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Curcumin-Loaded Transferosomes: Promising Strategy for Overcoming Poor Oral Bioavailability

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ABSTRACT: *Curcumin, a bioactive polyphenol derived from Curcuma longa, exhibits a wide range of therapeutic benefits, including anti-inflammatory, antioxidant, antimicrobial, and anticancer activities. Despite its potent pharmacological properties, curcumin's clinical application is significantly limited by its poor aqueous solubility, instability in the gastrointestinal tract, and low systemic bioavailability when administered orally. Transferosomes, a class of ultra-deformable vesicular systems, have emerged as a promising nanotechnology-based strategy to address these limitations,their flexible lipid bilayers enable deeper tissue penetration and enhanced drug absorption. This review comprehensively highlights the challenges associated with oral delivery of curcumin and evaluates the role of transferosomal drug delivery in improving its pharmacokinetic profile. It also explores recent research on curcumin-loaded transferosomes for therapeutic applications across various organ systems, with a particular emphasis on inflammation and wound healing. The findings underscore the potential of transferosomes to revolutionize curcumin-based therapy by offering targeted delivery, enhanced bioavailability, and improved therapeutic efficacy.*

KEYWORDS: *Curcumin, Bioavailability, Oral administration, Dissolution*

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I. INTRODUCTION:

Curcuma longa L., its derived extracts and even its major compound curcumin has a long history of use and doubtless effectiveness, reported through increasingly detailed *in vitro, ex vivo, in vivo* and even clinical trials. Regarding its biological effects, multiple health-promoting, disease-preventing and even treatment attributes has been remarkably highlighted. Clinical trials, although have increased in a progressive manner, significant disproportionalities have been stated in terms of biological effects assessment. In this sense, the present report aims to provide an extensive overview to curcumin therapeutic effects in human subjects. For that, clinical trials assessing the curcumin effect on inflammation, skin, eye, central nervous system, respiratory, cardiovascular, gastrointestinal, urogenital and metabolic disorders are here presented and discussed. A special emphasis was also given to curcumin activity on intoxications and multiple malignant diseases (1,2). Herbs and natural products have long been exploited by humans to combat numerous diseases since the dawn of time. The Indian subcontinent boasts diverse flora, including both aromatic and therapeutic species. After all, contributions should be made to analyze, standardize, and confirm Unani and Ayurvedic medication for potential, safety, and effectiveness prior to actually introducing them to the market as first-line drug delivery. Plant-based therapies are being used across all civilizations. Plant-based medicines are already extensively utilized, and several countries invest 40%–50% of their total health budget to produce novel drugs. Herbal medicines are assumed to have a beneficial effect on health without any side effects. (3,4)

The genus *Curcuma* has been employed from many years back due to its medicinal applications; it is composed of approximately 133 species worldwide. *C. longa* (Haridra), *C.aromatica* Salisb (Vana Haridra), *C. angustifolia* Roxb., *C. zanthorrhiza* Roxb., *C. amada* Roxb (Amaragandhi Haridra), *C. caesia* Roxb (Kali Haridra), and *C. zedoaria* Rosc (Zedoary) are common species of genus *Curcuma* found in several regions of the globe. *Curcuma longa* Linn. (*C. longa*) is the common tall herb that flourishes in tropical as well as in other Indian regions and is referred to as "Indian saffron or The Golden Spice of India" because of its use in a broad range of diseases in Indian homes as a spice, food preservative, and coloring source. *C. longa* belonging to the Zingiberaceae (ginger) family is a perennial plant commonly planted in Asian nations. It is among the oldest spices of India that have been used in Western and Southern parts for centuries, and is a significant part of Ayurvedic medicine. In Ayurveda, the therapeutic effects of *C. longa* have been well established and are discussed in Dashemani Lekhaniya (emaciating), Kusthagna (anti-dermatosis), and Visaghna (anti-poisonous) texts. It is known by many distinct names such as Haridra in Sanskrit, Haldi in Hindi, Jianghuang (yellow) due to shortcomings in the earlier published review articles, such as a lack of information on the therapeutic

potential of *C. longa* in relation to its major compound curcumin, we have attempted to provide in-depth information by highlighting knowledge gaps in traditional and scientific evidence about *C. longa* in relation to the therapeutic potential of curcumin against numerous disorders. (5, 6) This review mainly focuses on the distribution, cultivation, botany, nutritional composition, phytochemistry, toxicology, traditional and medicinal properties, and safety aspects including the pharmacological activities of *C. longa* in relation to its major compound curcumin. This review will further discuss the current advances in *C. longa* and curcumin, such as the utilization of nanocarriers to increase curcumin bioavailability and overcome all the disadvantages in relation to drug delivery. (7,8)

LIMITATIONS OF ORAL DRUG DELIVERY OF CURCUMIN (9, 10)

- **Gastrointestinal (GI) Degradation**

The gastrointestinal tract presents a highly acidic and enzymatic environment, particularly in the stomach. Curcumin is chemically unstable at low pH and undergoes degradation when exposed to gastric fluids. Additionally, the phospholipid bilayer of transferosomes can be hydrolyzed by digestive enzymes such as lipases and pepsin. This degradation reduces the integrity of the vesicles and can lead to premature leakage or destruction of the encapsulated curcumin, severely limiting its therapeutic efficacy when administered orally.

- **Low Stability in the GI Tract**

Transferosomes are ultra-deformable vesicles composed of phospholipids and edge activators (e.g., surfactants), making them structurally optimized for transdermal drug delivery. However, their stability in the gastrointestinal environment is limited. Bile salts and digestive enzymes can destabilize the vesicles by disrupting the lipid bilayer. Moreover, variations in pH and ionic strength throughout the GI tract can cause vesicle aggregation, fusion, or breakdown, making it difficult for the drug to remain encapsulated and intact until absorption.

- **Limited Mucosal Penetration**

For any orally administered drug, crossing the intestinal mucosal barrier is a critical step. Although transferosomes are deformable and capable of squeezing through narrow pores in the skin (in transdermal applications), their efficiency in penetrating the dense mucus layer and tight epithelial junctions in the gut is significantly lower. The size, charge, and surface characteristics of transferosomes may prevent them from effectively adhering to and penetrating the intestinal epithelium, resulting in reduced systemic absorption of curcumin.

- **Poor Bioavailability of Curcumin**

Curcumin inherently suffers from poor aqueous solubility, low absorption, and extensive first-pass metabolism in the liver and intestinal wall. Even when loaded into transferosomes, curcumin's systemic availability after oral administration remains low unless the formulation can protect it from metabolic enzymes and facilitate its transport across the gut barrier. Additionally, curcumin is rapidly conjugated into inactive metabolites (glucuronides and sulfates), which further diminishes its therapeutic activity *in vivo*.

- **Formulation Challenges**

Formulating transferosomes for oral use is more challenging compared to transdermal systems. The vesicles must remain stable throughout the entire GI transit time, resist enzymatic degradation, and retain their encapsulation efficiency. Techniques such as lyophilization (freeze-drying) and coating with polymers can be used to enhance stability, but they add complexity and cost. Additionally, ensuring reproducibility, scale-up, and shelf-life stability of oral transferosomal formulations is a significant hurdle for pharmaceutical development.

- **Dose-Limiting Factors**

Transferosomes have a limited drug-loading capacity, especially for hydrophobic compounds like curcumin. To achieve therapeutic plasma concentrations, relatively large doses may be required. However, the volume of the vesicular suspension that can be orally administered is limited, especially in humans. This restricts the total deliverable drug dose and may necessitate multiple administrations or combination with other delivery systems, which can reduce patient compliance and increase costs.

- **Lack of Targeting Capability**

Unlike some advanced delivery systems that include ligands for active targeting (e.g., nanoparticles with folate or antibody surface markers), standard transferosomes lack specific mechanisms to target curcumin to the site of action within the body after oral administration. Once released in the systemic circulation, the drug may distribute non-specifically, reducing its concentration at the desired target site and increasing the risk of off-target effects. This non-targeted distribution is particularly concerning in chronic diseases like cancer or inflammation, where localized drug action is often critical.

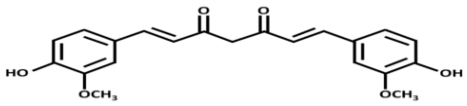
RATIONALE USE OF TRANSFEROSOMES (11,12,13)

Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility. Transferosomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.

This high deformability gives better penetration of intact vesicles. They are self-aggregates, with an ultra-flexible membrane which delivers the drug reproducibly into or through the skin. These vesicular vesicles are several orders of magnitude more elastic than the standard liposomes. Transferosomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipids of the stratum corneum. The concept of transferosomes as a carrier for transdermal delivery was first developed by Cevc and coworkers, in 1992. Transferosomes for potential transdermal application, contain a mixture of lipids and biocompatible membrane softeners. The optimal mixture leads to flexibility of the elastic liposomal membranes and to the possibility of penetration through channels of the skin, which are opened by the carriers. Transferosome is a supramolecular entity that can pass through a permeability barrier and there by transport material from the application to the destination site. These are more elastic than the standard liposomes and therefore are used as a novel carrier for effective transdermal drug delivery. They have easily deformable properties which make them easily squeeze out from the stratum corneum and the mechanism for penetration is the generation of 'osmotic gradient' due to the evaporation of water while applying the lipid suspension (transferosomes) on the skin surface. (14, 15, 16)

Transferosomes penetrate the stratum corneum by either intracellular route or transcellular route. With the excellent distribution properties of transferosomes, they have been widely used as a carrier for various proteins, anti-cancer drugs, anti-fungal drugs, analgesics, anaesthetics, corticosteroids, sex hormone, insulin, albumin etc. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes. They have high entrapment efficiency, which is nearly 90% in the case of lipophilic drug. They protect the encapsulated drug from metabolic degradation. They act as depot, releasing their contents slowly and gradually.

CURCUMIN PHARMACOLOGICAL PROFILE AND LIMITATIONS(3,17)
CHEMICAL STRUCTURE AND PROPERTIES:
Drug: Curcumin



Chemical structure of **Curcumin**
IUPAC Name: (1E,6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione
Molecular formula: $C_{21}H_{20}O_6$
Molecular weight:368.38 g/mol
Chemical Class: Polyphenol (Curcuminoid)
Source: Extracted from the rhizome of *Curcuma longa* (Turmeric)
Chemical name:(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione
Solubility: Practically insoluble in water; soluble in organic solvents like ethanol, acetone, and DMSO
Description: A yellow colour powder
Analytical profile: Spectrophotometry: Spectrophotometric determination of curcumin shows a maximum absorbance (λmax) at 427 nm in ethanol and PBS medium.
PHARMACOKINETICS
Absorption: Curcumin has poor oral bioavailability due to limited absorption, rapid metabolism, and systemic elimination. After oral administration, only about 1–2% of the dose appears in systemic circulation. Peak plasma levels are achieved in 1–2 hours post-administration.
Distribution: Curcumin has a high volume of distribution, indicating extensive tissue uptake. It is highly lipophilic and strongly binds to plasma proteins, including albumin.
Metabolism: Curcumin undergoes extensive first-pass metabolism in the liver and intestinal wall. It is primarily metabolized to glucuronide and sulfate conjugates, and to tetrahydro curcumin and hexahydro curcumin through reduction and conjugation pathways.
Elimination: Curcumin is predominantly excreted in bile as conjugated metabolites. The elimination half-life ranges from 1.5 to 2 hours. Less than 0.01% of the oral dose is recovered unchanged in urine.
Mode of Action
Curcumin acts through multiple mechanisms:

- Anti-inflammatory: Inhibits NF-κB, COX-2, and pro-inflammatory cytokines (e.g., TNF-α, IL-6).
- Antioxidant: Scavenges free radicals and boosts antioxidant enzymes like SOD and catalase.
- Anticancer: Suppresses cell proliferation and induces apoptosis by inhibiting STAT3, Akt, and VEGF.
- Immunomodulatory: Balances immune responses by reducing inflammatory mediators.

- Neuroprotective: Reduces beta-amyloid plaques and neuro inflammation.
- Antimicrobial: Disrupts microbial membranes and inhibits viral replication.

These actions contribute to its therapeutic effects in inflammatory, infectious, and degenerative diseases.

Indications and Usage

Curcumin, a polyphenolic compound derived from the rhizome of *Curcuma longa* (turmeric), is widely recognized for its anti-inflammatory, antioxidant, and anticancer properties. It is used:

- As an adjunct therapy in inflammatory conditions (e.g., arthritis, IBD).
- In the management of metabolic syndrome, diabetes, and obesity.
- For liver protection, neurodegenerative disorders, and cancer chemoprevention.
- In skin disorders due to its anti-inflammatory and wound-healing effects.

Dosage and Administration

- Typical oral doses: 500–2000 mg/day of standardized curcumin extract.
- Bioavailability enhancers (e.g., piperine, phospholipids) are often used to improve absorption.
- Dosage should be individualized based on clinical indication and patient tolerance.

Contraindications

- Hypersensitivity to curcumin or turmeric.
- Biliary obstruction or gallstones (due to stimulation of bile secretion).
- Pregnancy and lactation: Use with caution due to limited safety data.

Drug Interactions

- May inhibit or induce cytochrome P450 enzymes (CYP1A2, CYP3A4, CYP2C9), affecting drug metabolism.
- Increases bioavailability of certain drugs by inhibiting P-glycoprotein and CYP3A4.
- Anticoagulants/antiplatelets: May increase bleeding risk.
- May interact with chemotherapeutic agents, NSAIDs, antidiabetics, and immune suppressants—monitor closely

Adverse Reactions

- Generally well-tolerated at therapeutic doses.
- Mild GI disturbances: Nausea, diarrhoea, constipation, dyspepsia.
- High doses (>8 g/day) may cause abdominal pain or ulcers.
- Rare cases of allergic dermatitis or contact urticaria have been reported.
- Long-term high doses may contribute to iron chelation, leading to iron deficiency.

Uses in Dermatology

- Effective in psoriasis, eczema, acne, wound healing, and photoaging.
- Used in topical creams, masks, and cosmeceuticals for its anti-inflammatory and depigmenting effects.
- Research supports its role in melanoma and non-melanoma skin cancers, especially via NF-κB and MAPK pathway inhibition.

Other Potential Benefits

- Cardiovascular health: Lowers LDL, improves endothelial function, and reduces inflammation.
- Glycemic control: Improves insulin sensitivity and reduces blood glucose.
- Neuroprotection: Studied in Parkinson's, Alzheimer's, and depression due to modulation of inflammatory cytokines and oxidative stress.
- Gut health: Modulates gut microbiota and supports intestinal barrier function (8,9,10).

TRANSFEROSOMES: AN OVERVIEW (18,19,20)

Drug Delivery via the route is an interesting option in this respect because transdermal route is convenient and safe. They offers several advantages over conventional drug delivery system like avoidance of first pass metabolism, predictable and extended duration of action, minimizing undesirable side effects, utility of short half-life drugs, improving physiological and pharmacological response, avoiding the fluctuation in drug levels, inter-and intra-patient variations and most importantly, it provides patients convenience. Despite major research and development efforts in transdermal systems and the advantages of these routes, low stratum corneum permeability limits the usefulness of topical drug delivery.

To overcome this, various methods have been assessed to increase stratum corneum permeability. To date many physical and chemical approaches have been applied to increase the efficacy of the material to

transfer across the intact skin, by use of the penetration enhancers, iontophoresis, iontophoresis and the use of colloidal carriers such as lipid vesicles (liposome and pro-liposomes) and non-ionic surfactant vesicles (noisome and proniosomes). Vesicular system used in transdermal drug delivery such as liposomes, niosomes, or microemulsions usually remains confined to the skin surface and therefore do not transport drugs efficiently through the skin. The system delivers the drug with high efficiency depending on the choice of administration or application.

With the application of mechanical stress, they can enter through stratum corneum in self-adapting manner because of their high vesicle deformability. Flexibility or elasticity of transferosomes membrane is achieved by mixing suitable surface-active components (edge activator) in the proper ratios. When applied on the skin, the carrier searches and exploits hydrophilic pathways or pores between the cells, where it opens wide enough to permit the entire vesicle to pass through stratum corneum along with drug molecule, deforming itself extremely to accomplish this without losing its vesicular integrity. This enables them to cross various transport barriers efficiently. Transferosome penetrate the stratum corneum by either intracellular route or the transcellular route by the generation of “osmotic gradient” due to evaporation of water.

Other applications include the transport of small molecule drugs which have certain physicochemical properties which would otherwise prevent them from diffusing across the barrier. To overcome these problems, a new type of carrier system called "Transfersome", has recently been introduced, which is capable of transdermal delivery of low as well as high molecular weight drugs. Transferosomes are specially optimized, ultra deformable (ultra flexible) lipid supra molecular aggregates, which are able to penetrate the mammalian skin intact. Transferosome is a term registered as a trademark by the German company IDEA AG, and used by it to refer to its drug delivery technology. The name means “carrying body”, and is derived from the Latin word 'transferre', meaning “to carry across” and the Greek word “soma”, for a “body”. A Transferosome carrier is an artificial vesicle designed to be like a cell vesicle or a cell engaged in exocytosis, and thus suitable for controlled and potentially targeted, drug delivery.

MECHANISM OF SKIN PENETRATION BY TRANSFEROSOMES

1.The trans-appendageal route also known as shunt route. This route includes transdermal delivery using the hair follicles and their associated sweat glands and provides a continuous channel across the SC. It also provides a large surface area for the diffusion of solutes. Factors such as sweating and secretion from sebaceous and sweat glands can affect the permeation of solutes through this route. Additionally, it has been reported that hair follicles occupy only 0.1% of the surface area of the skin and therefore contribute very little toward TDD.

2.The intracellular route also known as transcellular route. In this mode of TDD, the solute permeates through the SC by passing through the corneocytes. Corneocytes are highly hydrated keratin containing dead cells (the level hydration being dependent on level of skin moisturization and the environmental temperature). This creates a suitable route for hydrophilic solutes. However, due to the lipid matrix surrounding the hydrated keratinocytes, the solute undergoes multiple steps of partitioning through the skin .

3.The intercellular route. In this route, diffusion takes place through the lipid matrix between the corneocytes. This route involves a tortuous route as compared to previous direct pathways for the delivery of the solute. Due to the water gradient in the SC as the drug crosses the epidermal layers, it undergoes multiple steps of partitioning and diffusion to reach the lower viable epidermis, the dermis and then the systemic circulation.

CHALLENGES FOR TRANSDERMAL DRUG DELIVERY (21,22,27)

To overcome some of the challenges with transdermal drug delivery, a combination of solid and liquid (oils) lipids with surfactants in an aqueous solution is often used. In addition to PCs and cholesterol from liposomes, edge activators are used to induce deformability to the vesicle. This mixture results in better drug loading, higher stability, better permeation through the skin and controlled drug delivery. This improved technology has various applications in dermatological cosmetic as well as the pharmaceutical industry. The high deformability of ultra-flexible LNPs is a valuable tool in transdermal drug delivery with better entrapment efficiency and stability of APIs. These properties can further be altered to make a new generation of ultra-flexible carriers known as transferosomes to enhance the skin permeability properties.

Transferosomes are supple or malleable vesicles invented in the early 1990s. The term “transferosome” is a combination of Latin and Greek, derived from the meaning “to carry the body”. Currently, the use of transferosomes-based TDD has attracted a lot of attention in the pharmaceutical research circles. Transferosomes are an attractive drug delivery carrier for transdermal treatment since they are able to transmit larger quantities of active compounds to the deeper parts of the skin. By creating an “osmotic gradient,” transferosomes enter the SC through the intracellular or the transcellular pathway. These carriers encapsulate both hydrophobic and hydrophilic molecules. This is advantageous for the simultaneous delivery of multiple drugs and phytochemical agents into the systemic circulation. Electron microscopy images have revealed that

the morphology of transferosomes is highly irregular but the carriers often appear oval shaped. Ultra-flexible LNPs can aid in the transfer of large molecules through the skin.

Transferosomes on the other hand, can deliver both high and low molecular weight drugs transdermally. Furthermore, they can accommodate drug molecules with variety of solubilities and is appropriate for regulated and targeted drug delivery. These ultra-flexible LNPs enhance the penetration through the skin barrier by overcoming the limitations presented by the solid LNPs and liposomes, provided they are applied in a non-occluded formulation. Deformable liposomes transdermal delivery was compared to ethosomes by Elsayed et al. ketotifen as a model drug; both formulations were prepared by film hydration method. Their results suggest that the deformable liposomes increased the permeation of ketotifen more than ethosomes formulation. Furthermore, deformable liposomes were able to enhance the permeation of both the entrapped and free ketotifen. Transferosomes, as compared to solid LNPs and liposomes, have a hydrophilic surface property which better entrapment of hydrophilic molecules. Due to the increased elasticity and surface hydrophilicity, the vesicles have additional stability by avoiding agglomeration and fusion under osmotic stress. These stability issues, however, are commonly experienced with conventional liposomes.

FORMULATION OF CURCUMIN LOADED TRANSFEROSOMES METHOD OF PREPARATION

A. Thin film hydration technique is employed for the preparation of transferosomes which comprised of three steps

1. A thin film is prepared from the mixture of vesicles forming ingredients that is phospholipids and surfactant by dissolving in volatile organic solvent (chloroform methanol). Organic solvent is then evaporated above the lipid transition temperature (room temp. for pure PC vesicles, or 50°C for dipalmitoyl phosphatidyl choline) using rotary evaporator. Final traces of solvent were removed under vacuum for overnight.
2. A prepared thin film is hydrated with buffer (pH 6.5) by rotation at 60 rpm for 1 hr at the corresponding temperature. The resulting vesicles were swollen for 2 hr at room temperature. 3. To prepare small vesicles, resulting vesicles were sonicated at room temperature or 50°C for 30 min. using a bath sonicator or probe sonicated at 4°C for 30 min. The sonicated vesicles were homogenized by manual extrusion 10 times through a sandwich of 200 and 100 nm polycarbonate membranes.

B. Modified hand shaking, lipid film hydration technique is also founded for the preparation of transferosomes which comprised following steps

1. Drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent.
2. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minutes at corresponding temperature. The transferosome suspension further hydrated up to 1 hour at 2-8°C

CHARACTERIZATION OF TRANSFEROSOMES (22)

1. Vesicle size distribution and zeta potential-Vesicle size, size distribution and zeta potential were determined by Dynamic Light Scattering system by Malvern Zeta sizer.

2. Vesicle morphology- Vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering (DLS) method. Samples were prepared in distilled water, filtered through a 0.2 mm membrane filter and diluted with filtered saline and then size measurement done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Transferosomes vesicles can be visualized by TEM, phase contrast microscopy, etc. The stability of vesicle can be determined by assessing the size and structure of vesicles over time. Mean size is measured by DLS and structural changes are observed by TEM.

3. No. of vesicles per cubic mm- This is an important parameter for optimizing the composition and other process variables. Non sonicated Transferosome formulations are diluted five times with 0.9% sodium chloride solution. Haemocytometer and optical microscope can then be used for further study. The Transferosomes in 80 small squares are counted and calculated using the following formula:

Total number of Transferosomes per cubic mm = (Total number of Transferosomes counted × dilution factor × 4000) / Total number of squares counted.

4.Entrapment efficiency-The entrapment efficiency is expressed as the percentage entrapment of the drug added. Entrapment efficiency was determined by first separation of the un-entrapped drug by use of mini-column centrifugation method. After centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol]. The entrapment efficiency is expressed as: Entrapment efficiency = (Amount entrapped / Total amount added) ×100

5. Drug content- The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) method using a UV detector, column oven,

auto sample, pump and computerized analysis program depending upon the analytical method of the pharmacopoeial drug.

6. Turbidity measurement- Turbidity of drug in aqueous solution can be measured using nephelometer. www.wjpps.com Vol 5, Issue 10, 2016. 443 Solanki et al. World Journal of Pharmacy and Pharmaceutical Sciences

7. Degree of deformability or permeability measurement- In the case of transferosomes, the permeability study is one of the important and unique parameter for characterization. The deformability study is done against the pure water as standard. Transferosomes preparation is passed through a large number of pores of known size (through a sandwich of different micro porous filters, with pore diameter between 50 nm and 400 nm, depending on the starting transferosomes suspension). Particle size and size distributions are noted after each pass by dynamic light scattering (DLS) measurements.

8. Penetration ability- Penetration ability of Transferosomes can be evaluated using fluorescence microscopy.

9. Occlusion effect- Occlusion of skin is considered to be helpful for permeation of drug in case of traditional topical preparations. But the same proves to be detrimental for elastic vesicles. Hydrotaxis (movement in the direction) of water is the major driving force for permeation of vesicles through the skin, from its relatively dry surface to water rich deeper regions. Occlusion affects hydration forces as it prevents evaporation of water from skin.

10. Surface charge and charge density-Surface charge and charge density of Transferosomes can be determined using zeta sizer.

11. In-vitro drug release- In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in vitro studies are used to optimize the formulation before more expensive in vivo studies are performed. For determining drug release, transferosomes suspension is incubated at 32^0C and samples are taken at different times and the free drug is separated by mini column centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

12. In-vitro Skin permeation Studies -Modified Franz diffusion cell with a receiver compartment volume of 50ml and effective diffusion area of 2.50 cm2 was used for this study. In vitro drug study was performed by using goat skin in phosphate buffer solution (pH 7.4). Fresh Abdominal skin of goat were collected from slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed and the skin was hydrated in normal saline solution. The adipose tissue layer of the skin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 0-40˚C. To perform skin permeation study, treated skin was mounted horizontally on the receptor compartment with the stratum corneum side facing upwards towards the donor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2.50cm2 and capacity of receptor compartment was 50ml. The receptor compartment was filled with 50ml of phosphate buffer (pH 7.4) saline maintained at 37 ± 0.5˚C and stirred by a magnetic bar at 100RPM. Formulation (equivalent to 10mg drug) was placed on the skin and the top of the diffusion cell was covered.

13. Physical stability- The initial percentage of the drug entrapped in the formulation was determined and were stored in sealed glass ampoules. The ampoules were placed at 4 ± 20C months. Samples from each ampoule were analyzed after 30 days to determine drug leakage. Percent drug lose was calculated by keeping the initial entrapment of drug as 100%.

IN -VITRO AND *EX-VIVO* DRUG RELEASE STUDIES

Wistar rats of about 250–300 g were obtained from the animal breeding center, The dorsal hair of the rats was carefully removed using a suitable depilatory cream then animals were killed using ketamine overdosage. Prior to the permeation study, the skin samples were hydrated in phosphate buffer (pH 6.8) at 4 °C overnight in a refrigerator.

Curcumin Skin Permeation Study

In vitro skin permeation study of curcumin across male Wistar rat skin was performed using modified Franz diffusion cell constructed in our lab. The upper epidermis with the dermis portion of the skin was carefully separated and mounted on the diffusion cell "with surface area of 4.91 cm^2" where the epidermis upside was facing the formulations to be permeated and the dermis portion was facing the acceptor buffer medium. The sink medium was composed of 100 mL phosphate buffer (pH 5.5): methanol 1:1 ratio and was maintained at constant temperature (37 ± 0.5 °C) and the cell was covered to minimize methanol vaporization. The niosomal formulations or the curcumin suspension were applied to the donor area. Samples of 1 mL were taken over a period of 24 h at different time intervals of 0.5, 1, 2, 4, 6, 8, and 24 h. The aliquots were replaced by fresh medium to maintain the sink conditions. The drug concentration was then determined using UV spectrophotometer at 450 nm. At the end of the permeation experiment the applied skin area was separated and

washed twice with distilled water. The rat skin was homogenized into fine pieces and extracted using methanol by sonication. The curcumin extract was then filtered using 0.45-µm filter and was analyzed spectrophotometrically at 450 nm. Methanol filtrate of homogenized rat skin and sonicated with methanol was used as blank

Drug Release Kinetics: The permeation kinetics of curcumin was examined using kinetic models in which the drug amount (Q) is plotted against time (t) and Q_0 is the initial drug concentration. The kinetic models to be followed are as following:

Zero order equation: $Q = Q_0 - k_0 t$

where, a plot of (Q) against time (t) will be linear, if curcumin release obeys the zero order equation.

First order equation: $\text{Log } Q = \log Q_0 - k_1 t/2.303$

A linear plot of Log (Q) against time (t) will be obtained, if the curcumin release obeys the first order equation.

Higuchi Kinetics equation: $Q = K_H t^{0.5}$

A linear plot of (Q) against the square root of time ($t^{0.5}$) will be obtained if the curcumin release obeys the Higuchi equation.

Korsmeyer-Peppas release model equation: $ft = K\ t^n$

where the fraction of curcumin permeation is (ft) at time (t), (k) is the permeation rate constant and (*n*) is the permeation rate exponent.

A linear plot of Log (% cumulative amount) against Log (time) will be obtained if curcumin permeation obeys the Korsmeyer-Peppas model equation.(26)

THERAPEUTIC APPLICATIONS OF CURCUMIN TRANSFEROSOMES (23-26)

Curcumin-loaded transferosomes have gained significant attention in recent years due to their ability to enhance the therapeutic efficacy of curcumin in inflammatory conditions and wound healing. Curcumin, the active compound derived from turmeric (*Curcuma longa*), possesses strong anti-inflammatory, antioxidant, and antimicrobial properties. However, its poor solubility in water, low stability, and limited systemic bioavailability significantly restrict its clinical applications. To address these challenges, curcumin is encapsulated into transferosomes, which are ultra-deformable lipid vesicles designed to enhance drug penetration through the skin and biological membranes.

In terms of anti-inflammatory effects, curcumin-loaded transferosomes have demonstrated superior efficacy compared to free curcumin. By suppressing these signaling pathways, curcumin reduces the production of inflammatory cytokines, thereby alleviating inflammation at the cellular and tissue levels. The transferosomal delivery system further enhances these effects by allowing the curcumin to penetrate deeper layers of the skin and inflamed tissue, providing a targeted and sustained release. This leads to a more effective and prolonged anti-inflammatory response with reduced systemic side effects. In the context of wound healing, curcumin-loaded transferosomes play a vital role across all stages of the healing process.

This makes curcumin-loaded transferosomes a promising non-invasive delivery system for managing chronic wounds, burns, diabetic ulcers, and other skin injuries, where both anti-inflammatory and regenerative actions are crucial. For thousands of years, turmeric has been used medicinally as a treatment for inflammatory disorders, particularly in the Ayurvedic tradition Early research, using cell cultures and mouse models, has focused on its established antioxidant and anti-inflammatory properties, as well as its possible anticarcinogenic capacities. Curcumin is believed to act pleiotropically on multiple molecular and cellular pathways, and this could explain its potential to combat multifactorial diseases such as cancer.

Review of evidence about the clinical validity of curcumin is complex because its therapeutic rationale has stirred up controversy. Despite the fact that in 2017, there were already over 15,000 manuscripts published examining the biological properties of curcumin, the results of this large pool of research have been mainly disregarded since curcumin's beneficial effects have not yet been proven in a randomized placebo-controlled clinical trial.

Oxygen-derived free radicals are generated as a normal part of the cellular aerobic process and one category of these, reactive oxygen species (ROS), serves as a necessary intermediate in many enzyme reactions. But despite this helpful role and because of their reactive nature, increased levels of ROS can be highly toxic to normal cells, damaging and interfering with the repair mechanisms of their DNA. In vitro studies have demonstrated curcumin's ability to impair the generation of ROS, preventing, among other things, its activation of the oncogenic effects of activator protein-1 (AP-1), a transcription factor that controls a number of cellular processes including proliferation and apoptosis .

As far as anti-inflammation is concerned, topical curcumin has historically been used to reduce wound-healing time and reduce scarring, as well as serving as an antimicrobial agent. Curcumin's anti-inflammatory actions are most likely linked to its ability to inhibit the expression of specific proinflammatory cytokines and enzymes, high levels of which have been shown to contribute to cancer development. For example, a pilot study of curcumin for women with obesity and a higher risk for breast cancer is currently seeking to determine if

different doses of curcumin will modulate proinflammatory biomarkers in this population in a randomized clinical trial. Inflammation in the cancer micro-environment not only aids in the formation of tumours, but also contributes to their progression and metastasis.

Preclinical cancer research has indicated that curcumin hinders tumorigenesis in a number of cancer types by inhibiting cell proliferation, inducing apoptosis and preventing metastasis. In vitro and in vivo studies specific to breast cancer have explored curcumin's effect on a variety of pathways and cellular activities such as its inhibition of telomerase activity in the MCF-7 breast cancer cell line. It has an anti-proliferative effect on MDA-MB-231 and BT-483 breast cancer cell lines, in a time- and dose-dependent manner, by down-regulating the genes that induce NFκB, a type of transcription factor that influences cell proliferation and cell survival. The apoptotic influence of curcumin was also tested on tumour suppressor and hormone receptor dysregulation in breast cancer cells, to positive results. Curcumin has been evaluated in combination with other phytonutrients as well, both *in vitro* and *in vivo*. This would enable us to create an innovative form of safe, natural, and "wearable" breast cancer prevention for testing in future clinical trials.

ADVANTAGES AND LIMITATIONS OF TRANSFEROSOMAL APPROACH

The transferosomal approach offers several significant advantages in drug delivery, making it a promising system particularly for transdermal and mucosal applications. One of the primary benefits is its enhanced penetration capability. Transferosomes are highly deformable vesicles composed of phospholipids and surfactants (edge activators), allowing them to pass through skin pores much smaller than their own diameter. This ultra-deformability enables deeper penetration into tissues, significantly improving drug absorption and therapeutic effectiveness. Additionally, transferosomes can enhance the bioavailability of drugs, especially those that are poorly water-soluble or rapidly metabolized, by avoiding the first-pass metabolism often encountered in oral delivery. They also provide a non-invasive delivery route, which is particularly advantageous for chronic disease management and for patients who prefer to avoid injections, such as children and the elderly. Moreover, transferosomes can offer targeted drug delivery to specific tissues, reducing systemic side effects and improving treatment efficiency. Their vesicular structure helps protect labile drugs like peptides and proteins from enzymatic degradation, thereby preserving their activity. Furthermore, these systems can provide a controlled and sustained release, which improves patient compliance by reducing the frequency of administration. Composed of biocompatible materials, transferosomes are generally well-tolerated and pose a low risk of toxicity. However, the transferosomal system is not without its limitations. One major concern is formulation and physical stability. Transferosomes are sensitive structures that may undergo aggregation, fusion, or leakage of the encapsulated drug over time, leading to reduced efficacy. Their preparation is technically complex, requiring precise control over the composition and process conditions, which can make the development process labour intensive. Moreover, the cost of production is relatively high compared to conventional delivery systems due to the need for sp

ecialized equipment and materials. These formulations often have strict storage requirements, sometimes needing refrigeration to maintain their structural integrity and prevent degradation. Another limitation is the restricted drug loading capacity; only drugs with certain physicochemical properties (like amphiphilic nature) can be efficiently incorporated into the vesicles. Additionally, scaling up the production process from laboratory to industrial scale can present challenges, especially in achieving consistent quality across batches. Finally, the surfactants used as edge activators may cause skin irritation or hypersensitivity reactions, particularly in individuals with sensitive skin. Despite these limitations, the advantages of transferosomes often outweigh the drawbacks, especially when tailored for specific therapeutic applications.

II. FUTURE PERSPECTIVES AND CLINICAL IMPLICATIONS

Lipid nanoparticles (LNPs) are biocompatible drug delivery systems that have found numerous applications in medicine. Their versatile nature enables the encapsulation and targeting of various types of medically relevant molecular cargo, including oligonucleotides, proteins, and small molecules for the treatment of diseases, such as cancer. Cancers that form solid tumours are particularly relevant for LNP-based therapeutics due to the enhanced permeation and retention effect that allows nanoparticles to accumulate within the tumour tissue. Additionally, LNPs can be formulated for both locoregional and systemic delivery depending on the tumour type and stage. To date, LNPs have been used extensively in the clinic to reduce systemic toxicity and improve outcomes in cancer patients by encapsulating chemotherapeutic drugs. Next-generation lipid nanoparticles are currently being developed to expand their use in gene therapy and immunotherapy, as well as to enable the co-encapsulation of multiple drugs in a single system.

Other developments include the design of targeted LNPs to specific cells and tissues, and triggerable release systems to control cargo delivery at the tumour site. It has realized significant success in the development of safer chemotherapy formulations, challenges remain to improve the overall efficacy of LNP formulations. One of the most important limitations, especially for targeted delivery of LNPs, is the inconsistent

delivery and therapeutic efficacy in human trials. The striking discrepancy between the success of nanotherapeutics in preclinical studies compared with clinical trials underlines significant drawbacks in the use of current quantitative methods, including animal tumours models, to study LNP targeting in complex tissue environments. Ectopic allogeneic or xenogeneic mouse models are not always representative of human tumours, especially when it comes to assessing the biodistribution of nanoparticles in subcutaneously established tumours due to the lack of characterization of the vascular morphology at different time points, as well as significant structural and functional differences with respect to orthotopic/ectopic mouse models and human cancers. The use of more representative models that mimic the cellular heterogeneity and TME features of human cancers should be considered especially for metastatic tumours. For instance, the recent development of prime editing technology may allow the development of cancer mouse models that are more representative of human cancers by recapitulating de facto driver mutations present in patients.

A thorough comparison between current animal model TME and human TME vasculature should be undertaken to identify relevant features or biomarkers that may be more predictive of clinical biodistribution and response rates, since nanoparticle transport into the TME appears to be highly dependent on the cancer type and anatomical location of the tumour, which can vary widely across species. Alternatively, tumour-on-a-chip models are currently being developed to help bridge the gap between preclinical and clinical discrepancies by helping with the development of more predictable nanoparticle targeting and transport approaches. The molecular basis for the differential accumulation of nanoparticles in some tumours, but not others, remains to be elucidated.

III. CONCLUSION:

Curcumin, while pharmacologically potent, has long faced the barrier of poor oral bioavailability, severely restricting its full clinical potential. The incorporation of curcumin into transferosomal systems offers a transformative approach to this challenge. Transferosomes, due to their high deformability, enable better penetration through biological membranes, prolonged systemic circulation, and targeted delivery, all of which significantly enhance the therapeutic performance of curcumin. Current research has demonstrated that curcumin-loaded transferosomes not only improve drug solubility and stability but also amplify anti-inflammatory, antioxidant, and wound healing effects in various preclinical and clinical models. This review concludes that transferosomes represent a promising frontier in nanomedicine for curcumin delivery. However, for widespread clinical acceptance, further investigations into long-term safety, large-scale production, and regulatory approvals are essential. Continued interdisciplinary efforts in formulation development, toxicological evaluation, and clinical translation will be crucial to harness the full therapeutic potential of curcumin via transferosomal delivery systems.

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