Review Article

Drug Delivery System: A Novel Approach to Formulation Development

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ABSTRACT

One of the fascinating fields of research territories in medical sciences is the development of novel drug delivery systems (NDDS) for the sustained release of medications to mitigate most of the limitations of standard treatments and improve the therapeutic efficacy of a specific drug. To ensure maximal therapeutic efficacy, the drug must be delivered to the target tissue in the appropriate amount and at the appropriate time, resulting in minimal toxicity and adverse effects. Successful treatment of most diseases is limited by a lack of safe and effective drug delivery methods. Drug pharmacological efficacy is significantly impacted by drug delivery techniques. Every drug has an optimum concentration range within which maximum benefit is derived, and concentrations above or below the range can be toxic or provide no therapeutic benefits at all. Therefore, the development of an efficient drug delivery system (DDS) remains a significant challenge in medicine, and this can be achieved only through multidisciplinary approaches to the mechanisms of delivery of drugs to targets in tissues. Consequently, a number of drug delivery and drug targeting systems are being created right now.

Keywords: Drug discovery, drug delivery, drug targeting.

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INTRODUCTION

Targeting is the ability to direct the drug(s) to the desired size. There are two primary mechanisms, viz., active and passive, for drug targeting, and several approaches are designed for distributing a therapeutic substance to the target site in a sustained release fashion. A truly intelligent delivery system must address the need for specific targeting, intracellular transport, and biocompatibility while integrating elements of responsive behavior to physiological environments and cognitive feedback control. Target and site categorical distribution with absolute precision can be achieved by annexing bioactive molecules to the liposome, bio-erodible polymer, implants, monoclonal antibodies, and various particulate [1,2]. One such approach is utilizing nanotechnology-based medications as carriers for drugs.

Nanotechnology-based formulations can be used for the sustained relinquishment of drugs, vaccines, antibiotics, and hormones. For example, by capitalizing on the characteristics of nanoparticles, beyond the fundamental benefits, the Nanoparticles could provide a more immensely colossal surface area and possess a more facile estimation of diffusion and mass transfer deportment [3]. Polymers have played an integral role in the advancement of DDS by providing controlled release of therapeutic agents in constant doses over long periods, cyclic dosage, and tunable release of both hydrophilic and hydrophobic drugs. The rational design of polymers engineered to perform specific biological functions and tailored for a specific cargo is now the foundation for modern advancements in drug delivery. Hierarchical progress in modern drug delivery begins with polymer carriers to elicit spatiotemporal release of therapeutics in both pulsatile dose delivery products and implanted reservoir systems. The ability to transfer into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, the release of the drug in a predetermined manner, and degradation within an acceptable time are just a few of the demanding requirements placed on these delivery systems. Nanoparticles made of biodegradable polymers demonstrate assurance in meeting these requirements [4]. Although conventional drug delivery formulations have contributed significantly to the treatment of disease, the emergence of potent and specific biological therapeutics has escalated the impetus for intelligent delivery systems[5].

1. Drug Delivery System: A Novel Approach to Formulation Development

A prospective drug delivery system can be defined as a mechanism to introduce therapeutic agents into the body or the process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals [6]. Every DDS may be defined as a system comprising of:

a. Drug formulation

b. Therapeutic method or dosage form/technology for administering drug inside the body

c. The mechanism for the release of the drug.

1.1 Skin

Skin plays the most crucial role in the transdermal and topical drug delivery system. Our body's largest organ, skin, serves as a barrier to prevent the entrance of foreign objects and potential pathogen invasion. The epidermis also stops the excessive loss of endogenous material like water.

1.1.1 Structure of Skin

The structural anatomy of human skin is about 0.5 mm thick and comprises two distinct layers, the inner dermis and the overlying epidermis. Connective tissue components can be found in the dermis, which makes up the majority of the epidermis and is 1-2 mm thick. The dermis contains pilosebaceous units, sweat glands, adipose cells, mast cells, and infiltrating leukocytes. It is also extremely vascular. The skin contains an uppermost layer, the epidermis, which has morphologically distinct regions; basal, spiny, stratum granulosum, and uppermost stratum corneum (SC), which is highly cornified (dead) cells, a continuous matrix of lipid membranous sheets. These extracellular membranes contain ceramides, cholesterol, and free fatty acids, making them special in their makeup [7].

The heterogeneous outermost layer of the skin, the stratum corneum, is 10–20 m thick. The thickness varies, however, and maybe a magnitude of order larger in areas such as the palms of the hand and soles of the feet, areas of the body associated with frequent direct and substantial physical interaction with the physical environment. It prevents the skin from being against the external environment. A barrier to shearing forces acting on the skin prevents the absorption of water from outside and the skin's loss of water and electrolytes [8].

1.1.2 Mechanism of Drug Absorption through the skin

Drug transport in the skin is a process involving several steps: a) dissolution and release of drug from the formulation; b) drug partitioning into the SC; c) drug diffusion across the SC, mainly by intercellular lipids; d) drug partitioning from the stratum corneum into viable epidermis layers; e) diffusion across the viable epidermis layers into the dermis, and f) drug absorption by capillary vessels, which achieves systemic circulation [9]. There are different possible routes for penetration of drugs via skin are paracellular (Transfer of substances across an epithelium by passing through the intercellular space between the cells), trans-cellular (the transportation of drug substance by a cell through a cell), and transappendgeal (transport via the sweat glands and along with hair follicles with their associated sebaceous glands) [10], [11]. The two major routes are identified for absorption of the drug through the skin as given below:

1.1.2.1 Trans-Epidermal Absorption

The trans-epidermal pathway is now widely accepted as being primarily responsible for diffusion across the epidermis. The resistance encountered along this pathway arises in the stratum corneum. Permeation by the trans-epidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoid route. The dermal region marks the last barrier to systemic entry. It is so regardless of whether permeation is trans-epidermal or by a shunt route. The ground substance's interlocking pathways allow it to permeate the dermis. Diffusion through the dermis is facile and without molecular selectivity since gaps between the collagen fibers are far too wide to filter large molecules [12].

1.1.2.2 Trans'-follicular (shunt pathway) Absorption

The skin s appendages offer only secondary avenues for permeation. Sebaceous and Acrine glands are the only appendages seriously considered shunts are bypassing the stratum corneum since these are distributed over the entire body. Though Acrine glands are numerous, their orifices are tiny and add up to a minuscule fraction of the body s surface. The current or flux is and terms of matter or molecules rather than electrons, and the driving force is a concentration gradient (technically, "a chemical potential" gradient) rather than a voltage drop. Membranes act as diffusion resistors. Resistance is proportional to thickness (h), inversely proportional to the diffusive mobility of matter within the membrane or the diffusion coefficient (D), inversely proportional to the fractional area of a route where there is more than one (F), and inversely proportional to the carrying capacity of a phase [13].

$$R = h/FDK$$

Were,

R =Resistance of diffusion resistor

F = Fractional area

H = Thickness

D = diffusivity

K = Relative capacity.

1.1.3 Basic Principles of Permeation

In the stage diffusion phase, drugs may be penetrated to the skin by the hair follicle, and -the opening of the sweat ducts and the follicular epithelium and sebaceous glands help towards the absorption of the drug molecules [14]. The stratum corneum plays a role to reaches the steady state by the diffusion of the molecules and making a dormant pathway for the drug towards absorption. The J is defined and calculated by the following equation

J= (DAKO/WrC) / h

Where,

J = Denotes the drug amount that passes through membrane system per unit/time.

D = Diffusion coefficient

A = Membrane area

C = concentration

Ko/w = Partition coefficient of the membrane

h = Membrane thickness.

1.1.4 Kinetics of Permeation

Knowledge of skin permeation is vital to the successful development of topical formulation. Permeation of a drug involves the following steps:

- Sorption by stratum corneum.
- Penetration of drug though viable epidermis
- Drug absorption via the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physicochemical properties. The rate of permeation across the skin (dQ/dt) is given by:

The Cd and Cr are the concentrations of skin penetrant in the donor compartment (e. g., on the surface of the stratum corneum) and the receptor compartment (e.g., body), respectively. Ps is the overall permeability coefficient of the skin tissues to the penetrant. The relationship gives this permeability coefficient:

$$Ps = Ks.Dss / Hs$$

Where Ks is the partition coefficient for the interfacial Partitioning of the penetrate molecule to form a solution medium onto the stratum corneum, Dss is the apparent diffusivity for the steady-state diffusion of the penetrate molecule through a thickness of skin tissues, and hs is the overall thickness of skin tissues. As Ks, Dss, and Hs are constant under given conditions, the permeability coefficient (Ps) for skin penetration can be considered to be persistent. From equation (1), it is clear that a constant rate of drug permeation can be obtained when Cd >> Cr, i.e., the drug concentration at the surface of the stratum corneum (Cd) is consistently and substantially more significant than the drug concentration in the body (Cr). The equation (1) becomes and the rate of skin permeation (dQ/dt) is constantly provided the magnitude of Cd remains relatively constant throughout skin permeation. For keeping Cd constant, the drug should be released from the device at a rate (Rr) that is either constant or greater than the rate of skin uptake (Ra), i.e., Rr >> R [15].

Penetration of drugs with low solubility and low permeability is harsh, so various polymers are used as penetration enhancers and solubility enhancers in the formulation to obtain better results. NDDS are developed to overcome the limitation of the conventional DDS to meet the stipulation of the healthcare vocation. These systems can be categorized as controlled drug release systems and targeted DDS. The various types of DDS utilized in drug discovery and formulation development are given below and elucidated in the subsequent section

a. Transdermal Drug Delivery Systems
b. Carrier-Based Drug Delivery Systems
c. Variable Release Drug Delivery Systems
d. Implantable Drug Delivery System
e. Nasal Drug Delivery Systems.

2. Transdermal Drug Delivery Systems (TDDS)

The Transdermal Drug Delivery System (TDDS) is a non-invasive system that can be exploited to go around the factors impacting the oral absorption of drugs, such as pH, nourishment consumption, and gastrointestinal motility. The biggest challenge with Transdermal Drug Delivery (TDD) is the obstacle nature of skin that stops the entry of most drugs. A few physical and chemical procedures have been tried and tested to beat the boundary of the stratum corneum (SC) to get higher transdermal penetrability [16, 17]. The non-invasive approaches for providing transdermal drug delivery of different therapeutic substances are depleted in [Table 1].

Table 1: Non-Invasive Approaches for Providing TDDS.

Non-Invasive Type of TDDS	Approaches
Drug and Vehicle Interaction	• Chemical potential adjustment • Ion pairs and complex co-acervates • Selection of correct drug or pro-drug • Eutectic systems
Stratum Corneum Modification	• Hydration. • Chemical penetration enhancers
Stratum Corneum Bypassed or Removed	• Micro-needle array [18]. • Stratum corneum ablated. • Follicular delivery.
Electrically Assisted Methods	• Ultrasound (Phonophoresis, Sonophoresis) [19]. • Iontophoresis. • Electroporation. • Magnetophoresis. • Photomechanical wave.

Vesicles and Particles	• Liposomes and other vesicles. • Niosomes. • Nano-trasfersomes (NTRF). • Solid lipid nanoparticles (SLNs).

2.1 Optimizing Transdermal Drug Delivery

The transdermal route has many potential benefits over traditional routes, including avoiding first-pass metabolism, predicting and extending the duration of the activity, minimising negative side effects, using drugs with short half-lives, improving physiological and pharmacological response, avoiding drug level fluctuations, inter and intra-patient valuations, and most importantly, providing patient convenience. But one of the major problems in transdermal drug delivery is the low diffusion rate through the outermost layer of the skin[20,21].

2.1.1 Non-Invasive Approaches of TDDS

There are various approaches used to avoid painful injections; the following are the common ways to deliver the drug non-invasively:

- **Micro-needles**

Micro-needle is a solid or hollow cannula with an approximate length of 50-900 mm and an outer diameter below 300 mm. Micro-needles can be adulterated in the patch for TDD. Patches having micro-needles have been assessed in the delivery of drugs, biopharmaceuticals, vaccines, etc. Micro-needles penetrate through the epidermis up to a bottom of 70–200 mm. Micro-needles are narrow and tiny and don't enter the dermis layer with nerves; therefore, painless application is achieved[22].

Table 2: Advantages and Disadvantages of Micro-needles.

Advantages	Disadvantages
• The administration of bulky molecules can be achieved. • Pain-free governance of the API • Avoidance of the first-pass metabolism • Quick-relief at the injection site compared with a hypodermic.	• Dosage correctness can be less with hypodermic needles. • Careful utilization of the device may be expected to prevent particles from bouncing off the skin surface, • The dose may escape or can enter the skin to varying degrees. • The heaviness of the stratum corneum varies penetration of the drug. • Hydration and other external environmental factors can affect delivery.

- **Transdermal Patch**

It is a patch filled with drugs placed under the skin supplying a specific dose of medicament to the systemic circulation. It includes a drug reservoir/polymer matrix, permeation enhancers, pressure-sensitive adhesive (PSA), backing laminates, release lining, and additional excipients such as plasticizers and solvents.

Table 3: Advantages and Disadvantages of Transdermal Patch.

Advantages	Disadvantages
• Prolonged duration of action. • Reduction in the dosing infrequency. • Constant peak plasma concentration enhance • Enhance bioavailability.	• Irritation at the application site may be observed. • Drugs or excipients may cause skin annoyance. • The skin's low permeability limits the drugs that can be delivered in this kind.

- **Iontophoresis**

Iontophoresis, also called electromotive drug administration, uses a small electric charge to deliver a medicine or other chemical through the skin. Iontophoresis is a transdermal drug delivery method that utilizes a voltage gradient on the skin. It enhances medication distribution through the skin via two main mechanisms: electro-repulsion and electro-osmosis. The effect of an electric field on a charged permeate is electro-repulsion. The second mechanism, electro-osmosis, results from the skin holding up a negative charge at 7.4 pH[23].

Table 4: Advantages and Disadvantages of Iontophoresis.

Advantages	Disadvantages
• The dose is not more depending on the thickness of the skin at the application site. • Fast-reacting administration kinetics, permitting the pulsatile administration and minimizing *in vivo* plasma profiles. • Skin irritation and membrane disruption are reduced. • Increase in the collection of drug candidates for TDDS.	• Because of the negative qualities of efficiently transporting the electric charge, the delivery and extraction of large molecules (such as proteins) are still limited. • The presence of the analyte at high levels in the skin. • Slight risk of electrode burns. • Time-consuming for administration.

- **Sonophoresis**

In sonophoresis, ultrasound improves the absorption of topical compounds into the epidermis, dermis, and skin extremities. Although sonophoresis is known to build skin permeability, the fundamental mechanism is yet not comprehended or described. A few proposed mechanisms of sonophoresis incorporate thermal effects of immersion of ultrasound energy, and cavitation outcomes brought about by breakdown and oscillation of cavitation rises in the ultrasound area[24].

Table 5: Advantages and Disadvantages of Sonophoresis.

Advantages	Disadvantages
• No gastrointestinal degradation. • No first-pass metabolism. • Steady delivery. • Better patient compliance.	• Low skin permeability. • Unable to deliver large (>500 Da) molecules. • Prominent lag time. • Skin sensitization.

- **Electroporation**

Electroporation is a layered phenomenon that consists of the fundamental nature of cell and mannered bilayers and increasingly attracts applications in biology, biotechnology, and medicine. The administration of well-designed electric field vibrations to cells and tissue leads to various structural changes to the cell membrane. Significant progress has been made by accepting that a portion of these advancements consist of impermanent fluid pathways (pores), with the electric field playing the dual role of causing pore formation and providing a local driving force to the ionic and molecular vehicles passing through the pores[25].

Table 6: Advantages and Disadvantages of Electroporation.

Advantages	Disadvantages
• It does not alter the biological structure or function of target cells. • It can be applied to a much broader section of cell type. • The capacity to operate in live creatures with minor DNA requirements • Time-efficient and easy to perform.	• May lead to Collateral damage • Can cause skin edema • Electroporation damage to the tumor. • Probable cell injury • Nonspecific transport of molecules in/out of the cell.

- **Magnetophoretic**

Magnetophoresis indicates the utilization of a magnetic field and goes about as an outer driving force to better the conveyance of drugs through the skin. It incorporates changes in the skin structure that could contribute to the rise in permeability. It is a technique with less heat generation[26].

Table 7: Advantages and Disadvantages of Magnetophoresis.

Advantages	Disadvantages
• Simple design, low cost, and easy operation. • Changeable by controlling the spin state induced by ligands and valence number. • It does not affect the properties of the sample solution (pH value, ion concentration, surface charge, and temperature).	• More prolonged exposure of the cells to the paramagnetic medium may affect cell integrity. • The pH value, tonicity, and nanoparticle surfactant optimization must be maintained for colloidal stability.

3. Nanotechnology-based Formulation techniques (using Novel vesicular system)

Nanotechnology is the advancing technology based on the study of manipulating matter on a nanoscale range, and it refers to the construction and engineering of functional systems at the atomic level. Vesicular delivery carriers are used in this approach to reduce the skin's barrier characteristics. Numerous vesicular carriers like liposomes, Trasfersomes, niosomes, virosomes, etc., have proven themselves a potential tool for the effective delivery of drugs and bioactive. These delivery vesicles have been discussed in detail in the next part. The rapid development in transdermal delivery formulations within the last few years is due to certain advantages offered by transdermal administration versus the conventional oral route, which increases the bioavailability of drugs because using the transdermal delivery, the active principle enters directly into the circulatory system, bypassing the hepatic metabolism, controlled drug input decreasing the variations in drug plasma levels, increases the patient compliance and minimizes the risk of trauma or any other injury of tissue [27,28]. The reason behind the use of vesicles in transdermal drug delivery is based on the fact that they act as drug carriers to deliver entrapped drug molecules across the skin, as well as act as penetration enhancers because of their composition. Moreover, these vesicles serve as a depot for the sustained release of active compounds in the case of topical formulations and a rate-limiting membrane barrier for the modulation of systemic absorption in the case of transdermal formulations [29].

3.1 Niosomes

Different carriers have been used for targeting drugs, such as immunoglobulin, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, and niosomes. Niosomes are one of the best among these carriers. These non-ionic surfactant-based vesicles are an affordable, biodegradable, more stable, and less toxic option to liposomes. When non-ionic surfactant of the alkyl or dialkyl polyglycerol ether family and cholesterol are combined, microscopic lamellar structures known as niosomes or non-ionic surfactant vesicles are produced [30]. Niosomes can improve the performance of the drug molecules by delayed clearance from the circulation, better availability to the particular site, just by protecting the drug from the biological environment and by controlled drug delivery at a specific site, and have unique advantages over liposomes. Niosomes are relatively stable structures, even in the emulsified form. The inclusion of cholesterol in

niosomes increases its hydrodynamic diameter and entrapment efficiency. These can be changed or modified by incorporating other excipients like cholesterol into the membrane, and they can possess one or more lipid bilayers encapsulating an aqueous core. The bilayered vesicular structure is made up of hydrophilic head groups in touch with the aqueous space in the centre and hydrophobic tails of surfactant monomers that are shielded from it. Niosome possesses an infrastructure consisting of hydrophobic and primarily hydrophilic together and accommodates the drug molecules with a wide range of solubility. The addition of cholesterol results in an ordered liquid phase formation, which gives rigidity to the bilayer Diacetyl phosphate is known to increase the size of vesicles, provide charge to the vesicles, and thus show increased entrapment efficiency. Other charge-inducers are stearyl amine and diacylglycerol, which also help in the electrostatic stabilization of the vesicles [31,32].

3.2 Liposomes

Liposomes are tiny, spherical manufactured vesicles that can be created using cholesterol and safe, natural phospholipids. In addition to biocompatibility, liposomes' size and hydrophobic and hydrophilic properties make them effective drug transport vehicles. The liposome size can vary from small (0.025 µm) to large (2.5 µm) vesicles. Liposomes are often distinguished according to their number of lamellae and size. There are three types of vesicles small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), and large multilamellar vesicles (MLVs) or multivesicular vesicles (MVVs). Large liposomes form a spontaneous process when phospholipids are dispersed in water above their phase transition temperature. The preparation of SUVs usually starts with MLVs, which are then transformed into small vesicles using an appropriate manufacturing technique, e.g., high-pressure homogenization [33,34].

The liposomes are characterized for their physical attributes, i.e., size, shape, size distribution, surface charge, percent capture, entrapped volume, lamellarity through freeze-fracture microscopy, P-NMR, phase behavior, and drug release, quantitative determination of phospholipids, and cholesterol analysis. Liposome has been extensively investigated for their potential application in pharmaceutics, such as drug delivery, drug targeting, controlled release, or increased solubility. They offer a substantial improvement in the therapeutic indices of the drug molecules entrapped in them. Due to their high biocompatibility, liposomes have been used as delivery systems for various molecules. Applications of the liposomes are in immunology, dermatology, vaccine adjuvant, eye disorders, brain targeting, infective disease, and tumor therapy [35].

3.3 Ethosomes

Ethosomes are novel carrier systems used to deliver drugs with low penetration through the biological membrane, mainly skin. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentrations, and water, primarily used for the transdermal delivery of drugs. Ethosomes have a higher penetration rate through the skin than liposomes; hence these can be used widely in place of liposomes. Although, the exact mechanism for better permeation into deeper skin layers from ethosomes is unclear. The synergistic effects of phospholipids and high ethanol concentration in vesicular formulations have been suggested to be responsible for deeper distribution and penetration in the skin lipid bilayers. The size range of ethosomes may vary from tens of nanometres to microns[36,37].

3.4 Nano-Trasfersomes (NTRF)

Nano-trasfersomes are a particular type of liposomes consisting of phosphatidylcholine and an edge activator. They are soft, malleable vesicles tailored for enhanced delivery of active agents [38]. Gregor Cevc first reported NTRF in 1992 as elastically deformable lipid vesicles. NTRF are defined as "self-adaptable ultra-deformable flexible elastic bilayer vesicles made up of phospholipids and edge activators like surfactants, e.g., sodium chelate, spans, tweens, etc. which are stress adaptable and able to pass across the pores of the skin even smaller than their size as these squeeze through the pores by deforming themselves and then reform after passing through pore [39,40].

❖ **Features of NTRF [41]**

- NTRF is capable of controlled and targeted types of drug delivery.
- They are amphiphilic and suitable for all drug molecules, especially water and lipid-loving drugs.
- The ability to release the drug sustainably for a prolonged time is an outstanding feature of Nanotrasfersomes.
- Because of their flexible and elastic nature, Nanotrasfersomes can deform and enter the bottom layer of skin through the narrow constriction of the stratum corneum.
- During penetration, its size can lead to 10 times lesser.
- Drugs having low and high molecular weight can penetrate through the skin by using that transferosomal carrier system
- Nanotrasfersomes have greater entrapment efficiency and can also defend the entrapped drug from metabolic decomposition.
- Nanotrasfersomes are biocompatible and easily removed from a biological system because the fundamental components employed in their manufacture are natural in origin.

4. Mechanism of Permeation and composition of NTRF

The first feature of the Transfersomal drug delivery system permits a transferosome to react strongly to the moisture gradient of this layer of the skin. When lipid aggregates act in the sensitized region of the skin, evaporation of water takes place in that area. Trasfersomes enter the body through the skin by hydro taxis [42]. NTRF are applied to the skin in a non-occluded manner and have been demonstrated to penetrate through the stratum corneum lipid lamellar regions due to the skin's hydration or osmotic pressure. They have been used as drug carriers for small molecules, peptides, proteins, and vaccines, both *in-vitro* and in-vivo. It has been claimed that intact Trasfersomes penetrate through the stratum corneum and the underlying viable skin into the blood circulation. However, this has not been substantiated by other research groups who have extensively probed the mechanism of penetration and interaction of elastic vesicles in the skin. Structural changes in the stratum corneum have been identified, and intact elastic vesicles have been visualized within the stratum corneum lipid lamellar regions, but no intact vesicles have been ascertained in the viable tissues [43,44]. Thus, these vesicles penetrate the more hydrated layer of skin, reaching the deeper layer of the epidermis and dermis; the description is explained [45,46].

Nano-transfersomes are composed of phospholipids like phosphatidylcholine, which self assembles into lipid bilayer in an aqueous environment and closes to form a vesicle. A bilayer softening component (such as a biocompatible surfactant or an amphiphilic drug) is added to increase lipid bilayer flexibility and permeability. This second component is called an edge activator. Surfactants are added in the proper ratios to provide flexibility to the transferosomes membrane [47,48]. The following [Table 8] shows the critical components of transferosomes vesicles.

Table 8: Composition of Trasfersomes.

Excipients	Examples	Applications
Phospholipids	Phosphatidylcholine, Soya Phosphatidylcholine, Egg phosphatidylcholine.	Vesicles wall forming agent.
Lipid	Cholesterol	Stabilizer
Dye	Rhodamine-123, 6-carboxyfluorescein, rhodamine red, isothiocyanate fluorescein.	The diagnosis market is used for confocal laser scanning microscopy.
Surfactant	Tween 80, span 80, Sodium cholate, Sodium deoxycholate	Flexibility enhancer.
Buffering agent	Phosphate buffer saline (pH 6.4)	Hydrant
Solvent	Methanol, ethanol, propanol, isopropanol, chloroform.	Solubilizer
Polyglycerol	Propylene glycol, Diethylene glycol monoethyl ether, glycerin	Penetration enhancer

4.1 Advantages and Disadvantages of Nano-transfersomes

Nano-transfersomes bears several advantages and disadvantages [49]; they are given in [Table 9]

Table 9: Advantages and Disadvantages of Nano-transfersomes.

Advantages	Disadvantages
Both hydrophobic as well as hydrophilic drugs can be incorporated Offer enhanced permeation. Safeguard the drug from the external environment by encapsulation. They are composed of biodegradable and biocompatible materials. It can be used for drugs targeting the skin. Sustain the drug release into the skin. Easy to speed up and has high market potential.	Chemically unstable due to predisposition to oxidative breakdown. Genuineness of natural phospholipids is challenging to achieve These compositions are unaffordable. Dermatitis, hypersensitivity, or irritates the skin in a few patients. Some products get lost because they are moved from alcoholic to aqueous media.

4.2 Methods of Nano-Nano-transfersomes Preparation

Present section deals with the several methods utilized for the formulation of nano-transfersomes.

- **Vortexing Sonication Method**

In this vortexing sonication method, lipids such as phospholipids, edge activators, and medicinal agents are added to the phosphate buffer and shaken to get a milky suspension. This suspension was then sonicated for 30 minutes, followed by the extrusion through a polycarbonate membrane filter [50].

- **Reverse-Phase Evaporation Method**

Dissolve phospholipid into the organic solvent in a round bottom flask. An aqueous blend of surfactants or edge activator is added under nitrogen purging to the organic solvent of phospholipid. The drug can be incorporated into the lipid or aqueous phase based on its solubility. The resultant mixture is then sonicated using a probe sonicator in the ice bath at 100°C for 15 minutes. Keep this system for 30 minutes after sonication. The organic solvent has vanished under reduced pressure, and a homogeneous viscous gel will form, which contains vesicles of transferase[51].

- **Freeze-Thaw Method**

This method involves exposing multilamellar vesicles to alternate cycling of low temperatures for freezing followed by very high temperatures. The suspension is transferred in a Pyrex tube and dipped in a nitrogen bath (-30°C) for a few seconds, then exposed to a high temperature. This process is to be continued nine times [52].

- **Rotary Film Evaporation Method**

This process entails dissolving phospholipid in an organic solvent (a mixture of chloroform and methanol), then adding edge activators to this solution in a specific ratio. The organic solvents in the mixture are evaporated in the Rota-Evaporator, followed by vacuum drying to the total elimination of the solvent's residue. This process leaves the thin vesicular film. This film was further hydrated with saline phosphate buffer pH 6.5 containing a therapeutic agent, rotating the flask for hot at room temperature. Then vesicles kept swelling for 2 h through sonication. The formed cysts are then removed through a series of filters of polycarbonates membranes with a pore size of 220 nm to 450 nm. Depending on its solubility, the drug is incorporated in either an organic or aqueous solution [53].

- **Ethanol Injection Method**

In this method, the aqueous solution of the drug is heated at a steady temperature with continuous stirring. On the other side, Phospholipids and edge activators are solubilized in ethanol, and that solution is injected drop-wise into the aqueous drug solution. When the ethanolic solution comes in contact with an aqueous solution, the lipid molecules are precipitated and form a bilayer structure. It is a simple and reproducible method [52].

4.3 Significance of Nano-transfersomes

The significance of transferase in various aspects of disorders [54] is included in the following [Table 10]:

Table 10: Significance of Nano-transfersomes.

Sr. No.	Applications
1.	Basal cell carcinoma: In the therapy of cancer
2.	Actinic keratosis: Ordinary skin ailment caused is treated using transfersome gel.
3.	AIDS: Indinavir sulphate transfersome in AIDS.
4.	Gout: Colchicine transdermal gel containing transferosome used for the treatment of gout.
5.	Insulin-dependent diabetes mellitus: Transfersome gel containing insulin is used to treat this kind of diabetes.
6.	Skin cancer: Transfersome as versatile and elastic nano-vesicular carriers in skin cancer therapy

The present research deals with the novel formulation strategy for drug-loaded nano-transfersomes to treat different kinds of fungal infections caused due to dermatophytes.

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