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Nano-Structured Lipid Carriers (NLCs) as a Novel Nanotechnological Strategy for Improving the Oral Drug Bioavailability

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General Background Nanotechnology has transformed pharmaceutical science by enabling nanoscale delivery systems that overcome major limitations in conventional oral drug administration, including poor solubility, instability, and extensive first-pass metabolism. Specific Background Among lipid-based nanocarriers, nanostructured lipid carriers (NLCs) have emerged as a second-generation advancement over solid lipid nanoparticles due to their mixed solid–liquid lipid matrix. Knowledge Gap Despite extensive research, the mechanisms by which NLCs enhance oral bioavailability and their comparative advantages across formulation techniques remain insufficiently synthesized. Aims This work consolidates current evidence on the structure, preparation, stability, and functional performance of NLCs as oral drug delivery systems. Results The review indicates that the imperfect or amorphous NLC matrix increases drug loading, modulates release kinetics, improves physicochemical stability, reduces required surfactant concentrations, and promotes lymphatic uptake while attenuating P-glycoprotein efflux. Novelty By integrating mechanistic, formulation, and biopharmaceutical insights, this synthesis highlights the multidimensional superiority of NLCs in enhancing the oral absorption of poorly soluble and labile drugs. Implications NLCs represent a promising platform for next-generation oral therapeutics, with potential to improve clinical efficacy, reduce dosing frequency, and expand the applicability of challenging drug molecules despite remaining manufacturing and regulatory hurdles.

Highlights:

1. NLCs provide higher drug loading and reduce crystallization-related leakage.
2. Their small particle size and lipid composition enhance oral absorption and lymphatic uptake.
3. Scalable manufacturing methods support consistent, controlled drug release.

Keywords: Nanotechnology, Oral Drug Delivery, Lipid-Based Nanocarriers, Nanostructured Lipid Carriers, Bioavailability.

A. Nanotechnology in Drug Delivery Science

Nanotechnology is the field that involve the development and application of physical, chemical and biological systems characterized by structural dimensions ranging from individual atoms or molecules to submicron scales, as well as the integration of resultant nanostructures into larger systems (1).Nanomaterials are characterized as substances that exhibit one or more dimensions at the nanoscale, namely within the range of 1 to 100 nanometers. Nanotechnology, the field

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of study focused on the science and applications of nanoparticles, is undergoing quick and persistent expansion. At this size, the characteristics of materials see substantial changes. Properties such as solubility, reactivity, spectroscopy, electrical and magnetic characteristics, along with membrane transport, generally differ from those displayed by the same substances at larger sizes. Nanomaterials' unique properties make them useful for a wide range of purposes and open up many possibilities for new research and development in many scientific and technical fields (2). The word "nano" comes from the Latin word for "dwarf." A nanometer (1 nm) is one billionth of a meter, which is the same as one billionth of a certain unit. Numerous examples from nature, such as water molecules, DNA, viruses, and red blood cells, exhibit nano-dimensions; also, history provides several instances demonstrating our exploitation of technological advantages in various forms. The word nanotechnology has been predominantly utilized in several scientific disciplines such as electronics, engineering, and physics for several decades (3).

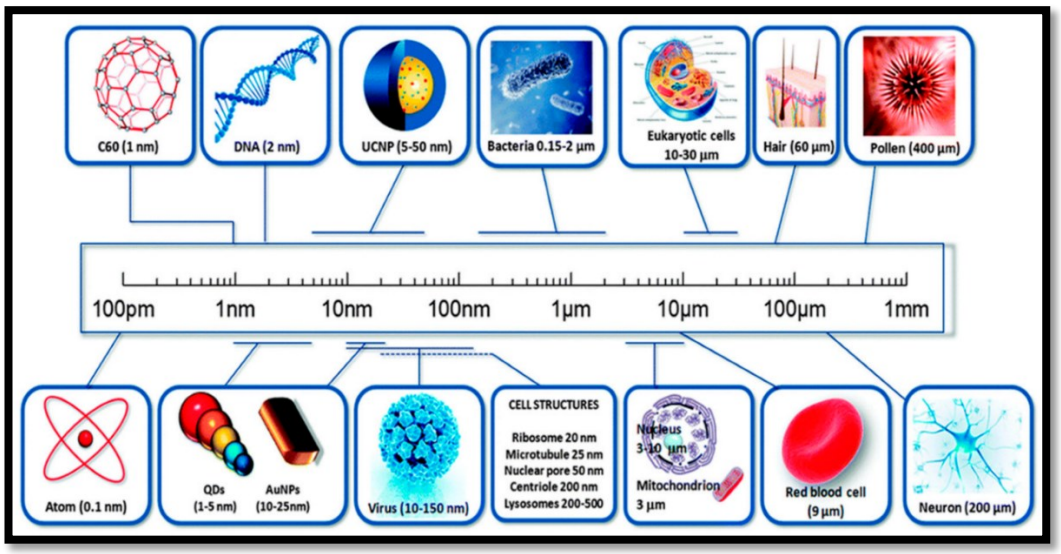

Figure 1: A comparison of sizes of nanomaterial (4)**.**

In recent years, nanotechnology has emerged as one of the most inventive and promising fields in medical and pharmaceutical science. The rising demand for enhanced bioavailability of challenging compounds due to their inadequate water solubility, low permeability, instability, or other limitations has led to the development of new specialized methods (5).

1.1. Nanoscience and nanotechnology hold significant potential in research and application within the pharmaceutical sector. The word "nanotechnology" was utilized in 1974. Any technology that operates at the nanoscale and possesses diverse applications will be classified as nanotechnology. Nanoscale materials exhibit significant differences in characteristics compared to their macroscale counterparts. The characteristics remained consistent with size reduction, although significant alterations were noted when the size fell below 100 nm. In most instances, size reduction is confined to the micron scale, exemplified by various medicinal dosage forms such as powders, emulsions, and suspensions. Nanometer-sized drugs improve efficacy across various dose forms. Size

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reduction can enhance bioavailability, diminish toxicity, improve solubility, and optimize formulation qualities of a medicine. The efficacy of the medicine in different dose forms may be improved by its nanometer-scale size (6).

1.2. Pharmaceutical nanotechnology has enabled more precise diagnosis and targeted therapy of diseases at the molecular level. Pharmaceutical nanotechnology is a highly inventive and specialized field that will transform the field of medicine in the near future. Pharmaceutical nanotechnology offers transformative prospects for combating various ailments. It aids in identifying antigens linked to conditions such as cancer, diabetes mellitus, and neurological illnesses, as well as in detecting bacteria and viruses related to infections. It is anticipated that the market within the next decade will be flooded with nanotechnology-based medication (7, 8). Nanotechnology-based systems could make bioactive compounds delivered through different routes more effective and powerful. This method is a good way to deliver drugs to specific areas and treat illnesses, as well as to prevent them, diagnose them, and treat them. Nanocarriers can be used to deliver medicine and also as biosensors to find and keep an eye on biomarkers or infections. This can be done by adding quantum dots (QDs) and dyes or using magnetic nanocarriers (9).

It is already well known that materials that are nanoscale in size have different physical, chemical, and biological properties than materials that are larger. The unique property of nanoparticulate formations has been thoroughly investigated for prospective applications of nanotechnology in medicine. One of the most exciting and promising uses of nanotechnology is for delivering medications. Nanotechnology systems can make treatments more powerful and effective when given in different ways. This chapter will focus on the use of nanotechnology systems for delivering drugs through the mouth (10).

B. Nanoparticles in Drug Delivery

Different kinds of nanoparticles have been made, and many of them are getting a lot of attention from businesses because they can be used in cosmetics and medicines to improve health. These include inorganic nanoparticles, polymeric nanoparticles, dendrimers, liposomes, carbon nanotubes, nanocrystals, and most importantly, lipid nanoparticles (11).

Nanoparticles (NP) were first used in the 1970s as carriers for vaccines and cancer-fighting drugs. Nanoparticles are a type of drug delivery technology that uses particles that are less than 1000 nm in diameter. Atoms and molecules behave very differently at the nanoscale and have some interesting properties that make classical physics useless. This leads to new properties and functions that aren't present at the macro scale, like changes in solubility, electrical conductivity, chemical reactivity, strength, mobility, and optical and magnetic properties. These changes could also create new safety concerns and risks (12).

2.1 The main goals in designing nanoparticles as a delivery system are:

1. Regulation of particle size, surface characteristics, and release of pharmacologically active compounds to attain site-specific therapeutic effects at a suitable rate and dosage.
2. Improving water solubility, which led to improved bioavailability.
3. Extending the duration of drug release within the body to augment its therapeutic efficacy

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and improve patient adherence.

4. Directing medicinal agents to their specific site of action leads to a simultaneous decrease in the required drug dosage and a significant reduction in drug toxicity, facilitating the safe administration of toxic therapeutic agents while protecting non-target organs and cells from severe side effects (13).

Table 1: Some Application of Nanoparticles (13).

N. O	Application	Medicament Studie
1	To increase the efficacy	Actinomycin–D, Amphotericin–B Pilocarpine, Cyclosporine and Metronidazole.
2	To reduce side effects	5 – fluorouracil
3	To reduce drug toxicity	Doxorubicin Dehydro emetine
4	To enhance therapeutic index	Doxorubicin
5	To improve/enhance bioavailability	pefloxacin mesylate and ofloxacin
6	For prolonged drug action	Insulin, influenza whole virus, influenza vaccine
7	For controlled release	Theophylline, indomethacin Ibuprofen and Propranolol
8	For targeting	Monoclonal Antibodies
9	Miscellaneous	Cyclosporin – A somatoliberin

C. Nanotechnology for oral drug delivery and targeting

One of the most promising and exciting techniques is the utilization of nanotechnology for the delivery of targeted orally administered drugs. Historically, the most accessible and commonly utilized method of medication delivery has been oral ingestion. Oral dosage forms are convenient, enhance patient compliance, and may be more cost-effective than alternative forms (14).

More than 70% of medicines are administered orally in the form of tablets, capsules, solutions, or suspensions. Oral drugs do not readily enter the systemic circulation to deliver their therapeutic effects, in contrast to parenteral medications. Instead, they must be metabolized in the gastrointestinal system before to entering the bloodstream. Consequently, drugs that taken through the oral route exhibits a delayed onset of action relative to the parenteral route or is entirely useless for medications that are unable to enter the bloodstream (15).

The oral route has been the most successful method for targeted drug delivery systems because

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gastrointestinal physiology allows for greater dosage form design flexibility (16).

3.1. Oral route

The oral route of administration is definitively the most patient-compliant method, circumventing the disadvantages associated with various drug delivery systems; for instance, the parenteral route raises the risk of infections in patients, includes pain, and incurs additional manufacturing and handling costs. Due to its exceptional attributes, such as minimal invasiveness, painless, ease of use, cost-effectiveness, repeatability and applicability across all age groups, the oral route of administration is the most preferred option (17).

Furthermore, a medicine exhibiting an optimal hydrophilic and hydrophobic balance for traversing the intestinal barrier without substantial alterations from gastrointestinal fluids is a suitable option for oral delivery. Nevertheless, the availability of such a medicine is uncommon. The majority of medications are metabolized, hydrolyzed, or degraded; hence, oral drug administration presents a challenge owing to the limited availability of intact and active drug and the anticipated pharmacological effect is rarely achieved (18).

Medication administered orally must effectively tackle many challenges, including stability in the stomach environment, inadequate aqueous solubility and targeted location of absorption. Nanotechnology-enabled drug delivery systems seem to be engineered to bypass and efficiently resolve these issues, ensuring the medication remains intact, is more readily absorbable at the site of absorption and has a programmable release profile (19).

3.2. Challenges in the delivery of therapeutics through oral rout

The bioavailability of oral medicines reflects the rate and degree of their absorption into the systemic circulation. Factors affecting medication bioavailability may be categorized into three parts (20):

1. physicochemical properties of the drug.
2. physiological aspects pertaining to the gastrointestinal system.
3. factors linked with the dosage form.

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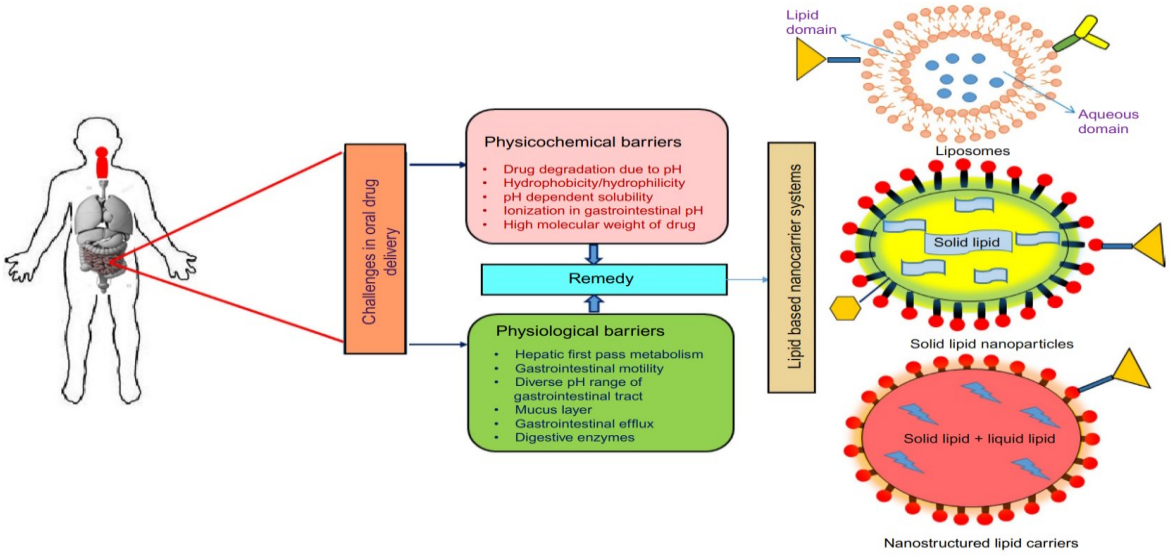

Figure 2: Obstacles in oral drug delivery and use of nanocarriers to overcome these obstacle (9).

3.2.1 Physicochemical characteristics of drugs affecting oral bioavailability

Drug absorption, can be simplified by the Fick's First law of diffusion: -

J = PC ------- (Eq. 1)

where the flux (J) of a given drug through the GI wall is related to the permeability coefficient (P) of the GIT wall and the drug concentration (C) in the GI fluid under sink conditions. The drug concentration in the GI lumen is related not only to its solubility, but also to its dissolution rate and stability in the GI environment (21). Assuming that a drug is stable in the GI fluids, information on drug solubility and intestinal membrane permeability can provide a better understanding of its oral subdivided into four categories in the Biopharmaceutics Classification System (BCS) as showing in (Figure 3) (22).

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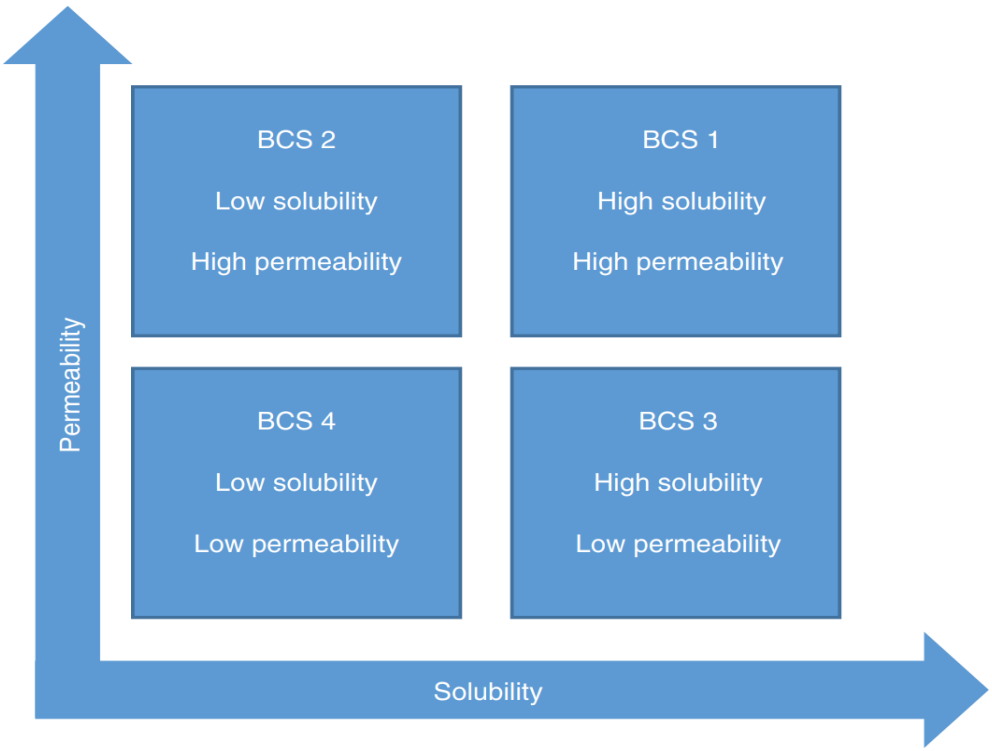

Figure 3: Biopharmaceutics Classification System (BCS) (22)**.**

The BCS classification is a powerful predictor for oral drug development. Poor oral bioavailability of medications may arise from poor solubility/dissolution rate (class II), low permeability (class III), or both (class IV) according to the BSC (23). New drug compounds in development appear to pose greater formulation challenges than marketed drugs: BCS II compounds increase from 30% to 50–60%, while BCS I compound decrease from 40% to 10–20%. Evidently, medicinal chemists are under greater pressure than past to improve solubility and bioavailability of new compounds (24).

This presents significant difficulties for some therapeutic classes, including HIV protease inhibitors, many anti-infective agents and anticancer medications, since their efficacy relies on interactions with highly lipophilic targets, complicating the maintenance of both potency and water solubility. In addition to medicinal chemistry strategies for enhancing drug solubility, pharmaceutical scientists possess many more techniques. Formulation approaches aimed at enhancing the solubility and/or dissolution rate of poorly soluble pharmaceuticals include the creation of solid solutions or dispersions, the use of cyclodextrins, and the stability of the drug in an amorphous state. In recent years, many nanotechnology methods, such as drug nanocrystals and self-emulsifying drug delivery systems, have shown efficacy for this purpose (25).

3.2.2 physiological factors influencing bioavailability

A drug encounters many physiological obstacles to absorption throughout its passage through the gastrointestinal system. Initially, drugs have to tolerate the acidic pH of the stomach. Furthermore, the drug may be broken down by enzymes located in the stomach and intestine,

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including those generated by the colonic bacterial flora. This kind of pre-systemic drug metabolism is termed luminal metabolism (26).

For the medicine to stay stable, it has to cross the mucus layer enveloping the epithelial cells of the gastrointestinal tract prior to absorption from the intestinal lumen. The current concern is that the medicine may fail to diffuse through this layer or may get bound and stuck in the mucus. For small molecule medications, a higher lipophilicity of the substance correlates with a slower diffusion through gastrointestinal mucus(27). The transmembrane efflux of pharmaceuticals may significantly restrict the flow of medications through the gastrointestinal membrane. This refers to the expulsion of a medication from the cell, specifically gastrointestinal epithelial cells, by a transport mechanism located on the cell membrane, such as P-glycoprotein (P-gp). P-glycoprotein is frequently found on the apical surface of several cell types, including those in the jejunal epithelium (28).

Furthermore, the medication may undergo first-pass intestinal metabolism, a pre-systemic metabolic process facilitated by enzymes located in the brush border or inside enterocyte cells of the gut. In addition to luminal and first-pass intestinal metabolism, medicines may also undergo first-pass hepatic metabolism; all medications, upon absorption, are first delivered to the liver via the portal circulation. Numerous medications may be processed by various liver enzymes (29). The liver performs essential metabolic functions to eliminate many endogenous chemicals and xenobiotics, resulting in the metabolism of several pharmacological molecules. First-pass metabolism is considered the primary reason for the inadequate oral bioavailability of several medicines. The predominant enzymes engaged in first-pass intestinal and hepatic metabolism are part of the cytochrome P-450 superfamily (30).

3.2.3 Factors related to the dosage form that influence bioavailability

Both physiological aspects and physicochemical properties of medicines affect their oral bioavailability. The type and qualities of the dosage form containing the drug may significantly influence its bioavailability. The quantity of drug entering the bloodstream may be precisely regulated by specific release methods. Delivery methods have been developed to enhance the bioavailability of poorly soluble pharmaceuticals (31).

D. Targeted oral drug delivery systems (TODDS)

The objective of the targeted oral delivery system is to attain optimal therapeutic efficacy, a goal frequently not achieved by traditional dosage forms. Nevertheless, patient compliance, dosage and dose frequency, and modified pharmacokinetic characteristics are significant factors that need careful attention (32).

The established method must guarantee drug stability in the gastrointestinal tract, minimize gastrointestinal-related side effects, decrease dosage and dosing frequency, maintain a constant plasma profile, and enhance the therapeutic index. Furthermore, targeted oral drug delivery systems (TODDS) have some notable disadvantages, including elevated costs, generally inadequate in vitro/in vivo correlation, potential for dosage dumping, and diminished capacity for dose modification or withdrawal in cases of toxicity. Oral drug targeting may traditionally be spatial or temporal, significantly involving time-dependent release and the specific site within the gastrointestinal tract (33).Various drug delivery systems that are functional responding to

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environmental, anatomical, and physiological factors can be classified as:

1. systems targeted to the stomach/duodenum.
2. system targeted to the colon or large intestine.
3. system targeted to the small intestine/lymphatic.

4.1. Systems targeted to the stomach/duodenum

Systems designed for targeting the stomach to enhance absorption or achieve localized pharmacological effects are fundamentally gastroretentive; hence, their gastric residence period is significantly extended. The system, together with the medicine, must be maintained in the stomach to achieve localized pharmacological effects and to avoid gastrointestinal degradation of the drug. Similarly, such systems might encourage the solubilization of drugs that are soluble at (low ph.). However, they have superior solubility in the stomach. Consequently, over the retention period, they are solubilized within the stomach and then supplied to the small intestine in a soluble state for enhanced absorption (9).

Targeting drug delivery systems to the stomach can be accomplished by developing the following systems.

4.1.1. Polymer-lipid hybrid systems

Polymer-lipid hybrid (PLH) systems have evolved as an effective technique that integrates the solubilization capabilities of lipid-based nanocarriers with the stabilizing properties of polymeric excipients in order to solve the limitations of traditional lipid-based delivery systems. The incorporation of polymers in lipid-based drug delivery systems offers numerous biopharmaceutical advantages for oral medication administration due to their capacity to:

1. Maintain stability of lipid colloids.
2. Precisely control the physicochemical properties.
3. Selectively modify delivery pathways to enhance oral absorption.

The biodegradable polymers utilized in the formulation of PLH systems are varied and encompass a range of natural, semisynthetic, and synthetic polymers with distinct physicochemical properties and bioactivities. Comprehensive study has demonstrated the efficacy of PLH systems in improving the oral absorption of permeable and poorly soluble bioactives, proteins, peptides, vaccines, and nucleic acids. They represent exciting carriers with potential clinical applications (34).

4.1.2. Mucoadhesive dendrimers

Drug delivery by Mucoadhesive techniques have attracted considerable attention. A mucoadhesive dendrimer (nanocarrier) for oral drug administration is an innovative strategy for enhanced oral medication delivery. Mucoadhesion often occurs via the following mechanisms: (a) penetration of the mucoadhesive into the tissue or the mucous membrane surface (interpenetration) and (b) close contact between the mucoadhesive and the membrane (wetting and swelling phenomena). This nanocarrier-based method offers numerous advantages, including the customization of cellular interactions through formulation design and the administration of dual drugs for a synergistic impact. These nanocarriers ensure the total protection of bioactives in acidic environments after adhering to the mucosal membrane,

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facilitate prolonged retention, and allow the medicine to reach and penetrate the infection site via diffusion (35).

The dendrimer (anion) reacts quickly with the mucin layer (cation). The benefits of dendrimers include a nanoscale molecular dimensions, ranging from 1 to 100 nm, which render them less vulnerable for uptake by the reticuloendothelial system (RES) (36).

4.2. Systems targeted to the colon/large intestine

Colon-restricted disorders require targeted delivery of medication to the colon for localized therapeutic effects or colon drug absorption. This technique employs intestinal microflora and pH levels to selectively release pharmaceuticals. The colon is essential for the administration and absorption of medication. In contrast to the small intestine, it favors the transcellular absorption of hydrophobic pharmaceuticals. A substantial population of commensal bacteria, exceeding 400 species, predominantly anaerobes, facilitates targeted medicine administration within the colon. The colon absorbs around 90% of the 2000 mL of water it receives each day (37). The colonic drug delivery system is used for some diseases localized in colon such as inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, constipation and colorectal cancer. A colon medicine delivery system is essential for treating these illnesses. Peptides and proteins may be given to the colon to improve systemic absorption since it has a less hostile bioenvironment than the gastrointestinal tract. The oral delivery of a majority of peptides and proteins and their systemic absorption thereafter is limited due to the following: (a)- degradation in the acidic milieu of the stomach, (b)- enzymatic degradation in the small intestine, (c)- decreased mucosal permeability, (d)-accelerated transit through the small intestine, and (e)- extensive first-pass metabolism.

The permeability of the colonic mucosa may be modified by using penetration enhancers to increase the bioavailability of protein and peptide pharmaceuticals, including growth hormone, calcitonin and interleukin. Drugs with low absorption may be directed to the colon, which has an extended residence duration and is particularly sensitive to penetration enhancers (38).

4.2.1. Current oral nanodrug delivery system–based approaches to inflamed colon

The better strategy for oral drug delivery has significantly improved the bioavailability of colon-targeted drugs, enabling these formulations to effectively reach and release the medication selectively in the colon. Pharmaceutical strategies using nanodrug delivery techniques as carriers for active ingredients have shown encouraging results in managing the physiological alterations associated with IBD, utilizing these changes to enhance targeted drug administration to affected tissues [35].

4.2.2. Active targeting–based strategies for oral nanodrug delivery

Active targeting includes altering specific ligands, antibodies, or other molecules on the nanoparticle surface to recognize and bind to certain cells or tissues at the target location, thereby enhancing the precision of drug delivery. The use of antibody-coated nanoparticles may detect and bind to particular antigens on the surface of tumor cells, facilitating more accurate medication administration. Active targeting is primarily categorized as antibody-based targeting, small-molecule-based targeting, peptide-based targeting, aptamer-based targeting. In the quest for appropriate ligands, antibodies were identified as the predominant choice for

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the progression of targeted ligand creation. Antibodies on the nanoparticle surface may selectively identify and bind to antigens on tumor cell surfaces, facilitating the active targeted transport of nanoparticles. A range of antibodies and antibody-drug conjugates (ADCs) have been registered and licensed for targeted drug delivery, including cetuximab for advanced colorectal cancer and rituximab for non-Hodgkin's lymphoma (39).

4.3. System targeting to the small intestine/lymphatics system

They are designed to circumvent the acidic conditions of the stomach and deliver the drug in the alkaline environment of the small intestine. These methods are used for pharmaceuticals that are (a) acid-labile, (b) irritative to the stomach mucosa, (c) preferentially absorbed from the small intestine, and (d) need a localized action inside the intestine (40).

Small intestine composed of three parts duodenum, jejunum, and ileum with length of 5.5–6.0m, and transit duration is 3–4 hours. Villi are fingerlike structures in the small intestine very important to increase absorption surface area by several folds. Small intestine pH is 6–6.5 fasting and 5–5.5 on feeding while Ileum has alkaline pH may be (7–8). Small intestine enzyme activity is not preferred for protein and peptidic medicines (41).

Peyer's patches are another rout of absorption that may absorb macromolecules and hydrophobic pharmaceuticals via the lymphatic route in the small intestine. Peyer's patches, structured mucosal lymphoid tissues in the GI tract, modulate the immune response to oral antigens. They are often seen on the antimesenteric or circumferential aspects of the intestinal wall and are larger and more abundant in the distal part of small intestine. The whole mucosa of the small intestine is adorned with lymphoid follicles inside Peyer's patches. Peyer's patches are recognized for their ability to uptake bacteria, marker proteins, and particulate debris. Specialized epithelial cells facilitate vesicular transport of soluble and colloidal particles into Peyer's patches. Certain Peyer's patch cells possess microfolds, known as microfolds (M cells) that have the ability to uptake antigens and high-molecular-weight soluble and colloidal proteins (42).

Peyer's patches may absorb large molecules, making them effective for the uptake of medicines with hydrophobic properties or unfavorable partition coefficients. Lymphatic movement necessitates a molecule with a high partition coefficient. The lymphatic system absorbs compounds via two mechanisms: chylomicron absorption and pinocytosis of large molecules. Chylomicrons, mostly consisting of dietary fat and cholesterol, are little spherical entities absorbed into lymphatic capillaries. Compounds integrated into chylomicrons are absorbed by the lymphatic system and its channels rather than passing via the liver to circumvent first-pass liver metabolism (43). This route can be used for the following:

1. Avoidance of initial hepatic metabolism.
2. Targeted therapy for illnesses and infections of the mesenteric lymphatic system.
3. Improved adsorption of macromolecules, including proteins and peptides.
4. Prevent of efflux transport mechanism.
5. Drugs that exhibit strong hydrophilicity and stability across all pH levels.
6. Oral delivery of antigens.

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There are several important approaches that can accomplish this purpose among the most significant of these nanocarrier approaches (44):

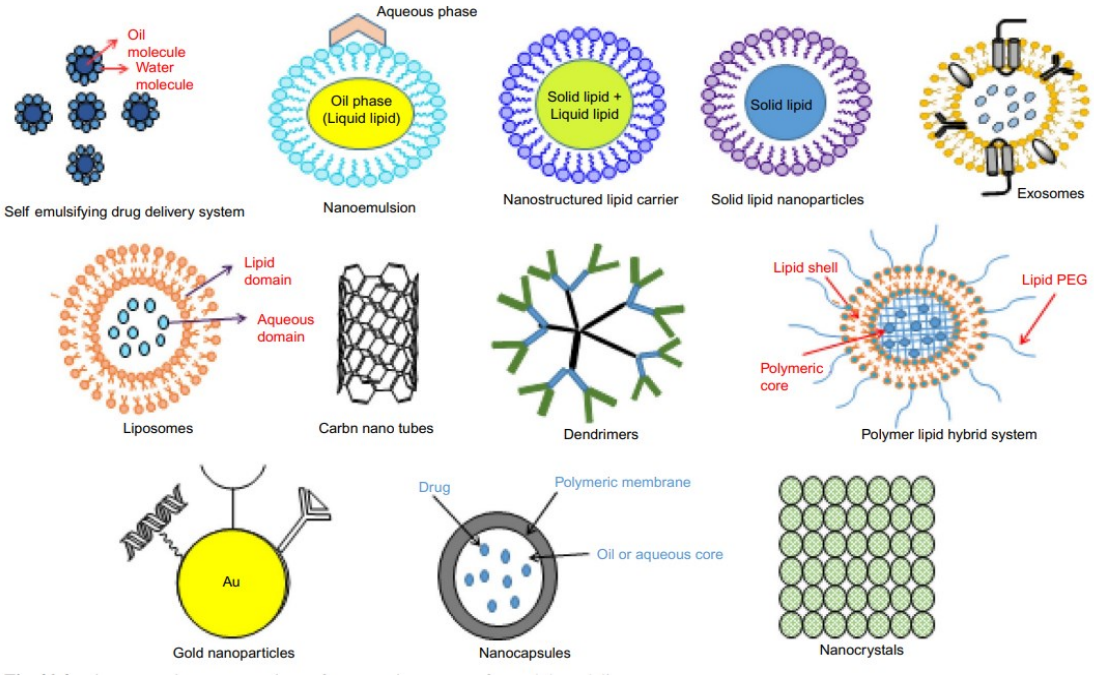

Figure 4: Diagrammatic depictions of nanocarrier systems for oral pharmaceutical delivery (9).

4.3.1. Polymeric systems These include nanoparticles, nanocapsules, nanospheres, and microspheres. These methods purportedly enhance the drug's absorption and stability

A-Nanocapsules

These tiny drug carriers have an oily or watery core and a thin polymer membrane. Nanocapsules carry active substances well. They shield encapsulated medicines from the environment and provide regulated release. Nanocapsules are potential for lymphatic targeting since they may be easily manufactured and have specific features. When supplied, lymphatic cells may readily capture nanocapsules covered with hydrophobic polymers because they are identified as foreign substances (45). Abu Abed et al. (2021) discusses the formulation of PEGylated Poly (ε-Caprolactone) (PCL)-based nanocapsules for the targeted administration of trypsin to the small intestine to provide sustained-release replacement treatment. A unique polymeric nanocapsules technology was created to deliver trypsin to the small intestine in a sustained, localized, and active manner continuously. All aspects influencing protein delivery were evaluated to minimize trypsin degradation and ensure its transport to the small intestine at the lowest feasible cost (46).

B-Polymeric carriers

Several polymeric particles have been developed for lymph medication targeting and delivery. Polymers are either natural, such chitosan, dextran, gelatin, alginate and hyaluronan, or synthetic, like poly lactide-coglycolide (PLGA), polymethyl methacrylate (PMMA), and poly-lactic

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acid (PLA). One or more polymers of 10–200 nm in size make up polymeric nanoparticles. The polymer may entrap or conjugate the medication depending on synthesis technique. Coadministration of polymeric carriers like dextran and albumin increases interstitial oncotic pressure and lymphatic absorption. Thus, biodegradable polymers are being widely examined for lymphatic targeting (47).

4.3.2. Lipid-based drug delivery systems

Lipid-based nanocarrier technologies may improve bioavailability of bioactive drugs with limited water solubility when administered orally. Lipid nanoparticle excipients like emulsifiers and surfactants may boost bioavailability. Self-emulsifying drug delivery systems (SEDDs), microemulsions, nanoemulsions, liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are types of these technology that encapsulate medicinal substances and improve their oral solubility and bioavailability (48).

A-Self-emulsifying drug delivery systems

SEDDS are commonly employ lipid nanocarriers to enhance oral medication bioavailability. An anhydrous isotropic mixture of oil, solubilizer, emulsifier, co-emulsifier, and active medicinal ingredient generated o/w transparent microemulsions with oil droplets from 100 to 250 nm following dilution by water with mild agitation (49).Their ability to self-emulsify in gastrointestinal fluid renders bioactive nanosized oil droplets available, and their large interfacial surface area enhances gastrointestinal dissolution. SMEDDS (self-micro emulsifying) and SNEDDS (self-nanoemulsifying) are two classifications of SEDDS. Following oral administration, SMEDDS yield transparent microemulsions with thermodynamically stable formulation, whereas SNEDDS are characterized by opacity or translucency with droplet sizes under 100 nm. The bioavailability of SEDDS active components is influenced by the ingredients, lipophilicity, droplet size and lipid digestibility of the bioactive agents. Commonly used techniques for the manufacture of SEDDS include low-energy emulsification, solvent displacement, phase inversion temperature and phase inversion composition (50).

Mechanism of self-emulsification

The process of self-emulsification is inadequately understood. Self-emulsification occurs when the entropy change facilitating dispersion exceeds the energy required to increase the dispersion's surface area. The free energy of a standard emulsion formulation is directly proportional to the energy required to create a new interface between both water and oil phases, as explained by the following equation:

$$DG = SN_i\ pr_i\ 2S \text{ ------- (Eq: 2)}$$

where DG denotes the free energy related to the operation, N represents the quantity of droplets of radius r, and S signifies the interfacial energy. The two phases of the emulsion typically separate over time to minimize the interfacial area and the system's free energy (51).

B-Nanoemulsions

Heterogeneous mixes of oil droplets in an aqueous media, stabilized by an emulsifier, are referred to as nanoemulsions. The resultant emulsified mixture is isotropic, transparent, and stable kinetically, without flocculation or coalescence over prolonged storage. The droplet

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dimensions vary from (20 to 200 nm). In contrast to SEDDs, nanoemulsions are produced by direct assembly instead of self-assembly. Bioactives may be encapsulated inside the oil cores of nanoemulsions to improve oral absorption (52).

The FDA has authorized nanoemulsions of some drugs with poor aqueous solubility as Estrasorb, Flexagon, and Restasis. Other than bioactives, nanoemulsions may deliver minerals and vitamins and offer various advantages over food systems. They can encapsulate lipophilic substances, have great physical stability, modulate product texture easily, and digest quickly. Stable nanoemulsions are made using high-energy and low-energy emulsification. High-energy stirring, ultrasonic emulsification, and high-pressure homogenization with microfluidics and membrane emulsification are prevalent. Low-energy strategies include phase inversion temperature, emulsion inversion point, and spontaneous emulsification (53).

Alshehri et al. (2023) developed a piperine-loaded nanoemulsion for improving solubility bioavailability, stability, and physicochemical characteristics. The results revealed increased in piperine release (from 72.5 ± 2.9 to 96.2 ± 3.5%) and bioavailability from nanoemulsion by 3.4-folds as compared with pure piperine suspension (54).

C-Liposomes

Liposomes are characterized as colloidal spherical structures, first identified in the 1960s by British hematologist Dr. Alec D. Bangham and his coworkers, created by the self-assembly of amphiphilic lipid molecules in solution, such as phospholipids. The liposomal membrane may have one or many lipid bilayers (lamellae) surrounding an internal aqueous core, with the polar head groups oriented towards the inner and outer aqueous phases. This organized configuration provides liposomes with the unique capacity to contain and convey molecules of diverse solubility. Hydrophilic molecules occupy the aqueous core, hydrophobic molecules embed inside the lipid bilayer, and amphiphilic molecules are situated at the interface of water and the lipid bilayer (55).

Liposomes have garnered significant interest as a medication delivery mechanism for several types of pharmaceuticals. The direct use of liposomes in medicine motivates researchers to develop innovative liposomes for the treatment and diagnostics of various illnesses and therapeutic applications (56). Daunoxome®, Myocet® and Doxil®, are examples of liposomal formulations that are already approved by the FDA. However, liposomes have a disadvantage of a relatively low loading capacity their formulation involves organic solvents, they're unstable in biological fluids and in aqueous solutions, and are highly expensive (57).

D-**Exosomes**

Exosomes are small, spherical vesicles ranging from 30 to 120 nm in diameter, secreted by all cellular types. Exosomes perform several vital roles in intercellular communication and tissue interaction throughout the human body. They may serve as effective biomarkers and therapeutic agents for early diagnosis, treatment response, and prognosis of several illnesses. The primary requirements for the large-scale clinical use of exosomes are rapidity, simplicity, high yield, elevated purity, safety, cost-effectiveness, and therapeutic efficacy. Exosomes may be extracted from diverse sources, such as bodily fluids, solid tissues, and cell culture media, using distinct methodologies (58).

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Recent studies show that extracellular vesicles such as exosomes have a particular cell tropism, can be used to target them to diseased tissues and/or organs. Agrawal et al. (2017) elucidated the use of milk-derived exosomes for the oral administration of the chemotherapeutic agent paclitaxel. Exosomes and paclitaxel-loaded exosomes demonstrated remarkable durability in simulated gastrointestinal fluids and during storage at −80°C. Their results demonstrated a prolonged release pattern of paclitaxel and a significant reduction of tumor development in human lung tumor xenografts. Moreover, paclitaxel-loaded exosomes exhibited significantly reduced systemic and immunogenic toxicity in comparison to paclitaxel treatment alone (59).

E. Solid lipid nanoparticles

SLNs have attracted heightened interest as an effective and safe alternative for lipophilic colloidal carriers, formulated with either lipids of physiologic origin or lipid molecules used as standard pharmaceutical excipients. SLNs were first developed by Schwarz et al. in the early 1990s. They comprise a solid lipid core covered by a monolayer of lipid that forms an external shell. Solid lipid nanoparticles (SLNs) consist mostly of a solid lipid matrix combined with various surfactants for emulsification purposes (60). Solid lipids used in the manufacture of solid lipid nanoparticles (SLN) include fatty acids (such as palmitic acid and stearic acid), triglycerides (such as tristearin), steroids (such as cholesterol), and waxes (such as cetyl palmitate). Poloxamer 188, sodium cholate, soybean lecithin and sodium glycocholate are often used as emulsifiers to stabilize lipid dispersions (61). Two primary techniques used for the production of solid lipid nanoparticles (SLNs) include high-pressure homogenization, as reported by Muller and Lucks in 1996, and microemulsion-based methods introduced by Gasco in 1993 with three drug inclusion models (62). The models include the homogeneous matrix model, the drug-enriched shell model, and the drug-enriched core model as shown in figure (4).

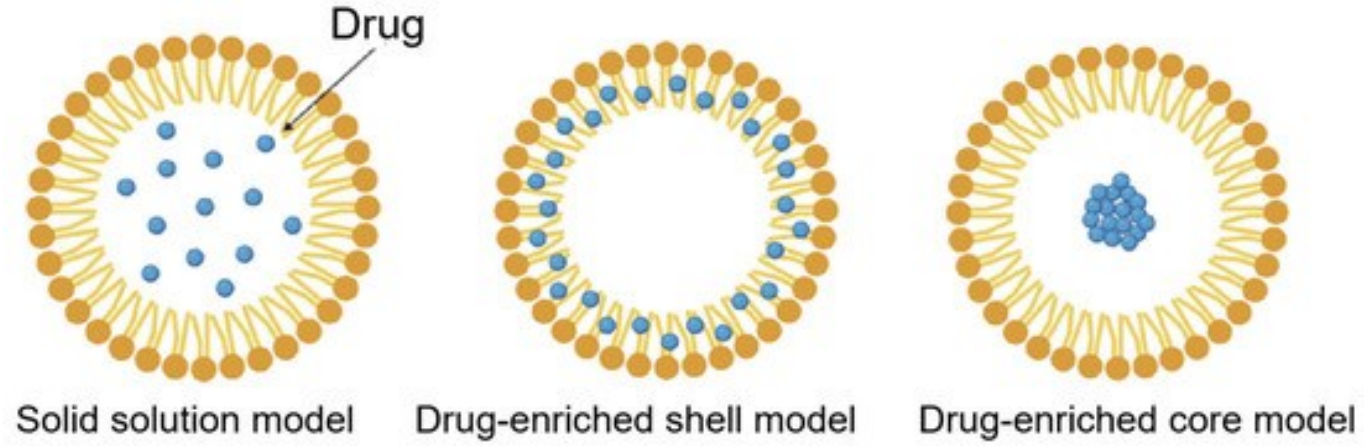

Figure 5: Models of drug inclusion into SLN (63).

Solid lipid nanoparticles (SLNs) ranging from 50 to 1000 nm in diameter are regarded as advantageous for the oral administration of several bioactive substances. The advantages of using solid lipid nanoparticles (SLNs) for the administration of oral bioactives include enhanced bioavailability, extended drug release, and protecting of chemically unstable compounds. Furthermore, SLNs are often considered as Safe (GRAS) duo to their biocompatible and biodegradable constituents, which exhibit low toxicity to mammalian cells. Previous studies on

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the oral antibiotic indicates that tobramycin exhibited inadequate intestinal absorption due to the P-glycoprotein efflux pumping. Incorporating tobramycin into solid lipid nanoparticles (SLNs) may diminish the function of the P-glycoprotein efflux pump, hence enhancing absorption and concentration at the site of infection via endocytosis (32).

F. Nanostructured lipid carriers NLCs

Second-generation lipid nanoparticles consist of a mixture of oil, solid lipids, emulsifying agent and water. The inclusion of liquid lipids disrupts the development of ideal lipid crystals, hence enhancing drug loading capacity; it decreases particle size, the danger of gelation, and leakage of drugs upon storage. NLCs facilitate the oral absorption of encapsulating bio-actives by selective uptake via lymphatic circulation or Peyer's patches. Moreover, the modulation of drug release from NLCs may be easily achieved by altering the ratio of solid to liquid lipids (64, 65).

Faiz et al. (2023) created pioglitazone-loaded nanostructured lipid carriers by the solvent emulsification-evaporation approach. Permeation experiments demonstrated increased permeability, while in vivo investigations validated the improved bioavailability of pioglitazone. The findings indicate that NLCs are effective methods for improving the bioavailability of poorly soluble Class II medicines (66).

Based on the lipid matrix structure, three categories of nanostructured lipid carriers (NLCs) can be derived, contingent upon the production technique and lipid blend composition, as illustrated in figure (6): (a) the imperfect type, (b) the amorphous or structureless type, and (c) the multiple oil-in-solid fat-in-water (o/f/w) type. In the imperfect type, lipid crystallization is modified by minor quantities of oils, whereas in the amorphous type, the lipid matrix remains solid yet non-crystalline. The solid lipid matrix in multiple type has several minuscule oil compartments. The composition and structure of NLCs facilitate a large drug load; the creation of a less ordered lipid matrix diminishes the burst impact, enhances the release qualities, and enhances stability during storage (67).

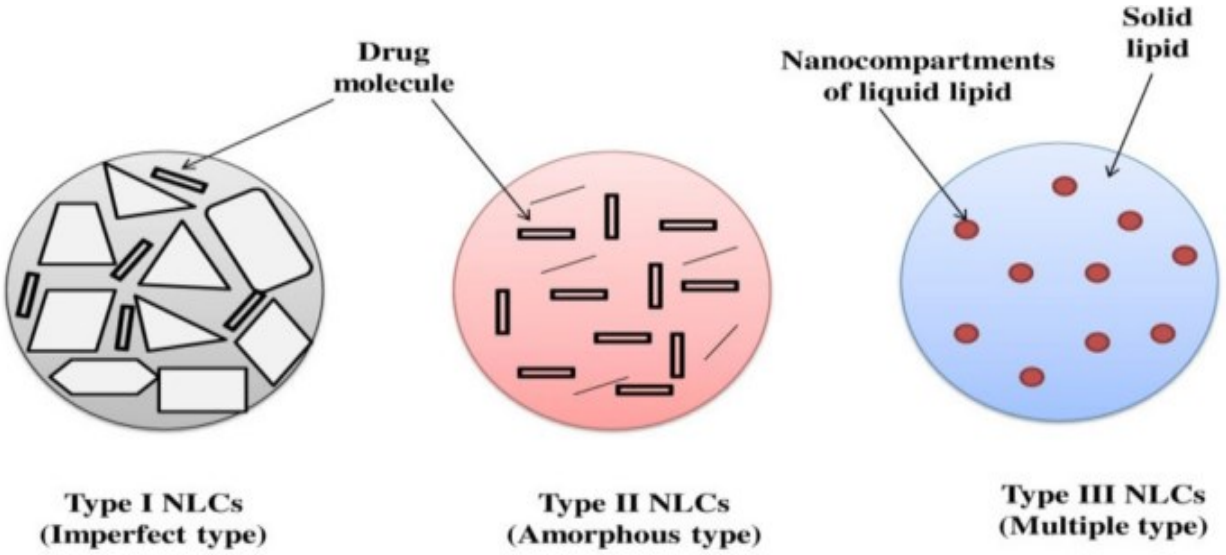

Figure 6: Types of NLCs depending on the structure of the lipid matrix (68).

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6.1. Advantages of Nanostructured Lipid Carriers

NLCs have notable benefits, including enhanced drug entrapment, extensive manipulation of drug release, prolonged stability, and the use of minimal surfactant concentrations with greater drug entrapment. The following topics are explored in depth below:

6.1.1. Improvement of Drug Loading Capacity.

In the manufacturing of SLNs, the concentration of pharmaceuticals in the lipid melt exceeds that of the final formulation, so a higher drug quantity is expected to result in a rapid drug release during cooling, but not for NLCs. The solid lipid matrix in NLCs contains nano-oil, which increases drug solubility compared to solid lipid melts and drug loading capacity. Therefore, liquid lipid components in the NLC matrix greatly increase drug entrapment. Because oil droplets form crystal defects in the solid lipid matrix, imperfections in the highly ordered crystal structure provide enough room for an enhanced drug load (69).

6.1.2. Drug Release Profile Modulation.

In NLCs, drug release occurs in bursts and then continuously from the lipid matrix. Liquid lipids in nanoparticle outer layers should generate a drug-enriched coating. This causes abrupt drug release. Liquid lipids in the exterior layer increase oil content to solubilize hydrophobic medicines. Thus, a high drug concentration is solubilized and loaded, then released by diffusion or matrix erosion (70). The solid lipid core releases drugs steadily after a fast release period. The lipid matrix determines drug release from nanostructured lipid carriers (NLCs), hence changing the liquid-to-solid lipid ratio may modulate drug release patterns (71).

6.1.3. Long Term Storage Stability of Entrapped Drug

The hypothesis behind the invention of NLCs is based on the concept that lipid crystallization results in drug expulsion. Because of this, these lipids are used in nanostructured lipid carriers (NLCs) that are solid but don't crystallize. These NLCs use certain combinations of solid and liquid lipids. The particles become solid when they cool down, but they don't crystallize. This lack of crystallinity affects the size distribution of the particles, how well they encapsulate drugs, and how quickly they release drugs in vitro. Also, adding liquid lipids to solid lipids in NLCs helps with long-term stability problems that come up when polymorphism develops. Liquid lipids are necessary to stop crystallization. Crystallization happens when something is supersaturated. Liquid lipids are thought to cause sub-saturation in solid lipids, which slows down crystallization (72, 73).

6.1.4. Decrease in the Used Amount of Surfactant

NLCs are distinctive nano-carriers that may be stabilized with little surfactant content, while exhibiting improved entrapment efficiency and an appropriate drug release profile. Stable NLCs containing lipophilic medicines may be achieved with a surfactant concentration of 0.5% to 1%. Notably, all available surfactants are suitable for the preparation of stable NLCs, in contrast to the limited acceptability range of surfactants for lipid emulsions and other formulations. Consequently, NLCs are a preferable drug delivery method over lipid emulsions due to the issues associated with the increased quantity and limited selection of surfactants (74).

6.2. Formulation Composition of NLC

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NLCs include a mixture of blended liquid and solid lipids in aqueous medium, accompanied by a surfactant or a combination of surfactants. Typically, solid lipids and liquid lipids are combined in a ratio ranging from 70:30 to 99.9:0.1. The surfactant concentration typically ranges from 1.5% to 5% (w/v) (75). Various mixtures of solid and liquid lipids, together with surfactants, have been documented throughout the literature study, with the majority shown in (Table 2). All of these building units are commercially marketed goods that are authorized by the American Food and Drug Administration (FDA) as generally recognized as safe (GRAS) components (76).

Table 2: List of Lipids and Surfactants Used to Prepare NLCs(77).

NLCs Components	Names
Solid lipids	Glyceryl palmitostearate, Glyceryl Di behenate, Cetyl palmitate, Stearic acid, Tripalmitin, Tristearin, Cholesterol and Glyceryl monostearate.
Liquid lipids	Medium chain triglycerides Caprylic/capric triglycerides, Vitamin E, Paraffin oil, 2-Octyl dodecanol Squalene and Oleic acid.
Surfactants	Lauryl polyoxylglycerides, Soy lecithin, Polyoxyl castor oil, Polyoxyethylene stearate, Macrogol-15-hydroxy stearate, Poloxamers and Polysorbates.

6.2.1. Lipids

Both solid and liquid lipids are used in the production of the inner cores of NLCs. The solid lipids often utilized for NLC preparation include triglycerides, waxes, fatty acids, and steroids, as seen in Table 3. These lipids are mostly solid at ambient temperature and melt at elevated temperatures throughout the production process (e.g., > 80°C) (78). The solubility of the drug in lipid matrix is essential, as it significantly influences drug entrapment efficiency and loading capacity, hence determining the efficacy of lipid nanoparticles for drug delivery (24 hr.) post-blending and their suitability for the formulation of stable NLCs (79).

The amount of liquid lipids has always been very important. It has a big effect on the size of the particles and the rate at which the medicine is released. It lowers the viscosity and surface tension of the solution, which makes the NLC particles smaller. This increases the surface area and makes it more likely that a larger percentage of the drug will be released over time (77). The overall ratio of the lipid matrix has a big effect on both the size of the particles and how well they hold drugs in NLCs. Using a larger lipid matrix leads to a bigger particle size and better drug entrapment. The higher viscosity of the fluid makes the particles bigger, and the higher lipid content makes it less likely for drugs to escape, which improves entrapment efficiency. Choosing the right amount of lipids is very important for making NLCs with better properties (80).

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Table 3 : Types of Solid Lipids Used in Formulating NLCs(78)**.**

NO.	Type of Lipids	Examples
1	Triacylglycerols	Tristearin, tricaprin, tripalmitin, trilaurin & trimyristin.
2	Acylglycerols	Glycerol, Glycerol monostearate, glycerol palmitostearate & behenate.
3	Fatty acids	Stearic, behenic palmitic & decanoic acid
4	Waxes	Cetyl palmitate, Beeswax & Carnauba wax.

6.2.2. Surfactants

Surfactants are necessary in the making of NLCs because they help mix two phases that don't mix well together. They stop particles from sticking together by covering their surfaces, which keeps them stable over time. They are also expected to make particles that are very small. They lower the interfacial tension between the two phases that don't mix, lipid and water. This makes the surface area of lipid droplets bigger and the particles smaller. The types and amounts of surfactants affect how well drugs are trapped and how quickly they are released. This aligns with the observation that surfactants reduce interfacial tension to a specific ratio, beyond which additional particle coating causes a decrease in zeta potential, resulting in particle agglomeration (81).

Choosing the right type and amount of surfactant is very important when making nanostructured lipid carriers (NLCs). These factors are important for making good NLC delivery systems that have controlled particle size, a narrow size range, and predictable drug release. Surfactants also give NLCs important properties. When used as a stabilizer in lipid nanoparticle formulation, Solutol HS 15 has a strong affinity for the P-glycoprotein (P-gp) efflux pump, which stops it from working. This is good for delivering drugs that are P-gp substrates, like etoposide and itraconazole. Surfactants are also known for their ability to break down intestinal membranes, which makes NLCs more permeable (82, 83).

G. Preparation Techniques of NLCs

Methods used for the manufacture of solid lipid nanoparticles (SLNs) can additionally be utilized for the production of nanostructured lipid carriers (NLCs). The choice of a technique for lipid nanoparticle manufacturing is contingent upon many aspects, including the physicochemical characteristics of the included drug, especially its solubility, the stability of both the active

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ingredient and the lipid nanoparticle dispersion, and the desired characteristics of the particles (84).

7.1. High-Pressure Homogenization (HPH) Method

HPH has been used as a reliable and effective method for the large-scale production of NLCs, LDCs, SLNs, and parenteral emulsions. In the HPH process, lipids pass through a small hole of a few microns with elevated pressure (100-200 bars). Shear stress and cavitation are the primary factors responsible for the disintegration of particles to the submicron range, with lipid content generally ranging from 5% to 10%. Unlike other manufacturing processes, HPH does not exhibit scaling-up issues. There are two primary approaches for manufacturing using HPH: hot and cold homogenization. In both methods, the medication is solubilized inside the molten lipid matrix at roughly 5-10ºC over the melting point of the used solid lipid.

A) - Hot Homogenization Technique: This process involves dispersing the medication with melted lipid in continual stirring using a mixer with high shear in an aqueous solution of surfactant maintained at an identical temperature. The resultant pre-emulsion is homogenized using a piston-gap homogenizer, and the resulting nanoemulsion then cooled to ambient temperature, causing lipid recrystallization and creation of lipid nanoparticles (85).

B) -Cold Homogenization Technique: in this technique the drug encapsulated in solid lipid, with cold homogenization developed to address the drawbacks of hot technique, including degradation of the drug payload due to temperature and partitioning to the aqueous phase through the homogenization stage. In both cold and hot methods, the starting step remains same. In the subsequent step, the liquefied lipid-based pharmaceutical is quickly chilled with ice or with liquid nitrogen to facilitate the dispersion of the medication inside the lipid matrix, as seen in figure (7). This cold homogenization procedure minimizes the heat exposure of the sample (86).

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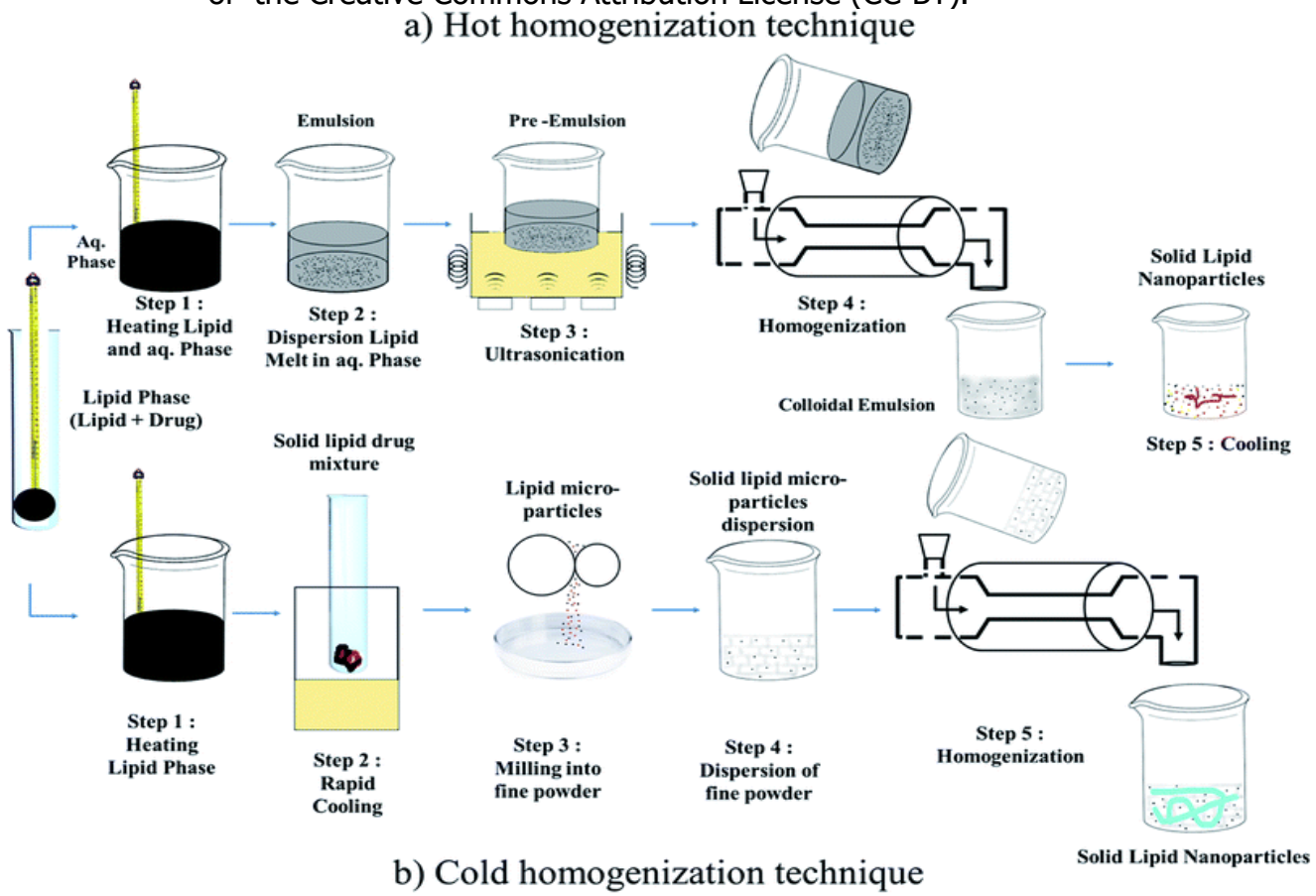

Figure 7 : Homogenization techniques: (A) Hot technique, (B) Cold technique (87).

7.2. High Shear Homogenization (HSH) and/or Ultrasonication (US) Technique

HSH and US are energy-intensive dispersion methods, where the nanoparticulates are produced by dispersed molten lipid in a heated aqueous solution of surfactant with high shear homogenization, and then by ultrasonication. This technique mostly includes heating a solid lipid to around 5–10 °C over its melting point. The liquefied lipid is distributed in an aqueous solution containing a surfactant at an equivalent temperature while being stirred vigorously to create an emulsion, followed by a sonication process to decrease the droplet size of the original emulsion. The gradual cooling of the heated emulsion less than the point of crystallization of the solid lipid produces a dispersion of lipid nanoparticles. Ultracentrifugation may produce concentrated dispersions of lipid nanoparticulates. The formation of particles occurs via the shear force between neighboring particles, as well as the development and implosive breaks of bubbles resulting from cavitation forces (88, 89).

7.3. Microemulsion (ME) Methods

This method leads to the spontaneous creation of the ME because there are more surfactants than lipids. The percentages of excipients are very important, and a lot of the time, pseudo-ternary diagrams are used to figure out where ME is made. This procedure is straightforward and executed via multiple phases. The molten lipids are first distributed in the heated surfactant solution, followed by gentle stirring until the microemulsion is established. In the subsequent phase, the heated ME is introduced to a substantial quantity of cold water (2–3°C) with

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moderate agitation. This induces the solidification of the liquid droplets. SLN or NLC produced by this approach have a spherical morphology with a restricted size range. This approach has significantly diluted final lipid nanoparticle dispersion relative to the hot emulsion and this may need an extra step to concentrate the final product using ultrafiltration or lyophilization. The excessive use of surfactants and co-surfactants is a significant disadvantage of this approach (90, 91).

7.4. Double Emulsion (w/o/w) Technique

The double emulsion (DE) was produced via a two-step emulsification method, wherein the drug intended for entrapment in the aqueous inner phase (W1) is solubilized in water alongside a stabilizer, followed by mixing with the intermediate oil phase (O) using a high-speed homogenizer at elevated temperatures to generate a primary (W1/O) emulsion. The heated primary (W1/O) emulsion is next distributed in the external aqueous surfactant solution to yield a final W1/O/W2 double emulsion at 2–3°C with mechanical agitation, resulting in lipid nanoparticulates that are then isolated via diafiltration (92, 93).

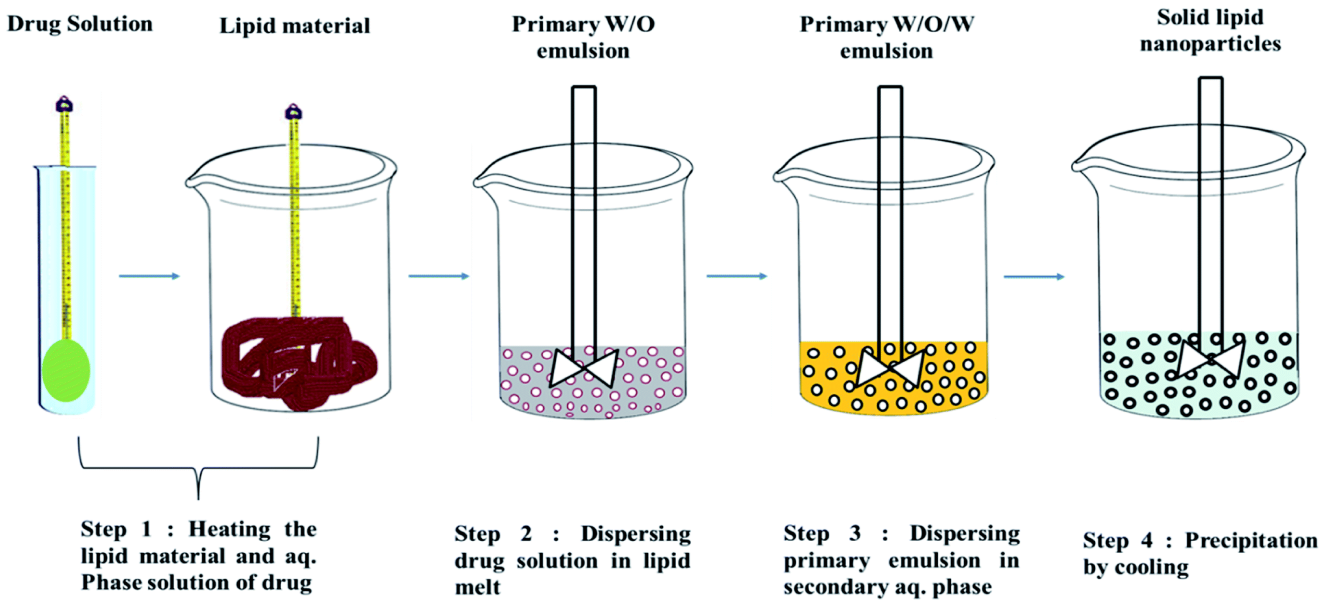

Figure 8 : Double emulsion technique (87)**.**

7.5 Organic-Solvent Based Methods

7.5.1. Emulsification Solvent Diffusion Technique

Several number of organic solvents that have partial solubility in water including butyl lactate, benzyl alcohol, isobutyric acid, tetrahydrofuran, and isovaleric acid, can be used to solubilize solid lipids and involve in the production of lipid nanoparticles. To achieve initial thermodynamic equilibrium, the organic solvents must be saturated with water. The transitory O/W emulsion is introduced into water with continuous agitation, resulting in the solidifying of the dispersed components and the formation of lipid nanoparticles owing to the organic solvent diffusion. The process of particle formation occurs via lipid solidification resulting from solvent migration from the inner organic phase toward the exterior aqueous medium (94).

7.5.2. Solvent Injection Technique

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This approach resembles to the solvent diffusion method; but the solvents employed are chosen from the group of highly water-miscible solvents (e.g., DMSO, ethanol), therefore precluding the possibility of emulsion formation. Initially, the lipids and the medication are dissolving in organic solvent, which follows their injection into an aqueous solution of surfactant with agitation, resulting in the fast escape of the organic solvent into the aqueous phase and the lipids precipitation. The resultant particle size is significantly influenced by the rate of extraction and, correspondingly, by the solvent hydrophilicity. Solvents with high hydrophilicity yields smaller particles but diminishes the solubilization capacity of lipids (95).

7.5.3. Emulsification –Solvent Evaporation Technique

Some types of organic solvent such as cyclohexane, dichloromethane, and chloroform) that are immiscible with water can be used to solubilize the lipophilic medicine followed by emulsification in aqueous solution containing. Then, the organic solvent is removed via evaporation at low-pressure (40-60 mbar)., the nanoparticulates are generated by precipitation of lipids in the aqueous medium. The emulsification in an aqueous medium accomplished by high-pressure homogenization (86, 94).

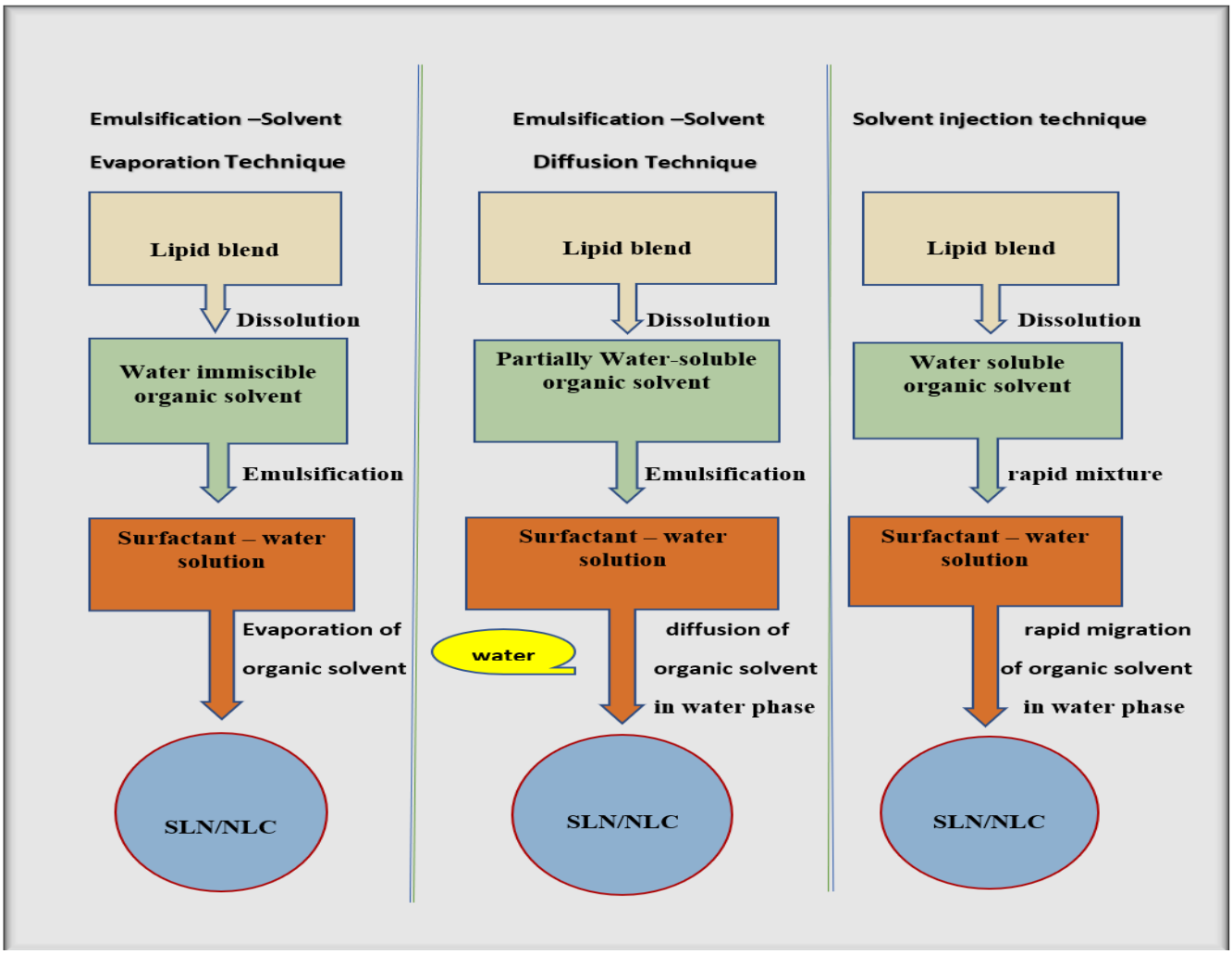

Figure 9 : Organic-solvent based methods (96).

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7.6. Supercritical Fluid (SCF) Technique

The process of producing lipid nanoparticles from emulsions via supercritical fluid technology is termed "supercritical fluid extraction of emulsions" (SFEE). The oil phase is created by dissolving the medicament and lipid component in an organic solvent, such as chloroform, followed by the addition of an appropriate surfactant. The organic phase is incorporated into an aqueous phase, potentially including a cosurfactant, and the resultant combination is further processed via a high pressure homogenization to generate an oil-in-water emulsion. The oil/water emulsion is supplied from one end of the extraction chamber (often the top) at a steady flow rate, while the supercritical fluid (e.g., CO2) is concurrently released from the bottom of the extraction column at a constant flow rate. Lipid nanoparticles are generated by removing organic solvent that diffuse from the oil-in-water emulsions to supercritical fluid as in (figure 10) followed by lipid solidification resulting from the oil phase expansion (97).

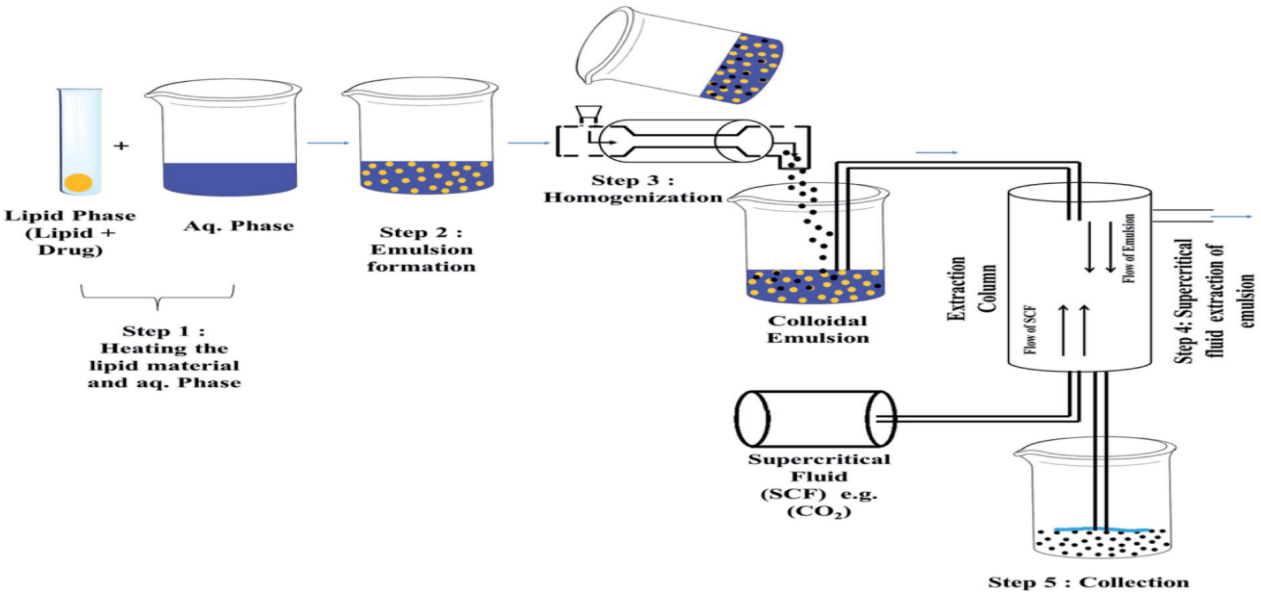

Figure 10: Super critical fluid technique (87).

7.7. Coacervation Technique

Lipid nanoparticles are generated by the acidifying of a micellar solution containing alkaline salt of lipids (figure 11). Prior to the creation of lipid nanoparticles, a polymeric stabilizer solution is generated after being heated in water bath. The fatty acid sodium salt is uniformly distributed in the solution of polymeric stabilizer, under heating to point greater than the Krafft point of the fatty acid salt and continuous agitation to achieve a clear solution. The medication, dissolved in ethanol, is then incorporated into the clear solution with continuous agitation until a homogeneous phase is achieved (98). The gradual addition of a coacervating solution (i.e., acidification of the solution) to this combination results in a suspension. Further cooling of the mixture while maintaining steady agitation produces uniformly distributed drug-loaded

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nanoparticles (99).

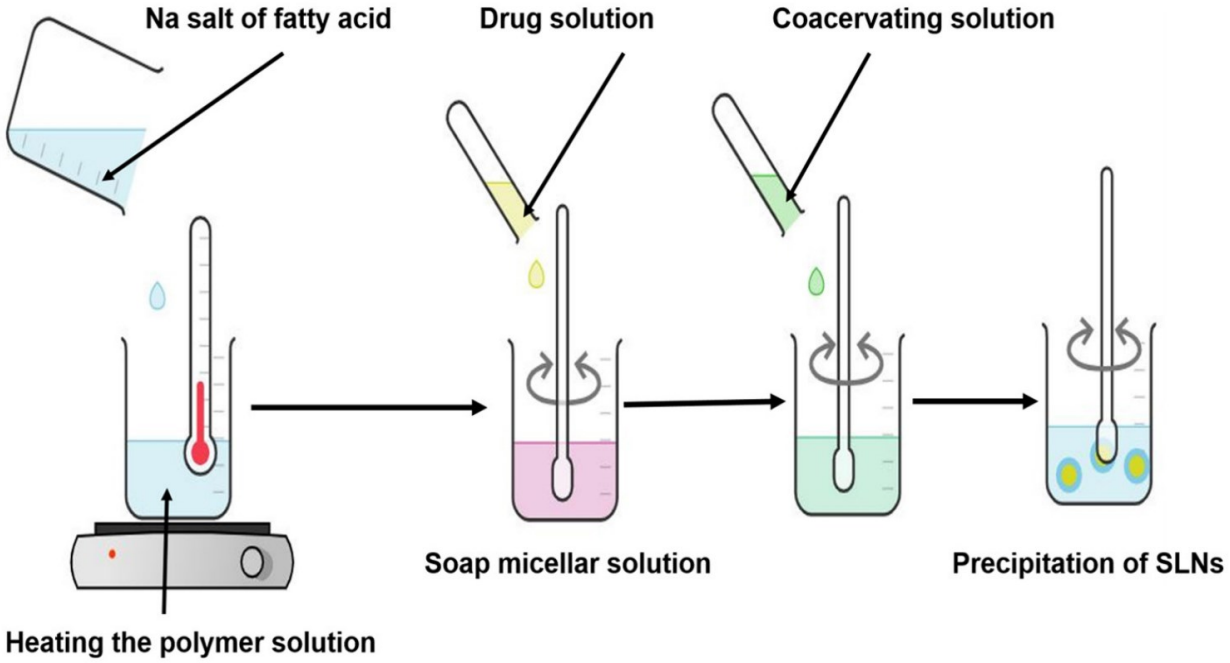

Figure 11 : Coacervation Technique (100).

7.8. Ultrasonication

This technique relies on the idea of particle size diminution by the utilization of sound waves. This approach employs both homogenization under elevated pressure and then ultrasonication to produce solid lipid nanoparticles (SLNs) ranging in size from 80 to 800 nm. Ultrasonication relies on cavities in aqueous dispersions induced by high-frequency ultrasound, often at or above 20 kHz. In the synthesis of SLN and NLC, an initial the pre-emulsion is created using molten lipid and heated solution of surfactant. The ultrasound is subsequently given via a sonotrode that contacts the liquid. Cavitation induces the fragmentation of the lipid portion to small droplets and the resultant heated microemulsion undergoes cooling to yield solid particles. The advantages of this approach include scaling up with flow cells, a smaller number of wetting and moving components (facilitating cleaning), and the ability to regulate the procedure by modulation of sound wave amplitude. The primary disadvantage, however, is the heightened

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danger of metal contamination, that escalates with prolonged sonication durations (97, 101).

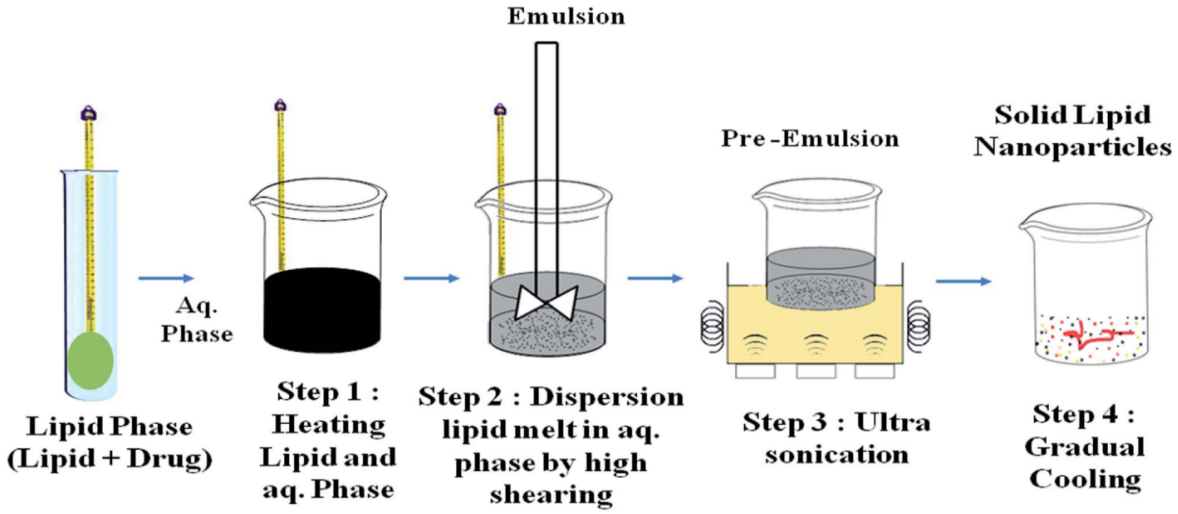

Figure 12: Ultrasonication Technique (87).

H. Stability of NLCs

Numerous more nanocarrier forms may similar to NLC dispersions, including liposomes, micelles, and nanoemulsions, which influence formulation stability. Aggregation may transpire during prolonged stability as a result of collisions leading to flocculation. In highly concentrated NLC dispersions, a pearl-like effect is seen owing to network development that prevents collision and flocculation. Upon dilution with stomach fluids or blood after administration, this network is destroyed, releasing unattached nanoparticles (102).

The NLCs Physical instability, including gelling or aggregation over prolonged storage, is a significant problem. All NLC dispersions must maintain their physical characteristics, particularly particle size, throughout storage and be kept safe against bacterial proliferation. To assure the physical stability of the NLCs during storage, two methods are employed: first, removing of water from the nanoparticle dispersion (e.g., freeze-drying); second, the incorporation of preservatives into the mixture (103).

A lyophilized product must retain a suitable appearance and quickly suspend again upon the addition of water within a brief reconstitution period. Furthermore, it must not alter the particle size of the nanoparticles and should preserve the efficacy of the encapsulated medicine. Aggregation has been seen in freeze-dried formulations without cryoprotectants. Various polymeric and saccharide-based cryoprotectants have been examined and used for the preservation of NLCs, including trehalose, mannitol, PVP, sucrose, sorbitol, dextrose, Microcelac®, lactose, and Avicel® RC591. Preservatives are used to maintain physical stability primarily in dermal products, which are mostly liquid or semisolid formulations using water as the dispersion medium. Nevertheless, preservatives may potentially compromise the stability of NLCs; thus, it is essential to evaluate various preservatives and their impact on physical stability. The destabilizing effect of preservatives is contingent upon many elements, including the hydrophobicity of the particles, the attachment of the preservative to the particle surface, the capacity to reduce zeta potential, the nature of the particle stabilizer, and its interaction with

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the preservative. To get preserved and stable NLCs, the preservative must be very hydrophilic and non-ionic to avoid interaction with the particle surface and to have no impact on zeta potential (104).

I. Characterization of NLCs

It is important to characterize nanostructured lipid carriers (NLCs) in the same way that you would characterize other colloidal carriers in order to assess the quality, stability, and release kinetics of the delivery system. Here are the main ways to characterize something:

9.1. Particle Size Distribution and Polydispersity Index

The best and most common ways to find out the size of lipid nanoparticles are photon correlation spectroscopy (PCS) and laser diffraction (LD). People often call PCS "dynamic light scattering." This method finds out how the intensity of scattered light changes when particles move. PCS is a technology that is fairly accurate and sensitive, but it can only measure sizes between a few nanometers and 3 µm. This size range is good enough to describe lipid nanoparticles. On the other hand, LD can measure larger particles (>3 µ). LD has a wider range of sizes, from the nanoscale to the lower millimeter range. This method is based on the idea that the diffraction angle depends on the particle radius. This means that smaller particles cause more intense scattering at higher angles than larger particles. It is advisable to use both PCS and LD methods concurrently, since neither approach directly measures particle sizes; instead, particle sizes are inferred from their light scattering effects. This is due to the mostly non-spherical morphology of particles. The size of particles adversely affects gastrointestinal absorption and clearance via the reticuloendothelial system; hence, precise measures of particle size are essential. Particle sizes below 300 nm are advised for intestinal transit (105, 106).

As SLNs/NLCs are usually polydisperse in nature, measurement of polydispersity index (PI) is important to know the size distribution of the nanoparticles. The lower the PI value, the more monodispersed the nanoparticle dispersion is. Mostly a PI value of less than 0.3 considered as optimum value. PI can be measured by PCS (105, 107)

9.2. Zeta Potential and Surface Charge

The zeta potential (ZP) signifies the overall charge acquired by a particle inside a particular medium. The stability of nanoparticle dispersion during storage may be anticipated from the zeta potential value. The ZP denotes the intensity of repulsion among proximate particles with analogous charges inside the dispersion. A high ZP value indicates strongly charged particles. Typically, a strong zeta potential (whether negative or positive) prevents particle aggregation by electrostatic repulsion, hence maintaining the dispersion of nanoparticles. Conversely, in instances of low ZP, the attractive force surpasses the repulsive force, resulting in the coagulation or flocculation of the nano dispersion. This assumption does not apply to sterically stabilized colloidal dispersions. The ZP value of (−30 or +30 mV) is sufficient for the satisfactory stability of nanoparticle dispersion (108). The zeta potential of colloidal dispersion may be measured by photon correlation spectroscopy (105, 109).

9.3. Particle Shape and Surface Morphology

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force

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microscopy (AFM) are effective techniques for assessing the form and surface morphology of lipid nanoparticles. These approaches can ascertain both the particle size and the particle size distribution. SEM use electron transmission from the sample's surface, while TEM utilizes electron transmission through the samples. Compared to PCS and LD, both SEM and TEM provide direct data on particle size and morphology. Numerous SEM and TEM investigations reveal spherical-shaped lipid nanoparticles. Although conventional SEM lacks great sensitivity to the nanometric size range, field emission SEM (FESEM) can detect sizes within this range. Nonetheless, sample preparation (e.g., solvent removal) may influence the morphology of particles. Cryogenic FESEM may be advantageous in this scenario, whereby the freezing of liquid dispersion is achieved using liquid nitrogen, and micrographs are captured under such conditions. The AFM method is increasingly being used for the characterization of nanoparticles (110, 111).This methodology yields a three-dimensional surface profile, in contrast to prior methods that provide a two-dimensional picture of the material. AFM delivers direct functional, structural, mechanical, and topographical surface information with resolution ranging from nanometers to angstroms. This approach produces a picture with a spatial resolution of up to 0.01 nm, derived from the interaction force between the sample surface and the AFM probe tip. Direct imaging of the original water or solvent-containing samples is feasible since no vacuum is used during operation, and sample conductivity is unnecessary. Zur Muhlen et al. conducted a comparative analysis of AFM and SEM, reporting identical nanoparticle sizes obtained from both methods (112, 113).

9.4. Differential Scanning Calorimetry (DSC)

This approach employs a sensitive device that facilitates the comprehension of a sample's structural features by quantifying heat exchanges (i.e., thermal energy absorption or emission) during the sample's melting or crystallization under regulated temperature circumstances. In Differential Scanning Calorimetry (DSC), a sample is first heated and then cooled at a regulated pace, while the heat flow, whether absorbed or released, is quantitatively measured. While extremely sensitive DSC devices may detect minimal temperature variations, they do not provide insights into the underlying causes of these changes. The causes of processes such as melting, polymorphic changes, sample dehydration, or decomposition may be ascertained via the use of several integral approaches, including microscopy, X-ray diffractometry, thermogravimetric analysis, or other spectroscopic techniques (114).

9.5. Powder X-ray Diffraction (XRD)

This approach involves analyzing the diffraction patterns of X-rays when they contact with the randomly arranged crystal lattices of particles. The resultant diffractogram displays the intensity of reflected X-rays in relation to the angular location of the incident X-ray beams. The diffractogram generates a distinct XRD pattern for a particular crystal form, which can be employed to identify or distinguish its polymorphic structures. Additionally, it can be utilized to identify various lipid polymorphic forms, such as glycerides, which exist in three primary polymorphic forms: α, β′, and β, in order of increasing thermodynamic stability (115).

9.6. Encapsulation Efficiency (EE)

The optimization of encapsulation efficiency is a crucial element in formulation design, since it influences both drug release and the cost-effectiveness of the formulation. The proportion of

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the medication quantity encapsulated in the nanoparticle, indicating the effectiveness of the NLC formulation. The entrapment efficiency is increased for lipophilic medicines due to their uniform solubilization inside the lipid matrix. Moreover, drug entrapment is enhanced due to the creation of a solid lipid particle during cooling, which retains the drug inside the lipid matrix. Elevated energy efficiency is seen in lipids exhibiting defects in their crystalline architecture. The inclusion of liquid lipids in NLCs enhances the defects in the lipid crystalline architecture, hence significantly augmenting the encapsulation efficiency (EE) (116).

9.7. In-Vitro Release Study of Medication

The regulated or sustained releasing of active medicinal agents from these nanocarriers will result in an extended the half-life and reduced degradation in systemic circulation by enzymes. The manufacturing temperature influences the releasing of medicine from formulation, along with the kind and ratio of surfactant and the proportion of oil incorporated into the lipid matrix (117).

The medication is released from NLCs in either a burst or continuous manner. A high drug concentration on the outer shell and surface of the NLCs particles results in a burst release, while a sustained release pattern occurs when the drug is integrated into the inner core of the NLCs particles. The sustained release of pharmaceuticals may be elucidated by considering the partitioning of medications through the lipid phase and aqueous medium, together with barriers function that provided by interfacial membranes. The techniques such as Franz cell and dialysis are often used for assessment of medication release in vitro from nanocarriers. The elucidation of drug releasing patterns in vitro must take into account the particular conditions present in the in vivo environment. The breakdown by enzymes of NLCs may be appropriately regulated by the composition of the particles (74, 118).

J. NLCs as a Potential Oral Drug Delivery System

The oral medication delivery system was the most preferred and convenient way of drug administration. Innovative strategies are being explored to mitigate risk concerns including restricted solubility of medication, small absorption window, rapid metabolic rate, significant fluctuations in medication plasma levels, and unpredictability associated with dietary effects. These conditions may provide unfavorable in vivo outcomes, hence resulting in the failure of oral administration methods (119). NLCs have been shown to be among the most advantageous techniques for the orally intake of drugs that have poor solubility in water with limited bioavailability. Additional benefits of using NLCs for oral administration including enhanced the loading capacity of medications, superior drug encapsulation, elevated compliance of patient and the greater particulates concentration (120). NLCs have garnered significant interest for enhancing the oral bioavailability of medicines. They may regulate P-glycoprotein-mediated efflux activity and significantly alter the pharmacokinetics of the delivered medication. Recent investigations indicate that different lipids and surface-active agents included in the manufacture of NLCs may impede P-glycoprotein-mediated medication efflux across the gastrointestinal wall. The surface-active agents such as tween 80, Cremophor-EL and Solutol 15, which may influence P-glycoprotein function. Moreover, pecerol, pluronic P85, and gelucire 44/14 are also capable of inhibiting P-glycoprotein. The precise mechanism through which these surfactants modulate P-glycoprotein (P-gp) activity remains unclear; various theories suggest that alterations in cell

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membrane integrity, competitive or noncompetitive blockage of binding sites, or allosteric interference with ATP hydrolysis, resulting in a futile ATP hydrolysis cycle, may contribute to the inhibition of P-gp efflux (90). A potential mechanism for improved drug bioavailability delivered in NLCs is the nanoscale particle size. The absorption by reticuloendothelial system has reduced for nanoparticulates within the range of 120-200 nm, hence improving the bioavailability of oral medicines. The augmentation of drug solubility owing to the shift from crystalline to amorphous forms is one mechanism contributing to increased oral bioavailability. Alternative hypothesized pathways for the absorbed of these nanocarriers from the colon include directly intake by the GIT, enhanced permeation via surface-active agents and decreased degradation and elimination (120).

Conclusion

Nanotechnology has become a revolutionary tool in modern pharmaceuticals, providing new ways to solve the problems that have plagued traditional drug delivery systems for a long time. Nanotechnology has enhanced the solubility, permeability, and bioavailability of drugs with suboptimal pharmacokinetic profiles by facilitating precise control over particle size, surface characteristics, and release dynamics. The transition from liposomes and solid lipid nanoparticles (SLNs) to nanostructured lipid carriers (NLCs) signifies a substantial progression in lipid-based nanocarriers. NLCs are better than SLNs because they can hold more drugs and don't break down when they crystallize. They combine solid and liquid lipids to make a less ordered matrix that holds more drugs and keeps them from leaking out during storage. They can be made using scalable methods like high-pressure homogenization, ultrasonication, and solvent-based methods, which makes them flexible enough for a wide range of pharmaceutical uses. NLCs are better than other types of drugs because they can release drugs in a controlled and long-lasting way, stay stable for a long time, need less surfactant, and improve lymphatic uptake, which helps them avoid first-pass metabolism. Recent studies show that they work well to improve the oral bioavailability of class II drugs, peptides, and biopharmaceuticals that don't dissolve well. This means that the drugs work better and patients are more likely to take them. Even though there are still problems to solve with large-scale production, getting regulatory approval, and making strong connections between in vitro and in vivo studies, NLCs are the best lipid-based platform for delivering drugs by mouth. Their multifunctional characteristics establish them as a fundamental component in the future of nanotechnology-driven pharmaceuticals, connecting laboratory advancements with clinical application.

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