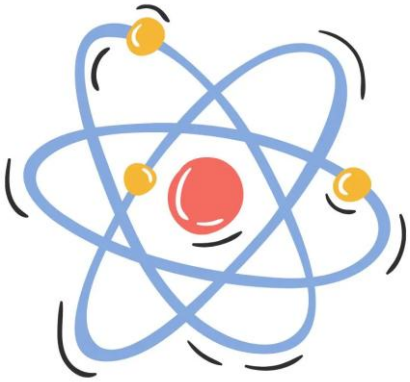

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Abstract: *Oral drug delivery is predominantly limited by the low aqueous solubility that leads to low dissolution rate and hence poor bioavailability. Lipid-based nanocarriers provide a logical answer to this challenges as they enhance solubilization, prevent drug degradation and escalate intestinal absorption. The classification, mechanisms, formulation techniques, and advantages and limitations of the major lipid-based systems (i.e., SLNs, NLCs, liposomes, niosomes SEDDSs and SNEDDS) are presented in this study. Especially self-nanoemulsifying systems are focussed because of its success in poorly water-soluble drugs. Comparative aspects of vesicular and non-vesicular systems are also highlighted. Solid SNEDDS and lipid-polymer hybrid nanocarriers are examples of future developments that have the potential to improve stability and performance. In general, lipid-based nanocarriers show promise as a means of improving oral bioavailability.*

Keywords*: Lipid-based nanocarriers; Solid lipid nanoparticles (SLN); Nanostructured lipid carriers (NLC); Self-nanoemulsifying drug delivery systems (SNEDDS); Poorly water-soluble drugs; Oral bioavailability; Hybrid nanocarriers.*

1. INTRODUCTION

One of the most suitable method of drug delivery is oral administration it is because it is safe, easy to use and have better patient compliance. Drugs may have difficulties in absorbing and dissolving due to the delicate microenviournment and a number of biological barriers such as mouth, oesophagus, stomach, small intestine, and colon's varied anatomy, mucin-biocarbonate layers, enzymatic degradation and change in pH [1].

A major barrier to oral drug delivery is poor aqueous solubility which affects drug dissolution, absorption and bioavilability. Approximately 70% of newly developed drugs have poor water solubilty and as we know that gastrointestinal permeability and solubillity are important factors

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that influence oral drug absorption. Hence improving solubility and dissolution rate is necessary to enhance the bioavailability of poorly soluble drugs [2].

Nanotechnology-based drug delivery approaches have emerged as an effective strategy to address several limitations associated with conventional therapeutic systems. Nanocarriers are colloidal delivery systems, typically ranging in size from 1 to 100 nm, that are engineered to transport therapeutic agents to specific biological sites. These systems exhibit favorable properties such as prolonged systemic circulation, acceptable biocompatibility and the ability to provide targeted as well as sustained drug release. Furthermore, modification of physiochemical parmeters, including surface characteristics and material composition, enables improved drug stability, enhanced solubility, and optimized pharmacokinetic behaviour while simultaneously reducing toxicity. Owing to these advantages nanocarriers are considered to be the promising platforms for improving drug delivery efficiency and overall therapeutic outcomes [3].

Lipid-based delivery systems are among the most effective nanocarrier platform for enhancing the oral delivery of lipophilic drugs. Lipid-based drug delivery systems(LBDDS) have attrracted considerable attention due to their favorable size-dependent properties and their ability to improve drug absorption. In addition these systems are widely preferred because of their high biocompatibility and formulation versatility. Lipid based formulations can be successfully developed for multiple routes of administration including parenteral, pulmonary, and topical delivery. Moreover, lipid formulations can be strategically modified to meet diverse product requirements such as disease-specific targeting, route of administration cost considerations, formulation stability, toxicity and therapeutic efficacy. Because of their proven safety and performance lipid based carriers have become valuable platforms for the development of pharmaceuticals, vaccines, diagnostic agents and nutraceuticals. In recent years the importance of LBDDS has further increased due to their ability to enhance the solubility and bioavailability of poorly water soluble drugs [4].

Self-nanoemulsifying drug delivery systems(SNEDDS) repersent an established lipid-based formulation approach that integrates principles of nanotechnology to overcome challenges associated with poorly water-soluble drugs. These systems are particularly effective in enhancing oral bioavailability by improving drug solublilization within the gastrointestinal environment. Upon exposure to gastrointestinal fluids and mild agitation, the biocompatible and biodegradable components of SNEDDS spontaneously from fine oil-in-water

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nanoemulsions. Due to their formulation stability, ease of scale-up and potential to enable controlled or sustained drug release, SNEDDS have emerged as a promising platform for improving therapeutic efficacy as well as patient compliance [5].

2. Classification and Mechanism of Lipid-Based Nanocarriers.

2.1 Classification Overview

Lipid-based nanocarriers encompass several distinct systems, including liposomes, niosomes, solid lipid nanoparticles(SLNs) and naostructured lipid carriers(NLCs). According to Weber et al., SLNs and NLCs were developed to address specific limitations associated with conventional colloidal delivery systems, such as polymeric nanoparticles, liposomes, niosomes and nanoemulsions. The solubility, bioavailability, pharmacokinetic parameters, intestinal absorption, skin penetrability, and ocular residence time of medications can all be significantly enhanced by lipid nanoparticles, which aids the molecule in overcoming physiological barriers and reducing adverse effects. Consequently, these drug delivery vehicles show a great deal of promise for use in pharmaceutical or medical settings. There are two types of lipid particulate drug delivery systems: SLNs and NLCs. At low drug-loading, SLNs have been found to exhibit slower drug release compared to NLCs. Nevertheless, there is no discernible difference in drug release from SLNs and NLCs at high drug loading. At 25°C, NLCs are more stable than SLNs [6].

2.2 Mechanism Of Solubilization And Absorption Enhancement

Lipid-based nanocarriers improve the solubilization of poorly soluble medications and make it easier for them to pass through the gastrointestinal barrier, which improves oral absorption. In order to prevent drug precipitation and promote dissolution in the intestinal environment—both of which are essential for absorption—these nanocarriers encapsulate lipophilic compounds within a lipid matrix [7]. The drug molecules are transported to the enterocyte surface by the natural solubilizing agents known as mixed micelles, which are created when monoglycerides and free fatty acids are released during lipid digestion by pancreatic enzymes and combine with endogenous bile salts [8].

Drugs may be facilitated into the intestinal lymphatic transport pathway by promoting chylomicron formation within enterocytes during the lipid digestion process.This avoids the hepatic first-pass metabolism and improves systemic bioavailability [7]. Additionally, lipid nanocarriers engage in a variety of interactions with the intestinal membrane to

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promote drug uptake, all of which enhance permeation efficiency. These mechanisms involve transcellular uptake via endocytosis, paracellular transport mediated by transient modulation of tight junctions and transcytosis through M cells [9]. In addition, surfactants and excipients present in lipid-based systems can enhance membrane fludity and inhibit efflux transporters, thereby further improving drug absorption [7]. Collectively enhanced solubilization through micellar systems, along with increased membrane interaction and lymphatic uptake, contributes to the enhanced oral bioavailability exhibited by lipid-based nanocarriers [7-9].

Comparison Of Lipid Based Systems

Stability, drug loading capacity, release kinetics, bioavailability enhancement, and scalability are some of the specific benefits and drawbacks of systems such as Liposomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) [4].Different types of lipid nanocarriers have different compostion, drug loading capacity, stability and many more different properties. Here is a comparison table of different types of lipid based system:

Lipid System	**Composition**	**Drug Loading**	**Stability**	**Example**
Solid Lipid Nanoparticles(SLN)	Solid lipids (triglycerides,fatty acids) stabilized by surfactants [10],	Moderate, limited by crystalline lipid matrix [10].	Good physical stability, possible polymorphic transitions and drug expulsion during storage [10].	Paclitaxel, Quercetin
Nanostructured Lipid Carriers(NLC)	Blend of solid and liquidslipids with surfactants[10].	Higher then SLN due to liquid lipid inclusion [10].	More stable than SLN, less drug expulsion [10].	Curcumin , Resveratrol

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Liposomes	Phospholipids and cholesterol [11].	Variable, encapsulate hydrphilic and lipophilic drugs [11].	Moderate stability, prone to fusion and leekage without stabilization [11].	Doxorubicin, Amphotericin B
Self-Nanoemulsifying Drug Delivery System (SNEDDS)	Oil surfactants, cosurfactants forming isotropic mixtures [12].	High capacity no crystallinity limitations [12].	Thermodynamically stable liquid and solid SNEDDS improve stability [12].	Tacrolimus, Cyclosporine

Table no.: 1

The table compares the main lipid-based drug delivery methods, such as liposomes, self-nanoemulsifying drug delivery systems (SNEDDS), solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs). It provides a summary of their physical and chemical stability, drug loading capacity, typical drug release profiles, physical states, formulation compositions, and representative example drugs.

Solid Lipid Nanoparticles (SLN)

Solid lipid nanoparticles(SLNs) are submicron colloidal carriers composed of biocompatible lipids that remain solid at room temperature, with particle sizes typically ranging from 50 to 1000 nm. By combining features of liposomes, lipid emulsions, and polymeric nanoparticles, SLNs provide enhanced drug protection, controlled release, and enhanced physical stability [13]. These systems enhance the stability and bioavailability of poorly water-soluble drugs through immoblization of the drug within the solid lipid matrix. Moreover, SLNs can be manufactured at a large scale using established techniques such as high-pressure homogenization or ultrasonication and are suitable for multiple routes of administration, including oral, parenteral, dermal, opthalmic, and pulmonary delivery [14]. High-pressure homogenization is one of the production techniques that enables scalable manufacturing with consistent particle size and encapsulation effectiveness. Surface changes to enhance targeting and pharmacokinetics are recent developments that establish SLNs as a flexible and viable platform for modern drug delivery applications [15].

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2.3 Composition And Preparation Technique

- **Composition**: Solid lipid nanoparticles (SLNs) are colloidal carriers composed of physiological and biodegradable lipids that remain solid at both room and body temperature. The basic components of SLNs include:

- **Lipids:** Solid lipids found in SLNs stay solid at body and room temperatures. Triglycerides (like tristearin), partial glycerides, fatty acids (like stearic acid and palmitic acid), steroids (like cholesterol), and waxes (like cetyl palmitate) are examples of frequently used lipids. These fats make up the central matrix that contains the medication [16].

- **Surfactants (emulsifiers)**: By lowering surface tension and inhibiting aggregation, surfactants stabilize the dispersion of nanoparticles. According to Maryam Hasan Zadeh, et al Poloxamer 188, Tween 80, lecithin, and Pluronic F68 are a few examples. The administration method and the intended physicochemical characteristics of SLNs determine the surfactant selection and concentration [17].

- **Co-surfactants and Aqueous Phase**: The dispersion medium is either water or aqueous surfactant solutions. Co-surfactants are occasionally added to enhance stability and particle size distribution [17].

- **Preparation Techniques:** Preparation techniques for solid lipid nanoparticles (SLNs) include several well-established methods, each with specific operational principles and advantages:

- **High-Pressure Homogenization (HPH):** Hot and cold homogenization are the two primary varieties of this most popular and scalable preparation method. In hot HPH, a pre-emulsion is created by melting the lipid above its melting point and dispersing it in a heated aqueous surfactant solution. After reducing the particle size through high-pressure homogenization at a high temperature, the mixture is cooled to crystallize the lipid matrix and create SLNs. In order to create nanoparticles, cold HPH entails quickly solidifying the lipid-drug mixture, then dispersing it in a cold surfactant solution and

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homogenizing it at room temperature or lower. This approach works well for medications that are heat-sensitive [18].

- **Microemulsion Technique:** With this technique, melted lipid, surfactant, co-surfactant, and aqueous phase are combined at a high temperature to create a microemulsion. Lipid crystallization and the creation of SLN occur when this microemulsion is rapidly diluted with cold water. In order to preserve lipid liquidity throughout processing, the microemulsion method mainly depends on temperature control [17].

- **Solvent Emulsification-Evaporation:** This process involves dissolving the drug and lipid in an organic solvent that is water-immiscible, emulsifying it in an aqueous surfactant phase, and then evaporating the solvent under low pressure. SLNs can be prepared using lipid precipitation techniques which are particularly useful when direct lipid melting is unsuitable for the formulation process [18].

- **Ultrasonication/High-Shear Homogenization:** In this method, molten lipids are disperssed into an aqueous surfactant phase through the application of ultrasonic energy or high shear forces, Although the techniques are simple to perform and cost-effective, they may lead to limited batch-to-batch reproducibility and relatively broad particle size distributions [17].

2.4 Advantages And Limitations Of SLN

- **Advantages:**
- Owing to their physiological lipoid composition, SLNs exhibit excellent biocompatibility and biodegradibility which contributes to reduced systemic toxicity [19].
- The formulation flexibility of SLNs allows the incorporation of both lipophilic and hydrophilic therapeutic agents, thereby broadening their application potentialc [20].
- SLNs are less immunogenic and cytotoxic than polymer-based nanocarriers [20].
- SLNs, especially those between 120 and 200 nm, are not easily absorbed by the cells that make up the RES (Reticulo Endothelial System), avoiding filtration by the liver and spleen [20].

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- By limiting drug degradation and preventing premature lekage SLNs enhance shelf life and improve consistency in therapeutic performance [15].

Limitations:

- **Limited drug loading capacity:** Because of the highly crystalline nature of SLNs, there is less room for drug molecules, which leads to lower drug loading, particularly for hydrophilic drugs [19]
- **Risk of drug expulsion:** During storage, polymorphic transitions and crystallization may cause the encapsulated drug to leak or expel, decreasing the therapeutic consistency [10].
- **Physical instability during storage:** Prolonged storage may lead to issues such as particle aggregation, gelation, or gradual praticle size growth which can negatively affect product quality and performance [21].
- **Unstudied long-term toxicity:** Comprehensive studies evaluating potential long-term toxicity and immunological effects remain limited, particularly for specific target tissues or route of administration, such as ocular or retinal delivery [19].

2.5 Applications Of SLN

- **Parenteral administration:** SLNs improve circulation time and enable controlled release of antiviral and anticancer drugs following intravenous administration [10].
- **Topical and dermal delivery:** SLNs enhance drug stability and skin penetration , supporting their use in dermatological and cosmetic formulations [22].
- **Targeted drug delivery:** Surface modification of SLNs enables site-specific delivery to organs such as the liver, brain, and tumor tissues, thereby improving therapeutic efficacy while reducing systemic adverse effects [16].
- **Vaccines:** SLNs and related lipid nanoparticle systems serve as effective vaccine carriers by enhancing antigen stability and immune response [23].
- **Anticancer therapy:** According to Albertsen, Camilla Hald, et al., SLNs facilitate the encapsulation of multiple chemotherapeutic agents, offering sustained drug release and reduced toxicity [22].

3. Nanostructured Lipid Carriers (NLC)

Nanostructured lipid carriers (NLCs) are second-generation lipid-based delivery systems composed of a mixture of solid and liquid lipids, forming a less ordereds lipid matrix. This structural modification was designed to overcome limitations of solid lipid nanoparticles, such as low drug loading and drug explusion during storage. The

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inclusion of liquid lipid creates imperfections within the solid matrix, therby enhancing drug accommodation and allowing greater control over release behavior [24].

Compared with conventional lipid carriers, NLCs exhibit improved stability, biocompatibility and biodegradability along with higher drug loading capacity and reduced drug leakage. These advantages have led to increasing attention in their use across multiple routes of administration including oral, parenteral, ocular, nasal and dermal delivery. In addition, surface modification of NLCs enables targeted delivery and controlled drug release, contributing tom improved bioavailibility and therapeutic efficacy [8]. NLCs can be produced on a large scale using established techniques such as high pressure homogenization, supporting their translational and industrial potential [25].

4.1 Composition And Preparation Techniques

- **Composition:** The composition of Nanostructured Lipid Carriers (NLCs) are composed of the following components:
- **Solid Lipids:** Solid lipids form the structural matrix of NLCs and remain solid at both room and physiological temperatures. Common examples include cetyl palmitate, glyceryl monostearate, and stearic acid [8].
- **Liquid Lipids:** Liquid lipids or oils are incorporated into the solid lipid matrix to create structural imperfections, which enhance dryg loading capacity and reduce drug expulsion during storage. Squalene, medium-chain triglycerides, almond oil, and oleic acid are examples of common liquid lipids. The normal range of the solid-to-liquid lipid ratio is 70:30 to 99.9:0.1 [18].
- **Surfactants**: By lowering surface tension, surfactants stabilize the lipid dispersion. Commonly used nonionic surfactants include lecithin, Tween 80, and Poloxamer 188. Using multiple surfactants frequently results in better stability and smaller particle sizes [25].
- **Aqueous Phase:** The continuous phase in which the lipid nanoparticles are distributed is made up of water or an aqueous surfactant solution. Additionally, the aqueous phase may contain preservatives or cryoprotectants [26].
- **Other Ingredients:** To improve stability and functionality, emulsifiers, antioxidants (like vitamin E), moisturizing agents, and preservatives may be added, depending on the needs of the formulation [27]

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- **Preparation Techniques:** Preparation Techniques of Nanostructured Lipid Carriers (NLCs) includes:
- **High-Pressure Homogenization (HPH):** This is the most widely used technique for preparing NLC. A hot aqueous surfactant solution is combined with liquid and solid lipids that have melted above their melting points, and the mixture is homogenized under high pressure. Cooling induces lipid recrystallization, leading to the formation of nanostructured lipid carriers. Cold homogenization is particularly suitable for heat-sensitive drugs and involves and solidifying the lipid-drug mixture prior to its dispersion in a cold surfactant solution, followed by homogenization at low temperatures [28].
- **Microemulsion Technique:** At elevated temperatures, solid and liquid lipids are melted and combined with surfactants to form a thermodynamically stable oil-in-water microemulsion. Rapid dispersion of this microemulsion into cold water under stirring includes lipid recrystallization, resulting in the formulation of NLCs. While this mild allows relatively mild processing conditions, precise temperature control is essential [25].
- **Solvent Emulsification-Evaporation:** This less commonly used method involves dissolving lipids in an organic solvent, emmulsifying the solution into an aqueous phase, and subsequently removing the solvent evaporation to form NLCs. It is suitable for thermoliable drugs; however careful control of solvent removal is required [8].
- **Additional Techniques**: Other emerging approaches include phase inversion, hot-melt extrusion, solvent injection, membrane contractor systems, and supercritical fluid techniques. These methods offer improved control over particle size and formulation parameters but often require specialized equipment [29].

4.2 Advantages And Limitations Of NLC

- **Advantages:**
- Compared with solid lipid nanoparticles(SLNs), nanostructured lipid carriers(NLCs) exhibit higher drug loading capacity and improved long term stability due to their less ordered lipid matrix, which reduces the likelihood of drug expulsion during storage [8].
- They are promising for large-scale pharmaceutical manufacturing because of their superior biocompatibility, simplicity in sterilization, and scalable production techniques [30].

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- NLCs can encapsulate hydrophilic and lipophilic medications, increasing their bioavailability and facilitating oral, topical, and nasal delivery, among other routes of administration [31].
- NLCs provide versatility for a range of therapeutic areas and enhance drug penetration in dermal applications [32].
- **Limitations:**
- **Regulatory Challenges:**Existing regulatory frameworks are largely designed for conventional formulations, making the approval of nanoscale systems such as NLCs more complex. This necessitates the development of standardized characterization methods and quality control guidelines, specific to NLC formulations which can increase development and manufacturing costs and ultimately affect product affordability [32].
- **Excipient related safety concerns:** The use of certain stabilizers including polysorbate 80(Tween 80), commonly employed in NLC formulations is limited due to their potential to cause skin irritation, partivularly in sensitive populations such as pediatric patient. Consequently through compatibility and safety evaluations are essentail during formulation development [32].
- **Scale-up and manufacturing issues:** Large scale production of NLCs remains challenging with risks of batch-to-batch variability arising from lipid crystallinity changes and the high senstivity of formulation and process parameters [33].

4.3 Applications Of NLC

- **Oral Delivery:** NLCs enhance drug solubility, permeability, and bioavailability while protecting drugs from gastrointestinal degradation and enabling controlled release. Absorption is facilitated through paracellular, transcellular, and M-cell-mediated pathways [9].
- **Dermal and Topical Delivery:** Due to their nanoscale size, NLCs closely intreact with the stratum corneum, improving skin hydration and drug penetration. They are widely applied in dermatology and cosmetic formulations for conditions such as inflammation ,acne and skin aging [29].
- **Cancer Treatment:** NLCs enable targeted delivery of anticancer agents with higher drug loading efficiency, controlled release, and reduced systemic toxicity [34].

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- **Antimicrobial Applications:** NLCs loaded with antimicrobial agents or essential oils demonstrate enhanced activity against resistant bacterial strains, providing an effective platform for infectious disease management [35].
- **Wound Healing:** NLCs are utilized in topical formulations that promote wound healing processes because of their enhanced occlusion, hydration, and drug penetration [32].

Comparison between SLN and NLCs

Feature	SLNs	NLCs	Reference
Lipid Matrix Composition	Composed purely of solid lipids.	Mixture of solid and liquid lipids, creating an imperfect matrix.	[18]
Stability	Generally more stable because of the solid matrix.	Because liquid lipid is present, it may be less stable.	[36]
Release During Storage	Unwanted drug leakage while being stored.	Drug release during storage is minimal.	[18]
Particle size control	Narrow size range but sometimes limited by lipid type.	Using a lipid mix makes controlling particle size easier.	[37]
Drug Loading	Lower due to compact structure.	Higher, due to matrix imperfections created by liquid lipid.	[38]
Manufacturing Complexity	Comparatively easier because of single-phase lipids,	Handling two distinct lipid phases makes it more complicated.	[36]

Table no.:- 2

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4. VESICULAR LIPID SYSTEMS:

Vesicular systems are highly organized structures composed of one or more concentric lipid bilayers formed through intreactions between amphiphilic molecules and aqueous media.These vesicles are capable of encapsulating both hydrophilic and lipophilic drugs, thereby enhancing drug stability and improving bioavailability. Because vesicular drug delivery systems localize drug activity at specific sites, they allow for targeted delivery, lowering systemic toxicity and maintaining drug action at a predefined rate [39]. Thus, several vesicular drug delivery systems have been created, including transfersomes, niosomes, and liposomes [40].

Liposomes, niosomes, and transfersomes are the major classes of vesicular lipid carriers differing mainly in composition and membrane flexibility. Significant benefits of vesicular lipid systems include better drug entrapment, protection against degradation of labile drugs, improved drug penetration through biological membranes, controlled and prolonged release, and fewer systemic side effects. They can be applied topically, transdermally, orally, and parenterally because of their structural resemblance to natural biological membranes, which promotes cellular uptake and targeted delivery [41].

5.1 Liposomes: Liposomes are spherical vesicles that self-assemble in aqueous environments and are primarily made up of one or more phospholipid bilayers, frequently including cholesterol and other lipids. Because phospholipids are amphiphilic, they can arrange into bilayers that enclose an aqueous core and divide the internal and external environments by forming a hydrophilic head and a hydrophobic tail. The composition and structural characteristics of liposomes affect their size, rigidity, and drug loading capacity. Liposomes are vesicular lipid-based nanocarriers that may be unilamellar, consisting of a single bilayer, or multilamellar, composed of multiple concentric bilayers [42].

They are widely used due to their ability to enhance drug solubility, protect encapsulated drugs from metabolic degradation, and improve bioavailability. Surface modification of liposomes enables targeted drug delivery, reducing systemic toxicity and enhancing therapeutic efficacy, particularly in cancer therapy [43]. In addition, liposomes exhibit favorable pharmacokinetic properties, high biocompatibility, low toxicity, and the capacity to encapsulate both hydrophobic drugs while allowing comntrolled and sustained release [44].

Notwithstanding their benefits, liposomes have drawbacks such as chemical and physical instability, the possibility of therapeutic agent leakage, oxidation susceptibility, and comparatively high production costs. Unless properly surface-engineered, unmodified

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liposomes may be quickly cleared by the mononuclear phagocyte system, reducing their in vivo circulation time and effectiveness [43]

5.2 Niosomes: Niosomes are vesicular drug delivery systems made of cholesterol and non-ionic surfactants that self-assemble into bilayer structures. Both hydrophilic and lipophilic medications can be encapsulated in these vesicles' aqueous core and bilayer membrane, respectively. Due to the chemical makeup of their constituents, niosomes have better physical and chemical stability than liposomes, which makes them attractive options for increasing the effectiveness of drug delivery and lowering toxicity [45].

Niosomes are lipid-based nanocarriers well documented for their low toxicity, biocompatibility, and ability to enhance drug stability and bioavailability. Their vesicular structure enables efficient encapsulation and controlled release of both hydrophilic and lipophilic drugs, including anti-inflammatory, anticancer and antimicrobial agents making them promising systems for targeted drug delivery and for overcoming poor solubility and instability issue [46].

Compared to liposomes, niosomes exhibit greater chemical stability due to their non-ionic surfactant composition and are biodegradable, non-immunogenic, and suitable for multiple routes of administration [47]. However challenges such as vesicle aggregation, drug leakage, and variability in encapsulation efficiency remain. Optimization of a surfactant type and cholesterol content is therefore essential to improve stability and drug release performance [48].

5.3 Transfersomes: Transfersomes are ultra-deformable vesicular lipid carriers composed of phospholipids and edge activators such as surfactant which enhance membrane flexibility. Their exceptional deformability allows them to penetrate narrow biological pores, particularly across the stratum corneum, making them highly effective for transdermal and systemic drug delivery. Compared with conventional liposomes and niosomes, transfersomes demostrate superior tissue penetration and can efficienctly transport both hydrophilic and lipophilic drugs [49].These advanced nanocarriers enable targeted and controlled drug delivery and are suitable for molecules with a wide range of molecular weights including proteins, peptides, corticosteroids, and anticancer agents. Transferosomal systems have been successfully explored for the delivery of insulin, antiviral drugs, anesthetics, and topical immunotherapies. Their non-invasive administration, sustained release potential, improved bioavailability, and avoidance of first-pass metabolism contribute to reduced dosing frequency and minimized systemic side effects particularly in transdermal applications [50].

Despite these advantages transfersomes face challenges such as complex formulation procedures, highers production costs, and susceptibility to oxidative degradation. Achieving optimal deformability and stability requires careful optimization of phospholipid-to-surfactant

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ratios and the use of specialized manufacturing equipment. Large-scale manufacturing and long-term stability are still issues that need to be resolved for regular clinical use [49].

5.4 Comparative features with non-vesicular systems:

Feature	Vesicular Lipid Systems [51]	Non-Vesicular Systems [52]
Structure	Liposomes and niosomes are examples of highly ordered lipid bilayer vesicles that encapsulate hydrophilic and lipophilic medications.	Solid lipid or polymeric colloidal nanoparticles without a bilayer structure.
Drug Encapsulation	Encapsulate lipophilic medications in a bilayer membrane and hydrophilic medications in an aqueous core.	Medication primarily loaded into a polymeric or solid lipid matrix.
Biocompatibility	Because of natural or synthetic lipids, it is biodegradable and biocompatible.	Lipid or polymer matrix that is biodegradable and biocompatible.
Stability	Prone to oxidation, fusion, and leakage; requires particular stabilization.	Chemically and physically stable; reduced drug leakage.
Drug Release	Membrane engineering makes controlled, targeted release possible.	Slower release kinetics and sustained release via a solid matrix.
Manufacturing Complexity	Complex formulation and scale-up processes.	Generally simpler, scalable production processes.
Applications	Used in vaccines, cancer therapy, gene delivery, ocular delivery.	Used for injectable, topical, and oral administration with improved stability.
Limitation	Short half-life, high cost, and stability problems.	Possible burst release and limited hydrophilic drug loading.

Table no.:- 3

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This table offers a succinct comparative summary of the key characteristics, benefits, and drawbacks that set vesicular and non-vesicular drug delivery systems apart, allowing for well-informed selection for certain pharmaceutical applications.

5. Self-Emulsifying and Self-Nanoemulsifying Drug Delivery Systems(SEDDS and SNEDDS)

Self-Emulsifying Drug Delivery Systems (SEDDS) are isotropic blends of oils, surfactants, and co-surfactants that, when gently agitated in gastrointestinal fluids, easily produce fine oil-in-water emulsions, improving the solubility and oral bioavailability of medications that are poorly soluble in water [53]. SNEDDS are a subtype of SEDDS that produce nano-sized emulsions with droplet sizes usually less than 200 nm, increasing surface area and improving rates of absorption and dissolution [54]. These lipid-based nanocarrier systems increase systemic drug availability by preventing enzymatic drug degradation, promoting lymphatic transport, and lowering first-pass metabolism [53]. Because of these benefits, SEDDS and SNEDDS have garnered a lot of interest as practical methods to enhance the oral delivery of lipophilic and poorly soluble medications [55].

6.1 Principle of Self-Emulsification: Self-emulsification in SEDDS is made thermodynamically favorable by a change in entropy that affects the process's free energy. $\Delta G = \sum N i \pi r^2 \sigma$, where ΔG stands for free energy, Ni is the number of droplets, r is the droplet radius, and σ is interfacial energy, gives the free energy needed to form the emulsion[56]. In aqueous media, such as GI fluids, this process enables spontaneous emulsification with low or negative free energy upon mild agitation [57].

6.2 Formulation Components: SEDDS/SNEDDS contain three main components: oils, surfactants, and co-surfactantsp[56].

Oils: MCTs, LCTs, vegetable oils solubilize lipophilic drugs [56].

Surfactants: Tween 80, Cremophor EL enable emulsification [56].

Co-surfactants: PEG 400, propylene glycol improve fluidity [56].

6.3 Formulation Methods: There are various ways to formulate Self-Emulsifying Drug Delivery Systems (SEDDS) and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) to meet various drug delivery requirements, as explained below:

Liquid SEDDS/SNEDDS: In the most basic form, the drug is directly combined with oils, surfactants, and co-surfactants to create a homogenous, isotropic liquid mixture. Soft gelatin capsules are then filled with this liquid. When administered orally, gentle

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gastrointestinal motility promotes rapid self-emulsification, leading to enhanced drug solublization and improved absorption [54].

Solid SEDDS/SNEDDS: Liquid SEDDS can be converted into solid dosage forms by adsorbing them onto solid carriers such as Aerosil®(colloidal silicon dioxide) using techniques like physical mixing or rotary evaporation. This process produces free-flowing powders suitable for capsule filling or tablet compression. Upon contact with gastrointestinal fluids solid SEDDS retain their self-emulsifying behavior while offering improved physical stability, ease of handling, and patient convenience compared with liquid formulation [54].

Self-Emulsifying Pellets (SEDDS/SNEDDS):Multiparticulate controlled-release systems are prepared using extrusion-spheronization techniques with polymers such as Eudragit® and hydroxypropyl methylcellulose (HPMC) [58].

Self-Emulsifying Tablets: Liquid SEDDS converted to solid formulation using crospovidone as carrier for improved stability [59].

6.4 Evaluation Parameters: The various evaluation parameters for SEDDS and SNEDDS are:

Self emulsification time: The time it takes for a SNEDDS pre-concentrate to create a transparent, homogenous nanoemulsion is known as the self-emulsification time. There are several ways to measure it. For instance, Ashfaq et al. evaluated it in 900 mL of phosphate buffer at 37 ± 5°C using USP Dissolution Apparatus II (paddle, 100 rpm) [60].

Droplet Size & PDI: Analyze using dynamic light scattering at 25°C after diluting 100 µL SEDDS in 50 mL of distilled water. Target droplet size <200 nm and PDI <0.4 [61].

Thermodynamic Stability: Six cycles of heating and cooling between 4°C in the refrigerator for 48 hours and 45°C in a stability chamber for 48 hours, followed by a centrifugation test at 3500 rpm for 30 minutes and three freeze-thaw cycles between -21°C and +25°C [56].

Dispersibility Test: Grade A emulsions (rapid formation <100 rpm) appear clear or bluish white. Bright white and slightly less turbid (clear bluish white) in grade B. Fine, milky white emulsions of grade C. Greyish white, dull emulsions of grade D. Grade E has a bright or white emulsion directly beneath a clear or slightly bluish white layer on top [56].

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6.5 Advantages and Application of SEDDS and SNEDDS:

Advantages:

Bioavailability Enhancement: 2-5 fold increase due to nano-sized droplets, rapid absorption, first-pass bypass [53].

Reduced inter/intra-subject variability: As a result of controlled droplet size and consistent GI absorption [54].

Improved physical stability: Unlike conventional emulsions, SEDDS/SNEDDS do not exhibit creaming, coalescence or phase seperation [62].

Simplified manufacturing: Formulation requires simple mixing without the need for high-pressure homogenization or complex equipment [63].

Food effect independence: Drug absorption remains consistent under both fed and fasted conditions [60].

Applications:

- **Immunosuppressants:** By avoiding first-pass metabolism and lowering dose variability for organ transplant recipients, cyclosporine A is formulated as SEDDS (Neoral®) to increase oral bioavailability from 30% (Sandimmune®) to 60–70% through lymphatic absorption[53].
- **Antiretrovirals:** Regardless of whether a patient is fed or fasting, ritonavir (Norvir® SEDDS) maintains therapeutic HIV viral suppression with fewer doses and better patient compliance[54].
- **Hypertriglyceridemia:** Fenofibrate is used for hypertriglyceridemia. Provides food-independent lipid lowering effect[53].
- SEDDS may transport macromolecules like peptides, hormones, enzyme, substrates and inhibitors[56].
- Protection from biodegradation[56].

6. **Challenges, Limitations and Future Perspectives:** Lipid-based nanocarriers such as SEDDS and SNEDDS have shown significant success in enhancing the oral bioavailability of poorly water-soluble drugs; however, several challenges limit their large scale commercialization. Drug precipitation upon extensive dilution in the gastrointestinal tract can reduce therapeutic efficacy, while the high surfactant levels(30-60% w/w) required for spontaneous emulsification may cause

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gastrointestinal irritation and mucosal toxicity [64]. In addition, scale-up remains challenging, as phase behavior optimized at the laboratory level often fails to translate directly to industrial production, resulting to batch-to-batch variability and reproducibility concerns [63].

7.1 Future Directions:

Hybrid Lipid Nanocarrier: Lipid-polymer hybrid nanoparticles(LPHNPs) are next generation nanocarriers composed of a polymeric core(eg., PLGA or chitosan) surrounded by a lipid or lipid-PEG shell, combining the advantages of both systems. This dual architecture provides mucoadhesion, enhanced colloidal stability, controlled and sustained drug release and reduced premature drug leakage [65,66]. LPHNPs enable efficient encapsulation of both hydrophilic and lipophilic drugs while improving drug loading, oral bioavailability, pharmacokinetic performance, and systemic exposure of poorly water-soluble compounds, making them promising platforms for advanced oral drug delivery [66].

Solid SNEDDS (S-SNEDDS): The development of solid self-nanoemulsifying drug delivery systems (S-SNEDDS) repersents an important advancement in lipid-based formulations, wherein conventional liquid SNEDDS are converted into solid dosage forms such as powders, pellets, or tablets using adsorbent carriers or solid matrices. This soldification preserves self-emulsifying behavior and solubility enhancement upon reconstitution while improving physical stability, handling, portability and shelf life. For example Dasatinib-loaded S-SNEDDS demonstrated approximately a two-fold increase in oral bioavailability compared with the free drug, along with stable nanoemulsion droplet size(~140 nm) after reconstitution [67]. Similarly, sorafenib-loaded solid SNEDDS exhibited enhanced stability, improved dissolution behavior and superior therapeutic efficacy. These findingd highlight the strong potential of S-SNEDDS for commercial oral dosage forms, as they effectively overcome key limitations of liquid SNEDDS, including formulation leakage, capsule incompatibility and storage instability [68].

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Conclusion:

Lipid-based nanocarriers play a vital role in improving the oral bioavailability, stability, and solubility of poorly water-soluble drugs. Delivery systems such as SLNs, NLCs, liposomes and SNEDDS protect drug from gastrointestinal degradation and enhance intetinal absorption with SNEDDS offering particularly effective self-emulsification and bioavailability enhancement, However, challenges related to surfactant content and formulation stability remain. Emerging approaches including solid SNEDDS and lipid-polymer hybrid systems, address these limitations by providing improved stability, controlled drug release, and better scalability. Cosequently, lipid-based nanocarriers are expected to continue shaping the future of oral drug delivery.

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