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Review Article

Novel Nanocarriers Microencapsulation: Current, Patents and Clinical Trials Comprehensive Review

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Abstract

The field of nanocarriers and microencapsulation has witnessed substantial growth, offering innovative solutions for drug delivery challenges. This comprehensive review explores the latest advancements in nanocarriers and microencapsulation technologies, focusing on their applications in enhancing drug stability, controlled release, and targeted delivery. The article highlights key breakthroughs, emphasizing their significance in addressing therapeutic inefficacies. A detailed analysis of current patents underscores the innovative strides in this domain, while insights into clinical trials provide a perspective on the translational potential of these technologies. This review article begins with a fundamental overview of microencapsulation, including its various types and characteristics. It intermediately delves into several formulation techniques associated with microencapsulation, examining the latest developments in prepared formulations, granted patents, and a selection of marketed products. Finally, the article addresses future prospects and the challenges that lie ahead in this field.

Keywords: microencapsulation; entrapment; microcapsules; nanocarriers; advancements.

1. INTRODUCTION

Controlled drug delivery technology is one of the most rapidly advancing fields, addressing the limitations of conventional dosage forms while enhancing crucial aspects such as targeted drug delivery to specific organs or tissues and regulating the rate of drug release at the target site[1-2]. Developing an oral controlled-release system poses significant formulation challenges due to its difficulty in maintaining localization within specific areas of the gastrointestinal tract. However, with appropriate modifications, such systems can sustain the desired drug concentration at the site of interest without requiring external intervention[3].

Nanocarriers and microencapsulation techniques have emerged as groundbreaking strategies in drug delivery, offering precise control over drug release, enhanced stability, and targeted delivery to specific sites. These advanced systems address critical challenges associated with conventional formulations, such as poor bioavailability (BA) and rapid degradation. Exploring their potential in improving therapeutic outcomes and addressing unmet clinical needs, the review provides a holistic perspective on the innovations shaping the future of drug delivery systems (DDs) [4-5]. In microencapsulation, microcarriers such as microspheres and microcapsules form a multiparticulate DDs designed to target specific organs and tissues through a controlled drug release mechanism. This mechanism ensures that the outer layer safeguards the inner core, which contains the active pharmaceutical ingredients, from external conditions until the drug is needed for release[6]. The major factors that influence the drug delivery for microencapsulation carriers are as Table 1 follows:

Table 1: List of the major factors that influence drug delivery in terms of microcapsules/microencapsulation[5-8]

Factor	Description	Impact on Drug Delivery
Core Material	The drug or active ingredient encapsulated within the microcapsule.	Determines the drug stability, solubility, and release profile.
Wall Material	The polymer or material used to form the outer shell of the microcapsule.	Affects the encapsulation efficiency, release rate, and protection of the drug.
Size and Shape	Physical dimensions and morphology of the microcapsule.	Influences drug release kinetics and biodistribution.
Encapsulation Method	Techniques like coacervation, spray drying, or solvent evaporation used to create microcapsules.	Impacts the uniformity, size, and stability of the microcapsules.
Drug Loading Capacity	The amount of drug incorporated into the microcapsule relative to its total weight.	Determines the dosage and efficacy of the formulation.
Release Mechanism	Methods like diffusion, erosion, or degradation by which the drug is released.	Controls the timing and duration of drug release.
Degradation Rate	The rate at which the wall material breaks down in the body.	Influences the release rate and biodegradability of the microcapsules.
pH Sensitivity	The microcapsule stability and release behavior under varying pH conditions.	Allows targeted delivery in specific regions of the gastrointestinal tract (GIT).
Stability	Physical and chemical stability of the microcapsule during storage and use.	Affects shelf life and therapeutic performance.
Surface Properties	Characteristics like hydrophobicity, charge, or roughness of the microcapsule surface.	Impacts interaction with biological environments and drug uptake.
Environmental Factors	External conditions such as temperature, humidity, and light during storage or application.	Influence the integrity and release profile of the microcapsules.

Advantages and Disadvantages of Microencapsulation: The various merits and demerits for the selection of microencapsulation discussed as below Table 2.

Table 2: List of advantages and disadvantages of microencapsulation [8-10]

Advantages	Disadvantages
Protects encapsulated ingredients from degradation by moisture, light, oxygen, etc.	High cost due to materials and sophisticated equipment.
Masks the bitter taste of the drug, improving palatability and patient compliance.	Core particle stability is affected by changes in process conditions like temperature, pH, or solvent evaporation.
Avoids incompatibilities in drug combinations.	Stricter quality control requirements.
Provides controlled release of active ingredients.	Polymer matrix degradation due to heat, hydrolysis, or biological agents.
Reduces major side effects like toxicity and gastrointestinal irritation.	Complex manufacturing process and limited drug-loading capacity.
Converts free-flowing liquids into solids or pseudo-solids, improving handling and storage.	Reduces the shelf life of hygroscopic drugs.
Preserves the volatility of compounds in the inner core.	Technique is not adaptable to all types of drugs.
Improves the flow property of the core drug.	Probability of discontinuous coating.
Masks unpleasant odors of certain drugs.	Single methods cannot be applied to all core materials. Difficulties in scaling up production processes (small-scale and large-scale). May not be suitable for parenteral routes due to size restrictions.

Need for Microencapsulation: The primary characteristic of microcapsules is their tiny particle size, which results in an extensive surface area. This increased surface area offers notable benefits, including enhanced absorption and desorption sites, facilitation of chemical reactions, and improved light scattering [11]. Microencapsulation techniques play a crucial role, enabling the development of various dosage forms, such as transforming liquids into solids. This transformation addresses a significant challenge in microencapsulation: safeguarding against environmental factors. Additionally, it aids in the separation of reactive pharmaceutical components and enhances the handling properties of materials [11-12]. In a variety, of cases there is a need for separation of the core from its surroundings because of the following reasons:

- Isolating vitamins from adverse effects
- Slowing down the evaporation of a volatile substance
- Enhancing the handling characteristics of a tacky material
- Protecting a reactive core from chemical exposure [13]

Microencapsulation, involving microspheres or microcapsules, is a critical advancement in DDs designed to address several challenges associated with conventional formulations. This technique enables controlled and sustained drug release, ensuring consistent therapeutic levels and reducing dosing frequency [13-14]. It enhances the stability of sensitive drugs, protecting them from environmental factors such as light, moisture, and pH variations. Microencapsulation also facilitates targeted delivery to specific sites, minimizing systemic side effects and improving patient compliance. To optimizing drug solubility, BA, and release kinetics, microencapsulation has become an essential tool in modern pharmaceutical development [15].

In some cases, the main objective is not to separate the core from the outer surroundings but to control the release of drugs in its surrounding environment which can be achieved by microencapsulation [16]. Overall microencapsulation enhances product functionality in various industries (Fig. 1) which are as follows: -

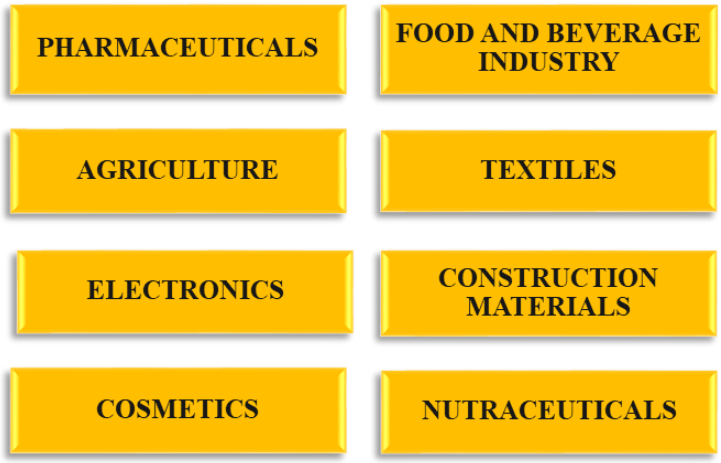


Figure 1: Application of microencapsulation

This comprehensive review article discuss the basics of microencapsulation with their structure, compositions and classifications on the types of carriers such as microcapsules and microsphere. The different methods of preparation involved in the formulation steps. The recent and current status in the preparation of nanocarriers with patent status and few marketed formulations. Lastly, the clinical trials on microencapsulation nanocarriers conducted in the targeting actions.

2. STRUCTURE, COMPOSITION & TYPES OF MICROENCAPSULATION NANOCARRIERS

Microencapsulation nanocarriers are advanced drug delivery systems designed to encapsulate active ingredients within nanoscale carriers for targeted delivery and controlled release. Their structure typically comprises a core containing the active substance, surrounded by a protective shell or matrix material [17-18]. The composition varies based on the application and may include biodegradable polymers (PLGA, chitosan), lipids (Phospholipids), or proteins. These nanocarriers are classified into different types, especially nanospheres (solid matrix systems) and nanocapsules (distinct core-shell structures) offering unique properties for specific therapeutic or industrial purposes [19]. The brief description about this as below following:

2.1. *Classification/Types of Microencapsulation*: Microencapsulation involves the encapsulation of active ingredients within a coating material to form small, discrete particles known as microcapsules or microspheres [20]. These two types differ in structure, function, and applications. The classification based on their characteristics as below discussion:

2.1.1. Microspheres

Microspheres are solid spherical particles with a uniform distribution of the active ingredient throughout the matrix. They do not have a distinct core-shell structure but provide controlled drug delivery and improved BA [21].

Microspheres are spherical particles, typically ranging in size from 1-1000 µm, composed of natural or synthetic materials. Apart from microcapsules, microspheres have a uniform matrix structure without a distinct core-shell design. They are commonly used in DDs due to their

ability to encapsulate active ingredients and provide controlled, sustained, or targeted release. Microspheres can be biodegradable (Made of PLA, PGA, or PLGA) or non-biodegradable (PMMA) [21-22]. Their applications extend to pharmaceuticals, diagnostics, and imaging, offering enhanced BA, reduced dosing frequency, and improved therapeutic outcomes.

2.1.2. Microcapsules

Microcapsules are spherical structures composed of a core material (API) surrounded by a distinct coating layer. The coating provides controlled release, protection from environmental factors, or taste masking [23].

Microcapsules are tiny spherical particles with a distinct core-shell structure, where the core contains the active ingredient, and the shell provides a protective coating. Their sizes range from 1 µm to several millimeters. The shell material, often made of polymers, lipids, or proteins, helps protect the core from environmental factors and allows controlled or sustained release of the encapsulated substance [22-24]. Microcapsules are widely used in pharmaceuticals, food, agriculture, and cosmetics for applications like drug delivery, flavor masking, and enhanced stability of volatile or sensitive compounds.

Microcapsules are categorized into controlled release types, designed for gradual drug or nutrient release, and burst release types, which rapidly deliver the core material. The manufacturing methods further classify them into chemical microcapsules (produced via coacervation or polymerization) and physical microcapsules (formed through spray drying or extrusion) [25]. These diverse types make microcapsules adaptable for pharmaceuticals, food, and industrial applications. Microcapsules classified in the various parts (Fig. 2) as below following

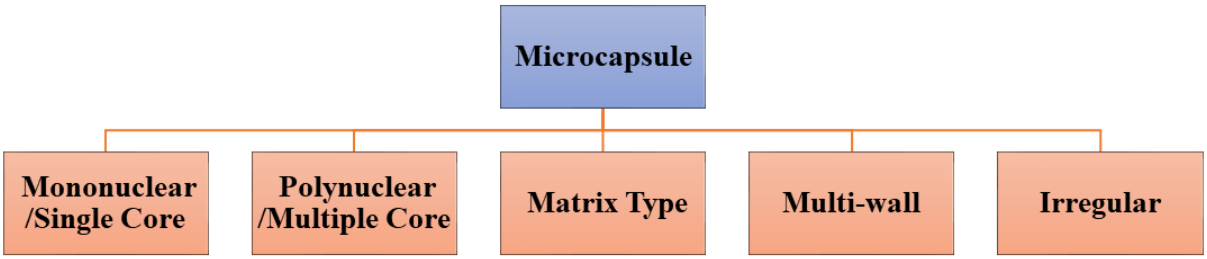
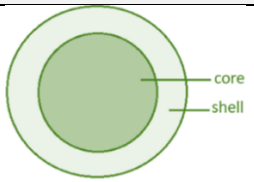
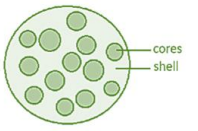
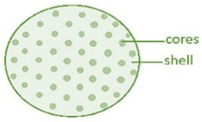
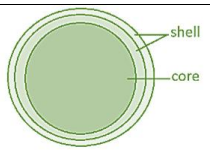
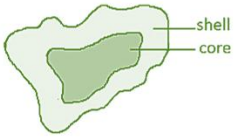


Figure 2: Representation of types of microcapsules nanocarrier

The description of the types of microcapsules mentioned in the given Table 3 as below following:

Table 3: List of description about the types and description of types of microcapsules [25-27]

Type of Microcapsule	Description	Structure
Mononuclear/Single Core	A single core containing the active ingredient is enclosed within a single shell. Made of organic compounds, artificial materials, or polymers.	
Poly-nuclear/Multiple-Core	Multiple core particles containing active ingredients are enclosed within a single shell. Provides consistent release due to the presence of multiple cores.	
Matrix Type	Core material is uniformly distributed throughout a solid matrix. Provides controlled release based on matrix composition.	
Multi-Wall Type	Core material is enclosed within multiple shell layers, offering enhanced protection and gradual release.	
Irregular Microcapsules	Core and shell are non-uniform or asymmetric in shape. Often used for burst release patterns.	

This classification highlights the diversity in microcapsule design, catering to various applications requiring controlled, sustained, or burst release. Microcapsules have a core-shell structure, where the API is enclosed within a protective shell, enabling controlled release or protection. Microspheres are solid matrix systems where the API is uniformly distributed throughout, allowing sustained or targeted release [28]. While microcapsules are ideal for applications requiring a distinct core-shell design, microspheres are better suited for uniform release profiles and enhanced BA [29]. Both systems serve diverse purposes in pharmaceuticals, diagnostics, and industrial applications. The comparison of microencapsulation brief discussed as below Table 4.

Table 4: The comparison Between Microcapsules and Microspheres [29-30]

Characteristic	Microcapsules	Microspheres
Structure	Core-shell	Matrix-like
Encapsulation Type	Single core surrounded by coating	Uniform distribution of core material
Release Profile	Controlled, burst, or delayed	Controlled, sustained release
Applications	Food, pharmaceuticals, cosmetics	Drug delivery, diagnostics, imaging

This classification highlights the diversity and adaptability of microencapsulation techniques in drug delivery and other industrial applications [31]. The both nanocarriers for microencapsulation have their several offering advantages and benefits in the loading and encapsulation of medicament and targeting treatment.

2.2. *Structure of Micro capsulation (Microsphere/Microcapsules)*: The structure of microencapsulation varies between microspheres and microcapsules. Microcapsules have a core-shell design, where the core contains the active ingredient, and the shell is made of protective materials like polymers, lipids, or proteins [32]. This design allows for controlled release, protection from environmental factors, and targeted delivery. Microspheres, on the other hand, lack a distinct core-shell structure; the active ingredient is uniformly distributed throughout a solid matrix [32-33]. This matrix-based structure provides sustained release and improved stability. The structure of microsphere and microcapsules represented in the given Fig. 3 as below.

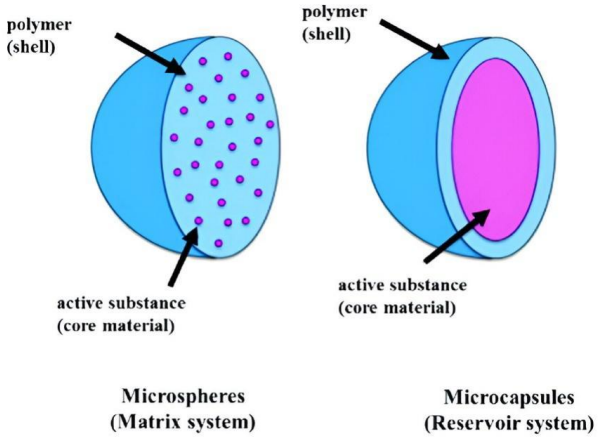


Figure 3: Representation of structure of microsphere/microcapsules with their parts [34]

The both structures are tailored for specific applications, such as drug delivery, diagnostics, or industrial use, by selecting appropriate materials and methods.

2.3. *Compositions of Microencapsulation (Microsphere/Microcapsule)*: The several composition parts of microencapsulation nanocarriers discussed as below description:

- **Core Material:** The core contains the active substance, which could be a drug, nutrient, flavor, or any bioactive compound. Core materials can be liquids (oils, solvents), solids (drugs, powders), or gases, depending on the intended application.
- **Wall/Coating Material:** The wall material encapsulates the core, providing protection, stability, and controlled release. The common wall materials include natural polymers (Gelatin, alginate), synthetic polymers (PLGA, PCL), lipids (Phospholipids), and proteins. The choice of wall material affects the release profile and the stability of the encapsulated substance [34].
- **Additives:** Additives such as surfactants, stabilizers, or plasticizers may be included to enhance the performance of the microencapsulation system, improve the release rate, or stabilize the encapsulated substance during storage.

The structure, composition, and types of microencapsulation nanocarriers play a crucial role in optimizing DDs. Their versatile designs, including core-shell and matrix structures, enable precise control over release profiles, enhanced stability, and targeted delivery [34-35]. Tailoring the composition and type such as nanospheres, nanocapsules, these carriers provide innovative solutions for therapeutic and industrial applications, ensuring efficiency and improved outcomes.

3. TECHNIQUES INVOLVED IN THE PREPARATION OF MICROENCAPSULATION

Microencapsulation techniques encompass a range of methodologies designed to enclose active substances within a protective coating or matrix, ensuring controlled release and stability. The common techniques include spray drying, coacervation (phase separation for capsule formation), emulsion-based methods (oil-in-water or water-in-oil emulsions for polymer encapsulation), and solvent evaporation/extraction (removal of solvents to solidify the capsule). Other advanced methods like fluidized bed coating, interfacial polymerization, and freeze-drying are also employed to tailor capsule size, release kinetics, and stability for specific applications [36]. The brief discussion about the techniques involved in the preparation of microencapsulation discussed as below following:

3.1. *Physical Methods:* The various physical methods involved in the preparation of microencapsulation discussed below description.

3.1.1. Spray Drying (rapid solvent evaporation) and Spray Cooling (Congealing)

In spray drying, the process begins with preparing a feed solution or dispersion by dissolving or dispersing the core material (API) in a suitable polymer solution or solvent system, ensuring uniform mixing. This solution is then fed into a spray dryer using a peristaltic pump, where it is atomized into fine droplets using a spray nozzle. The droplets are introduced into a hot air stream within the drying chamber, leading to rapid solvent evaporation and solid microsphere formation [37]. The dried particles are collected at the bottom of the cyclone separator, and, sieved or characterized for size and encapsulation efficiency %EE (Fig. 4) as below.

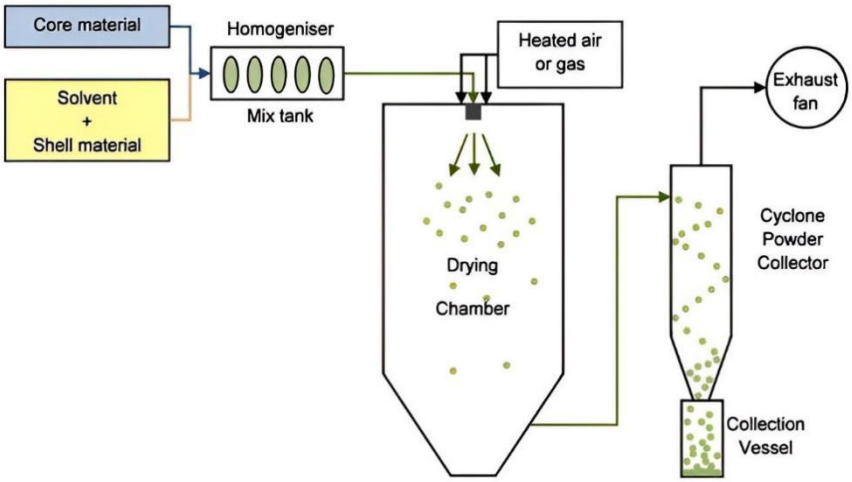


Figure 4: Representation of preparation of microencapsulation carrier by spray drying/cooling [38]

In spray cooling (congealing), the core material is dispersed or dissolved in a molten polymer matrix, which is maintained at an appropriate temperature to ensure liquidity. This molten mixture is atomized into fine droplets and introduced into a cooling chamber containing chilled air or another cooling medium. The droplets solidify upon cooling, forming microspheres or microcapsules. The solidified particles are then collected [39].

3.1.2. Ionic Gelation Method (IGM)

The IGM is a widely employed technique for the preparation of microspheres and microcapsules, particularly for hydrophilic polymers such as alginate, chitosan, or their derivatives. This method involves the crosslinking of polymer solutions with multivalent cations (Calcium ions for alginate) to form a gel matrix under mild conditions [39-40]. Typically, the polymer solution containing the drug or active ingredient is dropped into an ion-rich solution using a syringe or nozzle, forming spherical microspheres or microcapsules upon contact (Fig. 5) as below.

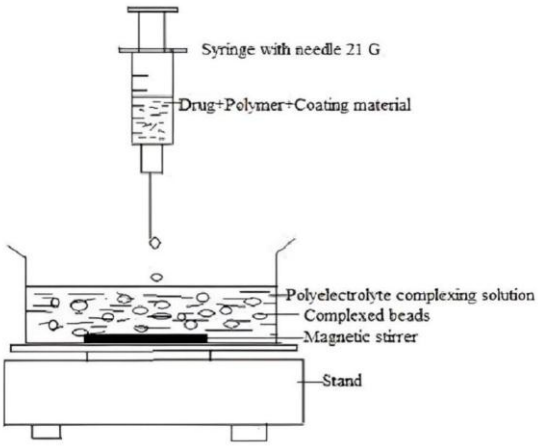


Figure 5: Representation of preparation of microencapsulation via IGM [40]

Additionally, ionic gelation enables controlled release properties by adjusting factors such as polymer concentration, crosslinking agent type, and gelation time [40]. The applications of this method span diverse fields, including drug delivery, nutraceuticals, and tissue engineering.

3.1.3. Centrifugal Extrusion Method (CEM)

The preparation of microspheres or microcapsules via centrifugal extrusion begins by preparing two immiscible liquids: the core material and the encapsulating polymer solution. These liquids are fed into concentric nozzles of a rotating extrusion head, with the core material in the inner nozzle and the polymer solution in the outer nozzle. As the head rotates, the liquids are extruded simultaneously, forming a liquid jet. The centrifugal force generated by the rotation causes the jet to break into uniform droplets [41-42]. These droplets are directed into a hardening or solidifying medium, typically a cooling bath or a crosslinking solution, where the encapsulating polymer solidifies to form stable microspheres or microcapsules. The formed particles are then collected, washed to remove residual materials, and dried (Fig. 6).

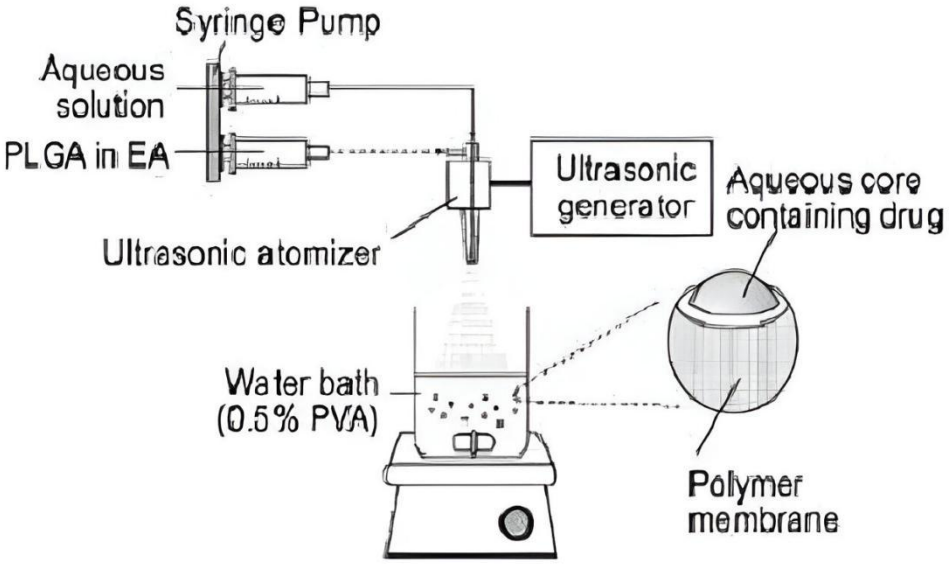


Figure 6: Representation of preparation of microencapsulation via CEM [40]

The parameters such as nozzle size, rotation speed, and the viscosity of the liquids are carefully controlled to achieve uniform particle size and %EE [42].

3.1.4. Emulsification

The emulsification method is a versatile and widely used technique for preparing microspheres or microcapsules, particularly for hydrophobic polymers and drugs. This process involves creating a stable emulsion by dispersing a polymer solution containing the active ingredient into an immiscible continuous phase, typically oil or water, under constant stirring. The emulsion droplets act as microreactors where the polymer solidifies, trapping the drug within. Polymer solidification can occur through solvent evaporation, solvent diffusion, or thermal gelation, depending on the system (Fig. 7) [43].

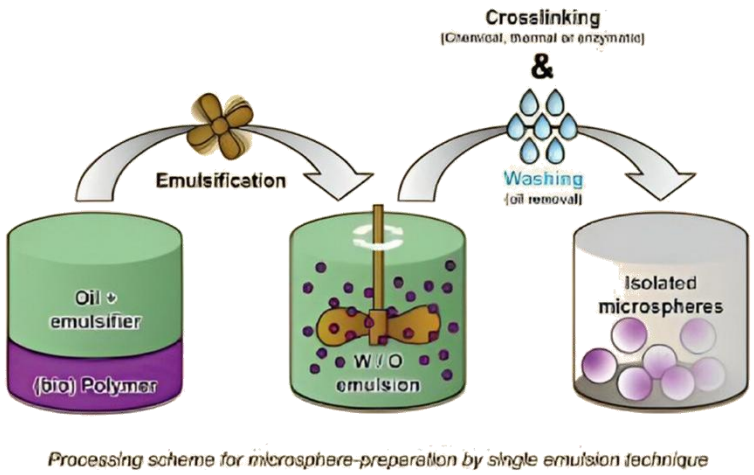


Figure 7: Representation preparation of emulsification for microemulsification [40]

The microspheres or microcapsules are then separated, washed, and dried.

3.1.5. Fluidized Bed Coating (FBC)

The preparation of microspheres or microcapsules via FBC involves suspending solid particles, which serve as the core material, in an upward stream of heated air within a fluidized bed chamber. A polymer solution or dispersion, serving as the coating material, is sprayed onto the fluidized particles using a nozzle. As the droplets of coating material come into contact with the particles, the solvent evaporates due to the heated air, leaving behind a uniform coating layer on the surface of the cores. The process is repeated in cycles to achieve the desired coating thickness (Fig. 8). Once coated, the microspheres or microcapsules are collected [44].

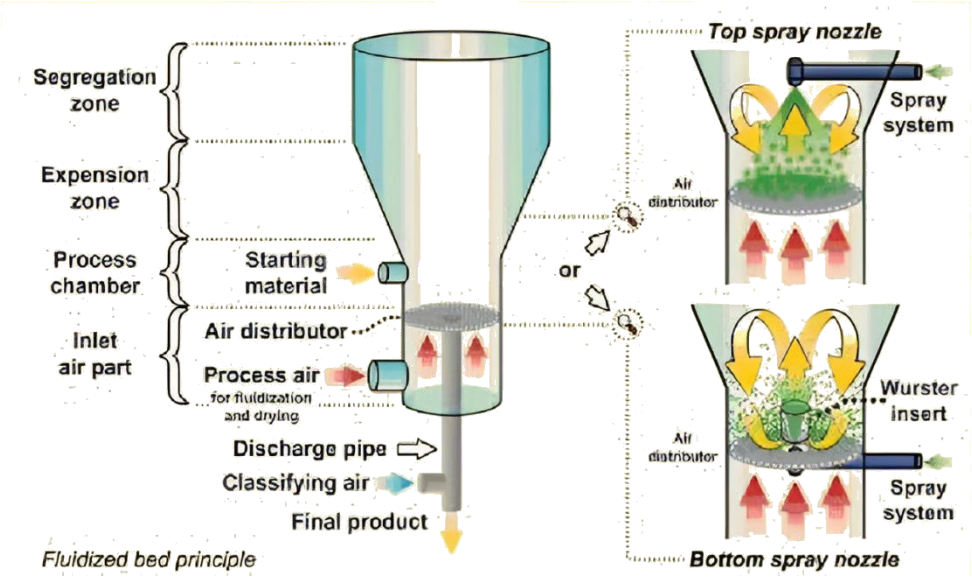


Figure 8: Preparation steps for microencapsulation carriers via FBC method [40]

3.1.6. Freeze-Drying (Lyophilization)

Freeze-drying, or lyophilization, is a specialized technique used to prepare microspheres or microcapsules, particularly when preserving the structural integrity of sensitive bioactive compounds is crucial. The process begins with the preparation of a polymer solution containing the drug or active ingredient, followed by its dispersion or emulsification into droplets. These droplets are rapidly frozen, typically using liquid nitrogen or a cryogenic freezer, to form solid particles. The frozen particles are then subjected to sublimation under reduced pressure in a freeze-dryer. This step removes water or other solvents by converting ice directly into vapour without passing through the liquid phase [45]. The result is dry, porous microspheres or microcapsules with improved stability and extended shelf life. Freeze-drying is ideal for heat-sensitive drugs or biologics, as it operates at low temperatures [45-46].

3.1.7. Hot-Melt Microencapsulation

The hot-melt microencapsulation method is a thermal-based technique for preparing microspheres or microcapsules, particularly for hydrophobic drugs and polymers with low melting points. The process begins by heating the polymer above its melting point to form a uniform molten phase. The drug or active ingredient is then dispersed or dissolved within this molten polymer. The polymer-drug mixture is subsequently emulsified into a continuous phase, typically an aqueous solution containing a stabilizer or surfactant, under vigorous stirring. Upon cooling, the molten polymer solidifies into discrete microspheres or microcapsules, encapsulating the drug within [47]. The solidified particles are collected by filtration or centrifugation, washed, and dried. This method avoids the use of organic solvents, making it suitable for environmentally sensitive applications. It offers the advantage of producing microspheres with high drug loading efficiency and controlled-release properties by varying polymer types, drug concentrations, and process parameters [46-47].

3.1.8. Extrusion/Emulsion-Solvent Evaporation/Solvent evaporation

The extrusion/emulsion-solvent evaporation/solvent evaporation method is a versatile and widely used technique for preparing microspheres or microcapsules, particularly for encapsulating both hydrophilic and hydrophobic drugs. The process typically involves several steps, starting with the preparation of a polymer solution containing the drug in a suitable solvent. In the extrusion step, the polymer-drug solution is extruded through a needle or nozzle to form droplets, which are then dispersed into an immiscible continuous phase, such as oil or an aqueous phase containing surfactants. This forms an emulsion where the droplets act as the microreactors for the formation of microspheres [48-49]. The emulsion is then subjected to solvent evaporation, where the solvent is gradually removed under reduced pressure or by stirring. As the solvent evaporates, the polymer solidifies, encapsulating the drug within solid microspheres or microcapsules (Fig. 9) as below.

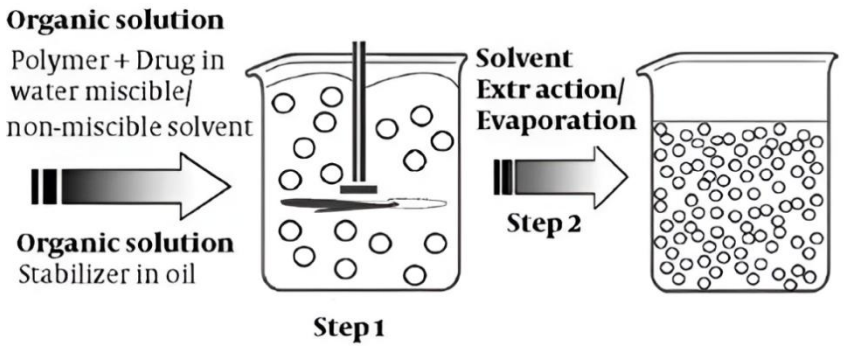


Figure 9: Representation of holt-melt Extrusion/Emulsion-Solvent Evaporation/Solvent evaporation [50]

After evaporation, the microspheres or microcapsules are collected, washed, and dried.

3.2. *Physico-Chemical Methods*: The various methods involved in the preparation of microencapsulation using physico-chemical methods describe as following:

3.2.1. Coacervation Phase Separation

In this method initially dissolving or dispersing the core material (API) in a suitable polymer solution. A non-solvent or a second polymer is gradually added under continuous stirring, inducing phase separation and leading to the formation of a coacervate (polymer-rich phase). The coacervate droplets deposit around the core material, encapsulating it to form a coating. The system is stabilized by adjusting parameters such as temperature, pH, or ionic strength to solidify the coacervate layer [51]. The encapsulated particles are then separated by filtration or centrifugation, washed to remove impurities, and dried to obtain the final microspheres or microcapsules (Fig. 10).

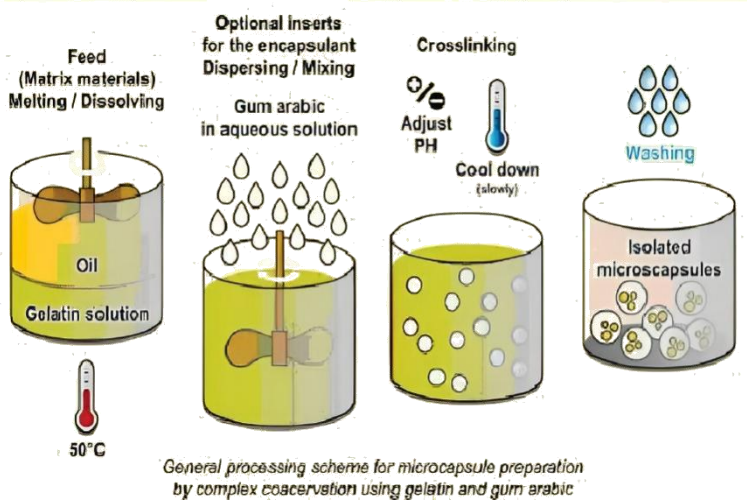


Figure 10: Preparation of microencapsulation via Coacervation Phase Separation [40]

3.2.2. Polymer encapsulation

The method begins with dissolving the core material in a suitable solvent and mixing it with a polymer solution. The mixture is emulsified in an immiscible continuous phase, such as water or oil, under vigorous stirring to form droplets containing the core material and polymer. Encapsulation is achieved through methods like solvent evaporation, solvent extraction, or crosslinking. In solvent evaporation, the organic solvent is removed by heating or applying a vacuum, causing the polymer to precipitate around the core material. In solvent extraction, the solvent diffuses into the aqueous phase, leading to polymer deposition, while in crosslinking, chemical agents or physical methods like UV light or heat solidify the polymer shell around the core [52-53]. The resulting microspheres or microcapsules are then collected and dried.

3.2.3. Hydrogel microspheres

The preparation of hydrogel microspheres involves dissolving or dispersing the core material in a hydrogel-forming polymer solution, such as alginate or chitosan. This solution is then extruded dropwise into a crosslinking or gelation medium, such as calcium chloride for alginate, where the polymer undergoes ionic or covalent crosslinking to form hydrogel beads encapsulating the core material [54-55]. The formed microspheres are collected, washed to remove residual reagents, and dried or stored in hydrated form, depending on the application.

3.2.4. Polymer-polymer incompatibility

The preparation of microspheres or microcapsules via polymer-polymer incompatibility involves dissolving two incompatible polymers in a common solvent, along with the core material. Under controlled conditions, one polymer precipitates due to phase separation, forming a polymer-rich coacervate that encapsulates the core

material. The second polymer remains in solution, stabilizing the dispersion. The system is further treated by solvent removal (evaporation or extraction) to solidify the encapsulating polymer layer. The resulting microspheres or microcapsules are collected by filtration or centrifugation, washed to remove residual materials, and dried [56].

3.3. *Other Methods:* The several others methods involving as below following:

- **Cyclodextrin Inclusion**: The preparation of microspheres or microcapsules using cyclodextrin inclusion begins by dissolving the core material (Hydrophobic drug) in a solvent, followed by the addition of cyclodextrin in an aqueous medium. The mixture is stirred thoroughly to allow the formation of inclusion complexes, where the hydrophobic core material is encapsulated within the hydrophobic cavity of cyclodextrin [57]. The resulting solution is filtered or centrifuged to separate the complexes, which are then washed to remove unbound materials. The final step involves drying the inclusion complexes, typically by freeze-drying or spray drying, to obtain solid microspheres or microcapsules [57-58].
- **Interfacial Polymerization**: In interfacial polymerization, microspheres or microcapsules are formed at the interface of two immiscible liquids. Initially, the core material is dispersed in one phase, typically the aqueous phase, while monomers are dissolved in the organic phase. Upon mixing, the two immiscible liquids form an emulsion with the core material in the dispersed phase. Polymerization is initiated at the interface of the droplets by adding a catalyst or adjusting the pH and temperature, resulting in the formation of a polymer shell around the core material. After completion of the reaction, the formed microspheres or microcapsules are washed to remove unreacted monomers and solvents, and then dried to obtain the final product [50-60].

These all above methods widely utilized in the formulation of microencapsulation such as microspheres and microcapsules of various drugs for the treatment of targeting. These techniques collectively enable innovative applications across pharmaceuticals, food, and cosmetic industries.

4. RECENT & CURRENT STATUS ON MICROENCAPSULATED NANOCARRIERS

Microencapsulated nanocarriers are at the forefront of modern DDs, offering enhanced therapeutic efficacy through controlled and targeted release. Recent advancements focus on developing biocompatible and biodegradable materials such as polymers and lipids for encapsulation, improving drug stability and minimizing side effects [61]. Innovations include stimuli-responsive nanocarriers that release drugs in response to pH, temperature, or enzymatic activity, and dual-functional carriers for combined therapy and imaging. Currently, their application spans pharmaceuticals, nutraceuticals, and cosmetics, with significant progress in cancer therapy, vaccines, and chronic disease management, demonstrating their transformative potential in personalized medicine [61-62]. The recent status in term of prepared microsphere/microcapsules with their details, granted patent status and few marketed formulations mentioned in the Table 5, Table 6 and Table 7 respectively as below description.

4.1. *Prepared Nanocarriers as Microencapsulation:* Prepared nanocarriers as microencapsulation refers to the innovative formulation approach where nanocarriers, such as microspheres and microcapsules are encapsulated within a microscale matrix or coating to enhance their performance. This dual-scale system combines the benefits of nanocarriers-such as high surface area, controlled drug release, and improved BA-with the protective and controlled-release properties of microencapsulation [63-64]. The different microencapsulation formulations such as microcapsules, microspheres preparation with their several details mentioned in the given Table 5 as below.

Table 5: List of prepared microencapsulated nanocarriers with their details

Microencapsulated nanocarriers	API /Drug	Methods of preparations	Compositions	Research Outcomes	Ref.
Microcapsules	Albendazole	---	Albendazole + sodium alginate + Chitosan + HPMC + $Cacl_2$	Albendazole-loaded chitosan alginate based microspheres can be effectively used for colon targeting	[65]
	Aceclofenac	Emulsion solvent evaporation method	Aceclofenac + Ethyl cellulose (EC)	They followed the Higuchi model and a released pattern of over 12 hr. was observed.	[66]
	Trihexypheni dyle HCl		Trihexyphenidyle + Methacrylic acid + Paraffin + Petroleum ether + Span80 + Acetone	Trihexyphenidyle microcapsules can be successfully designed to	[67]

		Solvent evaporation method		develop sustained drug-delivery capsules	
	Cefotaxime sodium (CFs)		CFs + Eudragit + Span80	*In-vitro* studies show that the release ratio kept ⇓ as the polymer ratio kept increasing, the drug was sustained release.	[68]
	Carvedilol	Orifice gelation and co-grinding technique	Carvedilol + Hydroxypropyl beta cyclodextrin + Sodium alginate + Eudragit NE30D(30)	*In-vivo* studies show that optimized formulation was effective in controlling hypertension for a period of 24 Hr.	[69]
	Diclofenac sodium (DS)	Emulsion solvent evaporation technique	DS + EC + Sodium carboxy methyl cellulose (CMC) + Chloroform + HCl + Methanol	In *in-vitro* studies, the drug release profile decreased on increasing polymer concentration, and in *in-vivo* studies still to be carried out on the animal model.	[70]
	Verapamil HCl	Hot melt technique	Verapamil HCl + EC acetate + Cyclohexane + n-hexane + Acetone	*In-vitro* sustained release of verapamil have been established and *in-vivo* release are still to be confirmed in trials.	[71]
	Valacyclovir HCl	Solvent evaporation	Valacyclovir HCl + Acetone + Liquid paraffin + Span 80	Good %EE and sustained released behavior were noticed in EC shell encapsulation.	[72]
Microspheres	Pantoprazole Sodium (PPs)	Nonaqueous solvent evaporation method	PPs + HPMC K100M + Eudragit S100 + Ethanol + Dichloromethane (DCM)	Micro particulate floating dose type of PPs can be effectively intended to give delayed arrival of medication and thus enhanced BA.	[73]
	5-Fluorouracil (5-FC)	Emulsion dehydration method and solvent evaporation method	5-FC + Chitosan + Distilled water/Isooctane/Acetone + Span80 + Eudragit S100 + Liquid paraffin + n-hexane	The prepared microspheres of 5-FC for colon targeting may reduce the side effects of the drug caused by its absorption from the upper part of GIT when given in conventional dosage forms.	[74]
	Telmisartan	Emulsion solvent evaporation method	Eudragit 100 + Sodium lauryl sulfate (SLS) + Disodium hydrogen phosphate + Potassium dihydrogen phosphate + Polyvinyl alcohol (PVA) + Chloroform/sodium hydroxide/Chloride/methanol/HCl	The formulations have shown good drug release in simulated intestinal medium, which is the desired medium for drug absorption.	[75]
	Famotidine	Ionotropic gelation technique	Crude A + nilotica gum + Sodium alginate + Acacia nilotica + $AlCl_3$/$BaCl_2$/$CaCl_2$ + distilled water	Formulation with A. nilotica gum may be utilized during pharmaceutical dose frames by giving support to	[1]

				drug delivery system and avoiding side effects for the patients.	
	Ciprofloxacin	Emulsion solvent diffusion evaporation method	Ciprofloxacin + EC HPMC (100M) + Carbomer (934P)	EC microspheres showed reproducible results, with good Mucoadhesive properties and good surface morphology.	[77]
	Diacerein	Ionotropic gelation method	Diacerein + $CaCl_2$ + sodium alginate + Chitosan	The B3 formulation was the optimized formulation that gave the best results.	[78]
	Glipizide	Emulsification phase separation technique	Glipizide + Chitosan + acetic acid + sodium acetate + dioctyl Sodium sulfosuccinate + Petroleum ether	Mucoadhesive microspheres of glipizide could sustain the release of the drug for more than 12 hours.	[79]
	Metformin HCl	Ionic gelation technique	Metformin HCl + xanthan gum + aluminium trichloride + NaCl + HCl	The microparticles formulated with xanthan gum could be successfully used for the controlled release of drugs but also for the protection of pH-sensitive active ingredients, which could be degraded under the acidic conditions of the stomach.	[80]
		Floating microspheres	Metformin HCl + Eudragit + HPMC	Showed excellent floatability, good buoyancy and prolonged drug release.	[81]
	Efavirenz	Solvent evaporation method	Efavirenz + EC N-22 + EC 100 CPS + Eudragit RS PO + Acetone	F14 contains Drug & Eudragit in the ratio of 1:1, which has a % yield of 94.12%,% %EE of 98.78% & the drug release of 96.82% at the end of 12 hrs when compared to other formulations.	[82]
	Sulforaphane	Spray drying Technique	Iron (II) chloride tetrahydrate/hexahydrate + Ammonium hydroxide + Bovine Serum albumin + Deionized water + Glutaraldehyde + R/S sulforaphane	Sulforaphane exerts anticancer activity in melanoma cells *in vitro*. Inhibition of HDAC was also observed when the cells were treated with sulforaphane, suggesting that this is a potential MOA, along with induction of apoptosis.	[83]
	Human insulin	Emulsion solvent evaporation technique	Human insulin + Glycerol + Zinc oxide + Aprotinin + HCl + Methacrylic acid (EudragitS-100) + DCM/ethanol/IPA/PVA + Purified water	Satisfactory performance of PVA-stabilized microspheres (F6) with respect to better %EE and delayed *in vitro* release at neutral pH for recombinant human insulin from Eudragit S100 microspheres.	[84]

	Stavudine	Emulsion solvent diffusion technique	Stavudine + Acetone + Light liquid paraffin + n-Hexane	The drug-to-polymer ratio and stirring speed are imperative to acquire sustained release and %EE.	[85]
	5-Fluorouracil	O/W emulsification solvent evaporation	5-FU + Eudragit S100 + Eudragit L 100 + PVA + Methylene chloride	At pH 7.4, nearly immediate release (within 30 min) was observed for pure S100, while mixtures enabled to prolong the release slightly.	[86]
	Flurbiprofen	Ionotropic gelation method	Flurbiprofen + HPMC + Sodium Alginate + $CaCl_2$ + Chitosan	Flurbiprofen shows maximum absorption in the lower GIT regions, and shows half-life 4-5 h, it shows low BA orally.	[87]
	Tinidazole	Emulsion cross linking method	Tinidazole + Bovine serum albumin + Span 80 + Glutaraldehyde + Toluene	When the polymer concentration increases, drug %EE also increases.	[88]
	Ketoprofen	Solvent evaporation technique	Ketoprofen + Acrycoat S 100 + PVA + Ethanol + DCM	Ketoprofen loaded Acrycoat S 100 microsphere may be useful to achieve sustained drug.	[89]
	Pantoprazole	Solvent evaporation and solvent extraction	Pantoprazole sodium + HPMC + Sod. Alginate + Liquid paraffin + IPA + NaOH + Acetone + DCM	The formulation B1 was considered as the best formulation as the percentage drug release was found to be 91.352% in the presence of PBS of pH 7.4 after 14hrs which is the greatest among all.	[90]
	Diltiazem HCl	Solvent evaporation method	Diltiazem HCl + Eudragit RS 100 + PEG 6000 + Liquid paraffin + Petroleum ether	Diltiazem HCl can be formulated as prolonged/sustained release drug delivery system with Eudragit RS 100.	[91]
	Metformin	Emulsion solvent evaporation method	Metformin + EC + DCM + Tween-80 + Span 80 + Guar gum	Microcapsules prepared with guar gum as matrix material could be a suitable CR dosage form of metformin having high DEE that may release less amount of drug in stomach minimizing the emergence of gastric adverse effects.	[92]

This Table 5 mentioned all details of prepared microencapsulation nanocarriers with their several details and enhanced the treatment of different disease and targeting.

4.2. *Granted Patents:* Granted patents under microspheres and microcapsules typically encompass innovations in drug delivery systems, focusing on controlled and targeted release mechanisms. These patents often detail the composition, preparation methods, and applications of microcarriers in pharmaceutical formulations [93]. The various patents status mentioned in the preparation of microencapsulation with their targeted details in the Table 6 as below.

Table 6: List of granted/published patent on microencapsulated nanocarriers with their targeting details

Types of Patent Category	Entitle	Application No./CBR/Grant No.	Patent No.	Applicants/Inventor	Filling Date	Published/Grant/Date of Patent
US	Microsphere Formulations Comprising Lurasidone and Methods for Making and Using the Same	17 / 679,385	US 2022/0265562 A1	Spencer et al.	Feb. 24, 2022	Aug. 25, 2022
	Method and apparatus for formulating microspheres and microcapsules	09/687,706	US 6,361,798 B1	Thanoo et al.	Oct. 13, 2000	Mar. 26, 2002
	Process for preparation of microspheres	193977	US4933105A	Jones W. Fong	May 13, 1988	Jun. 12, 1990
	Intravitreal microsphere drug delivery and method of preparation	455,091	US5718922A	Herrero-Vanrell et al.	May 31, 1995	Feb. 17, 1998
	Synthesis of functionalized carbon microspheres and their catalyst activity in C-O and C-N bond formation reactions	15/911018	US10195599	Ankush Venkatrao Biradar et al.	02-03-2018	05-02-2019
	Continuous process for preparing microspheres and microspheres prepared thereby	14 / 278, 035	US10195149B2	Kim et al.	May 15 , 2014	Feb. 5 , 2019
EP	Gastroretentive controlled release microspheres for improved drug delivery	98924438.9	EP0984774B1	ILLUM, Lisbeth et al.	22.05.1998	14.07.2004
	Method For Producing Microspheres Loaded With DruSgs And Microspheres Loaded With Drugs Produced Thereby	07808011.6	EP2063874B1	Hong Kee Sah	31.08.2007	03.04.2013
CA	Controlled release biodegradable micro- and nanospheres containing cyclosporine	1996/000017	CA2217462C	Zebunnissa Ramtoola	1996-04-02	2010-08-03
CN	Preparation method of drug-carrying microspheres	201110142359	CN 201110142359	朱利民聂伟申夏夏	2011-05-30	2013-01-02
WIPO (PCT)	Method of preparing microcapsules	2004/000803	WO2004105734A1	Patrice Hildgen et al.	2004-12-09	2004-12-09

This Table 6 above mentioned the several patent on the microencapsulation, with their all required details briefly. They may include novel polymeric materials, encapsulation techniques, or surface modifications to enhance BA, stability, and therapeutic efficacy [94].

4.3. *Marketed Products:* Marketed preparations under microspheres represent advanced drug delivery systems available for therapeutic use. These formulations leverage encapsulation techniques to provide controlled, sustained, or targeted drug release. These products improve patient compliance, reduce dosing frequency, and enhance therapeutic outcomes by optimizing drug BA and minimizing side effects [95]. The various marketed preparations on microencapsulation mentioned in the Table 7 as below following:

Table 7: List of several marketed preparation available microsphere for various targeting

API/Drug	Manufacturing Company	Commercial Marketed Name	Use/Application	Dose
Risperidone	Janssen Pharmaceuticals, Inc.	RISPERDAL CONSTA®	Schizophrenia	12.5, 25, 37.5, & 50 mg (3)
Naltrexone	Alkermes	Vivitrol®	Alcohol dependence	380 mg delivered intramuscularly (IM)
Paclitaxel	Abraxis BioScience	Abraxane ®	Cancer Treatment	260 mg/m^2 every 3 weeks
Octreotide acetate	Novartis Pharmaceuticals Corporation	Sandostatin® LAR	Alcoholism	50 mcg three times daily
Triptorelin	Pfizer	Trelstar™ depot Decapeptyl® SR	Prostate cancer	3.75 mg
Buserelin	Sanofi-Aventis	Suprecur® MP	---	---
Minocycline	Orapharma	Arestin®	---	---
Glatiramer Acetate	Teva Pharmaceutical Industries	Copaxone ®	Multiple Sclerosis	20 mg/day

This Table 7 explained the various marketed preparations mentioned in the above discussion with brief details. These preparations demonstrate the clinical utility and commercial success of microsphere and microcapsule technologies.

Recent developments have demonstrated their potential in enhancing therapeutic efficacy, improving drug stability, and enabling controlled release mechanisms. The growing number of patents highlights the increasing interest and investment in this field, reflecting significant progress in formulation techniques, scalability, and diverse applications [96]. These advancements, challenges such as scalability, regulatory complexities, and clinical translation remain key barriers. Continued research, innovation, and interdisciplinary collaboration will be crucial in addressing these hurdles, paving the way for the commercialization and widespread adoption of these promising technologies in pharmaceuticals, nutraceuticals, and other industries [95-97]. Microencapsulated nanocarriers stand poised to revolutionize healthcare, offering more effective, targeted, and patient-friendly therapeutic solutions.

5. CLINICAL TRIALS STAUS OF MICROENCAPSULATIONS

The clinical trial status of microencapsulation refers to the current phase and progress of clinical studies evaluating the safety, efficacy, and therapeutic benefits of drugs or bioactive compounds delivered through microencapsulation technology. Microencapsulation involves enclosing active ingredients within a protective coating to enhance stability, control release, and improve BA. Clinical trials in this area assess their applications in fields such as targeted drug delivery, sustained-release formulations, and protection of sensitive compounds, ensuring they meet regulatory requirements for human use [97-98].

The various clinical trials conducted for microencapsulation nanocarriers such as microsphere and microcapsules with their details mentioned in the Table 8 as below following.

Table 8: List of clinical trials data on microspheres/microcapsules/microencapsulation

Study Title	Study Type	NCT Number	Status	Conditions	Interventions	Sponsor
Yttrium Y 90 Resin Microspheres Data Collection in Unresectable Liver Cancer: the RESIN Study (RESiN)	Observational	NCT02685631	Completed	Localized Non-Resectable Adult Liver Carcinoma	Yttrium-90 Resin Microspheres	Vanderbilt-Ingram Cancer Center
Comparison of Pain After Uterine Artery Embolization Using Gelatin Microsphere		NCT05086770	---	Uterine Myoma, Uterine Fibroid	Device: Gelatin microsphere (Nexsphere™)De	Next Biomedical Co., Ltd.

or Tris-acryl Gelatin Microsphere					vice: Embosphere	
Progesterone Microspheres Pharmacokinetic - Pharmacodynamic (PK-PD) Study		NCT01176175	Phase-I	Infertility	Progesterone	Productos Científicos S. A. de C. V.
A Study Comparing Tretinoin Gel Microsphere, 0.1% and RETIN-A MICRO ® Gel Microsphere, 0.1% in the Treatment of Acne Vulgaris	Interventional	NCT04883736	Early Phase I	Acne Vulgaris	Tretinoin Gel Microsphere, 0.1%	Taro Pharmaceuticals USA
Bioequivalence Study for Crizotinib Encapsulated Microsphere Formulation (eMS)		NCT04856293	Phase 1	Healthy Participants	Crizotinib	Pfizer
Docetaxel Lipid Microsphere (DT-LM) for Injection in Chemotherapy Patients		NCT01611961		Advanced Cancer	DT-LM, Docetaxel	Shenyang Pharmaceutical University
Evaluate Taste and Relative Bioavailability of Two Microsphere Formulations of Crizotinib in Healthy Participants	Interventional	NCT03978143	Completed (Phase I)	Healthy Volunteers	Treatment A,B,C etc.	Pfizer

This Table 8 explained all clinical trials conducted and concluded the research in the field of microencapsulation. These trials often cover preclinical studies, Phase I (safety), Phase II (efficacy), and later phases for broader evaluations.

6. FUTURE PROSPECTUS AND CHALLENGES

The future prospectus of Novel Nanocarriers Microencapsulation and its potential to revolutionize DDs. The integration of nanocarriers with microencapsulation opens avenues for creating more efficient, targeted, and controlled-release formulations [99]. The future advancements may focus on:

- *Enhanced Precision Medicine:* Development of personalized therapeutic approaches using nanocarriers tailored for specific diseases or patient needs. Nanocarriers and microencapsulation technologies are paving the way for personalized medicine, allowing therapies to be tailored to individual patients based on their genetic profiles, disease conditions, and specific needs. By enabling targeted drug delivery, these systems reduce off-target effects and improve therapeutic outcomes, making treatments more effective and safer for patients.
- *Improved Drug Stability:* Designing encapsulation methods to protect drugs from degradation, enhancing shelf life and therapeutic efficacy. Microencapsulation enhances the stability of bioactive compounds by shielding them from environmental factors like light, oxygen, and moisture. This protective layer preserves the drug efficacy, extends shelf life, and ensures that the therapeutic agents remain active until they reach their target site, thereby improving the overall treatment success [100].
- *Expanding Applications:* Applications in diverse fields, including oncology, neurology, and vaccine delivery, for addressing unmet clinical needs. The versatility of nanocarrier microencapsulation enables its use in various fields, such as oncology for targeted cancer therapies, neurology for crossing the blood-brain barrier, and vaccine delivery for controlled antigen release. These technologies are addressing unmet clinical needs, particularly in challenging therapeutic areas where conventional approaches often fail.
- *Emerging Technologies:* Integration with AI and 3D printing for optimized formulation design and rapid prototyping of novel encapsulated systems. The integration of artificial intelligence (AI) and 3D printing is revolutionizing the design and prototyping of encapsulated drug systems. AI algorithms optimize formulation parameters, while 3D printing enables rapid and precise fabrication of complex nanocarrier systems, fostering innovation and reducing development timelines [100-101].

These innovations could lead to breakthroughs in healthcare, providing safer, more effective treatments for various diseases [102]. The various challenges include several technical, regulatory, and clinical trials discussed as below following:

- *Scalability and Manufacturing:* Transitioning from laboratory-scale preparation to large-scale

production of nanocarriers and microencapsulated systems while maintaining consistency and quality is complex and resource-intensive.

- *Stability Issues:* Ensuring the long-term stability of encapsulated drugs, particularly for sensitive bioactive molecules, is a significant challenge. The factors such as chemical degradation, aggregation, or leakage of the encapsulated substance can compromise the formulation efficacy and shelf life, necessitating advanced encapsulation techniques and stabilizers [103].
- *Regulatory Barriers:* The stringent regulatory frameworks governing nanotechnology-based systems pose hurdles to clinical approval. These systems require extensive safety, efficacy, and biocompatibility evaluations, often delaying commercialization due to the lack of clear, universally accepted regulatory guidelines.
- *Complexity in Patenting:* The intellectual property landscape for nanocarrier technologies is highly competitive, with overlapping innovations making patent claims ambiguous. This often leads to disputes, delays in filing, or challenges in securing exclusive rights, which can hinder the progress and adoption of novel formulations.
- *Clinical Translation:* Demonstrating the safety and efficacy of nanocarrier systems in human clinical trials is both time-consuming and expensive. High failure rates due to unforeseen toxicities, lack of significant therapeutic improvements, or inadequate scalability can further delay the translation of these technologies into real-world applications [104-105].

These challenges require interdisciplinary collaboration, advanced research, and supportive regulatory frameworks.

The field of nanocarrier microencapsulation presents significant opportunities for the evolution of drug delivery systems, providing cutting-edge solutions for targeted therapies, improved drug stability, and broader therapeutic uses. The incorporation of new technologies such as AI and 3D printing enhances its capability to transform precision medicine. Nevertheless, to fully harness this potential, it is crucial to tackle considerable challenges, including stability concerns, regulatory obstacles, patent intricacies, and the substantial costs associated with clinical implementation. Collaborative initiatives among research institutions, industry players, and regulatory bodies are vital to overcoming these challenges [106]. By capitalizing on technological advancements and addressing existing issues, nanocarrier microencapsulation has the potential to revolutionize healthcare, making treatments safer, more effective, and more accessible to meet a variety of medical needs [107-109].

CONCLUSION

The comprehensive review of novel nanocarriers and microencapsulation technologies highlights their transformative potential in drug delivery, offering solutions for enhanced bioavailability (BA), controlled release, and targeted delivery. Recent developments in drug delivery systems (DDs), such as liposomes, niosomes, solid lipid NPs, and polymeric formulations, highlight their versatility across a range of therapeutic fields. An increase in patent applications indicates a robust drive for innovation aimed at addressing current challenges in pharmacological treatments. Additionally, clinical trials are demonstrating the potential of these technologies in real-world applications, showing encouraging results in areas like oncology, infectious diseases, and chronic conditions. Future investigations need to tackle issues related to scalability, regulatory compliance, and long-term safety to facilitate the broader acceptance of these systems in clinical settings. By aligning technological advancements with patient-focused outcomes, nanocarriers and microencapsulation are poised to transform the future of modern therapeutics.

LIST OF ABBREVIATIONS

PPs: Pantoprazole Sodium; **BA:** Bioavailability; **HPMC:** Hydroxy Propyl methyl cellulose; **DCM:** Dichloromethane; **DDs:** Drug Delivery Systems; **AI:** Artificial Intelligence; **NPs:** Nanoparticle; **US:** United Sate; **EP:** European Patent; **CA:** Canada; **CN:** China; **WIPO:** World Intellectual Property Organization.

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