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NANOCAPSULE: THE WEAPONS FOR NOVEL DRUG DELIVERY SYSTEM

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***Abstract*:** Nanocapsule is defined as nanovascular system with a core-shell structure consisting of polymer membrane or coating and the target drug or food formulation is added within the cavity. Drug-filled polymeric nanocapsules have showed possible applications in the drug delivery systems. They have attracted great interest, due to the protective coating, which are usually pyrophoric and easily oxidized and delay the release of active ingredients. Nanocapsules have many uses, including promising medical applications for drug delivery, food enhancement, nutraceuticals, and for self-healing materials.

Introduction: A nanocapsule consists of shell and a space in which desired substances may be placed. Nanocapsules have more diagnostic and therapeutic potential and thus have demonstrated neuroprotective potential in vitro. Nano capsules having various advantages and disadvantages. Preparation of the nanocapsules are used as a two types of polymers 1) Natural polymers 2) Synthetic polymers.

Nanocapsules, as main class of nanoparticles, are made up of one or more active materials (core) and a protective matrix (shell)in which the therapeutic substance may be confined. Nanocapsules mainly developed as drug delivery systems for several drugs by different routes of administrations such as oral and parental. Reduce the toxicity of drugs. Polymeric nanoparticles are termed as nanocapsules when they contain a polymeric wall composed of non-ionic surfactants, macromolecules, phospholipids and an oil core.

Current Status of Nanocapsules: Materials and Formulation Techniques:

Common Materials for Preparing Polymeric Nanocapsules:

1. **Polymeric Shell:**

Shell materials play a important role in the development of polymeric nanocapsules to load, protect and release bioactive substances. The properties of polymers exert special influence on the stability, encapsulation efficiency, release profile and biodistribution of the nanocapsule as drug delivery system. Biocompatible polymeric materials have been extensively considered as appropriate candidates for nanocapsules development. In most cases, polymers should be biodegradable for the payload-releasing and elimination of nanoparticles. The Non-biodegradable, but biocompatible polymers such as polyethylene glycol (PEG), polyvinyl alcohol (PVA) have also been widely used to contribute to the fabrication of nanoparticles. They can assist drug release through diffusion, due to their hydrophilicity. Additionally, they could be cleared from blood via the reticuloendothelial system, eventually—despite not being degraded in smaller molecules.

Polysaccharides—one of the most important categories of natural polymeric materials—have been broadly used as drug carriers, profiting from biocompatibility, gelation conditions and mucoadhesive properties. Generally, polysaccharides are rich in deprotonated amino groups or carboxylic acid groups, resulting in cationic or anionic charges, to form the polymeric shell by electrostatic attractive interactions.

Chitosan, one of common natural polymers has been broadly used as drug carrier profiting from the biocompatibility, endogenous metabolizable degradable productions, gelation conditions and mucoadhesive properties. Nanocapsules formed or covered by chitosan can process a cationic surface charge benefiting from the rich amino groups of chitosan. The cationic surface can make the interaction between nanoparticles and the bacteria which process negative surface through electrostatic interactions

Alginate is one of the anionic natural polysaccharides which has been developed as drug carrier, taking advantages of its biocompatibility, low immunogenicity and mild gelation conditions. In addition to these well-known advantages, alginate is also a pH-responsive polymer, which can provide effective protection for payloads at acidic pH conditions, while achieving drug release at alkaline pH environment.

As a biocompatible and biodegradable polyanionic polymer, dextran sulfate has been widely used in pharmaceutical field in drug delivery application.

Moreover, common polysaccharides stated above, poly(cyclodextrin) , heparin hyaluronan and also other polysaccharides have been used to prepare nanocapsules as drug carrier for different pharmaceutic applications.

Protein-based polymers, as another kind of natural macromolecules, have been processed as polymeric shell for nanocapsules, due to their biocompatibility and tunable properties. Albumin is a water soluble and biodegradable protein which shows critical role in the circulating system. Human serum albumin has served as shell for nanocapsules. Besides controlling drug permeation rate, albumin corona can reduce the immunogenicity of nanoparticles and thus assist them to escape from the reorganization of reticuloendothelial system.

Moreover, poly (ethylene glycol) (PEG), a biocompatible hydrophilic synthesized polymer, has been widely used as polymeric coating for nanocapsules. PEGylation can be achieved either via self-assemble nanocapsule formulation by amphiphilic PEG copolymer such PLGA-PEG copolymer, or PEG coated after nanocapsules formed.

2. **Liquid/Solid/Hollow Core:-**

The core of nanocapsules may be hollow or consists in a liquid or solid phase, thus making it able to carry different drugs. Nanocapsules can present an oleic core highly suitable for the encapsulation of lipophilic molecules. Concerning the oily core, vegetable oil (such as soybean or palm oil) or fatty acids (such as medium chain triglycerides) are the optimal composition oleic phase for nanocapsules fabrication, because of its capacity to dissolve lipophilic drugs and the safety of oil phase.

Copaiba oil has been used as oily core of a PCL [Poly(ε-caprolactone)] nanocapsule in order to increase the solubility of imiquimod which is used as hydrophobic anti-cancer drug. Meanwhile, copaiba oil is mainly used for treatments of neoplastic melanoma, micropapillary carcinoma and also works as anti-inflammatory and analgesia.

Polymeric nanocapsules can also be manufactured by using aqueous core to act as good platform for sustained delivery of hydrophilic molecules. Hydrophilic anti-cancer drugs, such as gemcitabine hydrochloride and doxorubicin, have been successfully encapsulated into polymeric nanocapsules with aqueous core

METHOD OF PREPARATION

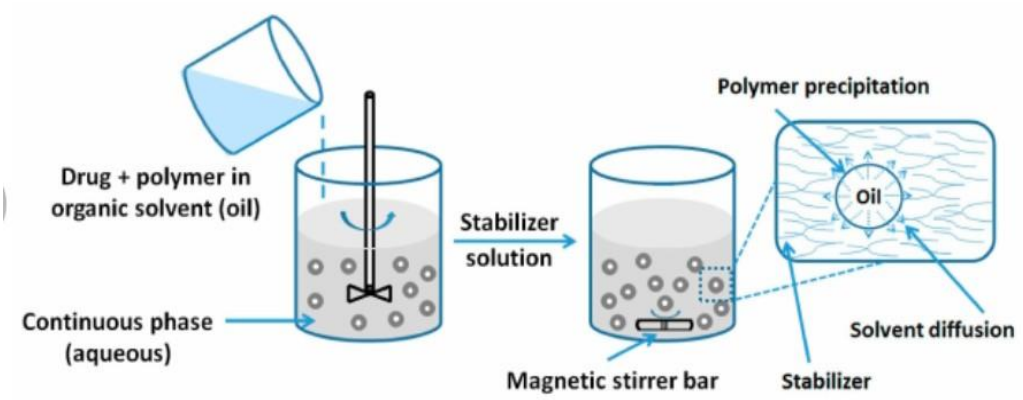
- **Solvent displacement method or interfacial deposition method:**

Interfacial deposition method, as well as nanoprecipitation, was widely used to fabricate nanocapsules. The method was first mentioned by Fessi et al. in 1989. Interfacial polymerization is an another term to bulk polymerization of condensation polymers, which would require high temperatures. 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.

Film formed polymeric substance can be dissolved in organic or water phase as per the property of the polymer. One or more surfactants could be added to increase the nanocapsules stability. The water suspension of formed nanocapsules is obtained by removing organic solvent through diffusion or evaporation.

The nanocapsules properties can be mainly influenced by polymer concentration, injection method of organic phase, volume ratio between organic and aqueous phase and also nature of materials. The interfacial deposition method has been used completely in the last decade, due to the simple operation without applied other high energy force and extensive applicability for various payloads.

A. Emulsion–diffusion/Evaporation Method:
One of the common methods for formulating polymeric nanocapsules via nanoemulsion is the emulsion–diffusion/evaporation method. It is based on emulsification of the organic phase into an inorganic phase and subsequent elimination of the organic solvent by diffusion into the external phase or evaporation. Nanocapsules are formed by a combination of polymer precipitation and interfacial phenomena during the diffusion—or an evaporation procedure. The polymers that can be used to formulate polymeric nanocapsules by emulsion–diffusion method must possess good solubility in an organic solvent, well miscible with water, such as acetone, ethanol or ethyl acetate, thereby, removing the organic solvent by diffusion into water. The nanocapsules were formed by using acetone and methanol in organic phase, and subsequently purifying by diffusion into the water phase; the hydrophobic amphotericin B was successfully encapsulated with an excellent encapsulation efficiency of 99.2 ± 1.3%. Moreover, nonpolar solvents such as chloroform or dichloromethane—which are immiscible with water—may be used in the organic phase in the emulsion–evaporation method.



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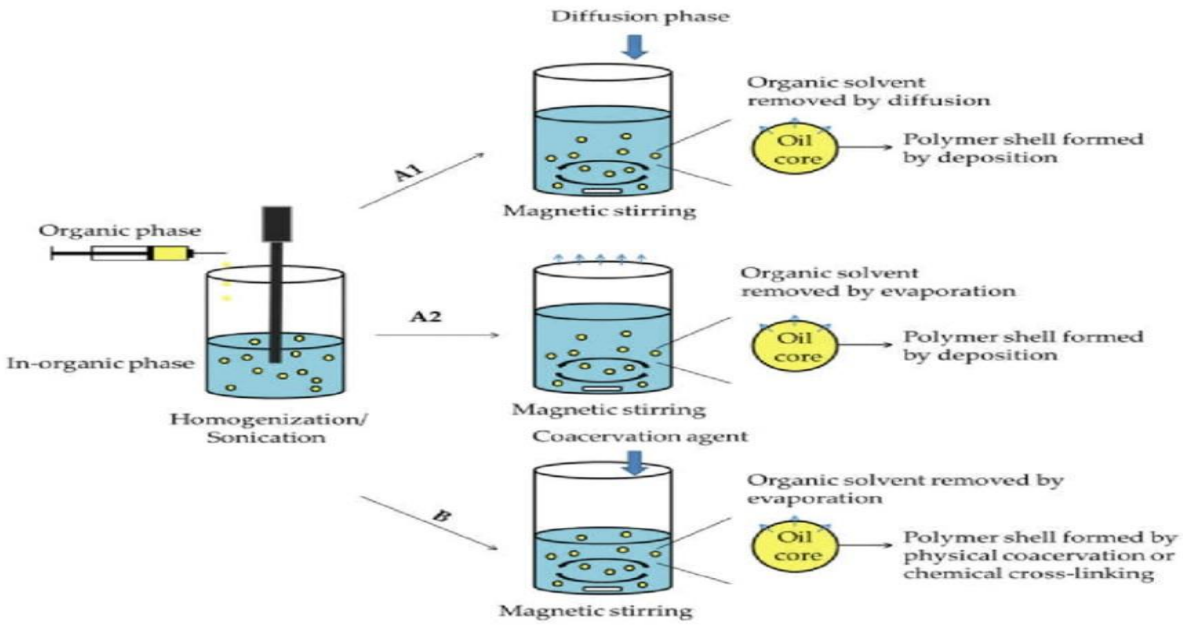
B. Emulsion–coacervation Method:

Emulsion–coacervation process is also based on nanoemulsion as template for nanocapsule formulation. However, compared with emulsion–diffusion/evaporation method, the different is the polymeric shell is formed and stabilized by either physical coacervation or chemical cross-linking. The emulsion–coacervation methods are principally used for polyelectrolyte materials or monomer/polymer possessing cross-linking function groups for nanocapsules fabrication. Electrostatic interaction as a physical coacervation strategy has been used to prepare a polyelectrolyte nanocapsules for encapsulation of brinzolamide to treat glaucoma. A cross-linked starch nanocapsules with aqueous core was developed as delivery system for hydrophilic dye by interfacial polymerization carried out using water in oil (W/O) mini-emulsion method. It indicates that with higher concentration of cross-linker, the nanocapsules can form a thinker polymeric shell to minimize the leakage of hydrophilic payload to the aqueous phase. Typically, an amphiphilic copolymer based on same monomer further used for polymeric shell was synthesized to act as template core and also stabilizer for nanoemulsion preparation. A random copolymer consisting of butyl acrylate and acrylic acid was pre-synthesized as macroRAFT agent. N,N-(dimethylamino)ethyl methacrylate or tertiary butyl methacrylate with methyl methacrylate were used to preform nanocapsules. The hollow core was obtained by hydrolysis of trifluoroacetic acid. The nanocapsules showed a rapid drug release at pH 6.5 responding to the pH sensitive property of the polymer.



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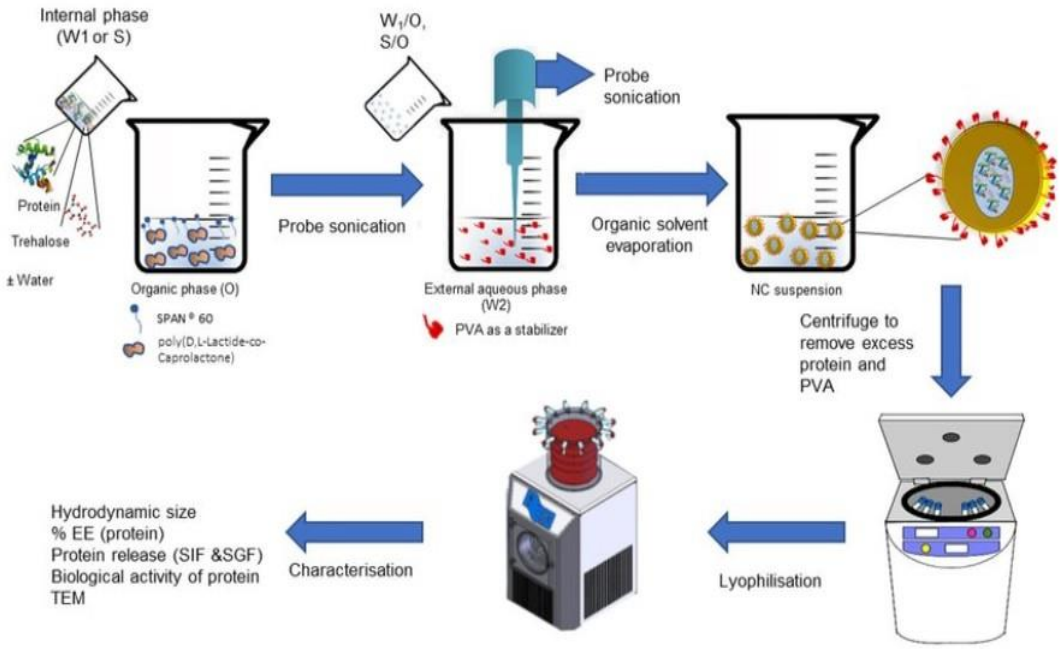
C. Double Emulsion Method:

Based on the principle of emulsion diffusion/evaporation and coacervation method, resulting nanoemulsion can be continually emulsified into the third phase to perform emulsions of emulsions, as well as double emulsion method. Double emulsions are categorised into two major classes, water in oil in water (W/O/W) and oil in water in oil (O/W/O) according to the phase sequence. The principle of double emulsion methods is choosing suitable surfactants to give a good stability

between the interfaces of both internal and external emulsion. Erdmann et al. Developed a poly(alkyl cyanoacrylate)-based nanocapsule by this method.

The shell was formed by interfacial polymerization of n-butyl cyanoacrylate and propargyl cyanoacrylate. W/O/W double emulsion has been mostly applied for development of nanocapsules containing aqueous core, which is beneficial to encapsulation and sustained release of hydrophilic drugs. Two anticancer drugs hydrophilic doxorubicin and hydrophobic paclitaxel were encapsulated into a poly(methacrylic acid)/polyvinyl alcohol-based nanocapsules to improve cancer therapy. Both of the hydrophilic and hydrophobic payloads achieved excellent encapsulation efficiency about 72% and 91%, respectively. Similar result was achieved by Balan. That doxorubicin and magnetite were incorporated into the nanocapsules simultaneously by double emulsion methods.



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CHARACTERIZATION OF NANOCAPSULES:

1. Particle Size: The smaller particles have greater surface area; so, most of the therapeutic agents associated at or near to the surface particle, begins instant drug release, whereas, the larger particles having the large core surfaces gradually diffuse out . The size of nanocapsules ranges between 5 to 1000 nm, but generally they are 100–500 nm. It is a submicroscopic colloidal drug carrier system. Nanocapsules can be made by using natural or synthetic polymers.
2. Determination of the pH of Nanocapsule :- Nanocapsules formulation pH was measured using a digital pH meter at room temperature. Nano capsules dispersion pH values ranges between 3.0-7.5.
3. Determination Of drug Content:-**D**rug content was find out by dissolving 1ml of prepared nanocapsules in 20ml acetonitrile. Suitable quantity of sample was then subjected to the UV Spectrophotometer at 232nm. The absorbance for each sample was measured and compared with the standard values.
4. Structural characterization:-**S**tructural characterization can be done by using field emission scanning electron microscopy (FE-SEM) and transmission electron microscopy (TEM) to determine the various elements like shape, size and surface morphology. Micrographs of the nano capsules were obtained using a Phillips Cm 200 operated at 20-200 kv while the Fe-SEM was carried out using Hitachi S-4800 FE-SEM equipped with energy dispersion spectrometer (EDS)
5. In-vitro drug release:- In vitro dissolution studies were carried out using USP type 11 dissolution apparatus. The study was carried out in 100 ml of buffer (pH-30). The Nano capsules suspension was placed in dialysis membrane and dipped in dissolution medium which was kept inert thermostatically at 37±0.50C. The stirring rate was maintained at 100 rpm. At predetermined time intervals 5ml of sample were withdrawn and assessed for drug release spectrophoto metrically. After each withdrawal 5 ml of fresh dissolution medium was added to dissolution jar.

APPLICATIONS

Nanocapsules, which measure 1/1000 of mm, can be coated with an antibody on the surface, which assists in directing them from the blood stream to induced tumor. At the site of tumor, an instant blast occurs that makes the capsules to open up and discharge its 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 have a impact in drug delivery such as controlled release and targeting of drugs for the protection of enzymes, proteins, and foreign cells. The drugs find difficulty in marketing due to their undesirable side effects, so they are placed inside the core of the nanocapsule which delivers the drug directly to the target site. The increased delivery of bioactive molecules through the targeted delivery utilizing a nanocapsule provides various difficult challenges and opportunities for the research and future development of novel improved therapies. Alginate-based polymeric nanocapsules are prepared by loading curcumin to make it more bioavailable to overcome problems like poor bioavailability, low solubility, and low permeability. It is a natural polyphenolic compound having antiinflammatory, chemotherapeutic, and antioxidant properties.

Lipid nanocapsules can be thought of as a cross between liposomes and nanoemulsion particles. The external wall of Liquid nanocapsule is thicker over a conventional nanoemulsion particle permitting functionalization and more controlled delivery. LNCs are made up of a liquid, oily core (such as medium-chain triglycerides) bordered by hydrophilic and also lipophilic surfactants. They were patented in 2001 for therapeutic uses, and an effective, solvent-free phase-inversion technique for their synthesis has been developed. Stealth LNCs also have been prepared utilizing Polyethylene glycol for improving circulation time. Furthermore, LNCs have been working for delivery of therapeutic compounds as well as radionuclides across the Blood brain barrier through attachment of antibodies or antibody fragments. LNCs have been used for delivery of various anticancer drugs (paclitaxel, docetaxel, etoposide, hydroxytamoxifen, doxorubicin, etc.), which are released according to a sustained design. Similarly, David et al. developed a platform of siRNA LNCs by using different cationic lipids, combining the properties of LNCs (siRNA protection and targeting) and lipoplexes (efficient siRNA delivery into the cell). These novel siRNA LNCs is a size of 55 nm with a neutral surface charge and siRNA encapsulation efficiencies up to 65% representing appropriate characteristics for systemic administration. Groo et al. carried out investigation using encapsulated paclitaxel in various LNC formulations to compare their pharmacokinetic and efficacy on a subcutaneous isograft model in rats. This investigation spotlights the significance of efficacy studies along with pharmacokinetic studies for nanomedicines on resistant tumor.

Conclusion:

Nanocapsules have great diagnostic and therapeutic potential and so they have demonstrated neuroprotective potential in vitro. Nanocapsules are addition to the methodological development for formulation by various methods, mainly the interfacial polymerization and interfacial nano-deposition. Nanocapsules also have the significant applications in various fields of the agrochemicals, wastewater management, genetic engineering, cosmetics, cleaning products, and also in adhesive component. They are also used in encapsulation of enzymes, adhesives, catalysts, polymers, oils, inorganic micro and nanoparticles, latex particles, and even the biological cells.

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