Drug delivery through nanocapsules: An overview

Jayanti Mukherjee, Shivani Khoware

Department of Pharmaceutical Chemistry, Shri Bherulal Pharmacy Institute, Indore

Corresponding author

Email: jayantispandan@gmail.com

Introduction

Nanocapsules, a characteristic class of nanoparticles, are made up of one or more active materials (core) and a protective matrix (shell)[1] in which the therapeutic substance may be confined. These have been developed as drug delivery systems for several drugs by different routes of administrations such as oral and parental by reducing the toxicity of drugs. Polymeric nanoparticles are named nanocapsules[2] when they contain a polymeric wall composed of non-ionic surfactants, macromolecules, phospholipids[3]and an oil core[4].

Current research practices employs nanotechnology approaches to improve the solubility, bioavailability and bio efficacyof active pharmaceutical ingredients (5). Nano phytomedicines prepared from active standardized extracts are used as forefficacy and bioavailability thus minimizing the side effects and toxicity of administered drugs(6). Polymeric nanoparticles are named nanocapsuleswhen they contain a polymeric wall composed of non-ionic surfactants, macromolecules, phospholipids (7-9) and an oil core(10). These are prepared mostly by two technologies: the interfacial polymerization and interfacial nano-deposition. The interest in research on magnetic nanocapsules has increased considerably because of their intermediate states between mass and atomic materials. These materials may present different magnetic behaviors from their corresponding counterparts. Researchers in China have succeeded in synthesizing a new type of inter-metallic nanocapsules that can be applied in cryogenic magnetic refrigerator devices (8). Some drugs find difficulty in marketing due to their unpleasant side effects. However, when they are placed inside the cavity of nanocapsule, they deliver drug directly to the target site in a reducible dosage (10,000 fold) and thus lead significantly to the

removal of any side effects or at least an appropriate acceptable level (11).Nanocapsules, holds the biomedical interest because they can be used, for the controlled release and targeting of drugs against the protection of enzymes, proteins, and foreign cells(12).The preparation of nanocapsules involving the organic phase constitutes solvent, polymer, oiland drug penetration into the pores of an ultrafiltration membrane via the filtrate side and then it is pressed. The aqueous phase containing water and surfactant circulates inside the membrane module, and removes the nano-capsules forming at the pore outlets.

METHOD OF PREPARATION

- **Solvent displacement method or interfacial deposition method**

Interfacial polymerization is an alternative to bulk polymerization of condensation polymers, which would require high temperatures[13]. It comprises of two immiscible solvents, in which monomer in one solvent instantaneously reacting with monomer of the other solvent or it may depend on the time scale. Higher molecular weights of monomers are obtained since it is more likely to stumble upon a growing chain than the opposing monomer. For instance, the nanocapsules can be formulated by using the aqueous core containing oligonucleotides of isobutylcyanoacrylate in a W/O emulsion. The resultant nanocapsules are then purified by ultracentrifugation followed by resuspending in water to yield a dispersion of aqueous core nanocapsules. Both solvent (organic phase) and non-solvent phases (aqueous phase) are used in the synthesis of nanocapsules. Solvent phase contains solvents (ethanol, acetone and hexane), polymers (natural or synthetic polymer), the drug molecule and oils. On the other hand, the non-solvent phase consisting of a non-solvent or a mixture of non-solvents for the polymers, supplemented with one or more naturally occurring or synthetic surfactants. The solvent is an organic medium, while the non-solvent is mainly water. In the solvent displacementmethod, the nanocapsules are obtained as a colloidal suspension formed when the organic phase is added slowly with continuous moderate stirring to the aqueous phase. In the Solvent displacement method, commonly used biodegradable polymers are poly-e-caprolactone (PCL)

- **Polymerisation method**

The monomers are polymerized in an aqueous solution to form nanocapsules followed by placing the drug either by dissolving in the medium of polymerization or by the adsorption of

nanocapsules. Ultracentrifugation method, which has been utilized for purifying the nanoparticle suspension, removes various stabilizers and surfactants employed for polymerization. The nanocapsules are then resuspended in an isotonic surfactant free medium for making polybutylcyanoacrylate or polyalkylcyanoacrylate nanoparticles [14].

- **Emulsion Polymerisation**

Pre-emulsion preparation for one of the nanocapsules (M-6) is provided as an example here [15]. The preemulsion was synthesized by blending two parts; Part I contained 40 g styrene, 0.8 g DVB (divinylbenzene), 0.82 g AIBN (2,2′- azobisisobutyronitrile) and 40 g Desmodur BL3175A; and Part II contained 1.71 g SDS (sodium dodecyl sulfate), 1.63 g Igepal CO-887, and 220 g water. Parts I and II were magnetically blended in separate containers for 10 minutes. Part II was then added to Part I under mechanical agitation and the contents were stirred at 1,800 rpm for 30 minutes. The resulting preemulsion was cooled to <5°C before sonication using a Misonixsonicator 3000 (until a particle size <250 nm was achieved). The pre-emulsion was transferred to a three-necked round bottom flask, which was equipped with a mechanical stirrer, reflux condenser, and a nitrogen inlet, and degassed for 30 minutes. The temperature was increased to 70°C and preserved for 8 hours to complete the polymerization.

- **Miscellaneous methods of Preparation**

Other preparation methods for nanocapsules include electron irradiation deposition, chemical vapor deposition [16], laser vaporization-condensation [17], charge transferring [18], organic reagent assisted method [19], solution-liquid-solid method and catalytic vapor-liquid-solid growth [20].

Characterization of nanocapsules

- ✓ **Particle size**

Particle size and size distribution plays a crucial role in nanocapsule systems and it establishes the *in vivo* distribution, bioavailability, toxicity and the targeting capacity of nanoparticulate systems. It also quite often influences the capacity of drug loading, drug release and the stability of nanoparticulate systems. Depending on the particle size, the effect of releasing dosage and the time lapse of pharmacological action forms the basis. The smaller particles have greater surface

area; therefore, most of the therapeutic agents associated at or near to the surface particle, lead to instant drug release, whereas, the larger particles having the large core surfaces gradually diffuse out (21). Particle size can also affect the polymer degradation. For example, the rate of poly (D, L-lactide-co-glycolide) (PLGA) polymer degradation revealed an enhancement with an increase in particle size *in vitro* (21). Photoncorrelation spectroscopy or dynamic light scattering are used to determine the particle size (23).

- ✓ **Scanning Electron Microscopy (SEM)**

The architecture of the hierarchical branching aggregates, characterized from nanocapsules, may be of flocculent structure, small clusters, big clusters and big branches step by step at different scales, which confirms the self-similar attributes of the structure (24). It is characterized by a scanning electron microscope (SEM) which shows at a high magnification the clear morphology of small clusters. The clusters are composed of flocculent structure formed by the small particles adhered together (25). A low-magnification SEM image may reveal the coral-like architecture that contains hierarchical branching characteristics along the axial and lengthwise directions.

- ✓ **Differential Scanning Calorimetry (DSC)**

DSC analysis is conducted in both open samples (no lid) and closed samples (pan capped possessing a small hole in the center). Both methods have similar thermal behavior as per the observations reported (26).

- ✓ **Transmission Electron Microscopy (TEM)**

TEM is a microscopic technique in which a beam of electrons is transmitted through an ultra-thin specimen, interacting with the specimen as it passes through. An image is formed from the interaction of the electrons transmitted through the specimen; the image is magnified and focused onto an imaging device. TEM forms a major analysis method in a range of scientific fields, in both physical and biological sciences. TEM finds application in cancer research, virology, materials science as well as pollution, nanotechnology and semiconductor research (27, 28).

- ✓ **X-Ray Photoelectron Spectroscopy (XPS)**

X-ray photoelectron spectroscopy measurements are performed with a monochromatic X-ray source (an aluminium Kα line of 1486.6 eV energy and 150 W) to describe the valency of surface aluminium atoms present on the nanocapsules at a depth of 1.6 nm. The XPS technique is highly specific to the solid surface due to the narrow range of photoelectrons that are excited.

The excited energy of the photoelectrons emitting from the sample is determined by using a concentric hemispherical analyzer (CHA) which demonstrates a spectrum with a serial levels of the photoelectron peaks. The binding energies of the peaks are characteristic to each element. The peak areas are utilized (with equivalent sensitivity factors) to demon-strate the composition of the surface materials. The shape of each peak and binding energy can be slightly varied by the emitting atom of chemical state. XPS technique provides the chemical bonding information as well (29).

- ✓ **FT-IR analysis**

The presence of characteristic peaks is confirmed by using the FTIR analysis. It is used to determine the nature of associated functional groups and structural features. The calculated spectra clearly reflect the characteristic functional groups of compound (30,31).

Evaluation of nanocapsules

- **Determination of the pH of nanocapsule**

Nanocapsules formulation pH used to be measured using a digital pH meter at room temperature. Nanocapsules dispersion pH values fall within a range of 3.0-7.5.

- **Determination of drug content**

Drug content is determined by dissolving accurately weighed prepared nanocapsules in a suitable organic solvent. Appropriate quantity of sample was then subjected to the UV Spectrophotometer or through HPLC at the maximum wavelength of the compound. The absorbance for each sample has to be measured thereafter and compared with the standard.

- **In-vitro drug release**

In vitro dissolution studies is carried out using Franz diffusion cell. The study was carried out in 100 ml of phosphate buffer (pH 7.4). The nanocapsule formulationhas to be placed in dialysis membrane and dipped in dissolution medium needs to maintain thermostatically at 37 ± 0.5^{0}C. The stirring rate is maintained at 100 rpm. At predetermined time intervals 5ml of sample should be withdrawn and assessed for drug release spectrophotometrically. After each withdrawal 5 ml of fresh dissolution medium has to be added to diffusion cell.

- **Determination of particle size (PS) and polydispersion index(PDI)**

PS distribution and PDI are determined by the laser light scattering technique at a 90°fixed angle at a temperature of 25°C using a Zetasizer Nano Series (Malvern, UK). The dispersions were diluted in Milli-Qwater, according to the volume frequency histogram. All measurements are required to perform in triplicate.

- **Determination of zeta potential (z)**

Zeta potentialis estimated for all the systems prepared using a Zetasizer Nano Series (Malvern, UK) after appropriatedilution in Milli-Q water. Measurementswere made at 25 C in triplicate.

- **Morphological studies**

NCs samples were separated from the external phase by three ultracentrifugations (at 45,000g for 30 min) in order to eliminateexcess stabilizer. A droplet of this concentrated suspension wasspread on a glass surface and dried. Finally, the dried samples weremounted on stubs and shadowed in a cathodic evaporator witha gold layer (w20 nm) using a JFC-1100 Sputter Coater (JEOL, Tokyo,Japan), and were then observed under a low vacuum scanningelectron (LV-, JSM 5600 LV) with a resolution of5 nm. The NCs micrographs were obtained with equipment settings of 20 kV electron acceleration voltage and a pressure of 12e20 Pa inthe specimen.

Applications of nanocapsules

The nanocapsules are found to be suitable for various applications (Table 1). Due to the micronized size, they have a wide range of applications and high reproducibility, which can be used significantly in life-science applications. They have the potential applications in various fields like agrochemicals, cosmetics products, genetic engineering techniques, wastewater treatments, cleaning products, and componential adhesive applications. They also find applicability in encapsulating the enzymes, organic or inorganic catalysts, oils, adhesives, surface polymers, inorganic micro-particles and nano-particles, latex particles, or even biological cells.

Table 1: Applications of nanocapsules in the arena of medicines

Applications	Drugs	Mode of Preparation
Agrochemicals	Abamectin-nanocapsules Cypermethrin nanocapsules Pyrethrum Nanocapsules	Emulsion polymerization Microemulsion polymerization
Anti-inflammatory drugs	Diclofenac sodium Indomethacin loaded nanocapsules	Sol-gel method Interfacial polymerization
Antiseptics	Monodisperse polymer nanocapsule	Interfacial polymerization
Cosmetics	Hinokitiol-loaded poly (epsilon-caprolactone) nanocapsules	Emulsion-diffusion method
Diabetes	Insulin loaded Biodegradable poly (isobutyl-cyanoacrylate) nanocapsules	Interfacial polymerization
Nanocapsules for cancer	Artemisinin Camptothecin (CPT) and doxorubicin Cisplatin Indomethacin-loaded polyisobutylcyanoacrylatenanocapsules Lipid nanocapsules loaded with	Nanoencapsulation method Sol-gel method Repeated freezing and thawing of a concentrated solution of Cisplatin in the presence of negatively charged phospholipids. nterfacial polymerization Phase-inversion process

	Rhenium-188 (LNC188Re-SSS) .	
Nanocapsule for Topical use	Chlorhexidine	Interfacial Polymerization method

- **Nanocapsules for drug delivery**

Nanocapsules, which measure 1 thousandth of a milli-meter, can be coated with an antibody on the surface, which assists in directing them from the blood stream to an induced tumor. After reaching to the tumor, an instant blast occurs that makes the capsules to open up and discharge their therapeutic contents. On the surface of the polymer, there are tiny gold particles in the range of 6 nm i.e. 6 millionth of a millimeter which stick across and are specific to the laser light and lead the capsules to position their drug load capacity at the desired time. The rupturing of the capsule can be seen when near infrared light hits the gold spots and they melt instantaneously without harming the content.

- **Nanocapsules for oral delivery of peptides and proteins**

Nanocapsules are used as carriers for oral administration of peptides and proteins, particularly biodegradable poly (isobutylcyanoacrylate) nanocapsules (32,33). However, the development of suitable carriers remains as a challenging technique due to the characteristic bioavailability of these molecules. They are restricted due to the gastrointestinal barriers of the epithelium and by their degradation of digestive enzymes. By the technique of encapsulation which provides the bioactive molecules from enzymatic and hydrolytic degradation e.g., the loaded insulin nano-particles, the impact has been observed in diabetic rats following the oral administration (34). The nanocapsules are suitable for the entrapment of bio-active peptides.

- **Treatment of hormone dependent breast cancer**

The study(35) shows that specific siRNAs encapsulated in nanocapsules can be used to target estrogen receptor alpha (ERα). The intravenous injection of these nanocapsules into estradiolstimulated MCF-7 cell xenografts led to a significant decrease in tumor growth and a

decrease in ERα expression in tumor cells. This indicates that a novel strategy, based on ERα−siRNA delivery, could be developed for the treatment of hormone dependent breast cancers.

- **Nanocapsules for self-healing materials**

Damages in the materials of coating of the polymer, components of adhesives, and microelectronics, as well as structural composites can span longer durations (36). The new method of self-healing has been achieved using polymer microcapsules that contain the healing agent. It also possesses adequate strength, longer shelf life, and excellent binding to the host material. Nanocapsules with functionalized surface areas and their walls with the possibility of forming and taking nano-meter sized objects, have become popular to forward future with miniaturized tool leading completely to novel therapeutic applications in the research of medicine and technology.

- **Nuclear nanocapsules treatment for cancer by using radioactive materials**

The radioactive compound Astatine, like radium and uranium, emit high velocity alpha particles by the procedure of radioactive decay, which is about 4,000 times faster than the beta decay of the emitted electrons, and is most commonly used to treat cancer. The unique combination of the low penetrating power as well as large particle size make the alpha particle unique for targeting tumor at the single cellular level (37).

- **Sun screen cosmetics comprising TiO_2 nanocapsules**

A UV blocking cosmetic product containing TiO2 nano capsule, which is produced by dispersing TiO2 with surfactant, is provided to improve the stability and UV protection effect without any harm to the body. The oleophilic surface treatment is performed with surface treating agent containing isostearic acid or aluminum stearate.

Conclusion

This paper has reviewed recent knowledge and built a data base of nanocapsules. Our review highlights on an overview of nanocapsules based upon the types, synthesis, characterization

methods and wide range of applications. Our study concludes that nanocapsules have tremendous growth in recent years. Upcoming projects of nanotechnology offering cost effectiveness, natural and eco-friendly means are yet to usher on large scale.

Conflict of Interest

There is no conflict of interest in publishing this article.

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