REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Surfactant-Based Nanovesicles as Drug Delivery System

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Abstract

Over the past few decades, the systemic delivery of numerous active compounds through buccal mucosa has increased significantly. A prolonged residency time provides for more medication penetration after mucoadhesion. Wafers have a higher drug load than cast films because of their porous construction. These mucoadhesive buccal dosage forms provide painless administration, direct access to the systemic circulation via the inner jugular vein, the ability to use permeation enhancers or pH modifiers in the established systems, avoidance of potential gastrointestinal enzyme degradation, and the possibility of therapy discontinuation. Edge activators (EAs) and non-ionic surfactants make up most of the elastic surfactant-based vesicles known as nanospanlastics—the deformable nanocarriers known as spanlastics were created by Kakkar and Kaur and are based on surfactants. Non-ionic surfactants and EAs constitute the majority of spanlastics. By squeezing through various pores of the biological layers without rupturing, EAs increase the flexibility and permeability of the vesicular membranes of nanocarriers, destabilizing them and increasing their flexibility and cross-membrane permeability. Inert, biodegradable, and safe deformable nanovesicles are called spanlastics. They also have more chemical stability than standard liposomes.

Keywords: Solubility; nanovesicles; surfactants; spanlastics; drug delivery.

1. Introduction

Peptic ulcers (PU) commonly cause gastrointestinal morbidity and mortality. They are a group of persistent symptoms that compromise the mucosal integrity of the stomach lining and/or duodenum (Fikree and Byrne 2021). This acid-induced digestive system lesion is characterized by a denuded mucosa defect extending into the submucosa or muscularis propria.

Statistics show that for every 100,000 people, there are 200–250 instances of PU worldwide, with developing countries having the greatest prevalence. Although both sexes are equally affected by PU, which can start at any age, the disorder usually shows symptoms between the ages of 10 and 15. Functional gastrointestinal diseases are conditions that impact

every component of the digestive system. The normal neuromuscular function of the affected digestive tract is compromised and/or causes discomfort; the pathophysiological mechanisms underlying them, in addition, lack an anatomical or traumatic defect that could cause dysfunction. Furthermore, they are not connected to a metabolic abnormality like hypothyroidism and frequently result in vague and challenging symptoms to localize. Special focus is placed on conditions more common in tropical areas, including tropical enteropathy, tropical sprue, gastroenteritis, TB and intestine, malabsorption, and conditions like ulcers and intestinal intussusception. Improved sanitation and socioeconomic conditions have reduced the burden of infectious diseases and increased previously uncommon tropical disorders. Digestion problems are among the low areas' most prevalent health problems (Groenen et al., 2009). Malfertheiner et al. further stated that a big reason this ailment, despite substantial breakthroughs, continues to be a clinical problem is the growing popularity of low-dose aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Due to the rapidly declining incidence of Helicobacter pylori infection, PUD is today much less common than it was twenty years ago (Malfertheiner et al. 2009, 2022).

However, with an aging population and extensive use of complex anti-thrombotic medications, management has become more challenging. This is due to concerns about the rise of antimicrobial resistance globally. Diagnosing and curing peptic ulcers that do not result from an infection with the H pylori bacteria or from taking non-steroidal anti-inflammatory drugs is now very difficult. The inner lining of the GI tract is disrupted by peptic ulcer disease (PUD), which may be brought on by pepsin or gastric acid release. The muscularis propria layer of the stomach epithelium is penetrated (Lanas and Chan 2017).

Over the past ten years, the prefix "nano" has become more and more applicable to several branches of knowledge. A large public, including non-experts, is now familiar with many new nano-containing phrases used often in scientific reports, popular books, and newspapers. These terms include nanoscience, nanotechnology, nanomaterials, and nano-chemical. It is used to denote a reduction factor of 109 times according to the International System of Units (SI) norm. The nanosized universe, therefore, covers systems with sizes that are above molecular dimensions and below macroscopic ones (usually > 1 nm and 100 nm) and is often measured in nanometers (1 nm equivalent to 10-9 m). Nanotechnology is the study of very small objects. It involves the usage and tinkering of the matter. At this scale, atoms and molecules function differently, providing various unexpected and fascinating applications. Although it is frequently called the "tiny science," nanotechnology encompasses more than extremely tiny objects and materials.

Drugs made from nanoparticles can function as therapeutic agents or as carriers for delivering other therapeutic agents to specific bodily regions. Nanoparticle-based medications offer a promising method for modifying the biopharmaceutical and pharmacokinetic characteristics of the molecule to achieve desired drug-specific qualities (2009).

NPs have many benefits, such as simplicity in preparation, improved bioavailability, prolonged absorption, and site-specific drug targeting (Khosa et al., 2018). Drugs made from nanoparticles can function as therapeutic agents or as carriers for delivering other therapeutic agents to specific bodily regions.

1.1. Nanoparticles

Drug carriers that are solid, submicron in size, and either biodegradable or not are referred to as pharmaceutical nanoparticles (Paiva-Santos et al., 2021). Colloidal drug delivery systems called nanoparticles (NP) are made of natural, synthetic, and semi-synthetic polymers. The diameter of NP particles varies from 10 nm to 1,000 nm (Gardouh et al. 2021).

1.1.1. Polymeric nanoparticles

The features of polymeric nanoparticles (NPs), which result from their small size, have generated much interest in recent years (Bennet et al. 2014). Polymeric NPs are advantageous as drug carriers because they can be used for controlled release, shield drugs and other molecules from the environment, increase their bioavailability, and have a higher therapeutic index. These two varieties of polymeric NPs are known as a matrix system (nanosphere) and a reservoir system (nano-capsule). Additionally, polymeric particles demonstrated their usefulness in stabilizing and shielding medicinal molecules like proteins, peptides, or DNA molecules against degradation caused by various environmental dangers (Gardouh et al., 2022). Therefore, these polymers offer the possibility of different protein and gene delivery (Jarai et al. 2020; Zielińska et al. 2020).

1.1.2. Solid lipid nanoparticles

At typical room temperature, SLNs are lipids that remain in the solid phase. SLNs have particles that

range in size from 50 nm to 1,000 nm. SLNs comprise a single phospholipid covering layer and a solid hydrophobic core (Ghasemiyeh and Mohammadi-Samani 2018). In addition to showing many features like improved biodegradability, higher bioavailability, and drug targeting in the brain, SLNs are stabilized by various surfactants for emulsification. For the creation of SLNs, many lipid types are utilized.

1.1.3. Liposomes

Cholesterol and phospholipids are the main components of liposomes. These are vesicles with a hydrophilic core encased in a bilayer of hydrophobic lipids. Liposomes exhibit a wide range of uses in cosmetic and medicinal compositions. The particle size of nano-liposomes, which are also vesicular in shape, is in the nanometer range. The design of the liposomes, the particle size, the charge on the surface, and the formulation process are some of the variables that affect the properties of liposomes (Ahmed et al., 2019).

1.1.4. Noisome

As an alternative to liposomes, niosomes or non-ionic surfactant-based vesicles have been investigated (Muzzalupo and Tavano 2015). Niosomes are created from non-ionic surfactants in aqueous media, resulting in closed bilayer structures. Niosomes and liposomes, compared to phospholipid vesicles, offer greater chemical stability, reduced prices, and a wide range of surfactant classes. Because the vesicles can serve as drug-containing reservoirs, drug delivery systems utilizing vesicular systems, such as liposomes or niosomes, benefit from conventional dosage forms (Khafagy et al., 2022).

1.1.5. Transferosomes

Deformable liposomes (Transferosomes), elastic nanovesicles made of phospholipids, are so-called. They represent the first generation of introduced elastic nanovesicles (Shamma and Elsayed 2013). Phospholipids comprise most of the constituents in transferosomes, with 10–25% being edge activators such as sodium cholate only when administered in non-occlusive circumstances where they are said to penetrate undamaged skin and transport the medicines.

1.1.6. Ethosomes

They are elastic nanovesicles made of phospholipids with a high ethanol concentration (20–45%). To create the elastic nanovesicles, ethanol, a well-known permeation enhancer, was introduced to the vesicular systems (Chauhan et al. 2022). It has the potential to interact with the polar head group region of lipid molecules, lowering the melting point of the SC lipid and raising lipid fluidity and cell membrane permeability as a result. Due to the additional ethanol's high degree of flexibility, elastic vesicles can squeeze through significantly smaller pores than their diameters. Ethosomal systems are far more effective in quantity and depth at delivering chemicals to the skin than a hydroalcoholic solution or standard liposomes (Paiva-Santos et al., 2021). Ethosomes, however, may experience issues with inconsistent purity and expensive phospholipids.

1.2 Studies on Spanlastics (SNVs)

Kakkar and Kaur were the first to design a new elastic nano vesicular system (nano spanlastics) utilizing Span 60 and Tween 80 as edge activators. They are vesicles made of non-ionic span 60 surfactants with a nanoscale edge activator. The edge activator incorporates additional hydrophilic surfactant molecules that create gaps in the lipid bilayer membranes of nano-plastic lipid bilayers, destabilize the lipid bilayers, and ultimately increase the deformability of the vesicles. Non-ionic surfactants and EAs are the major constituents of spanlastics. EAs act as a destabilizing factor of nanocarriers' vesicular membranes, increasing their flexibility and permeability across the biological membranes by squeezing through different pores of the biological layers without rupture. Nanospanlastics are non-immunogenic, biodegradable, and safe deformable nanovesicles. Moreover, they are more chemically stable than conventional liposomes (Zaky et al., 2022).

1.2.1 Fenoprofen Calcium loaded spanlastics

Several edge activators (EAs) were used to prepare FPCa-loaded spanlastics utilizing the thin film hydration process. Using Design-Expert® software, a factorial design was used to examine the effects of various formulation factors on vesicle properties, including entrapment efficiency %EE, vesicle size, and in vitro drug release. Trans tympanic administration of ciprofloxacin via non-invasive spanlastics.

1.2.2 Ciprofloxacin SNVs

This was accomplished by utilizing multiple edge activators (EAs) at a Span 60: EA weight ratio of 8:2 to create ciprofloxacin nanovesicles or spanlastics. Span 60: EA weight ratio, kind of EA, and other formulation factors were optimized using a full factorial design (3^2) and Design-Expert® software (Al-mahallawi et al. 2017). Physical stability tests and ex-vivo permeation tests (via rabbit ear skin and TM) were then performed on the ideal formulation. The non-invasive trans tympanic distribution of ciprofloxacin may therefore be made possible by spanlastics, which could also be a potential nano-carrier.

1.2.3 Clotrimazole SNVs

A promising nano vesicular ophthalmic formulation of Clotrimazole (CLT) made only of surfactants was successfully prepared. CLT; is a water-insoluble antifungal drug. The nano vesicular carriers were formulated using Span 60 with one of the following edge activators (EA): Tween 80 (T80), sodium cholate (SC) or sodium deoxycholate (SDC). A 3^2-full factorial design was used to study the effect of two independent variables: the type of edge activator and the ratio of Span 60 to edge activator. The effects of these parameters on the mean particle size, entrapment efficiency (EE) and zeta potential (ZP) were investigated as dependent variables. As dependent variables, it was explored how these parameters affected the mean particle size, entrapment efficiency (EE), and zeta potential (ZP) (Abdelbari et al. 2021).

The best-optimized formulation developed after optimization was carried out, consisting of SDC as an EA at a ratio of 90:10 (Span 60: EA), with an average diameter of 479.60 nm, EE of 87.92%, and ZP of -33.7 mV. The differential scanning calorimetry analysis showed that the optimised nano vesicular carriers were spherical unilamellar vesicles containing CLT in an amorphous state. It was investigated how efficiently CLT suspension and niosomal formulations inhibited the growth of Candida albicans. The antifungal impact of CLT-loaded nano vesicular carriers lasted for 12 hours. After testing for ocular tolerance, the AUC of the optimised formulation was 3.09 times greater than that of the drug suspension, with no indication of discomfort.

1.2.4 Epigallocatechin gallate SNVs

Natural plants are a significant and reasonably priced source of valuable medications that can successfully treat various ailments. The anti-inflammatory, antioxidant, and anti-tumorigenic properties of EGCG are beneficial. Sadly, it has a low oral bioavailability because of its weak stability and minimal penetration. To examine the effects of several independent factors on entrapment efficiency (EE%), percent of drug released after 12 h (Q12h), and particle size (PS), ethanol-loaded spanlastics containing EGCG were made using a 2^3 factorial design. The optimised formula (F4) showed longer drug release than the comparable niosomes and a notable improvement in the EE%, permeability, deformability, and stability. The pharmacokinetic study looked at how F4 differed from traditional niosomes and free medicines in that it gradually released pharmaceuticals and had a higher bioavailability (Mazyed et al. 2021).

1.2.5 Sodium valproate SNVs

The sodium form of valproic acid (VA) is called sodium valproate (SV), also known chemically as 2-propyl pentanoate. A common treatment for epilepsy, migraines, bipolar illnesses, and many seizure disorders is SV, a histone deacetylase inhibitor. Weight gain, tremors, liver dysfunction, gastrointestinal issues, thrombocytopenia, metabolic acidosis, and hair loss are typical side effects of oral valproate treatment. The gradual rise in dose is thought to be a key element in preventing SV-induced hair loss. Topical application of valproate demonstrated efficient hair regeneration, in contrast to oral administration of SV, which results in hair loss. (SV) is a common antiepileptic medication used to treat various seizure disorders (Badria et al., 2020). The Wnt/-catenin pathway is activated by topical SV, which also induces the anagen phase and has the potential to regenerate hair. That investigation's goal was to create SV nanospanlastics that would enhance cutaneous delivery by prolonging the effects of the medicine and enhancing permeability for the treatment of androgenic alopecia (AGA).

1.2.6 Carvedilol SNVs

Another study attempted to create a mucoadhesive buccal drug delivery system by encapsulating the model beta-blocker antihypertensive carvedilol in nano-spanlastics and then incorporating it into a 1% CMC wafer.

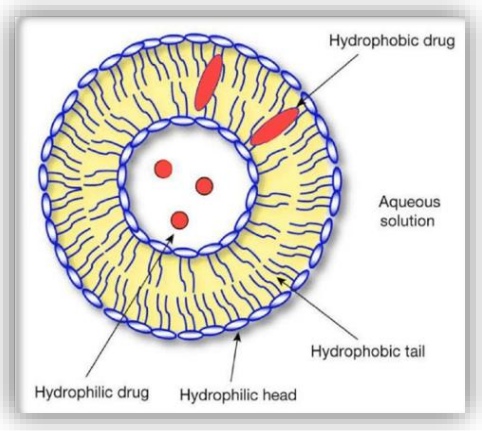

Figure I: Structure of spanlastics (Chauhan and Verma 2017)

1.2.7. Thymoquinone SNVs

The pleiotropic thymoquinone (TQ), discovered in the Nigella sativa seeds, holds much promise as a chemotherapeutic treatment for many malignancies. However, its weak stability and restricted water solubility limit its clinical use. TQ was encapsulated within spanlastics created with Span 60 and other edge activators to overcome

these obstacles. Particle size, polydispersity index, zeta potential, drug entrapment effectiveness, and in vitro drug release were assessed for the spanlastics. TQ's anticancer efficacy was examined vitro using the MCF-7 breast cancer cell line. Spherical TQ-loaded spanlastics with negative zeta potential (between 12 and 25 mV) and particle sizes between 92-285 nm were present. The type and concentration of the edge activator utilized greatly impacted the particle size and zeta potential. Additives. The smallest particle size was in tween 80 spanlastics (between 90 and 110 nm). These findings support the notion that Tween 80 spanlastics may represent an effective nano-delivery strategy for boosting the anticancer activity of TQ or other anticancer medications.

1.3 Administration of drugs via buccal route

There is great interest in the systemic administration of various active compounds via buccal mucosa. The buccal mucosa is a functional, extended, and still mucosa. Therefore, utilizing this method, the development of unidirectional or multidirectional drug delivery devices could be considered viable. Buccal drug delivery systems have several advantages, including easier medication administration, better patient compliance, and accessibility. They also provide excellent substitutes for individuals who are nauseous, aged, or young (Sallam et al. 2021b).

1.4 Mucoadhesive drug delivery system

Numerous investigations on longer and increased medicine interaction with the mucosal membrane led to the creation of mucoadhesive drug delivery methods, such as patches, film, and wafers. Hydrogels, films, patches, ointments, and mucoadhesive tablets are some examples of buccal dosage forms. Each has disadvantages. For instance, semi-solid ointments and hydrogels have insufficient hardness to survive tongue retraction and poor dosing accuracy. Mucoadhesive tablets can increase precision, but their release and long-term residency lengths are shortened by their sometimes-unpleasant size. These issues can be resolved by using films, patches, and wafers.

1.4.1 Films

Currently, buccal films are the most popular commercial dosage form for extended transmucosal delivery; their effectiveness depends on delayed matrix erosivity, good mucoadhesiveness, and appropriate drug loading. However, these carriers have enough water to encourage microbial contamination or the breakdown of sensitive APIs.

1.4.2 Wafers

Wafers are comparatively new formulations created by lyophilizing (freeze-drying) polymeric gels or solutions to easily produce solid porous cakes that may be applied to the buccal mucosa. There are numerous advantages of freeze-dried wafers over conventional crushed pills (Gm et al. 2014). They are lighter due to lyophilization preparation, which would improve patient compliance. When applied to the buccal mucosa, the sponge-like structure of these wafers promotes quick hydration and gelation, which reduces the sense of a foreign body. Wafers have a longer residence time than semi-solid polymer gels that flow easily after application and can hold their swelling gel structure for longer, allowing for more efficient medication absorption.

Compared to thin and continuous solvent-cast films, they have a better drug-loading capacity because of their larger surface area and porous construction. They have been utilized in various drug delivery systems, including controlled-release wafers, quick-dissolving wafers, and wound-healing dressings. Lyophilized wafers offer the benefits of improved drug loading and little residual moisture for medicines with low solubility. Extended-release wafers are only now available in noncommercial formulations, however.

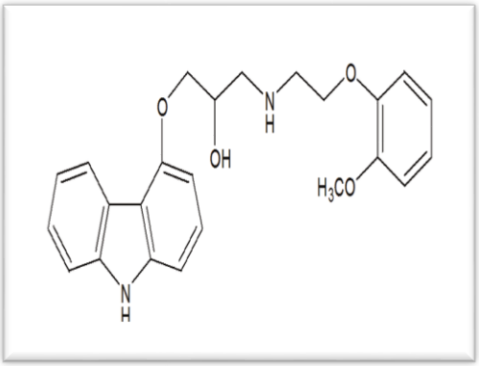

Figure II: Structure of carvedilol (Arzani et al. 2015)

1.5 Nanosponge

Targeted drug delivery to particular places is the main issue the investigators are dealing with. These issues should be solved by developing new nanoparticle carriers known as nanosponges (Hanna et al. 2019). A brand-new and emerging breakthrough called nanosponge enables the topical delivery of regulated substances. Nano-sponges are essential for the regulated distribution of pharmaceuticals. Medications could be stuffed inside nanosponges to direct drug delivery (Sallam et al. 2021a). All pharmaceuticals that are hydrophilic and lipophilic could be placed onto

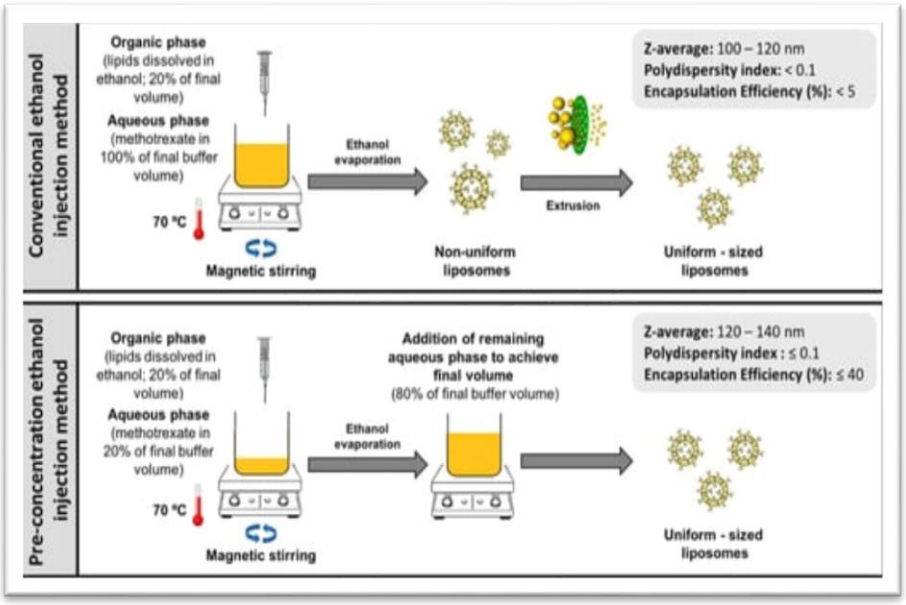

Figure III: Conventional and pre-concentration ethanol injection method (Guimarães et al. 2020)

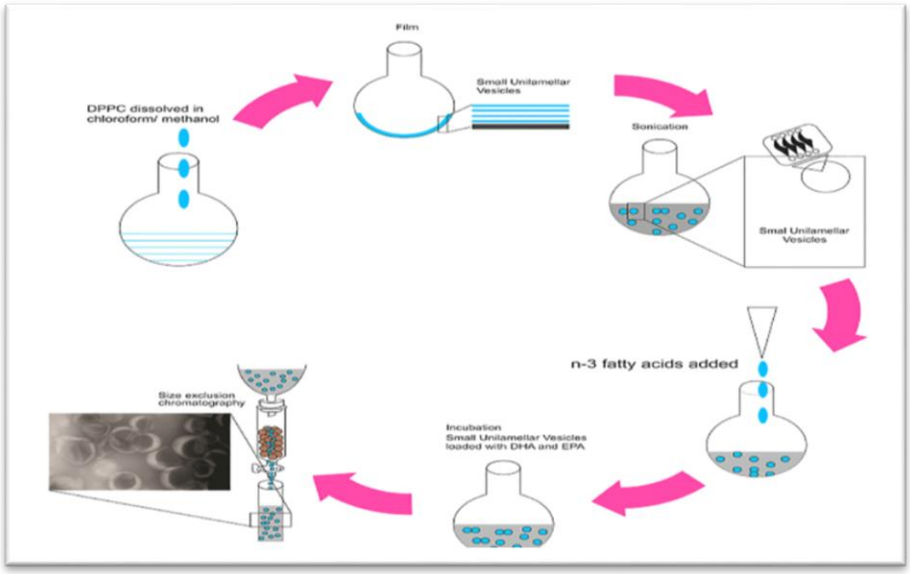

Figure IV: Thin film hydration technique (Elhabak et al. 2021)

nanosponges. One of the many prosperous fields of life in current science has appeared to be the medicine delivery method, Nanosponge (Nitish et al. 2021).

Targeting drug delivery systems has long been a goal in achieving desired results. The Nanosponge medication delivery system initially only had surface use, but in the twenty-first century, it is also possible to administer Nanosponges orally and intravenously (IV**)** (Al-Maghrabi et al. 2020).

These tiny particles can contain both hydrophilic and lipophilic medication substances, which increases the stability of pharmacological substances or compounds that are weakly water-soluble (Bhowmik et al., 2018).

It is an encapsulating nanoparticle that keeps the medication molecule in the core. The crosslinker's functional groups and their concentration modify the NSs' porosity, which results in flexible polarity (Gardouh et al. 2020; Desoqi et al. 2021).

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Figure V: Cooling centrifuge for determination of entrapment efficiency of SNVs (Abdelbari et al. 2021)

Table I: Drugs for peptic ulcers

(El-Dakroury et al. 2022)

Drugs that reduce gastric acid secretion	
H2 receptor antagonist	**Proton pump inhibitors**
Cimetidine	Omeprazole
Ranitidine	Lansoprazole
Famotidine	Pantoprazole
Nizatidine	Rabeprazole
Roxatidine	Esmoprazole
Loxatidine	
PG analogues	**Anticholinergics**
Misoprostol	**propantheline**
Enprostil	Oxyphenonium
Rioprostil	Pirenzipine, Telenzepine

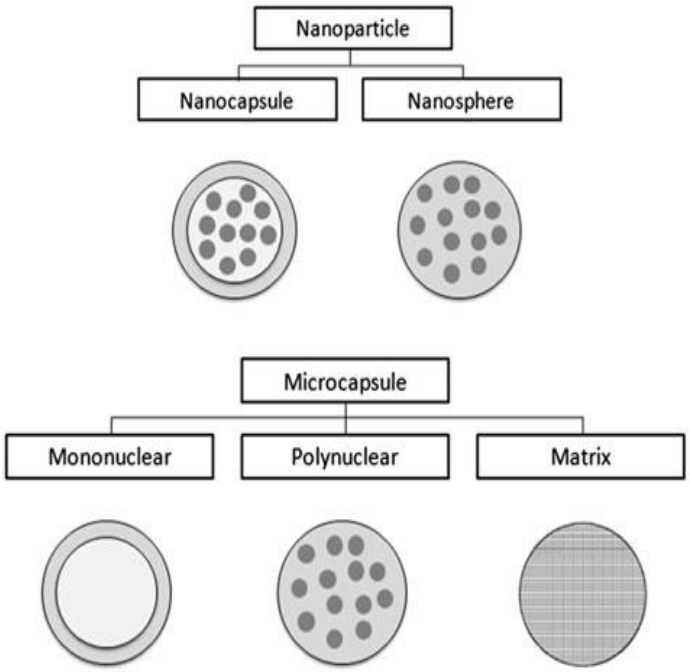

Figure VI: Types of nanoparticles (Mokhena et al. 2020)

Table II: Parameters needed for characterization technique (Mourdikoudis et al. 2018)

Entity characterized	Characterization techniques suitable
Size (structural properties)	TEM, XRD, DLS, NTA, SAXS, HRTEM, SEM, AFM, EXAFS, FMR, DCS, ICP-MS, UV-Vis, MALDI, NMR, TRPS, EPLS
Shape	TEM, HRTEM, AFM, EPLS, FMR, 3D-tomography
Elemental-chemical composition	XRD, XPS, ICP-MS, ICP-OES, SEM-EDX, NMR, MFM
Crystal structure	XRD, EXAFS, HRTEM, electron diffraction
Size distribution	DCS, DLS, SAXS, NTA, ICP-MS, FMR, superparamagnetic relaxometry, DTA, TRPS, SEM
Growth kinetics	SAXS, NMR, TEM, cryo-TEM, liquid-TEM
ligand binding/composition/density/arrangement	XPS, FTIR, NMR, SIMS, FMR, TGA, SANS
Surface charge	Zeta potential, EPM
concentration	ICP-MS, UV-Vis, RMM-MEMS, PTA, DCS
Agglomeration state	Zeta potential, DLS, DCS, UV-Vis, SEM, Cryo-TEM, TEM
Optical properties	UV-Vis-NIR, PL, EELS-STEM

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