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Nanostructured Multiparticulate Drug Delivery System.

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ABSTRACT:
Pharmaceutical development and research are increasingly focusing on delivery technologies that help patients achieve their therapeutic goals while minimising negative effects. Recent trends suggest that multiparticulate drug delivery technologies are particularly well suited to creating controlled or delayed release oral formulations with low dose dumping risk, blending flexibility to achieve varied release patterns, and a repeatable and short gastric residency time. The amount of drug released from microparticles is determined by a number of factors, including the carrier utilised to generate the multiparticles and the amount of medication inside. As a result, multiparticulate drug delivery methods open up a world of possibilities for creating new controlled and delayed release oral formulations, broadening the scope of future pharmaceutical development.
Nanostructures are crucial in the development of new functions and the improvement of medications. Nanostructures are materials or structures with at least one dimension of 1 to 100 nanometers. Because designing and developing novel pharmacological entities is difficult and time-consuming, it comes at a significant expense. As a result, enhancing the solubility qualities of conventional medications could be a good way to boost the bioavailability of drugs that are poorly water soluble. Without sophisticated production methods, nanosizing pharmaceuticals in the form of nanoparticles, nanocrystals, or nanosuspensions can be utilised as a simple technique to boost medication dissolving rate and hence bioavailability. The use of these systems has enhanced the dissolution rate and, as a result, the bioavailability following oral administration.Solubility, bioavailability, and dissolution rate of medications are critical parameters for achieving efficiency, hence this study examines several nanostructured forms that have been used or could be employed as multiparticulate drug delivery systems.

I. INTRODUCTION:

Multiparticulate drug delivery also known as multi-unit dosage form was introduced in 1950[(2)]. It aids in the development of diverse dosage forms because of its unique features, which make production more versatile. Single-unit dose forms include immediate/delayed-release tablets, extended-release, coated/uncoated tablets, or osmotic tablets, whereas multi-unit (multiparticulate) dosage forms include pellets, microencapsulation, or compressed tablets [1]MDDS is made up of several small distinct particles, each of which has eccentric properties with the characteristic unit, allowing for regulated drug release. Pellets, granules, microparticles, and nanoparticles formulations are examples of multiparticulate techniques that have been employed for particular drug delivery. Some of the procedures used to entrap or layer drug particles onto and around surfaces include pelletization, in situ polymerization, interfacial polymerization, phase inversion, coacervation, solvent evaporation, spinning disc, co-extrusion, hot melt, granulation, spray drying, and spray congealing.

Microcapsules, beads, pellets, or microparticles, as well as microcapsules, beads, pellets, or microparticles, and mini-tablets, are discrete small, repeated units of drug particles that may or may not be of comparable pharmacological patterns. Their size that has been reported ranges from 150 m in diameter for taste-masked multiparticulate to 2–3 mm in diameter for mini-tabs (3).

Multiparticulate formulations can range from orally dissolving particles to immediate-release and modified-release formulations, and might include a single medication or numerous pharmacological combinations. After combining with additional excipients and compression, multiparticulate systems are administered as a single dose of the medicine or pharmaceuticals in the form of hard-shell capsules, sachets, tablets, or other formulations. Because multiparticulates are less attracted to GI Predicted Time, they reduce the

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risk of dose quick release, systemic toxicity, irritation, and an unlimited variance in bioavailability. Furthermore, the technologies that are used by the Scientists and regulators are well-versed in the technologies involved in the production and manufacturing of tablets and capsules. In recent years, many drug products have been marketed with multiparticulate drug delivery technology. The following are a few of the major advantages of MDDS:

(a) When compared to single-unit dosing forms, dose-weight proportionality is easier.

(b) Formulations for fixed-dose combination formulations that are flexible.

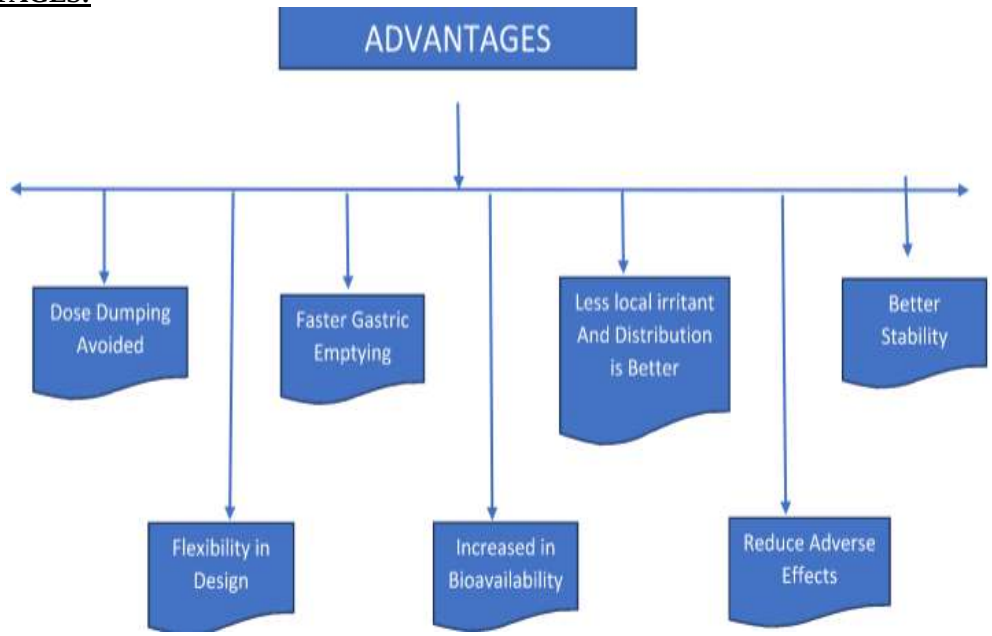
(c) Less variance in stomach emptying rate and overall gastrointestinal transit time reduces intra- or inter-subject variability.

(d) Dose titration flexibility without jeopardizing drug release, which can be an issue with extended-release monolithic tablets.

(e) In the case of juvenile and geriatric populations, flexibility in mixing them with food for easy swallowability.

II. ADVANTAGES AND DISADVANTAGES:

ADVANTAGES:



III. DRUG RELEASE MECHANISM FROM MULTI PARTICULATES:

MDDS has three mechanisms: osmosis, diffusion, and erosion.

3.1 Osmosis:

With the help of osmotic pressure created within the particle, the medicine is released out into the environment through the coating.

Osmotically controlled DDS (CDDS)-based devices are the most compatible CDDS, especially for oral route drug delivery, because they use osmotic pressure to verify drug release in a regulated manner. Various osmotic agents, such as excipients, semipermeable membranes, and drugs, are used in the systems.

3.2 Diffusion:

When a drug comes into contact with the GI tract, water diffuses into the particle, causing the drug to dissolve.

The reservoir device and the monolithic device are two methods for obtaining diffusion-controlled release. Drug product products spread in a matrix in monolithic devices, and diffusion may occur through a polymer mer matrix or by bridging between the polymer chain and the molecular level. A reservoir device is an example of a device in which a medication is encapsulated or cored within a polymer sheet.

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3.3 Erosion

Wherever coatings are specifically intended to wear away gradually over time, allowing medications contained within the particle to be administered via erosion. Polymer coverings that dissolve progressively as a function of GIT parameters such as pH and motility can be used to accomplish erosion.

- **MULTIPARTICULATE DRUG DELIVERY SYSTEMS COME IN MANY FORMATS**:

1. Pellets.
2. Minitablets.
3. Spheroids..
4. Granulation.
5. Components with nanostructures.
6. Spray drying.
7. Spray congealing.

Pellets:

Pellets are available in sizes ranging from 0.2mm to 2.0mm. They are small, free-flowing, systematically created spheres or semispheres made from fine powders or granules using various pelletization techniques.

Orally administered pellets in hard gelatin capsules/disintegrating tablets release the medicine in the stomach and spread it throughout the GIT system without losing any of its effects.

Minitablets:

Minitablets are small tablets with a diameter of 1.0-3.0 mm. Mini-tablets are flat or slightly curved tablets that can be put in capsules or compacted into a giant tablet and inserted into a sachet. (6). Minitablets are a terrific alternative to pellets and are very appealing. These mini-tablets are made using small matrices and tableting processes (7).

Spheroids:

Water-insoluble pharmaceuticals are a controlled-release pharmacological composition that can be given to people or animals, according to a recent invention. The term "spheroid" refers to an aspherical granule with a diameter of 0.5mm to 2.5mm, preferably 0.8mm. By spheronisation, MCC, a non-water-soluble medicinal excipient, is employed to produce spheroids. The higher the MCC content, the easier it is to create spheroids. Microcrystalline cellulose, on the other hand, has less control over drug release and so cannot exhibit controlled release features.

This flaw can be remedied by:

1. Applying a controlled release polymer to the spheroids.
2. MCC content is reduced to 50% w/w or less than the excipient weight, and an excipient is introduced that does not affect drug release at a concentration of 10% or greater than the excipient weight. In both cases, disadvantages are present.

Granulation :

Granulation is the process of converting powder into microscopic particles with a diameter of 0.2-0.4mm. Granulation aids in the modification of powder drug flow qualities, compression characteristics, packing arrangement, and dissolution-disintegration parameters. Granulation can be classed as dry granulation or wet granulation depending on the procedures used. In wet granulation, a compact mass of powder is created by adding liquid or water to the medication, which is subsequently sieved to the desired size granules. Granules are created without the use of liquid ingredients in dry granulation. Granule effectiveness is influenced by the type and volume of binder used, the amount of time required to prepare the wet mass, the amount of force exerted, and the rate at which the granules dry. The following are the most popular new granulation techniques:

1. Pneumatic dry granulation
2. Freeze granulation
3. Foamed binder technology
4. Steam Granulation
5. Moisture activated dry granulation
6. Melt granulation technology
7. Thermal adhesion granulation process

• LIMITATIONS OF MPS:

There are some limitations, such as low drug loading capability, a disproportionately higher requirement for process variables in comparison to others, the inclusion of a large number of formulation processes, and a higher cost in terms of production. Aside from that, production requires advanced technology as well as trained/skilled personnel.

NANOSTRUCTURED COMPONENTS:

Nanostructures are structures with a molecular scale of 1 nm to 100 nm in at least one dimension. The majority are synthetic and can be built into a variety of physical qualities. Common nanostructures include nanosurfaces, cylindrical nanotubes, and nanospheres.

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Nanostructures are created by arranging nanoparticles atom by atom or electron by electron arrangement utilizing deposition and lithography processes.

- **ADVANTAGES OF NANOSTRUCTURES**:

The following are some of the advantages of nanostructures:

1. An increase in the dissolution rate
2. Increase in Bioavailability
3. Increase in rate of absorption of poorly water-soluble drugs,
4. Extended circulation times
5. Active targeting capabilities,
6. Protecting from opsonization
7. Clearance in the bloodstream,
8. Toxicity reduction
9. Reducing side effects of drugs

NANOSTRUCTURES LIST:

• **Gradient multilayer nanofilm (GML nanofilm):**

A GML nanofilm is a group of quantum dot films with a gradient in nanoparticle size, composition, or density built in. Solar cells[1][2][3] and energy storage devices are both benefiting from the properties of such nanostructures. GML nanostructures can be implanted in organic materials (polymers) or combine two or more materials to form quantum dots.

• **Icosahedral twins**:

An icosahedral twin is a type of atomic cluster nanostructure. These twenty-faced clusters are made up of ten interconnected dual-tetrahedron (bowtie) crystals that are usually connected along with triangular faces with three-fold symmetry. On size scales where surface forces outnumber bulk forces, a variety of nanostructures (e.g. condensing argon, metal atoms, and virus capsids) take on an icosahedral shape. Face-centered-cubic (FCC) metal-atom clusters, for example, have a twinned version of these nanostructures.

• **Gold nanocages**:

Nanocages are hollow and porous gold nanoparticles with sizes ranging from 10 to 150 nanometers. The reaction of silver nanoparticles with chloroauric acid (HAuCl4) in boiling water produces silver nanoparticles. Gold nanoparticles absorb visible light (about 550 nm), whereas gold nanocages absorb near-infrared light, which biological tissues absorb the least. Because gold nanocages are biocompatible, they could be used as a contrast agent in optical coherence tomography. The photothermal effect causes gold nanocages to absorb light and heat up, killing cancer cells in the surrounding area. Nanocages have been functionalized using cancer-specific antibodies.

• **Nanocomposite:**

A multiphase solid material with one, two, or three dimensions of less than 100 nanometers (nm) or structures with nano-scale repetition intervals between the distinct phases that make up the material is referred to as a nanocomposite.

• **Nano fabrics**:

Nano fabrics are textiles made composed of microscopic particles that have been developed to offer ordinary materials features like superhydrophobicity, odor and moisture elimination, enhanced elasticity and strength, and bacterial resistance. A Nano fabric is made from nanoscopic threads called nanofibers or by adding a solution containing nanoparticles to a conventional fabric, depending on the desired feature.

• **Nanoparticle:**

Nanoparticles are particulate dispersions or solid particles having a diameter of 10 to 1000 nanometers. A medication is dissolved, entrapped, encapsulated, or connected to a nanoparticle matrix in one of several ways. Nanoparticles, nanospheres, and nanocapsules can be made depending on the method of preparation. The main goals of nanoparticle design as a delivery system are to manage particle size, surface characteristics, and release of pharmacologically active substances to produce site-specific drug activity at the therapeutically appropriate rate and dose regimen. The following are some of the benefits of employing nanoparticles as a drug delivery system:

1. Nanoparticle size and surface properties can be easily adjusted after parenteral delivery to accomplish both passive and active medication targeting.
2. They control and maintain the drug's release during transportation and at the site of localization, modifying the drug's organ distribution and subsequent clearance to improve drug therapeutic efficacy and reduce side effects.
3. The choice of matrix constituents can easily modulate controlled release and particle degradation characteristics.

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• **Nanogels:**

A "Nanogel" is a nanoparticle made up of a hydrogel and a cross-linked hydrophilic polymer network. Nanogels (nanosized hydrogels) are swollen small particles made up of flexible hydrophilic or amphiphilic polymer networks that are mechanically or chemically cross-linked. Anionic or ionic polymer networks are possible. They act as drug carriers and are built in such a way that they can easily absorb physiologically active chemicals through biomolecular interactions such as salt bonds, hydrophobic or hydrogen bonding. By tailoring the molecular composition, size, and shape of these nanogels, they may easily encapsulate multiple classes of biomolecules, ensuring the regulated release of therapeutic molecules in vivo. When nanogels are disseminated in aqueous environments, their inflated networks soften, allowing them to encapsulate a certain volume of water. [5]

• **Niosome**s:

A hydrating mixture of cholesterol and nonionic surfactants produces nonionic surfactant vesicles, which are known as niosomes. It can transport both amphiphilic and lipophilic medicines. The medication is enclosed in a vesicle in the niosomes drug delivery mechanism. Niosomes are biodegradable, biocompatible, and non-immunogenic, and their structural characterization is flexible. The major goal of this review is to look at how niosome technology is being utilized to treat a variety of ailments. Niosomes have a lot of potential in research and are valuable to both researchers and pharmaceutical companies. Because niosomes are stable and cost-effective, they appear to be a preferable drug delivery technique over liposomes. Niosomes also have a lot of medication delivery potential for anti-cancer and anti-infective medicines. Novel drug delivery concepts such as proniosomes, discomes, and aspasomes can improve the niosome's drug delivery capacity.

As a result, more study and research are needed in these areas to bring out or createcommercially accessible niosomal preparations.

• **Nanoemulsions**:

These are emulsions that are made up of nanoparticles.

Nanoemulsions are submicron-sized emulsions that are being investigated as pharmaceutical carriers for improved therapeutic agent delivery. They're the most advanced nanoparticle methods for delivering biologically active compounds to the body for targeted drug delivery. Nanoemulsions are a thermodynamically stable isotropic system in which two immiscible liquids (water and oil) are mixed with an appropriate surfactant or surfactant mixture to generate a single phase with a droplet diameter of 0.5-100 um. The diameter of nanoemulsion droplets is typically 20-200 nm, with a narrow size distribution. Nanoemulsions have applications in cosmetics, diagnostics, pharmaceutical therapy, and biotechnologies.

• **Nanoliposomes:**

The word nanoliposome was recently used to refer to nanoscale lipid vesicles alone. Nanoliposomes have the same physical, structural, and thermodynamic features as liposomes, as well as the same manufacturing and creation procedure. The hydrophilic–hydrophobic interaction between phospholipids and water molecules is the underlying process for the creation of liposomes and nanoliposomes. Nanoliposomes, also known as submicron bilayer lipid vesicles, are a relatively new technology for encapsulating and delivering bioactive substances. Pharmaceuticals, cosmetics, and nutraceuticals are just a few of the bioactive materials that can be incorporated into nanoliposomes. Nanoliposomes have potential uses in a wide range of industries, including nanotherapy, cosmetics, food technology, and agriculture, due to their biocompatibility and biodegradability, as well as their nanosize.Bioactive drugs' efficacy can be improved by using nanoliposomes, which improve solubility and bioavailability, in vitro and in vivo stability, and reduce undesired interactions with other compounds. Nanoliposomes can also deliver a delayed release of an encapsulated medication, resulting in increased efficacy and persistent exposure to the site of action. Hydrophilic medications are usually added to the aqueous compartment, while lipophilic pharmaceuticals are added to the phospholipid layer. Nanoliposomes, on the other hand, do not degrade and are not cleared by liver macrophages as quickly as liposomes. Nanoliposomes are essential for tailored medication delivery. It can be utilized in both passive and active targeting scenarios. [8]

• **Nanofibers:**

Because of the benefits it provides, nanotechnology has become a popular choice in contemporary research. Exploring and/or

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implementing diverse methodologies for the creation of nanostructured drug delivery systems is the focus of current pharmaceutical development research. Electrospinning nanotechnology has established itself as a preferred method for producing nanofibers for a variety of applications. Electrospinning is an innovative, reliable, and efficient production technology that is generally recognized and utilized to produce nanofibers with unique characteristics such as a length of several kilometers and a diameter of less than 300 nm.

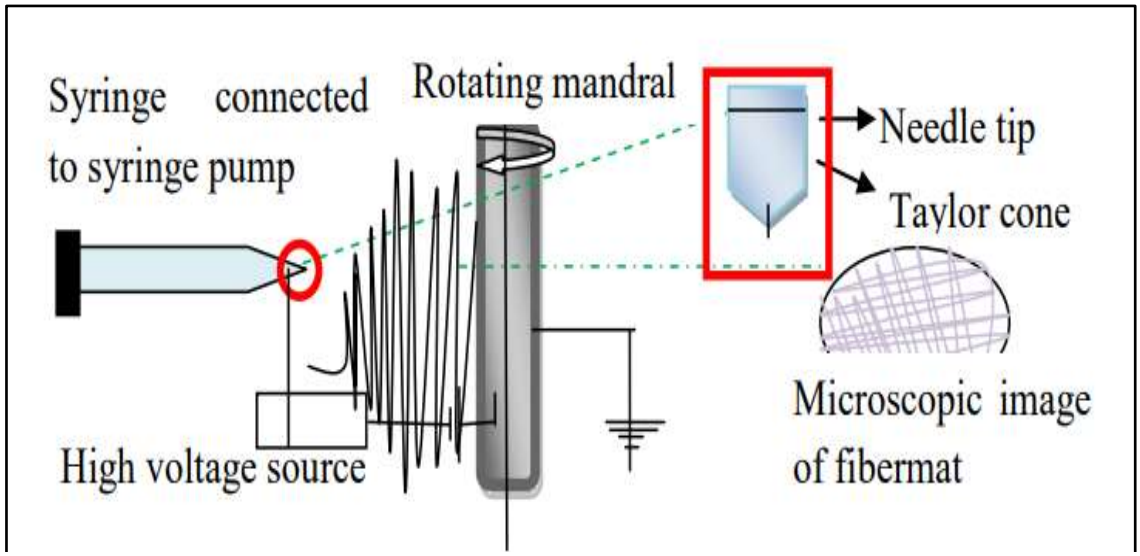

Fig.3: Electrospinning of nanofiber

Nanofibers have a high surface-area-to-volume ratio and high porosity, making them a strong and appealing candidate for a variety of sophisticated applications.Nanofibers are described as fibers with a length-to-thickness ratio of less than 1000:1. "Nanofiber is defined as nanomaterials with at least one dimension, that is, 100 nm or fewer," according to the American National Science Foundation. Nanofiber formulations can be created by selecting appropriate polymers, practical additives, and appropriate manufacturing processes based on a variety of essential characteristics that determine their ability to meet the needs of their specific application area. Electrospinning, self-assembly, drawing, melt blowing, template synthesis, phase separation, melt spinning, and centrifugal spinning are some of the processes used to make nanofibers. [9,10]

• SOLID LIPID NANOPARTICLES:

Solid lipid nanoparticles (SLNs) are made from lipids that can return to their solid-state when cooled. In comparison to typical polymeric nanoparticles, these nanoparticulate formulations are created from physiologically acceptable lipids, making them a safe and effective alternative((9). SLNs for oral drug delivery is used to improve the therapeutic efficacy of medicines with limited water solubility or bioavailability by increasing in vivo solubilization and absorption by the lymphatic system, avoiding first-pass metabolism. They are also capable of maintaining medication release for a long time, which aids patient compliance, and they are suitable for lymphatic system localized treatment. Size reduction techniques such as homogenization (hot and cold) and ultrasonication, solvent emulsification/evaporation, and the supercritical fluid approach are among the various SLN fabrication technologies.

1) Homogenization and ultrasonication:

Homogenization and ultrasonication are common methods for reducing the size of lipid droplets in an emulsion (10,11). The medication is dissolved/dispersed in lipid melt, which is then placed into an aqueous phase containing surfactants (as an emulsion stabilizer) and kept at a temperature above the lipid's melting point to prevent it from solidifying. This combination is then homogenized using a high-pressure homogenizer, ultrasonication with an ultrasonicator, or high shear mixing with an ultra-turrax for a sufficient period at the same

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temperature. The oil droplets are reduced to the nanoscale during this procedure. It's worth noting that the amount of surfactants applied must be sufficient to stabilize the oil droplets, which have a massively increased surface area after being reduced in size.The resulting product is a nanoemulsion, which is subsequently cooled to allow the lipids to crystallize into solid lipid nanoparticles. Because of the small particle size and the presence of emulsifiers, the crystallization process in the aqueous phase may be slowed even when the emulsion is heated to well below the lipid's melting point. The term "super-cooled melt" refers to lipid in this physical state. Solid-state characterization of samples should be carried out using X-ray diffraction and differential scanning calorimetry to avoid misinterpretation of such a 'nanoemulsion' as a 'nanosuspension' [12]. The key issues with the above approach are drug leaking into the aqueous phase, temperature-induced drug degradation, crystal alteration, and the formation of super-cooled melts.To address these difficulties, cold homogenization was used, in which a solid solution/dispersion containing medication dissolved/dispersed in bulk lipid was milled to microparticles using ball or mortar milling [13,14]. These microparticles are subsequently disseminated in a surfactant solution and homogenized at or below room temperature using high-pressure homogenization. When compared to heat homogenization, the particle size achieved by this process is usually larger.

2) Solvent emulsification/evaporation:

The drug-lipid mixture is dissolved in a water-insoluble organic solvent in this process [15,16]. The solution is then put into a surfactant-containing aqueous phase and homogenized at a temperature high enough to evaporate the solvent. As the organic solvent evaporates, the lipid precipitates in the aqueous environment, forming nanoparticle dispersion. The size of the nanodispersion particles is determined by the lipid concentration in the system. The usage of organic solvent, which must be eliminated until its concentration is within acceptable limits, is the method's principal flaw.

3) The method of supercritical fluids:

To create a homogeneous mixture of medication and lipid, organic solvents are often utilized in the manufacturing of solid lipid nanoparticles. These solvents may be toxic to administer if they are not eliminated according to regulatory criteria. The supercritical fluid approach was used to generate organic solvent-free solid composite lipid/drug nanoparticles. The lipid and medication are dissolved in an organic solvent to generate a solution in this method. This is then emulsified in an aqueous media to produce an emulsion with a discontinuous micelle phase containing an organic solvent, drug, and lipid, as well as a continuous phase. Finally, under proper conditions, the emulsion is treated with a supercritical fluid, which removes the organic solvent from the micelles, resulting in the precipitation of solid composite lipid/drug nanoparticles [17].

The above-mentioned process produces an aqueous dispersion as the ultimate form of the product. In this physical state, the SLNs' stability is jeopardized because they are prone to particle aggregation and drug leakage into the exterior dispersion phase. As a result, it is suggested that the aqueous dispersion be lyophilized into a dry powder form. Lyophilization of the SLN dispersion is commonly done with the right amount of cryoprotectants such sorbitol, mannose, trehalose, glucose, and polyvinylpyrrolidone to avoid interaction between discrete lipid nanoparticles and extend the shelf life of the product. The dispersion could also be spray-dried into a powder and crushed into tablets with the requisite excipients [18]. The aqueous dispersion can also be used as a granulating agent for tablets, a wetting agent in the extrusion process, or as a coating agentin the pelletization (Wuster) process.

Other than solid lipid, the most important excipient for SLN manufacturing is an emulsifier at the right concentration, which serves to lower surface tension between the lipid and aqueous phases and ensures formulation stability. Certain polymers, such as polyvinyl alcohol, have also been shown to prevent particle agglomeration by providing viscosity to the dispersion medium, which helps to stop particle movement [19].

Oral drug administration employing SLNs as carriers has piqued researchers' interest in recent decades, owing to the several therapeutic advantages it has shown over the traditional drug delivery strategy. Unfortunately, this delivery system is still in its early stages, since it has been unable to reach patients due to several manufacturing challenges on a large scale. To avoid an increase in particle size, the lipid content of the SLN dispersion should preferably not exceed 5% w/v of the aqueous phase during manufacture [20]. As a result, the overall amount of surfactant

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required per drug dose (particularly at higher doses) to stabilize the dispersion is quite large, ranging from 1 to 4% w/v of the aqueous phase. This is important to consider since too much surfactant can disrupt the normal physiology of the gastrointestinal barrier(21).This limitation also limits the use of this dosage form for high-potency medicines (like nanodispersion), which can only be supplied with a small amount of surfactant per dose. Furthermore, the additional expense of developing a nano-delivery system's formulation must be justified by its improved therapeutic effects over the already existing traditional dosage form. Furthermore, the potentially harmful health effects of these nanoparticles associated with human exposure have not been well investigated, as there is a risk that they may induce unintended human exposure with unknown health consequences that are now unknown [26].

- **SOME OF THE FORMULATIONS THAT USED NANOSTRUCTURED MULTI PARTICULATE DRUG DELIVERY ARE GIVEN BELOW:**

1) Carlo Vecchio, Matteo Cerea, Franco Pattarino, Andrea Foglio Bonda, Luca Palugan, Lorena Segale- Extrusion/spheronization was used to make multiparticulate systems out of crospovidone, low viscosity hypromellose, microcrystalline cellulose, micronized medication, and water. The micronized medication was suspended in water with polysorbate 20 and nanosized by a high-pressure homogenization to increase the release performance of the multiparticulate systems (HPH). Spray-drying the suspension of drug nanoparticles made it easier to handle the drug and prevented over-wetting of the powders during extrusion/spheronization processes. Preparation of multi-particulate systems for the oral delivery of a poorly soluble micronized or nanosized drug (28)
2) Mayuri K. Magar, Monica RP Rao*, Monica RP Rao*, Monica RP Rao*, Monica RP Rao*, Monica RP Rao*, Monica (ETH): Various solvents, including methanol, ethanol, acetone, and chloroform, were used to make nanosuspensions, which were made utilising an anti-solvent precipitation procedure including probe sonication. This nanosuspension could also be delivered in multiparticulate solid dose forms. (27)
3) Watnasirichaikul et al. - Made insulin-loaded nanocapsules using agitated interfacial polymerization. Using ethyl 2-cyanoacrylate, insulin poly(ethyl 2-cyanoacrylate) nanocapsules were produced within a microemulsion for oral medication delivery (29)
4) Wang et al. - In situ polymerizations of styrene and methacrylic acid at 85 C in the presence of nano-Fe3O4 in styrene, utilising lauroyl peroxide as a thermal initiator for polymerization, produced carboxyl-functionalized magnetic microspheres. (30)
5) Brown et al. - Using urea-formaldehyde microcapsules containing dicyclopentadiene produced by in situ polymerization in an o/w emulsion, they prepared microencapsulated therapeutic agents with acceptable strength, long shelf life, and excellent bonding to the host matter. (31)

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