Palestinian Medical and Pharmaceutical Journal (PMPJ). 2023; 8(3): 221-240

# An Overview of Nanocapsule and Lipid Nanocapsule: Recent Developments and Future Prospects

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Received: (8/6/2022), Accepted: (20/11/2022)

## ABSTRACT

Nanocapsules are colloidal particles with dimensions measured in nanometers and generally obtained in the range of 100 to 500 nm through nanoencapsulation technologies. Nanoencapsulation encapsulates nano-sized particles in liquid or solid form to create nanocapsules or nanoparticles. Generally, six classical methods are involved in nanocapsule formation: nanoprecipitation, emulsification-diffusion, double emulsification, emulsification-coacervation, polymer coating, and layer-by-layer. Nanocapsules are prepared from different monomers and cross-linked polymers, contributing to their stability during and after encapsulation. They are segregated into ionic and non-ionic by the surface formal charges, which then influence the type of applications. The applications of nanocapsules usually range from developing targeted drug delivery systems, self-healing materials, and the encapsulation of nutritive additive compounds in nutraceutical products. Nowadays, people turn their attention to natural resources. Therefore, the polymer matrix and the active substances in nanocapsules have been adopted with various natural polymers such as protein, lipids, polysaccharides, plant metabolites, plant exudates, or plant extracts. Since nanotechnology products are predicted to be broadly utilized in the future, major key players must work collectively to handle the issue of safety regulation and user acceptance as well as optimum scale production of nanocapsules in industries.

**Keywords:** Nanocapsule, Encapsulation, Capsule, Drug delivery system, Nanotechnology, Emulsion.

## INTRODUCTION

In recent years, nanocapsules have become a promising candidate in advanced nanotechnology research and have successfully played their part in the numerous means of human life in many scientific fields, which include pharmaceuticals, the food industry, healthcare, nanomaterials, nanodevices, etc. (1, 2). The availability of nanotechnology-based products in the commercial markets has been extended worldwide (3). Nanocapsules are polymeric-surrounded membranes of nano-vesicular systems designed with a typical inner core and confined with active substances in their reservoir (4).

Vesicular systems such as nanocapsules have become promising candidates in pharmaceutical, nutraceutical, and food research to ease and improve the existing system. Nanocapsules are systems that imprison active substances like drugs in a cavity that is made up of an inner core such as solid, liquid, and gas or molecular dispersion surrounded by a polymer membrane (5, 6). Meanwhile, Mohanraj and Chen (2006) stated that nanoparticles are solid particles that range in size from 10 to 1000 nm, in which the drug will be encapsulated in their matrix (6).

Nanoencapsulation involves the process of entrapping nano-sized particles in the state of liquid or solid to obtain nanocapsules or nanoparticles (7). According to Wagle et al, (2020), nanoencapsulation can be carried out by physical and chemical methods (8). Physical methods include spray drying, fluidized bed and centrifugal extrusion processes, while chemical methods comprise *in situ* polymerization, interfacial polymerization and complex coacervation (8, 9).

As the nanoencapsulation process is mostly used in drug delivery systems, the main goals of nanoparticle design are to control particle size, surface properties, and the release of pharmacologically active agents to achieve site-specific drug action at a therapeutically optimal rate and dose regimen (6, 10). This is a revolutionary technique due to the limitations of employing liposomes as drug carriers.

A few advantages of using nanoparticles in drug delivery systems listed by Patra et al, (2018) include easily manipulated particle sizes and surface properties. Also, high efficacy in drug therapeutics reduces the side effects, which is attributed to their ability to regulate drug release and particle degradation through matrix constituents readily. In addition, site-specific targeting can be performed and is applicable for various routes of administration such as oral, nasal, parenteral, intraocular, etc (11).

Apart from these advantages, nanoparticles exhibit several limitations, as agreed by Shah et al. (2017), which include particle aggregation as a result of small particle size and large surface area, which can lead to the complications of physical handling in liquid and dry states, as well as limited drug loading and burst release (12).

### *Nanocapsules preparation and formation methods*

Typically, there are six classical methods used in the preparation of nanocapsules, as reviewed by Mora-Huertas et al. (2010), which are: nanoprecipitation, emulsification-diffusion, double emulsification, emulsification-coacervation, polymer-coating, and layer-by-layer (13). However, emulsion evaporation and procedures for polymer liposome preparation have also been applied. In the case of the emulsion-evaporation method, it has been agreed that this method is not recommended for nanoencapsulation as it is normally done through microencapsulation technology, thus triggering the alternative research work for nanocapsule production (14).

In contrast, polymer-based liposomes or polymersomes have become promising candidates for drug encapsulation because of their resemblance to the structures of lipids in membrane cells, which could enhance their biological action and targeted nanoparticle design (15, 16). Despite the favorable response to polymersomes, their use in drug delivery has been limited because of their low encapsulation efficiency, quick leakage of water-soluble medicines in the presence of blood components, and poor storage stability (17).

Many criteria should be considered in choosing matrix materials: the size of nanoparticles required, inherent properties of the drug (aqueous solubility and stability), surface characteristics (charge and permeability), degree of biodegradability, biocompatibility, and toxicity, drug release profile desired, and antigenicity of the final product (18). It has also been stated that nanocapsule production and particle size depend on the concentration of employed surfactants and stabilizers (19). As reported by Lima et al. (2021), the synthesization of nanocapsules required both solvent (organic) and non-solvent (aqueous) phases (20). The general processing requirements involved in nanocapsule formation are shown in Table 1.

**Table (1):** General processing requirements in preparing nanocapsules from both phases.

| **Solvent (organic) phase** | **Non-solvent (aqueous) phase** |
|---|---|
| Organic medium | Water |
| Film-forming substance: polymer (synthetic or natural) | Film-forming substance |
| Active substance | One or more naturally occurring or synthetic surfactants |
| Oil | |
| Lipophilic tensioactive | |
| Active substance solvent | |
| Oil solvent (if needed) | |

**Nanoprecipitation**

The nanoprecipitation technique is also known as solvent displacement or interfacial deposition. As a result, this method produces nanocapsules as a colloidal suspension when the organic phase is added slowly and with moderate stirring to the aqueous phase (20). It also involves three stages: nucleation, growth, and aggregation, in which the formation depends on the polymer aggregation in stabilized emulsion droplets.

**Emulsification-diffusion**

According to the research, this method involves lipophilic and hydrophilic active ingredient nanoencapsulation. There are three phases involved: organic, aqueous, and dilution. The organic medium would act as a solvent for various components in the organic phase. The aqueous phase is an aqueous dispersion of a stabilizing substance, while the diluting phase is often water (21-23). Vibrant agitation in the aqueous phase resulted in the emulsification of the organic phase. After adding water to the system, the nanocapsule would form as the solvent is diffused into the external phase.

**Double emulsification**

Double emulsification is divided into water-oil-water emulsion (w/o/w) and oil-water-oil emulsion (o/w/o) (24). It involves a two-step emulsification process by applying two surfactants (hydrophobic and hydrophilic). The normal steps to synthesize nanocapsules through this system consist of a primary emulsion and a second emulsion that would eventually leave hardened nanocapsules in an aqueous medium (20).

**Emulsification-coacervation**

The emulsification-coacervation technique prepares nanocapsules from naturally occurring polymeric materials such as sodium alginate and gelatine. The process begins with the o/w emulsification of an organic phase with an aqueous phase through mechanical stirring or ultrasound, followed by a simple coacervation step (25). Lastly, the coacervation process is completed with additional cross-linked steps until a rigid nanocapsule shell structure is produced (26).

**Polymer coating**

A few approaches can be used to deposit a thin layer of polymer on the nanoparticle surface. Nevertheless, Zhuang et al. (2017) suggested beginning the procedure with the organic phase, an aqueous phase comprising a stabilizing agent and an aqueous polymer coating solution. The o/w nanoemulsion will be formed after the organic and aqueous phases are mixed under moderate stirring by solvent displacement. The evaporation of solvents under vacuum to the rate of a specific volume is then followed by the polymer's prior formation of coated nanoemulsion through simple incubation in the polymer solution (27).

**Layer-by-layer**

The layer-by-layer method obtains vesicular particles called polyelectrolyte capsules. According to Yan et al. (2021), to prepare oil-loaded polyelectrolyte nanocapsules, high-pressure homogenization is used in the first part to prepare an emulsion of modified starch that acts as an emulsifier of the oily phase and the first negatively charged polyelectrolyte layer of the shell and oil, followed by the addition of the solution of the second polyelectrolyte under stirring, which is followed by injecting the third polyelectrolyte solution into the system under the same conditions. Once the addition has settled, the nanocapsule dispersion will be treated by high-pressure homogenization prior to the final centrifugation of the dispersion (28).

**Natural resources in nanocapsule development**

The encapsulation process that involves nanoparticles in the nanocapsules synthetization can be performed from various materials, including synthetic and natural polymers. Synthetic polymers could be polylactide (PLA), polyglycolide (PGA), polylactide, polymalic acid, co-polyglutamic acid, etc (29). On the other hand, natural polymers comprise lipids, proteins, and polysaccharides (30). With polysaccharides becoming the

most widely used material, starch and their derivatives, such as amylose, maltodextrins, amylopectin, polydextrose, dextrins, syrups, and cellulose with their derivatives are also widely used (31).

Materials include plant exudates and extracts such as gum Arabic, gum tragacanth, gum karaya, mesquite gum, galactomannans, pectins, and soluble soybean polysaccharides. In addition to marine extracts like carrageenans and alginate, microbial and animal polysaccharides like dextran, xanthan, chitosan, and Magellan are also employed. Other than that, fatty acids, fatty alcohols, waxes (beeswax, carnauba wax, and candellia wax), glycerides, and phospholipids have also been used. Moreover, other selected inorganic materials used are polyvinyl pyridine, paraffin, and shellac (32). However, natural resources are also adapted from plant metabolites and polyphenols used in encapsulation (33).

Menezes et al. (2017) have successfully developed a new version of nanocapsules from lipids through interfacial deposition using a polymer technique known as lipid-core nanocapsules (34). They were made of sorbitan monostearate and medium-chain triacylglycerol dispersion and were encased in poly(-caprolactone), an aliphatic polyester, as a polymeric wall in the core. By incorporating lipophilic medicines into their core, this novel nanocapsule design shows improved loading capacity over their pure oil-core parent nanocapsules.

Coradini et al. (2015) have attempted to co-encapsulate two natural polyphenols, which are resveratrol and curcumin, in lipid-core nanocapsules by using the identical method of nanocapsule preparation as Venturini et al. (2011) (35, 36). Resveratrol is derived from grape seed and red wine, whereas the extracted compound from turmeric (Curcuma longa), curcumin, has been applied in Ayurvedic medicine for inflammatory treatment. This novel approach has shown their potential as oedematogenic agents in treating chronic inflammatory diseases like arthritis, as the co-encapsulated polyphenols exhibited the most significant effects on Complete Freund's adjuvant (CFA)-induced arthritis in rats.

Lobato and his research team (2013) adopted the same technique as Venturini et al. (2011); they successfully produced natural plant-origin nanocapsules to be used in food applications, which were obtained from the annatto seeds (bixin) with high encapsulation efficiency (37). Bixin is a carotenoid that acts as a primary coloring component in annatto. There are also previous works on bixin encapsulation by Parize et al. (2008) and Barbosa et al. (2005) with natural resources from animal polysaccharides and plant exudates, respectively (38, 39). These two studies used spray drying to prepare microcapsules with chitosan as an encapsulating agent (39). On the other hand, Barbosa et al. (2005) encapsulated bixin with gum Arabic or maltodextrin (38).

Another example of natural resources used for nanoencapsulation is in drug delivery systems, as Gnanadhas et al. (2013) demonstrated. This research team intended to develop an effective drug delivery system by combining two types of animal polysaccharides (Chitosan and Dextran). Chitosan-dextran sulfate nanocapsules are synthesized using a layer-by-layer ciprofloxacin method to inhibit Salmonella infection. Based on these findings, chitosan-dextran sulfate nanocapsules have been chosen as a potential drug carrier against intraphagosomal and vacuolar pathogens (40).

Similar research was carried out using the ionic gelation method using chitosan as a nanocapsule material. Chitosan is incorporated with alginate, a type of marine extract, to encapsulate essential oils such as turmeric and lemongrass oil as nanocarriers for future biomedical and pharmaceutical purposes (41). Interestingly, there has been research work by Kumar et al. (2008) on developing natural polymer-based nanocapsules to encapsulate insecticides within them that later would be crucial in agricultural sustainability, specifically in controlled-release formulations of pesticides (42). Moreover, alginate and chitosan are chosen to be incorporated into nanocapsules loaded with acetamiprid by ionic regulation and polyelectrolyte complexation methods (43).

Another study by Quiroz-Reyes et al. (2014) used polyphenolic extract from cocoa

to be loaded into animal protein-based nano-encapsulation known as gelatine nanoparticles. This process is carried out through the nanoprecipitation method to develop a nanoscale system that is capable of sustaining and preserving active forms of polyphenols extracted from cocoa, such as procyanidins and flavonols, prior to being consumed and released within the body. Further, several investigations and research projects are ongoing to produce new natural-based nanocapsules for future human and environmental sustainability (44).

**Polymeric nanoparticles**

Nanocapsules are polymeric nanoparticles with a polymeric wall comprised of non-ionic surfactants, macromolecules, phospholipids, and an oil core (45, 46). These are created primarily through interfacial polymerization and interfacial nano-deposition. Polymeric nanoparticles are named nanocapsules containing a polymeric wall composed of non-ionic surfactants, macromolecules, phospholipids, and an oil core. These are mostly prepared by two technologies: interfacial polymerization and nano-deposition (46, 47).

The methods of preparation of lipid nanocapsules are simple and easily scalable. In addition, it is a promising method in treating cancer, Alzheimer's disease, and other applications.

**Lipid nanocapsules**

Lipid nanocapsules (LNCs) are the most recently produced and patented nanocarriers; they resemble lipoproteins (48). LNCs feature an oily core composed of medium-chain triglycerides surrounded by a stiff, tensioactive membrane composed of lecithin and a pegylated surfactant. LNCs are characterized by a hybrid structure comprised of polymer nanocapsules and liposomes, as well as a diminutive size (20 to 100 nm) (49).

Lipid nanocapsules offer great potential, particularly in oral drug delivery, because of their reported stability in simulated gastrointestinal fluids (50), diffusion in intestinal mucus (51), a direct effect on P-glycoproteins (P-gp) (52), and potential internalization via active endocytic processes that likely allow transcytosis and gastrointestinal transport of the encapsulated drug (53). Moreover, the transcellular crossing of the Caco-2 cell membrane by intact LNC was recently confirmed by two complementary techniques employed: Förster resonance energy transfer (FRET) and nanoparticle tracking analysis (NTA) (54).

LNCs have lately demonstrated remarkable promise as medication nanocarriers for parasitic diseases. This has reportedly occurred with ivermectin (55) and abendazole (56). Further, it was reported earlier that the incorporation of miltefosine (MFS), an alkylphosphocholine with proven antischistosomal activity in LNCs, significantly enhanced its efficacy against *S. manosoni* in infected mice (57).

**LNC Preparation**

Lipid nanocapsules were introduced by Heurtault et al. (58). They exhibit a core-shell structure composed of a liquid oily core and an amorphous surfactant shell. The formulation process is based on the phase inversion temperature (PIT) method plus the temperature cycling treatment.

The PIT method is a low-energy and solvent-free method that uses the particular ability of emulsions stabilized by polyethoxylated (PEO) non-ionic surfactants to undergo a phase inversion following a temperature variation. The so-called *transitional* phase inversion occurs when, at a fixed composition, the relative affinity of the surfactant for the different phases is changed and controlled by the temperature. The temperature cycling has been proven to increase the quality of the nanoemulsions (in terms of size and polydispersity index) by increasing the surfactant amount at the water/oil interface. This leads, in fact, to droplets exhibiting an effective quantity of surfactants in the interfacial region (59, 60).

Usually, the surfactant is forced to migrate towards the interface at each temperature cycle. At low temperatures, non-ionic surfactants will have a high affinity for water, leading to an o/w emulsion. In contrast, at higher temperatures, the surfactant is dehydrated and has less affinity for water, so the interactions of surfactant with oil will be superior to the interactions of surfactant with water, which involve the formation of a w/o

emulsion. A bicontinuous microemulsion phase is formed at the transitional region, where the surfactant exhibits ultra-low interfacial tension and a very low droplet curvature. The final formulation (nanocapsules) is reached by a sudden dilution with water. At this translational phase, which usually corresponds to a temperature below the non-ionic surfactant melting point (30°C), shell crystallization occurs.

Therefore, Ostwald ripening is significantly reduced, even more than the simple nanoemulsion (61). Thus, the structure of these particular nanoemulsions is specific and typical due to the formulating method and the physicochemical properties of their adequate components, mainly medium-chain triglycerides (caprilic triglycerides) as the oil phase, a polyoxyethylene-660-12-hydroxy stearate as the PEO non-ionic surfactant, and water plus NaCl as the aqueous phase. An additional neutral component, such as lecithin, was introduced in the formulation and has been shown to significantly increase LNC stability (62), creating a 'framework' in the shell.

## Characterization of Lipid Nanocapsules

The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties, and release of pharmacologically active agents to achieve the drug's site-specific action at the therapeutically optimal rate and dose regimen (63).

### *Colloidal properties*

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine nanoparticle systems' in vivo distribution, biological fate, toxicity, and targeting ability. In addition, they can also influence the drug loading, drug release, and stability of nanoparticles (63). Many studies have shown that sub-micron-sized nanoparticles are a better way to deliver drugs than microparticles (64, 65).

Dynamic Light Scattering (called Photon Correlation Spectroscopy or Quasi-Elastic Light Scattering) is a technique for measuring the size of particles, typically in the submicron region.

Photon correlation spectroscopy (PCS) has become a powerful light-scattering technique for studying the properties of suspensions and solutions of colloids, macromolecules, and polymers (66) that is absolute, non-invasive, and non-destructive (67).

Colloidal-sized particles in a liquid experience random (Brownian) motion due to numerous collisions with thermally propelled liquid molecules. The fluctuating scattered light intensity from these diffusing particles carries information about the particles' diffusion coefficient (68). The rate at which these intensity fluctuations occur will depend on the size of the particles. The particle size measurement instrument based on the DLS principle and has gained popularity for industrial applications is the Zetasizer range from Malvern Instruments Ltd., Malvern, Worcestershire, UK (69). This range of instruments is widely used to measure the hydrodynamic size as one of the parameters, along with the polydispersity, surface charge, and molecular weight of the nanoparticles.

Most applications for DLS in particle sizing are the rapid routine measurements of mean sizes in quality control and research laboratories (70). Manufacturers of latexes, pigments, emulsions, micelles, liposomes, nanoparticles, vesicles, oils, and silica can track the consistency of the desired particle sizes rapidly and accurately, independent of different operators and different instruments. According to the composition of LNC, the average hydrodynamic diameter ranges from 10 to 100 nm (71), with a polydispersity index of 0,01 and showing a monomodal particle size distribution.

Zeta potential measurements were also performed using photon correlation spectroscopy (PCS). Zeta potential, or potential, is an abbreviation for electrokinetic potential in colloidal systems. Theoretically, zeta potential is the electric potential in the interfacial double layer of a dispersed particle or droplet versus a point in the continuous phase away from the interface. In other words, the zeta potential is the difference between the potential of the mobile dispersion medium and the potential of the layer of the mobile dispersion medium attached to the dispersed particle (72).

The effects of ζ potential on the stability

of emulsions are well explained by the Derjaguin–Landau–Verwey–Overbeek theory (DLVO), which states that the stability of colloidal systems depends on the balance between the different forces acting on the interface. These include electrostatic repulsive forces and van der Waals attractive forces due to the surface charge (73). High ζ potential, either positive or negative, is generally required to ensure stability. In general, systems with ζ potential of greater than ±30 mV are considered pharmaceutically stable (73), and due to the presence of PEG dipoles in the shell of LNC (74) and the negative contribution of phospholipid molecules (75), LNCs have a slightly negative surface charge (-1 to -2 mV).

### *Morphological aspects*

The nanocapsules were characterized in terms of their morphological aspects. Transmission electron microscopy (TEM) is a common technique used for this purpose because of the high resolution it can reach (76).

TEM uses a beam of electrons that passes through an ultra-thin specimen and returns an image formed from the interaction of the electrons with the specimen. The high resolution is due to the small de Broglie wavelength of electrons, which enables them to detect fine details. TEM investigation was performed to confirm particle formation, as well as their size and shape, and to gain more information about our product, such as surface morphology and copolymer behavior in the nanoprecipitation process. Scanning electron microscopy (SEM) was also used in the first attempt to characterize nanospheres and nanocapsules, but it was successful only with nanospheres. A TEM of LNC revealed that lipid nanocapsules were spherical, with different diameters ranging from 25 to 60 nm or more. The lipid core was homogeneous, limited by an electron-dense interface and an external clear layer. The capsules were surrounded by a large continuum corresponding to the large quantities of added water and free polyethylene glycol (73).

### *Encapsulation Efficiency*

The encapsulation efficiency (EE%) is defined by the concentration of the incorporated material (such as active ingredients, drugs, fragrances, proteins, pesticides, antimicrobial agents, etc.) detected in the formulation over the initial concentration used to make the formulation (64).

Encapsulation efficiency (EE %) was calculated using the following:

$$EE\ \% = (Wt/Wi) \times 100\%$$

Wt is the total amount of the incorporated material, and Wi is the total quantity of incorporated material added initially during the preparation. Wt and Wi can be determined using spectroscopic or chromatographic methods. If the capsule shell material is a polymer, it can be dissolved in the solvent, and the incorporated molecule will become soluble to be quantified. If the incorporated molecule is not soluble in that solvent, it can be extracted by adding the capsules to a liquid in which the target molecule is soluble (also by multiple extraction). Suppose the core material is a liquid (such as emulsions). In that case, the amount of the encapsulated material can be evaluated after induced separation of the liquid dispersed phase and liquid continuous phase (i.e., simple emulsions) or in the outer liquid phase (i.e., W2 in water-in-oil-in-water (W1/O/W2) emulsions). The amount of water retained within the oil droplets during emulsification is also significant for double emulsion (64). In this case, differential scanning calorimetry (DSC) was used to measure the outer water phase conductivity (77).

The encapsulation efficiency can be influenced by (i) the partition coefficient of the target molecule in the solvents used in the preparation of the formulation, (ii) the method used to carry out the encapsulation process (temperature, pH, mechanical stress), and (iii) the size distribution of the capsules (78).

LNC shows the encapsulation of hydrophilic species alone, using examples of very different molecular weights, such as a dye (methylene blue) and a protein (BSA-isothiocyanate fluorescein-labeled), and (iii) showing the simultaneous encapsulation of hydrophilic (methylene blue) and lipophilic (also a dye, red Sudan III) species (72).

## Special applications of Nanocapsules

The application of nanotechnology to medicine can provide several benefits, especially in oncology, and this has resulted in the emergence of a new field called Nano-oncology (79). Drug-loaded nanoparticles provide a promising solution by selectively targeting tumor cells, thereby preventing damage to healthy cells (80). Nanoparticles can be engineered to incorporate various chemotherapeutic or diagnostic agents, creating flexibility in their design that is impossible with other drug delivery systems (81).

Nanocapsules (NC) are potential nanocarriers for several strategies in oncology. An NC is a vesicular system that exhibits a typical core-shell structure in which active molecules are confined to a reservoir or cavity surrounded by a polymer membrane or coating. The cavity can contain an active substance in liquid or solid form or as a molecular dispersion. The NC zeta-potential (ZP) is an important index for the stability of a nanoparticle suspension, representing the electric potential at the NC shear plane that depends on the chemical nature of the polymer, the stabilizing agent, and the medium pH (82).

### *LNCs in cancer chemotherapy*

Cancer is a major public health problem worldwide, with breast cancer being the most frequent cancer affecting women. Despite advances in detection and treatment, mortality rates remain high. Therefore, new approaches to breast cancer treatments are necessary. Doxorubicin-loaded lipid-core nanocapsules (DOX-LNC) were a promising way to treat breast cancer, opening up new ways to study the drug in living organisms (83).

Replacing injured neurons by the selective stimulation of neural stem cells in situ represents a potential therapeutic strategy for treating neurodegenerative diseases. The peptide NFL-TBS.40-63 (NFL) was adsorbed on lipid nanocapsules (LNC) whose targeting efficiency was evaluated on neural stem cells from the subventricular zone (brain). NFL-LNC was incubated with primary neural stem cells in vitro or injected in vivo in the adult rat brain and showed specific interactions towards neural stem cells of the subventricular zone (84).

The nanocapsules were an effective drug delivery and tumor cell theranosis agent. Nanocapsules containing protein-functionalized gold nanoclusters (AuNCs) as the shell and the hydrophobic drug curcumin could synergistically inhibit tumor cell growth and induction of cell apoptosis (85).

Liquid lipid nanocapsules (LLN) represent a promising new generation of drug-delivery systems. They can carry hydrophobic drugs in their oily core, but the composition and structure of the surrounding protective shell determine their capacity to survive in the circulatory system and to achieve their goal of penetrating tumor cells (86). By a layer-by-layer method, pectin-based hollow nanocapsules were obtained. Because they are sensitive to pH, have good colloidal stability, and kill cancer cells, they have much potential as new drug carriers (87).

### *LNCs as targeted carriers for anticancer drugs*

LNCs are useful as drug carriers. Erlotinib is an anticancer drug incorporated into PEGylated polypeptide lipid nanocapsules to enhance the anticancer efficacy of erlotinib in non-small cell lung cancer. The core-shell polypeptide-based lipid nanocapsules enhanced the antitumor efficacy of erlotinib and offered a promising approach in lung cancer therapy (88). Folate-receptor-targeted hybrid lipid-core nanocapsules comprise a hybrid lipid core lodging tanespimycin (TNP) and a polymeric corona lodging doxorubicin (DOX) (F-DTN). This nanocarrier could deliver DOX and TNP sequentially, as demonstrated by an in vitro release study (89).

Combining targeting with therapy remains a major challenge in cancer treatment. To address this subject, the lipid nanocapsules (LNC) surface was modified by grafting cRGD peptides, known to be recognized by v3 integrins expressed by tumor endothelium and cancer cells. The peptide-grafted LNC remained in the blood circulation for up to 3 h with reduced capture by the RES organs. These results show that cRGD grafted to LNC has created a promising tumor-targetable nanocarrier for cancer treatment (90).

Tretinoin-loaded lipid-core nanocapsules overcome the triple-negative breast cancer

cell resistance to tretinoin and show synergistic effects on cytotoxicity induced by doxorubicin and 5-fluorouracil. This work shows the possibility of using nanocapsules to improve the antitumoral activity of TT for its use either alone or in combination with other chemotherapeutic drugs, especially considering the chronic effect (91).

### *Nanocapsules for targeted brain drug delivery*

The blood-brain barrier (BBB) represents a significant and important barrier between the central nervous system (CNS) and the periphery. For this reason, the BBB preserves the CNS from potentially being exposed to toxic substances that may otherwise have access to it through systemic circulation. Nevertheless, it also signifies a major challenge in the delivery of drugs due to the tight junctions present in the BBB (92, 93).

The BBB prevents approximately 98% of small and 100% of large-molecule drugs from entering the brain under normal conditions. This indicates that brain tumors are a significantly difficult health challenge due to their fast development and poor prognosis. Current treatments have increased life expectancy. However, they carry the unwelcome risk of non-selectively destroying normal healthy cells and not fully suppressing cancer cells. Recent research has pointed towards the passive and active targeting of cancer cells through nanoparticles; these allow the direct targeting of tumor cells while carefully leaving healthy tissue (94).

Alzheimer's disease (AD) is the most common form of dementia. It is characterized by extracellular deposition of a specific protein, beta-amyloid peptide fibrils, and is accompanied by extensive neuronal loss in the brains of affected individuals. Although the pathophysiologic mechanism is not fully established, inflammation appears to be involved. Neuroinflammation has been known to play a critical role in the pathogenesis of chronic neurodegenerative disease in general and AD in particular (95). Over the past decade, numerous attempts have focused on this pivotal problem by designing strategies to aid drug passage across the BBB. Nanotechnology-based approaches have gained significant momentum since some can effectively transport drugs across the BBB. One such strategy is the use of nanoparticles for controlled drug delivery and release (74), such as the use of polymeric nanocapsules (76). A significantly higher efficiency was achieved by delivering indomethacin-loaded lipid-core nanocapsules (IndOH-LNCs). Hence, the combination of indomethacin and the LNC-based delivery system may pave the path for future therapeutic interventions in Alzheimer's disease (73).

It is well known that a healthy diet may delay the occurrence of age-related neurological disorders such as Alzheimer's, Parkinson's, and stroke. Resveratrol, and its preferred form, trans-resveratrol, has been found in various foods, including red grapes and berries. Resveratrol demonstrated pleiotropic activities such as antioxidant, anti-inflammatory, and inhibitory effects, indicating that it is one of the most promising compounds for developing AD therapies. Several intracellular targets of resveratrol have also been identified. However, the poor absorption of resveratrol makes the development of analogs very challenging (96).

Different strategies, such as nanotechnologies, have been shown to improve the solubility and stability of polyphenols, at least in rodents. Hence, various methods, such as the use of lipid-core nanocapsules containing resveratrol, have been shown to improve the efficacy of resveratrol. These new technologies should be used to confirm if resveratrol is a potential therapeutic agent in age-related neurodegenerative disorders (96, 97).

### *LNCs in Cosmetics and Topical Drugs*

LNCs have been used via different routes of administration, including oral, parenteral, and transdermal routes. Improved bioavailability, increased drug targeting, achieving controlled drug release, increasing the stability of the entrapped drugs, low biotoxicity, and good biocompatibility are some of the advantages reported for LNCs (98).

The Lipid Nanocapsule showed excellent transdermal delivery. The small size of LNCs ensures close contact with the stratum corneum, increasing the amount of drug penetrating through the skin. Therefore, in some topical applications, LNCs are preferred.

LNCs showed a 13-fold increase in the permeability of ketorolac compared to conventional gels. The partition coefficient of the drug between the stratum corneum and the vehicle was significantly higher than what is reported for NLCs of this drug (98).

On the other hand, LNC seems to allow quercetin delivery to viable epidermis, which holds promise for skin inflammatory disorders such as psoriasis (99). Quercetin is a plant flavonoid with strong antioxidant and anti-inflammatory properties that are particularly interesting for skin protection. However, its poor water solubility limits its penetration and so its efficiency on skin. Lipid nanocapsules present a promising strategy to deliver quercetin to skin tissue and can be of value for other poorly water soluble drug candidates (99, 100).

### *LNCs as potential new adjuvant for vaccines*

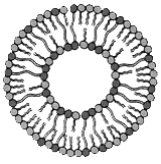
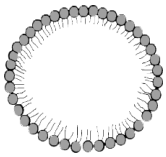
The term "adjuvant" originates from the Latin word "adjuvare: meaning "to help," and is assigned to compounds that enhance the host's humoral and/or cellular immune response toward a coadministered antigen. Modern vaccine development has turned toward the application of distinct, purified, subunit, and synthetic antigens as vaccines. These vaccines are typically poor immunogens and require the assistance of adjuvants to generate a robust and persistent immune response (101).

Polymeric antigen-based nanocapsules are particularly attractive for improving vaccines as an antigen–adjuvant delivery system to target key cells of the immune system, particularly in the liver (102). A novel nanocapsules (NCs) with surface-chelated nickel (Ni-NCs) as a vaccine delivery system for histidine (His)-tagged protein antigens can bind Histidine-tagged proteins and have the potential to be used as an antigen delivery system capable of generating strong antigen-specific antibodies at doses much lower than with aluminum-based adjuvants (103).

### Nanoformulation

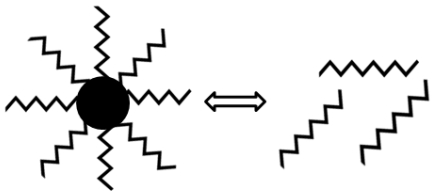
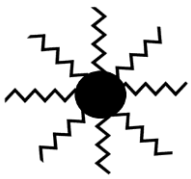
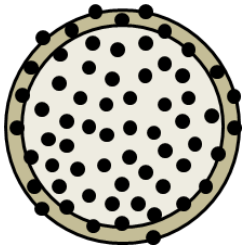
There are many obstacles to conventional pharmaceutical formulation for drug administration that could limit the bioavailability and absorption of the active agents into the body system. Thus, scientists have come up with a new solution to overcome this problem, which is the application of nanotechnology-based drug delivery systems (104). As reported by Bhatia (2016), there are four main types of technologies involved in the development of nano-based drug delivery systems, which are nanoparticles, nanocrystals, polymer therapeutics, and dendrimers. Moreover, many forms and shapes of nano-objects are introduced, as presented in table 2 (a, b), which shows numerous forms of nanotechnology-based drug delivery systems (105).

**Table 2(a):** Different forms and shapes of nano-objects of lipid based nano-delivery systems.

| Particle Type & Shape | Description |
|---|---|
| Nano delivery systems: lipid based | |
|  | Nanoliposomes / archaeosomes<br>Bilayer lipid vesicles |
|  | Micelle<br>Single layer lipid vesicles |

| Particle Type & Shape | Description |
|---|---|
|  | Nanocochleates<br>Lipid layer sheet rolled up in spiral fashion |

**Table 2(b):** Different forms and shapes of nano-objects of polymer based nano-delivery systems.

| Particle Type & Shape | Description |
|---|---|
| Nano delivery systems: polymer based | |
|  | Micelle<br>Aggregated copolymers |
|  | Nanosphere<br>Aggregated copolymers generating a solid central core |
|  | Nanocapsule/Polymersome<br>Polymer membrane surrounding a central cavity:<br>• Nanocapsule: oily liquid cavity, single layer membrane<br>• Polymersome: aqueous cavity, bilayer membrane (similar to nanoliposome) |

However, Chen et al. (2011) have presented three main strategies used in nanoformulation for drug delivery purposes. They are drug nanocrystals, nanoemulsions, and polymeric micelles. Drug nanocrystals are nanoscopic crystals of the parent compound with less than 1 μm in dimensions, invented to increase the oral bioavailability of hydrophobic drugs. It is prepared through several methods, including nanoprecipitation, high-pressure homogenization (HPH), and media milling. Drug nanocrystals are commonly formulated into conventional dosage forms such as tablets, capsules, pellets, and injectable suspensions (104).

The second strategy, which is nanoemulsion, is designed with oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules (104). The application of nanoemulsions could increase drug loading and enhance bioavailability. Among the methods used to synthesize nanoemulsions are HPH, microfluidization, ultrasonication, and spontaneous emulsification (106). The use of nanoemulsions comprises intravenous delivery of lipophilic drugs, transdermal delivery of lipophilic drugs, and sublingual and intranasal drug delivery. Moreover, polymeric micelles are nano-sized supramolecular constructs with a size range of 20–100 nm (107). They are formed from the self-assembly of amphiphilic block copolymers in aqueous environments. In water, a semi-solid core is formed from the hydrophobic segment of the

block copolymer while the hydrophilic segment of the copolymer transforms into a coronal layer (108). For hydrophilic segments, polyethylene glycol (PEG) is the most commonly chosen, while other polymers include Poly (N-vinylpyrrolidone) and Poly (N-isopropylacrylamide) (109). Polyesters and poly (L-amino acids), such as poly (lactic acid), poly (-caprolactone), poly (L-aspartic acid), and poly (L-glutamic acid (110). Polymeric micelles are suitable for intravenous administration to transport various cytotoxic drugs in cancer chemotherapy (111). All of these nanoformulation strategies have brought significant advantages to biological applications for drug-carrier purposes.

**Medicinal Product Formulation Market Trend**

In the past two decades, research and development investments, industrial production, sales, and consumption of medicinal products have exhibited an increasing trend in the European Union (EU) (112). Merck (MSD outside of North America) announced a 14% increase in global sales to $15 billion in the third quarter of 2022, compared to $13.15 billion in the same quarter of the previous year. Pharmaceutical sales during the quarter totaled $13 billion compared to $12.7 billion in Q3 2021, representing a 13% increase (113).

**Nanoformulation market trend**

According to Cientifica (2007), nanotechnology-enabled drug delivery systems will conquer the major share of the market after 2015, up to nearly 90% of the drug delivery market. This scenario will subsequently bring a total change to the way drug delivery systems are formulated. Looking into the market growth of nanotechnology, nano-enabled drug delivery systems already dominate a $3.39 billion market. The amount of money invested in nanotechnology's research and development demonstrates its significant advancement. In 2019, the United States National Nanotechnology Initiative (NNI) projected a budget of $27 billion (114).

## CONCLUSION

In conclusion, nanocapsules and lipid nanocapsules have played a crucial role in the development of nanotechnology through their outgoing applications in numerous areas such as the food industry, sustainability of agricultural systems, healthcare, textiles, maritime, and medicine. Further research and advancements in the aspects of nanocapsules and lipid nanocapsules synthetization methods, materials selection, and bioactive compounds to be loaded into nanocapsules and lipid nanocapsules production are then required without abandoning the risk assessment and public safety of the drugs to consumers. These considerations are vital to gaining a better understanding of the mechanisms of biological interactions and particle engineering of nanocapsule and lipid nanocapsule production. Thus, scientists, researchers, and engineers should all work together to improve and make it easier to make a lot of nanoformulated drugs by controlling the size and physiochemical properties of the drugs at each step of the nanoformulation process.

***Ethics approval and consent to participate***

N/A (This study has no human or animal participants; therefore, no consent was required).

***Consent for publication***

The authors give the Publisher the Author's permission to publish the work.

***Data Availability***

All data generated for this study are included in the article.

## *Author's contribution*

**Nagib Elmarzugi**: Writing-original draft, investigation, supervision, visualization, and writing review & editing.

**Rokoya Amara**: Writing-original draft, investigation, visualization, and writing review & editing.

**Malak Eshmela**: Writing-original draft, investigation, visualization, and writing review & editing.

**Ahmad Eid**: Conceptualization, writing-original draft, data curation, investigation, supervision, methodology, validation, visualization, and writing review & editing.

***Competing Interests***

None.

**FUNDING**

None.

**ACKNOWLEDGMENTS**

None.

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