Review Article

Nanocapsule

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ABSTRACT

Nanocapsules are vesicular system in which the drug is confined to a cavity consisting of an inner liquid core surrounded by a polymeric membrane. Nanotechnology is the science of small. Nano derives from Greek word "Nano" which means 'dwarf size'. Nanocapsules having various advantages and disadvantages. Preparation of nanocapsules can be used as a two types of polymers 1) Natural polymers 2) Synthetic polymers. Nanocapsules are prepared by different methods those are a) Solvent evaporation b) Nano precipitation c) Solvent Diffusion d) Salting out e) Dialysis f) Supercritical fluid technology. Dispersed polymer nanocapsules can be used as Nano sized drug carriers to get controlled release as well as efficient drug targeting. Nanocapsules existing in miniscule size range from 10 nm to 100 nm.

Keywords: Nano-scale, Nanocapsules, Encapsulation, Bioavailability, Controlled release, Drug targeting etc.

INTRODUCTION

Nanotechnology derived from the Greek word "Nano" which means the very small. It comprises Nano technological development on the nanometer scale, usually 0.1 to 100nm. Nano materials have found many important applications in biomedical, pharmaceutical, electronic and molecular diagnostic fields. Nano capsules are vesicular systems in which the drug is confined to a cavity consisting of an inner liquid core surrounded by a polymeric membrane.[1] Nanotechnology is the study of small particles. A Nanocapsule is a Nanoparticle that is spherical, hollow structure with a diameter less than 200nm in which desired substance may be placed. They can be filled with a solvent, either polar or non- polar.[2]

Nanocapsules can be different from other Nanoparticles because they have well defined core and shell, whereas the latter do not. When it is made from polymers, Nanocapsules can be referred as hollow polymer nanostructures.[3] Technologies for microencapsulating materials have been around for several years, primarily for applications involving minimization of hygroscopic and chemical interactions, elimination of the oxidation, and controlled release of nutraceuticals. Preparation of Nano capsules can be used as a two types of polymers: [1]

Natural polymers and Synthetic polymers. Polymers are large molecules composed of repeated chemical units. The smallest repeating unit is called a mer. The term polymer is derived from the Greek words *poly* and *mers* meaning "many parts."[4]

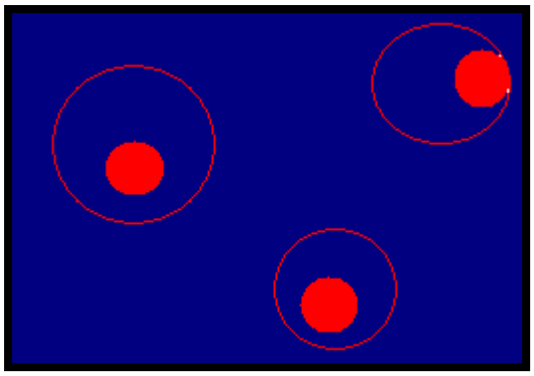

Figure 1: Nanocapsules

1) Natural polymer:

Proteins, enzymes, muscle fibers, polysaccharides and gummy exudates are the natural polymer being used effectively in formulating the variety of pharmaceutical products. The well-known natural polymer used in pharmacy and other fields are chitosan[5], carrageenan[6], is paghula[7], acacia[8], agar[9], gelatin[10], shellac, guar gum and gum karaya.[11] These natural polymers are widely used in pharmaceutical industry as emulsifying agent, adjuvant and adhesive in packaging; and also, well suited for pharmaceutical and cosmetic product development. Alginic acid [6] is a natural polymer composed of beta-1, 4-linked-D-Mannuronic acid and alpha-1, 4-linked L-guluronic acid molecules and is obtained by alkali treatment of seaweeds. It serves as an excellent extra granular disintegrant when it is added before compression.[12]

2) Synthetic polymer:

Synthetic polymers are the human-made polymers. From the utility point of view they can be divided into four main categories:thermoplastics, thermosets, elastomers and

synthetic fibers. They are found commonly in a variety of the consumer products such as money, super glue, etc. A wide variety of synthetic polymers are available with variations in main chain and side chains. The back bones of common synthetic polymers such as polythene, polystyrene and poly acrylates are made up of carbon-carbon bonds, whereas hetero chain polymers such as polyamides, polyesters, polyurethanes, polysulfides and polycarbonates have other elements (e.g. oxygen, sulfur, nitrogen) inserted along the backbone. Also silicon forms same materials without the need of carbon atoms, such as silicones through siloxane linkages; these compounds are thus said to be an inorganic polymers. Coordination polymers may contain a range of metals in the backbone, with non-covalent bonding present.

Some familiar household synthetic polymers contains: Nylons in textiles and fabrics, Teflon in non-stick pans, Bakelite for electrical switches, polyvinyl chloride (PVC) in pipes, etc. The common PET bottles are made of synthetic polymer, polyethylene terephthalate. The plastic kits and covers are mainly made of synthetic polymers like polythene and tires are manufactured from Buna rubbers.[13] However, due to the environmental issues created by these synthetic polymers which are the mostly non-biodegradable and often synthesized from petroleum, alternatives like bioplastics are also being considered. They are however expensive when compared to the synthetic polymers. [14, 15]

THE PROPERTIES OF POLYMERIC NANOCAPSULES

1. Polymeric nanocapsules can be made in the specific sizes, shapes, and in reasonable quantities.

2. Nanocapsules can be made to function in different ways.

3. They can be produced like monodisperse particles with exactly defined biochemical, electrical, optical, and magnetic properties.

4.They can be tailored to suit the complexity of whatever application they are intended for, such causing the release of the contents in response to the particular bimolecular triggering mechanism in targeted drug-delivery systems.[2]

TECHNIQUES OF PREPARATION

Nano capsules are prepared by various methods those are a) Solvent evaporation b) Nano precipitation c) emulsification/Solvent diffusion d) Salting out e) Dialysis f) Super critical fluid technology. [1]

The appropriate method for the preparation of nanoparticles depends on the characteristics of polymer and the drug that is to be used in the Nano preparations therefore in order to achieve the properties of interest the mode of preparation plays a vital role. Different techniques employed in preparation[16-19] and synthesis of nanoparticles is divided below:

Solvent evaporation

Solvent evaporation (**Figure no. 2**) was the first method that developed for the preparation of nanoparticles, in this technique the polymer solutions [20] were prepared in the volatile solvents and emulsions [21] were formulated by employing dichloromethane and chloroform, but now it is replaced with ethyl acetate that is shows a much better toxicological profile to obtain polymeric particles less than 500 nm in size. During the preparation, emulsion is converted into the nanoparticle suspension on evaporation of the solvent, after that the solution is allowed to diffuse through the continuous phase of the emulsion to carry out conventional mode of methods i.e. single emulsions e.g., oil-in-water (o/w) and double emulsions[21] e.g., (water-in-oil)-in-water, (w/o)/w. Such type of methods utilize high-speed homogenization or ultrasonication, followed by the evaporation of solvent [22-23], either by continuous magnetic stirring at room temperature or under reduced pressure resulting in the formation of solidified Nanosized particle collected by ultracentrifugation followed by washing to remove surfactants and at last the product is lyophilized.

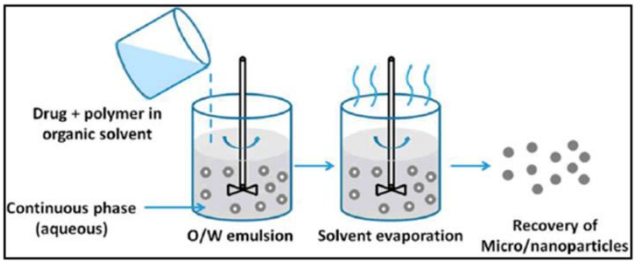

Figure 2: Solvent Evaporation

Single emulsion and Double emulsion has been widely used for the pharmaceutical applications [24] to obtain clinically applicable drug delivery systems, encapsulation of various hydrophilic and hydrophobic anticancer drugs, anti-inflammatory drugs, antibiotic drugs, proteins and amino acids and their applications in theranostics. In solvent evaporation technique[25], efforts are being made in clinics to develop more specific, individualized therapies for different diseases, and to combine diagnostic and therapeutic capabilities into a single agent.

Nano-precipitation

Nano-precipitation (**Figure no. 3**) is a facile, mild, and low energy input process to carry out polymeric nanoparticles synthesis [26] which is also termed as solvent displacement[27-28] method. The process of preparing involves preformed polymer of organic solution (acetone, ethanol, or methanol) and then in the presence or absence of surfactant[29] the organic solvent is allowed to diffuse generally using polymer Poly-Lactic Acid (PLA).

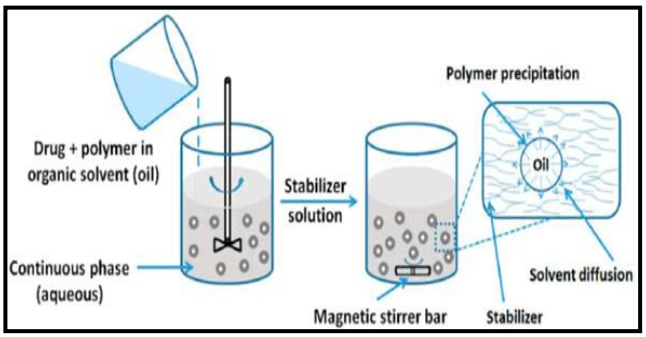

Figure 3: Nano-precipitation

The polymer PLA of intermediate polarity is allowed to dissolved in a water-miscible solvent, resulting in formation of Nanospheres [30-31] and the solution is injected into an aqueous solution containing stabilizer as a surfactant as to result the formation of nanoparticles due to interaction between the water and the organic solvent. The nanoparticles synthesized through the process are of submicron size (<210 nm) with of low polydispersity. Biodegradable Nano-carriers [32-36] such as lipid or polymer based nanoparticles that were designed to enhance the efficacy of nanoparticles and reduce the toxic effects of drugs [37] that results from therapeutic delivery of drugs for treatment of diseases. The Nano-precipitation, without using surfactant of hydrophobic compounds in a non-solvent solutions leads to scattering of nanoparticles with effect of Nanosized particles and such process is termed as "Ouzo" effect.

Emulsification Diffusion

Emulsification or solvent diffusion (ESD) technique (**Figure no.4**) is the modification of solvent evaporation method which utilizes water miscible solvent [38-41] and a small amount of water immiscible organic solvent due to the spontaneous diffusion of immiscible solvents that generate turbulence [42] between the two phases results the formation of Nanosized particles. The formation of nanoparticles depends only on the diffusion of the solvent of the dispersed phase [43-44] and the formation of nanospheres or nanocapsules [45], according to the oil-to-polymer ratio in which an aqueous solution containing stabilizer [46] successfully leads to solvent diffusion to the external phase[47] of the solution for nanoparticle formation.

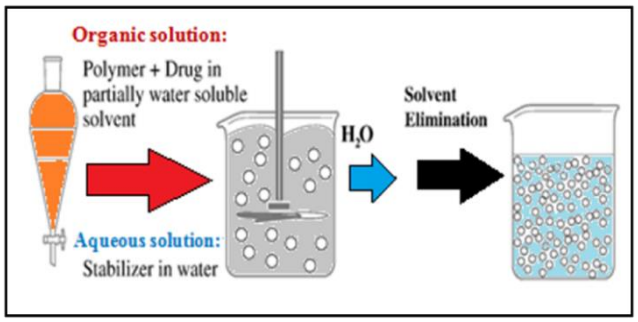

Figure 4: Emulsification Diffusion

ESD presents many advantages such as high encapsulation efficiencies [48,] no homogenization required, high batch-to-batch reproducibility [49] ease of scale-up, simplicity, narrow size distribution.[50-51] As drug loaded nanoparticles can be prepared by ESD technique [52] thus hydrophobic or hydrophilic drugs [53] can be used for medical and electronical importance. Similarly, several other nanoparticles such as mesotetra porphyrin-loaded PLGA (p-THPP) nanoparticles [52, 54-58], doxorubicin-loaded PLGA nanoparticles, plasmid DNA-loaded PLA nanoparticles, coumarin-loaded PLA nanoparticles, indocyanine [59-61] can also be used for a number of applications.

Salting Out

The salting out (**Figure no.5**) is modification of emulsification solvent diffusion technique [62-66] in which water miscible solvent is separated from aqueous solution through salting out process where, initially polymer and drug are dissolved in a solvent such as acetone, then it emulsifies into an aqueous gel consisting a salting-out agent in it as electrolytes such as magnesium chloride, calcium chloride, and magnesium acetate, or non-electrolytes such as sucrose. Importance of technique depends upon the type of salting out agent used, as it play an important property of encapsulating efficiency [67] of the drugs because the solvent and the salting out agent [68-69] are then eliminated by cross-flow filtration.

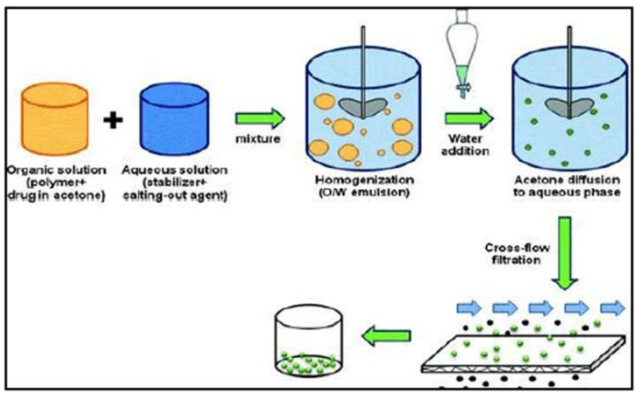

Figure 5: Salting Out

Dialysis

Dialysis is a simple and effective method for the preparation of small, narrow-distributed nanoparticles synthesis [70, 71] in which polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut off and the displacement of solvent inside the membrane is followed by the progressive aggregation of polymer [72] due to a loss of solubility and the formation of homogeneous suspensions [73] of nanoparticles. The mechanism of dialysis [74] (**Figure no. 6**) is similar to Nano-precipitation [75] whereas, it is based on the use of a physical barrier, specifically dialysis membrane [76] or common semi permeable membranes that allow the passive transport of solvents to slow down the mixing of the polymer solution with a non-solvent; the dialysis membrane [77,78] contains the solution of the polymer.

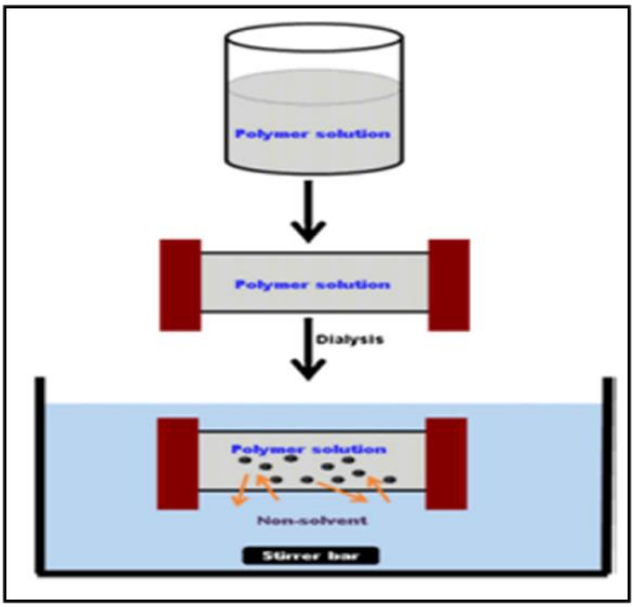

Figure 6: Dialysis

Supercritical Fluid Technology (SCF)

Supercritical fluid (**Figure no. 7**) is defined as a solvent at a temperature above its critical temperature, at which the single phase regardless of pressure moreover; the technology has been used as an alternative to prepare biodegradable[79] micro and nanoparticles because supercritical fluids[80] are environmentally safe. Supercritical CO_2 is most widely used as supercritical fluid because of its mild conditions, non-toxicity, non-flammability where this fluid along with dense gas technology [81] are expected to offer an interesting and effective technique of particle production [82], avoiding most of the drawbacks of the traditional methods (**Figure no. 7**). This technique is environmentally friendly, suitable for mass production and is more expensive.

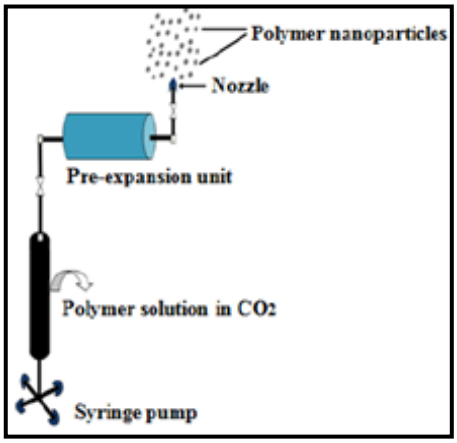

Figure 7: Supercritical Fluid Technology (SCF)

Nanocapsules, as characteristic class of nanoparticles, are made up of one or more active materials (core) and a protective matrix (shell) [83] in which the therapeutic substance may be confined.

PREPARATION OF NANOCAPSULES

Nanocapsules comprise of an oily or an aqueous core, which is surrounded by a thin polymer membrane.[84] Two technologies have been utilized for obtaining such nanocapsules: the interfacial polymerization for monomer and the interfacial Nano-deposition method for preformed polymer. The development in technologies in pharmaceutical research field has been spread widely in designing of the tumor targeting Nano-scale vectors, capable of delivering radionuclides. Among them, the lipid nanocapsules (LNCs) as a nanovector-based formulation with bio-mimetic properties [85] shows to be an applicable therapeutic option for HCC (Hepatocellular carcinoma) treatment. [86] It is composed of a liquid lipid core, which is surrounded by a shell of tensioactive. LNCs results in the encapsulation of a lipophilic composite of radioactive Rhenium-188. [87]

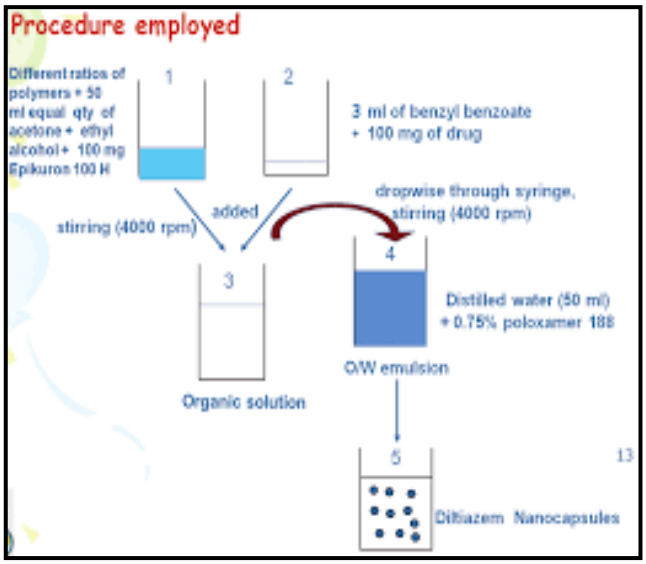

Figure 8: Nanocapsules composition

The capsules are constructed in several steps layer by layer:

1. In capsule preparation, the positively or negatively surface charged polymer addition comprises the first actual step.
2. Second step utilizes layer by layer self-assembling to form an ultrathin polymer film. Each new layer has the opposite charge to that of previous layer. The polymer coating is thrown by electrostatic gravities. They create shells of well ordered polyelectrolyte complex layers. This will result in capsule walls with 4 to 20 layers with a thickness of 8-50 nm.

The completed capsules will possess precise properties. Additional functions are often taken on by their surfaces for instance to provide connections for antibodies to dock.

It is optional that in the case of demand, the core of the capsule can be removed or various substances can fill the empty capsule shells.

Researchers suggest a number of approaches for preparing nanocapsules, but mostly four different approaches are utilized, namely: methods of interfacial polymerization or interfacial precipitation or interfacial Nano-deposition, and self-assembly methods. For designing the optimized drug carrier systems, each procedure offers its advantages and disadvantages. Nanocapsules can also be prepared according to the Nano-precipitation method.

The preparation of nanocapsules involving the organic phase which constitutes solvent, polymer, oil, and drug is penetrated 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 nanocapsules forming at the pore outlets.

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. Depend on the particle size the effect of releasing dosage and the time lapse of pharmacological action is 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.[88] Particle size can also affect the polymer degradation. For example, the rate of poly (D, L-lactide-co-glycol ide) (PLGA) polymer degradation revealed an enhancement with an increase in particle size in vitro.[89] Photoncorrelation spectroscopy or dynamic light scattering are used to determine the particle size.[90]

Surface properties of the nanocapsules

In view of drug targeting by means of nanocapsules, it is which is succeeded by (a) surface coating of nanocapsules with addition of hydrophilic polymers and/or hydrophilic surfactants, and (b) formulation of nanocapsules with their bio-degradable copolymers of hydrophilic segments like poly-ethylene glycol (PEG), poly-ethylene oxide (PEO), poly-oxamer, polo-xamine and poly-sorbate 80 (Tween 80). The zeta potential of nanocapsule is efficiently used to characterize charge on the surface property of nanocapsule.[91] Necessary to diminish opsonization and lengthen their circulation in vivo.[92]

Fluorescence quenching

Quenching of fluorescence[93] is mainly utilized to confirm the localization of nanocapsules, which contains the aqueous core containing oligonucleotides. [94]

EVALUATION STUDIES

X-Ray Diffraction (XRD) studies

Phase analysis of the products is performed by powder XRD on a Rigaku D/max-2000 diffractometer with graphite monochromatized CuKα (λ = 0.154 056 nm) at a voltage of 50 kV and a current of 250 mA. The XRD pattern shows the phase composition of prepared products. [95]

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. [96] It is characterized by a Philips XL-30 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.[97] 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.[98]

Transmission Electron Microscopy (TEM)

The transport of particularly insulin-loaded nanocapsules across the epithelium can be assessed by transmission electron microscopy after their oral administration to experimental rats when they are subjected to in vitro and in vivo studies.[99] TEM observations indicate the intestinal absorption of biodegradable nanocapsules leading to the transport of insulin across the epithelium mucosa.

High-Resolution Transmission Electron Microscopy (HRTEM)

The detailed morphology of the corresponding nanocapsules examined by means of high-resolution transmission electron microscopy clearly shows the shell/core structure of the nanocapsules.[100]the morphology of nanocapsules constructing the aggregates is tested from the low-magnification TEM images.

X-Ray Photoelectron Spectroscopy (XPS)

X-ray photoelectron spectroscopy measurements are performed on an ESCALAB-250 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 demonstrate 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.[101]

Superconducting Quantum Interference Device (SQUID)

The magnetic properties of nanocapsules are measured by using Quantum Design MPMS-7s or MPMS-5s superconducting quantum interference device. SQUIDs are the most sensitive detectors in detecting the tiny changes in magnetic flux, which take an account to the wide spectrum of application potential of SQUID devices.[102]

Multi Angle Laser Light Scattering (MALLS)

Vaults have a capsule-like structure with a very thin shell (approximately 2 nanometers) surrounding a large internal cavity. The vault particle in a nanocapsule has an incredible potential for compound encapsulation, protection, and delivery. [103] Vault conformation in solution is probed using the multiangle laser light scattering[104] to determine conditions that can stimulate the interconversion of opened and closed conformers. These studies enable the control of entrapment and release of encapsulated materials. Vaults containing binding sites for the toxic metals have importance in environmental and medical detoxification.[105]

FT-IR analysis

The presence of characteristic peaks is confirmed by using the FTIR analysis. The peaks indicate the characteristic functional groups of compound.[106, 107]

APPLICATIONS OF NANOCAPSULES

The nanocapsules are found to be suitable for various applications (Table no. 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

Application	Drug	Mode of Preparation	References
Agrochemicals	Abamectin-nanocapsules	Emulsion polymerization	Shang et al 2006[108]
	Cypermethrin nanocapsules	Microemulsion polymerization	Cheng et al 2008[109]
	Pyrethrum Nanocapsules	Microemulsion polymerization	Wu et al 2008[110]
Anti-inflammatory drugs	Diclofenac sodium	Sol-gel method	Adriana et al 2008,[111] Kortesuo et al 2000[112]
	Indomethacin loaded nanocapsules	Interfacial polymerization	Bernardi et al 2009[113]
Antiseptics	Monodisperse polymer nanocapsule	Precipitation	Umapom et al 2007[114]
Cosmetics	Hinokitiol-loaded poly (epsilon-caprolactone) nanocapsules	Emulsion-diffusion method	Hwang et al 2008[115]
Diabetes	Insulin loaded Biodegradable poly (isobutylcyanoacrylate) nanocapsules	Interfacial polymerization	Huguette et al 2002[116], Graf et al 2009[117]
Nanocapsules for cancer	Artemisinin	Nanoencapsulation method	Andrieu et al 1989[118]
	Camptothecin (CPT) and doxorubicin	Sol-gel method	Shen et al 2010[119]
	Cisplatin	Repeated freezing and thawing of a concentrated solution of Cisplatin in the presence of negatively charged phospholipids.	Burger et al 2002[120]
	Indomethacin-loaded polyisobutylcyanoacrylate nanocapsules.	Interfacial polymerization	Andrieu et al 1989[118], Raffin et al 2002[121], Guterres et al 2000[122]
	Lipid nanocapsules loaded with Rhenium-188 (LNC188Re-SSS)	Phase-inversion process	Vanpouille et al 2011[123]
Nanocapsule for Topical use	Chlorhexidine	Interfacial Polymerization method	Lboutounne et al 2004[124]

The Use of Nanocapsules as Smart Drugs

Nanocapsules can be used as a smart drug that have specific chemical receptors and only bind to specific cells. It is the receptor that makes the drug 'smart,' allowing it to target cancer or disease. The advantages of the nanoencapsulation technologies for pharmaceutical applications include:

1. Higher dose loading with smaller dose volumes
2. Longer site-specific dose retention
3. More rapid absorption of active drug substances
4. Increased bioavailability of the drug
5. Higher safety and efficacy
6. Improved patient compliance

CONCLUSION

Nanocapsules are a contribution to the methodological development formulation by various methods, mainly the interfacial polymerization and interfacial Nano-deposition. They can also be release as the monodisperse particles with well-defined biochemical, electrical, optical as well as magnetic properties. Nano-materials have found many important applications in biochemical, pharmaceutical, electronic and molecular diagnostic filed. Due to micronized size, they have a wide range of applications and high reproducibility, which can be used in life science application. Nanocapsules have efficient application in different field like agrochemicals, cosmetics products, genetic engineering technique, waste water treatment and cleaning product. They also applicable in encapsulating the enzymes, organic or inorganic catalyst, oil nanoparticles, adhesives, surface polymer or even biological cells. Nanocapsules can be used as smart drug.

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