

# LIPONOVEL PREPARATION OF MICROENCAPSULATION DRUG DELIVERY SYSTEM

## Abstract

There are several advantages when contrasting innovative drug delivery systems with conventional multi-dose therapy. Research aimed at developing novel drug delivery methods has given a lot of attention to controlled release and sustained release dosage forms. A lot of work is currently being done to deliver the medicine in a way that will have the greatest positive effects. There are numerous techniques for continuously regulating the delivery of a therapeutic substance to the target area. One such method is the use of microspheres as drug delivery systems. During the microencapsulation process, small discrete solid particles or tiny liquid droplets are encased and contained by an intact shell. Microencapsulation is used to modify pharmaceutical dosage forms and delay the drug releases from those dosage forms. The well-established field of microencapsulation focuses on the preparation, properties, and applications of individually encapsulated novel small particles, as well as significant improvements in tried-and-true techniques relevant to micro and nano-particles and their use in a wide range of industrial, engineering, pharmaceutical, biotechnology, and research applications. Its scope includes all other small particle systems, including self-assembling structures that need to be modified beforehand, in addition to conventional microcapsules. An effective controlled drug delivery system can reduce side effects while addressing some of the problems with conventional therapy. If altered, it is the reliable way for consistently and precisely delivering the medication to the target site while keeping the required concentration at the site of interest. The

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persistent release of microspheres and their capacity to deliver anti-cancer drugs directly to the tumour garnered a lot of attention. The purpose of this technology is to demonstrate how important microencapsulation technique may be in the development of innovative medication delivery systems.

**Keywords:** Niosomes, Microencapsulation, Microspheres, Transfersomes, Microparticles.

## I. INTRODUCTION

With a continuous layer of polymeric components, tiny particles with sizes ranging from less than 1 micron to several hundred microns are created via the technique of microencapsulation, which involves encasing or wrapping solids, liquids, or even gases in a second substance.

Various pharmaceutical dosage forms are routinely modified and delayed in their release of drugs using the microencapsulation method. Regardless of the specific outer and/or inner structures, "microparticles" refers to particles having a diameter ranging from 1 to 1000 m. There are numerous types of microparticles. Within the broader category of microparticles, "Microspheres" designates spherically formed microparticles. Microcapsules are microscopic particles that are coated or walled in a distinct substance and have a solid, liquid, or even gas-filled core.

**1. Microcapsules are divided into three categories:** Containing the shell around the core (mononuclear). The microencapsulation techniques which can prepare several different varieties of microcapsules are:

Extrusion, emulsification, fluidized bed coating, cyclodextrin inclusion, spray drying, and spray chilling. The materials that surround the components in the microcapsules are referred to as coating materials, wall materials, shell materials, or membrane. The components that are enclosed or enveloped within the microcapsules are known as core materials, pay-load materials, or nucleus.

### 2. Advantages of microencapsulation

- Protecting the enclosed active agents or core ingredients from the environment.
- Microcapsules can be used to convert liquids and gases into solid particles.
- Surface and colloidal properties of different active agents can be altered.
- Alter and postpone drug release from various pharmacological dose forms
- Modifying or delaying the release of encapsulated active agents or core materials can be used to create prolonged controlled release dosage forms.

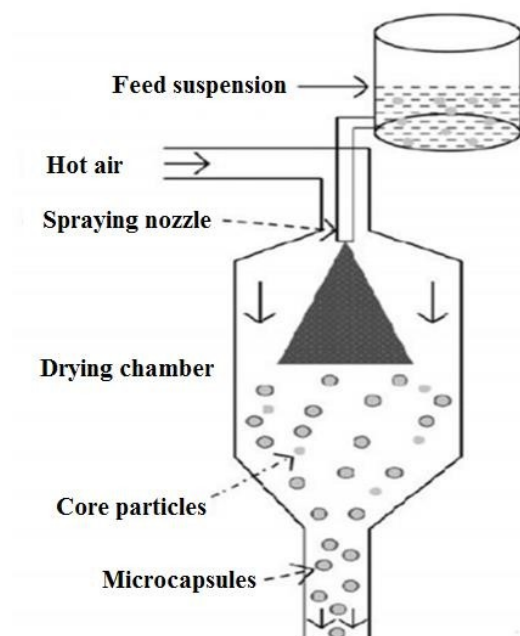
### 3. Disadvantages of Microencapsulation

- Expensive methods.
- Hygroscopic agents' shelf life is shortened as a result of this.
- The uniformity of the microencapsulation layer can affect the release of encapsulated components.

### 4. Methods of microencapsulation:

- **Air suspension:** The air suspension technique for microencapsulation involves dispersing solids and particulate core materials in a supporting air stream, then spray-coating the air suspended particles (Fig. 2).

Within the coating chamber, suspended particle core materials are flowing upward in an air stream. The coating chamber's operational features and design have an impact on the recirculating flow of particles through the coating zone, where a coating material is sprayed onto the moving particles.

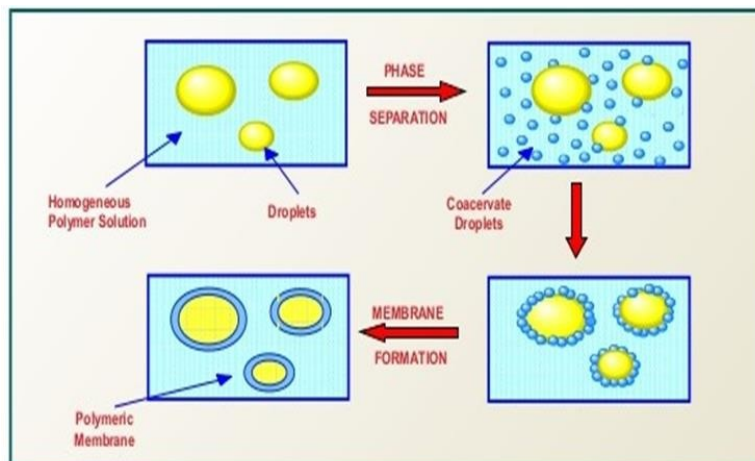


**Figure 2:** Microencapsulation (through air suspension method)

## II. COACERVATION

Three phases make up the microencapsulation by coacervation phase separation method:

- The development of the liquid manufacturing, core material, and coating material phases, which are three immiscible phases.
- The core material is coated with a liquid polymer.
- Creating microcapsules by heating, crosslinking, or desolving the coating to make it hard. A liquid polymer coating is coated all around the interface formed between the core material and the liquid vehicle phase (Fig. 3). Phase separation of the polymers can be caused by physical or chemical changes in the coated polymer solutions under various conditions. The formation and coalescence of droplets of concentrated polymer solutions will result in a two-phase liquid-liquid system.



**Figure 3:** Microencapsulation (through coacervation phase separation)

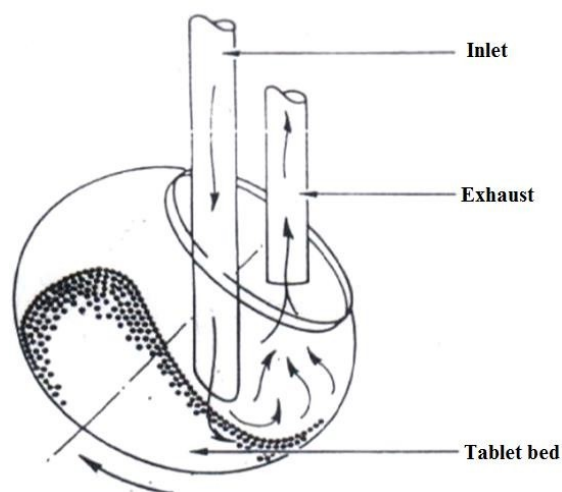
- 1. Pan Coating:** The pan coating method, which is commonly used in the pharmaceutical sector to create controlled release particulates, may microencapsulate rather large particles (greater than 600 in diameter).

In this process, various spherical core materials, such as nonpareil sugar seeds, are coated with a selection of polymers (Fig. 4).

In actual use, the coating is sprayed as a solution or an atomized spray to the selected solid core material in the coating pan.

While the coatings are being applied in the coating pans, warm air is blown over the coated components to eliminate the coating solvent.

In some circumstances, the drying oven is used to complete the final solvent removal process.



**Figure 4:** Microencapsulation (through pan coating method)

**2. Fluidized-Bed Technology:** This technique for microencapsulation encapsulates solid core materials, including liquids absorbed into porous solids.

Medication capsules are frequently created using this microencapsulation technique. After being sprayed with a liquid coating solution, the solid particles are suspended in a jet of air.

The capsules are sent to a site where cooling or solvent vaporisation is used to cement the shells of the capsules.

Up until the capsule wall achieves the required thickness, the suspending, spraying, and chilling processes are repeated.

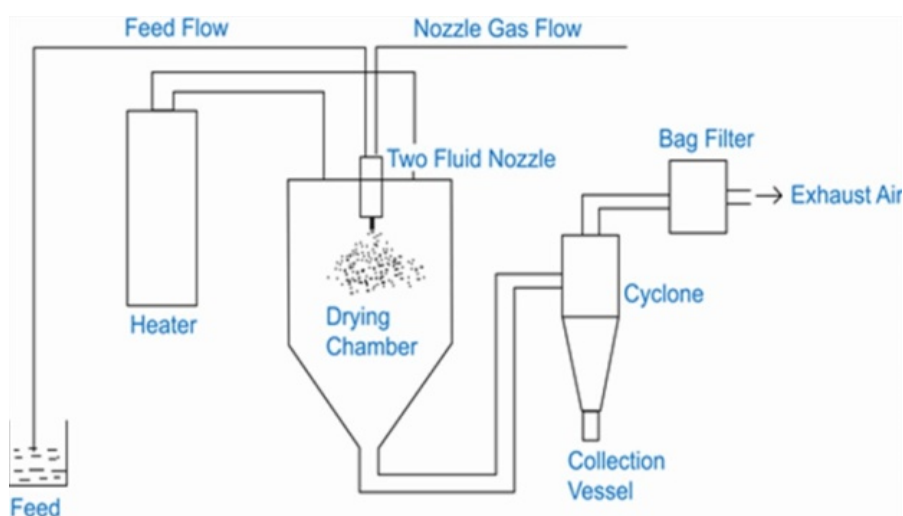
The Wurster technique is used when the spray nozzle is placed at the bottom of the fluidized bed of particles.

Both the spray drying and the spray congealing techniques for microencapsulation involve dispersing the core material in a liquid coating agent and spraying or introducing the core coating mixture into a condition where the coating's relatively quick solidification is influenced (Fig. 5).

The key difference between these two microencapsulation processes is how firm the covering becomes.

The solvent's rapid evaporation has an impact on how quickly the coating ingredient solidifies during the spray drying process. Coating solidification is achieved by thermally congealing molten coating material or, in the case of spray congealing, by injecting the coating core material mixture into a non-solvent.

Sorption extraction or evaporation techniques are frequently used to remove non-solvent or solvent from coated materials.



**Figure 5:** Microencapsulation (through spray drying method)

**3. Multi-orifice Centrifugation:** In the multiorifice-centrifugation method of microencapsulation, a core particle is propelled through an enclosing membrane by centrifugal forces.

The multiorifice-centrifugation method involves a number of processing variables, including the cylinder's rotational speed, the flow rates of the core and coating materials, and the concentration, viscosity, and surface tension of the core material.

Using a variety of coating materials, the multiorifice centrifugal process may microencapsulate liquids and solids in a range of sizes.

In the hardening media, the encapsulated product may be given as a slurry or as a dry powder.

### III. EVAPORATION OF SOLVENT

By stirring together two immiscible liquids, the solvent evaporation process can be used to create a liquid manufacturing vehicle (O/W emulsion).

The microcapsule coating (polymer) is dissolved in a volatile solvent during the solvent evaporation process, which is incompatible with the liquid production vehicle phase.

A core substance (drug) to be microencapsulated is dissolved or dispersed in the coated polymer solution.

The core-coating material mixture is disseminated in the liquid manufacturing vehicle phase by agitation to produce the desired sized microcapsules. When the solvent separates into the aqueous phase and evaporation removes it, the system is stirred. This process results in the toughening of microcapsules. Various methods can be used to disperse the oil phase in the continuous phase. The most common method is a propeller-style blade connected to a variable-speed motor.

The rate of solvent evaporation for the coating polymer(s), temperature cycles, and agitation rates are only a few of the process variables that affect how dispersions are made. The most important factors to take into account while creating microcapsules utilizing the solvent evaporation technique are the solvent recovery systems, vehicle phase, and solvent for the polymer coating.

Numerous liquid and solid core materials can be microencapsulated using the solvent evaporation technique. As core materials, substances that are soluble or insoluble in water may be used. Coatings can be made in a variety of methods using film-forming polymers.

**1. Polymerization:** Protective microcapsule coverings are made in situ using the polymerization method of microencapsulation. The process involves the reaction of monomeric units situated at the interface between a continuous phase and a scattered core material.

The polymerization reaction occurs at the liquid-liquid, liquid-gas, solid-liquid, or solid-gas interfaces because the continuous or core material supporting phase is frequently a liquid or gas.

2. **Interfacial Cross-linking:** The tiny bifunctional monomer containing active hydrogen atoms is substituted by a biosourced polymer, such as a protein, in the interfacial cross-linking process of microencapsulation. When the reaction takes place at the emulsion's interface, the acid chloride reacts with the protein's different functional groups, resulting in the development of a membrane. For pharmaceutical or aesthetic applications, the interfacial cross-linking process of microencapsulation is extremely adaptable.

#### IV. APPLICATIONS OF MICROENCAPSULATION

1. Microencapsulation can be utilised to create a Variety of prolonged controlled release dosageforms by changing or delaying the release of encapsulated active agents or core materials.
2. Microencapsulation can also be used to create enteric-coated dosage forms, which allow medications to be absorbed selectively in the intestine instead of the stomach.
3. Drugs that cause stomach irritation are being microencapsulated to lessen the risk of discomfort.
4. Microencapsulation techniques can be used to conceal the taste of bitter medication candidates.
5. Liquids and gases can be converted into solid particles in the form of microcapsules using microencapsulation.
6. To solve the challenges of sticky granulations and direct compression, microencapsulation can be used to help with the addition of oily pharmaceuticals to tableteddosage forms.
7. To reduce volatility, microencapsulation can be utilized.
8. A volatile chemical that has been microencapsulated can be held for prolonged periods of time without evaporation.
9. Microencapsulation protects encapsulated active substances from a variety of environmental factors such as light, heat, humidity, oxidation, and so on.
10. Microencapsulation can minimise the hygroscopic properties of several core materials.
11. Microencapsulation is a technique for separating incompatible chemicals. Microencapsulation, for example, can be used to separate pharmacological eutectics. This is a situation where two materials come into direct touch and form a liquid. Microencapsulating both aspirin and chlorpheniramine maleate before combining improves the stability of the incompatible mixture.



Microencapsulation is utilised to reduce the risk of handling harmful substances. Herbicides, insecticides, pesticides, and fumigants, for example, can be effectively reduced in toxicity after microencapsulation.

## V. PARTICULATES (NANOPARTICLES AND MICROPARTICLES)

Anoparticle- <1 micrometre Microparticle- >1 micrometre. The maximum size limit for microparticles for ophthalmic administration is roughly 5-10 micrometres, above which ocular instillation might cause a scratching sensation in the eye.

As a result, micro and nanoparticles are prospective medication carriers for use in ophthalmology.

Emulsion polymerisation produces nanoparticles.

The most often utilised ophthalmic nanoparticles are polyalkyl cyanoacrylate.

Many anti-glaucoma medications have been put onto nanoparticles for efficacy testing. sity pellets can resist stomach peristaltic motions, extending the gastrointestinal tract time from 5.8 to 25 hours, according to Garg and Gupta.

Despite the fact that this technique has the potential to increase GRT, designing high-density pellets holding high-dose medications is difficult.

Furthermore, there are just a few clinical trials on high-density pellet formulations in the literature; as a result, the clinical significance of these formulations is unknown. Gastro retentive systems are still debatable.

As a result, future research should concentrate on animal trials to determine the clinical importance of such dosage formulations.

## VI. LIPOSOMES

The Greek words lipo, which translate to "fatty constitution," and soma, which means "structure," are the sources of the word liposome, which Alec D. Bangham originally identified in the early 1960s.

Liposomes are incredibly small particles, with sizes ranging from 50 nm to several m. One or more phospholipid bilayers completely encapsulate the aqueous core of these spherical vesicles. It has the unusual capacity to entrap substances that are both hydrophilic and lipophilic.

While hydrophilic molecules can be confined in the aqueous centre, hydrophobic or lipophilic molecules are injected into the bilayer membrane. Due to its biocompatibility, biodegradability, low toxicity, capacity to trap both hydrophilic and lipophilic drugs, and ease of site-specific drug administration to cancer tissues, liposomes have gained favour as an exploratory and commercial drug delivery technique.

Numerous studies on liposomes have been conducted to lessen drug toxicity and/or target particular cells.

### 1. Advantages

- Suitable for the administration of hydrophobic, hydrophilic, and amphipathic agents, such as cytrabine and amphotericin B.
- Liposome improves the therapeutic index and efficacy of the medication actinomycin-D.
- Liposomes' encapsulation increases stability.
- Suitable for the delivery of targeted drugs.
- Capable of providing targeted activity in a specific tissue.
- Suitable for administration by a number of routes
- Liposomes assist in lowering the amount of hazardous medication exposure to delicate tissue

### 2. Disadvantages

- Liposomes are inert once administered.
- The potential for dosage dumping as a result of subpar administration techniques.
- Encapsulated drug leakage while being stored.
- Limited solubility
- High production costs.

### 3. Classification (based on structural parameters)

- Multi-lamellar massive vesicles (MLV), to start. 0.5  $\mu\text{m}$ . There are numerous bilayers.
- OLV: 0.1–1  $\mu\text{m}$  oligo lamellar vesicles.  
Two to ten lipid bilayers surround a vast inner volume.
- UV: unilamellar vesicles of every size.
- SUV: a small, 30-70 nm-diameter unilamellar vesicle made of a single lipid bilayer. MUV: medium unilamellar vesicle
- Large unilamellar vesicle > 100 nm. Giant unilamellar vesicle > 1  $\mu\text{m}$ .
- MV stands for multivesicular vesicle, which is a vesicle with more than one vesicle.

### 4. Classification (Based on method of preparation)

- REV: reverse phase evaporation process produces single or oligo lamellar vesicles
- MLV-REV: multilamellar vesicle produced via reverse phase evaporation
- SPLV stands for stable plurilamellar vesicle, and FATMLV stands for frozen and thawed plurilamellar vesicle.
- MLV: Large enough vesicles may host one or more internal (inner) vesicles. If they are concentrically arranged, the vesicles are oligo- or multilamellar, OLVs or MLV. Vesicles with non-concentrically arranged internal vesicles are called multivesicular vesicles
- VET: vesicle obtained by extraction dehydration-rehydration method

**5. Classification (Based on composition and application):** Conventional Liposomes (CL): Neutral or negatively charged phospholipid and cholesterol.

- **Fusogenic Liposomes (RSVE):** Reconstituted Sendai virus envelopes.
- **pH sensitive Liposomes:** Phospholipid such as PE or DOPE with either CHEMS or OA.
- **Cationic Liposomes:** Cationic lipids with DOPE.  
Long Circulatory (stealth) Liposomes.
- **Immuno-Liposomes:** Immuno-liposomes have a specific antibody on their surface that helps them bind to their target sites.

**6. Preparation of liposomes**

- Lipid hydration in the presence of a solvent
- Ultra-sonication French pressure cell,
- Technique of solvent injection:
  - method of injecting ether
  - a method of injecting ethanol
- Dialysis, column chromatography, biobeads, and dialysis: methods for removing detergent.
- The use of reverse phase evaporation
- Extrusion under high pressure
- Other different techniques
  - Chaotropic ion removal
  - Freeze-Thawing

**7. Characterization of Liposomes**

- **Physical Characterization:** assesses size, shape, surface characteristics, lamellarity, phase behaviour, and drug release profile among other things.
- **Chemical Characterization:** on the other hand, refers to investigations that determine the purity and potency of specific lipophilic elements.
- **Biological Characterization:** determines the formulation's safety and suitability for therapeutic use.

**8. Applications**

- **Chemotherapy for Cancer:** Liposomes have been effectively employed to encase anticancer medicines. This prolongs the life of the circulatory system and protects it from metabolic deterioration.
- Liposomes as medication carriers in oral treatments
- Arthritis-related steroids can be integrated into big MLVs.
- Oral administration of liposome-encapsulated insulin resulted in a change in blood glucose levels in diabetic rats.
- **Topical use of Liposomes:** Topical liposomes can successfully include drugs such as triamcinolone, methotrexate, benzocaine, and corticosteroids.

- **Liposome for Pulmonary Delivery:** Nebulizers and other inhalation devices are used to create an aerosol of liposome-containing particles.

## VII. NIOSOMES

Niosomes are a special form of drug delivery where the substance is contained in a vesicular structure. Niosomes are vesicles composed of a non-ionic surfactant bilayer. The niosomes are miniscule and extremely small (on a nanometric scale). Despite sharing a structural similarity with liposomes, they have many advantages.

**1. Advantages of Niosomes:** Despite sharing a structural similarity with liposomes, they have many advantages.

- The vesicles might function as a drug storage system that releases medication over time.
- They increase the stability of the medicine that is entrapped and are osmotically active and stable.
- By delaying their removal from circulation, protecting them from the biological environment, and restricting their actions to target cells, they improve the therapeutic effectiveness of drug molecules. Surfactants that are biodegradable, biocompatible, and non-immunogenic are used.
- They improve the oral bioavailability of poorly absorbed medications and boost pharmaceutical penetration via the skin. You can administer them topically, parenterally, or orally to deliver them to the area of action.
- Surfactants can be handled and stored without extra precautions.
- As a result of their special structure, which combines hydrophilic, amphiphilic, and lipophilic moieties, drug molecules with a variety of solubilities can be accommodated.
- To control the drug delivery rate and administer normal vesicles in an external non-aqueous phase, niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase.

**2. Disadvantages of Niosomes:** The main drawback of the noisy drug delivery technique is the physical instability of the noisy vesicles.

- **Aggregation:** Another drawback to take into account is the accumulation of the noisy vesicles. The homogeneity of the size of the niosome vesicles will be affected by the fusion of the niosomal vesicles to form loose aggregates or to fuse into larger vesicles.
- **Entrapped drug leakage:** The niosomes' intended qualities will be impacted if entrapped medicines leak from the polymer system.
- Drugs that are encapsulated undergo hydrolysis, reducing the shelf life of the dispersion.

**3. Types of Niosomes:** The size of the niosomes or the number of bilayers (MLV, SUV, etc.) determines how they are categorized. (LUV, SUV, for example) or based on the manner of preparation (REV, DRV).

- **Multilamellar Vesicles (MLV):** These are made up of several bilayers that enclose

each of the compartments for aqueous lipids independently. These vesicles have a diameter that ranges from 0.5 to 10 micrometres. The most common niosomes are multilamellar vesicles. These vesicles are ideal for using as lipophilic compound medication carriers.

- **Large Unilamellar Vesicles (LUV):** These niosomes have a high aqueous/lipid compartment ratio, allowing for the very efficient usage of membrane lipids to entrap larger amounts of bioactive molecules.
- **Small Unilamellar Vesicles (SUV):** SUVs are primarily made from multilamellar vesicles using the French press extrusion method and the sonication method. Dicetyl phosphate is added to 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes for electrostatic stabilisation.

**4. Applications of Niosomes:** The following are some examples of niosome uses in various diseases where research is either ongoing or has already been established:

Niosomes are frequently utilised to target medications to the reticulo-endothelial system. Niosome vesicles are taken up preferentially by the reticulo-endothelial system (RES). Opsonins, molecules found in circulating serum, regulate the uptake of niosomes.

The niosome is marked for clearing by these opsonins.

Such medication localisation is used to treat animal cancers that are known to spread to the liver and spleen. This medication localisation can also be used to treat parasite liver infections. Niosomes can be used to direct medications towards organs other than the RES.

Niosomes can be directed to particular organs by attaching a carrier system (such as antibodies) to them because immunoglobulins bind to the lipid surface of niosomes with ease.

Niosomes can take advantage of the innate aptitude that many cells have to recognise and bind particular carbohydrate determinants in order to route the carrier system to specific cells.

## VIII. ANTI-NEOPLASTIC THERAPY

The majority of antineoplastic medications have detrimental side effects. Niosomes can change drug metabolism, extend drug circulation, and extend drug half-life, all of which reduce drug side effects.

Niosomal entrapment of the medications Doxorubicin and Methotrexate (in two different investigations) shown advantages over the untrapped pharmaceuticals, including a lowered rate of tumour proliferation and higher plasma levels with a slower rate of clearance. Leishmaniasis is a disease caused by a species of parasites called Liver and spleen cells are invaded by leishmania. Antimony derivatives (antimonials), which can harm the heart, liver, and kidneys in higher amounts, are frequently prescribed medications for the condition. Niosomes were used in experiments to demonstrate that it was possible to provide

bigger doses of the medication without causing the side effects, allowing for better therapeutic efficacy.

**1. Peptide Drug Delivery:** It has long been difficult to avoid the enzymes that would break down peptides used in oral medication administration. It is being researched if niosomes may successfully shield peptides from gastrointestinal peptide degradation. Oral administration of a vasopressin derivative trapped in niosomes shown in an in vitro investigation by Yoshida et al. that drug entrapment considerably improved the stability of the peptide. Niosomes are employed to research the nature of the immune response triggered by antigens because of their immunological selectivity, low toxicity, and higher stability.

**2. Niosomes as Haemoglobin Carriers:** Niosomes can act as haemoglobin carriers in the blood. In anaemic patients, the niosomal vesicle, which is permeable to oxygen, can serve as a carrier for haemoglobin.

### 3. Advantages of Nanoparticles

- Improves the stability of any volatile pharmacological substances, which can be quickly and inexpensively manufactured in large quantities using a variety of ways.
- They provide a significant efficiency and efficacy boost over standard oral and intravenous administration methods.
- Delivers a higher concentration of a medicinal substance to a targeted area
- Because of the polymer used and the ability to control drug release, polymeric nanoparticles are great candidates for cancer therapy, vaccine administration, contraception, and antibiotic delivery.

### 4. Preparation of nanoparticles from polymerization of monomers

- Emulsion
- Mini emulsion
- Micro emulsion
- Interfacial polymerization
- Controlled/Living radical polymerization
- Ionic gelation or coacervation of hydrophilic polymers

### 5. Application of Nano Particulate Drug Delivery Systems

- Vaccination Adjuvant
- Delivery of DNA
- Eye delivery
- **Internalisation:** Carbon nanotubes that have been functionalized can be internalised by mammalian cells.
- **Vaccine Delivery:** Peptides may be conjugated to produce structures for vaccine delivery.
- **Gene Delivery:** Using molecular dynamics simulations, it has been predicted that the flow of water molecules through surface-functionalized carbon nanotubes can deliver

genes and be easily used as small molecule transporters in transporting DNA, indicating potential use as a gene delivery tool.

Drug substances, including peptides and nucleic acids, are delivered.

Because they are more soluble, carbon nanotubes containing carboxylic or ammonium groups are more suited to transport peptides, nucleic acids, and other medicinal compounds.

Less harmful side effects and increased effectiveness.

- **Cancer Treatment:** This technique is currently being assessed for cancer treatment. When exposed to infrared photons from an external source, nanoshells are calibrated to absorb them, which causes them to get heated and destroy tissue. On numerous cell lines, this has been looked into in vitro and in vivo.
- **Diagnostic Uses:** They are helpful in whole blood immunoassays for diagnostic purposes. A few examples include detecting immunoglobulins in plasma and whole blood by coupling gold nanoshells to antibodies.

## IX. CONCLUSION

Globally, scientists are working to create the best delivery system possible so that drugs can be targeted to a specific spot in an efficient and controlled manner.

By using new methodologies, the likelihood of more effectively targeting medications at the real spot can be increased. At present, an optimum knowledge of microparticles and its types are known and are also been constantly evolved.

The important property of the various types of microparticles is their flexibility, which enable them to cross biological membranes without rupturing. Much research shall be further done to increase the vesicle flexibility whichd stabilizes the lipid bilayers of the vesicles but maintains their stability even during enlarged deformations.

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