the encapsulated drug. Nanocapsules are submicron-sized vesicular systems ranging typically from 10 to 1000 nm in size. They are a type of nanoparticle drug delivery system characterized by a core-shell structure, where the core can encapsulate active substances (e.g., drugs, essential oils, proteins), and the shell or wall surrounds the core, controlling the release and providing protection.

Nanocapsules are widely used in pharmaceutical, cosmetic, agricultural, and food applications due to their ability to enhance the stability, bioavailability, and targeted delivery of encapsulated agents.

Polymeric nanoparticles are named nanocapsules [183] when they contain a polymeric wall composed of non-ionic surfactants, macromolecules, phospholipids [184,184] and an oil core [186]. These are prepared mostly by two technologies: the interfacial polymerization and interfacial nano-deposition.

Nanocapsules, holds the biomedical interest because they can be used, for the controlled release and targeting of drugs against the protection of enzymes, proteins, and foreign cells, etc. [187].

Nanocapsules are also made up of either inorganic or polymeric nanostructures with spherical in shape and drug molecules can be inserted inside the solid/liquid core by a protective outer membrane made of polymer nanomaterials while the hollow core offers great opportunities for encapsulating different therapeutics [188]. Porous NCs of PCL polymer have been used to encapsulate siRNA for enhanced siRNA transfection on HepG2 using EGFP (enhanced green fluorescent protein) [189].

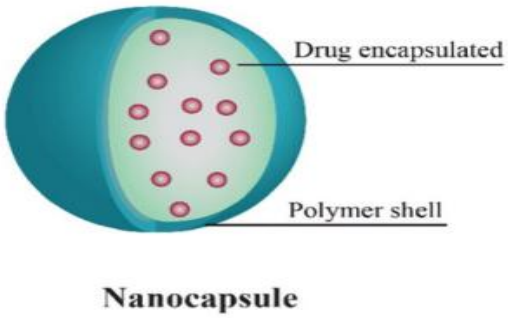


Figure 1.3: Nanocapsules Structure

The interest in research on magnetic nanocapsules has increased considerably because of their intermediate states between mass and atomic materials. These materials may present different magnetic behaviors from their corresponding counterparts. Researchers in China have succeeded in synthesizing a new type of intermetallic nanocapsule that can be applied in cryogenic magnetic refrigerator devices [190].

Some drugs find difficulty in marketing due to their unpleasant side effects. However, when they are placed inside the cavity of nanocapsule, they deliver drug directly to the target site in a reducible dosage (10,000 fold) and thus lead significantly to the removal of any side effects or at least an appropriate acceptable level [191].

Due to the miniscule size, nanocapsules possess greater capability to take on an extensive range of applications with extremely high efficient reproducibility. The production of nanocapsules depends on their application and pharmaceutical, biochemical, electrical, optical or magnetic characteristics. The enhanced delivery of bioactive molecules through the targeted delivery by means of a nanocapsule provides numerous challenges and opportunities for the research and future development of novel improved therapies.

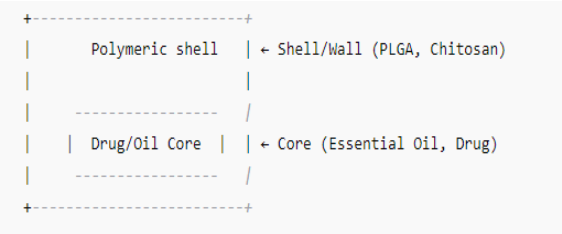
3.1. Structural Features

The typical size of the nanocapsule used for various applications ranges from 10-1000 nm. However, depending on the preparation and use of the nanocapsule, the size will be more specific [192].

Nanocapsules typically consist of:

- Shell/Wall: Made of natural or synthetic biodegradable polymers (e.g., PLGA, chitosan, alginate) or lipids (e.g., phospholipids). This layer:

- Controls drug release
- Protects the core from environmental degradation
- Provides surface functionality for targeting
- Core: Contains the active ingredient. This can be an oil, aqueous solution, or solid material depending on the application.



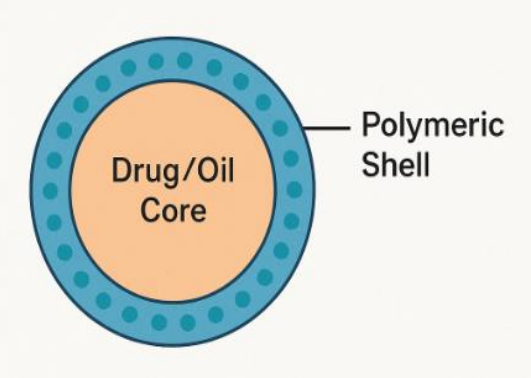


Figure 1.4: schematic representation of Nanocapsules

I. Polymeric Shell

The shell of a nanocapsule plays a pivotal role in dictating the performance of the drug delivery system. Shell materials are critical for encapsulation, protection, and controlled release of bioactive compounds. The physicochemical characteristics of the polymer—such as molecular weight, hydrophilicity, degradability, and charge—significantly influence the stability, encapsulation efficiency, release kinetics, and biodistribution of nanocapsules.

Both biodegradable and non-biodegradable but biocompatible polymers are employed for nanocapsule formulation. Biodegradable polymers facilitate payload release and eventual degradation within the body, which is essential for systemic applications. Common examples include poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and alginate. In contrast, polymers such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA), although not biodegradable, are widely used due to their hydrophilicity, biocompatibility, and ability to promote drug diffusion and circulation clearance via the reticuloendothelial system [193,194].

To meet diverse formulation goals, polymers used as nanocapsule shells are broadly categorized into natural and synthetic types.

V. NATURAL POLYMERS

Polysaccharides, as a major group of natural polymers, are extensively utilized due to their biocompatibility, biodegradability, mucoadhesive properties, and ability to form gels under mild conditions. These polymers, rich in amino or carboxylic acid groups, exhibit ionic charges that facilitate electrostatic assembly into nanocapsular shells [195-197].

- Chitosan, a widely studied natural cationic polymer, is valued for its biodegradability, mucoadhesion, and endogenous metabolite safety [198,199]. Chitosan-coated nanocapsules possess a cationic surface charge, which enhances interaction with negatively charged bacterial membranes. For example, PLGA nanocapsules coated with chitosan show improved adhesion to *S. aureus* and *M. abscessus* compared to uncoated versions [200]. However, the strong cationic surface may also induce aggregation, plasma protein adsorption, and rapid clearance from systemic circulation [195,196,201]. To overcome these issues, anionic polymers such as poly(acrylic acid) (PAA) [202], PVA [203], and anionic polysaccharides [204,205] are often co-formulated with chitosan.
- Alginate, an anionic polysaccharide, offers biocompatibility, low immunogenicity, and pH-sensitive drug release properties [206-208]. It protects encapsulated drugs under acidic gastric conditions and enables release at alkaline intestinal pH, making it ideal for oral, colon-targeted delivery [209,210].
- Dextran sulfate, a polyanionic natural polymer, is frequently used with chitosan to form multilayer nanocapsules through electrostatic interaction [211,212]. The release profile can be tailored by adjusting the chitosan-to-dextran ratio, enabling improved gene delivery performance [213-215].

Other polysaccharides used include poly(cyclodextrin) [216], heparin [217], and hyaluronan [218], all of which offer specialized

functionalities for targeted delivery and bioactive molecule protection.

Protein-based polymers, such as albumin, offer another class of natural shell materials due to their biological origin, water solubility, and tumor-targeting capabilities [219-221]. Albumin-coated nanocapsules not only enhance permeation and retention in tumor tissues via albondin receptor targeting but also help reduce immune recognition [222]. Additionally, engineered protein nanocages, such as those based on HspG41C mutants or dihydrolipoyl acyltransferase (E2), form uniform, virus-like nanostructures with tight size distribution for efficient delivery of anticancer drugs like doxorubicin [223,224].

VI. SYNTHETIC POLYMERS

Synthetic polymers offer advantages over natural materials due to their reproducibility, tunable chemistry, and tailorability for specific drug delivery requirements [225]. Aliphatic polyesters such as PLA, PLGA, and PCL are commonly used due to their biodegradability, biocompatibility, and approval by regulatory authorities. Among them, PCL offers a longer degradation time, making it preferable for long-term drug delivery systems, and it is also more cost-effective [226-228].

Eudragit® polymers, synthetic copolymers of acrylates and methacrylates, are valued for their pH-responsiveness and ionic modifiability. For example, Eudragit® RS100 has been used to encapsulate dihydromyricetin, providing quaternary ammonium groups that enable DNA binding and facilitate cellular uptake [229,230].

Poly(ethylene glycol) (PEG) is a widely used hydrophilic polymer applied either as a co-polymer (e.g., PLGA-PEG) or as a surface coating. PEGylation enhances the colloidal stability, systemic circulation, and immunological stealth of nanocapsules [231,232].

II. Core

The internal core of nanocapsules can vary in structure hollow, liquid-filled, or solid enabling the encapsulation and delivery of a wide range of therapeutic agents.

✧ Oleic Core:

Nanocapsules commonly feature an oleic (oil-based) core, which is particularly suitable for encapsulating lipophilic (hydrophobic) drugs. Oils such as soybean oil, palm oil, and medium-chain triglycerides are often employed due to their excellent solubilizing properties for lipophilic compounds and their established safety profiles in pharmaceutical applications [233,234]. Beyond acting as solvents, these oils may also provide therapeutic benefits themselves. For instance, *copaiba oil* has been used as the oil phase in PCL nanocapsules to enhance the solubility of imiquimod, a poorly water-soluble anticancer drug. In addition to improving solubility, copaiba oil also exerts therapeutic effects, including anti-inflammatory, analgesic, and antitumoral activity, particularly in conditions like melanoma and micropapillary carcinoma [235].

Similarly, nanocapsules made with Eudragit® RL 100 and *açai oil* (AO) as the core not only encapsulated desonide, an anti-inflammatory agent, but also leveraged the intrinsic anti-inflammatory and antiproliferative properties of AO to enhance therapeutic outcomes [234]. Other essential oils such as turmeric oil and lemongrass oil are frequently utilized for their antibacterial, antifungal, antioxidant, and anticancer activities [236].

✧ Aqueous Core:

Alternatively, polymeric nanocapsules can be formulated with an aqueous core, facilitating the encapsulation and controlled release of hydrophilic drugs. Compounds like gemcitabine hydrochloride and doxorubicin have been successfully incorporated into such systems, yielding enhanced anticancer efficacy compared to their free forms [237-239]. Aqueous-core nanocapsules also offer protective benefits for sensitive biomolecules such as mono- or oligo-nucleotides, which typically suffer from poor stability and limited cellular uptake. Encapsulation within an aqueous core can safeguard these molecules from enzymatic degradation and enhance their intracellular delivery, thereby improving bioavailability [240,241]. Furthermore, this type of nanocapsule is well-suited for delivering water-soluble proteins such as albumin [242].

✧ Hollow Core:

Nanocapsules can also be designed with a hollow internal cavity. Typically, this involves the initial formation of a sacrificial solid template that is later removed following shell assembly. This technique allows the development of nanocapsules with precise size and morphology, often incorporating multiple polymeric layers. The sacrificial core must be removable under mild conditions to prevent damage to the encapsulating shell. Various

materials have been explored as templates: iron oxide [243,244] and gold [245] nanoparticles can be dissolved using hydrochloric acid or potassium cyanide; calcium carbonate templates are eliminated by chelation with ethylenediaminetetraacetic acid (EDTA) at neutral pH [246]; silica can be dissolved using hydrofluoric acid [247]; and polystyrene nanospheres are removable with trichloromethane [248]. These hollow structures enable modulated drug release and improved biocompatibility.

✧ Solid Core:

Nanocapsules may also be fabricated with a solid-state core composed of polymeric matrices. These solid cores serve as reservoirs for drug loading and controlled release. For example, pectin gel cores have been used to formulate nanocapsules for ocular drug delivery in glaucoma treatment [249,250]. The porous and hydrophilic nature of pectin gels supports high drug-loading efficiency and enhances patient compliance during administration. Despite these benefits, solid-core nanocapsules remain less explored compared to their oleic or hollow counterparts.

3.2 Method of Preparation of Nanocapsules

Nanocapsules are typically prepared using top-down or bottom-up techniques that allow for the formation of a core-shell structure at the nanoscale. The choice of method depends on the type of polymer, core material (oil, water, solid), desired size distribution, drug loading efficiency, and release profile. The most commonly used methods include:

1. Interfacial Deposition Method

The interfacial deposition method, also known as nanoprecipitation, is one of the most widely employed techniques for the preparation of nanocapsules. Initially introduced by Fessi et al. in 1989 [251], this method offers a straightforward and efficient approach to encapsulation without the need for high-energy input. The typical procedure involves two immiscible phases: an organic phase, composed of a polymer (either oil-soluble or water-soluble), the active pharmaceutical ingredient, and an appropriate organic solvent; and an aqueous phase, often containing a surfactant to stabilize the formed nanocapsules (Figure 1.5).

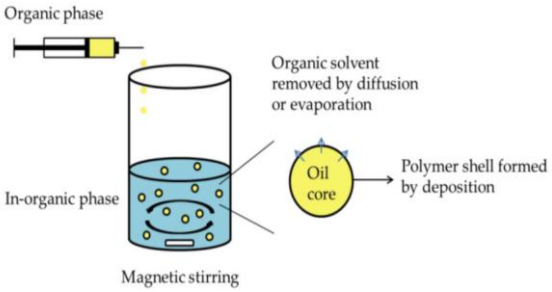


Figure 1.5: Nanocapsule formulation by interfacial deposition method

In this method, the polymer is deposited at the interface of an emulsion (O/W or W/O) by means of solvent exchange or phase inversion. The oil phase contains a polymer dissolved in a water-immiscible solvent along with the active ingredient. This is emulsified in the aqueous phase and subsequently hardened by solvent evaporation or by adding a non-solvent.

During formulation, the organic phase is slowly injected through a fine needle into the aqueous phase under moderate agitation. Upon contact, rapid diffusion of the solvent into the aqueous medium induces polymer precipitation at the interface, resulting in the formation of a polymeric shell around the core material. The final nanocapsule suspension is obtained by removing the organic solvent via diffusion or evaporation.

The physicochemical properties of the resulting nanocapsules—including size, polydispersity, encapsulation efficiency, and stability—are influenced by several factors: polymer concentration, rate and method of organic phase injection, organic-to-aqueous phase volume ratio, and the nature of the core and shell materials [252-254].

Due to its versatility and ease of use, this method has gained significant attention in the past decade, particularly for its applicability across a wide range of therapeutic agents. For instance, Veragten et al. successfully developed oleic-core nanocapsules loaded with olanzapine, demonstrating enhanced mucoadhesive properties and potential for improved oral bioavailability [255]. Additionally, nanocapsules incorporating antimicrobial essential oils have been fabricated using this technique, highlighting its utility in encapsulating volatile and lipophilic compounds [256].

Moreover, hollow nanocapsules can also be produced using this method by omitting the oily core and using only volatile organic solvents in the organic phase. Once the polymeric shell is formed,

evaporation of the solvent results in a void interior, thereby forming hollow-structured nanocapsules.

Advantages:

- Produces nanocapsules with strong, impermeable shells.
- Suitable for unstable actives.

Limitations:

- Toxicity of monomers and reaction by-products.
- Requires careful control of polymerization conditions.

Applications: Used to create nanocapsules from polyurethanes, polyamides, and polyalkylcyanoacrylates.

2. Layer-by-Layer Method

The layer-by-layer (LBL) technique has emerged as a promising strategy for the fabrication of nanocapsules composed of multiple polymeric layers. A general schematic of the LBL process for polymeric nanocapsule preparation is illustrated in Figure 1.6. This method enables precise control over the targeting and release characteristics of nanocapsules by modulating the composition and thickness of the polymeric shell layers [257]. The formulation mechanism typically involves electrostatic interactions, whereby alternating layers of polycations and polyanions are sequentially deposited onto an inorganic template core. Following the construction of the multilayered shell, the core is sacrificially removed to yield a hollow nanocapsule.

Payload encapsulation within these core-sacrificed LBL nanocapsules is generally achieved post-fabrication. Hydrophilic molecules are incorporated through diffusion, while hydrophobic substances are typically entrapped via hydrophobic interactions or electrostatic binding. For instance, the hydrophilic anticancer drug doxorubicin hydrochloride was successfully loaded into chitosan–pectin-based nanocapsules fabricated using the LBL approach. The drug-loading process involved incubating the empty nanocapsules in an aqueous doxorubicin solution for 24 hours, resulting in an encapsulation efficiency of approximately 76% [258].

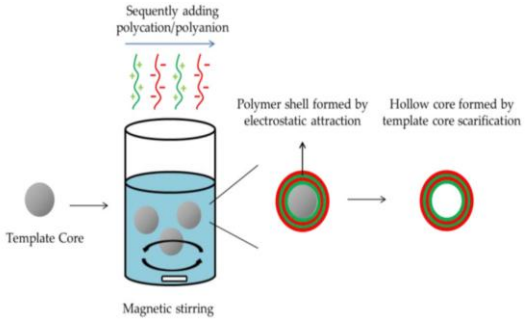


Figure 1.6: Nanocapsules formulation by LBL method

Belbekhouch et al. demonstrated the development of multilayered nanocapsules via electrostatic assembly of cationic poly(cyclodextrin) and anionic alginate around a colloidal gold nanoparticle, which was subsequently removed to form a hollow core. The hydrophobic compound 4-hydroxy-tamoxifen was incorporated by incubating the nanocapsules in an ethanol solution, and it was found to retain its biological activity post-encapsulation [216]. Similarly, the antibiotic amoxicillin was effectively loaded into hollow polyelectrolyte nanocapsules prepared by the LBL technique. The nanocapsules were suspended in an amoxicillin acetate buffer solution, enabling the drug to interact with the polymeric shell via electrostatic absorption, yielding an encapsulation efficiency ranging from 62% to 75% [202].

Recently, the layer-by-layer (LBL) technique has been effectively combined with the nanoemulsion method, utilizing oil-in-water (O/W) nanoemulsions as template cores for the fabrication of polyelectrolyte nanocapsules. This approach allows for the efficient encapsulation of lipophilic substances by dissolving them in the organic (oil) phase of the nanoemulsion [213]. To facilitate the deposition of polyelectrolyte layers, nanoemulsions are typically stabilized using positively or negatively charged oleic surfactants, which provide a charged interface suitable for subsequent layer formation [259].

A key advantage of the LBL approach lies in its ability to construct nanocapsules with a hierarchical multilayer-core structure, enabling the co-encapsulation of different therapeutic agents in distinct regions of the nanocapsule. For example, Ledo et al. designed a multilayer polymeric nanocapsule capable of simultaneously delivering a chemokine and an RNA interference (RNAi) sequence for immunotherapeutic applications. In this system, the chemokine was loaded into the lipid core, while the RNAi sequence was

incorporated into outer polyelectrolyte layers composed of polyarginine and hyaluronic acid [260].

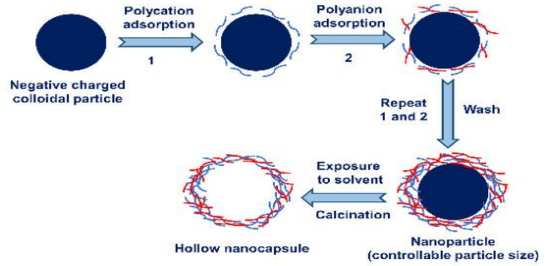


Figure 1.7: schematic diagram of the preparation of nanocapsules using layer-by-layer self-assembly

Moreover, the sequence and composition of the polyelectrolyte layers in LBL nanocapsules can be strategically arranged to achieve pH-responsive drug release behaviors. This characteristic is particularly beneficial for oral drug delivery applications, as it enables modulation of drug release at different regions of the gastrointestinal tract [261–263]. For instance, a pH-sensitive multilayer system composed of poly-L-arginine, sodium alginate, chitosan, and Eudragit L100 was developed using the LBL method. When chitosan was used as the outermost layer, the nanocapsules exhibited delayed drug release at pH 1.2 and sustained release at pH 7.4. This behavior was attributed to the protonation of chitosan under acidic conditions and its deprotonation under neutral to basic conditions, which influence its solubility and permeability.

3. Nanoemulsion Template Method for Nanocapsule Preparation

Over time, the development of high-energy instrumentation has significantly enhanced the ability to produce nanoemulsions, which can then be further processed into nanocapsules through various techniques, most notably organic solvent diffusion/evaporation or monomer coacervation. In the nanoemulsion preparation process, an organic or aqueous phase is emulsified into the opposite phase (aqueous or organic) in the presence of suitable surfactants, with continuous energy input—typically via ultrasonication or high-pressure homogenization. During this emulsification process, surfactants spontaneously self-assemble at the interface of the immiscible phases, minimizing interfacial tension and stabilizing the system.

Depending on the desired formulation properties, components such as polymeric shell materials, active pharmaceutical ingredients (APIs), oils, and other functional agents may be either dissolved or suspended in the dispersed phase or continuous phase. This flexibility in composition enables the design of nanocapsules tailored to specific physicochemical and therapeutic requirements [264].

A. Emulsion–Diffusion/Evaporation Method

The emulsion–diffusion/evaporation technique is among the most commonly employed methods for the fabrication of polymeric nanocapsules via nanoemulsion templates. As illustrated in Figure 1.8 A, this method involves emulsifying the organic phase into an aqueous external phase, followed by the removal of the organic solvent either through diffusion or evaporation[264,265]. Nanocapsules form as a result of polymer precipitation and interfacial phenomena during the solvent removal process.

Polymers suitable for this method must exhibit good solubility in organic solvents that are partially or fully miscible with water—such as acetone, ethanol, or ethyl acetate—to allow efficient diffusion and removal of the organic phase into the aqueous medium[266,267].

For example, Sombra et al. developed nanocapsules from propionated *Sterculia striata* polysaccharides using Miglyol® L812 oleic oil as the core carrier for amphotericin B[268]. The nanocapsules were prepared with a mixture of acetone and methanol as the organic phase, which was subsequently diffused into an aqueous phase. The system achieved an impressive encapsulation efficiency of 99.2 ± 1.3% for the hydrophobic drug.

In contrast, the emulsion–evaporation method may utilize nonpolar organic solvents such as chloroform or dichloromethane, which are immiscible with water. In one study, nanocapsules composed of poly(DL-lactide-co-glycolide) (PLGA) and polyethylene glycol (PEG) were prepared by dissolving the polymers in dichloromethane and homogenizing this organic phase into an aqueous phase to form a nanoemulsion[269]. Solvent removal was carried out through evaporation. Notably, the core of these nanocapsules was composed of perfluorooctyl bromide, a compound capable of acting as a cavitation nucleus under ultrasound, allowing for both in vitro and in vivo monitoring of nanocapsule collapse.

B. Emulsion–Coacervation Method

The emulsion–coacervation technique also utilizes nanoemulsions as structural templates for

nanocapsule fabrication. However, in contrast to the emulsion–diffusion/evaporation method, this approach involves the formation and stabilization of the polymeric shell through either physical coacervation or chemical cross-linking mechanisms[270-273] (Figure 1.8B). This method is particularly suitable for polyelectrolyte materials or polymers/monomers containing functional groups that facilitate cross-linking reactions.

In physical coacervation, electrostatic interactions between oppositely charged polymers can drive shell formation. For instance, polyelectrolyte nanocapsules have been developed for encapsulating brinzolamide, a drug used to treat glaucoma. In this formulation, positively charged chitosan and negatively charged pectin were incorporated into a nanoemulsion, where they coacervated via electrostatic attraction, ultimately forming the nanocapsule shell.

Compared to physical coacervation, chemically cross-linked shells typically yield nanocapsules with enhanced structural integrity and stability. An example is the fabrication of cross-linked starch nanocapsules with aqueous cores designed to deliver hydrophilic dyes, achieved through interfacial polymerization using a water-in-oil (W/O) mini-emulsion system[274]. This study demonstrated that increasing the concentration of the cross-linker led to the formation of thicker polymer shells, thereby reducing the leakage of hydrophilic payloads into the aqueous phase.

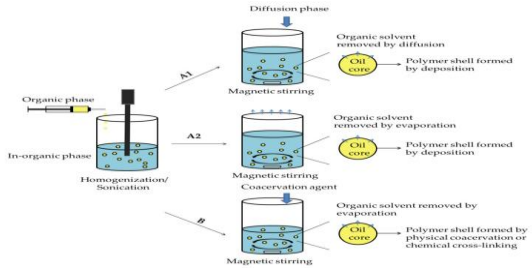


Figure 1.8: Schematic representation of nanocapsule formulation by nanoemulsion methods: (A). nanoemulsion–diffusion/evaporation method; (B). nanoemulsion–coacervation method

Moreover, advanced polymerization techniques such as reversible addition–fragmentation chain-transfer (RAFT) and atom transfer radical polymerization (ATRP) have been employed to create nanocapsules via the emulsion–coacervation method. In these strategies, amphiphilic copolymers synthesized from the same monomers used in the nanocapsule shell serve both as nanoemulsion stabilizers and template cores. The shell is formed by introducing monomers, cross-linkers, and initiators, triggering shell formation via free radical polymerization. Subsequently, the amphiphilic copolymer template is removed (e.g., by hydrolysis), yielding a hollow-core structure[275-277].

As an illustrative case, pH-sensitive nanocapsules were prepared using RAFT polymerization. A random copolymer composed of butyl acrylate and acrylic acid was first synthesized as a macroRAFT agent[278,279]. Monomers such as *N,N-dimethylaminoethyl methacrylate* or *tert-butyl methacrylate*, in combination with methyl methacrylate, were polymerized to form the capsule shell. The hollow core was subsequently generated via hydrolysis using trifluoroacetic acid. These nanocapsules exhibited pH-responsive behavior, showing accelerated drug release under mildly acidic conditions (pH 6.5), highlighting their potential for targeted drug delivery in tumor microenvironments or inflammatory tissues.

C. Double Emulsion Method

Based on the principles of emulsion diffusion/evaporation and emulsion–coacervation techniques, nanoemulsions can be further emulsified into a third phase to create more complex systems, such as multiple emulsions—commonly referred to as double emulsions. These are primarily categorized into two types based on their phase sequence: water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O). A key factor in the successful formation of double emulsions is the careful selection of compatible surfactants that ensure stability at both the internal and external interfaces [281,282]. The polymeric shell of nanocapsules in such systems can be formed through mechanisms including solvent diffusion, evaporation, coacervation, or a combination thereof.

Campos et al. successfully developed a fluorescent polymeric nanocapsule using the double emulsion–evaporation method [283]. Similarly, Erdmann et al. created polymeric nanocapsules based on poly(alkyl cyanoacrylate) via the double emulsion technique, in which the shell was formed by interfacial polymerization of n-butyl cyanoacrylate and propargyl cyanoacrylate [284]. The W/O/W emulsion approach has been extensively employed in fabricating nanocapsules with aqueous cores, facilitating the encapsulation and sustained release of hydrophilic drugs. Furthermore, the double emulsion method presents a versatile platform for

the simultaneous encapsulation of both hydrophilic and hydrophobic substances [285].

4. Solvent Evaporation Method

The solvent evaporation method involves emulsifying a volatile organic solvent (e.g., dichloromethane, chloroform) containing the polymer and the active ingredient into an aqueous surfactant phase to form a nanoemulsion. The solvent is then evaporated under reduced pressure or ambient conditions, leaving behind solid nanocapsules [286].

Mechanism:

- Organic phase with drug and polymer is emulsified in an aqueous phase.
- Solvent evaporation leads to polymer precipitation and nanocapsule formation.

Advantages:

- Suitable for thermally stable drugs.
- Scalable and simple.
- Can encapsulate both hydrophilic and hydrophobic drugs (via W/O/W or O/W).

Limitations:

- Use of toxic organic solvents.
- Not suitable for thermolabile compounds.
- Requires surfactant removal or purification steps.

Applications: Suitable for drugs like paclitaxel, dexamethasone, and hydrophobic vitamins [287].

5. Nanoprecipitation (Solvent Displacement)

Nanoprecipitation involves the spontaneous formation of nanocapsules upon mixing a polymer–solvent solution with a miscible nonsolvent (usually water). The difference in solvent miscibility leads to rapid precipitation of the polymer around the drug.

Mechanism:

- Drug and polymer are dissolved in a water-miscible organic solvent (e.g., acetone).
- Injected into an aqueous phase under agitation.
- Rapid diffusion causes polymer precipitation.

Advantages:

- Easy, fast, and reproducible.
- No need for high shear or high temperature.

Limitations:

- Limited to low viscosity solvents and hydrophobic drugs.
- Lower encapsulation efficiency for hydrophilic drugs.

Applications: Ideal for poorly water-soluble drugs such as curcumin, quercetin, and anticancer agents [288].

3.3Characterization of Nanocapsules

1. Particle Size

Particle size and its distribution are critical parameters in nanocapsule systems, influencing in vivo distribution, bioavailability, toxicity, drug targeting, and therapeutic performance. Smaller particles offer a higher surface area, often resulting in rapid drug release due to surface-associated drug molecules. Conversely, larger particles enable sustained release through gradual diffusion from the core [289]. Particle size also affects polymer degradation; for instance, the degradation rate of PLGA increases with particle size in vitro [290]. Dynamic light scattering (DLS), also known as photon correlation spectroscopy, is commonly used for size determination [291].

2. Surface Properties

Surface characteristics are essential for effective drug targeting via nanocapsules. To prolong systemic circulation and reduce opsonization, surface modification is employed through hydrophilic polymer or surfactant coatings. Polymers such as PEG, PEO, poloxamers, poloxamines, and polysorbate 80 are frequently used for this purpose [292]. Zeta potential measurement is widely used to assess surface charge and colloidal stability [293].

3. Fluorescence Quenching

Fluorescence quenching is a valuable tool for confirming the localization of nanocapsules, especially those encapsulating aqueous-core contents such as oligonucleotides. This method validates the structural integrity and internalization behavior of Nanocapsules [294-296].

3.4 Evaluation Studies of Nanocapsules

The characterization of nanocapsules is essential to understand their physicochemical properties, which directly influence drug loading, release profiles, bioavailability, and therapeutic efficacy. A variety of analytical and imaging techniques are employed to evaluate parameters such as morphology, particle size, crystallinity, surface charge, thermal stability, and chemical composition. The following techniques provide a comprehensive evaluation of nanocapsule systems:

1. X-Ray Diffraction (XRD)

XRD is a vital tool for determining the crystalline or amorphous nature of nanocapsules. It reveals the phase composition by analyzing the diffraction

patterns produced when X-rays interact with the crystal lattice of materials. Sharp, intense peaks indicate a crystalline structure, while broad humps suggest amorphous phases. For instance, a Rigaku D/max-2000 diffractometer using CuKα radiation (λ = 0.154 nm) operates at 50 kV and 250 mA to analyze the sample's phase transitions and structural integrity after encapsulation [297].

2. Scanning Electron Microscopy (SEM)

SEM provides high-resolution surface images to evaluate the morphology and topography of nanocapsules. It is particularly useful in observing the formation of flocculent structures, small and large clusters, and hierarchical branching patterns. These morphological features reflect the self-similar and potentially fractal nature of aggregates formed by nanocapsules [298,299]. Such analysis helps in understanding agglomeration, uniformity, and overall particle architecture.

3. Differential Scanning Calorimetry (DSC)

DSC measures heat flow associated with phase transitions, such as melting and crystallization, which can affect the stability and behavior of nanocapsules. It helps in identifying the thermal behavior of encapsulated drugs and polymers. Whether run in open or sealed pans, DSC provides consistent thermal transition data, which is essential for verifying the physical state of drugs (amorphous vs crystalline) post encapsulation [300].

4. Transmission Electron Microscopy (TEM)

TEM is a powerful tool for visualizing the internal structure of nanocapsules. It offers insights into particle size, distribution, and core–shell architecture. TEM studies have confirmed the transport of insulin-loaded nanocapsules across epithelial barriers, providing evidence of oral bioavailability and mucosal absorption [301,302]. Such findings underscore the utility of TEM in assessing intracellular delivery mechanisms.

5. High-Resolution Transmission Electron Microscopy (HRTEM)

HRTEM offers even finer resolution than conventional TEM, enabling visualization at the atomic scale. It distinctly reveals the core–shell morphology of nanocapsules and confirms uniformity in structure. HRTEM has been used to validate the spherical structure and shell thickness of nanocarriers, ensuring consistency in encapsulation and drug distribution [303,304].

6. X-Ray Photoelectron Spectroscopy (XPS)

XPS is used to study the surface elemental composition and chemical states within a depth of a few nanometers. It utilizes photoelectron emission to identify and quantify elements and their binding energies. This is particularly useful in assessing the presence of functional groups, oxidation states, and the effect of surface modifications on nanocapsules [305]. Such information is crucial for applications requiring surface-sensitive interactions, such as targeted drug delivery.

7. Superconducting Quantum Interference Device (SQUID) Magnetometry

SQUID magnetometry is employed to study the magnetic properties of nanocapsules, especially those designed for magnetically guided drug delivery or hyperthermia treatment. SQUID devices can detect extremely small magnetic flux changes, offering insight into magnetic responsiveness and potential biomedical applications [306].

8. Multi-Angle Laser Light Scattering (MALLS)

MALLS is used to determine the molecular weight and size distribution of nanocapsules in solution. It is particularly valuable in characterizing vault-like nanocapsules with large internal cavities and thin shells. MALLS can monitor conformational changes that affect the release or encapsulation of therapeutic agents, thereby offering real-time insights into formulation behavior under different conditions [307,308].

9. Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopy is a standard technique to identify functional groups and confirm chemical structure. The appearance of characteristic absorption bands verifies the presence of specific chemical bonds within the nanocapsule material and confirms successful drug encapsulation or polymer interaction. It is widely used to study polymeric compatibility and detect chemical modifications [309,310].

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