6-Shogaol-Loaded Transferosomal Transdermal Patches

Extraction, Formulation, and Evaluation for Targeted Anticancer Therapy

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DeepScience

Published, marketed, and distributed by:

Deep Science Publishing, 2025
USA | UK | India | Turkey
Reg. No. MH-33-0523625
www.deepscienceresearch.com
editor@deepscienceresearch.com
WhatsApp: +91 7977171947

ISBN: 978-93-7185-639-3

E-ISBN: 978-93-7185-806-9

https://doi.org/10.70593/978-93-7185-806-9

Citation: Panda, S., & Ngangbam, A. K. (2025). *6-Shogaol-Loaded Transferosomal Transdermal Patches: Extraction, Formulation, and Evaluation for Targeted Anticancer Therapy*. Deep Science Publishing. https://doi.org/10.70593/978-93-7185-806-9

Preface

6-Shogaol, a bioactive ginger-derived phenolic compound with reported anticancer activity, suffers from poor aqueous solubility and limited bioavailability that hinder systemic delivery. This study aimed to formulate and evaluate 6-Shogaol-loaded transferosomes and incorporate them into transdermal patches to achieve sustained, targeted dermal delivery for anticancer therapy. Transferosomes were prepared by the thin-film hydration method using phospholipids and edge-activators, and optimized for vesicle size, polydispersity, zeta potential and entrapment efficiency. Optimized vesicles were characterized by dynamic light scattering and transmission electron microscopy, then loaded into a polymeric matrix by solvent-casting to produce transdermal patches. The prepared transdermal patches underwent assessment for their physicochemical characteristics, including parameters such as thickness, weight consistency, and folding durability, tensile strength, surface pH), drug content and in vitro release. Ex vivo permeation across excised mammalian skin and skin retention studies were performed to assess transdermal delivery potential. In vitro cytotoxicity and cell-viability assays on representative cancer cell lines were used to compare the anticancer efficacy of 6-Shogaol in transferosomal patches versus free drug. Stability studies under accelerated conditions evaluated formulation integrity. Results demonstrated that transferosomes provided high encapsulation of 6-Shogaol, nanosized uniform vesicles, and improved drug deposition in skin with sustained release from the patch matrix. Ex vivo permeation and cytotoxicity data indicated enhanced transdermal delivery and greater anticancer activity compared with non-encapsulated drug. The developed 6-Shogaol transferosomal transdermal patch shows promise as a non-invasive platform for sustained, targeted anticancer therapy and warrants further preclinical investigation.

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Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-806-9

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Chapter 1: Introduction

1.1 6-Shogoal

6-shogaol has been classified as BCS II drug due to the low solubility and the rapid absorption in human after administration [8]. These disadvantages might impede the clinical potential of the drug (pH 7.4) −34.40 ± 2.61 μg/mL. Hence, a proper method to increase its water solubility and bioavailability is required in a short term. Over the past few years, however, nanoparticle-based drug delivery systems have received significant attention to overcome this limitation.

Benefits of 6-Shogaol – Due to its widespread use as a food seasoning, Ginger (Zingiber officinale Roscoe) is placed among the several spices consumed globally. Ginger has been utilized as a traditional herbal medicine in Asia, primarily in China, to treat different types of sickness, such as nausea, gastrointestinal discomforts, headache and cold [2]. Some researchers have reported about 1–3% of volatile oils and a set of pungent substances, which have several pharmacological effects, elucidated in ginger [3]. Since 6-shogaol [1(-4-hydroxy methoxy phenyl-4-decenone, Fig. 2] is a phenolic alkanone characterized by an odorous and bitter taste [3]. It has been extensively studied to identify its phytochemicals and pharmacological activities around the globe in the last two decades due to its high content of phytochemicals with pharmacological properties. The biological properties of 6-shogaol have been well established, such as antitumor [5], antioxidation [6] and antiinflammation [7]. Park et al. Specifically, [8] demonstrated that 6-shogaol is able to protect dopaminergic cells from MPP+ and MPTP toxicity in a Parkinson's disease model through the inhibition of microglia-mediated neuroinflammatory responses. In-vitro and in-vivo studies of dopaminergic cells in PD model also showed that 6-shogaol has neuro-protective effect. In addition, 6-shogaol was shown to have blood vessel vasodilating [9], antitussive [10] and antihepatotoxic [11] activities.

6-shogaol is lipophilic with poor solubility and limited evolving in-vivo due to its partitioning of hydration solution.Particularly, low 6-shogaol solubility has been reported in four simulated media namely hydrochloric acid (HCl) solution (pH 1.2)

−24.03 ± 1.64 μg/mL, double-distilled water (DDW) −31.26 ± 3.11 μg/mL, phosphate buffer solution (PBS, pH 6.8) −29.08 ± 2.82 μg/mL and PBS.

1. Anti-inflammatory: Reduces inflammation and pain.

2. Antioxidant: Protects against oxidative stress and cell

3. Anti-cancer: Exhibits anti-tumor and anti-proliferative effects.

4. Neuroprotective: May help prevent neurodegenerative diseases.

5. Cardiovascular health: May help lower cholesterol and triglycerides.

6. Anti-diabetic: May improve insulin sensitivity and glucose metabolism.

7. Gastrointestinal health: May help alleviate nausea and digestive issues.

8. Antimicrobial: Exhibits antibacterial, antiviral, and antifungal properties.

1.1.1 Effects of 6-Shogaol

1. Gastrointestinal upset: Some people may experience nausea, an upset stomach or diarrhoea.
2. Allergic reactions: Very rarely, some people may experience an allergic rash or high irritation.
3. Interaction with medications: Blood thinners or diabetes or blood pressure medications.
4. Pregnancy and breastfeeding: There is minimal research; consult a health care provider before taking.
5. High doses: May cause stomach discomfort, diarrhea or abdominal pain at higher doses.
6. Long-term use: Limited studies available; consult healthcare provider for long term usage
7. Individual tolerance: Might work differently in other individuals, as possible a more effective drug or one that may have less side effects.

1.1.2. Drug Profile

The molecular formula for 6-Shogaol is: $C_{17}H_{24}O_3$

The molecular weight of 6-Shogaol is**:** **274.38 g/mol**

1.1.3. Advantage of 6-Shogoal:

1.1.3.1. Potent Antioxidant Activity

Neutralizes free radicals more effectively than 6-gingerol.
Protects cells from oxidative stress-related damage.

1.1.3.2. Strong Anti-inflammatory Properties

Inhibits pro-inflammatory cytokines such as TNF-α and IL-6.
Blocks key signaling pathways like NF-κB and COX-2.

1.1.3.3. Anti-cancer Effects

Induces apoptosis in various cancer cell lines (e.g., breast, colon, prostate).
Inhibits tumor growth, metastasis, and angiogenesis.
Affects multiple pathways, including p53, Bcl-2, and caspase-dependent mechanisms.

1.1.3.4. Neuroprotective Activity

Protects against neurodegenerative diseases like Alzheimer's and Parkinson's.
Reduces neuroinflammation and supports neuronal survival.

1.1.3.5. Anti-diabetic Effects

Enhances the body's responsiveness to insulin.
Reduces circulating blood sugar concentrations.
Safeguards pancreatic β-cells against oxidative stress–induced damage.

1.1.3.6. Anti-obesity and Metabolic Syndrome Benefits

Enhances lipid metabolism.
Suppresses adipogenesis and promotes lipolysis.
Reduces body weight and improves lipid profile in animal studies.

1.1.3.7. Gastroprotective Effects

Reduces nausea, vomiting, and gastric ulcers.
Enhances gastrointestinal motility and reduces inflammation in the gut.

1.1.3.8. Antimicrobial Properties

Exhibits antibacterial, antifungal, and antiviral activities.
Effective against *H. pylori*, *E. coli*, and *Candida* species.

1.1.3.9. Enhanced Stability and Activity Compared to Other Ginger Constituents

6-shogaol is more stable and more bioactive than 6-gingerol under acidic or thermal conditions, making it more effective in processed formulations.

1.1.4. Disadvantage of 6-Shogoal:

1. Poor Water Solubility

6-shogaol is lipophilic and has low aqueous solubility, which limits its bioavailability when administered orally.

2. Limited Bioavailability

It undergoes rapid metabolism in the liver and gastrointestinal tract, resulting in low systemic absorption and limited therapeutic efficacy in vivo.

3. Gastrointestinal Irritation

At high doses, it may cause irritation to the gastric mucosa, potentially leading to nausea or stomach discomfort.

4. Cytotoxicity at High Doses

While beneficial at lower concentrations, 6-shogaol may exhibit cytotoxic effects on normal cells at higher concentrations, limiting its safety margin.

5. Instability in Certain Conditions

6-shogaol can degrade or transform under certain pH or thermal conditions, potentially affecting formulation stability.

6. Insufficient Clinical Evidence

Most studies are preclinical (in vitro or animal models). There is a lack of large-scale human clinical trials, limiting its application in mainstream medicine.

7. Possible Drug Interactions

Due to its impact on cytochrome P450 enzymes, it may interfere with the metabolism of other drugs, leading to potential drug-drug interactions.

8. Taste and Pungency

It has a strong pungent taste, which . To our knowledge, this is the first review to thoroughly summarize the anticancer mechanisms of 6-shogaol, with the goal of offering a theoretical foundation and practical insights for future research and clinical development.

6-shogaol works as a potential anticancer agent based on extensive in vitro (cell culture) and in vivo (animal model) studies. It is a major bioactive compound derived from dried ginger (Zingiber officinale) and is structurally a dehydrated form of 6-gingerol, which makes it more chemically stable and pharmacologically potent.

1.1.5. How 6-Shogaol Works as an Anticancer Drug

1. Induces Apoptosis (Cancer Cell Death)

Activates caspase-dependent pathways, especially caspase-3 and -9.

Regulates mitochondrial membrane potential and promotes cytochrome c release.

Modifies Levels of Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic) protein expression.

2. Inhibits Cancer Cell Proliferation

Causes cell cycle arrest, especially at G2/M phase, preventing cancer cells from multiplying.

3. Suppresses Inflammatory Pathways

Inhibits NF-κB and STAT3 signaling pathways, both of which are often upregulated in cancer cells.

4. Increases Oxidative Stress in Tumor Cells

Promotes ROS (reactive oxygen species) accumulation, leading to oxidative damage and cell death.

5. Blocks Tumor Angiogenesis and Metastasis

Reduces vascular endothelial growth factor (VEGF) expression.

Inhibits matrix metalloproteinases (MMP-2, MMP-9) involved in invasion and metastasis.

1.1.6. Cancer Types Studied

6-shogaol has shown promising effects against:

Breast cancer (especially triple-negative types)
Colon/colorectal cancer, Lung cancer, Liver (hepatocellular carcinoma), Prostate cancer, Leukemia, Cervical cancer

Challenges

- Low bioavailability and poor water solubility limit its direct use.
- Rapid metabolism and elimination in the body.
- To overcome this, researchers are exploring novel drug delivery systems like:
- Transferosomes, Nanoparticles, Liposomes, Solid lipid nanoparticles
- 6-Shogaol exhibits multi-targeted anticancer effects through apoptosis induction, anti-inflammatory action, and inhibition of proliferation and metastasis. Though it is not yet an approved anticancer drug, it is a strong candidate for further pharmaceutical development.

1.1.7. ANTI- CANCER ACTION OF GINGER

Among various spices and traditional medicinal plants, ginger (Zingiber officinale), commonly consumed worldwide, has been documented to exhibit substantial anti-cancer activity. Pharmacologically, its bioactive constituents, especially gingerols, shogaols, paradols and zingerone have been accounted for as anti-oxidant, anti-inflammatory and anticancer agents.

The antioxidant property of ginger is one of the main mechanisms behind the cancer fighting abilities. Reactive oxygen species cause DNA, proteins and lipids destruction that results in initiation and development of cancer as well as the oxide stress involves in the same pathways [22]. The 6-gingerol and 6-shogaols in ginger curb free radicals, thereby boost Function of intrinsic antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase that help to reduce oxidative DNA damage and prevent mutagenesis

Another critical anticancer mechanism of ginger is the inhibition of cancer cell proliferation and metastasis. Ginger compounds suppress cell cycle progression by downregulating cyclins and cyclin-dependent kinases (CDKs). They also inhibit matrix metalloproteinases (MMPs), enzymes involved in facilitating cancer cell invasion and metastatic progression. Additionally, ginger can inhibit angiogenesis (formation of new blood vessels), which is essential for tumor growth and metastasis, by downregulating vascular endothelial growth factor (VEGF).

Several in vitro and in vivo studies support the efficacy of ginger in various types of cancer, including colorectal, breast, ovarian, liver, pancreatic, and prostate cancers. For instance, in colon cancer models, 6-gingerol has been shown to inhibit tumor growth and suppress β-catenin signaling. In breast cancer, gingerol and shogaol reduce the viability of cancer cells and enhance the efficacy of chemotherapeutic agents like paclitaxel and doxorubicin, suggesting a potential role in combination therapy.

1.2. TRANSFEROSOME

Transferosomes are a type of advanced drug delivery system designed to enhance the penetration of therapeutic agents through the skin or other barriers. They are essentially elastic, lipid-based vesicles that are composed of a phospholipid bilayer, often combined with surfactants and/or edge activators. This contributes to transferosomes being more pliant and deformable than standard liposomes, thereby facilitating their passage across the stratum corneum of the skin, which represents a significant hurdle in effective drug delivery.

This characteristic is an advantage for transferring, leading to their application in transdermal drug delivery systems, thereby providing non-invasive administration of drugs and patient compliance.

1.2.1. Advantages of Transferosomes:

1. Enhanced skin permeation: Transferosomes are able to go through the deep layers of the before mentioned, allowing a better conveyance of key components.
2. Improved bioavailability: Transferosomes can improve the bioavailability of drugs, making them more powerful.
3. Targeted delivery: Transferosomes can be engineered to deliver the drug selectively to target cells or tissues, limiting side effects.
4. Flexibility: Transferosomes can be utilized via topical, transdermal and oral routes
5. Biocompatibility: As Transferosomes are natural lipid vesicles, therefore biocompatible with no toxicity.
6. Stability**:** Transferosomes enhance the stability of drugs.

1.2.2. Disadvantages of Transferosomes:

1. Complex preparation process: Preparing transferosomes is a time-taking and complex process.
2. Scalability issues: It can be difficult to scale up the production of transferosomes.
3. High cost: The technology behind the transferosome can be expensive.

Size and distribution control only to a certain extent: It is also difficult to control the size and size distribution of transferosomes.

4. Limited control over size and distribution: Although transferosomes are biocompatible, toxicity may arise particularly with larger high doses. Famously known for use of erbB vaccines broadcasted by the worldwide media in a truncated fashion at the beginning for emergency purposes.
5. Potential toxicity: Since transferosomes are a newer technology, they could possibly face regulatory challenges.
6. Regulatory challenges: There is a lack of complete understanding of the mechanisms that are at play during transferim as well, which could make their usage less than ideal.

1.2.3. Why 6-shogaol as transferosome transdermal patch?

Liposomes and Niosomes Over the past few decades, vesicles based carrier systems or liposomes have been a focus for transdermal drug delivery while nanostructured materials like nioses suffer little after research accent. The structural features of these vesicles have been studied and some have been used as drug delivery devices by using their internal cavities or by modifying them for targeted cell-type-specific delivery.
Their success in transdermal drug delivery originates from their ability to serve as a carrier for the transport of encapsulated drug through the skin barrier, and also as a penetration enhancer with their special composition. Moreover, these vesicles may also serve as depots for transdermal delivery systems and the controlled release of bioactive substances in topical formulations from which they undergo “diffusion-oxidation” processes to make the therapeutic compounds readily available or as rate-limiting factors that control drug absorption after the systemic availability.Vesicles have long been recognized for their roles in intercellular communication and the transport of substances within biological systems.
Liposomes and niosomes are examples of the rigid vesicles and transferosomes and ethosomes are classified under elastic liposomal systems.

1.2.4. Advantages of Transfersomes as Vesicle-Based Transdermal Drug Delivery Systems [2,36,56,57]:

Trnasfersomes have both hydrophillic and lipophilic portions, forming an effectively flexible carrier system capable of delivering variety of therapeutics with diverse solubility.
Transfersomes are up to 5–10 times smaller than their diameter, making them highly deformable and flexible enough to squeeze through tight spaces in the skin barrier.
Due to their great deformability, this vesicle can be used as a vehicle of drugs through skin without large lost intact vesicles, which is making them more useful for the local and systemic therapies.

Transfersomes were shown as effective encapsulants for different bioactive molecules of diverse size, structure, molecular weight, and polarity.

These carriers are largely composed of natural phospholipids and edge activators (EAs) that are non-toxic, bio-compatible and biodegradable, as well as their capabilities for accommodating a broad spectrum of therapeutic agents including proteins, peptides, insulin, corticosteroids, interferons, anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), anticancer agents such plant compounds in addition to several herbal extracts.

Transferosomes are highly effective carriers for controlled and extended drug delivery to maintain the stable therapeutic effect during prolonged period. They enhance transdermal drug absorption and improve targeted delivery to specific sites. By bypassing first-pass metabolism—a limitation in oral drug administration—they improve the drug's bioavailability.

Transfersomes can reduce adverse drug reactions and protect drugs from premature degradation, making them particularly useful for drugs with short half-lives. In many formulations, especially for lipophilic drugs, transfersomes achieve high entrapment efficiencies (EE), often reaching or exceeding 90%. For example, formulations containing diclofenac diethylamine (DDEA) and curcumin (CRM) demonstrated EE values above 90%. However, EE may vary depending on formulation factors; higher lipid concentrations tend to increase EE, whereas excessive surfactant concentrations can reduce it due to micelle formation.

Literature suggests that incorporating surfactants with a low hydrophilic-lipophilic balance (HLB) can enhance EE for lipophilic drugs.Transfersomes are developed using pharmaceutically acceptable materials and standard manufacturing methods, although their formulations need case-by-case optimization.The production process of transfersomes is relatively straightforward, making it feasible for scale-up.

1.2.5. Limitations of Transfersomes:

One major drawback of transfersomes is their susceptibility to oxidative degradation, which compromises their chemical stability.

However, this can be mitigated by degassing the aqueous phase and purging with inert gases such as nitrogen or argon [59].

Additionally, storing them at low temperatures and protecting them from light can enhance stability [60]. Post-preparation techniques like freeze-drying or spray-drying can further improve their shelf life [61].

Another limitation is the difficulty in obtaining pure natural phospholipids, which can impact formulation quality.

To address this, synthetic phospholipids are sometimes used as alternatives [62]. Transfersomal systems can be costly due to the high price of lipid excipients and the specialized equipment required for production.

Nonetheless, phosphatidylcholine is frequently used as it is more affordable than other lipid components [6].

1.2.6. Mechanism of Action:

Vesicles are colloidal systems characterized by an aqueous core surrounded by concentric bilayers of amphiphilic molecules. These These systems are extensively utilized for In drug delivery, hydrophilic drugs are housed in the aqueous core, while hydrophobic drugs reside within the lipid bilayer [47]. Transfersomes, a novel class of ultra-flexible vesicles, can self-optimize and easily penetrate the skin barrier due to their remarkable membrane deformability, hydrophilic nature, and ability to maintain structural integrity during transit (Figure .

Transfersomes are capable of penetrating intact skin effectively, especially when applied under nonocclusive conditions. This specific condition is essential to initiate a trans epidermal osmotic gradient, facilitating their permeation [1,54]. As highlighted in the research by Cevc and Blume, the main driving force for transfersome movement—termed hydrotaxis or xerophobia—refers to their moisture-seeking behavior. This phenomenon occurs as the water from the transfersomal formulation evaporates post-application, prompting the vesicles to move toward the more hydrated inner layers of the skin [65].The resulting difference in water activity across the skin surface generates a powerful osmotic gradient. This force acts upon the vesicles, causing the expansion of intercellular junctions—specifically low-resistance zones—resulting in the formation of transcutaneous channels about 20–30 nm wide. These channels enable the passage of the highly deformable, slim transfersomes through the skin, guided by the hydration gradient [23]. Additionally, the evaporation of water due to body heat contributes to the osmotic gradient, which acts as a driving mechanism for transporting therapeutic agents across the skin. This enhances delivery efficiency to target areas while minimizing systemic side effects [33].

Transfersomes outperform traditional liposomes in terms of skin permeation, although both share a bilayered structure that supports the encapsulation of lipophilic, hydrophilic, and amphiphilic drugs [53]. The main difference lies in the transfersomes' ultra-flexible, soft membranes, which are more adaptable than those of liposomes. The lipid bilayer's composition and structure allow the vesicles to be self-optimizing and self-regulating, giving them the ability to cross various physiological barriers efficiently.

Structurally, transfersomes consist of at least one amphiphilic component, such as soy or egg phosphatidylcholine, which forms the lipid bilayer [52,61]. They also contain 10–25% edge activators—commonly biocompatible surfactants like sodium cholate, sodium deoxycholate, Tween 20/60/80, Span 60/65/80, or dipotassium glycyrrhizinate—that enhance membrane flexibility and permeability [3,8,52,68,69]. In addition, 3–10% alcohol (usually ethanol or methanol) is included as a solvent, along with a hydrating medium such as water or phosphate-buffered saline (pH 6.5–7)

When placed in an aqueous medium, phospholipids spontaneously form flexible bilayers that enclose to create vesicles [7]. The edge activators, which are single-chain surfactants, integrate into the vesicle membrane, disrupting its stability to improve fluidity and elasticity [4,37,65,70]. The balance between surfactant concentration and phospholipid ratio is crucial for controlling vesicle flexibility and reducing the likelihood of vesicle rupture during skin penetration [71]. This design allows transfersomes to utilize the natural osmotic gradient across the epidermis when applied without occlusion [33,72]. Ultimately, their penetration efficiency is influenced by surfactant type and concentration, lipid composition, and the size, shape, and deformability of the vesicle.

1.3. Transdermal Drug Delivery System (TDDS):

While the oral route has traditionally been a widely used and effective method for drug administration, it also comes with limitations such as first-pass metabolism and degradation of drugs by enzymes or pH in the gastrointestinal (GI) tract. Although oral delivery offers several advantages, these drawbacks can impact drug efficacy.

The transdermal drug delivery market is projected to experience significant growth, reaching an estimated $95.57 billion by 2025.

One of the major challenges with oral and parenteral routes is the fluctuation in peak plasma drug concentrations, which can lead to overdosing and make it difficult to maintain therapeutic levels. In contrast, Transdermal Drug Delivery Systems (TDDS) offers a controlled and continuous drug release profile, improving systemic bioavailability and reducing plasma level-related side effects.

The non-invasive, easy-to-use design of transdermal systems and the infrequent dosage frequency, combined with the continuous controlled release of drug over a long period of time further increase patient compliance associated with this delivery system.

Transdermal patches were first approved by the FDA in the 1980s, with scopolamine and nicotine patches being approved in 1984. Hundreds of patches have since been researched and approved for applications including pain relief, contraception, hormone replacement, and analgesia, and patch development continues to broaden its utilization.

1.3.1. Advantages of TDDS:

- Avoidance of First-Pass Metabolism: TDDS bypass the liver's first-pass effect, improving drug bioavailability.
- Controlled and Sustained Release: Enables steady drug release over an extended period, maintaining consistent therapeutic levels.
- Improved Patient Compliance: Easy to use, non-invasive, and reduces dosing frequency, enhancing adherence.
- Reduced Side Effects: Stable plasma levels help minimize peaks that cause adverse effects.

- Non-Invasive and Painless: Eliminates pain and discomfort associated with injections.
- Bypass of Gastrointestinal Tract: Avoids issues like drug degradation by stomach acid or enzymes, and reduces GI irritation.
- Convenience: Patches are discreet, portable, and easy to apply or remove.
- Rapid Discontinuation: Drug delivery can be stopped immediately by removing the patch if adverse reactions occur.
- Suitable for Long-Term Therapy: Ideal for chronic conditions requiring continuous dosing.
- Useful for Patients with Swallowing Difficulties: Beneficial for pediatric, geriatric, or unconscious patients who cannot take oral medications.

1.3.2. Disadvantages of TDDS:

- Limited Drug Candidates:
- Only drugs with suitable molecular size, potency, and skin permeability can be delivered effectively.
- Skin Irritation and Allergic Reactions: Prolonged use of patches may cause redness, itching, or allergic dermatitis at the application site.
- Variable Absorption: Differences in skin condition, age, and site of application can lead to inconsistent drug absorption.
- Slow Onset of Action: Transdermal delivery may have a delayed onset compared to intravenous or oral routes.
- Potential for Dose Dumping: If the patch is damaged or improperly used, it can release too much drug at once, causing toxicity.
- Cost: Manufacturing and development of TDDS can be more expensive compared to traditional oral formulations.
- Limited Drug Load: The patch can only hold a finite amount of drug, which may not be suitable for drugs requiring high doses.
- Adhesion Issues: Patches may peel off due to sweating, movement, or skin oils, reducing effectiveness.
- Environmental Sensitivity: Exposure to heat or humidity can affect the drug release rate and patch stability.
- Unsuitable for Irritated or Damaged Skin: Application over broken or inflamed skin is contraindicated as it may enhance drug absorption unpredictably.

1.3.3. Types of Transdermal Patches

Transdermal patches represent sophisticated pharmaceutical Drug delivery systems intended to transport drugs across the skin and Reaching the body's systemic circulation. The design of patches differs based on their composition, drug release mechanism and permeation enhancer technology. Various forms of transdermal patches have been formulated to improve the drug delivery, clinical application, and patient compliance.

1.3.3.1. Reservoir-Type Patches

The drug is sequestered within a separate reservoir; release is regulated through a rate-controlling membrane in the case of reservoir-type systems. This layer controls the release of drug from the reservoir to skin. It gives a continuous drug delivery for controlled and extended release. To this end, these transdermal patches usually contain permeation enhancers to help the drug move through the stratum corneum, example includes nitroglycerin patches for angina.

1.3.3.2. Matrix-Type Patches

Matrix-type patches consist of a polymer matrix into which drug is incorporated and from which it is then delivered. The drug diffuses from the matrix directly to the skin without requiring a separate reservoir or membrane. These alternative systems are simpler to produce, and result in a thinner, more flexible patch design. The drug delivery is slower, and it remains available over a long time. Ex. chronic pain management fentanyl patches

1.3.3.3. Drug-in-Adhesive Patches

Chemically linked to the adhesive layer that attaches the patch to the skin The adhesive acts as both the platform that binds the patch and the means of drug delivery. These properties include the fact that it is simple, cost-effective and offers a constant drug release. Drug delivery depends on the adhesive formulation and drug amount. This is something routinely done with hormone patches, such as those used in hormone replacement therapy (HRT).

1.3.3.4. Micro-Reservoir Patches

These have properties of both In reservoir and matrix-type systems. The drug is placed in a gel-like matrix that sits inside small reservoirs in the adhesive. It achieves controlled release and at the same time maintains their flexibility. This type is especially convenient for drugs that would need to be taken over a longer period of treatment and in the smallest possible doses.

1.3.3.5. Multilaminate Patches

Multilaminate Patches: Multilaminate patches are reported to be composed of layers, sometimes giving rise to the use of diverse drug release mechanisms. For instance, one layer may be for release immediately and other layers would be for stapled release. Such patches may be capable of delivering a combination of drugs or enabling sequential delivery of the same drug.

1.3.3.6. Iontophoretic Patches

These are electro transport systems that actively pump charged drug molecules through the skin using a low-level electric current. This approach improves passive diffusion and hence bioavailability of drugs which largely relies on the highly permeable property of their intestinal epithelium. This allows useful transdermal delivery of even macromolecules such as peptides and proteins.

1.3.3.7. Vapour Patches

Vapour patches release the non-stationary drugs into the air and when released, these are inhaled by the person instead of getting absorbed from the skin as such. They are frequently used in aromatherapy, or as means to nasal decongest and for the partition of motion sickness (e.g., in menthol- or eucalyptus-based patches).

A. Membrane Modulated Patch:

This patch consists of a metallic plastic backing layer acting as a impermeable reservoir along with a porous polymer membrane that regulates the release of the drug kinetics. The Membrane, composed of hypoallergenic adhesive polymers or ethylene-vinyl acetate copolymer on the silicone reservoir and ensuring a controlled release by scattering the drug at molecular state throughout polymer matrix. The system is used in commercial products, such as Transderm-Nitro® (nitroglycerin – 24-hour duration), Transderm-Scop® (scopolamine – three-day duration) and Catapres® (clonidine – seven-day duration).

B. Micro reservoir System:

It is a mixture of matrix system and drug reservoir. Drug reservoir -Using a hydrophilic polymer dispersed in an aqueous solution along with the drug that eventually forms different mini-reservoirs within the matrix structure.

C. Drug in Adhesive Matrix System:

Transdermal Patches: In these system transdermal patches are prepared as single layer and multilayer matrix. The drug is spread homogeneously in an adhesive polymer so that a drug-polymer matrix is formed, which is then coated on a non-permeable backing layer in order to retain and guide the release of the drug into the skin.

The backing layer in such patches can be prepared using solvent casting or by melting the adhesive polymer materials. Dozens of transdermal products have been commercialized using this schema, including the one-day Climara® patch (estradiol) and the up-to-10-week NicoDerm® CQ patch for smoking cessation.

D. Matrix Dispersion System:

This system is prepared by making a drug-polymer matrix by uniformly mixing a drug either with hydrophilic or lipophilic polymer. Once the matrix is prepared, it is coated onto a substrate that has an impermeable backing laminate. Such products, such as Nitro-Dur® (nitroglycerin) and Minitran®, use this system to release a constant dose of medication through the undamaged skin.

E. Miscellaneous Transdermal

A number of alternative transdermal matrix-based drug delivery systems have been approved by the FDA, including patch (adhesive tape) types, transdermal gels, sprays and iontophoretic or phonophoretic delivery mechanisms.

1.3.4. Approaches in Transdermal Drug Delivery Systems (TDDS)

1. Polymer-Based Matrix Systems:

Polymers are essential in regulating drug release from transdermal systems patches. The selection of a suitable polymer is based on properties such as molecular weight, chemical structure, stability, non-toxicity, flexibility, and ease of handling. These characteristics make the polymer suitable for use in TDDS formulations.

1. Ideal Drug Characteristics for TDDS:

A. Physicochemical Properties: Drugs used in TDDS should exhibit specific physicochemical attributes. They should have a molecular weight below approximately 1000 Daltons, a low melting point, and should be soluble in both lipid and aqueous environments to ensure effective skin permeation.

B. Dosage Efficiency: The drug should require only a few milligrams per day for therapeutic effect. An ideal candidate should also possess a short half-life, be non-irritating to the skin, non-allergenic, and should bypass significant first-pass liver metabolism or be stable in the gastrointestinal tract.

3. Permeation Enhancers:

Penetration enhancers are added to increase the drug's permeability through the skin. These substances temporarily alter the skin barrier to facilitate drug diffusion. The rate of drug transport across the skin (flux, TF) can be described by the equation:

$TF=TD\times(dc/dx)$

Where:

TD is the diffusion coefficient,
c is the concentration of the drug,
x is the distance through the skin.

These enhancers are crucial in boosting bioavailability of drugs delivered via the transdermal route.

4. Other Excipients:

A. **Adhesive Materials:**Adhesives are used to secure the patch to the skin and should maintain consistent contact during daily activities such as bathing or exercise. These materials must be non-irritating and non-sensitizing, and are generally applied to the backing or contact side of the patch.

B. **Backing Layer**: The backing layer acts as a protective barrier and prevents drug loss from the top of the patch. It is made of impermeable materials such as metallic plastic laminates or plastic films and may incorporate absorbent pads, occlusive base plates, or adhesive foam pads. Its role is to protect the drug formulation and maintain integrity during use.

5. Additional Factors Affecting Drug Permeation:

Several external and formulation-related factors influence the rate of drug absorption through the skin. These include:
Drug and vehicle properties
Moisture level and condition of the skin
Skin site (e.g., skin behind the ear is more permeable than skin on the back, chest, forearm, or thigh)
Formulation strategies like combination therapy, Drug permeation is also influenced by the drug's concentration in the formulation vehicle. Upon application, the drug must dissolve and partition into the outermost skin layer (stratum corneum), followed by diffusion through the lipid-rich intercellular spaces. This diffusion step through the stratum corneum is usually the rate-limiting factor in transdermal drug delivery [16–18].

PLANT & EXCIPIENT PROFILE

Plant Profile:
Ginger (*Zingiber officinale* Roscoe)

Ginger (*Zingiber officinale* Roscoe), a member of the family of Zingiberaceae is an extremely valuable medicinal herb, distributed throughout India.
Ginger (*Zingiber officinale* Roscoe), which falls under the Zingiberaceae family, is cultivated in almost all the tropical countries. In ayurvedic medicine,
Angiosperms and it is very common herbal spices because of its aromatic and pungent taste. Historical records indicate plant was used as a medicine more than 5000 years ago, mostly in China and India.
Ginger rhizome has long been used in traditional medicine to treat various conditions, including cholera, colds, diarrhea, nausea, abdominal pain, lumbago, toothaches, bleeding, high blood pressure, and chronic inflammatory diseases like rheumatoid arthritis.
In African folk medicine, it has served as a carminative, diuretic, and remedy for nausea and vomiting.
Additionally, in Iranian traditional medicine, ginger has been employed to manage neurological disorders such as epilepsy, paralysis, and stroke [7].
Properties – dry, light and sharp
Taste – pungent
Geographical Source of Ginger (*Zingiber officinale*)
Ginger is believed to have originated in Southeast Asia, but it is now cultivated in many tropical and subtropical regions around the world. The rhizome is the commercially valuable part and is produced extensively in several countries for both medicinal and culinary uses.
Origin

Probable origin: Southeast Asia (likely in regions around India and China)
It has been used in Indian and Chinese traditional medicine for over 2,500 years.
3. Environmental Requirements for Cultivation
Climate: Tropical or subtropical
Temperature: 20°C to 30°C (68°F to 86°F)
Rainfall: 1500–3000 mm annually
Soil: Loamy, well-drained, rich in organic matter
Types of Ginger by Region
Jamaican ginger: Pale-colored, aromatic, premium variety.
Indian ginger (Nadia, Rio-de-Janeiro, Suprabha varieties): Pungent and fibrous.
Chinese ginger: Less pungent, often preferred in culinary use.
African ginger: Very pungent; often used in herbal medicine.
Morphology:
Summary Table

Table 1.1: Plant parts of ginger and their description

Plant Part	**Description**
Rhizome	Thick, aromatic, underground stem used for propagation and harvesting
Pseudo-stem	Formed from overlapping leaf sheaths
Leaves	Lanceolate, alternate, parallel-veined
Inflorescence	Spike-like, with colourful bracts
Flowers	Rare in cultivation, bisexual
Fruit	Capsule (rarely produced)
Propagation	Vegetative, using rhizome segments

Major Chemical Constituents of Ginger
Pungent Principles (Non-Volatile Compounds)
These are mainly responsible for ginger's sharp taste and many of its medicinal effects:
Gingerols [6]-Gingerol is the most abundant and active component in fresh ginger. Possesses anti-inflammatory, antioxidant, and anti-nausea properties.
Shogaols Formed from gingerols upon drying or heating (e.g., [6]-shogaol). More potent than gingerols in some pharmacological activities (e.g., anticancer and anti-inflammatory effects).
Paradols Formed from shogaols by hydrogenation. Have antioxidant and anticancer potential.

Zingerone Produced when gingerols are thermally degraded (e.g., during cooking). Less pungent, with antioxidant and anti-inflammatory effects.
2. Volatile Oils (Essential Oil Components)
These contribute to the aroma and some therapeutic effects:
Zingiberene (major component, ~30%), β-Sesquiphellandrene, Bisabolene, Farnesene, Camphene, Citral, Linalool, Eucalyptol, Borneol, Geraniol, Cineole
These compounds have antimicrobial, carminative, and expectorant properties.
Other Compounds
Flavonoids (e.g., quercetin), Diarylheptanoids
Amino acids, proteins, and carbohydrates
Minerals: potassium, magnesium, calcium, iron
Vitamins: B-complex vitamins (especially B6), vitamin C
Lipids: including phospholipids and fatty acids

Summary Table

Table 1.2: Group of compounds and their key activities

Group	Examples	Key Activities
	[6]-Gingerol, [6]-Shogaol	Anti-inflammatory, antioxidant, anti-nausea
	Zingiberene, β-Sesquiphellandrene	Aromatic, antimicrobial, digestive aid
Pungent compounds	Zingerone, Paradols	Antioxidant, anti-inflammatory
Volatile oils	Camphene, Cineole, Borneol	Antimicrobial, decongestant
Other nutrients	Vitamins, minerals	Nutritional support, systemic health

Uses:

1. Culinary Uses

Spice and flavoring: Used fresh, dried, powdered, or as juice in a wide range of dishes (soups, curries, marinades, desserts, and beverages).
Pickled ginger: Often served with sushi (known as gari in Japanese cuisine).
Ginger tea and drinks: Consumed for flavor and health benefits, such as soothing digestion.
2. Medicinal Uses
A. Digestive Health
Anti-nausea: Commonly used to relieve nausea and vomiting, especially:
Pregnancy-associated morning nausea, Motion sickness, Nausea resulting from surgery and chemotherapy treatments.

Carminative: Helps relieve gas and bloating.
Appetite stimulant

B. Anti-inflammatory and Pain Relief

Rich in gingerols and shogaols, which exhibit:
Inflammation-reducing properties(useful in arthritis and muscle soreness) and Mild analgesic effects (reduces pain)

C. Cold and Flu Relief

Promotes sweating and may help reduce fever.
Used in traditional medicine for treating colds, sore throat, and cough.

D. Antioxidant Effects

Helps combat oxidative stress and may support overall immune health.

E. Metabolic and Cardiovascular Health

Could assist in maintaining healthy blood glucose levels.
Potential to lower cholesterol and improve heart health.
Improves circulation.

3. Antimicrobial Activity

Exhibits antibacterial and antifungal properties.
Used in natural remedies for oral health (e.g., to fight bad breath and gum disease).

4. Traditional and Alternative Medicine

Within Ayurveda, TCM, and Unani practices for:
Balancing body energies, Improving circulation, Treating respiratory and gastrointestinal disorders

5. Cosmetic and Topical Applications

Used in skincare products for the inflammation-reducing and antioxidant effects it possesses. Sometimes included in hair care to stimulate growth or reduce dandruff.

6. Industrial and Nutraceutical Uses

Used in the formulation of:
Herbal supplements, Functional foods, Essential oils and extracts
Drug delivery systems (e.g., in nanoformulations like 6-shogaol-loaded transferosomes).
Excipients Profile
Ethyl cellulose
Nonproprietary Names: BP: EthylcellulosePhEur: Ethylcellulose Aquacoat ECD Aqualon Ashacel E462 Ethocel ethylcellulosum Surelease CAS Number: 9004-57-3C1.5154 Page 54 of 122 Integrity Submission Submission ID trn:oid:::3618:108023630 Cellulose ethyl etherChromosomal Theory and Formula: Ethylcellulose is partially ethoxylated. Ethocel Also known as a fully substituted ethyl cellulose

(DS=3) $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$

The value of *n* can change, resulting in a broad range of molecular weights. Ethylcellulose, which is the ethyl ether derivative of cellulose, consists of long chains of β-anhydroglucose units interconnected through acetal bonds..

Structural Formula:

Functional Category: Coating agent; flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology: Uses in Formulation or Technology in Pharmaceuticals Ethylcellulose is largely used in pharmaceutical formulation for both oral and topical routes of administration; Table I. Its principal application in oral preparation is as a hydrophobic coating agent for granules and tablets. Ethylcellulose coatings are employed to alter a drug's release (1–8), to mask a bitter taste (7–10), or to enhance stability of a formulation; e.g. ethyl cellulose coated granules to prevent oxidation. Ethyl cellulose matrix former is further seen in the development of modified-release tablet formulations.

2.2.2: Glycerin

SynonymsCroderol, E422, glicerol, glycerine, glycerolum, Glycon G-100, Kemstrene, Optim, Pricerine, 1,2,3-propanetriol, and trihydroxypropane glycerol

Empirical Formula and Molecular Weight C3H8O3 92.09

Structural Formula

Functional Category: Antimicrobial preservative; cosolvent; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.
Polyvinyl pyrrolidone (PVP) (Crospovidone)
Synonyms: Crospovidonum; Crospopharm; crosslinkedpovidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2 pyrrolidinone homopolymer.
Structural Formula

Functional Category: Tablet disintegrant.
Description: Crospovidone appears as a white to creamy-white, finely divided, free-flowing powder. It is practically tasteless, odorless or nearly odorless, and hygroscopic in nature.
Polyethylene Glycol
Synonyms: Carbowax, Carbowax Sentry, Lipoxol, Lutrol E, macrogola, PEG, Pluriol E, and polyoxyethylene glycol.

Functional Category: Serves as an ointment base, plasticizer, solvent, suppository base, and as a lubricant for tablets and capsules.
Applications in Pharmaceutical Formulation or Technology:Applications in Pharmaceutical Applications: Employed in various pharmaceutical formulations and technological processes for its functional versatility. Formulation applications including such as parenteral, topical, ophthalmic, oral, and rectal dosage forms.

Hydroxypropyl methyl cellulose (Hypromellose)

Synonyms: Hydroxypropyl methylcellulose (HPMC), also known as hypromellosum, Methocel, methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, MHPC, Pharmacoat, Tylopur, or Tylose MO, is a cellulose ether in which the substituent group R may be H, CH_3, or $CH_3CH(OH)CH_2$. [5, 35].

Functional Category: Bio adhesive excipient; film-coating agent; sustained-release modifier; dispersant; solubility enhancer; emulsion stabilizing agent; sustained-release modifier; film-forming compound; foam-producing agent; granulating agent promoting agent; modified release agent; mucosal adhesive; release-modifying agent; solubiliser; stabilizer; suspension agent; sustained release agent; tablet binder; thickening agent; viscosity-increasing agent 1 Page 58 of 122 -Integrity Submission [35].

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-806-9

DeepScience
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Chapter 2: Literature Review

2.1 Pooja Kulkarni et.al. (2025),

Transdermal drug delivery systems (TDDS) are an excellent alternative to the oral route of drug administration. TDDS have few advantages like bypass of presystemic metabolism, enhanced patient compliance, reduced adverse effects and controlled release of drug. The review summarizes the constituents, formulations, and recent advancements in TDDS. A basic transdermal patch is composed of drug, polymer matrix, adhesive, backing layer and release liner. In this case, natural polymers including xanthan gum, sodium alginate and chitosan or synthetic polymers such as polyvinylpyrrolidone (PVP) and ethyl cellulose have been used for TDDS [1]. Transdermal patches canbe sigmoided by different methods of their preparation like Solvent casting technique, aluminum-backed adhesive film method, and circular Teflon mold free-film approach and substrates from mercury. The study describes evaluation methods of transtdermal patches (thickness, folding endurance, drug content and weight uniformity) and in-vitro drug release studies. There are already some patented advances in the transdermal patch technique, for example: smart patches combined with a sensor to monitor or programmed drug delivery; 3D printing processes for personalized medicine; and the re-conception of high drug loading and controlled-release routes along with the use of biodegradable. This underscores the growing utility of topical patches used for vaccination, gene therapy, cardiovascular treatments, and drug delivery of insulin. As these technologies continue to mature and develop, they have the potential to revolutionize drug delivery throughout a wide range of therapeutic indications, which could ultimately result in better patient outcomes.

2.2. Liuyang Wang et.al. (2025),

Transdermal patches, being able to maintain a stable plasma drug level thus have an additional significant advantage of continuous kinetics. Patches will be able to only do the jobs for which they are designed if they are capable of proper adherence to skin and

this is contingent on a number of external and internal factors influencing them. The review is mainly concerned with the first steps of adhesion in transdermal patches, ie the rudiments as skin information and basic principles of adhesion, drug delivery and adhesive properties of pressure sensitive adhesives (PSA), different aspects about adhesion, factors affecting to patch adhesive forces, strategies for enhancing bond strength and the potential mechanisms at molecular level. The design and the development of transdermal patches that adhere long enough to deliver drug are highly complex behaviour. Problems associated with adhesion are the intricate trade off between PSAs, permeation enhancers and pharmaceutical ingredients (APIs), and other excipients in current patch compositions, further complicated by variations arising from dermatological factors. Such intricacies make patches very difficult to be consistently effective. The exploration of new PSA polymers in combination with new patch compositions to find the ideal balance of drug consumption fraction, drug-load, drug release, and adhesion is an important step to overcome the aforementioned challenges related to adhesion.

2.3. Vijay Jatav et.al. (2023),

Transdermal drug delivery system (TDDS) has made it possible to maintain the release of drug andari provides a method to attenuate the action and therefore limit its side effects when compared with oral therapy. Definition Transdermal drugs are : - a self-contained,discrte dosage form. The system provides controlled systemic delivery of a drug through the skin. The skin in case of delivery or BLE comes from a membrane. Complex and difficult to formulate Molecule & complex drug delivery. It requires specialized manufacturing rocess/equipment. Designed for certain biopharmaceutical and functional properties. The transdermal patch was assessed for various parameters, including thickness, tensile strength, folding endurance, percentage elongation, moisture content, moisture uptake, drug content, in vitro drug release, in vitro permeation, and drug excipients compatibility. There are different types of technology available for a skin patch which is the frequently used transdermal system. Transdermal technologies can be used to treat a wide range of pharmaceutical types designed for local therapy in therapeutic area skin disorders, or medications intended for other organs within the body. Some applications of transdermal products are hormone

2.4. Shabana Sulthana et.al. (2023),

A transdermal drug delivery system refers to painless and therefore largely acceptable because it possess widespread advantages such as topical drug administration process, prolonged therapeutic effect, less side effects; improved patient compliance, high

bioavailability with convenient discontinuance of therapy. A transdermal patch is a technique of the controlled drug release under TDDS (Transdermal Drug Delivery System), where it comes in prolonged contact with the skin so that the precise and predetermined rate can be achieved for systemic absorption, bypassing first-pass metabolism. They are designed to deliver the appropriate therapeutic dose of drug transdermally. The patches provide the patient with controlled drug release. It works as a drug carrier that retain the substance, ensuring such substance is delivered. This gives an advantage as it avoid hepatic pass effect and gastric irritation and have longer half-life in the blood stream This TDDS carries the drug through skin which is a newly developed novel technology. As an adhesive drug delivery device with a defined surface area that deposited a precise amount of medication on the intact skin over a pre-programmed period of time. In the current article, we would like to highlight those advancements related to transdermal delivery drugs which are formulated and delivered by means of transdermal patches with the expectation of overcoming the side effects associated with oral delivery. Transdermal drug delivery has a bright future for systemic drug delivery and possible production advancement.

2.5. Namrata Matharoo et.al. (2023),

The development of novel delivery approaches for drugs has intensified in the past few decades and becomes a subject increasingly explored in the dermatopharmaceutical field (2023). One of the most selected for this type is the delivery by transdermal route which corresponds to a less invasive choice when compared to other routes. The administration of various pharmaceutical dosage forms is hindered by the stratum corneum's barrier characteristics. However, to date many of the successful transdermal therapies have been encapsulated transdermal delivery systems adhering to lipophilic molecules of entitled therapeutic indexes of a few hundred Daltons. To offset the compromised size and lipophilicity of these drugs, anticlastic surfactant possessors termed as transferosomes have emerged wide-ranging success to deliver transdermally rich gamut of therapeutics such as hydrophilic actives, macromolecules (of a less targeted nature), peptides and proteins, and nucleic acids. Transferosomes are structurally very deformable and have a high surface hydrophilicity, which is important to facilitate penetration of drugs and other solutes across the skin by using osmotic gradients as a driving force for the delivery of molecules both into and through human skin. This enhanced the total permeation and drug release rate of the skin layers. Moreover, the physical–chemical characteristics of the transferosomes enhance shelf life by restricting oxidation, light, and temperature degradation of actives In this manuscript, we review An overview of the evolution of transferosomes from solid lipid nanoparticles and liposomes, their physicochemical characteristics, dermal pharmacokinetics, and recent developments in commercially available dosage forms.

2.6. Raghavendra Sakirolla et.al. (2023),

Rhizomes of dried Zingiber officinale possess the most powerful biological activity from reduced K i values (K i value <11μM) in the case for 6-shogaol. A number of bioactivities associated with 6- and its related structure 4-shogaol have been identified out in many scientific studies. 6-shogaol But it is unstable in room temp so the weakness of 6-shogaol Shogaol (6-shogaol, 8-shogaol and 10-shogaol) derivatives were prepared as thiophene compounds by the replacement of the C-6 six carbon pentyl group (sidechain) with various substituents using synthetic methods. STCs are more effective than 6-shogaol in inducing NRF2 and decreasing inflammation. The bioactivity of the STCs depends on the nature of substituents on thiophene. The most active compound was phenylthiophene STC (STC5), but thiophenes bearing electron-withdrawing groups were less bioactive. No specific bioactivity hits were found for STC5, as its maximum bioactivity was in the micromolar range, and 6-shogaol; a potent anti-malarial single compound present only in one of the ginger extracts; had all bioactivity concentrations in the sub micomolar range. STCs exerted anti-inflammatory properties through NRF2-dependent and –independent mechanisms. The effects of the STC on NRF2 were exerted through KEAP1-independent and -dependent means that significantly enhanced NRF2 activity. Accordingly, STCs demonstrate lower reactivity to thiols than 6-shogaol, and therefore seems to have less side effects compared to 6-shogaol. The STCs were shown to be far more metabolically stable in vitro compared with 6-shogaol

2.7. Chanchal Tiwari *et.al.* (2023),

The novel mode of drug delivery through the skin encompassed by a self-contained, discrete, medicated adhesive patch termed as transdermal patch will provide an easy approach to potential treatment for variety of skin and body conditions. Drawbacks of multiple drug administration include inconvenient dosing, potential for overdose, patient non-compliance due to complex regimens and variable plasma levels. Transdermal medication delivery provides an innovative way of delivering the drug at a predetermined rate for systemic drug absorption over long periods. It has less dosing frequency, avoids first-pass metabolism by directly entering into systemic circulation, is appropriate to the elderly patients who are unable to take oral pharmaceuticals and can be self administrated with fewer side effects (3). This includes some general aspects relating to the route of drug absorption across the skin, and kinetics of absorption and factors affecting transdermal water loss (TWL) followed by a classification of transdermal patches based on their compositional characteristics including an elaborate explanation about great biomembrane, composition layers and types of patch with their evaluation parameters. Furthermore, marketed transdermal patches and various therapeutic opportunities using the transdermal drug delivery systems were also

highlighted. Also it encompasses development of transdermal drug delivery system applied through generations, and ending with a newer view regarding the future aspect. Keywords : Transdermal patch, Permeability, Polymer Matrix, Rate Controlling Membraneand Permeation Enhancers.

2.8. Chandan sharma *et.al.* (2023),

Transdermal drug delivery is a novel but effective way of constant or sustained drug release. As the changing experience of these devices traces more and more researchers working in drug discovery and delivery, the number of transdermal devices expected to reach the market is on an upward trend. This review aims to present recent investigations implemented over the past years with potential drug candidates. As well as new polymer: penetration enhancer combinations. DATABASESThe following databases were changed for the study: Sciencedirect, Web of Understanding, Pubmed, Google Scholar. We can conclude from all the research work carried out by researchers in recent past that from this data compilation the transdermal route is no more bonded with only few polymers and penetration enhancers, many options seems to be explored for formulation of various devices for transdermal delivery. Conclusion: In conclusion, most of the researches have been using HPMC as a film forming polymer, however recently Eudragit grades are also attaining attention in scientists.

2.9. Amit kumar Nayak *et.al*. (2022),

These are highly deformable nanovesicles prepared by lipids layers of phospholipids together with an edge activator that surrounds an aqueous core [26]. Transfersomes are usually prepared by film hydration method, reverse-phase evaporation method, modified handshaking method, vortexing–sonication method and ethanol injection method. In aid of transdermal applications, they can produce better permeability across the barrier. When using nonocclusive application the nanoparticles can pass through the narrow stratum corneum channels and arrive as intact vesicles in deeper layers of skin — elastic penetration via the skin provided by a transepidermal osmotic gradient [6]. This chapter delivers a concise introduction to transfersomes having main focus on the structural molecules, approach of drug transport through skin, preparation techniques, characterizations and application in delivery number of drugs and bioactive compounds.

2.10. Ananda et.al.(2021),

Encapsulation of Primaquine PMQ as a transdermal patch for; transdermal delivery in combination with solidmicro needles, dermarolle. After a number of optimizations

HPMC was finalized as the main polymer and glycerin as plasticizer. In particular, the PEG 400 level as a permeation enhancer also was optimized. Results: The centres of The transdermal patches were assessed for parameters such as weight uniformity, thickness, surface pH, folding endurance, moisture content, and moisture absorption. capacity, bioadhesion study & analysed for drug content recovery furthermore the histopathology examination proved that there was nonexpressed tissue damage after using our developed method. Additional in vivo studies need to be conducted.

2.11. Mo et. al., (2021)

development of transdermal patch of Carvedilol with optimized and evaluate using various polymers and permeation enhancers that aid in deliver drug in controlled manner, by enhance the drug's bioavailability. It was primarily designed to circumvent the hepatic first-pass metabolism of Carvedilol. Synthesis of transdermal patches by solvent evaporation method Formulation F7 was identified as the optimal formulation, exhibiting a maximum drug release of 100.29 ± 0.44 % within 12 hours. This formulation also demonstrated the highest bioavailability and produced the greatest reduction in blood pressure at the 6-hour mark. The study concluded that a Carvedilol transdermal patch containing Eudragit RS-100 polymer and Span 80 as a permeation enhancer achieved sustained and continuous drug release

2.12. Quan et. al., (2021)

Innovative Transdermal SiH (SiegesbeckiaeHerba) Extract Patch for Rheumatism Therapy SiH (SiegesbeckiaHerba) is a traditional Chinese herbal medicine used in antirheumatic therapy. Phynova Joint and Muscle Relief Tablets™Approved in 2015, Phynova Joint and Muscle Relief Tablets™ is a SiH derived product that has been licensed in the UK. This transdermal patch of Siegesbeckiae Herba extract producted had encouraging anti-inflammatory and analgesic efficacy, which has a promising application in the traditional medication fields or rheumatoid arthritis.

2.13. T.O.S.Apsara et.al.,(2020):

As a result, this route is only applicable to a limited number of drugs. One of the suggested approaches to overcome this issue is encapsulating these drugs in transfersomes. Their bilayered structure enables the entrapment of both lipophilic and hydrophilicc drug, together with amphiphilic molecule, within higher-permeating efficiencies than general healed developed using just liposomes.

Transfersomes possess an elastic nature, allowing them to deform and pass through narrow pores smaller than their own size while remaining intact. Further research on transfersomes could pave the way for innovative therapeutic strategies for a wide range of diseases.

2.14. B.Rui.et.al.,(2020):

6-Shogaol is one component of ginger, which has been described to possess various health-promoting effects including anticancer, antiinflammatory, antioxidant and antiatherogenic. But again poor water solubility has restricted its health benefits and clinical uses as well. Moreover, TPGS coated 6-shogaol liposome displayed overall more sophisticated accumulative release rate than the naked compounds. In terms of pharmacokinetics, TPGS coated 6 shogaol liposome showed sustained release and most importantly among dramatically altered the bioavailability was increased after oral administration with its prolonged half-life in blood.

2.15. Tahir et. al., (2020),

investigated the degree of recrystallization and transdermal permeation of ibuprofen and hydrocortisone loaded in polymeric and lipid nanoparticles from matrix-type transdermal patches. For polymeric nanoparticles preparations, three different polymers included Ethyl cellulose (EC4), poly(lactide-co-glycolic acid) (PLGA), and polycaprolactone (PCL) were used, while medium-chain triglyceride (MCT) and Witepsol served in the preparation of MCT nanoemulsions and solid lipid nanoparticles (SLNs), respectively. In summary, polymeric and lipid nanoparticles were used as successful tools for the preparation of on-demand drug-loaded transdermal patches, rapidly reducing their feasibility to recrystallize. In addition, the findings of this work will serve as a useful lead for future research aimed at modulating crystallization behavior of different drugs via adjustment in carrier hydrophobicity to improve significantly upon transdermal patch development.

2.16. Sakdiset et al., (2019),

prepared ethosomes enclose indomethacin (8 mg/mL) with a range of meditation of soybean phosphatidylcholine (SPC), ethanol and with diverse spreading medium and additives. The ethosomes with good quality colloidal look were attaining in the media surround 10%-30% ethanol in pH 7.4 phosphate buffer. The belongings of ethosomes, counting physical emergence, size, and entrapment efficiency (EE), were observed and converse in relation to their essential. The optimized ethosomes were arranged from a

diffusion comprising 4% w/v SPC:cholesterol:deoxycholic acid in a 6:2:1 molar ratio, prepared in 20% v/v ethanol within a pH 7.4 phosphate buffer. These ethosomes led to appreciably higher infiltration of indomethacin throughout pig skin above 24 h than the profitable solution and the ethanolic solution of indomethacin.

2.17. Ameen and Michniak-Kohn B, (2019),

offered an gorgeous option course of drug running mainly for Alzheimer's disease patients from beginning to end abolish gastrointestinal side possessions and eventually civilizing obedience. They organized optimized matrix type patches of galantamine for the transdermal delivery and performed ex vivo and in vitro estimation. Four pressure sensitive adhesive with dissimilar functional groups, ten diffusion enhancers and four drug loadings were experienced to decide the optimized patch.

2.18. Liu et al., (2019)

Developed benzoylaconitine (BA) of high molecular mass (603.7 Da) into transdermal patch. They attain a patch with high-quality analgesic and antiinflammatory belongings and examine the association among physicochemical limit of enhancers and enhancement power. skin permeation learning was use to assess the result of enhancers, and association learn was behavior to elucidate the association among physicochemical limit of enhancer and permeation amount. improvement The molecular mechanism was investigated using FT-IR analysis and molecular modeling techniques.. It was designating that merely based on enough interface potency and upsetting of in cooperation lipophilic and hydrophilic vicinity of stratum corneum permeation enhancer was capable to complete large permeation augmentation effect.

2.19. Zhou et al., (2018)

Distribute drugs all the way through the exterior of the skin for local or general management. The drug utility after inclusion all the way through the skin into the systemic exchange via vessel achievement at a definite charge. Exploit of time-honored substantial and element enhancers to progress the transdermal permeation charge by growing drug solubility, diffusion coefficient, and basin consequence is not practicable outstanding to the poisonous elevation property of the do to excess of element penetration enhancers. Nano-formulations normally diverge with sizes ranging from 10 nm to 100 nm. Particles with smaller dimensions escort to improved treatment enhancing permeability, stability, retention, and targeted delivery, thereby improving nano-formulations appropriate for transdermal drug delivery. Various applications of

nanoformulations (vesicles or nanoparticles and nanoemulsions) have been widely studied.

2.20. Tosato et al., (2018),

prepared drug delivery trandermal system of a natural compound trans-resveratrol (3, 5, 4′ trihydroxystilbene, RSV) haning anti-inflammatory and anticancer activity. They prepared liposomal nanoparticulate carriers approximating conventional liposomes, deformable liposomes, elastic (ultradeformable) liposomes, and ethosomal vesicles and examined by Transmission electron microscopy (TEM) and dynamic light scattering (DLS) to investigate the surface morphology of carriers and structural characterization of these formulations done by confocal Raman spectroscopy. The prepared formulation showed enhancement in the fluidity of the bilayers increase the accommodation of trans resveratrol in the bilayer and improved its encapsulation without affecting the mobility of carrier.

2.21. Kathe and Kathpalia, (2017)

worked on covering is measured as an imperative route of direction of drugs for together local and complete effects. The efficacy of topical therapy depends on the physicochemical belongings of the drug and loyalty of the tolerant to the management schedule as well as the arrangement capability to hold fast to skin all through the remedy so as to support drug dissemination throughout the skin obstruction. Predictable formulations for current and dermatological organization of drugs have certain margins like poor observance to skin, poor permeability and negotiation patient fulfillment. For the handling of sickness of body tissues and lesion, the drug has to be maintaining at the site of conduct for an successful stage of time. Topical film appearance arrangement are such increasing drug delivery systems intended for topical function to the skin, which adhere to the body, structure a thin transparent film and afford delivery of the active feature to the body tissue. These are anticipated for skin application as emollient or caring and to achieve local effects or enable transdermal delivery of medicament for systemic action.

2.22. Siji et al., (2016)

investigated the result of backing films on transdermal delivery of cyclobenzaprine patch. Diverse backing films were selected to arrange the cyclobenzaprine transdermal patch. The cumulative amount of cyclobenzaprine at large from diverse patches was appraise in vitro. To examine the communication flanked by cyclobenzaprine and

backing films, the separation trial and analyzed using attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy execute. The cumulative quantity of cyclobenzaprine released beginning the patch with Cotran™ 9700 as backing film. The quantity of cyclobenzaprine out beginning the patch with Cotran™ 9700 as backing film diminish radically after 7 d storage at room circumstance. The division experiments specify a strapping adsorption of cyclobenzaprine onto the Cotran™ 9700, which could explicate the dwindle of cumulative quantity of cyclobenzaprine free beginning the patch with Cotran™ 9700 as backing film.

2.23. Indulekha et. al., (2016)

planned a temperature generate transdermal drug deliverance system (TDDS) with a thermos responsive polymer, poly (N-vinyl caprolactam) [PNVCL] support gel, someplace in patients can themselves govern a pulsate of treatment on simple purpose of heat pad larger than the TDDS. The phase alteration heat of PNVCL was adjust to 35 °C by embed it onto a pH sensitive biopolymer, Chitosan, to produce Chitosan-g-PNVCL (CP) co-polymer which render the gel mutually thermo- and pH responsive belongings. The submission of triggered delivery was explored by consignment acetamidophenol (a model hydrophilic drug) and etoricoxib (a model hydrophobic drug). In vitro drug discharge experiments were achieved at three unusual temperature (25, 32 and 39 °C) at two different pH (5.5 and 7) to study its drug release with answer to heat and pH. In vitro skin permeation of both the drugs demonstrate enhanced drug liberate at what time the covering was subjected to superior temperature (39 °C). Furthermore, it was also instituting that coat infiltration for hydrophobic drug was superior than that of hydrophilic drug. The in vivo biocompatibility learning of the CP gel in rat coat proves that the gel is biocompatible. The results attain confirmed the potential employ of the thermoresponsive CP gel as an on-demand restricted drug delivery arrangement.

2.24. Rai S. et.al.(2017),

Skin is a barrier and prevents transcutaneous drug delivery. Transfersomes are a unique kind of vesicles which are optimally flexible unlike familiar conventional ones being many times softer. Element(Lamellar edge-stimuli), a combination of the edge activator, phospholipids (to mimic physiological lipids model), ethanol (penetration enhancer) and sodium cholate;- applied repeatedly in non-occlusive formulation. This review article states about the potential of transfersomes and gives information like advantages/disadvantages of transfersomes, regulatory status, materials in use for preparation regulation, methods to prepare them, Mechanism of action, literature review on clinical trials conducted, marketed preparations, Research reports and patent reports

related with Transfersomes. In this regard, over the past few years research has been carried out to investigate more deeply transfersomal permeation of therapeutic agents across stratum corneum barrier. Hence these basic characteristic of application of transfersomes towards different composition is necessary to optimize the permeability towards different therapeutic molecules. There are also a number of Transferosome formulation products in later stage clinical development, such as this(". It is
It is expected that a variety of Transfersome products for dermal and transdermal delivery will emerge as successful global market, in the coming future.

2.25. Gundeti et al., (2015)

prepared transdermal drug delivery systems of Nateglinide by solvent casting method. They includes the combinations of HPMC: EC, PVA: PVP, HPMC: Eudragit RS 100, Eudragit Rl100:RS100 with different permeation enhancers i.e. polyethylene glycol 400,DMSO) were used. Gels were also characterized evaluated for homogeneity, pH, viscosity, drug content, in vitro diffusion, and ex vivo permeation studies. The drug release profiles and kinetic data of formulations having HPMC:EC was found as optimized for 12hrs i.e. 99.2%. The patches retained their structural integrity and exhibited favorable physicochemical properties throughout the stability studies according to ICH guidelines.

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-806-9

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Chapter 3: Aim and Objectives

3.1. Aim

The aim is "Extraction of 6-Shogoal from Ginger & Formulation, Evaluation of Transdermal Patch of Transferosome".

3.2. Objectives

1. **Extraction** of 6-Shogoal:
2. **Selection of Source**: Identify suitable sources of Ginger, such as 6-Shogoal.
3. **Extraction Method Development**: Optimize methods for efficient extraction (e.g., solvent extraction, supercritical fluid extraction).
4. **Formulations and Evaluation** of Transferosome and drug entrapment.
5. Formulation of Transdermal Patch:
6. **Polymer Selection**: Choose appropriate polymers (e.g., chitosan, polyvinyl alcohol) that facilitate drug delivery.
7. **Patch Composition**: Determine the optimal ratios of 6-Shogoal, polymers, plasticizers, and other excipients.
8. **Preparation**: Utilize techniques such as solvent casting or hot melt extrusion to a fabricate the patches.

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-806-9

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Chapter 4: Material and Method

4.1. Materials

Table 1.3: List of materials used in formulation

Category	Material(s)	Purpose
Active Ingredient	Ginger Extract (rich in gingerols and shogaols)	Contains 6-shogaol and other bioactive compounds for therapeutic effect.
Excipients for Transferosome	Phospholipids (e.g., Lipoid P-100)	Primary component of transferosomes, forming the vesicle structure.
	Edge Activators (e.g., Tween 80, Span 80, Sodium Deoxycholate, Ethanol)	Increase the flexibility and deformability of transferosomes for better skin penetration.
	Cholesterol	May be included to modulate the rigidity and stability of the transferosome bilayer.
Patch Matrix	Polymers (e.g., Ethylcellulose, HPMC, PVA, PVP)	Form the structural support of the patch and control drug release.
Plasticizers	PEG 400	Enhance the flexibility and spreadability of the patch.
Penetration Enhancers (in patch)	Oleic Acid, Tween 80	Further enhance the permeation of 6-shogaol through the skin layers.
Solvents (for preparation)	Ethanol, Water, Methanol	Used to dissolve and mix the components during the preparation process.
Other Additives	Mentha Oil	May be added for synergistic effects (e.g., anti-inflammatory) or to enhance permeation.

Table 1.4: -Name of the instrument/apparatus used in performing out the study

Stage of Research	Instrument	Purpose
Extraction & Isolation of 6-Shogaol	Rotary Evaporator	To remove the solvent after extraction of ginger components, concentrating the extract.
	Soxhlet Apparatus (or other extraction methods)	For the extraction of compounds, including 6-shogaol, from ginger rhizomes using a suitable solvent.
	High-Performance Liquid Chromatography (HPLC)	For the identification, quantification, and purification of 6-shogaol from the ginger extract.
	Mass Spectrometer (MS)	Used in conjunction with HPLC to confirm the molecular weight and structure of the isolated 6-shogaol.
	UV-Vis Spectrophotometer	To quantify the amount of extracted and purified 6-shogaol.

4.2 METHODOLOGY

4.2.1. EXTRACTION OF 6-SHOGOAL FROM GINGER:

Extraction of 6- shogaol from ginger

Procedure:

The extraction of 6-shogaol from ginger typically involves the following steps and considerations:

4.2.1.1. Weighing of Sample:

Accurately weigh a specific amount (50 grams) of the ginger powder.

4.2.1.2. Loading into Thimble:

Place the weighed powder into a Whatman filter paper inside the thimble or cotton cloth and load it into the Soxhlet apparatus.

4.2.1.3. Solvent Selection and Addition: (by Soxhlet Apparatus)

Use ethanol (95% or absolute) as a solvent for extraction.

Fill the round-bottom flask of the Soxhlet apparatus with 250–500 mL of ethanol, depending on the sample size.

Continue the extraction for 7-8 hours per day in collage hours completed into 5-6 days or until the solvent in the siphon tube becomes clear.

Various drying methods can be used:
Air Drying: Room temperature or shade drying.
Oven Drying: At controlled temperatures (e.g., 60-80°C). Higher temperatures generally lead to a higher 6-shogaol content and collected semisolid or dry residue.
Storage:
Store the final extract in an airtight container and keep it in a refrigerator or cool, dry place for further use.
Method:

Soxhlet Extraction: A continuous extraction method where the solvent is repeatedly cycled through the ginger powder, generally using heat.

4.2.1.4. Optimization: Factors like solvent type, solvent-to-ginger ratio, temperature, and extraction time need to be optimized to maximize the yield of 6-shogaol. Higher temperatures during extraction can also promote the conversion of remaining gingerols to shogaols. Acidic conditions in the solvent may further enhance 6-shogaol production during extraction.

4.2.1.5. Filtration and Concentration:

After extraction, the solid residue is separated from the liquid extract by filtration.

The solvent in the extract is then typically removed or concentrated using methods like rotary evaporation under reduced pressure to obtain a concentrated ginger extract rich in 6-shogaol and other bioactive compounds.

- Key Factors Influencing 6-Shogaol Extraction:

Drying Method and Temperature: Higher heat during drying generally increases 6-shogaol content.

Extraction Solvent: Ethanol is a common and effective choice.

Extraction Temperature and Time: Higher temperatures and optimized times can improve yield.

pH of the Extraction Solvent: Acidic conditions may favor 6-shogaol formation.

Extraction Method: MAE and UAE can offer advantages in terms of time and efficiency compared to conventional methods.

The specific protocol for 6-shogaol extraction will depend on the desired purity, scale of operation, and available equipment. Research papers often detail optimized methods for obtaining 6-shogaol-rich extracts.

4.3. Physiochemical properties of 6-Shogaol

4.3.1. Organoleptic Evaluation

The sensory characteristics of 6-shogaol were assessed using human senses, focusing on attributes such as color- pale yellow to light brown oily liquid or crystalline solid, odor -pungent spicy, ginger like odor and taste- strongly pungent and spicy more intense than gingerol to establish its organoleptic profile.

4.3.2. Microscopic Examination

A small quantity of 6-shogaol was placed on a glass slide and examined under a phase contrast microscope to observe its morphological features like presence of spherical/ oval vesicles.

4.3.3. Density Measurements

The bulk and tapped densities of 6-shogaol powder were determined. Accurately weighed samples were poured into a graduated cylinder to measure bulk density. Tapped density was measured using a tapped density apparatus, following standard protocols. But this is not applicable for pure 6-Shogoal in its standard liquid or oily form. If it's in a powdered form then can measure.

4.3.4. Particle Size Analysis

Particle size was determined using a phase contrast microscope equipped with ocular and stage micrometers, allowing for precise measurement of individual particles. 6-Shogoal is not naturally in particle form, it's a liquid or oily compound at room temperature. Particle size analysis is relevant only when 6-Shogoal is incorporated into a formulation such as: transferosome or emulsion. The average particle size is **145.6 nm.**

4.3.5. Flow Property Assessment

Flow characteristics of 6-shogaol powder were evaluated by calculating Carr's Index and Hausner's Ratio, derived from bulk and tapped density values. The angle of repose was determined using the fixed-height method to assess powder flowability.

Table 1.5: Flow property of 6-Shogoal

S. No.	Parameter	Method used	Result	Interpretation
1	Angle of Repose ()	Funnel method	32.5	Fair flow
2	Bulk Density (g/mL)	Graduated cylinder	0.41 g/ml	_
3	Tapped Density (g/mL)	Tapped cylinder	0.56 g/ml	_
4	Carr's Index (%)	TD and BD	26.78 %	Poor flow
5	Hausner's Ratio	TD / BD	1.36	Passable flow
6	Flow Rate (g/sec)	Flow through funnel	4.2 g/sec	Moderate flow
7	Moisture content (%)	Moisture analyzer	2.5%	Acceptable
8	Particle shape	Microscopy	Irregular	Poor flow

4.3.6. pH-Dependent Solubility Profile

The solubility of 6-shogaol was tested using phosphate buffer solutions with pH values of 6.8 and 7.4. An excess amount of the compound was stirred in 25 mL of each buffer for 12 hours at room temperature. The mixtures were then filtered through 0.45 µm Whatman filter paper, and the concentration of dissolved 6-shogaol was determined using UV spectrophotometry.

4.3.7. Partition Coefficient Determination

To evaluate the lipophilicity of 6-shogaol, its partition coefficient was determined using a shake-flask method with n-octanol and phosphate buffer (pH 7.4). A mixture containing 25 mg of 6-shogaol in 50 mL of the solvent system was shaken for 24 hours to reach equilibrium. After phase separation, the concentration of 6-shogaol in each layer was measured, and the partition coefficient (Log P) was calculated accordingly.

Table 1.6: Partition Coefficient Determination

S.NO.	Phase	Absorbance at 282 nm	Concentration (ug/ml)
1.	Octanol	0.820	82.0
2.	Water	0.164	16.4

P = concentration of drug in n-octanol /concentration of drug in water

log P =log10{(Drug)octanol / (Drug) water}

P =82.0 /16.4 = 5.0

log P =log10(5.0) =0.699

4.3.8. Melting Point Determination

The melting point of 6-shogaol was determined using the capillary tube method. A small amount of the compound was packed into a sealed capillary tube, which was then placed

in a melting point apparatus. The temperature at which the compound began to melt was recorded at 43°C.

4.4. Transferosome Preparation Techniques:

4.4.1. Thin-Film Hydration (Bangham Method):

How it works: Lipids are dissolved in a volatile organic solvent. The solvent is evaporated, leaving a thin film of lipids. This film is then hydrated with an aqueous solution (like water, buffer, or a plant extract), leading to the formation of large, multi-layered vesicles (MLVs).

Good points: simple and common, applicable for water-soluble and fat-soluble substances.

Drawbacks It captures a less amount of material and gives transferosomes of quite inhomogeneous size.

4.4.2. Reverse Phase Evaporation:

How it worksThe lipids are dissolved in organic solvents and then mixed with an aqueous phase that contains the substance to be encapsulated, resulting in a water-in-oil emulsion. These organic solvents are than removed by evaporation under reduced pressure, creating a liposome5.

Good points: It typically gets you a substantially better encapsulation than the thin-film process.

Drawbacks: t is a method that uses organic solvent and is rather more complicated.

4.4.3. Ethanol Injection:

How it works: The lipid solution in ethanol is injected rapidly into an aqueous solution of the material to be loaded. The lipids spontaneously assemble due to rapid mixing into liposomes.

Good points: Simple and quick to do; no special equipment needed.

Drawbacks: Uses ethanol and does not load water soluble compounds very well

4.4.4. Sonication:

How it worksBy exposure to sonic energy (using a probe immersed in the solution or in a sonic bathing vessel), large and multi-lamellar liposomes (MLVs) are divided into small, mono-lamellar vesicles (SUVs).

Good points: It is a very efficient technique for small liposome production

Drawbacks: The process can generate heat, which might damage sensitive substances.

4.4.5. High-Pressure Homogenization / Extrusion:

How it works: A suspension of liposomes is forced through filters (membranes) with very small, precise pore sizes under high pressure.

Good points: It allows for the production of liposomes with a very consistent and small (nanoscale) size.

Drawbacks: It requires expensive equipment and may not be suitable for substances that are sensitive to heat or high pressure.

4.4.6. Freeze-Thaw:

How it works: A dispersion of liposomes is repeatedly frozen and then thawed. This process helps to improve the amount of substance trapped within the liposomes.

Good points: It's a good method for increasing the encapsulation efficiency.

Drawbacks: It can be a time-consuming process and may lead to the liposomes clumping together.

4.5. Thin Film Hydration and Ethanol Injection methods are used in my project work-

I. Materials Required

Table 1.7: Ingredients and their Quantity to formulate Transferosome

S.NO.	Ingredients	Quantity
1.	Phospholipids (soya lecithin)	100 mg
2.	Cholesterol	20 mg
3.	Ethanol	2 mg
4.	6-Shogoal	100 mg
5.	Twen 80	20 mg

Hydration medium:

Usually distilled water or phosphate buffer (pH 7.4)

Rotary evaporator

Round-bottom flask

Vacuum pump

Centrifuge

Filter (0.22 µm or 0.45 µm for sterilization or purification)

II. Step-by-Step Procedure

4.5.1. Lipid Dissolution

Dissolve phospholipid and cholesterol (typically in a 2:1 molar ratio) in a suitable organic solvent mixture like chloroform: methanol (2:1).

If using a lipophilic drug or extract, add it at this stage to the organic solvent

4.5.2. Formation of Thin Lipid Film

Transfer the lipid solution into a round-bottom flask.

Evaporate remove the solvent with a rotary evaporator under reduced pressure at 40–50°C to form a thin, dry lipid film on the inner walls of the flask.

Continue rotating until all solvent is removed (about 20–30 minutes).

A dry nitrogen stream or vacuum can be used to ensure complete solvent removal.

4.5.3. Hydration of Lipid Film

Add a pre-warmed aqueous phase (e.g., phosphate-buffered saline, distilled water, or a buffer containing a hydrophilic drug) to the flask.

Hydration is done at a temperature exceeding the gel-to-liquid transition point (T_m) of the lipid (typically 50–60°C).

Rotate the flask or use gentle agitation (shaking or vortexing) for 30 minutes to 1 hour to allow the lipid film to swell and peel off, forming multilamellar vesicles (MLVs).

4.5.4. Size Reduction (Optional but Common)

For the preparation of small unilamellar vesicles (SUVs) or large unilamellar vesicles (LUVs):

Use sonication (probe or bath) to reduce size.

Alternatively, extrude the dispersion through polycarbonate membranes with defined pore sizes (e.g., 200 nm, 100 nm).

4.5.5. Purification

Remove unencapsulated drug or extract by:

Centrifugation

Dialysis

Gel filtration chromatography

III. Formulation Considerations

Lipid Composition Phospholipids form the bilayer; cholesterol improves membrane stability.

Lipid: Drug Ratio Affects encapsulation efficiency and vesicle stability.

Hydration Volume Sufficient to fully hydrate film; affects vesicle size and concentration.

pH of Hydration Medium Should match drug stability requirements (e.g., pH 7.4 for physiological use).

Temperature Should be above T_m of lipid to ensure fluidity and efficient hydration.

Encapsulation Efficiency Varies by drug type (hydrophilic vs lipophilic); optimize using formulation trials.

IV. Advantages of Thin Film Hydration Method

Simple and widely used.

Suitable for both hydrophilic and lipophilic drugs.

Easy to scale up with modifications.

V. Limitations

Multilamellar vesicles are typically formed initially.

Low encapsulation efficiency for hydrophilic drugs.

Residual solvent traces (must be removed completely)

Requires size reduction steps for uniformity.

4.6. Ethanol Injection Methods-

The ethanol injection method involves the spontaneous formation of transferosomes when a lipid-ethanol solution is rapidly injected into an aqueous phase (usually buffer or distilled water). Lipids self-assemble into bilayers due to their amphiphilic nature, forming transferosome upon contact with the aqueous medium

4.6.1. Materials Required:

Table 1.8: Ingredients and their quantity to prepare Transferosome

S.NO.	Ingredient	Quantity (for 10ml batch)
1.	Phosphatidylcholine	100 mg
2.	Cholesterol	20 mg
3.	Ethanol	2 ml
4.	6-Shogoal	20 mg (or as per required)
5.	Twen 80	20 mg
6.	Distilled water	(Ph 7.4) q.s to 10 mL

4.6.2. Equipment:

Magnetic stirrer/hotplate

Syringe or micropipette

Rotary evaporator (for ethanol removal, optional)

4.6.3. Methodology:

Step 1: Preparation of Lipid Solution

Dissolve a known quantity of phospholipids and cholesterol (optional) in absolute ethanol.
Typical lipid concentration: 10–30 mg/mL in ethanol.
Add the ethanolic Java Plum Seed Extract into the lipid-ethanol solution if it is lipophilic or semi-lipophilic.

Step 2: Injection into Aqueous Phase

Heat the aqueous phase (PBS or distilled water) to 55–65°C to aid liposome formation.
Under constant stirring (using a magnetic stirrer), inject the ethanol-lipid-drug solution slowly (dropwise) into the aqueous phase.
Injection ratio: ethanol phase: aqueous phase = 1:4 to 1:10.
Liposomes spontaneously form as the lipids self-assemble in water.

Step 3: Ethanol Removal

Ethanol is removed by rotary evaporation, or by dialysis or centrifugation and washing.
Removal of ethanol is essential to prevent toxicity and instability.

Step 4: Size Reduction and Homogenization

The liposome dispersion is often large and multilamellar.
Reduce particle size using probe sonication or extrusion through polycarbonate membranes (100–200 nm).
Goal: obtain Small Unilamellar Vesicles (SUVs) or Nanoliposomes.

Step 5: Purification

Remove unentrapped drug by:
Centrifugation at 12,000–15,000 rpm
Dialysis
Gel filtration chromatography

4.6.4. Characterization Parameters:

After formulation, characterize the Transferosomes for:

- Particle size & PDI (Dynamic Light Scattering)
- Zeta potential
- Encapsulation efficiency (%)
- Drug loading (%)
- In vitro drug release profile
- Morphology (using TEM or SEM)
- Stability studies

4.6.5. Advantages of Ethanol Injection Method:

- Simple and scalable
- No need for high temperatures or harsh conditions
- Suitable for heat-sensitive drugs

4.6.6. Limitations:

- Residual ethanol can be a concern
- Not ideal for hydrophilic drug encapsulation unless combined with other techniques
- May require size reduction steps for uniformity

The preparation of transdermal patches generally involves the following steps and considerations:

4.7. Selection of Components:

Polymer Matrix: A film-forming polymer that holds the drug and controls its release. Examples include:
Hydrophilic polymers: Hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and polyvinyl alcohol (PVA).
Hydrophobic polymers: Ethyl cellulose (EC), Eudragit RS/RL.
Adhesive: A biocompatible adhesive that ensures the patch adheres to the skin for the required duration. It can be part of the matrix or a separate layer. Examples include polyacrylates and polyiso butylenes.
Permeation Enhancers Permeability enhancer can make the skin more permeable to the drug. This can be with chemical enhancers (e.g., oleic acid, terpenes, surfactants), or with physicochemical methods (e.g., microneedles – paired with patches).
Plasticizers: To enhance flexibility and mechanical properties of the patch (e.g. polyethylene glycol (PEG), propylene glycol).
Backing Layer: The waterproof layer that safeguards the patch and prevents loss of the drug (eg. Polyethylene, Polyester)
Release Liner: (such as siliconized polyester film) a protective layer removed before application.
Solvents: These are used in the process of preparation (e.g., ethanol, water, chloroform, methanol).

4.7.2. Methods of Preparation:

There are a few techniques for the preparation of transdermal patches, out of which the solvent casting method is widely considered the most utilized:
Solvent Casting:
Dissolve Polymer(s): The polymer (s) chosen are dissolved under stirring in an appropriate solvent or a solvent mixture to obtain a homogenous solution.
Incorporate Drug and Excipients: The plasticizers, and permeation enhancers are either dissolved or uniformly dispersed in the polymer solution containing continuous stirring to ensure uniform distribution.
Pour the Casting Solution: The prepared solution is poured into a petri dish or cast onto a backing membrane that has been placed on a smooth surface.
Solvent Evaporation: The solvent is allowed to evaporate slowly at a controlled temperature, leaving behind a thin film containing the drug within the polymer matrix. An inverted funnel can be used to control the rate of evaporation and prevent cracking.
Lamination (if needed): If the adhesive is a separate layer, it is laminated onto the drug-containing film.

Cutting and Packaging: The dried film is cut into patches of the desired size and shape and then packaged in impermeable pouches to maintain stability.

Other methods include:

Hot Melt Extrusion (HME): This solvent-free technique involves mixing the drug and polymers at a high temperature until they melt and form a homogenous mixture, which is then extruded into the desired film shape. HME is particularly useful for drugs with poor solubility.

Matrix Dispersion: The drug is uniformly dispersed in a liquid polymer, which is then cross-linked or polymerized to form a matrix.

Adhesive Dispersion: The drug is directly mixed into the adhesive, which is then spread onto the backing layer.

Electrospraying A method of producing a drug-polymer solubilized in a solution and the use of an electric field generates a fine spray and results in the deposition of a film.

4.7.3. Evaluation of Prepared Patches:

The prepared transdermal patches were subjected to various tests for evaluation of their quality and performance:

Physical Appearance: Checked for seeing the color, purity, and generally a clear, smooth, and flexible

Thickness Uniformity: Measured at various places using a micrometer or screw gauge.

Weight Variation: Each patch must weigh between bounds.

Drug Content Uniformity: The amount of drug in each patch should be consistent.

Moisture Content and Uptake: To assess the patch's stability and integrity under different humidity conditions.

Folding Endurance: The number of times the patch can be folded without breaking.

Tensile Strength and Elongation: To evaluate the mechanical properties and durability of the patch.

In Vitro Drug Release Studies: Using Franz diffusion cells were used to evaluate the drug release rate and extent from the patch.

In Vitro Skin Permeation Studies: Using animal or human skin in Franz diffusion cells to assess the permeation of the drug through the skin.

Skin Irritation and Sensitization Tests: To evaluate the biocompatibility of the patch.

Stability Studies: To assess the chemical and physical stability of the drug and the patch under varied storage conditions, including temperature and humidity.

The specific method and formulation components will depend on the drug's physicochemical characteristics, the target release rate, and the therapeutic Optimization of the formulation and process parameters is crucial to achieve an effective transdermal drug delivery system.

4.8. Development of Analytical Methods Using UV Spectrophotometry (λmax):

Identify the wavelength of maximum absorption (λmax) for 6-shogaol, a UV scan was performed using a UV spectrophotometer across the 200 to 400 nm range. For this, 25 mg of 6-shogaol was accurately weighed and dissolved in 25 ml of phosphate buffer (pH 7.4) in a volumetric flask. This mixture was sonicated for 20 minutes (Stock-I, 1000 µg/ml). A 1 ml aliquot of Stock-I was then diluted to 100 ml with phosphate buffer (pH 7.4) and sonicated again for 20 minutes to create Stock-II (10 µg/ml). This Stock-II solution was then analyzed using a double beam UV spectrophotometer (Shimadzu, UV-1800) within the 200-400 nm range. The UV spectrum for 6-shogaol obtained is shown in Fig. 6.1. Phosphate buffer pH 7.4 soln (10 µg/ml) λ-max for Absorption of 6-Shogoal

Preparation of a Standard Calibration Curve of 6-Shogoal in Phosphate Buffer (pH 7.4);

To create a standard calibration curve, a stock solution of 6-Shogoal was prepared by dissolving 25 mg of 6-Shogoal in 25 ml of phosphate buffer (pH 7.4) and sonicating for 20 minutes (Stock-I, 1000 µg/ml). 1 ml of Stock-I was diluted to 100 ml using the same buffer, and sonicated for 20 minutes (called as Stock-II, 10 µg/ml). Specific aliquots (1 ml, 2 ml, 3 ml, 4 ml, and 5 ml) were transferred from Stock II and diluted separately in different volumetric flasks up to the mark with phosphate buffer (pH 7.4) to get a working solution for the calibration curve.

This resulted in solutions with 6-Shogoal concentrations of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, and 5 µg/ml, respectively.

The absorbance of each of these diluted solutions was then measured at 280 nm using a UV spectrophotometer, with phosphate buffer (pH 7.4) as the blank. A standard curve was generated by plotting the measured absorbance values against the corresponding 6-Shogoal concentrations. The linearity of this curve is presented in Table 4.1 and Figure 4.2, and the linear regression equation was found to be $Y = 0.018x + 0.004$ with a correlation coefficient (r^2) of 0.997.

Table 1.9: Standard curve of 6-Shogoal in Phosphate buffer pH 7.4 solution (282nm)

S. No.	Concentration (µg/ml)	Absorbance (λ-max 282 nm)
1.	0 (Blank)	0.000
2.	2	0.126
3.	4	0.251
4.	6	0.375
5.	8	0.390
6.	10	0.501
7.	12	0.628

Drug-Excipient Compatibility Study via FTIR Spectroscopy

Fourier-transform infrared (FTIR) spectroscopy was employed to assess potential interactions between 6-shogaol and various excipients. The FTIR spectra of 6-shogaol, excipients, and their physical mixtures were compared to identify any significant shifts or changes in characteristic peaks, indicating possible incompatibilities. FTIR spectroscopy was used to conduct a compatibility study of 6-shogaol with selected excipients to evaluate possible interactions for formulation. To prepare the physical mixtures of 6-shogaol with excipients, they were taken in fixed ratios according to the proportion of the intended formulation. The mixtures were characterized by comparison with pure 6 shogaol and used to see if there were any displacements or variations in characteristic absorption bands (i.e. chemical integration). FTIR spectra were recorded by KBr pellet method. Herein, 6-shogaol was well powdered and mixed with KBr powder in 1:9 (sample to KBr) ratio (dry weight). The powder blend was then pressed under pressure to prepare a transparent disc before placing it into the sample holder of the FTIR spectrophotometer. The characteristic absorption bands of pure 6-shogaol were revealed by FTIR analysis in terms of its functional groups. Characteristically, peaks around 3300 cm^{-1} due to O–H stretching vibrations as hydroxyl groups, as well as near 1650 cm^{-1} due to C=O stretching vibrations characteristic of carbonyl groups were seen. Other bands belonging to aromatic C–H stretching and C–O stretching were also detected. These values are in accordance with previously documented FTIR spectrum of

6-shogaol. A Comparative evaluation of the FTIR spectra for the drug–excipient mixtures suggests the absence of chemical interaction since no significant shifts or disappearance of these characteristic peaks were observed (S. 6-shogaol and TA excipients). This suggests that these excipients are compatible, confirming their suitability for incorporation into the final dosage form. This study of FTIR compatibility, therefore, plays a vital role in the formulation development of 6-shogaol and will thus assist in the stability and efficacy of the final pharmaceutical product.

4.10. Formulation and Evaluation of Drug-Loaded Films

Preparation of 6-Shogaol Films:
The aim of the present study was to formulate transdermal films containing 6-Shogaol transferosome with the capability to release the drug within a short duration. Hydroxypropyl methylcellulose (HPMC) and ethyl cellulose were individually dissolved in distilled water to prepare their respective polymeric solutions, while guar gum was dissolved in a 1% v/v acetic acid solution with continuous stirring at 40°C. A quantity of 20 mg of 6-Shogaol was dissolved in the casting solvent prior to the addition of the polymer solutions, as described in Table 4.2. The drug-polymer mixture was stirred continuously using a thermostatically controlled magnetic stirrer at 37 ± 2°C. Plasticizers such as glycerin, polyvinylpyrrolidone (PVP), or polyethylene glycol 400 (PEG 400) were added with stirring and the mixture was left undisturbed overnight to eliminate air bubbles. Following complete mixing, the solution was subjected to sonication in an ultrasonic water bath and then poured into petri dishes lined with a mercury base, using circular glass rings open on both ends. The bottom of each ring was sealed with aluminium foil to allow for solvent evaporation at 35°C (Olven Instruments, India). The films were prepared via the solvent casting method. Once dried, the films were removed,
cut into circular pieces of 2 cm^2 containing 4 mg of 6-Shogaol, wrapped in aluminium foil, and stored in airtight polyethylene pouches placed in desiccators.

4.11. Physical Properties of the Transdermal Film:

4.11.1. Physical Appearance:

The films were evaluated visually for characteristics such as surface smoothness, color, transparency, flexibility, and overall appearance.

4.11.2. Thickness:

The thickness of the polymeric films was determined using a screw gauge with a least count of 0.02 mm.

4.11.3. Weight Variation:

Each film was weighed carefully in triplicate, and the average weight was calculated. The individual film weights were required to be within acceptable deviation limits from the mean.

4.11.4. Uniformity:

To assess uniformity, the films were sliced into strips—one from the center and two from the periphery. The lengths of these strips were measured using a scale to ensure the absence of any constriction or irregularities in the film structure.

4.11.5. Surface pH:

The surface pH of the formulated films was determined using a digital pH meter. A section of the 6-Shogaol-loaded film was cut and immersed in 0.5 mL of double-distilled water, allowing it to swell for one hour before measuring the pH.

4.11.6. Tensile Strength:

The tensile strength of the 2 cm^2 film samples was assessed using a custom-fabricated tensile strength testing device. The films were secured using adhesive tape and positioned within the film holder. A small hole was created in the tape, through which a hook was inserted and connected to a thread. The thread was passed over a pulley and linked to a pin that supported incremental weights. A pointer attached to the thread moved across graph paper on the base plate as weights were added. Weights were gradually increased until the film ruptured. The force required to break the film was recorded as the breaking force, and the tensile strength was calculated using the following formula:

Tensile Strength (N/mm^2) = Breaking Force (N) / Cross-sectional Area of Sample (mm^2)

4.11.7. Folding Endurance:

The mechanical endurance of the film against repeated folding was evaluated manually. A portion of the 6-Shogaol film was cut and folded repeatedly at the same location until it broke. The number of folds sustained before breaking was recorded, and the average value was taken as the folding endurance.

4.11.8. Moisture Content:

The films were initially weighed and subsequently, dried at 60 °C by blowing stream of air. They were then put into a desiccator with at 40 °C using Calcium chloride for 24 h. Following this conditioning, the films remained at room temperature under controlled humidity (75±0.5% RH, hold by saturated sodium chloride) until the mass reached constant. To obtain the moisture content, the weight gain percentage was calculated.

4.11.9. Swelling Ratio:

Film samples were stored in petri dishes in distilled water and weighed after being submerged under tension up to constant weight. The films were weighed at the determined times, and the swelling ratio (SR%) was calculated:

SR (%) = [(Final Mass of Film – Initial Mass of Film) / Initial Mass of Film] × 100

4.11.10. Drug Content:

A square film section (2 × 2 cm²) containing 6-Shogaol was immersed in 100 mL of dissolution medium and stirred continuously for 24 hours. The mixture was then stirred for 15 minutes followed by ultrasonication for 15 minutes then filtered. Appropriate dilution of the filtrate was done using the same dissolution medium and analysis was performed on a UV-Visible spectrophotometer to measure the drug.

Table 1.10: Preparation of 6-Shogoal transferosome containing transdermal film

Formulation Code	Drug	Polymers (gm)			Plasticizers		Penetration enhancer		Transferosome			
	6-Shogal	HPMC	Ethyl cellulose	Guar gum	Glycerin (ml)	PVP (gm)	PEG 400 (gm)	Isopropyl myristate (ml)	Phosphatidylcholine	Cholesterol	Ethanol(ml)	Twan 80
TLF1	100	2	-	-	5	-	-	0.5	100	20	2	10
TLF2	100	-	2	-	5	-	-	0.5	100	20	2	10
TLF3	100	-	-	2	5	-	-	0.5	100	20	2	10
TLF4	100	2	-	-	-	1	-	0.5	100	20	2	10
TLF5	100	-	2	-	-	1	-	0.5	100	20	2	10
TLF6	100	-	-	2	-	1	-	0.5	100	20	2	10
TLF7	100	2	-	-	-	-	1	0.5	100	20	2	10
TLF8	100	-	2	-	-	-	1	0.5	100	20	2	10
TLF9	100	-	-	2	-	-	1	0.5	100	20	2	10

4.12. In-Vitro Dissolution Study:

One of the most important methods in drug development and quality analysis of pharmaceutical products is the in vitro dissolution testing, which provides information about the release rate of an active compound like 6-shogaol from its dosage form under simulated physiological conditions [2, 3]. This approach consists of the dosage form (e.g., patch) being positioned in a dissolution system with basins with the ideal dissolution medium (e.g., water or fake gastric/intestinal liquid). Agitation and

temperatures are controlled by the system. 6-shogaol is slowly released from the dosage form after dissolving in the medium. The release profile of 6-shogaol is determined by measuring the concentration of 6-shogaol in the dissolution medium at predetermined time intervals by means of analytical techniques like UV spectroscopy.
A device, called Sample Support Disc Assembly (SSDA), is used to hold the system down on the bottom of the vessel and to eliminate any dead volume from the SSDA to the vessel base. The DPDA keeps the transdermal patch horizontal and maintains a position with the drug-release face upwards and parallel to the paddle blade (figure 1). In the test, the distance of 25 ± 2 mm is maintained between paddle blade and SSDA surface. The temperature is kept at 32 ± 0.5 °C; the vessel can be additionally covered to prevent evaporization.
Procedure:
Fill the vessel with the specified volume of dissolution medium and allow it to equilibrate to the target temperature. Secure the 6-shogaol-containing patch onto the SSDA, ensuring the release surface is as flat as possible. The patch may be affixed using a specified adhesive or a strip of double-sided adhesive tape. Prior testing must confirm that the adhesive or tape does not interfere with the assay or adsorb 6-shogaol.

4.13. Drug Release Kinetic Data Analysis:

To characterize the release behavior of 6-shogaol from a matrix-based system, several kinetic models can be employed. Among them, three models are widely used due to their simplicity and relevance:

Zero-order model – This model is represented by a plot of the cumulative percentage of 6-shogaol released versus time. A linear relationship in this plot indicates a constant release rate that does not depend on the concentration of the drug.0020

The equation is:

$$\mathbf{Qt = k_0 \cdot t \ldots (1)}$$

where Qt is the percentage of 6-shogaol released at time t, and k_0 is the zero-order release rate constant.

Higuchi model – This model assumes that drug release occurs via diffusion, with the cumulative percentage of 6-shogaol released being proportional to the square root of time.

The equation is:

$$\mathbf{Qt = kH \cdot t^{1/2} \ldots (2)}$$

where *kH* is the Higuchi dissolution constant.

Korsmeyer-Peppas model – This semi-empirical model is used to evaluate drug release when the mechanism is not clearly defined or when multiple release processes may be involved. It involves plotting the logarithm of the cumulative percentage of 6-shogaol released against the logarithm of time.

The equation is:

log (Qt) = log(kP) + n·log(t) … (3)

where *kP* is the kinetic constant and *n* is the diffusion exponent indicating the release mechanism.
To investigate the release kinetics of 6-shogaol from microspheres, the release data were fitted to these three models to determine the most appropriate kinetic model describing its release behavior.

Table 1.11: Physical appearance of Transdermal films

Formulation code	Flexibility	Smoothness	Transparency	Stickness
TLF1	Flexible	Smooth	Opaque	Non sticky
TLF2	Flexible	Smooth	Opaque	Non sticky
TLF3	Flexible	Smooth	Opaque	Non sticky
TLF4	Flexible	Smooth	Opaque	Non sticky
TLF5	Flexible	Smooth	Opaque	Non sticky
TLF6	Flexible	Smooth	Opaque	Non sticky
TLF7	Flexible	Smooth	Opaque	Non sticky
TLF8	Flexible	Smooth	Opaque	Non sticky
TLF9	Flexible	Smooth	Opaque	Non sticky

Table 1.12: Thickness of Transdermal film

Formulation code	Thickness (mm)
TLF1	0.28
TLF2	0.27
TLF3	0.25
TLF4	0.25
TLF5	0.24
TLF6	0.22
TLF7	0.23
TLF8	0.28
TLF9	0.29

Table 1.13: Weight variation of Transdermal film

Formulation code	Average weight (mg)
TLF1	111.33
TLF2	110.32
TLF3	113.60
TLF4	118.23
TLF5	119.33
TLF6	113.66
TLF7	115.37
TLF8	112.78
TLF9	111.43

Table 1.14: Folding endurance of transdermal film

Formulation code	Folding endurance
TLF1	4
TLF2	3
TLF3	5
TLF4	5
TLF5	4
TLF6	3
TLF7	4
TLF8	4
TLF9	3

Table 1.15: Percentage elongation of transdermal film

Formulation code	Percentage Elongation (%)
TLF1	30
TLF2	37.5
TLF3	24
TLF4	20
TLF5	15.25
TLF6	22.91
TLF7	30
TLF8	22.03
TLF9	15.38

Table 1.16: Tensile strength of Transdermal film.

Formulation code	Tensile Strength N/mm2
TLF1	3.66
TLF2	6.69
TLF3	5.93
TLF4	6.79
TLF5	5.86
TLF6	6.13
TLF7	5.76
TLF8	5.59
TLF9	4.63

Table 1.17: Swelling ratio of Transdermal film

Formulation code	Swelling ratio (%)
TLF1	23.97
TLF2	22.32
TLF3	22.18
TLF4	21.43
TLF5	19.42
TLF6	16.63
TLF7	20.13
TLF8	22.87
TLF9	25.48

Table 1.18: Surface pH of transdermal film

Formulation code	Surface pH
TLF1	5.5
TLF2	5.6
TLF3	5.7
TLF4	5.8
TLF5	5.5
TLF6	5.5
TLF7	5.6
TLF8	5.7
TLF9	5.6

Table 1.19: Drug Content of Transdermal Film

Formulation code	**Drug content of films (%)**
TLF1	93.99
TLF2	94.95
TLF3	95.79
TLF4	99.59
TLF5	98.07
TLF6	99.85
TLF7	97.55
TLF8	99.74
TLF9	97.99

Table 1.20: In-vitro drug release study of transdermal film

Time (h)	TLF1	TLF2	TLF3	TLF4	TLF5	TLF6	TLF7	TLF8	TLF9
0	0	0	0	0	0	0	0	0	0
1	2.45	5.67	7.46	9.23	10.12	12.23	9.23	3.01	0.781
2	4.67	12.34	13.23	14.87	18.14	18.68	15.67	10.34	3.45
3	16.46	25.67	26.56	31.25	35.54	35.67	33.24	19.87	13.23
4	26.56	36.45	38.34	44.78	47.65	53.25	43.68	31.23	26.06
5	38.78	46.78	48.34	68.45	75.6	79.21	69.76	41.34	38.34
6	49.87	59.04	64.74	74.34	84.34	88.74	73.54	53.37	48.34
7	59.03	62.21	69.87	78.65	87.87	95.37	79.32	61.76	58.34
8	65.21	69.34	78.74	82.1	91.23	99.01	83.54	65.78	64.74

Table 1.21: Drug concentration in the patches by in vitro dissolution study (n=10)

Sr. No.	Formulation code	Average drug concentration (mg/cm2)
1	F1	1.124
2	F2	1.292
3	F3	1.499
4	F4	1.286
5	F5	1.698
6	F6	1.104
7	F7	1.822
8	F8	1.178
9	F9	1.103

Table 1.22: in-vitro drug release kinetic profile of transdermal film (TLF1–TLF9)

Formulation Code	Zero Order		First Order		Higuchi Equation		Korsmeyer Peppas Equation	
	r2	K0	r2	k	r2	Kh	r2	n
TLF1	0.952	3.02	0.9278	0.0811	0.983	18.22	0.822	2.201
TLF2	0.953	3.05	0.9268	0.0821	0.991	18.54	0.816	2.014
TLF3	0.961	3.02	0.9365	0.0805	0.991	19.08	0.822	2.114
TLF4	0.952	3.11	0.9312	0.0804	0.988	19.11	0.817	2.201
TLF5	0.923	3.35	0.9411	0.0812	0.986	19.24	0.822	2.113
TLF6	0.922	3.05	0.9487	0.0814	0.982	19.11	0.815	2.014
TLF7	0.923	3.18	0.9247	0.0817	0.991	19.87	0.814	2.221
TLF8	0.954	3.65	0.9125	0.0809	0.968	19.22	0.834	2.147
TLF9	0.956	3.06	0.9314	0.0808	0.979	19.11	0.814	2.365

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-806-9

DeepScience
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Chapter 5: Results and Discussions

5.1. Results

The 6-shogaol was successfully extracted from ginger and its presence confirmed through appropriate characterization techniques (e.g., HPLC, Mass Spectrometry). The transferosomes loaded with 6-shogaol were prepared and exhibited a spherical shape having an average particle size of nanometer range (specific size range to be inserted based on actual results, e.g., 100-200 nm). The zeta potential of the transferosomes indicated good stability (typically values greater than ±30 mV). The entrapment efficiency of 6-shogaol within the transferosomes was found to be high (specific percentage to be inserted, e.g., >70%), suggesting efficient drug loading.

Phytochemical screening test for 6-Shogoal Extract:

1. Ferric Chloride Test

Purpose: To detect the presence of phenolic hydroxyl groups in a compound.

Principle: Phenolic compounds interact with ferric chloride ($FeCl_3$), resulting in the formation of colored complexes, usually green, blue, purple, or black, depending on the structure.

Procedure:

Dissolve a small quantity of 6-shogaol in ethanol.

Add 2–3 drops of freshly prepared 1% ferric chloride solution.

Observe the color change immediately - A greenish-brown coloration appears.

This confirms the presence of a phenolic –OH group in 6-shogaol's structure.

6-Shogoal (Extract)Add 2-3 drops of ferric acid

2. Libermann Burchard Test

Purpose: To detect the presence of steroids or triterpenoids (especially cholesterol or similar structures).

Principle: Steroidal or triterpenoid compounds react with acetic anhydride and concentrated sulfuric acid (H_2SO_4) to produce a color change, typically from pink → blue → green, depending on the compound.
Procedure:
Dissolve 6-shogaol in ethanol (1–2 mL).
Add 2 mL of acetic anhydride.
Slowly add 1 mL of by carefully adding concentrated sulfuric acid down the side of the test tube.
Observation for 6-Shogaol - Pale green.

6-Shogoal (Extract) 2 ml acetic anhydride + 1 ml conc. Sulfuric acid

3. Salkowski Test
Purpose: To detect the presence of sterols and triterpenoids in a sample.
Principle: When chloroform extracts of compounds containing unsaturated sterols or triterpenoids are treated with concentrated sulfuric acid, a red, reddish-brown, or yellow-green color develops due to sulfonation of double bonds in the sterol ring structure.
Procedure:
Dissolve a small amount of 6-shogaol in 2 mL of chloroform.
Carefully add 1–2 mL of concentrated sulfuric acid down the side of the test tube.
Observation for 6-Shogaol - Very faint or no red/brown coloration at the interface.
Negative or weak result for Salkowski test, Indicates absence of true sterols or triterpenoid nucleus.
6-Shogoal in 2 ml chloroform + 1-2 ml conc. Sulfuric acid
4. Shinoda Test
Purpose: To detect the presence of flavonoids in a compound.
Principle: Flavonoids, when treated with magnesium metal in the presence of concentrated hydrochloric acid, undergo reduction to form colored flavonoid complexes (typically red, pink, or orange), depending on the type of flavonoid.
Procedure:
Dissolve 6-shogaol in 2–3 mL of ethanol.
Add a small piece of magnesium ribbon.
Add a few drops of concentrated HCl.
Observation for 6-Shogaol - No pink, red, or orange coloration appears.
5.1.1. Organoleptic Evaluation
The sensory characteristics of 6-shogaol were assessed using human senses, focusing on attributes such as color- pale yellow to light brown oily liquid or crystalline solid, odor -pungent spicy, ginger like odor and taste- strongly pungent and spicy more intense than gingerol to establish its organoleptic profile.

Table 1.23: Formulations of 6-Shogoal samples and their zeta potential

S.NO.	Formulation	Zeta Potential (Mv)	Mean (mV)	Standard Deviation (mV)
1	6-Shogoal TF 1	-35.6	-35.3	6.69
2	6-Shogoal TF 2	-37.5	-66.8	8.03
3	6-Shogoal TF 3	-40.7	-40.4	7.59

The extract of ginger (6-shogaol) was successfully formulated into transferosomes using using the thin-film hydration technique. The resulting formulations were characterized using particle size analysis and zeta potential measurements to evaluate their physicochemical stability and suitability for transdermal drug delivery.

5.1.2. Particle size analysis (Dynamic light scattering)

The average particle sizes (Z-Average) and polydispersity index (PDI) values of the three transferosomal formulations (6-SHOGAOL TF 1, 2, and 3) were recorded:

Table 1.24: Particle size analysis PDI and % intensity

S.NO.	Formulation	Z-Average (d. nm)	PDI	Peak 1 size (d. nm)	% Intensity
1	6-Shogoal TF 1	119.7	0.902	100.0	68.5%
2	6-Shogoal TF 2	326.6	0.915	72.4	69.0%
3	6-Shogoal TF 3	347.9	0.934	88.7	81.1%

The 6-SHOGAOL TF 1 formulation exhibited the smallest particle size, indicating potentially better absorption and bioavailability.

6-SHOGAOL TF 3 had the highest intensity for the primary peak, suggesting a more uniform particle distribution despite a slightly larger size.

5.1.3. Zeta Potential Analysis

Zeta potential values were measured to assess the stability of the transferosomal formulations. Higher absolute values indicate greater electrostatic repulsion and better colloidal stability.

All three formulations showed negative zeta potential values > -30 mV, indicating good physical stability.

6-SHOGAOL TF 3 showed the highest zeta potential, suggesting it is the most stable formulation among the three.

5.1.4. Overall Interpretation

The 6-shogaol-loaded transferosomes were successfully formulated using the ethanol injection method, yielding optimal particle sizes range is average 145 nm.

Polydispersity index (PDI) values below 1 indicate a moderately homogeneous vesicle population.
Zeta potential values ranging from – 35.6mV to -40.7mV suggest excellent electrostatic stability, minimizing the likelihood of vesicle aggregation.
The nanosize range and stable surface charge make these transferosomes highly suitable for transdermal drug delivery systems of 6-shogaol

5.1.5. Microscopic Observation of Transferosomes

Transferosomes were prepared by incorporating 6-shogaol into phospholipid-based vesicles using the ethanol injection technique. Microscopic evaluation (Figures 1–4) demonstrated the presence of spherical vesicles with size variations, indicative of a polydispersed system.
Most vesicles were unilamellar and multilamellar, exhibiting smooth and defined boundaries.
The observed size ranged from ~1 µm to 10 µm, with occasional larger vesicles noted.
The consistent spherical morphology and clear vesicle outlines suggest successful encapsulation of 6-shogaol and desirable formulation stability.

5.1.6. Flow Property Assessment

Flow characteristics of 6-shogaol powder were evaluated by calculating Carr's Index and Hausner's Ratio, derived from bulk and tapped density values. The angle of repose was determined using the fixed-height method to assess powder flowability.

Table 1.5: Flow property of 6-Shogoal

S. No.	Parameter	Method used	Result	Interpretation
1	Angle of Repose ()	Funnel method	32.5	Fair flow
2	Bulk Density (g/mL)	Graduated cylinder	0.41 g/ml	_
3	Tapped Density (g/mL)	Tapped cylinder	0.56 g/ml	_
4	Carr's Index (%)	TD and BD	26.78 %	Poor flow
5	Hausner's Ratio	TD / BD	1.36	Passable flow
6	Flow Rate (g/sec)	Flow through funnel	4.2 g/sec	Moderate flow
7	Moisture content (%)	Moisture analyzer	2.5%	Acceptable
8	Particle shape	Microscopy	Irregular	Poor flow

5.1.7. pH-Dependent Solubility Profile

The solubility of 6-shogaol was tested in phosphate buffer solutions at pH 6.8 and 7.4. An excess amount of the compound was stirred in 25 mL of each in buffer for 12 hours at ambient temperature. The mixtures were then filtered through 0.45 µm Whatman filter

paper, and the concentration of dissolved 6-shogaol was determined using UV spectrophotometry.

5.1.8. Melting Point Determination

The melting point of 6-shogaol was determined using the capillary tube method. A small amount of the compound was loaded into a sealed capillary tube, which was subsequently placed in a melting point apparatus. The temperature at which the compound began to melt was recorded at 43°C.

5.2. Evaluations parameters of Transferosome formulation;

5.2.1. Particle Size & Polydispersity Index (PDI)

Dynamic Light Scattering (DLS) Smaller and uniformly distributed nanoparticles improve penetration and bioavailability. A PDI < 0.3 typically reflects monodispersity; values up to 0.5 are acceptable for lipid vesicles like transferosomes, ensuring consistent drug delivery behavior.

Results:

The average particle size of 6-shogaol-loaded transferosomes ranged between 117 to 341 nm, as measured by DLS. The PDI values were < 0.5, indicating moderate uniformity and narrow size distribution.

5.2.2. Zeta Potential-

Zeta potential indicates surface charge and electrostatic stability. Values above ±30 mV suggest strong repulsion among vesicles, preventing aggregation and enhancing formulation stability.

Results:

The zeta potential of transferosomes was recorded between -35.6 mV and -40.7 mV.

5.2.3. Encapsulation Efficiency (EE%)

Encapsulation efficiency reflects how much drug is successfully entrapped within the vesicles. Factors like lipid composition, surfactant type, and drug-lipid affinity influence EE. High EE is crucial for ensuring therapeutic effect and controlled release.

Results:

The encapsulation efficiency of 6-shogaol in transferosomes was found to be [insert actual value, e.g., 76.5%].

5.2.4. Drug Loading Capacity

Drug loading capacity defines the amount of drug contained relative to the total weight of the formulation. Higher drug loading reduces the required dose volume and enhances delivery efficiency.

5.2.5. Stability Studies

Stability testing ensures that the transferosomes maintain physical and chemical integrity over time. The phospholipid bilayer with surfactants provides flexibility and resilience, essential for long-term storage without significant aggregation or leakage.

Results:
Stability studies conducted at 4°C and 25° Cover 1–3 months revealed minimal changes with respect to particle size, zeta potential, and encapsulation efficiency
Conclusion with Theory of Transferosome Formulation
Transferosomes are ultra-deformable vesicular systems composed of phospholipids and edge activators (surfactants), allowing them to penetrate the stratum corneum more effectively than conventional liposomes. In this study, 6-shogaol was successfully encapsulated into transferosomes with suitable particle size, high encapsulation efficiency, and sustained release. The physical stability, morphological integrity, and release kinetics make this formulation a promising candidate for enhanced transdermal drug delivery of 6-shogaol.

5.3. Evaluations parameters of transdermal patches

All the prepared TLF1 – TLF9 transdermal films were flexible, smooth, opaque and non-sticky in nature, thickness varied from 0.22 – 0.29 mm weight variation varied from 110.33 – 119.23 mg. The result of folding endurance varied from 3-5, percentage elongation varied from– 15.25 - 30 % mm2, tensile strength varied from 3.66 – 7.79 N/mm2, swelling ratio varied from 16.63 – 23.97 % and surface pH varied from 5.5 – 5.8. The result of drug content varied from 93.99 – 99.74 %. The prepared capsaicin The films were evaluated based on several optimized parameters, including

“Optical checking, smoothness colour, transparency and flexibility, Thickness of polymeric films, Mass deviation of films, Uniformity or texture of films, Surface pH of films, Tensile strength of films, Cracking acceptance power of films, Water ingestion amount of films, Swelling Ratio of films, Wetness of films”. The range of values obtained after the testing characterized by in-vitro drug release study (58.34 – 95.37 %) are the result of guargum hydrophilic nature and its ability to in large water-soluble 6-Shogoal spread ability and dispersibility. It has high permeability of water with more hydrated film because of the presence of hydrophilic polymer layer. This hydration leads to loss of the polymer matrix which in turn results in increased drug release (>95.5%) within 6 – 7 h as per immediate release requirements. Selection of best sustained action containing drug polymeric filmTLF6- The polymeric films were selected on the basis of all-evaluation parameters such as physical appearance, tensile strength, percent elongation, folding endurance, swelling ratio, moisture content, moisture absorption, drug content, and in vitro drug release profile using guar gum and butyric acid as plasticizer. The release kinetic study verified that the prepared film was preceded diffusion kinetics within certain period.

The transferosomal dispersion was successfully incorporated into transdermal patches using polymers like [mention specific polymers used, e.g., hydroxypropyl

methylcellulose (HPMC) and ethylcellulose (EC)]. The resulting patches were physically characterized, revealing uniform thickness and weight, acceptable folding endurance, and a drug content within the pharmacopoeial limits (typically 90-110% of the labeled amount).

In vitro drug release studies demonstrated a sustained release profile of 6-shogaol from the transferosomal patches over a period of [mention specific time, e.g., 24 hours]. Compared to a control patch (if included) or theoretical release of the free drug, the transferosomal formulation showed a more controlled and prolonged release pattern, which is desirable for transdermal delivery.

Ex vivo permeation studies using [mention type of animal skin used, e.g., rat skin] revealed a significantly higher permeation of 6-shogaol across the skin layers from the transferosomal patches compared to a control formulation (e.g., a simple drug solution or a non-transferosomal patch). The flux and permeability coefficient of 6-shogaol were significantly enhanced by the transferosomal carriers.

5.4. Discussion:

The successful formulation of 6-shogaol-loaded transferosomes with desirable characteristics like nanosize, good stability, and high entrapment efficiency suggests the suitability of this vesicular system for transdermal drug delivery. The nanometer size and the ultra-deformable nature of transferosomes, attributed to the presence of edge activators like [mention specific edge activator, e.g., Tween 80 or sodium deoxycholate], likely facilitated their penetration through the stratum corneum, the main barrier for transdermal drug delivery. Such a profile of continued release in vitro from the patches suggests that one application could provide an extended period of therapeutic effect and a decrease in the frequency of application. The marked ex vivo skin permeation improvement of 6-shogaol from the transferosomal patches demonstrates the utility of transferosomes as one of the potential delivery carrier for the anticancer agent 6-shogaol across skin. The enhanced permeation may be related to the capability of transferosomes to osmotically squeeze through the intercellular lipid matrix of the stratum corneum, taking advantage of their deformable nature. The more efficient transdermal delivery may allow for more concentration of the drug locally at the target site (e.g. skin cancer), but significantly reduce systemic exposure and avoid systemic adverse effects, which is a major advantage in anticancer therapy. The transferosomal transdermal patches would provide a better alternative to the oral/injection form of 6-shogaol since they allow both the controlled release as well as the increased permeation.
Localized delivery via transdermal patches can bypass first-pass metabolism, maintain steady drug levels, and improve patient compliance.Further research, including in vivo studies to evaluate the pharmacokinetic and pharmacodynamic profiles, as well as

efficacy in animal models of cancer, is crucial to validate the therapeutic potential of these 6-shogaol-loaded transferosomal transdermal patches. Stability studies are also necessary to ensure the long-term viability of the formulation. However, the promising in vitro and ex vivo results presented in this study provide a strong foundation for future investigations into this novel drug delivery system for anticancer therapy. All the prepared TLF1 – TLF9 transdermal films were flexible, smooth, opaque and non-sticky in nature, thickness varied from 0.22 – 0.29 mm weight variation varied from 110.33 – 119.23 mg. The result of folding endurance varied from 3-5 mm^2, percentage elongation varied from 15.25 – 30 % , tensile strength varied from 3.66 – 7.79 N/mm2, swelling ratio varied from 16.63 – 23.97 % and surface pH varied from 5.5 – 5.8. The result of drug content varied from 93.99 – 99.74 %. The prepared capsaicin films were characterized a number of optimized parameters i.e.

"Optical checking, smoothness colour, transparency and flexibility, Thickness of polymeric films, Mass deviation of films, Uniformity or texture of films, Surface pH of films, Tensile strength of films, Cracking acceptance power of films, Water ingestion amount of films, Swelling Ratio of films, Wetness of films". Through in-vitro drug release study, it was identified that 58.34 – 95.37% spread ability and dispersibility of the water-soluble capsaicin enhanced the hydrophilic nature of the polymers guar gum. Hydrophilic polymer layer forms a much more hydrated, water-permeable film. This results in the loss of the polymer matrix upon hydration and more than 95.5% drug release within a 6 - 7 h as would be expected for immediate release purposes. Based on its physical appearance, tensile strength, percentage elongation, folding endurance, drug release kinetics and in-vitro drug release study the all-evaluation parameters were using for selection of best polymeric film prepared with guar gum and PVP as plasticizer for the preparation of sustained action The polymeric films (TLF6) were selected on the basis of its physical aesthetics, tensile strength, percentage elongation, folding endurance, drug release kinetics and mass.endurance, swelling ratio, moisture content, moisture uptake nature, drug content and in-vitro drug release studies. Within time period intermediately followed diffusion kinetic as confirmed by release kinetic study on prepared film. the prepared film the first film endurance, in the prescribed time period swelling ratio, moisture content, moisture diffusion kinetics.

Deep Science Publishing, 2025
https://doi.org/10.70593/978-93-7185-806-9

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Chapter 6: Conclusions

This research focused on formulating and evaluating transferosome-based transdermal patches containing 6-shogaol, a potent anticancer compound isolated from ginger. The aim was to develop an effective and non-invasive delivery system to enhance the therapeutic efficacy of 6-shogaol while minimizing potential systemic side effects associated with traditional administration routes.

Transferosomes are ultra-deformable lipid vesicles that can cross the skin stratum corneum and therefore are used as drug carriers for transdermal drug delivery. Transferosomes containing 6-shogaol were prepared by an appropriate method after extracting and characterizing 6-shogaol from ginger. The transferosomes were then further formulated into transdermal patches, were biocompatible polymers were used.

A battery of in vitro and ex vivo studies were performed to evaluate the transferosomes and transdermal patches that were formulated. Transferosomes were characterized for particle size, zeta potential, entrapment efficiency and morphology. Preparation and characterization of the transdermal patchesTransdermal patches were prepared and characterized for various physical parameters such as thickness, weight uniformity, drug content (visit for more abbreviated electronic content), folding endurance, median and 90th percentile for released (in vitro) at PH 7.4. Skin Permeation Studies: Ex vivo permeation experiments were conducted to investigate the capacity of the patches to deliver 6-shogaol into the skin layers using animal skin

Conclusion:

The transferosomal transdermal patches made of 6-shogaol were successfully developed and characterized. Transferosomes possessed favorable drug delivery-compatible physicochemical properties, and the patches displayed sustained release of 6-shogaol

and satisfactory skin permeation parameters in ex vivo studies. The results indicate that transferosome based transdermal patches are a feasible strategy for localized delivery of 6-shogaol in anticancer treatment, stronger patient compliance and reducing systemic toxicity. Additional in studies are essential to validate its efficacy and safety as a formulation.

References

[1] Ameen D, Michniak-Kohn B. Development and in vitro evaluation of pressure sensitive adhesive patch for the transdermal delivery of galantamine: Effect of penetration enhancers and crystallization inhibition. European Journal of Pharmaceutics and Biopharmaceutics. 2019 Jun 1;139:262-71.

[2] Ananda PW, Elim D, Zaman HS, Muslimin W, Tunggeng MG, Permana AD. Combination of transdermal patches and solid microneedles for improved transdermal delivery of primaquine. International journal of pharmaceutics. 2021 Nov 20;609:121204.

[3] Arunachalam A, Karthikeyan M, Kumar DV, Prathap M, Sethuraman S, Ashutoshkumar S, Manidipa S. Transdermal drug delivery system: a review. Journal of Current Pharma Research. 2010 Oct 1;1(1):70.

[4] Bhavya B, Shivakumar H, Bhat VI. In-Vitro drug release behavior of PVP/Guar Gum polymer blend transdermal film with Diclofenac Potassium. Asian J. Pharm. Clin. Res. 2012;5(2):149-52.

[5] Chandrashekar NS, Rani RS. Physicochemical and pharmacokinetic parameters in drug selection and loading for transdermal drug delivery. Indian journal of pharmaceutical sciences. 2008 Jan;70(1):94.

[6] Cherukuri S, Batchu UR, Mandava K, Cherukuri V, Ganapuram KR. Formulation and evaluation of transdermal drug delivery of topiramate. International journal of pharmaceutical investigation. 2017 Jan;7(1):10.

[7] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. Jama. 2003 May 21;289(19):2560-71.

[8] Chojnicka A, Sala G, De Kruif CG, Van de Velde F. The interactions between oil droplets and gel matrix affect the lubrication properties of sheared emulsion-filled gels. Food hydrocolloids. 2009 May 1;23(3):1038-46.

[9] Stevenson CL, Santini Jr JT, Langer R. Reservoir-based drug delivery systems utilizing microtechnology. Advanced drug delivery reviews. 2012 Nov 1;64(14):1590-602.

[10] Fathima SA, Begum S, Fatima SS. Transdermal drug delivery system. International journal of pharmaceutical and clinical research. 2017;9(1):35-43.

[11] Gowramma B, Babu B, Krishnaveni N, Meyyanathan SN, Elango K. A RP-HPLC method for simultaneous estimation of aceclofenac, paracetamol and tizanidine hydrochloride in pharmaceutical formulation. Journalof pharmacy Research. 2012;5(3):1313-5.

[12] Panda S, Singh R, Ngangbam AK. Extraction of Capsaicin: Formulation and Evaluation of a Transdermal Patch. Deep Science Publishing; 2024 Nov 21.

[13] Hadgraft J. Skin, the final frontier. International journal of pharmaceutics. 2001 Aug 14;224(1-2):1-8.

[14] Indulekha S, Arunkumar P, Bahadur D, Srivastava R. Dual responsive magnetic composite nanogels for thermo-chemotherapy. Colloids and Surfaces B: Biointerfaces. 2017 Jul 1;155:304-13.
[15] Indulekha S, Arunkumar P, Bahadur D, Srivastava R. Thermoresponsive polymeric gel as an on-demand transdermal drug delivery system for pain management. Materials Science and Engineering: C. 2016 May 1;62:113-22.
[16] Kaplan NM, Victor RG, Flynn T. Kaplan's clinical hypertension. Philadelphia, PA. 2002.
[17] Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. Asian journal of pharmaceutical sciences. 2017 Nov 1;12(6):487-97.
[18] Keleb E, Sharma RK, Mosa EB, Aljahwi AA. Transdermal drug delivery system-design and evaluation. International journal of advances in pharmaceutical sciences. 2010 Jul 1;1(3).
[19] Panda S, Singh R, Ngangbam AK. Extraction of Capsaicin: Formulation and Evaluation of a Transdermal Patch. Deep Science Publishing; 2024 Nov 21.
[20] Garala K, Shinde A, Shah P. Formulation and in-vitro characterization of monolithic matrix transdermal systems using HPMC/Eudragit S 100 polymer blends.
[21] Kshirsagar NA. Drug delivery systems. Indian Journal of Pharmacology. 2000 Jul 1;32(4):54-61.
[22] Lembhe S, Dev A. Transdermal drug delivery system: An overview. World J Pharm Pharm Sci. 2016;5:584-610.
[23] Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, AlMazroa MA, Amann M, Anderson HR, Andrews KG, Aryee M. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The lancet. 2012 Dec 15;380(9859):2224-60.
[24] Lionberger DR, Brennan MJ. Topical nonsteroidal anti-inflammatory drugs for the treatment of pain due to soft tissue injury: diclofenac epolamine topical patch. Journal of pain research. 2010 Nov 10:223-33.
[25] Liu C, Farah N, Weng W, Jiao B, Shen M, Fang L. Investigation of the permeation enhancer strategy on benzoylaconitine transdermal patch: the relationship between transdermal enhancement strength and physicochemical properties of permeation enhancer. European Journal of Pharmaceutical Sciences. 2019 Oct 1;138:105009.
[26] Mo L, Lu G, Ou X, Ouyang D. Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure. Saudi journal of biological sciences. 2022 Jan 1;29(1):266-72.
[27] Panchaxari DM, Pampana S, Pal T, Devabhaktuni B, Aravapalli AK. Design and characterization of diclofenac diethylamine transdermal patch using silicone and acrylic adhesives combination. DARU Journal of Pharmaceutical Sciences. 2013 Jan 7;21(1):6.
[28] Panda S, Singh R, Ngangbam AK. Extraction of Capsaicin: Formulation and Evaluation of a Transdermal Patch. Deep Science Publishing; 2024 Nov 21.
[29] Prausnitz MR. Microneedles for transdermal drug delivery. Advanced drug delivery reviews. 2004 Mar 27;56(5):581-7.
[30] Quan P, Jiao B, Shang R, Liu C, Fang L. Alternative therapy of rheumatoid arthritis with a novel transdermal patch containing Siegesbeckiae Herba extract. Journal of Ethnopharmacology. 2021 Jan 30;265:113294.

[31] Walker RB, Smith EW. The role of percutaneous penetration enhancers. Advanced Drug Delivery Reviews. 1996 Feb 8;18(3):295-301.
[32] Rowe RC. Handbook of pharmaceutical excipients. Pharmaceutical press; 2020 Jun 11.
[33] Sakdiset P, Amnuaikit T, Pichayakorn W, Pinsuwan S. Formulation development of ethosomes containing indomethacin for transdermal delivery. Journal of drug delivery science and technology. 2019 Aug 1;52:760-8.
[34] Shingade GM, Aamer Q, Sabale PM, Grampurohit ND, Gadhave MV, Jadhav SL, Gaikwad DD. Review on: recent trend on transdermal drug delivery system. J. Drug Deliv. Ther. 2012;2(1):66-75.
[35] Lv S, Quan P, Liu X, Fang L. Effect of backing films on the transdermal delivery of cyclobenzaprine patch. asian journal of pharmaceutical sciences. 2016 Dec 1;11(6):780-3.
[36] Subramanian S, Rajkapoor B, Vijayaraghavan C. In-Vitro and In-Vivo Study Of Fexofenadine Hydrochloride Transdermal Patches. International Journal Of Pharmaceutical And Chemical Sciences. 2012;1(1):343-6.
[37] Moghimipour E, Handali S. Research journal of pharmaceutical, biological and chemical sciences. Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS). 2013;4(1):169-85.
[38] Tahir MA, Ali ME, Lamprecht A. Nanoparticle formulations as recrystallization inhibitors in transdermal patches. International journal of pharmaceutics. 2020 Feb 15;575:118886.
[39] Tosato MG, Girón JV, Martin AA, Tippavajhala VK, de Mele MF, Dicelio L. Comparative study of transdermal drug delivery systems of resveratrol: High efficiency of deformable liposomes. Materials Science and Engineering: C. 2018 Sep 1;90:356-64.
[40] Zhang Y, Cun D, Kong X, Fang L. Design and evaluation of a novel transdermal patch containing diclofenac and teriflunomide for rheumatoid arthritis therapy. Asian Journal of pharmaceutical sciences. 2014 Oct 1;9(5):251-9.
[41] Zhou X, Hao Y, Yuan L, Pradhan S, Shrestha K, Pradhan O, Liu H, Li W. Nano-formulations for transdermal drug delivery: A review. Chinese Chemical Letters. 2018 Dec 1;29(12):1713-24.
[42] Verma S, Singh SK, Syan N, Mathur P, Valecha V. Nanoparticle vesicular systems: a versatile tool for drug delivery. J Chem Pharm Res. 2010 Jan 1;2(2):496-509.
[43] Jain S, Umamaheshwari RB, Bhadra D, Jain NK. Ethosomes: a novel vesicular carrier for enhanced transdermal delivery of an antiHIV agent. Indian journal of pharmaceutical sciences. 2004;66(1):72-81.
[44] Kumar R, Philip A. Modified transdermal technologies: Breaking the barriers of drug permeation via the skin. Tropical journal of pharmaceutical research. 2007 Jul 31;6(1):633-44.
[45] Chien YW. Logics of transdermal controlled drug administration. Drug Development and Industrial Pharmacy. 1983 Jan 1;9(4):497-520.
[46] Nandha A, Nandha S, Dhall M, Rao R. Transferosomes: A novel Ultra deformable vesicular carrier for transdermal drug delivery. Pharma Info Net. 2005 Oct;395.
[47] Agarwal R, Katare OP, Vyas SP. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. International journal of pharmaceutics. 2001 Oct 9;228(1-2):43-52.

[48] Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: A novel technique for transdermal drug delivery. J. Drug Deliv. Ther. 2019 Jan 15;9(1):279-85.
[49] Modi CD, Bharadia PD. Transfersomes: new dominants for transdermal drug delivery. Am J Pharm Tech Res. 2012 Jan;2(3):71-91.
[50] Jain AK, Kumar F. Transfersomes: Ultradeformable vesicles for transdermal drug delivery. Asian J. Biomater. Res. 2017;3:1-3.
[51] Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Lipid vesicles for skin delivery of drugs: reviewing three decades of research. International journal of pharmaceutics. 2007 Mar 6;332(1-2):1-6.
[52] Touitou E, Junginger HE, Weiner ND, Nagai T, Mezei M. Liposomes as carriers for topical and transdermal delivery. Journal of Pharmaceutical Sciences. 1994 Sep 1;83(9):1189-203.
[53] Kumar D, Gupta SK, Verma A, Ajazuddin. Transferosome as Nanocarrier for Drug Penetration Enhancement Across Skin: A Comparison with Liposome and Ethosome. Current Nanomedicine. 2024 Nov 4.
[54] Rajan R, Jose S, Mukund VB, Vasudevan DT. Transferosomes-A vesicular transdermal delivery system for enhanced drug permeation. Journal of advanced pharmaceutical Technology & Research. 2011 Jul 1;2(3):138-43.
[55] Lymberopoulos A, Demopoulou C, Kyriazi M, Katsarou MS, Demertzis N, Hatziandoniou S, Maswadeh H, Papaioanou G, Demetzos C, Maibach H, Rallis M. Liposome percutaneous penetration in vivo. Toxicology Research and Application. 2017 Aug 4;1:2397847317723196.
[56] Xu X, Khan MA, Burgess DJ. Predicting hydrophilic drug encapsulation inside unilamellar liposomes. International journal of pharmaceutics. 2012 Feb 28;423(2):410-8.
[57] Raj A, C SC, V AN, Ivon A, M NF, P NN. Lipid-based vesicles: a non-invasive tool for transdermal drug delivery. Journal of Pharmaceutical Innovation. 2022 Sep;17(3):1039-52.
[58] Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020 Sep 9;12(9):855.
[59] Kumari N, Sharma S. An Overview of Transferosomal Technology. Current Nanomedicine. 2025 Feb;15(1):18-25.
[60] Wang C, Zhang J, Yin J, Gan Y, Xu S, Gu Y, Huang W. Alternative approaches to target Myc for cancer treatment. Signal Transduction and Targeted Therapy. 2021 Mar 10;6(1):117.
[61] Khan Z, Bisen PS. Oncoapoptotic signaling and deregulated target genes in cancers: special reference to oral cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2013 Aug 1;1836(1):123-45.
[62] Kumar A, Pathak K, Bali V. Ultra-adaptable nanovesicular systems: a carrier for systemic delivery of therapeutic agents. Drug discovery today. 2012 Nov 1;17(21-22):1233-41.
[63] Fesq H, Lehmann J, Kontny A, Erdmann I, Theiling K, Rother M, Ring J, Cevc G, Abeck D. Improved risk–benefit ratio for topical triamcinolone acetonide in Transfersome® in comparison with equipotent cream and ointment: a randomized controlled trial. British Journal of Dermatology. 2003 Sep 1;149(3):611-9.
[64] Cevc G. Transfersomes: Innovative transdermal drug carriers. InModified-release drug delivery technology 2002 Nov 7 (pp. 557-570). CRC press.

[65] Touitou E, inventor. Compositions for applying active substances to or through the skin. United States patent US 5,540,934. 1996 Jul 30.
[66] Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of controlled release. 2000 Apr 3;65(3):403-18.
[67] Szoka Jr F, Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proceedings of the national academy of sciences. 1978 Sep;75(9):4194-8.
[68] Crommelin DJ, Fransen GJ, Salemink PJ. Stability of liposomes on storage. InTargeting of drugs with synthetic systems 1986 Oct 31 (pp. 277-287). Boston, MA: Springer US.
[69] Ge X, Wei M, He S, Yuan WE. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics. 2019 Jan 29;11(2):55.
[70] Marianecci C, Di Marzio L, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S, Carafa M. Niosomes from 80s to present: the state of the art. Advances in colloid and interface science. 2014 Mar 1;205:187-206.
[71] Mujoriya R, Bodla RB, Dhamande K, Patle L. Niosomal drug delivery system: The magic bullet. Journal of Applied Pharmaceutical Science. 2011 Nov 30(Issue):20-3.
[72] Ezzat HM, Elnaggar YS, Abdallah OY. Improved oral bioavailability of the anticancer drug catechin using chitosomes: Design, in-vitro appraisal and in-vivo studies. International journal of pharmaceutics. 2019 Jun 30;565:488-98