REVIEW ARTICLE

Drug Delivery System That Self-Emulsify: Transportation of Drug From Gut to Target Organs

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ABSTRACT

Microemulsions are highly popular for their specific uses, including vivid applications and this is due to their special properties, which include very high interfacial interactions with demonstrated stability from a thermodynamics point of view, and on the other hand, also very low interfacial tension, which is required to solubilize highly immiscible dispersions. This review's goal is to briefly outline potential uses of micro-emulsion systems, their uses, limitations and possible *in-vitro* and *in-vivo* techniques. To characterise such dispersion systems, it is commonly known that adding the right surfactant or surfactant mixture can combine large amounts of two non-dissolving-target liquids, such as water and oil, into a single phase that is macroscopically homogeneous but microscopically heterogeneous. Owing to the advantages of lymph drug delivery, the drug-lipid conjugates, when they enter the lymph route, become an ideal approach for enhancing the absorption of such drugs to combat metastatic cancers of the lymph nodes and their drainage to specific organ systems where the cancer is already spread. As the route of lymph delivery is important where a tumor has already been cancerous, this formulation approach has distinct opportunities to transport needy molecules to cancerous sites in various organs, which also includes the lymph nodes. This review, particularly, lays more stress on an overview of microemulsions in general, the *in-vivo* and *in-vitro* characterization methods and potential applications related to target drug delivery via the lymphatic circulatory system.

Keywords: Self-emulsify microemulsions, Lymphatic drug delivery, *In-vitro* and *in-vivo* characterization, Thermodynamic stability, Emulsions *in-situ* behavior.

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INTRODUCTION

Microemulsions (ME) are highly popular as mixtures of highly stabilized thermodynamic isotropic systems consisting of oil, water, a combination of surfactants and co-surfactants added to maintain their thermodynamic stability. They have the advantages of easy manufacturing, clear appearance, easy drug incorporation, and easy scaling. The average droplet size range is less than 100 nm, making it a perfect carrier to enhance the transportation of vivid hydrophobic molecules, owing to fast absorption time, solubilization of drug molecules being least soluble (at drug concentrations, which are high), and accompanied with increased intestinal permeability. In the universal oral bioavailability classification system, hydrophobic drugs soluble in ethanol, PEG 400 and propylene glycol belong to Class III. With the fast progress of medicines and pharmaceutical technology, microemulsions have received great attention in the development of drug self-emulsifying microemulsions (SMEDDS).

In the rapid drug-solubilization process, such dispersions contribute to overcoming the fed/fasted state of the human body and further promote drug participation in lymphatic absorption. Thus, self-nano-emulsion preparations (SNEDDS) have even been used in enhancing patient health.[1] With the ability to inhibit or bypass the P-glycoprotein, both SNEDDS and SMEDDS have been regarded as important vehicle systems to promote the oral bioavailability of a variety of hydrophobic drugs.[2]

Pharmaceutical self-emulsifying microemulsion dispersions are mixtures that are isotropic in properties, comprising oil, surfactant, and cosurfactants. They can be used for solubilizing various hydrophobic drugs, enhancing drug bioavailability, and profoundly being utilized in the preparation of micro-sized drug dispersions. In this review, the study of the history of pharmaceutical self-emulsifying microemulsions, their beneficial characteristics, and their industrial applications will be discussed.

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Definition of Self-Emulsifying Microemulsions

Many of the drug compounds that are too large to dissolve can have high solvation energy even if solubilized in a simple microemulsion. This can lead to the drug compound partitioning out of the microemulsion during dilution, which in turn can lead to a potential decrease in the bioavailability of the compound. To minimize this risk, the particle size distribution should be kept as small as possible. The high solvation energy can be quite pronounced for some almost solubilized drugs. This is partly because several drugs are slower to dissolve in abundant systems and partly because liquid crystals have more solvent energy than non-taper inflammation steady states formed with much larger oil droplets. Since this is inherent to microemulsions, it is essential to test the stability of the microemulsion as a function of oil chain length, surfactant or co-surfactant type, counterion type, temperature, and macromolecule control on the final physical appearance of microemulsion formulations. By using another type of system, it may be possible to improve the number of drug compounds that can be solubilized at the highest effective concentration. Consequently, we could develop more compounds that can also be drug compounds. The development of pharmaceutical self-emulsifying microemulsions/gels is the main motivation of this book on industrial applications.[3]

Microemulsions were referred to as self-emulsifying before the term self-microemulsifying drug delivery systems (SMEDDS) was introduced. This altered because of the widespread usage of microemulsions for particulate systems and drug-loaded particles. Thus, the production of a mixed liquid crystal phase microemulsion with particles smaller than 50 nm and their quick emulsification time are the main characteristics of self-emulsifying microemulsions. On average, this microemulsion forms within less than a second of coming into touch with the dilution media. Because of the instantaneous incorporation of the aqueous media, the dispersed and dispersion phase contact surface, the emulsion forms instantaneously. When weak, low-temperature microemulsions meet the emulsion's warmer components, they may easily transform into microemulsions.[4]

Microemulsion production involves the addition of surfactants, co-surfactants and or electrolytes in order to attain a stable formulation. The pharmaceutical industry has shown a great deal of interest in manufacturing such self-emulsifying microemulsions because of their potential to enhance the dissolution of lipophilic drugs[5] (and research work by Tenjarla).[6] When oil, water, and emulsifier are mixed, these systems arise spontaneously. Such formulation was observed to be highly transparent and stable as well. According to research by Texter & Ziemer[7] in 2004, microemulsions have several benefits over conventional dosage forms, such as improved solubility and bioavailability of poorly water-soluble medications, stabilizing degradation-prone compounds, and their unique application to deliver drug molecules to target places of organ system.

The formulation and physicochemical characteristics of microemulsions have been extensively studied. Microemulsions typically comprise hydrophobic (oil-based), and hydrophilic (water-based) phases, and amphiphilic surfactants that stabilize the interface between the two immiscible liquids. The actual interface energies drive the spontaneous formation of microemulsions at the two phases 1) disperse phase 2) dispersion phase. This is achieved through the careful selection and optimization of the components.[8] Various factors, but not limited to e.g., the type and surfactants concentration presence of co-surfactants and the oil and water proportion, will contribute a vital role in the characteristics of the microemulsions. Microemulsions in past decades have been predominantly researched for its delivery of vivid lipophilic compounds, such as drugs, vitamins, and nutraceuticals[9]. The ability of microemulsions to solubilize and protect these compounds can significantly enhance their bioavailability and therapeutic efficacy.

Limitations of Self-emulsifying microemulsions

- Stability issues: Self-emulsifying microemulsions can be prone to stability issues such as phase separation, creaming, or drug precipitation over time, which can affect the efficacy of the formulation.
- Limited drug loading capacity: Self-emulsifying microemulsions have limited drug loading capacity, which may restrict the formulation of high-dose drugs or drug combinations.
- Size limitations:[10] The size of self-emulsifying micro-emulsions may be limited, which can affect drug solubilization and absorption in certain cases.
- Drug compatibility: Some drugs may not be compatible with the components of self-emulsifying microemulsions, leading to formulation challenges and potential drug interactions.
- Regulatory constraints: Regulatory approval for pharmaceutical self-emulsifying microemulsions may be difficult to obtain due to the complex nature of the formulations and potential concerns over stability and efficacy.
- Manufacturing constraints: The manufacturing process for self-emulsifying microemulsions can be complex and may require specialized equipment, which can increase manufacturing costs and limit scalability.
- Limited clinical data: There may be limited clinical data available on the safety and efficacy of pharmaceutical self-emulsifying microemulsions, making it challenging to establish their clinical utility and potential side effects.
- Patient compliance: Self-emulsifying microemulsions may require specific administration instructions or have a less favorable taste or texture, which could affect patient acceptance and compliance.

Self-emulsifying microemulsions are a specific formulation type that enhances both inherent solubility and absorption of lipophilic drugs. Microemulsions consist of base vehicles like e.g., oil, and a lipoidal surfactant, cosurfactant combination, which spontaneously form a O/W type emulsion when

dispersed *in-situ* inside GUT. This induces and leads to enhanced absorption of lipophilic drugs, which may have poor solubility in aqueous environments.

Pharmaceutical companies are using self-emulsifying microemulsions more frequently to create lipophilic medications because they can enhance oral bioavailability and promote drug dissolution. Improved stability, less variation in medication absorption, and the possibility of controlled-release formulations are just a few benefits of these microemulsions. All things considered, self-emulsifying microemulsions are a promising approach to creating lipophilic medications, and their application in drug research is probably only going to increase going forward. Lipophilic chemicals are essential to the pharmaceutical and cosmetic industries since they guarantee the stability and effectiveness of different formulations. These substances are objectively intended to enhance the inherent solubility and permeability of active components, particularly those that are poorly soluble in water because of their affinity for fats and oils. Self-emulsifying microemulsions are one of the best ways to add lipophilic chemicals to formulations. These complex systems, which are made up of water, oil, co-surfactants, and surfactants, can solubilize lipophilic substances and increase their bioavailability by forming stable micron-sized droplets.

Self-emulsifying microemulsions: what are they?

Self-emulsifying microemulsions are water and oil dispersions that are thermodynamically stable and stabilized by co-surfactants and surfactants. Because these systems can improve both the permeability and solubility of oil-soluble molecules, they are highly popularised in the cosmetic and pharmaceutical areas. The interfacial tension in self-emulsifying microemulsions is decreased by an increase in concentrations of surfactants and co-surfactants, but only to a particular concentration.

Classification scheme for microemulsions that self-emulsify

Microemulsions that self-emulsify are generally categorized according to their structure and composition. The most often used classification scheme divides these systems into three primary categories as follows:

Type-I

O/W systems, comprising the oil phase, which is distributed throughout the aqueous (hydrophilic) phase, are type I microemulsions. These microemulsions are distinguished by their clear appearance and tiny droplet size, which is often less than 100 nm. Pharmaceutical formulations frequently employ type I microemulsions to increase the solubility of lipophilic medications.

Type-II

W/O systems, comprising aqueous phase which is distributed throughout the oil (lipophilic) phase are type II microemulsions. It is well known that these microemulsions have excellent stability and may effectively solubilize hydrophilic to improve the distribution of active chemicals in cosmetic formulations, type II microemulsions are frequently utilized.

Third-class microemulsions, bi-continuous microemulsions, or type III microemulsions: are distinguished by their special structure of interpenetrating water and oil phases. These systems exhibit good solubility for both hydrophilic and lipophilic molecules and are thermodynamically stable. Because of their versatility, type III microemulsions can be applied in many different contexts, such as medication delivery and pesticide formulations.

Advantages of Self-emulsifying microemulsions

For formulators and producers, self-emulsifying microemulsions have several benefits. The following are some of the main advantages of these systems:

- Increase in oral absorption and drug bioavailability.
- Increase solubility of lipophilic compounds.
- Increase stability and shelf-life of formulations.
- Simple and economical manufacturing technique.
- Broad range of uses in agrochemicals, cosmetics, and medicine.

To sum up, self-emulsifying microemulsions are an effective method for creating lipophilic chemicals and improving their functionality in a range of settings. Formulators can refine their formulations and generate highly effective medicines that fulfil customer expectations by understanding the classification system of these complicated systems.

Lymphatic transportation: Mechanism of Absorption - highly lipophilic molecules

The absorption mechanisms of oil-soluble molecules through the lymph route of transportation are complex and multifaceted, involving various processes that impact drug intake and metabolism. One crucial aspect is the transportation and metabolic activities within enterocytes, which can influence drug transportation and metabolite formation.

Lipids play a significant role in enhancing absorption mechanisms, with mechanisms such as dissolution in gastric fluid creating lamellar packages (e.g. packages like structured micelles, vesicles and mixed structured micelles, which finally demonstrate enhancement of absorption).[11] Moreover, the formation of drug-lipoprotein complexes allows for their transportation across the basement membrane and subsequent trafficking into lymphatics following enterocyte exocytosis.[11] Studies have shown that oil-miscible molecules can be transported into the lymphatic circulatory system, i.e., across enterocyte cell layers, highlighting the importance of the lymphatic system in drug absorption.[12] Additionally, the physicochemical properties of drugs, including solubility and particle size, contribute greatly to their absorption, with lipid-based formulations addressing challenges such as limited solubility by improving the solubility of molecules in the presence of a lipoidal environment. The utilization of orally ingested lipoidal drug-delivery carrier systems has gained the center of attraction to conduct more research because for their potential to enhance drug bioavailability, as indicated by various studies.[13]

In-vitro & *In-vivo* techniques to characterize self-emulsifying emulsions

In-view to study advanced drug delivery, its highly important to deeply understand the different absorption models through which usually the oil-soluble molecules are being transported through physiological membranes. Research has shown that the addition of peanut oil significantly enhances the transportation of rifampicin, mirroring the effects of fat-rich meals on drug absorption through the lymphatic system.[14] Conversely, Pluronic L-81 has been found to inhibit the transportation of rifampicin, suggesting a potential role of certain excipients in modulating drug absorption pathways[14]. These findings underscore the importance of exploring innovation-based drug-excipient carrier systems that can modulate lymphatic drug transportations, as demonstrated in an *in-vitro* model wherein specialized excipient like Intralipid® enables to induce absorption highly oil soluble drugs *via* the lymph circulatory system. Furthermore, the association of drug-lipoprotein complexes with chylomicron, VLDL, and HDL fractions within lymphatic fluid highlights the intricate pathways involved in the transport of lipophilic compounds across the lymphatic system, shedding light on potential strategies in the same research field. The progress, including validation of *in-vitro* models for estimating drug transportation via the lymphatic system, as evidenced by the close resemblance to *in-vivo* uptake of various drugs, offers valuable insights for designing an optimized orally ingested drugs-lipids career system. By considering the physicochemical properties of drugs, the influence of different food on the solubility of drug, and the contribution of the protective lipid against therapeutic outcomes in clinical settings.

In-vitro Techniques

- Transmission electron microscopy
- Turbidity index (%)
- Visual inspection for phase separation on storage
- Higher dilutions of emulsions by purified water and check for phase separation
- Dynamicl scattering instrumentation technique
- Electrophoretic light scattering instrumentation technique
- Laser diffraction technique
- Percent drug release in dissolution apparatus
- Nanoparticle tracking analysis etc.

Of the most effective methods have been Emulsions can be characterized by vivid instrumentation techniques like light scattering techniques (dynamic type) (DLS), and wave spectroscopy (diffusing type) (DWS). Particle size distributions, dynamics, structure, and rheological characteristics of emulsions can all be measured with these methods. DWS can offer a more thorough comprehension and quantitative assessment of the variables influencing an emulsion's stability. Various light scattering techniques are employed to examine the internal structural changes and average bubble or droplet size of emulsions by means of light scattering by the gas-liquid or liquid-liquid interfaces. These methods are essential for researching soft matter because they are non-invasive and can yield insightful data regarding the characteristics and dynamics of emulsions.

Tong *et al*., in 2015, cryogenic-transmission based electron microscopy (Cryogenic TEM, i.e., `cryo-TEM`) and X-ray scattering (small-angle) were used for studying and demonstrating the mechanism of nanoemulsion generation. During the dilution of the microemulsion, because of the inversion phenomenon, highly small-sized dispersed globules were immediately formed however, the stability was compromised when the temperature was increased. Their stability was greatly increased upon cooling to room temperature because the collision frequency rate decreased, and the oil/water interface's stabilization improved. The practical applications of nanoemulsions are limited because, even after prolonged storage, Ostwald ripening still causes droplets of the nanoemulsions to develop. Thermodynamic systems characterize W/O microemulsions.

In-vivo Techniques

Studying the behavior and impacts of microemulsions in living things is known as "*in-vivo* characterization." Studies have demonstrated that microemulsions can display distinct structures and characteristics, including droplet-type oil-in-water microemulsions[15], ordered bi-continuous microstructures, and size distribution variations that affect oil extraction efficiency. The intricacy of contemporary microemulsions, comprising complex polymers, nanoparticles, and surfactants, demands thorough characterization through sophisticated methods such as transmission enzymatic degradation in the gastrointestinal tract. Researchers can tailor lipoidal preparations to improve the absorption of drugs and optimize electron microscopy, rheometric, and small-angle X-ray scattering.[16] In addition, variables like temperature, catalyst quantity, and surfactant type can be used to regulate the preparation and characteristics of microemulsions. Comprehending these attributes is imperative in evaluating the possible uses of microemulsions in pharmaceutical delivery, cosmetics, and oil extraction procedures.

Other techniques, which also cover:

- Morphology study
- Atomic force microscopy
- Zeta potential assessment
- Analysis *via* FTIR
- Fluorometry

Meng Yu *et al*.,[17] researched in 2014 that the unmet need of designing an appropriate drug-carrier delivery mechanism laying emphasis on specific delivery in skin and on the other hand being safe, hampered applications of topical skin treatments. The aim of their research was to develop and refine nanoemulsion preparations to improve metronidazole-targeted localization in epidermal layers. The preparations were optimized through *in-vitro* investigations, and a series of experimental trials were conducted for confirm of therapeutic efficaciousness of metronidazole-loaded emulsions.

Wan-Hsuan Hung *et al*.,[18] in their research work studied that vivid azelaic acid formulations, categorically of oil

dispersed in the dispersion phase of water, intended for topical route, the azelaic acid's permeability was determined for its inflammation-reducing properties on rat skin. Comparing the experimental formulation to the negative control group, there was no discernible skin irritation. Furthermore, after 30 days of storage, the drug-loaded formulation demonstrated both chemical and thermodynamic stability, too. The microemulsion formulations not only demonstrated considerable efficacy but were also found to be stable and non-irritant to the skin.

Evdokia D *et al*.,[19] 2022 studied O/W emulsions which were using various concentrations of Curcumin derivatives, initially, tested for pH, viscosity, dynamic light scattering (DLS), and microscopy drew significant conclusions on formulation attributes from a stability point of view. Additionally, research was carried on how active cosmetic ingredients affected the produced emulsions' antioxidant, antibacterial, and sun protection factor (SPF) qualities. Emulsions containing curcumin powder exhibited unstable behavior due to the agglomerate formation, whereas emulsions containing curcumin extract and complex of curcumin-β-cyclodextrin. Demonstrated excellent pH stabilization effect, accompanied with viscosity after ninety days of storage experimental condition.

Suparna SB *et al*.,[20] studies in 2015 revealed that cilnidipine based drug carrier system, wherein the drug is intrinsically weakly soluble in water, demonstrated an increase in drug release because of being formulated as microemulsions (with self-emulsifying properties named SEDDS). After screening a variety of vehicles, the drug-liquid SEDDS were formulated with Tween-80, transcutol-HP and Capryol-90. Created dispersions were analyzed in terms of their drug release (%), globular diameter size, the duration for the system, to emulsify on its own, stability on dilution and percentage of transmittance. Neusilin (i.e., adsorbent) was utilized for conversion of optimum SEDDS, into granules that flowed freely.

With respect to oral route of delivery, lipoidal preparations are mainly used for the improvement of the solubility of the drug, because it has been observed that poor water-soluble medicine's oral absorption can be improved when given with lipid-rich meals.[21] lipoidal preparations are presumed as viable for enhancing the absorption and water solubility of lipophilic medications. Preserving the medications in solution within the GI system is the primary objective of these formulations.[22]

Emulsion dispersions were extensively researched for the oral route of delivery. As previously indicated, several studies have demonstrated that SMEDDS significantly increased the percent drug release and extent of absorption especially highly less soluble molecules, in water. Emulsions that are presumed to self-emulsify are preferable to conventional liquid emulsions in that they simplify industrial manufacturing, lower production costs, increase patient compliance, and improve stability. Above all, SMEDDS can be used with great flexibility to create a variety of solid dosage forms that can be administered parenterally or orally. Furthermore, it is possible to provide regulated or sustained medication release and prevent GI irritation.[23]

Lymphatic Drug Delivery: The Transportation of Drug from GUT to Target Organs

Lymphatic drug delivery (LDD) can be an effective tactic to target anticancer and immunomodulatory agents (Khan *et al*., 2013)[24]. According to Zhang *et al*.,[25], LDDS can localize drugs to the lymphatic system through intraluminal injections or by means of lymph nodes and tissues. Therefore, LDD is used as an effective method to deliver targeted agents categorically in auto-immune disorders, anti-biotics and in chemotherapy segments to the lymphatic system (Franco *et al*., 2020).[26]

LDD mainly depends on several prerequisites, just like the molecule's lipophilic nature, the overall average particle diameter and most importantly, the electrostatic charges on the surface of the dispersed phase and all such factors will decide the development approach of such nano-substances. The anticancer drugs reach to the tumor cell outer surface and induce cytotoxic effects. In addition, to form pegylated-lipid nano-particulates (PEG-LNPs Conjugates), which are prepared by modifying polyethylene glycol (PEG), they also demonstrate an increase in stability. Even though conventional dispersion systems succeed in delivering drugs to target sites, they have yet been limited due to the existence of many other trace unwanted impurities/substances. Therefore, naturally sourced lipids from plant origin are preferential over the synthetic class of lipids in view to formulate target-specific delivery. In principle, over the years research in pharmaceutical and biological drug carrier systems has led to lot of opportunities to transport not only pharmaceuticals but also biologics (small and large molecular weights) through lipoidal bases.

Drains of the Living Body: Lymph Circulatory System

The lymphatic circulatory system of the body is a portal for fatty acids, vitamins (oil soluble) and highly lipophilic compounds transportation/absorption. In addition, the lymphatic system acts as a drainage system to return wastes and proteinaceous substances to the central systemic circulatory system. In addition, the lymph circulatory system plays a vital role by transporting antigen-presenting cells to lymphatic nodal globules of the human body.

In 2008, Trevaskis *et al*., researched that lymphatic endothelial cell receptors are single-layered cells with small tight junctions when compared to blood vessels.[27] The lymphatic system promotes cell-to-cell signaling between the lymph nodes and tissues through a specific transport system called as "active-and-passive" processes. During lymphatic transportation, the fatty acids and/or oil-soluble vitamins transport through the paracellular, immune cell and/or intracellular means.

Molecules can cross intercellular junctions paracellularly *via* a pathway that is active or transcytosis. Lymphatic transportation contributes to many highly lipophilic molecules like lycopene, retinoids, cyclosporine, probucol, testosterone, proteins, and many more prodrugs. Large macromolecular

drugs and/or biologics are more prone to transport through the lymphatic system because of their higher lipophilicities. Similarly, even intra-dermal injection promotes high lymph absorption because the skin has a high lymph flow. In this range of 10 to 100 nm, intramuscular or intradermal drug injections of 10 to 100 nm inject into lymphatic vessels, while others below 10 nm are mainly into blood vessels. Nasally inoculated nanoparticles interact with the lymphatic tissue associated with the nose and induce protective immune responses. This opens the doors to a new space of opportunity to increase the oral absorption and delivery of niche therapeutic segment molecules like immunomodulatory, anticancer, and antibiotics. Here, different regions of the lymphatic system with exceptional concentrations may be of therapeutic interest. In addition, lymphatic absorption contributes to multiple pharmacokinetics of orally administered drugs.

Site-target Drug Delivery Approach

Given the above-discussed likelihood of ingestion of complete particles, it is extremely desirable to transfer particles with payloads orally to locations outside the gastrointestinal tract. Following M cell ingestion, particles that make it to the lymphatic system proceed in a sequential manner from the right lymph node to the pulmonary artery and subclavian vein. Eventually, they arrive at several organs and tissues, such as the kidney, lung, liver, and spleen, as well as tumors and inflammatory sites.[28] An apparent increase of intact glycan particles was observed in tissues and organs rich in macrophages, such as the Peyer's patches, bone marrow, spleen and lymph nodes, and, according to a groundbreaking study on the particles in yeast.[29] There have already been reports of therapeutic distant targeting using lymphatics.

Solid lipid nanoparticles (SLNs) containing oral WGA-conjugated paclitaxel exhibit a nature to deposit in the lung's tissues, with local drug levels approximately ~6.2 times more than pure solution of paclitaxel.[30]

Nano-particulates of "PLGA tagged to the Chitosan Protein-Rifampicin" effectively treated fungal infections and increased drug levels in lung tissues by more than ten times.

Lung Cancer

The ability of the Peyer's patches to remove monocytes may be important, even though the underlying transport processes are unknown, a significant part in the movement of particles. The initial site for particle retention is the lung, which is where the mesenteric lymph node meets the blood. As evidenced by using nano-particulates of sorafenib in the therapy of hepatocellular cancer, the globules achieve high targeting efficiency after exiting the lungs and distributing to other macrophage-enriched inflammatory (MPS) organs, such as the liver.[31]

Novel approaches for drug delivery to lymph nodes are being developed because of growing research work in this specific approach which in turn helps in understanding cancer prognosis, vaccination immune responses, and the presence of HIV and various other infectious diseases in the lymph nodes. Current research is looking for new ways to get medicines along with additional carriers to the lymphatic system. Many solid malignancies spread primarily through cancer lymphatics. The state of the patient's lymph nodes plays a crucial role in the diagnosis of cancer metastases. The accurate staging of the lymphatic system is the primary determinant of a patient's suitable course of treatment. But, evidence suggests that patient survival is getting better. Raghuveer R *et al*., in 2024 in their research work, explained that the intra-nasal nanoformulation of Piribedil was observed to be highly soluble (nearly more than seven times more than conventional formulations, which in turn indicated the potential advantages of nano-size emulsions.[32] Similarly, research work published by Patil M R *et al*., in 2024 explains the preparation of vivid formulations of Itraconazole which were microemulsions and exhibited tremendous intrinsic solubility and dissolution characteristics in the light that explains the versatility of microemulsions and their applications.[33]

HIV

HIV, referred to as the human immunodeficiency virus, is a marker of primary HIV infection that appears early and is rapidly declining in plasma, accompanied by an immune system reaction specific to HIV. High amounts of HIV can be discovered in mononuclear cells in lymph nodes long after the virus is discovered in the blood. It has been reported that the rate of viral replication in these lymph nodes is between ~10 and ~100 times more than that of peripheral blood mononuclear cells. It is challenging to give medications to these lymph node mononuclear cells via oral or intravenous means. Even after 30 months of highly effective antiretroviral therapy (HAART), active virus can still be isolated from lymph nodes even though HAART can reduce the plasma virus count of HIV-infected patients by 90%. Current research is looking for new ways to get medicines along with additional carriers to the lymphatic system

Filaria

Lymph nodes of filaria are essential parts of many parasites' life cycles, including filaria. Adult worms may be present in the lymphatic arteries and lymph nodes of infected individuals. The distal extremities of the infected lymph node enlarge because of this mature filaria's obstruction of lymphatic drainage. Elephantiasis is the term given to the limb-swelling symptoms that filarial disease patients experience. Adult worms are rarely eliminated from lymph nodes, and when they are, it usually takes extremely lengthy therapy regimens to be successful. Current research is looking for new ways to get medicines along with additional carriers to the lymphatic system.

Anthrax

In the wake of anthrax-related fatalities, new anthrax treatments have gained significant attention in the United States. When an anthrax infection occurs, Bacillus anthracis endospores enter the body and are phagocytosed by macrophages en route to local lymph nodes. It is within these lymph nodes that the endospores germinate and turn into vegetative bacteria.

Current research is looking for new ways to get medicines along with additional carriers to the lymphatic system.[34]

Tuberculosis

Medicine therapy for tuberculosis (TB) may be shorter if newer techniques are used to target these lymph nodes with the medicine. Because tuberculosis has trouble getting medications to the TB sites, treatment for the disease must last a long time, at least six months.[35] Current research is looking for new ways to get medicines along with additional carriers to the lymphatic system.

Future Trends

Because micro-emulsions can solubilize non-polar active compounds, they are suggested for use in many pharmacy applications as prime drug delivery systems, as prima facia. The potential uses of such emulsions in various therapeutic domains or in the creation of skin- and hair-care products is extremely bright. One of the many uses is in drug delivery, where they function as "effective carriers" for bioactive compounds and macromolecules, too, allowing administration through a variety of routes. Apart from distinct uses of lipids in target drug delivery, the other major benefits arising are the stabilization of proteins from harsh gastric conditions wherein the peptides are encapsulated in lipoidal membranal structures which bypasses the pre-systemic metabolism. The major factors demonstrating that absorption is more overly dependent on the fate of the drug-lipid conjugate and its physiological journey right starting from the point of ingesting the formulation and until it reaches its target place in the organ system. The resurgence of interest in the formulation of herbal drugs suggests that they could be the perfect delivery system for these challenging-to-formulate phytopharmaceuticals. The potential of microemulsions rests in their creative formulation.

CONCLUSION

Due to their many benefits for drug delivery, micro-emulsions are becoming more and more popular as drug carriers to enhance the transportation of pharmaceutical actives. They have potential in several industries, like biotechnology, cosmeceuticals, and therapeutics, as they can be applied to nearly every delivery method. This new technology may be used to address the issues with some phytopharmaceutical's poor miscibility with the lipids found in cell membrane linings and their poor absorption. The SMEDDS formulation may improve intestinal absorption of oil-soluble drug molecules and those who face oral bioavailability challenges. SMEDDS is a potentially effective method for formulating medications with low water solubility. SMEDDS are well known these days to enhance oral absorption of lipophilic compounds and facilitate the distribution of lipophilic drugs.

REFERENCES

1. Chen CH, Chang CC, Shih TH, Aljuffali IA, Yeh TS, Fang JY. Self-nanoemulsifying drug delivery systems ameliorate the oral delivery of silymarin in rats with Roux-en-Y gastric bypass surgery. International Journal of Nanomedicine. 2015:2403-2416. Available from: doi.org/10.2147/IJN.S79522
2. Nakmode D, Bhavana V, Thakor P, Madan J, Singh PK, Singh SB, Rosenholm JM, Bansal KK, Mehra NK. Fundamental Aspects of Lipid-Based Excipients in Lipid-Based Product Development. Pharmaceutics. 2022;14(4):831. Available from: doi.org/10.3390/ pharmaceutics14040831.
3. Jaiswal P, Aggarwal G, Harikumar SL, Singh K. Development of self-microemulsifying drug delivery system and solid self-microemulsifying drug delivery system of telmisartan. International Journal of Pharmaceutical Investigation. 2014;4(4):195-206. Available from: doi.org/10.4103/2230-973X.143123.
4. Tartaro G, Mateos H, Schirone D, Angelico R, Palazzo G. Microemulsion Microstructure(s): A Tutorial Review. Nanomaterials. 2020; 10(9):1657. Available from: doi.org/10.3390/ nano10091657.
5. Nielloud F, Marti-Mestres G, Salager J. 1st Edition. Pharmaceutical Emulsions and Suspensions; 2000.
6. Ceschel G, Bergamante V, Maffei P, Borgia SL, Calabrese V, Biserni S, Ronchi C. Solubility and Transdermal Permeation Properties of a Dehydroepiandrosterone Cyclodextrin Complex from Hydrophilic and Lipophilic Vehicles. Drug Delivery. 2008; 12(5) :275–280. Available from: doi.org/10.1080/10717540500176563
7. Texter J, Ziemer P. Polyurethanes via Microemulsion Polymerization. Macromolecules. 2004; 37(16):5841–5843. Available from: doi.org/10.1021/la970990a
8. Szumała P, Kaplińska J, Makurat-Kasprolewicz B, Mania S. Microemulsion Delivery Systems with Low Surfactant Concentrations: Optimization of Structure and Properties by Glycol Cosurfactants. Molecular Pharmaceutics. 2023;20(1):232-240. Available from: doi.org/10.1021/acs.molpharmaceut.2c00599
9. Aungst BJ. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. Journal of Pharmaceutical Sciences. 1993; 82(10):979-987.
10. Mundada V, Patel M, Sawant K. Submicron Emulsions and Their Applications in Oral Delivery. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2016; 33(3):265-308. Available from: doi. org/10.1615/CritRevTherDrugCarrierSyst.2016017218.
11. Rezhdo O, Speciner L, Carrier R. Lipid-associated oral delivery: Mechanisms and analysis of oral absorption enhancement. Journal of Controlled Release. 2016; 240 (10):544-560. Available from: doi.org/10.1016/j.jconrel.2016.07.050.
12. Yáñez JA, Wang SW, Knemeyer IW, Wirth MA, Alton KB. Intestinal lymphatic transport for drug delivery. Advanced Drug Delivery Reviews. 2011;63(10):923-942. Available from: doi. org/10.1016/j. addr.2011.05.019.
13. Preeti, Sambhakar S, Saharan R, Narwal S, Malik R, Gahlot V, Khalid A, Najmi A, Zoghebi K, Halawi MA, Albratty M, Mohan S. Exploring LIPIDs for their potential to improves bioavailability of lipophilic drugs candidates: A Review. Saudi Pharmaceutical Journal. 2023; 31(12):1-20. Available from: doi.org/ 10.1016/j. jsps.2023.101870.
14. Yousef M, Park C, Henostroza M, Bou Chacra N, Davies NM, Löbenberg R. Development of a Novel In-vitro Model to Study Lymphatic Uptake of Drugs via Artificial Chylomicrons. Pharmaceutics. 2023; 15(11):2532. Available from: doi.org/ 10.3390/ pharmaceutics15112532.
15. Fu Y, Xiao S, Liu S, Chang Y, Ma R, Zhang Z, He J. Atomistic Insights into the droplet size evolution during self

microemulsification. Langmuir. 2022 ;38(10):3129-3138. Available from: doi.org/10.1021/acs.langmuir.1c03099.
16. Lombardo D, Calandra P, Kiselev MA. Structural Characterization of Biomaterials by Means of Small Angle X-rays and Neutron Scattering (SAXS and SANS), and Light Scattering Experiments. Molecules. 2020; 25(23):5624. Available from: doi.org/10.3390/molecules25235624.
17. Yu M, Ma H, Lei M, Li N, Tan F. In-vitro/in-vivo characterization of nano-emulsion formulation of metronidazole with improved skin targeting and anti-rosacea properties. European Journal of Pharmaceutics and Biopharmaceutics. 2014 ;88 (1) :92-103. Available from: doi.org/10.1016/j.ejpb.
18. Hung WH, Chen PK, Fang CW, Lin YC, Wu PC. Preparation and Evaluation of Azelaic Acid Topical Microemulsion Formulation: In-vitro and In-vivo Study. Pharmaceutics. 2021;13(3):410. Available from: doi.org/10.3390/pharmaceutics13030410.
19. Dalla E, Koumentakou I, Bikiaris N, Balla E, Lykidou S, Nikolaidis N. Formulation Characterization and Evaluation of Innovative O/W Emulsions Containing Curcumin Derivatives with Enhanced Antioxidant Properties. Antioxidants. 2022 ;11(11):2271. Available from: doi.org/10.3390/antiox11112271.
20. Bakhle SS, Avari JG. Development and Characterization of Solid Self-emulsifying Drug Delivery System of Cilnidipine. Chemical and Pharmaceutical Bulletin. 2015; 63(6):408-417. Available from: doi.org/10.1248/ cpb.c14-00326.
21. Zhang Z, Lu Y, Qi J, Wu W. An update on oral drug delivery via intestinal lymphatic transport. Acta Pharmaceutica Sinica B. 2021;11(8):2449-2468. Available from: doi.org/10.1016/j.apsb.2020.12.022.
22. Williams HD, Ford L, Igonin A, Shan Z, Botti P, Morgen MM, Hu G, Pouton CW, Scammells PJ, Porter CJH, Benameur H. Unlocking the full potential of lipid-based formulations using lipophilic salt/ionic liquid forms. Advanced Drug Delivery Reviews. 2019;142 (3) :75-90. Available from: doi.org/10.1016/j.addr.2019.05.008.
23. Akula S, Gurram AK, Devireddy SR. Self-Microemulsifying Drug Delivery Systems: An Attractive Strategy for Enhanced Therapeutic Profile. International Scholarly Research Notices. 2014; 14:1-11. Available from: doi.org/10.1155/2014/964051.
24. Ling SS, Magosso E, Khan NA, Yuen KH, Barker SA. Enhanced oral bioavailability and intestinal lymphatic transport of a hydrophilic drug using liposomes. Drug Development and Industrial Pharmacy. 2006;32(3):335-345. Available from: doi.org/ 10.1080/03639040500519102.
25. Ye JY, Chen ZY, Huang CL, Huang B, Zheng YR, Zhang YF, Lu BY, He L, Liu CS, Long XY. A Non-Lipolysis Nano emulsion Improved Oral Bioavailability by Reducing the First-Pass Metabolism of Raloxifene, and Related Absorption Mechanisms Being Studied. International Journal of Nanomedicine. 2020; 8(15): 6503-6518. Available from: doi.org/10.2147/IJN.S259993.
26. Ryšánek P, Grus T, Šíma M, Slanař O. Lymphatic Transport of Drugs after Intestinal Absorption: Impact of Drug Formulation and Physicochemical Properties. Pharmaceutical Research. 2020;37(9):1-7. Available from: doi.org/10.1007/s11095-020-02858-0.
27. Harisa GI, Sherif AY, Alanazi FK. Hybrid Lymphatic Drug Delivery Vehicles as a New Avenue for Targeted Therapy: Lymphatic Trafficking, Applications, Challenges, and Future Horizons. The Journal of Membrane Biology. 2023; 256(3):199-222. Available from: doi.org/10.1007/s00232-023-00280-2
28. Parayath NN, Nehoff H, Müller P, Taurin S, Greish K. Styrene maleic acid micelles as a nanocarrier system for oral anticancer drug delivery - dual uptake through enterocytes and M-cells. International Journal of Nanomedicine. 2015; 10: 4653-4667. Available from: doi.org/10.2147/IJN.S87681.
29. Hong F, Yan J, Baran JT, Allendorf DJ, Hansen RD, Ostroff GR, Xing PX, Cheung NK, Ross GD. Mechanism by which orally administered beta-1,3-glucans enhance the tumoricidal activity of antitumor monoclonal antibodies in murine tumor models. The Journal of Immunology. 2004;173(2):797-806. Available from: doi.org/10.4049/ jimmunol.173.2.797.
30. Pooja D, Kulhari H, Kuncha M, Rachamalla SS, Adams DJ, Bansal V, Sistla R. Improving Efficacy, Oral Bioavailability, and Delivery of Paclitaxel Using Protein-Grafted Solid Lipid Nanoparticles. Molecular Pharmaceutics. 2016;13(11):3903-3912. Available from: doi.org/10.1021/acs.molpharmaceut.6b00691.
31. Colino CI, Lanao JM, Gutierrez-Millan C. Targeting of Hepatic Macrophages by Therapeutic Nanoparticles. Frontiers in Immunology. 2020;11(3):218. Available from: doi.org/10.3389/fimmu.2020.00218.
32. Chekkilla B, Raghuveer P. Development of Nasal In-situ Gel containing Piribedil SLN. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):199-209. Available from: doi.org/10.25258/ijpqa.15.1.31.
33. Patil MR, Kshirsagar SK. Formulation, Optimization and Evaluation of Solid SMEDDS of Itraconazole in Effervescent Granules Form. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):273-287. Available from: doi.org/10.25258/ijpqa.15.1.42.
34. Suttee A, Singh G, Yadav N, Pratap Barnwal R, Singla N, Prabhu KS, Mishra V. A review on status of nanotechnology in pharmaceutical sciences. International Journal of Drug Delivery Technology. 2019; 9(1): 98-103. Available from: doi.org/ 10.25258/ijddt.9.1.16.
35. Dinanti FP, Erawati T, Hariyadi DM. Development of Inhaled Tuberculosis Microparticle using Polysaccharide Polymers Containing Rifamycin Groups: In-vitro and In-vivo Study. International Journal of Drug Delivery Technology. 2024;14(2):1116-1123. Available from: doi.org/10.25258/ijddt.14.2.77