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TARGET DRUG DELIVERY SYSTEM: AN ADVANCE APPROACH OF PHARMACEUTICALS

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ABSTRACT
In light of their special physicochemical and biological characteristics, nanomaterial-based drug delivery methods are frequently utilised to increase the safety and therapeutic effectiveness of encapsulated medicines. Targeted drug delivery is an advanced technique that delivers medications to patients in specific sequences that increase the concentration of the drug delivered to the targeted body part of interest (organs, tissues, or cells). This reduces side effects associated with drug administration and enhances treatment efficacy. Targeted medication delivery essentially helps the drug molecule go to the appropriate location. This technique's intrinsic benefit allows for the delivery of the necessary medication at a lower dose with fewer adverse effects. Research and development in the clinical and pharmaceutical domains are giving careful thought to the innate benefit of tailored drug delivery systems as the foundation of both treatments and diagnostics. Nano-targeted delivery systems were developed to overcome the primary limitations of conventional drug treatment, such as inadequate stability and solubility, lack of transmembrane transport, short circulation time, and undesirable toxic effects. Therapeutic drugs and nanoparticles were combined using rational targeting pathways. In this article, we examined the most current advancements in therapeutic techniques and targeted design tactics using a variety of nanomaterial-based systems. We also spoke about the prospects and difficulties of using smart technologies to accurately target various extravascular and intravascular illnesses.

KEYWORDS: Nanoparticles, Targeted drug delivery, Spanlastic, Transferosomes, Liposomes.

1. INTRODUCTION

Approximately 25% of the primary medicinal chemicals and their derivatives that are now on the market come from natural sources. New drug discoveries start with natural molecules that have diverse chemical bases. In the field of natural product-based drug development, creating synthetically accessible lead compounds that closely resemble their counterparts' chemistry has been popular recently. Natural products have many amazing qualities, including decreased toxicity, astonishing chemical variety, and chemical and biological capabilities with macromolecular precision. Because of this, they are good leads for the development of new medications. Pharmaceutical corporations are reluctant to allocate additional resources towards medication delivery and discovery processes based on natural products, despite the numerous benefits. Instead, they prefer to investigate the libraries of chemical compounds that are already accessible for drug discovery.

But currently, a number of serious illnesses, which includes as cancer, diabetes, cardiovascular disease, inflammatory disorders, and microbial infections, are being investigated as potential treatments for natural substances. This is mostly due to the special benefits that come with natural medications, which include reduced toxicity and adverse effects, affordability, and strong therapeutic potential. The toxicity and biocompatibility issues surrounding natural substances, however, make their use as medicine more difficult. As a result of these issues, several natural substances are failing to advance past the clinical trial stages. Large-sized material distribution presents a number of significant hurdles, including as in vivo instability, low solubility and bioavailability, poor absorption in the body, problems with target-specific delivery and tonic efficacy, and potentially harmful pharmacological side effects.

The term "drug delivery" describes the procedures, formulations, technologies, and techniques used to move a pharmaceutical material through the body in order to provide the intended therapeutic effect. It includes methods of delivering medication to both humans and animals in order to achieve therapeutic efficacy. The focus of recent advancements in drug delivery systems has mostly been on smart drug delivery systems, which aim to provide drugs at the right time, dose, and place for optimal safety and effectiveness. The development of Novel drug delivery systems has garnered significant interest lately.

By using nanostructures and nanophases in a variety of scientific domains, particularly in nanomedicine and nano-based drug delivery systems, where these particles are of great interest, nanotechnology has demonstrated its ability to bridge the gap between the biological and physical sciences. A substance that ranges in size from 1 to 100 nm is referred to as a nanomaterial. Materials of this size have an impact on several aspects of nanomedicine, including tissue engineering, drug delivery, biosensors, microfluidics, and microarray testing. To create nanomedicines, nanotechnology uses therapeutic molecules at the nanoscale level. Nanoparticles have been the driving force behind the discipline of biomedicine, which includes tissue engineering, medication delivery, nanobiotechnology, and biosensors. Because they are materials created at the atomic or molecular level, nanoparticles are typically tiny nanospheres.

As a result, they have greater mobility within the human body than larger materials do. Particles at the nanoscale have special biological, mechanical, chemical, electrical, magnetic, and structural characteristics. The ability to use nanostructures as delivery agents to encapsulate or attach therapeutic pharmaceuticals and transport them more precisely to target tissues with a regulated release has led to the increased appreciation of nanomedicines in recent years. The use of information and methods from nanoscience to medical biology, disease prevention, and treatment is a rapidly developing discipline known as nanomedicine. It involves the use of materials of nanoscale dimensions, such as actuating materials in living cells and nanorobots and nanosensors for delivery, diagnostic, and sensory applications.

Drug delivery directed delivery systems, or Targeted Drug Delivery systems, integrate several scientific disciplines, including molecular biology, polymer science, pharmacology, and bioconjugate chemistry, to deliver a medication to a particular site rather than the entire body or organ. The goal of Targeted Drug Delivery systems is to regulate and manage the pharmacokinetics, pharmacodynamics, immunogenicity, a specific toxicity, and bio-recognition of medicinal substances. The ultimate objective is to lessen adverse effects while increasing therapy efficacy. Targeted Drug Delivery systems are distinct from conventional or traditional Drug Delivery systems in that the former rely on drug absorption through biological membranes, while the latter get site-specific release of pharmaceuticals from a dosage form.

2. Basic Principles and Applications of Targeted Drug-Delivery Systems

Bringing a high concentration of medication at the intended site while minimising its concentration in the non-targeted region is the fundamental idea underlying drug targeting. By reducing the negative effects brought on by non-target concentrations, increased dosages, and multi-target interactions, this concept helps to maximise the therapeutic effects of the medication. Additionally, targeting reduces undesired medication interactions with bioenvironmental elements that impact drug delivery to specific body locations. Coordinated drug behaviour, the targeted location, and the pharmaceutical carrier make up drug targeting. The target is the particular organ, cell, or collection of cells that the medicine will interact with and that are in a chronic or acute condition that has to be treated. The carrier is a specifically designed system or molecule that is necessary for the loaded medicine to be transported effectively towards predetermined locations. Both in vivo and in vitro, a drug-targeting combination should ideally be atoxic, nonimmunogenic, biochemically inert, biodegradable, biocompatible, and physicochemically stable. It should also be quickly and swiftly removed from the body, have a limited amount of drug leakage during transit, and have a predictable and regulated pattern of drug release. Its manufacture should also be fairly straightforward, repeatable, and economical.

Targeted drug products should be created with the unique qualities of target cells and the makeup of transport carriers, or vehicles, that deliver the drug to certain receptors, in mind, in order to ensure the fulfilment of these ideal attributes. Physicochemical properties, enzymes, electric fields, physiological environment, drug concentration, particulate location and distribution, surface morphology (shape, charge, size, and density) of the carrier system, and enzymes are some of these important parameters. For efficient targeting of targeted cells or tissue, physiological factors like tissue architecture and blood flow for intravenous drug delivery should be managed in conjunction with physicochemical characteristics like carrier geometry, avidity, composition, and functionalization.

Effective tumor-targeted therapy also depends on extravasation, intratumoral distribution, clinical increased permeability and retention (EPR) impact, tumour heterogeneity, and overexpression features. Effective application of Targeted Drug-Delivery Systems in novel nanomedicine and therapies is possible provided that the optimal qualities are fulfilled and formulation considerations are taken into account. Targeted Drug-Delivery Systems has a wide range of applications in the treatment of infectious and chronic disorders, but because of its superior microphage penetration and increased

concentration at the infection site, it is particularly useful in the treatment of malignant tumours. Cancer treatment, vaccine adjuvant, ocular and brain delivery, DNA and oligonucleotide delivery, intracellular and systemic targeting, oral and transdermal distribution, enzyme immunoassays, and radio imaging are among the promising uses and applications of Targeted Drug-Delivery Systems. Reduced toxicity, better uptake, longer systemic circulation with increased bioavailability and drug impact, increased immunoresponse, improved drug absorption and permeability, improved drug retention, and decreased washout are often reported benefits associated with these uses.

3. TARGETED DRUG DELIVERY TYPES

As was previously said, the goal of drug targeting is not only to boost a medication's therapeutic efficacy but also to reduce its associated toxicity so that lower dosages of the medication may be employed in therapy. Targeting drug categorization and other similar approaches are two widely utilized methods for meeting such requirements.

3.1. Passive targeting

It describes the build-up of a medication or drug-carrier system in a particular location, such as an anti-cancer medication, the cause of which may be traced to pharmacological or physicochemical aspects of the illness. Therefore, in order to maximise circulation times and targeting ability during cancer therapy, the size and surface features of drug delivery nanoparticles must be properly managed to avoid absorption by the reticulo-endothelial system (RES). In summary, passive targeting is a misnomer for a straightforward medication delivery method that involves blood circulation. The liver is not one of the body's designated places for medication release or activity, such as a tumour. Additional instances comprise the use of antimalarial medications to treat *candidiasis, brucellosis,* and *leishmiansis*.

3.2. Active targeting

Active targeting, which only happens after blood circulation and extravasations, refers to a particular ligand–receptor type interaction for intracellular localization. Three distinct degrees of targeting may be distinguished using this active targeting technique, and they are as follows:

- First order targeting, such as compartmental targeting in the lymphatics, peritoneal cavity, multiple cavities, cerebral ventricles and eyes, joints, etc., refers to the confined distribution of the drug carrier systems to the capillary bed of a predefined target location, organ, or tissue.
- Second order targeting is the process of selectively delivering medications to particular cell types, such as cancer cells, rather than to healthy cells. An example of this would be the administration of pharmaceuticals to the liver's kupffer cells.
- Third order targeting is the process of delivering a medicine selectively to a target cell's intracellular location, such as by endocytosis or receptor-based ligand-mediated entrance of a drug complex into a cell.

3.3. First-, Second-, Third-, and Fourth-Order Targeting

Three (or four) distinct orders of targeting can be used to further categorise drug targeting. The drug-carrier system's distribution to the target site's capillary bed is restricted in first-order targeting. The term "second-order targeting" describes the deliberate administration of medications to particular cell types, such tumour cells. Drugs that target macromolecules like DNA and proteins are sometimes designated as having fourth-order targeting, whereas third-order targeting denotes a special focus on intracellular locations.

3.4. Inverse, Dual, Double, and Combination Targeting

Inverse targeting is the process of inhibiting the reticuloendothelial system's normal action using a blank colloidal carrier in order to minimise passive drug absorption. This will cause the system to become saturated with defence mechanism suppression. By delivering a carrier molecule with a distinct therapeutic action, dual targeting increases the drug's (synergistic) therapeutic impact. Double targeting combines temporal and spatial approaches, i.e., temporal delivery at a regulated pace and spatial placement to certain places. Combination targeting is a targeted delivery method that offers a direct path to a target by using carriers, polymers, and homing devices with molecular specificity.

3.5. Physical, Chemical, and Biological Targeting

Systems that localise agents to target locations based on their size, content, or other non-biological receptor-specific properties are referred to as physical targeting systems. Chemical targeting is the process of localising agents to specific regions by employing prodrugs that are unique to a given place. Moreover, agents can be targeted to certain regions by means of enzymatic or chemical processes that result in the agent’s-controlled release or activity, or in the targeting of a vehicle. By using antibodies (Abs), peptides, proteins, or other biomolecules that have a particular affinity for receptors, sites, or other biological targets, localised agents can target specific regions through the process of biological targeting. Via vector systems, gene expression may also be targeted to certain regions by using cells, tissue, or other particular promoters.

3.6. Local and Systemic Targeting

The primary objective of locally targeted systems, which are non-invasive targeting techniques, is to deliver drugs to the local location for the therapy of local diseases. Delivery of such therapeutic systems by an invasive method, such as intravenous infusion of nano-technological systems, is possible with systemic targeting. Once the medicine is distributed throughout the body, these systems administer it through systemic

circulation. The main drawbacks of these systems derive from the harmful effects of the medications in a particular tissue.

4. WIDELY USED VEHICLES FOR TARGETED MEDICATION DELIVERY

Drug carriers come in a variety of forms, including colloidals, polymers, NPs, cells, and monoclonal Abs. The choice of carrier to be utilised depends on the drug's composition, the target, and the stage of the disease. Targeting moieties include charged compounds, proteins, lipoproteins, hormones, and polysaccharides combined with carriers.

4.1. Colloidal Carrier Systems

Colloidal dispersant tablets (NDDSs) are nanoscaled particle targeting vesicles or vesicular dosage forms. They consist of numerous emulsions, liposomes, niosomes, nanospheres, and ceramics. These kinds of drug vectors have the capacity to change the distribution profile by sequestering, transporting, and holding onto the active medication as it elutes or is delivered within or close to the target. They are frequently divided into two groups: microparticulate and vesicular systems.

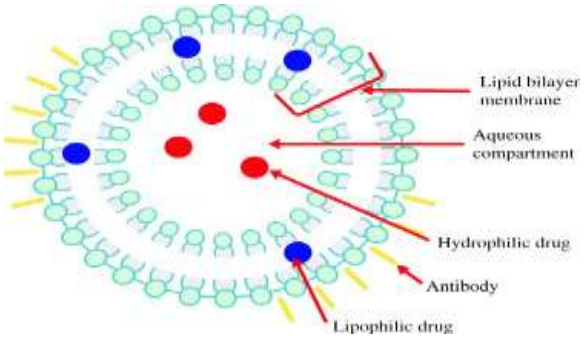

Fig 1: Colloidal Carrier Systems.

4.2. Systems of Vesicular Carrier

The goal of novel vesicular drug delivery systems is to distribute the medication according to therapeutic requirements in a rate- and site-controlled way. These carriers have recently surfaced and provide a variety of delivery methods for controlled and targeted doping. The therapeutic index, solubility, stability, and quick breakdown of drug molecules are all enhanced by vesicular drug delivery systems. The most well-known development in vesicular carrier systems is that of nanosomes. They are tiny, vesicular carriers that carry medications to the intended location. They come in many forms, such as ethosomes, liposomes, niosomes, and transferosomes. Each of these vesicular carriers is a generation of nanosomes that differs from the others in terms of the vesicular composition and properties during manufacture, storage and preparation circumstances, and intended therapeutic uses.

4.2.1. Niosomes

Arguably these carriers, niosomes are among the best. Researchers working in the cosmetics business initially reported on the self-assembly of non-ionic surfactants into vesicles in the 1970s. Niosomes, also known as non-ionic surfactant vesicles, are tiny lamellar structures that are created when cholesterol and non-ionic surfactant belonging to the alkyl or dialkyl polyglycerol ether class are combined. Because non-ionic surfactants are amphiphilic, they need energy, such as heat or physical agitation, to create a closed bilayer vesicle in aqueous fluids. While the hydrophilic heads of the bilayer structure stay in touch with the aqueous solvent, the hydrophobic portions of the structure are orientated away from it. By altering the vesicles' composition, size, lamellarity, tapping volume, surface charge, and concentration, one may modify their characteristics.

The physicochemical characteristics of niosomes and liposomes are comparable, albeit there are minor variations based on the manufacturing techniques and bilayer composition. Niosomes mostly consist of surfactants, whereas liposomes are made up of phospholipids. Since niosomes are far more stable than liposomes, they don't require any particular preparation or storage conditions. But liposomes and niosomes have different properties, particularly because the former are made from cholesterol and uncharged single-chain surfactant, while the latter are made from double-chain phospholipids (neutral or charged). Liposomes contain a far higher quantity of cholesterol than niosomes do. Consequently, liposomes' drug entrapment effectiveness declines relative to that of niosomes. In addition, liposomes are costly and their constituents, such phospholipids, are chemically unstable due to their propensity for oxidative destruction; therefore, these need particular treatment and storage, and the quality of natural phospholipids varies. This may lower the cost of manufacture. Niosomes and liposomes are not as suitable for transdermal distribution due to their poor skin permeability, aggregation and fusion of vesicles, shattering of vesicles, and drug leakage.

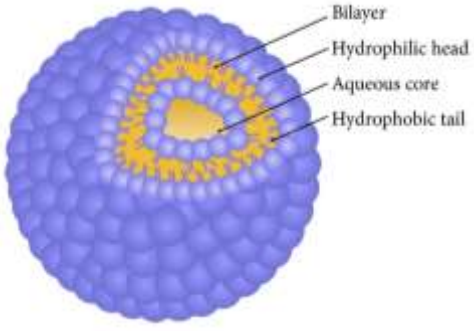

Fig 2: Niosomes.

4.2.2. Liposomes

Liposomes are drug-based, self-assembling phospholipid-based vesicles that surround a core aqueous compartment in the shape of a concentric sequence of several bilayers (multilamellar) or a bilayer (uni-lamellar). Liposomes are between 30 and micrometres in size, having a phospholipid bilayer that is 4-5 nm thick.

British scientist Alec Bangham and associates at Babraham Cambridge established the science of liposomology in the middle of the 1960s, publishing the structure of liposomes for the first time in 1964. Since then, liposomes have been thoroughly studied for their potential as delivery systems for imaging agents, proteins, nucleic acids, and small molecules. To increase treatment effectiveness and patient compliance, several delivery methods, including parenteral, pulmonary, oral, transdermal, ocular, and nasal routes, have been devised. In addition, liposomes have been widely applied in the fields of food and cosmetics.

Liposomes are exceptional drug delivery systems because they shield the enclosed materials from physiological deterioration, prolong the drug's half-life, regulate drug molecule release, and have high levels of safety and biocompatibility. Moreover, liposomes can use passive or active targeting to deliver their payload to the sick site selectively, reducing systemic adverse effects, increasing the maximum tolerated dose, and enhancing therapeutic benefits.

Sphingomyelin (SM), cholesterol (Chol), and glycerolphospholipid (GP) are the main ingredients found in commercially available products. Glycerol, which connects two hydrophobic fatty acid chains and a hydrophilic polar head group, is present in GP. Different head groups generate liposomes with neutral (PC and PE) or negative (PA, PS, PG, and cardiolipin) charges at physiological pH levels. Considering GPs have an impact on liposome biophysical characteristics (drug encapsulation, stability, and release), as well as the pharmacokinetic and pharmacodynamics in vivo, they are crucial to formulation. The bilayer's thickness and fluidity, phase transition temperature, and rate of drug release are determined by the hydrocarbon chains' length, symmetry, inter- and intramolecular interactions, branching, and degree of unsaturation. For the most part, a longer hydrocarbon chain may result in tighter membrane packing and increased drug retention, whereas a higher degree of unsaturation or branching may result in looser membrane packing. This is likely due to the fact that cholesterol preferentially interacts with saturated phospholipids rather than unsaturated ones.

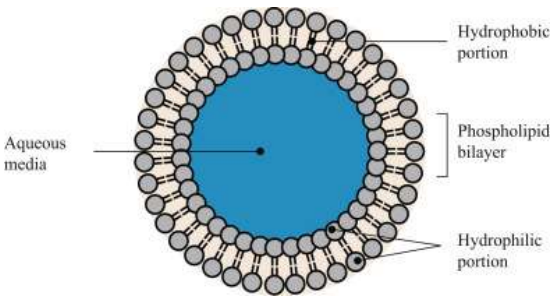

Fig 3: Liposomes.

4.2.3. Transferosomes

Transferosomes are a unique kind of liposome that are made up of an edge activator and phosphatidylcholine. These are flexible, soft vesicles designed to improve the delivery of active drugs. IDEA AG, a German business, registered them and uses them to refer to its own unique medication delivery technique. The Latin term "transfere," which means "to carry across," and the Greek word "soma," which means "body," are the sources of the name, which means "carrying body." An artificial vesicle called a transferosome carrier is made to resemble a cell vesicle or a cell undergoing exocytosis, making it appropriate for targeted and controlled drug administration. A transferosome is a complex aggregate that is extremely flexible and sensitive to stress. Its ideal shape is a very malleable vesicle with a complex lipid bilayer around an aqueous centre. The vesicle is both self-regulating and self-optimizing due to the interdependency of the bilayer's structure and local composition. Because of this, transferosomes are able to effectively pass through a variety of transport barriers and function as drug carriers for targeted, non-invasive drug delivery and therapeutic agent release that is maintained. Using vesicle formulations as skin delivery systems is one of the most contentious approaches of medication administration via the skin.

Transferosomes are self-aggregates that transfer drugs into or through the skin in a repeatable manner. They have a very flexible membrane. Compared to regular liposomes, these vesicular vesicles are orders of magnitude more elastic. Transferosomes squeeze themselves along the intracellular sealing lipids of the stratum corneum to get around the barrier of skin penetration. Transferosomes are composed of a blend of lipids and biocompatible membrane softeners, which may be applied transdermally. The ideal combination causes the elastic liposomal membranes to become flexible and opens the door for penetration through the skin's channels, which are opened by the carriers. A supramolecular structure known as a transferosome has the potential to cross permeability barriers and transfer materials from the application site to the destination location.

Under the right circumstances, transferosomes have the ability to move 0.1 mg of lipid per hour and square centimetre over undamaged skin. Compared to the value usually dictated by the transdermal concentration gradients, this value is significantly greater. This high flux rate is caused by "transdermal osmotic gradients," which are naturally existing gradients that are available across the skin but are significantly more pronounced. The skin penetration barrier creates an osmotic gradient that keeps the viable portion of the epidermis (75% water content) and the almost dry stratum corneum (15%) close to the skin's surface from losing water. This gradient also keeps the skin from drying out.

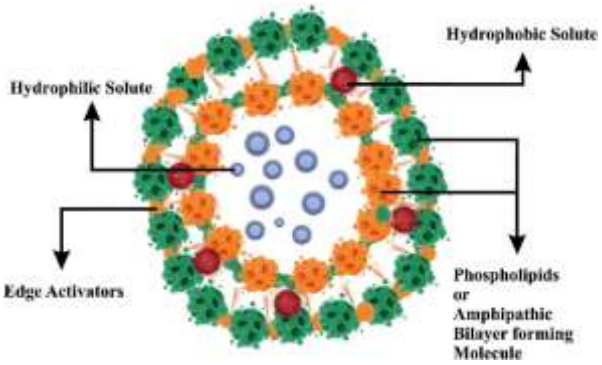

Fig 4: Transferosomes.

4.2.4. Spanlastics

Spanlastics are a unique drug delivery device that traps the medication as a bilayer in the core cavity. The phrase "Spanlastic" (Span + Elastic) was initially used in 2011. These carriers resemble transfersomes in that they are elastic and extremely malleable. Compared to drug solution, these deformable vesicular carrier systems exhibit enhanced permeability. They are amphiphilic, meaning that the drug is contained in a vesicle formed by a non-ionic surfactant. Spandex is quite tiny and minuscule in size. These unique nanovesicles eliminate the drawbacks of liposomes, namely their tendency to become unstable chemically. The varying purity of phospholipids and liposomes' susceptibility to oxidative degradation are the causes of their chemical instability. The inclusion of edge activators in their structure is responsible for the vesicles' elastic character.

4.2.4.1. Advantages of Spanlastics

- Spanlastics are biodegradable and non-immunogenic in nature.
- Enhancement of Bioavailability: The drug's protected support allows it to reach the intended location without being broken apart, resulting in increased bioavailability compared to the conventional form.
- Target Specific: By protecting the drug from the environment and reducing its impact on the intended spot, they improve the healing efficacy of medicated particles. They boost the stability of the medication that is entrapped and are both osmotically active and stable.
- Handling and storage of surfactants require no special condition.
- Their purpose is to accomplish activity particular to the site.
- Unlike liposomes, these vesicles are chemically stable and can target the retinal pigment epithelium, vitreous cavity, and choroid in both the anterior and posterior segments of the eye due to their elastic nature, which allows them to squeeze through the corneal membrane.

4.2.4.2. Components of Spanlastics

Spanlastics and traditional liposomes are structurally similar. These resemble Transfersomes, which are elastic liposomes that are extremely malleable. Two essential components of spanlastics are an edge activator and a nonionic surfactant. These vesicles have been dubbed spanlastics because they are mostly made of spans, or surfactants.

- **Non-ionic Surfactant**

Lowering the interfacial tension between two liquids—the aqueous phase and the oily phase—is the goal of surface active agents, or surfactants. The head of a nonionic surfactant is devoid of any charged groups. Spans, or sorbitan alkyl esters, are a significant subclass of non-ionic surfactants. The organisation of Spans into concentric bilayers creates the vesicular structure of spanlastics. There are several sorts of spans, such as Span 80 (monooleate), Span 60 (monostearate), Span 40 (monopalmitate), and Span 20 (monolaurate), depending on the kind of fatty acid linked to the polyoxyethylene sorbitan component of the molecule. When forecasting the stability of the vesicular formulation, the kinds of Span are crucial.

- **Edge Activators**

These surfactants belong to a unique class that exhibits high hydrophilicity or HLB value. These are single chain surfactants that reduce the interfacial tension of the vesicles, destabilising them and making the bilayer vesicles more deformable. As a result, they provide these vesicles' lipid bilayer membranes flexibility. EAs typically form more spherical vesicles, which result in lower particle sizes. By adding an edge activator (Tween 80), the vesicles' elastic properties would be amplified, enabling them to momentarily expand the biological membranes' pore size. This would enable somewhat larger vesicles to enter and improve drug penetration.

- **Ethanol**

The characteristics of these nano-vesicular carriers are improved by ethanol. It helps to enhance the drug's entrapment and partitioning inside the vesicles. Ethanol's capacity to condense membranes results in a decrease in vesicular membrane thickness, which in turn reduces vesicular size. Ultimately, this modifies the net charge of the system towards a negative zeta potential, resulting in a degree of steric stabilisation.

4.2.4.3. Morphology

They can be either multilamellar (MLVs) or unilamellar (ULM). These can be either (SUVs) Small unilamellar (10-100 nm) or (LUVs) Large unilamellar (100-3000 nm) depending on the size of the vesicles. According to reports, MLVs retain information longer than SUVs with equivalent lipid composition. Spheroid structures called spanlastics are made of amphiphilic molecules that function as appropriate matrix for bioencapsulation.

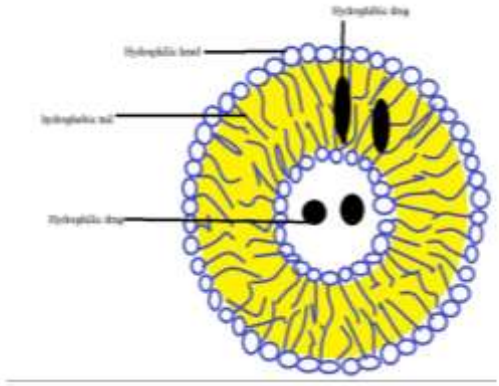

Fig 5: Spanlastics.

Methods to fabricate nano-particles

The appropriate and adequate technique is determined by the physicochemical properties of the polymer and the chosen medication.

1. Salting out method

This technique has the benefit of lowering the stress on the protein involved in the synthesis of encapsulants, and it produced high efficiency and was simple to scale up. The extraction of water miscible solvent from such an aqueous solution is what causes the salting-out phenomenon. The first phase involves dissolving the drug as well as the polymer in a vehicle, which would be subsequently emulsified into such an aqueous gel with salting out reagent and a colloidal stabiliser. Colloidal stabilisers and salting out agents, including electrolytes and non-electrolytes, have indeed been employed.

By using this method, an oil/water emulsion is created, that is then diluted with additional water to improve solvent diffusion inside the aqueous phase and facilitate the production of nano-spheres. The manufacture of ethyl cellulose, PLA, and poly-methacrylic acids nano-spheres uses the salting out method.

2. Solvent evaporation method

This method depends on both how soluble the polymer is and how hydrophobic the organic solvent is. Ibuprofen's better skin absorption and betulinic acid nanoparticles as an alternate treatment for visceral leishmaniasis are two examples.

The first step is the emulsification of a polymer solution in an aqueous phase, which is proceeded by the evaporation of the solvent of the polymer, which causes the polymer to precipitate as nano-spheres. The drug-polymer mixture is emulsified inside an aqueous solution that includes a surfactant or emulsifying agent to create oil in water (o/w) emulsion. Once a stable emulsion has been established, the organic solvent then is evaporated either by constant stirring or by lowering the pressure. To create tiny particle sizes, ultrasonication or high-speed homogenization may well be utilised. Nanoparticles are gathered by ultracentrifugation, and then any free drugs or stabiliser residue is removed by washing them in distilled water. For preservation, nanoparticles are even further lyophilized.

3. Emulsions–diffusion method

Excellent encapsulation efficiency, the absence of homogenization, high batch-to-batch repeatability, ease of scaling up, ease, and limited size range are just a few advantages of this method. This method was utilised to create poly lactic acid and make PLGA nanoparticles that were loaded with oestrogen.

The encapsulating polymeric is saturated with water after being mixed in a solvent that is partially water-miscible. Next, based on the oil-to-polymer proportion, the polymer-water saturated solvent phase is emulsion in an aqueous solution that contains a stabiliser, resulting in solvent diffusion to the outer phase as well as the creation of nano-spheres or nano-capsules. Based on the solvent's boiling point, the solvent is eliminated in the final phase either through evaporation or filtration.

4. Double emulsion and evaporation method

Examples of drug nano-formulations created using the double emulsion approach includes oleuropein with increased stability and Rose Bengal for the treatment of breast carcinoma.

The double emulsion method is used to load the lipophobic medication. Drug solutions are added to an organic solution that contains the polymer while being stirred constantly to create a w/o emulsion. The second aqueous phase then gradually incorporates the created emulsion. Continue spinning until the w/o/w emulsion forms. After the solvent has evaporated, high-speed centrifugation may be used to separate the nanoparticles.

5. Coacervation or ionic gelation method

Two distinct aqueous phases have been prepared, one for the polymer and the other for the polyanion sodium tripolyphosphate, and it varies depending on the strong electrostatic attraction between both the positively charged amino group of chitosan and the negatively charged tripolyphosphate to shape coacervates with a magnitude in the nano-meter range.

6. Polymerization method

Diffusion in the polymerization medium or adsorption onto to the nanoparticles after completion polymerization is the two ways that drugs are introduced during the polymerisation. An isotonic medium devoid of surfactants can be utilized to re-disperse the nanoparticle suspension after ultracentrifugation to remove the various stabilisers and surfactants that were employed throughout polymerization.

7. Nano spray drying

A quick, easy, repeatable, and expandable drying method known as spray drying provides for moderate ambient temperature that are ideal for heat-sensitive

biopharmaceutical molecules. In contrast to certain other drying techniques, spray drying is a continual process that turns various liquids into solid particles while providing for alterations in dimension, distribution, structure, porosity, density, and chemical properties.

Four steps are involved in spray drying: heating the drying gas, producing droplets, drying the droplets, and collecting the particles.

8. Supercritical fluid technology

Although supercritical fluid technology is suitable for large-scale production and is ecologically beneficial, it requires specialised, expensive gear. Supercritical fluids are fluids that, even at temperatures higher than their critical temperature, maintain their homogeneity. Due to its moderately critical conditions, non-flammability, high cost, and safety, supercritical CO2 (SC-CO2) is the supercritical fluid that receives the most applications.

Future of nanomedicine and drug delivery system

Although nanoparticles and nano-drug delivery systems are widely understood, their actual impact on the healthcare system—including in the treatment and diagnosis of cancer—remains quite restricted. In the end, the use of nanoparticles will develop along with our growing understanding of diseases at the cellular scale or that reflect a nanomaterial-subcellular scale equivalent biomarker identification to open up new pathways for diagnosis and treatment. Therefore, developing nanoparticle applications for the future will require knowledge of the molecular fingerprints of disease.

Theoretical mathematical models of prediction, technologies for the evaluation of these processes, drug effect in tissues/cellular level, and the concept of controlled release of specific medications at the troubled locations are not yet reached their full potential.

Animal experiments and interdisciplinary study, which takes a lot of time and money, will yield valuable information that might be used in drug therapy and diagnostic studies. The search for more accurate treatments and diagnoses is an expanding worldwide trend, as well as the development of nanoparticles and nano-drug delivery system appears to be promising.

The creation of nanorobots and nanodevices that work in tissue diagnostic and repair mechanisms with full external methods of control has generated a significant amount of attention. But just as with their advantages, nanomedicines' possible drawbacks must also be thoroughly investigated, both for humans and the ecosystem as a whole. Therefore, a thorough examination of the potential acute or long-term harmful consequences of novel nanomaterials on people and the environment is necessary. The accessibility of nanomedicines would be another topic of study that requires more study input as they become more and more widespread.

CONCLUSION

The application of nanotechnology to medicine, particularly more particularly to the administration of drugs, is expected to grow quickly. Pharmaceutical sciences have used nanoparticles to lessen the toxicity and adverse effects of drugs for many years. It wasn't known until recent that the carrier systems itself could present dangers to the patient. Further than the typical risks given by compounds in delivery matrix, new risks are added by the use of nanoparticles for medication administration. Unfortunately, there is currently no scientific framework for the potential (adverse) reaction of nanoparticles, and we know very little about the fundamentals of how nanoparticles react with living organisms, tissues, and animals.

For the future development and application of sustainable nanomaterials in medication delivery, a conceptual understanding of biological responses to nanoparticles is required. In order to advance this topic, strong cooperation between individuals involved in particle toxicology and drug delivery is required for the exchange of ideas, techniques, and knowledge.

Author's Contribution

All authors have equal contribution on conceptual writing of the paper.

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