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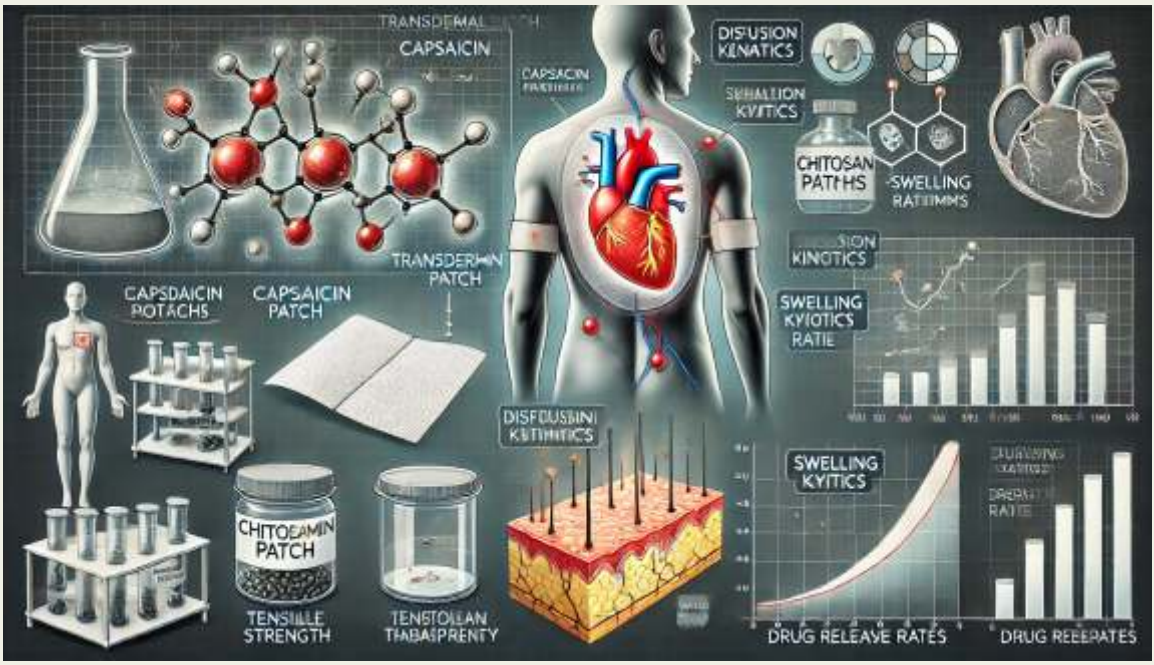

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Preface

Ethyl ester prodrug of non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor capsaicinat is the proposed model drug capsaicin. These hypothesized TDDs managed ventricular arrhythmias and had short biological half-life, low oral bioavailability, dosage, and molecular weight for better drug absorption. The suggested transdermal patch combines a slow-release calcium channel blocker with a sustained-release capsaicin angiotensin converting enzyme inhibitor. The prepared capsaicin film was characterized by “optical checking, smoothness color, transparency and flexibility, thickness of polymeric films, mass deviation, uniformity or texture, surface pH, tensile strength, cracking acceptance power, water ingestion amount, swelling ratio, wetness, and in-vitro drug release study”. Hydrophilic polymers chitosan increased water-soluble capsaicin spreadability and regulated drug release by 95.5% in 12 hours. The polymeric films (TLF6) were chosen for their look, tensile strength, percentage elongation, folding endurance, swelling ratio, moisture content, moisture uptake nature, drug content, and in-vitro drug release study parameters. Release kinetics showed that the produced film followed diffusion kinetics and released immediately. The release kinetic investigation showed that the patch followed super case II diffusion kinetics with sustained release over time. After regression analysis, slope values were calculated from the graph and r^2 values indicated linearity.

Keywords: Transdermal patches, Capsaicin, Anti-inflammatory, Endurance test, Permeation enhancer, TDDS.

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Chapter 1

Introduction

Topical drug delivery system

Easy use and good patient compliance make oral drug administration the most popular. Its drawbacks include hepatic first-pass metabolism requiring greater medication dosages and stomach discomfort from surfactants in lipid-based formulations. Unintended adverse effects are common with systemic drug delivery. Non-invasive, non-painful, and non-irritating topical drug delivery devices may overcome these constraints. These systems use targeted drug delivery to lower systemic toxicity, first-pass metabolism, gastrointestinal irritation, and percutaneous absorption, and boost bioavailability with sustained release characteristics. Despite these benefits, typical transdermal formulations including ointments, creams, and lotions have stickiness, poor spreadability, and stability concerns that cause patient non-compliance. Topical medication distribution is difficult because the stratum corneum is difficult to penetrate. This 40% protein, 40% lipid, and 20% water layer with tight intercellular connections is a stronger barrier than the gastrointestinal, rectal, buccal, nasal, and vaginal membranes. Despite these obstacles, topical medication administration can be used for site-specific or systemic effects when other routes fail. It effectively treats fungal infections. Recent advances in semisolid transparent gel compositions have broadened cosmetic and medicinal applications. These compositions improve stability, spreadability, and aesthetics over standard preparations. Formulation scientists still struggle to create efficient topical dose formulations.

Topical drug delivery systems are unique ways to deliver drugs directly to the skin or mucosal surfaces for localized and systemic effects. This approach is used for skin problems, pain treatment, and cosmetics. Topical drug delivery systems avoid first-pass metabolism and reduce systemic side effects, making them a good alternative to oral or injectable drugs. These devices' ease of use and non-invasiveness improve patient compliance, making them popular in clinical and consumer sectors. Topical drug delivery systems can transport medications directly to the skin's surface or deeper layers, depending on the therapeutic impact. The stratum corneum, the skin's outermost layer, protects it from foreign contaminants. Advanced formulations use penetration enhancers, lipid-based systems, and nanotechnology to bypass this barrier. These technologies allow active medicinal compounds to infiltrate the skin and reach their targets, enhancing efficacy and lowering the need for greater dosages.

Recently developed topical drug delivery systems use nanocarriers such liposomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers. Drug encapsulation, degradation protection, and controlled release are the goals of these nanocarriers. Liposomes imitate skin lipids to improve medication penetration. Solid lipid nanoparticles provide medicine stability and controlled release appropriate for chronic skin disorders including eczema and psoriasis. Nanotechnology in topical formulations has enhanced medicine distribution and created new treatment pathways for difficult ailments. Due to their high water content, biocompatibility, and capacity to deliver hydrophilic and hydrophobic medicines, hydrogel-based systems have garnered attention in recent years. Hydrogels can heal wounds and distribute systemic drugs via transdermal patches. These cooling and relaxing devices are ideal for inflammatory skin disorders. They can also be loaded with nanoparticles or other sophisticated carriers to boost efficacy.

Bioresponsive and stimuli-responsive topical medication delivery technologies are also growing. Advanced formulations release the medicine in reaction to pH, temperature, or enzymes at the application site. For acne and infections, where the local pH is altered, pH-sensitive formulations are being investigated. Body heat releases painkillers from temperature-responsive gels. Smart delivery technologies ensure precision and reduce drug waste, advancing individualized therapy. Adding biologics like peptides, proteins, and nucleic acids to topical medication formulations is fascinating. Recent formulation advances have permitted skin administration of these complex compounds, which were previously difficult because to their size and stability. To bypass the stratum corneum and reach therapeutic levels, microneedle patches are being developed to deliver biologics gently into the skin. This technology has great potential for vaccine distribution, hormone replacement therapy, and autoimmune disease treatment.

Digital methods in topical medicine delivery are another advancement. Wearable and smart patches are being developed to monitor and manage medicine administration in real time. These systems use sensors to monitor temperature and moisture and modify medicine release. Smart dressings can monitor chronic wound healing and release antimicrobial medicines as needed, lowering infection risk and speeding recovery. Topical drug delivery and digital health technologies are changing treatment administration and monitoring. Topical medication delivery methods are important in cosmetic and dermatological industries as well as medicine. Popular goods in this segment include anti-aging creams, sunscreens, and hyperpigmentation treatments. Modern carriers like liposomes and nanoparticles have increased cosmetic formulation efficacy and stability. Consumers want eco-friendly products, therefore research into plant-based and biodegradable delivery systems is driven by demand for natural and sustainable components.

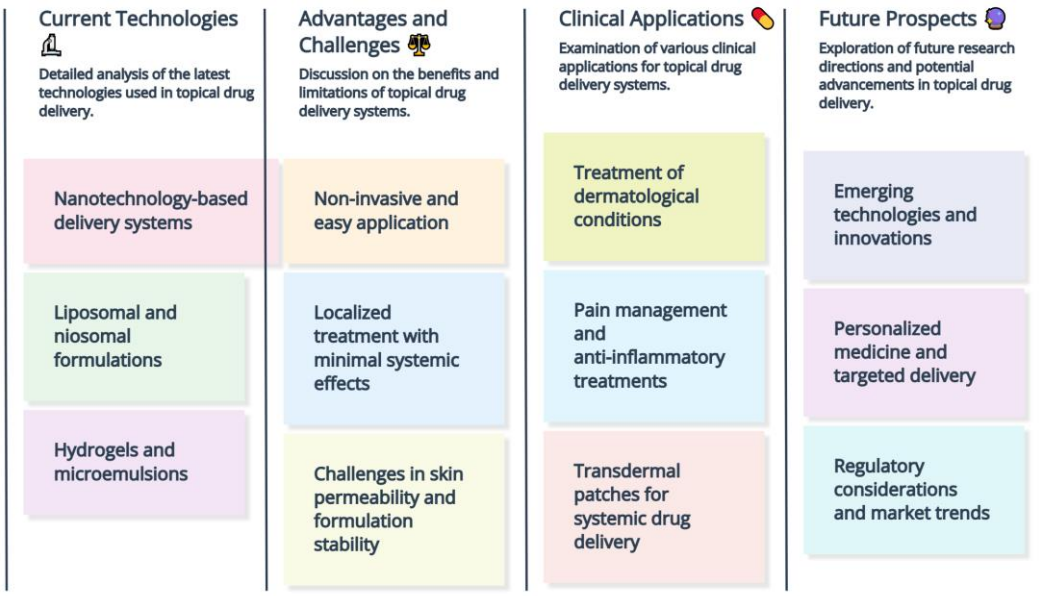

Fig. 1 Topical drug delivery system

Despite these advances, topical medication delivery system research and commercialization remain difficult. Delivering drugs consistently across skin types and circumstances is a major challenge. Topical formulations can be affected by skin permeability, which is affected by age, moisture, and disease. Patient adherence can be difficult, especially for chronic illnesses that necessitate frequent product use. Dermatologists, formulation scientists, and engineers must collaborate to solve these problems. Topical drug delivery system development also depends on regulations. FDA and EMA approval requires formulas to be safe, effective, and stable. Advanced technologies like nanocarriers and biologics require updated rules to meet strict safety criteria. For reliable evaluation of new formulations, standardized skin penetration and drug release testing methodologies are needed. The rise of personalized medicine will influence topical medication delivery technologies. Biomarkers that predict medication responses are being found thanks to genetics and proteomics. This knowledge can be utilized to create patient-specific formulations that maximize therapeutic benefits and minimize side effects. For instance, genetic insights can help create targeted treatments for psoriasis, whose causes differ by individual.

Future topical medicine delivery technologies must also address environmental sustainability. The pharmaceutical and cosmetic sectors are adopting green chemistry and producing biodegradable formulations to reduce their environmental impact. This

involves drug delivery via natural polymers like chitosan and alginate. These biocompatible, eco-friendly materials support global sustainability efforts.

A rapidly growing and essential part of pharmaceutical science, topical drug delivery systems provide therapeutic chemicals directly to the skin or mucosal surfaces for localized or systemic effects. This approach is popular since it is non-invasive, easy to use, and delivers medications exactly to the target location. This discipline has advanced due to the need for improved medication bioavailability, patient compliance, and creative treatment solutions for challenging therapeutic issues. Topical drug delivery methods deposit APIs onto or within the skin to address localized diseases or achieve systemic absorption. These systems avoid the gastrointestinal tract and first-pass metabolism, decreasing systemic side effects from oral or injectable approaches. The stratum corneum, the skin's outermost layer, prevents medication penetration. Penetration enhancers, new formulation methods, and nanocarriers have been used to solve this difficulty. Today's topical formulations demonstrate this delivery method's versatility. Creams, ointments, gels, and lotions are still popular due to their simplicity and affordability. More advanced technologies including transdermal patches, liposomes, and solid lipid nanoparticles provide regulated and sustained medication release. Transdermal patches have become popular for systemic drug delivery because they release medication slowly and reduce dosage. These patches help with chronic illnesses like pain, hormone replacement, and nicotine addiction.

Nanocarriers including liposomes, niosomes, and nanostructured lipid carriers have transformed topical medication delivery. These carriers stabilize drugs, prevent API degradation, and improve skin penetration. Lipid bilayer vesicles called liposomes resemble skin lipids, enhancing medication permeability and retention. Solid lipid nanoparticles combine the benefits of classic emulsions with the stability of solid particles, making them appropriate for hydrophilic and hydrophobic medicines. These advances allow for new treatments for difficult dermatological disorders like psoriasis, atopic dermatitis, and fungal infections. Hydrogels are promising topical medication delivery vehicles. Hydrogels soothe and cool burns, wounds, and inflammatory skin conditions due to their high water content, biocompatibility, and capacity to deliver a variety of medications. Hydrogel technology has enabled hybrid systems that mix hydrogels with nanoparticles or other carriers to improve medicine delivery and efficacy. Silver nanoparticle-loaded hydrogels are useful for wound care and infection prevention due to their antibacterial properties.

Stimuli-responsive medication delivery devices are innovative topicals. Drug release is triggered by pH, temperature, or enzymes in these systems. To treat acne, pH-sensitive formulations are being created since the acidic environment can release drugs. In pain

management, temperature-responsive gels release medicine when heated. These smart technologies increase drug targeting, waste reduction, and patient outcomes, advancing personalized medicine. Adding biologics to topical medication delivery devices is another innovation. Due to their bulk, fragility, and disintegration, biologics like peptides, proteins, and nucleic acids are difficult to distribute. Innovative formulation methods like microneedle encapsulation and lipid-based carriers have made skin delivery of complicated compounds possible. Microneedle patches generate skin channels that allow biologics to bypass the stratum corneum and reach therapeutic levels. This method has great potential for vaccine administration, gene therapy, and autoimmune disease treatment.

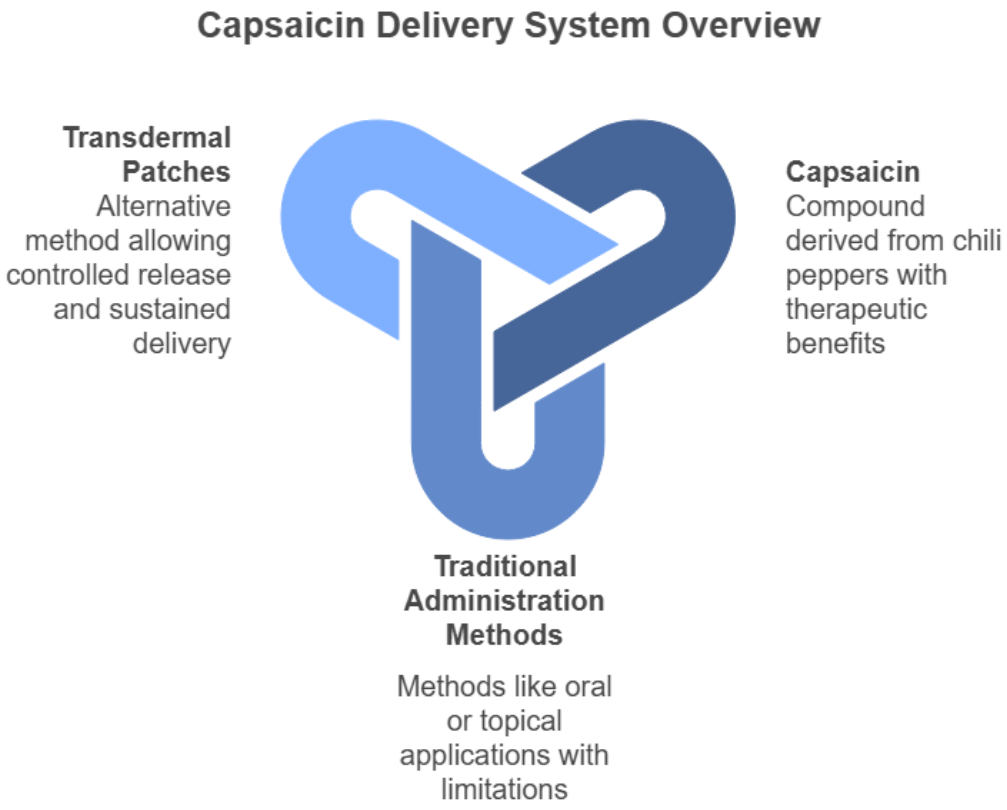

Fig. 2 Capsacin Delivery System

Digital innovations in topical medicine delivery devices have expanded this field. Wearable and smart patches are being developed to monitor and manage medicine administration in real time. These devices monitor physiological conditions including temperature, moisture, and pH to modulate medication delivery. In chronic wound

management, smart dressings can monitor healing and release antimicrobial agents only when needed, eliminating overmedication and speeding recovery. Digital health and topical medicine administration are improving treatment efficiency and personalization. Cosmetic and dermatological sectors use topical medication delivery technologies. Formulation science has improved anti-aging creams, sunscreens, and hyperpigmentation treatments. Nanocarriers in cosmetics improve active ingredient penetration and stability, resulting in longer-lasting and more effective outcomes. To satisfy ecologically conscious consumers' need for natural and sustainable ingredients, plant-based and biodegradable delivery technologies have been developed.

Table 1 Topical drug delivery systems

Sr. No	Aspect	Description	Examples	Challenges	Future Directions
1	Formulations	Various formulations designed for skin application.	Creams, gels, ointments, patches, transdermal systems	Stability, patient compliance, and aesthetic properties	Advanced formulations with nanotechnology and bio-responsive materials.
2	Mechanism of Action	How the drug acts when applied topically.	Local delivery (e.g., corticosteroids for inflammation) and systemic delivery (e.g., nicotine patches)	Limited skin penetration due to the stratum corneum barrier	Enhancing penetration using microneedles, iontophoresis, and chemical enhancers.
3	Drug Release Dynamics	Studies focusing on the release rate of active compounds.	Controlled-release mechanisms	Ensuring sustained release and avoiding burst release	Incorporating polymers for time-controlled drug delivery.
4	Targeted Applications	Specific diseases or conditions targeted through topical applications.	Psoriasis, eczema, acne, transdermal hormone therapy	Achieving site-specific action without systemic side effects	Smart delivery systems with environment-triggered release.

5	Carrier Systems	Development of delivery carriers to enhance drug efficacy.	Liposomes, niosomes, ethosomes, nanoemulsions	High cost and scalability issues	Development of cost-effective, biodegradable, and biocompatible carriers.
6	Permeability Studies	Research on drug penetration through skin layers.	Franz diffusion cells, microdialysis	Variability in skin types and conditions affecting permeation	Use of advanced imaging techniques like confocal microscopy for tracking drug penetration.
7	Safety and Toxicity	Assessing safety for long-term use or high-potency drugs.	Patch testing, in vitro cytotoxicity tests	Hypersensitivity reactions, irritation, and unforeseen long-term effects	Advanced biocompatibility tests and use of natural ingredients for reduced adverse reactions.
8	Regulatory Considerations	Guidelines for formulation approval and commercialization.	FDA, EMA, and ISO standards	Lengthy approval processes and high costs	Harmonization of global regulatory standards for expedited approvals.
9	Patient-Centric Design	Focus on user-friendliness and patient adherence to treatment regimens.	Non-greasy formulations, odorless creams	Difficulty in balancing therapeutic efficacy with aesthetic properties	Developing AI-driven customization of formulations for individual patient needs.
10	Nanotechnology Integration	Use of nanoscale systems for improved drug delivery.	Nanoparticles, dendrimers, and quantum dots	Uncertain long-term safety profiles of nanoparticles	Exploration of green nanotechnology for sustainable and safe systems.
11	Bioavailability	Enhancing drug absorption and effectiveness.	Prodrug approaches, enzymatic activation	Achieving desired systemic concentrations for	Personalized medicine approaches using AI for optimal

				transdermal systems	bioavailability predictions.
12	Market Trends	Current industry trends and research focus.	Natural and organic ingredients, anti-aging formulations	Meeting consumer demands while adhering to regulatory standards	AI and machine learning for predicting market demands and tailoring products accordingly.
13	Sustainability	Environmentally friendly materials and production processes.	Biodegradable packaging, minimal synthetic chemicals	Balancing efficacy with ecological responsibility	Fully biodegradable systems and eco-label certifications for topical drug formulations.
14	Advanced Delivery Methods	Techniques to improve the penetration and targeting of drugs.	Microneedles, iontophoresis, ultrasound-mediated drug delivery	High costs, technical complexity, and potential irritation to the skin	Miniaturized and wearable devices for continuous delivery and monitoring.
15	Personalized Medicine	Customized topical treatments based on individual characteristics.	AI-based skin profiling, DNA-driven formulations	High cost and lack of standardized platforms	Integration of AI for real-time formulation adjustments and precision treatment.
16	Pharmacokinetics	Study of absorption, distribution, metabolism, and excretion of drugs via topical delivery.	Drug metabolism modeling for transdermal drugs	Limited tools for accurately simulating skin metabolism	Development of advanced simulation tools for predicting drug performance in different skin types.
17	Antimicrobial Resistance	Role of topical systems in addressing or contributing to resistance.	Antimicrobial gels, antibiotic creams	Risk of overuse leading to resistance development	Focus on developing non-antibiotic antimicrobial agents such as

					peptides or natural extracts.
18	Immunological Aspects	Exploring immune responses triggered by topical agents.	Topical vaccines, immunosuppressive creams	Potential risk of allergies and immune overactivation	Developing immunomodulatory agents for controlled immune responses.
19	Combination Therapies	Use of multiple drugs in a single topical formulation.	Acne creams with benzoyl peroxide and clindamycin	Compatibility and stability of multiple drugs	Research into synergistic drug combinations for enhanced efficacy.
20	Digital Health Integration	Incorporating technology to monitor and optimize topical drug delivery.	Wearable sensors with topical patches	Data security, user acceptance	Internet of Medical Things (IoMT) integration for real-time monitoring and adaptive drug delivery.

Despite these advances, topical medication delivery system research and commercialization are difficult. Due to age, moisture, and underlying diseases, skin permeability varies greatly, making drug distribution challenging. A careful combination of science and art is needed to design medications that are effective and attractive to patients. Nanocarriers and biologics must meet strict safety and efficacy standards before being sold, which presents regulatory challenges. These issues emphasize the necessity for ongoing research and collaboration between scientists, physicians, and regulators. Topical drug delivery will evolve with customized medicine, biotechnology, and sustainability. Biomarkers that predict drug reactions are being identified by genomes and proteomics, allowing for personalized formulations that maximize efficacy and reduce side effects. Genetic knowledge of disorders like psoriasis can help design personalized medicines that target molecular pathways. In parallel, the pharmaceutical sector is applying green chemistry concepts to generate biodegradable and eco-friendly formulations. Biocompatible and sustainable carriers like chitosan and alginate are being investigated.

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Chapter 2

Literature review

Literature review

Ananda et al. (2021) formulated a transdermal patch for the delivery of Primaquine (PMQ) combined with solid microneedles and a dermaroller. HPMC and glycerin were chosen as the principal polymer and plasticizer after significant optimization. Polyethylene glycol 400 (PEG 400) concentration was tuned to improve permeability. The transdermal patches were tested for weight hom ogeneity, thickness, surface pH, folding durability, moisture content, absorption, bioadhesion, and medication content recovery. Patch delivery caused no tissue injury, according to histopathology. The study showed promising results, but in vivo testing is needed to confirm them.

Mo et al. (2021) designed and tested a Carvedilol transdermal patch employing polymers and permeability enhancers to modulate drug release and maximize bioavailability without first-pass metabolism. Formulation F7, which contained Eudragit RS-100 as the rate-controlling polymer and Span 80 as a permeation enhancer, produced the best solvent-evaporated patches. Formulation F7 showed the largest drug release (100.29 ± 0.44%) within 12 hours, highest bioavailability, and maximum blood pressure reduction at six hours post-administration. A Carvedilol transdermal patch containing Eudragit RS-100 and Span 80 released medication sustainably and controlledly, according to this investigation.

Quan et al. (2021) created a transdermal patch with Siegesbeckiae Herba (SiH) extract for rheumatoid arthritis. In 2015, the UK licensed Phynova Joint and Muscle Relief Tablets™, a derivative of SiH, a traditional Chinese anti-rheumatic herbal treatment. The transdermal patch showed good anti-inflammatory and analgesic benefits, suggesting a non-invasive rheumatoid arthritis treatment.

Tahir et al. (2020) examined the recrystallization and transdermal penetration of ibuprofen and hydrocortisone in matrix-type transdermal patches loaded with polymeric and lipid nanoparticles. Polymeric nanoparticles were made from ethyl cellulose (EC4), poly(lactide-co-glycolic acid) (PLGA), and polycaprolactone (PCL), whereas MCT nanoemulsion and solid lipid nanoparticles were made from MCT and Witepsol. These nanoparticles reduced recrystallization and enabled on-demand drug loading. Controlling

carrier hydrophobicity can optimize medication stability and release characteristics in transdermal patches, according to the study.

Sakdiset et al. (2019) created indomethacin (8 mg/mL) ethosomes utilizing SPC, ethanol, and additives as spreading media. With 10–30% ethanol in pH 7.4 phosphate buffer, ethosomes had higher colloidal quality. Using 4% w/v SPC:cholesterol:deoxycholic acid (6:2:1 molar ratio) in 20% v/v ethanol, the ethosomes' physical characteristics, size, and entrapment efficiency (EE) were optimized. These ethosomes penetrated indomethacin better than commercial and ethanolic solutions over 24 hours, suggesting they are better transdermal drug delivery.

Ameen and Michniak-Kohn (2019) proposed an innovative approach for drug delivery tailored primarily for Alzheimer's disease patients, aimed at eliminating gastrointestinal side effects and improving patient compliance. They developed optimized matrix-type patches of galantamine for transdermal delivery and conducted ex vivo and in vitro evaluations. The study tested four pressure-sensitive adhesives with varying functional groups, ten diffusion enhancers, and four drug loadings to determine the optimal patch formulation.

Liu et al. (2019) developed a transdermal patch for benzoylaconitine (BA), a high molecular weight compound (603.7 Da), exhibiting strong analgesic and anti-inflammatory properties. They studied the relationship between the physicochemical properties of permeation enhancers and their enhancement efficacy using skin permeation studies. Further investigations using FT-IR and molecular modeling elucidated the enhancement mechanism, revealing that effective interaction and disruption of both lipophilic and hydrophilic domains of the stratum corneum were critical for achieving significant permeation improvement.

Zhou et al. (2018) explored transdermal drug delivery systems for local and systemic drug administration. They highlighted that conventional physical and chemical enhancer, while effective at improving drug solubility and diffusion, often cause toxicity due to excessive enhancer penetration. Nano-formulations, ranging from 10 to 100 nm in size, were suggested as a promising alternative. Their smaller size enhanced treatment permeability, stability, and targeting. Applications of nano-formulations, such as vesicles, nanoparticles, and nanoemulsions, were extensively studied for transdermal drug delivery.

Tosato et al. (2018) developed a transdermal drug delivery system for trans-resveratrol (RSV), a natural compound with anti-inflammatory and anticancer activity. Using liposomal nanoparticulate carriers, including conventional, deformable, and ultradeformable liposomes, they performed detailed characterization with techniques like

transmission electron microscopy, dynamic light scattering, and confocal Raman spectroscopy. The formulations enhanced bilayer fluidity, improved drug encapsulation, and maintained carrier mobility, offering potential for efficient transdermal delivery.

Kathe and Kathpalia (2017) emphasized the importance of topical drug delivery systems, which rely on the drug's physicochemical properties and the adherence of formulations to the skin. They addressed limitations of traditional systems, such as poor skin adhesion and permeability, by developing topical film formulations. These systems formed thin, transparent films that adhered to the skin and provided sustained drug release, enhancing therapeutic efficacy and patient satisfaction.

Siji et al. (2016) investigated the effect of backing films on the transdermal delivery of cyclobenzaprine patches. Various backing films were evaluated for drug release rates using in vitro studies. ATR-FTIR spectroscopy revealed strong adsorption of cyclobenzaprine onto certain backing films, such as Cotran™ 9700, which affected drug release after storage. Their findings highlighted the importance of material compatibility in transdermal patch design.

Indulekha et al. (2016) developed a temperature-responsive transdermal drug delivery system (TDDS) using a thermoresponsive polymer, poly(N-vinyl caprolactam) (PNVCL). The system allowed controlled drug release via heat application. By incorporating PNVCL into a pH-sensitive chitosan biopolymer, the team created a co-polymer gel responsive to both temperature and pH. Drug release studies demonstrated enhanced permeation at elevated temperatures, and biocompatibility testing confirmed the system's safety.

Gundeti et al. (2015) formulated transdermal patches for Nateglinide using a solvent casting method and various polymer combinations. The patches were characterized for homogeneity, drug content, and permeation properties. The optimized formulation achieved sustained drug release for 12 hours (99.2%) and maintained stability per ICH guidelines.

Zhang et al. (2014) optimized a transdermal patch for Diclofenac using organic amine salts as permeation enhancers. Using excised rabbit skin in diffusion cells, they determined that Diclofenac triethylamine salt exhibited superior penetration compared to other salts, demonstrating the importance of enhancer selection for effective transdermal delivery.

Laxmi et al. (2014) prepared bilayer films for wound healing, combining a Diclofenac-loaded upper layer and a drug-free lower layer for controlled release. In vitro studies

showed sustained drug delivery, highlighting the potential of bilayer films for prolonged therapeutic effects.

Panchaxari et al. (2013) evaluated transdermal patches of Diclofenac diethylamine using silicone and acrylic adhesives. They concluded that an optimal adhesive combination provided sustained drug release, improved permeation, and robustness.

Bhavya et al. (2012) developed a potassium Diclofenac transdermal system using polyvinylpyrrolidone and guar gum polymers. Kinetic studies indicated sustained drug release following a non-Fickian model, validating the system's sustained action potential.

Shingade et al. (2012) reviewed transdermal drug delivery methods, emphasizing their ability to bypass hepatic first-pass metabolism and maintain steady plasma drug levels, improving therapeutic efficiency.

Subramanian et al. (2012) formulated a matrix patch for Fexofenadine Hydrochloride with controlled release properties. In vitro studies showed 94% drug release in 23 hours, while in vivo studies confirmed 99% release in 24 hours, following zero-order kinetics.

Lion and Brennan (2010) reviewed the clinical effectiveness of Diclofenac epolamine topical patches for treating soft tissue injuries. They noted the advantages of lower plasma drug concentrations and fewer systemic side effects compared to oral NSAIDs.

Kevin et al. (2009) developed a monolithic matrix transdermal formulation of Tramadol HCl and demonstrated sustained release through in vitro studies using Franz diffusion cells.

Chandrashekar and Sobha (2008) discussed the criteria for selecting drugs suitable for transdermal delivery, focusing on pharmacokinetic and physicochemical parameters.

Capsaicin, the main ingredient in chili peppers, is of interest to pharmaceutical and biomedical researchers. Effective analgesic and anti-inflammatory qualities make capsaicin essential in pain management formulations. New extraction technologies and transdermal drug delivery systems can improve bioavailability, therapeutic effects, and systemic side effects. This section review examines capsaicin extraction, transdermal patch composition, and evaluation. Capsaicin purity and efficacy for pharmaceutical uses depend on chili pepper extraction. Soxhlet extraction and maceration use organic solvents such ethanol, methanol, and acetone. These procedures are time-consuming and may degrade thermolabile components. Modern methods are more efficient and eco-friendlier. Supercritical fluid extraction (SFE) uses carbon dioxide as a solvent to produce pure capsaicin with high yields and low environmental effect. This approach is useful since it preserves the compound's bioactivity at lower temperatures.

Another new method, ultrasound-assisted extraction (UAE), disrupts plant cell walls to liberate capsaicin. UAE improves extraction efficiency, processing time, and solvent use, according to studies. Microwave-assisted extraction (MAE) is used for uniformly heating the extraction medium, maximizing capsaicin production. Pharmaceutical research is emphasizing green chemistry and sustainable practices, which these improved methods support. Transdermal Patch Formulation

Transdermal drug delivery systems (TDDS) are promising alternatives to conventional medication delivery. These systems bypass the gut, lowering first-pass metabolism and increasing bioavailability. Transdermal capsaicin patches provide capsaicin locally to the pain site, reducing systemic exposure and side effects. Capsaicin is added to a polymeric matrix, the patch's drug reservoir. Biocompatibility and mechanical strength make HPMC, ethyl cellulose, and PVA popular. The patch's adhesiveness, medication release, and efficacy depend on the polymer. Recent studies have examined how nanotechnology can improve capsaicin transdermal patches. Drug dispersion and controlled release are improved by adding nanoparticles and nanofibers to the polymeric matrix. Capsaicin's poor water solubility can be improved by adding lipid-based nanoparticles. Adding permeation enhancers like menthol and ethanol helps capsaicin penetrate the stratum corneum, the outermost layer of the skin.

Transdermal patches are evaluated for physicochemical qualities, drug release kinetics, and therapeutic efficacy. Patch thickness, tensile strength, wetness, and medication loading efficiency matter. Drug delivery and patient compliance are congruent with these qualities. In vitro investigations are essential for understanding capsaicin patch medication release. Franz diffusion cells are used to test capsaicin penetration through synthetic membranes or animal skin. These experiments illuminate the patch's zero-order kinetics release profile for sustained medication administration. Bioadhesive polymers also increase the patch's skin residence period, boosting its therapeutic potential. Clinical trials are essential for capsaicin transdermal patch efficacy and safety. They effectively treat neuropathic pain, osteoarthritis, and postherpetic neuralgia, according to recent studies. A capsaicin 8% patch randomized controlled trial showed considerable pain reduction in diabetic neuropathy patients. These experiments further emphasise the need of patch design optimization to reduce skin irritation and burning.

Despite hopeful advances, capsaicin transdermal patch composition and evaluation remain difficult. Capsaicin's pungency and skin irritation require cautious excipient and permeation enhancer selection. Scalability of modern extraction and patch manufacturing methods is another issue for commercial production. Researchers are investigating microencapsulation and co-crystallization to solve these problems. Capsaicin is microencapsulated in a biocompatible shell to control release and reduce discomfort.

However, co-crystallization with proper co-formers improves capsaicin solubility and stability. Hydrogel-based technologies and bio-responsive polymers could lead to next-generation capsaicin patches. High water content and flexibility make hydrogels ideal for long-term usage due to their comfort and adherence. Bio-responsive polymers that release medications in reaction to temperature or pH could improve pain management. Additionally, patch design and optimization are increasingly using AI and ML. These methods forecast medication release profiles, optimize formulation parameters, and speed development. Research discoveries should be translated into clinically viable products faster using such advancements.

Table 2 Review on extraction of capsaicin: formulation and evaluation of a transdermal patch

Sr. No.	**Aspect**	**Description**	**Importance**	**Methods Used**	**Challenges**
1	Capsaicin Overview	A bioactive compound found in chili peppers responsible for their pungency.	Used for its analgesic and anti-inflammatory properties in pain management.	Extraction through solvents like ethanol or methanol.	Ensuring purity and avoiding degradation during extraction.
2	Transdermal Patch Concept	A medicated adhesive patch delivering drugs through the skin into systemic circulation.	Provides controlled drug release and avoids gastrointestinal side effects.	Polymer matrix systems, adhesives, and permeation enhancers.	Achieving consistent drug delivery and adhesion issues.
3	Extraction Process	The method of isolating capsaicin from natural sources like chili peppers.	Ensures high-quality active pharmaceutical ingredient for patch formulation.	Soxhlet extraction, maceration, or ultrasonic-assisted methods.	Cost of extraction and yield optimization.
4	Formulation Techniques	Combining extracted capsaicin with polymers, plasticizers,	Improves drug stability and ensures effective	Mixing, casting, and solvent evaporation techniques.	Maintaining uniformity and avoiding phase separation.

		and other excipients.	transdermal absorption.		
5	Evaluation Parameters	Tests conducted to assess the effectiveness of the patch, including drug release and adhesion.	Ensures safety, efficacy, and compliance with regulatory standards.	In vitro release studies, skin permeation studies, and stability tests.	Replicating human skin conditions in experimental setups.
6	Mechanism of Action	Capsaicin interacts with TRPV1 receptors to provide analgesic effects.	Key to understanding its therapeutic potential in pain relief.	Study of pharmacodynamics and receptor interactions.	Limited understanding of long-term effects.
7	Skin Permeability	The ability of capsaicin to penetrate the skin barrier and enter systemic circulation.	Affects the efficiency of drug delivery through transdermal systems.	Use of permeation enhancers and carrier systems.	Variation in skin permeability among individuals.
8	Polymers Used	Materials like HPMC, PVP, or ethyl cellulose in the patch matrix.	Provide structural integrity and regulate drug release rate.	Polymer selection and compatibility testing.	Balancing mechanical strength and drug release properties.
9	Safety Considerations	Addressing potential irritation or allergic reactions from capsaicin patches.	Ensures patient compliance and regulatory approval.	In vivo irritation studies and clinical trials.	Minimizing adverse effects while maintaining efficacy.
10	Regulatory Guidelines	Standards for approval of transdermal patches	Ensures compliance with pharmaceutical regulations	Adherence to FDA, EMA, or local regulatory frameworks.	Meeting stringent documentation and testing requirements.

		containing capsaicin.	and quality assurance.		
11	Dosage Optimization	Determining the correct amount of capsaicin for effective transdermal delivery.	Critical for balancing therapeutic benefits and minimizing side effects.	Controlled release studies and pharmacokinetic analysis.	Variation in individual absorption rates.
12	Role of Permeation Enhancers	Substances used to improve skin permeability for capsaicin absorption.	Increases bioavailability and enhances drug delivery efficiency.	Use of solvents like ethanol, propylene glycol, or DMSO.	Risk of skin irritation and toxicity.
13	Storage and Stability	Assessing how the patch retains its efficacy over time under different conditions.	Ensures long shelf life and effectiveness during use.	Stability testing under various temperature and humidity levels.	Preventing degradation of capsaicin and patch materials.
14	Patient Compliance	Evaluating the acceptability and ease of use of the transdermal patch.	Ensures higher adherence to treatment protocols.	User feedback and usability studies.	Managing variability in skin sensitivity among users.
15	Cost-Effectiveness	Analysis of production costs and affordability of the patch for mass adoption.	Ensures wide accessibility and economic viability.	Cost analysis of materials and manufacturing techniques.	Balancing affordability with quality and efficacy.
16	Combination Therapy	Potential to combine capsaicin with other active ingredients for enhanced	Broadens the scope of applications, such as in multi-symptom treatments.	Co-formulation studies and compatibility testing.	Avoiding interactions and ensuring uniform delivery.

		therapeutic effects.			
17	Environmental Impact	Assessing the sustainability of materials and methods used in patch production.	Promotes eco-friendly practices in pharmaceutical development.	Use of biodegradable polymers and green extraction techniques.	Managing waste and resource consumption.
18	Drug Release Kinetics	Understanding how capsaicin is released over time from the patch.	Helps in optimizing the formulation for sustained or controlled release.	In vitro drug diffusion studies using Franz diffusion cells.	Achieving desired release profiles consistently.

Due to its analgesic, anti-inflammatory, and anti-obesity characteristics, capsaicin, a bioactive chemical found in chili peppers of the family Capsicum, is an important molecule in pharmacological research. It works by attaching to TRPV1 receptors to desensitize pain and heat. Its medicinal potential is well known, but poor water solubility, skin permeability, and irritation require new administration techniques such transdermal patches. Capsaicin-based transdermal patches bypass the gastrointestinal system and deliver this ingredient sustainably at the application site. Extracting capsaicin from natural sources is crucial to medicinal use. Chili peppers' dried fruit contains capsaicin, which varies by species, maturity, and climate. Soxhlet extraction and maceration use organic solvents such ethanol, methanol, or acetone. Recently developed green chemistry methods like supercritical fluid extraction (SFE) employing carbon dioxide preserve capsaicin's bioactivity without solvents. Solvent polarity, extraction temperature, and duration are tuned for optimal yield and purity, which are essential for product efficacy.

Capsaicin must be characterized to ensure purity and chemical composition after extraction. HPLC, GC-MS, and FTIR are commonly used. These methods check capsaicin purity and discover related chemicals like dihydrocapsaicin, which may affect its pharmacological characteristics. Pharmaceutical formulation repeatability and scalability require extraction and analytical methodology standardization. Capsaicin's hydrophobicity and low molecular weight must be addressed while making a transdermal patch. Transdermal patches administer capsaicin to systemic circulation or specific regions. To increase skin permeability, ethanol, propylene glycol, or natural terpenes must be added. The patch matrix, made of HPMC, ethyl cellulose, or polyvinyl alcohol, provides structural stability and controls capsaicin release.

Excipients and patch manufacture affect capsaicin patch medication release kinetics. Solvent casting, where drugs and polymers are dissolved in a solvent and cast onto a backing membrane, is common. Advanced fabrication methods including electrospinning and 3D printing improve patch matrix medication distribution precision. To improve stability, bioavailability, and skin irritation, capsaicin has been encapsulated in lipid nanoparticles or nanospheres. Capsaicin transdermal patch performance evaluation requires in vitro, ex vivo, and in vivo research. Franz diffusion cells assess drug penetration via synthetic membranes or excised animal skin in vitro. These investigations reveal release profile, permeation rate, and penetration enhancer effects. Ex vivo investigations on human or animal skin recreate patch-biological tissue interaction more realistically. To ensure patient compliance and comfort, adhesive strength, patch flexibility, and water vapor transmission rate are assessed. Capsaicin patch efficacy and safety must be assessed in vivo. Capsaicin pharmacokinetics and pharmacodynamics are studied in animals. Optimizing the formulation involves measuring Tmax, half-life, and bioavailability. Phased human clinical trials evaluate the patch's safety, efficacy, and side effects in specific populations. Due of capsaicin's skin irritation and burning effects, dose optimization and soothing medications are needed.

Capsaicin transdermal patches can treat osteoarthritis, postherpetic neuralgia, and sports medicine irritants. Locally acting capsaicin lowers systemic adverse effects, making it safer than oral or injectable analgesics. Transdermal patches also prolong therapeutic benefits, eliminating the need for frequent administration. Capsaicin and other medications, such as NSAIDs, are being studied in a patch for pain control synergy. Despite these benefits, capsaicin transdermal patch development is difficult. Skin irritation is a major issue, especially in sensitive people. Reducing capsaicin concentration, adding anti-inflammatory drugs, or inventing controlled-release encapsulation technologies can help. Another issue is skin permeability, which varies by age, ethnicity, and skin condition. These concerns are being addressed by personalizing patch compositions to patient demands.

Capsaicin patches need regulatory approval to be sold. FDA and EMA quality control standards must be met by the patch. Displaying medication content consistency, release uniformity, and stability under various storage circumstances. Since adverse events and user input inform future product developments, post-marketing surveillance ensures long-term product safety and efficacy. With continuous research enhancing formulation and delivery, capsaicin-based transdermal patches have a bright future. Biomaterials like bioadhesive polymers and stimuli-responsive hydrogels can improve capsaicin patch performance. Wearable technology like patches with sensors that monitor drug release or skin problems are fresh approaches to personalized treatment. Combining capsaicin with

new drug delivery methods like microneedles or iontophoresis may overcome transdermal delivery's limitations.

Chili peppers contain capsaicin, an alkaloid with analgesic, anti-inflammatory, and anti-obesity characteristics that have garnered attention in the pharmaceutical and biomedical industries. Chili peppers' pungency comes from this bioactive molecule, which has been researched for its pain-relieving properties. Capsaicin works by attaching to sensory neuron TRPV1 receptors. These receptors desensitize pain and heat, making capsaicin an excellent treatment for neuropathic pain, osteoarthritis, and postherpetic neuralgia. However, capsaicin oral administration can cause gastrointestinal irritation and low absorption, requiring other delivery routes. Controlled release and patient compliance make transdermal patches a viable option. This topic covers capsaicin extraction, transdermal patch formulation, and complete evaluation.

Capsaicin extraction is essential for pharmaceutical applications. The most common chili peppers used to make capsaicin are Capsicum annuum and Capsicum frutescens. Capsaicin concentration in chili peppers depends on species, cultivation, and harvest maturity. Maceration, Soxhlet, and supercritical fluid extraction have been used to extract pure capsaicin. Maceration and Soxhlet extraction dissolve capsaicin from dried chili powder using organic solvents such ethanol, methanol, or acetone. These technologies work, but they require substantial solvent recovery and purification, making them less environmentally friendly. However, supercritical fluid extraction, especially utilizing carbon dioxide, has become popular due to its eco-friendliness and ability to preserve capsaicin bioactivity. High pressures and moderate temperatures allow SFE to selectively extract capsaicin without thermal degradation. To maximize yields and purity, pressure, temperature, and co-solvent type (ethanol) are tuned. This method improves extraction efficiency and follows green chemistry, making it suited for large-scale production. No matter the method, post-extraction purification with chromatography removes contaminants and related chemicals like dihydrocapsaicin, which might affect the product's pharmacological effects.

Characterizing extracted capsaicin is essential for pharmacological use. HPLC, GC-MS, and FTIR are used to determine capsaicin purity, content, and structural integrity. These procedures give researchers complete analytical profiles to standardize the chemical for formulation. Maintaining therapeutic efficacy and reducing impurity adverse effects requires high purity. The formulation of capsaicin into a transdermal patch requires materials science, pharmacology, and drug delivery engineering. Drugs are delivered using transdermal patches, bypassing the gastrointestinal route and liver first-pass metabolism. Capsaicin's hydrophobicity and low molecular weight hinder skin penetration. The patch recipe includes penetration boosters such ethanol, propylene

glycol, or natural terpenes to solve these difficulties. These enhancers disturb the stratum corneum, the outermost skin layer, allowing capsaicin to penetrate deeper.

Another important formulation design concern is patch matrix polymer selection. Due to its biocompatibility, flexibility, and drug release control, HPMC, ethyl cellulose, and polyvinyl alcohol are widely employed. The patch matrix must be strong enough to stick to the skin and remove painlessly. Transdermal patches are often made via solvent casting. After dissolving the medication and polymers in a solvent and casting them onto a backing layer, they dry to produce a homogeneous matrix. New methods like electrospinning and 3D printing provide precise medication distribution and patch shape, improving system performance.

New nanotechnology has enhanced capsaicin transdermal patches. Encapsulating capsaicin in lipid nanoparticles, liposomes, or polymeric nanospheres improves stability, bioavailability, and skin permeability. These nano-carriers restrict capsaicin release, minimizing skin irritation from high concentrations. Biocompatibility and adverse reactions can be improved by adding natural polymers like chitosan or alginate to the patch matrix. Capsaicin transdermal patches are tested in vitro, ex vivo, and in vivo for safety, effectiveness, and performance. Franz diffusion cells assess drug penetration via synthetic membranes or excised animal skin in vitro. These investigations reveal capsaicin release kinetics, penetration enhancer effects, and patch medication delivery effectiveness. Ex vivo experiments on human or animal skin imitate the patch's interaction with biological tissues, revealing its irritation, adherence, and flexibility.

In vivo studies are needed to assess capsaicin patch pharmacokinetics and pharmacodynamics in animals and humans. Optimizing the formulation involves analyzing Tmax, elimination half-life, and bioavailability. Phased human clinical trials evaluate the patch's safety and efficacy in selected populations. To reduce patient discomfort, capsaicin's well-known adverse effects—burning and skin irritation—require dose adjustment and soothing medicines like aloe vera or menthol. Therapeutic uses of capsaicin transdermal patches go beyond pain treatment. These patches may help treat diabetic neuropathy, rheumatoid arthritis, and weight loss by modulating energy metabolism. Localized capsaicin patches lessen systemic adverse effects, making them safer than oral or injectable analgesics. Transdermal patches' continuous release prolongs therapeutic benefits, reducing administration frequency and boosting patient adherence.

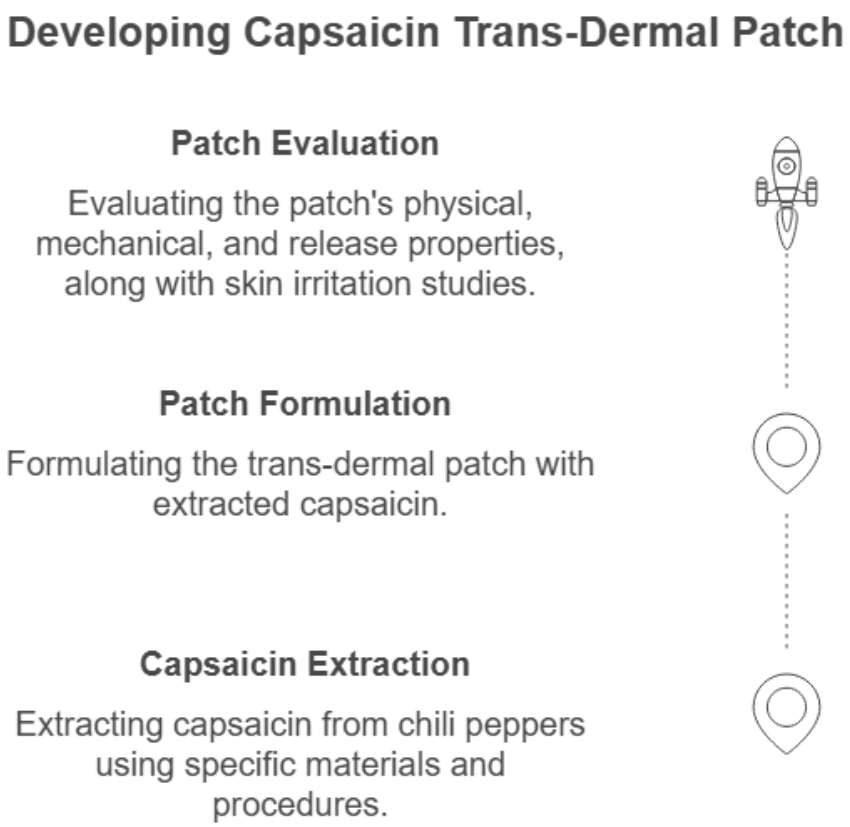

Fig. 3 Developing Capsaicin Trans-dermal Patch

For widespread usage, capsaicin transdermal patches must overcome many obstacles. Skin irritation is a major problem, especially for sensitive skin or dermatological diseases. Reducing capsaicin levels, adding anti-inflammatory medications, or encapsulating drugs can help. Another issue is skin permeability, which varies by age, ethnicity, and skin wetness. Personalized patch design, including patches for individual skin types or disorders, is being investigated to address these variances. Regulatory approval is crucial for capsaicin transdermal patch development. The FDA and EMA require these items to meet strict quality criteria. Displaying medication content consistency, release uniformity, and stability under various storage circumstances. Post-marketing surveillance guarantees product safety and efficacy, and user input informs future developments. Capsaicin transdermal patches will benefit from new materials and technologies. Stimuli-responsive hydrogels which release drugs when temperature or pH changes provide regulated and targeted administration. A unique approach to personalized medicine uses wearable sensors in patches to monitor drug release or skin problems in real time. In a patch,

capsaicin and other medicinal medicines like NSAIDs may work synergistically to treat complex disorders like rheumatoid arthritis.

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Chapter 3

Methods and materials

Extraction of Capsaicin

Procedure:

1. 500 gm green chilies are dried in sun light to remove the moisture.
2. Grind the chilies into a fine paste using mortar and pestle.
3. Place the ground chilies paste into a glass jar or container. Pour the ethanol over the paste to cover it completely for 42 hr to allow capsaicin to dissolve into the solvent.
4. After the soaking period, filter the mixture to separate the solid plant material into liquid solvent contaning the capsaicin.
5. To isolate the capsaicin from the solvent, the evaporate the solvents using a rotary evaporator or a simple distillation. Or gently heat the solvent in a well-ventillated area to evaporate it, leaving behind a resinous capsaicin extract.

Aim & Objective

Aim

The aim is “Extraction of Capsaicin and Formulation, Evaluation of Trans-Dermal Patch”.

Objectives

1. Extraction of Capsaicin:
    - Selection of Source: Identify suitable sources of capsaicin, such as chili peppers.
    - Extraction Method Development: Optimize methods for efficient extraction (e.g., solvent extraction, supercritical fluid extraction).
2. Formulation of Transdermal Patch:

- Polymer Selection: Choose appropriate polymers (e.g., chitosan, polyvinyl alcohol) that facilitate drug delivery.
- Patch Composition: Determine the optimal ratios of capsaicin, polymers, plasticizers, and other excipients.
- Preparation: Utilize techniques such as solvent casting or hot melt extrusion to fabricate the patches.

3. Evaluation of Transdermal Patch:
    1. Physical Properties: Assess thickness, tensile strength, and moisture content of the patches.
    2. Release Studies: Conduct in vitro release studies to evaluate the release profile of capsaicin.
    3. Stability Testing: Evaluate the stability of the patches over time under various storage condition.

Plan of Work

Pre-formulation studies

- Organoleptic Identification
- Microscopic examination
- Bulk & Tapped Density
- Particle size
- Flow properties
- Solubility determination
- Partition coefficient
- Melting point
- Drug excipients compatibility study etc.

Analytical method development

- Determination of absorption maxima (λmax)
- Preparation of calibration curve

Validation of Analytical method

- Specificity
- Precision (Repeatability and Intermediate precision)
- Accuracy

Preparation of Transdermal Patches

Evaluation of the formulations

- Physical appearance of Patch
- Thickness of Patch
- Weight variation of Patch
- Surface pH of Patch
- Tensile strength of Patch
- Swelling Ratio of Patch
- Drug content of Patch
- in-vitro perfusion analysis

Result and discussion

Extraction of Capsaicin

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4. After the soaking period, filter the mixture to separate the solid plant material into liquid solvent contaning the capsaicin.
5. To isolate the capsaicin from the solvent, the evaporate the solvents using a rotary evaporator or a simple distillation.
6. Or gently heat the solvent in a well-ventillated area to evaporate it, leaving behind a resinous capsaicin extract.

Development of analytical methods by UV Speectrophotometry analysis (λmax):

The absorption maxima of capsaicin were discovered by UV scanning a drug solution with a double-beam ultraviolet spectrophotometer (Shimadzu UV-1800, Shimadzu Corporation, Japan) at 200–400 nm. An precisely weighed 25 mg drug sample was dissolved in 25 mL of pH 7.4 phosphate buffer in a volumetric flask. After sonicating the solution in a bath for 20 minutes, Stock-I was created with a concentration of 1000 µg/mL. 100 mL volumetric flask was used to dilute 1 mL of Stock-I with phosphate buffer (pH 7.4) to the mark. The diluted solution was sonicated for 20 minutes to create Stock-II at a final concentration of 10 µg/mL. Stock-II solution was examined at 200- 400 nm in the UV spectrophotometer. Fig. shows capsaicin UV spectrum.

Capsaicin Standard Calibration Curve in Phosphate Buffer (pH 7.4)

Weigh precisely 25 mg of capsaicin and transfer it to a 25 mL volumetric flask. Add phosphate buffer (pH 7.4) to the flask and mix thoroughly. Sonicate the solution in a bath sonicator for 20 minutes to ensure complete dissolution. This prepared solution, referred to as Stock-I, has a concentration of 1000 µg/mL. From Stock-I, pipette 1 mL and dilute it to 100 mL with phosphate buffer (pH 7.4) in another volumetric flask. Sonicate this diluted solution for an additional 20 minutes. This new solution, labeled Stock-II, has a concentration of 10 µg/mL. To prepare the calibration curve, aliquots of 1.0, 2.0, 3.0, 4.0, and 5.0 mL of Stock-II were each diluted to 10 mL with phosphate buffer (pH 7.4) in volumetric flasks. The resulting solutions have concentrations of 10 µg/mL, 20 µg/mL, 30 µg/mL, 40 µg/mL, and 50 µg/mL, respectively. The absorbance of each solution was measured at 280 nm, using phosphate buffer (pH 7.4) as the blank. A standard calibration curve was then plotted by recording the absorbance data against the corresponding concentrations. The calibration curve for capsaicin follows the equation Y=0.018x+0.004 with a high correlation coefficient of r^2 =0.997, indicating excellent linearity.

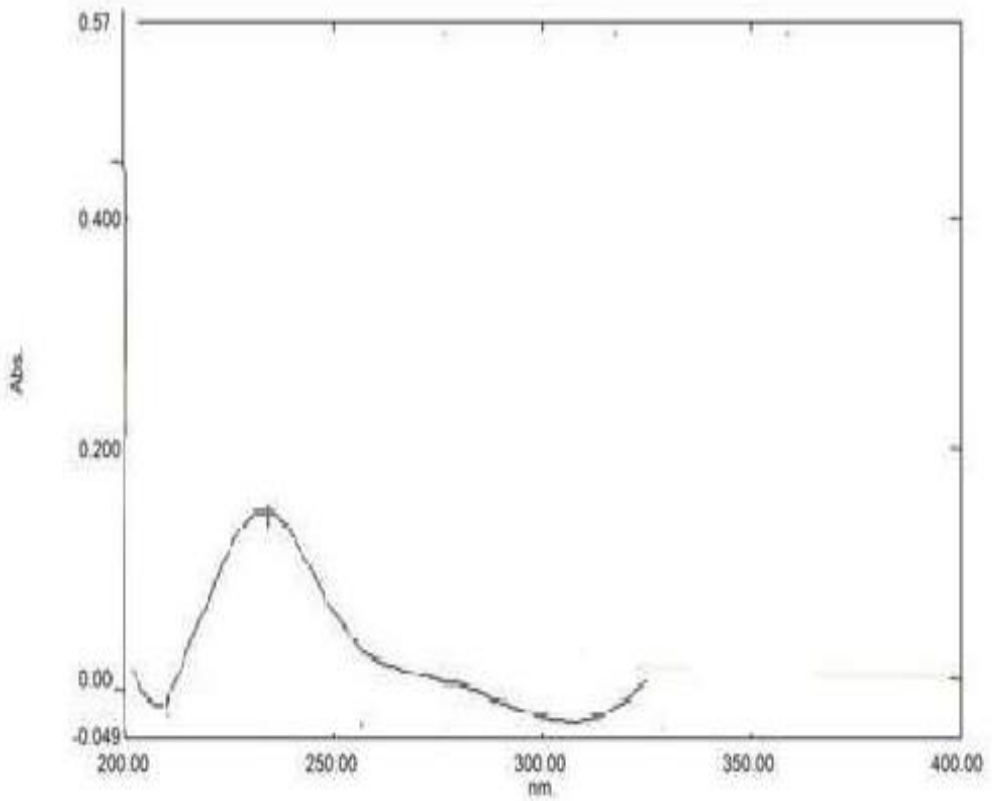

Fig. 4 Absorption maxima (λ-max) of capsaicin in phosphate buffer pH 7.4 solution (10 µg/ml)

Table 3 Standard curve of capsaicin in Phosphate buffer pH 7.4 solution (221 nm)

S. No.	Concentration (µg/ml)	Absorbance (λ-max 221 nm)
1	0	0
2	2	0.041
3	4	0.081
4	6	0.117
5	8	0.147
6	10	0.182

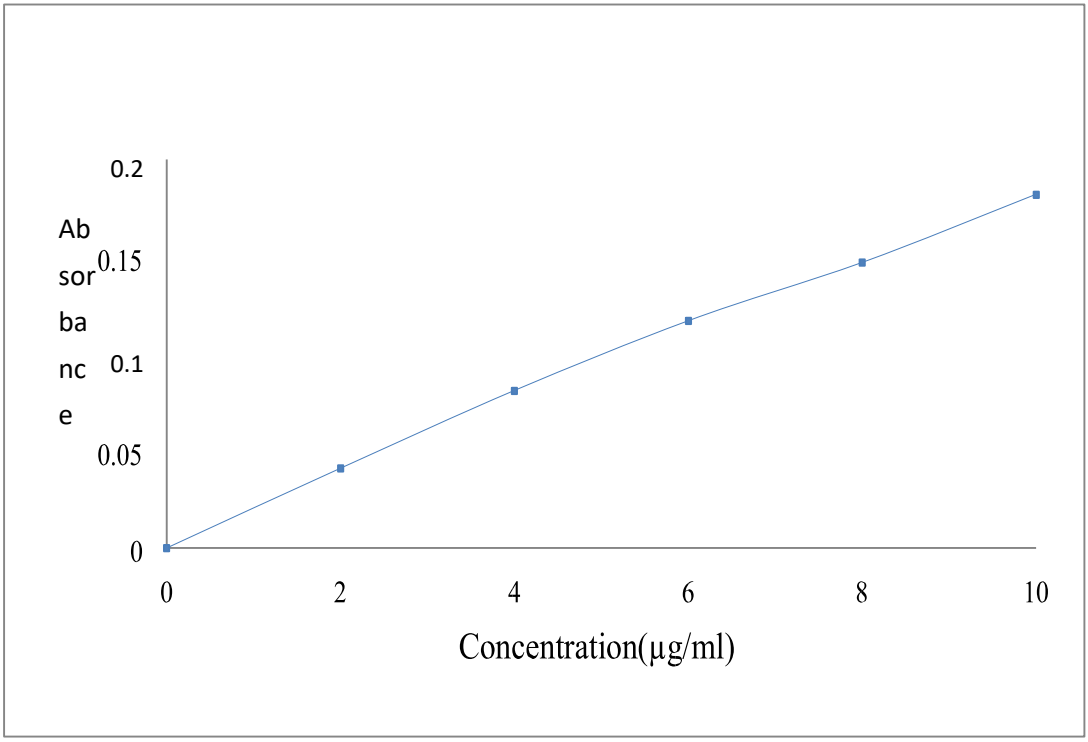

Fig. 5: Standard Curve of Capsaicin in Phosphate Buffer (pH 7.4) Measured at 221 nm

Preformulation study:

Organoleptic Identification Test:

The sensory identification of capsaicin was carried out using organoleptic evaluation methods, assessing attributes such as color, odor, and taste.

Phase Contrast Microscopic Study of Drug Samples:

A small quantity of the capsaicin sample was placed on a glass slide and observed under a phase contrast microscope. The light effects were utilized to enhance the visualization of the sample's structural properties.

Density Determination:

The capsaicin powder was accurately weighed and carefully poured through a glass funnel into a graduated cylinder to record its volume. Bulk density was calculated based on the recorded weight and volume. Tapped density was determined using a tapped density apparatus, ensuring consistent compaction during measurement.

Particle Size Analysis:

The particle size of the capsaicin sample was analyzed using a phase contrast microscope equipped with an ocular micrometer and a stage micrometer for precise measurement.

Flow Properties:

The flow properties of the capsaicin powder were characterized by determining Carr's Index, Hausner's Ratio, and the angle of repose. The angle of repose (θ) was measured using the fixed height method. Carr's Index (CI) and Hausner's Ratio (HR) were calculated using the following equations to assess flow behavior:

Carr's Index (IC) = ρTapped - ρBulk / ρTapped Hausner's ratio (HR) = ρTapped / ρBulk

Angle of repose (θ) = $\tan^{-1}$ 2 H / D

Where H is the surface area of the free-standing height of the powder pile and D is diameter of pile that formed after powder flow from the glass funnel.

pH Solubility Profile

The solubility of capsaicin (TL) was analyzed in aqueous media at different pH levels, specifically phosphate buffer solutions with pH 6.8 and pH 7.4. An excess amount of the drug was introduced into 25 mL of each buffer solution and stirred continuously at room temperature for 12 hours. The resulting mixtures were filtered using Whatman filter paper (pore size: 0.45 µm). The solubilized drug concentration in each medium was quantified using a UV spectrophotometric method.

Partition Coefficient

The partition coefficient of capsaicin (TL) was evaluated to determine its hydrophobicity and hydrophilicity. A mixture of n-octanol and phosphate buffer (pH 7.4) in a 1:1 ratio (50 mL each) was prepared in a separating funnel. A 25 mg sample of the drug was added, and the mixture was shaken vigorously for 24 hours to ensure equilibrium. The funnel was then left undisturbed for 2 hours to allow phase separation. Afterward, the n-octanol and phosphate buffer layers were separated and individually collected, followed by filtration. The drug concentration in the phosphate buffer phase was measured using a UV spectrophotometric method, and the drug amount in the n-octanol phase was calculated by subtracting the concentration in the buffer phase from the total initial amount. The partition coefficient was computed using the formula:

$$LogP\ (n-oct\ /\ pH\ 7.4) = Log\ (COct\ /\ CpH\ 7.4)\ equilibrium$$

Melting Point

The capillary tube method determined the drug sample's melting point. A capillary tube was loaded with a little amount of powdered drug sample and tapped evenly. The flame-sealed capillary tube was constructed earlier. When full, the tube was placed upright in a melting point apparatus. The medication sample's melting temperature was measured, and the experiment was carefully executed to assure accuracy.

FTIR Drug-Excipient Compatibility Study

Drug-excipient compatibility tests were conducted using FTIR spectroscopy to identify potential interactions for formulation design. For analysis, the drug-excipient ratio was the same as in the formulation. FTIR spectra of the combination and pure medication were compared. Infrared spectroscopy identified drug sample functional groups.

The potassium bromide (KBr) disc method with a Shimadzu IR Spectrophotometer was used for analysis. The medication powder was completely blended with potassium bromide powder 9:1. Pressure formed a disc from the mixture, which was placed in the FTIR spectrometer's sample container for scanning. This approach accurately identified functional groups and assured drug-excipient compatibility.

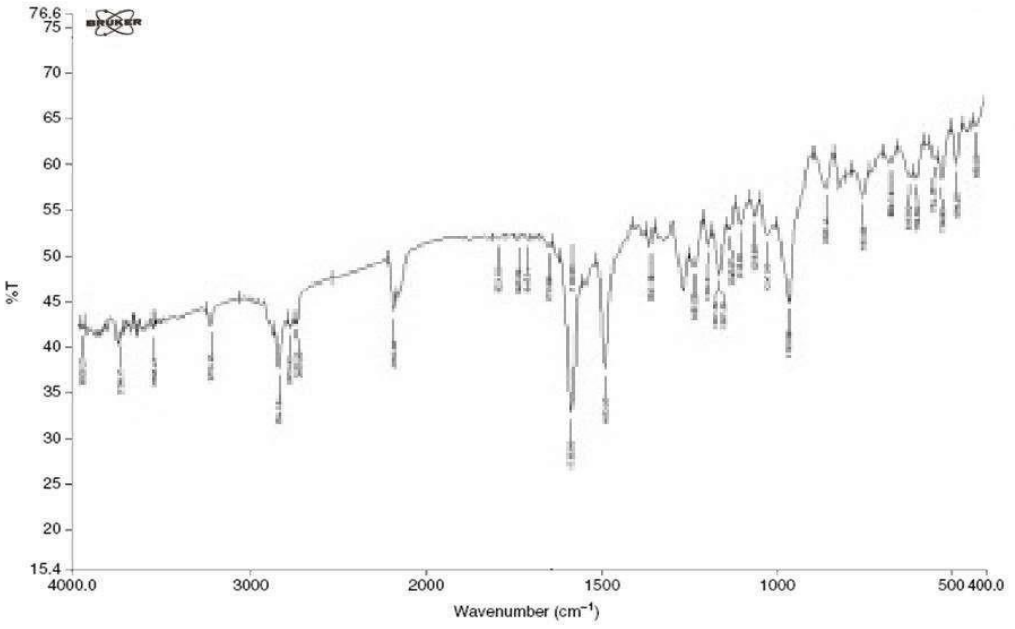

Fig 6. The I. R. Spectrum of capsaicin sample (S1)

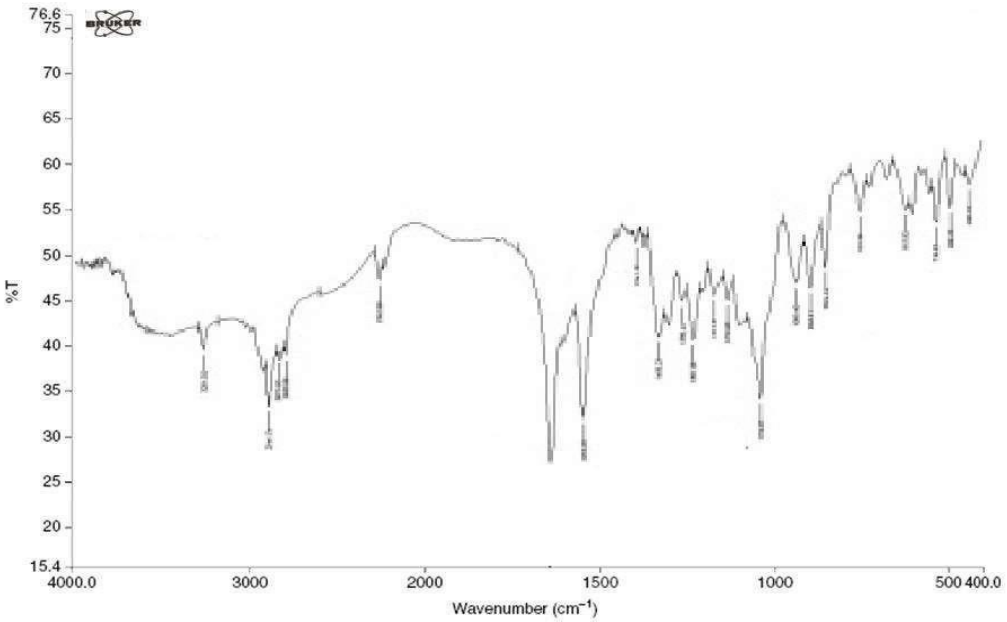

Fig. 7 The I. R. Spectrum of capsaicin drug and all excipient (S2)

Formulation and Evaluation of Drug-Containing Films

Preparation of Capsaicin Films:

The aim of this study was to develop transdermal films containing capsaicin, designed for rapid drug release. Hydroxypropyl methylcellulose (HPMC) and ethyl cellulose solutions were prepared individually by dissolving the required amounts in distilled water. Guar gum solution was prepared by dissolving the polymer in a 1% v/v acetic acid solution with continuous stirring at 40°C. Capsaicin (20 mg) was dissolved in the solvent prior to being incorporated into the respective polymeric solutions, as outlined in Table.

The drug-polymer mixture was continuously stirred using a thermostatic magnetic stirrer at 37 ± 2°C. Plasticizers, including glycerine, polyvinylpyrrolidone (PVP), or polyethylene glycol 400 (PEG400), were added during stirring. The mixture was left to stand overnight to eliminate air bubbles. After stirring, the solution was sonicated in an ultrasonic water bath and poured into petri dishes lined with a mercury base and circular glass bangles open on both sides. The bottom of the bangles was sealed with aluminum foil to facilitate solvent evaporation at 35°C (Olven Instruments, India). The films were produced using the solvent casting method. Once dried, the films were removed and cut into circular pieces (2 cm^2, equivalent to 4 mg of drug). These pieces were wrapped in

aluminum foil and stored in air-tight polyethylene bags within desiccators to ensure stability.Physical Properties of Transdermal Films

Physical Appearance:

The films were evaluated for key parameters, including optical properties, smoothness, color, transparency, and flexibility.

Thickness:

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

Weight Variation:

The films were weighed in triplicate, and the mean weight was calculated. Individual film weights were compared to ensure they were within the permissible limits of the mean weight.

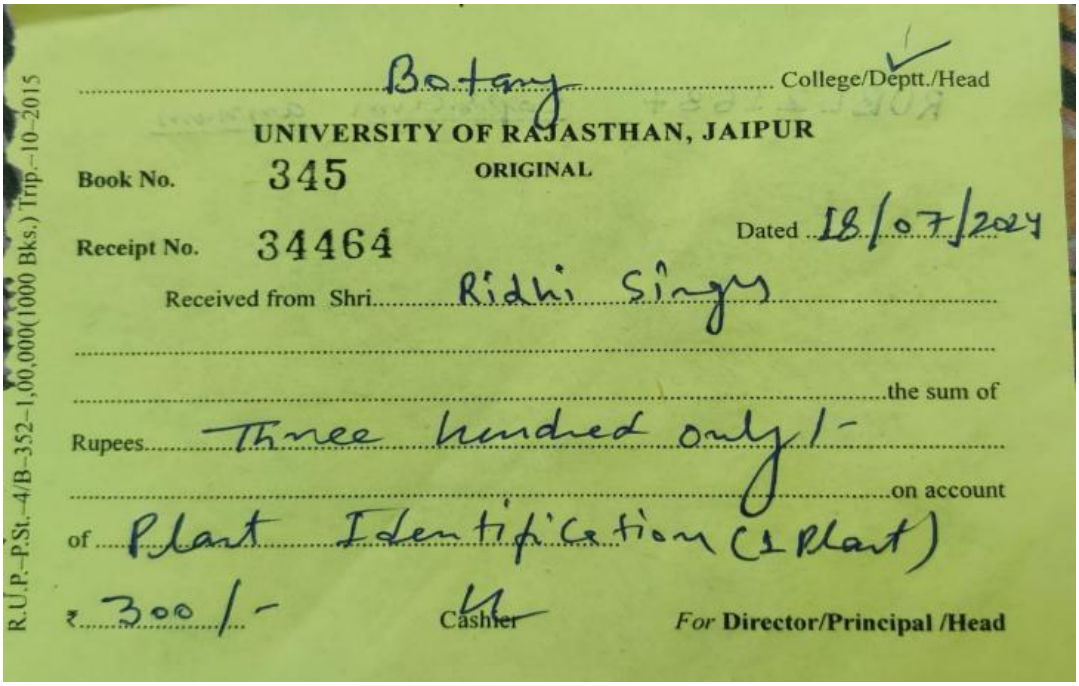

Fig. 8 Research relevant images

Fig. 9 Research Relevant Images: 170461-170495.

Uniformity:
The films were cut into strips—one from the center and two from the edges. The lengths of the strips were measured using a scale, ensuring there were no constrictions or irregularities in the films.

Table 4 Preparation of capsaicin containing transdermal film

Formulation Code	Drug	Polymers (gm)			Plasticizers			Penetration enhancer
	Capsaicin mg	HPMC	Ethyl cellulose	Guargum	Glycerin (ml)	PVP (gm)	PEG 400 (gm)	Isopropyl myristate (ml)
TLF1	100	2	-	-	5	-	-	0.5

TLF2	100	-	2	-	5	-	-	0.5
TLF3	100	-	-	2	5	-	-	0.5
TLF4	100	2	-	-	-	1	-	0.5
TLF5	100	-	2	-	-	1	-	0.5
TLF6	100	-	-	2	-	1	-	0.5
TLF7	100	2	-	-	-	-	1	0.5
TLF8	100	-	2	-	-	-	1	0.5
TLF9	100	-	-	2	-	-	1	0.5

Surface pH:

The surface pH of the prepared films was determined using a digital pH meter. A small piece of the film was cut, immersed in 0.5 mL of double-distilled water, and allowed to swell for 1 hour before measurement.

Tensile Strength:

The tensile strength of a 2 cm^2 film was assessed using a custom-designed tensile strength testing apparatus. The films were secured in place with adhesive tape and mounted in a film holder. A small opening was created in the tape to allow the insertion of a hook, which was connected to a thread. This thread extended over a pulley and terminated at the other end with a small pin for holding weights. A pointer, attached to the thread, moved across graph paper affixed to the base plate, enabling precise measurement. Incremental weights were added, starting from a low value, until the film reached its breaking point. The force required to rupture the film was recorded as the breaking force, and the tensile strength was subsequently calculated using the appropriate formula.

Folding Endurance:

The folding endurance of the prepared film was determined manually. A piece of the film was repeatedly folded at the same spot until it broke. The number of folds the film withstood without breaking was recorded as its folding endurance. The results were expressed as the mean number of folds.

Moisture Content:

The moisture content of the films was assessed by first weighing the films and then drying them in an air current at 60°C. The films were subsequently stored in a desiccator containing calcium chloride at 40°C for 24 hours. After drying, the films were equilibrated at room temperature and 75 ± 0.5% relative humidity, maintained using a saturated solution of sodium chloride. The films were weighed again, and the percentage increase in weight was calculated to determine the moisture content.

Swelling Ratio (SR):

The swelling behavior of the films was evaluated by immersing them in a petri dish containing distilled water until they reached a constant weight. The films were weighed at regular time intervals to monitor the swelling process. The degree of swelling (SR%) was determined using the formula

Drug Content Determination:

A square segment of the prepared film (2 × 2 cm) was immersed in 100 mL of dissolution medium and subjected to continuous stirring for 24 hours to ensure complete drug release. Following this, the mixture was ultrasonicated for 15 minutes and subsequently filtered. The filtrate was then diluted with the dissolution medium, and the drug content was determined using a UV spectrophotometric analysis.

In-Vitro Dissolution Study:

In-vitro dissolution testing is a critical method used in pharmaceutical development and quality control to evaluate the release rate of active ingredients from dosage forms under simulated physiological conditions. The dosage form, such as a film, is placed in a dissolution apparatus containing a dissolution medium (e.g., water, simulated gastric, or intestinal fluid) maintained at controlled temperature and agitation. The active ingredient's concentration in the medium is measured at regular intervals using analytical techniques like UV spectroscopy.

This testing helps to:

Assess the performance and quality of drug formulations.

Ensure consistency in drug release between batches.

Optimize formulations during development.

Compare generic drugs with innovator products to demonstrate bio-equivalence.

For this study, a dissolution test procedure was conducted using the FDA-adapted paddle method (USP Apparatus 2). A transdermal patch was positioned in the dissolution vessel by sandwiching it between a watch glass and an aluminum wire screen. Dissolution profiles of marketed brands (e.g., nitroglycerin patches) were studied over 24 hours. All samples were analyzed via UV spectroscopy.

Procedure for the In-Vitro Drug Release Study

Apparatus and Film Placement:

A USP type V dissolution apparatus was used, consisting of a basket, paddle, and glass slide. A specific portion of the prepared film was cut to fixed dimensions, which were noted for drug release calculations. The adhesive side of the patch was affixed to a glass slide, which was then placed in the basket.

Dissolution Medium:

The basket was immersed in 500 mL of dissolution medium (phosphate buffer, pH 7.4), maintained at 32 ± 0.5°C.

Agitation Settings:

The paddle was positioned 2.5 mm above the membrane surface and rotated at 50 rpm.

Sample Collection:

At fixed intervals up to 24 hours, 5 mL samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium to maintain sink conditions.

Analysis:

The absorbance of each sample was measured at 221 nm using a UV spectrophotometer. The cumulative percentage of drug release was calculated based on the standard calibration curve. This systematic approach ensures accurate and reproducible determination of the dissolution profile and drug release kinetics.

Drug Release Kinetic Data Analysis

To characterize the release behavior of drugs from a matrix, several kinetic models are commonly employed due to their simplicity and wide applicability. Among these, the most frequently used models are:

Zero-Order Model

The zero-order model assumes that the release rate of the drug is independent of its concentration. When a graph of cumulative drug release percentage against time is plotted, a linear relationship indicates zero-order kinetics. The equation for this model is:

$Qt = k0 * t$

Here, Qt represents the percentage of drug released at time t, and k0 is the zero-order release rate constant.

First-Order Model

The first-order model assumes that the drug release rate is directly proportional to the amount of drug remaining in the matrix. The equation is expressed as:

$\ln(100 - Qt) = \ln(100) - kI * t$

Where kI is the first-order release rate constant, and Qt is the cumulative percentage of the drug released at time t.

Higuchi Model

The Higuchi model is based on Fickian diffusion and describes drug release as a square-root time-dependent process. The relationship is given by:

$Qt = kH * t^{(1/2)}$

Here, Qt represents the drug released at time t, and kH is the Higuchi release rate constant.

Korsmeyer-Peppas Model

The Korsmeyer-Peppas model is applied to analyze drug release from systems where the mechanism is not well understood or involves multiple processes. The equation is:

$Qt/Q\infty = kKP * t^n$

Where $Qt/Q\infty$ is the fraction of drug released at time t, kKP is a constant related to the structural and geometric characteristics of the matrix, and n is the release exponent.

The release exponent (n) provides insight into the drug release mechanism:

n = 0.5: Fickian diffusion (Case I transport).

0.5 < n < 1: Anomalous transport (non-Fickian, involving both diffusion and matrix relaxation).

n = 1: Zero-order release (Case II transport).

n > 1: Super Case II transport, indicating mechanisms such as polymer erosion or swelling.

The n value is determined from the slope of a log(Mt/M∞) versus log(t) plot, where Mt and M∞ are the amounts of drug released at time t and infinity, respectively.

Data Analysis

To investigate the drug release kinetics from microspheres, release data were fitted to these equations. The selection of the appropriate model is based on the goodness of fit and the linearity of the corresponding plots:

Zero-Order Plot: Cumulative percentage drug release vs. time.

Higuchi Plot: Cumulative percentage drug release vs. square root of time.

Korsmeyer-Peppas Plot: Log cumulative percentage drug release vs. log time.

Each model provides specific insights into the release characteristics and mechanisms, ensuring a comprehensive understanding of the drug delivery system.

Table 5 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 6 Thickness of Transdermal film

Formulation code	Thickness (mm) Mean ± SD; n = 3
TLF1	0.29±0.03
TLF2	0.26±0.02
TLF3	0.25±0.03
TLF4	0.24±0.02
TLF5	0.23±0.01
TLF6	0.22±0.01
TLF7	0.23±0.03
TLF8	0.25±0.03
TLF9	0.26±0.02

Table 7 Weight variation of Transdermal film

Formulation code	**Average weight (mg) Mean ± SD; n = 3**
TLF1	111.32.±1.154
TLF2	110.33±1.156
TLF3	112.60±0.144
TLF4	119.23±1.154
TLF5	118.33±1.155

TLF6	114.66±1.165
TLF7	116.37±1.154
TLF8	113.78±0.111
TLF9	112.43±1.152

Table 8 Folding endurance of ransdermal film

Formulation code	**Folding endurance Mean ± SD; n = 3**
TLF1	75-80
TLF2	79-80
TLF3	86-91
TLF4	92-95
TLF5	93-97
TLF6	91-94
TLF7	90-93
TLF8	94-98
TLF9	99-101

Table 9 Percentage elongation of transdermal film

Formulation code	**Percentage Elongation Mean ± SD; n = 3**
TLF1	93.74±0.15
TLF2	94.81± 0.02
TLF3	101.42± 0.09

TLF4	116.52± 0.02
TLF5	118.12± 0.03
TLF6	119.11±0.02
TLF7	95.91±0.15
TLF8	104.72±0.15
TLF9	102.72±0.15

Table 10 Tensile strength of Transdermal film

Formulation code	**Tensile Strength N/mm^2 Mean ± SD; n = 3**
TLF1	3.66±1.18
TLF2	6.69±0.23
TLF3	5.93±0.13
TLF4	6.79±0.23
TLF5	5.86±1.18
TLF6	6.13±0.13
TLF7	5.76±1.18
TLF8	5.59±0.23
TLF9	4.63 ±0.13

Table 11 Swelling ratio of Transdermal film

Formulation code	**Swelling ratio (%) Mean ± SD; n = 3**
TLF1	23.97± 0.43
TLF2	22.32 ± 0.39
TLF3	22.18 ± 0.58
TLF4	21.43 ± 0.49
TLF5	19.42 ± 0.57
TLF6	16.63 ± 0.54
TLF7	20.13 ± 0.55
TLF8	22.87 ± 0.46
TLF9	25.48 ± 0.45

Table 12 Surface pH of transdermal film

Formulation code	**Surface pH Mean ± SD; n = 3**
TLF1	5.5 ± 0.14
TLF2	5.6 ± 0.14
TLF3	5.7 ± 0.12
TLF4	5.8± 0.12
TLF5	5.5 ± 0.13
TLF6	5.5 ± 0.14
TLF7	5.6 ± 0.14

TLF8	5.7 ± 0.14
TLF9	5.6 ± 0.12

Table 13 Drug content of transdermal film

Formulation code	**Drug content of films (%) Mean ± SD; n = 3**
TLF1	93.99±0.8
TLF2	94.95±0.9
TLF3	95.79±0.10
TLF4	99.59±0.11
TLF5	98.07±0.12
TLF6	99.85±0.13
TLF7	97.55±0.14
TLF8	99.74±0.15
TLF9	97.99±0.16

Table 14 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

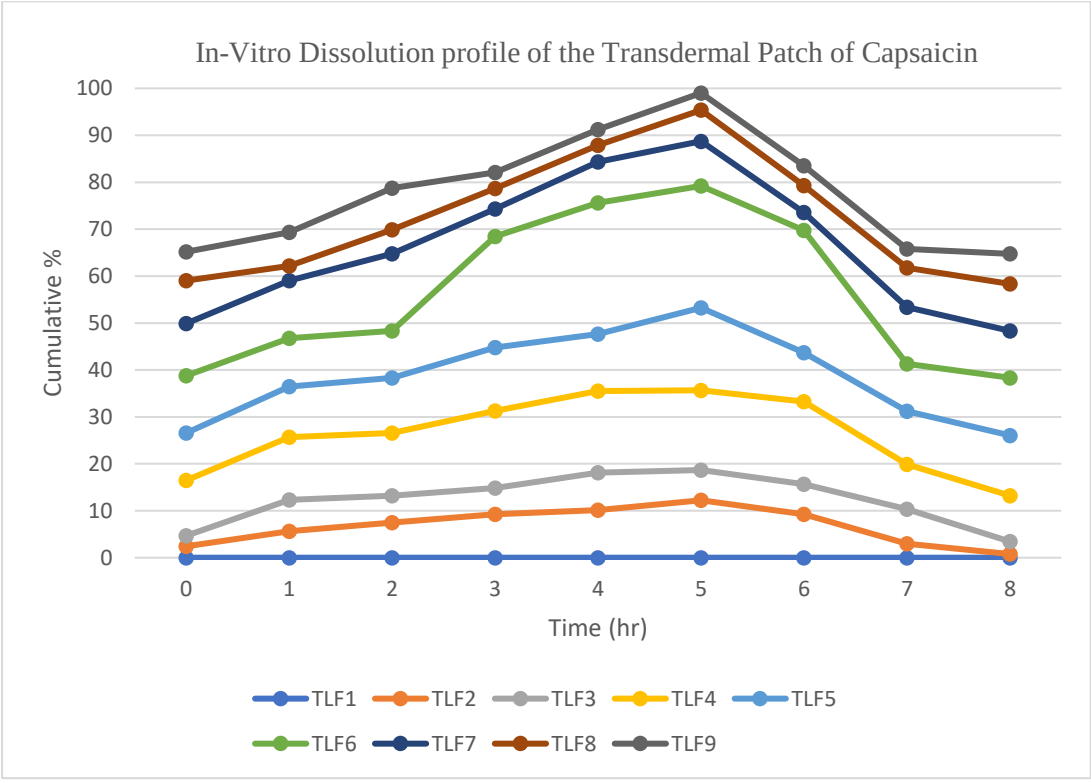

Fig. 10. In-Vitro Dissolution profile of the Transdermal Patch of Capsaicin

Table 15 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 ± 0.055
2	F2	1.292 ± 0.031
3	F3	1.499 ± 0.031
4	F4	1.286 ± 0.081
5	F5	1.698 ± 0.059
6	F6	1.104 ± 0.075
7	F7	1.822 ± 0.019
8	F8	1.178 ± 0.076
9	F9	1.103 ± 0.072

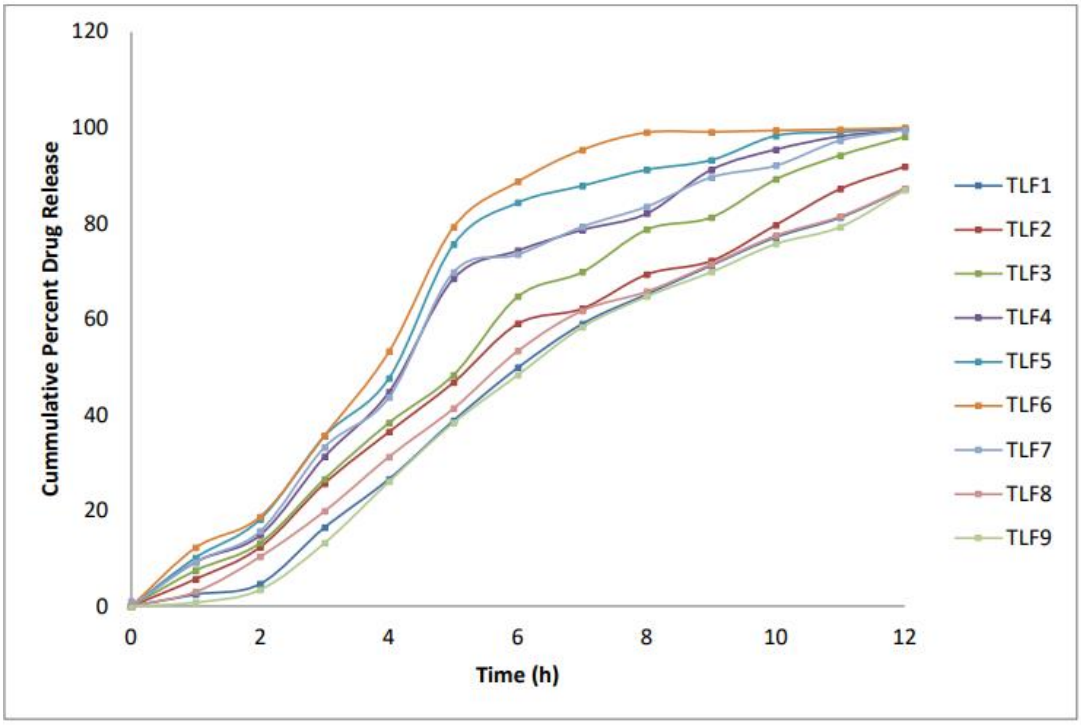

Fig. 11 In vitro drug release profile (Zero-order) of transdermal film (TLF1 – TLF9)

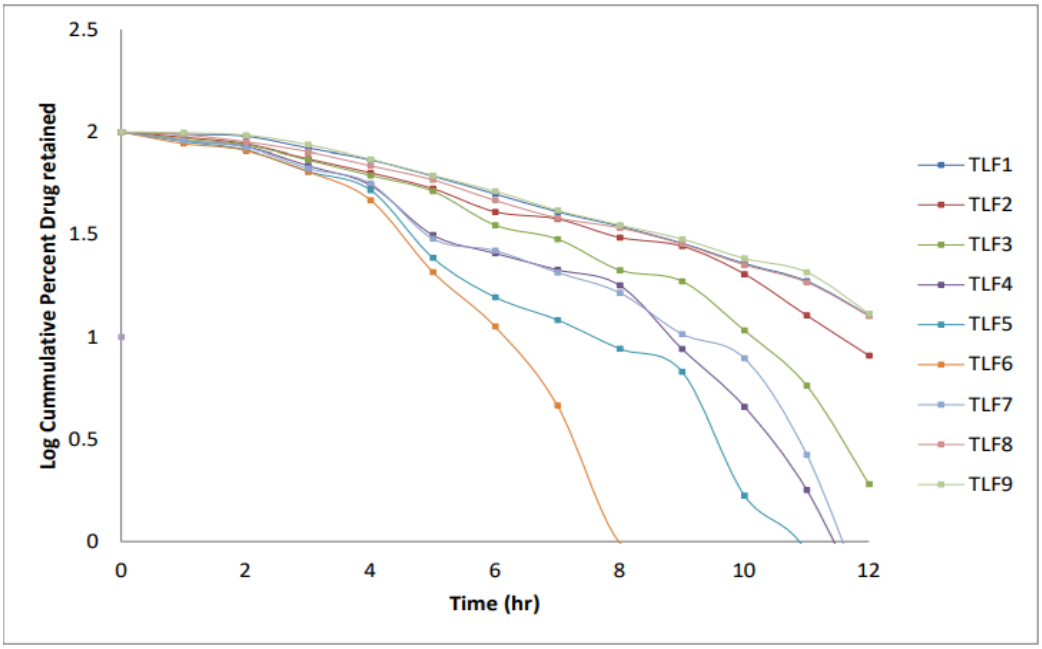

Fig. 12 In vitro drug release profile (First-order) of transdermal film (TLF1 – TLF9)

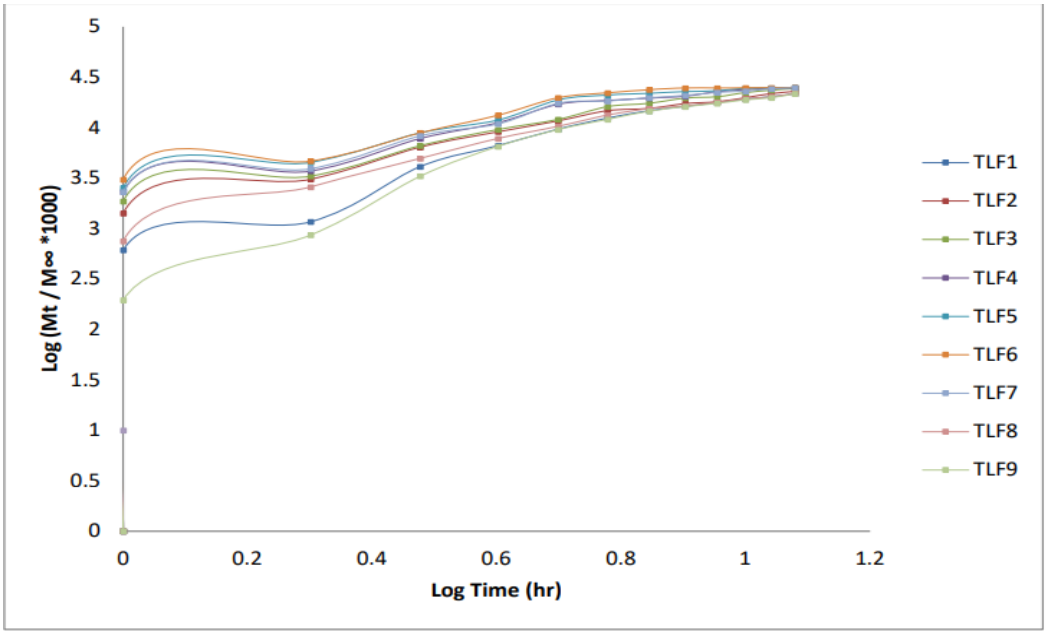

Fig. 13 In vitro drug release profile (Korsmeyer-peppas) of transdermal film (TLF1 – TLF9)

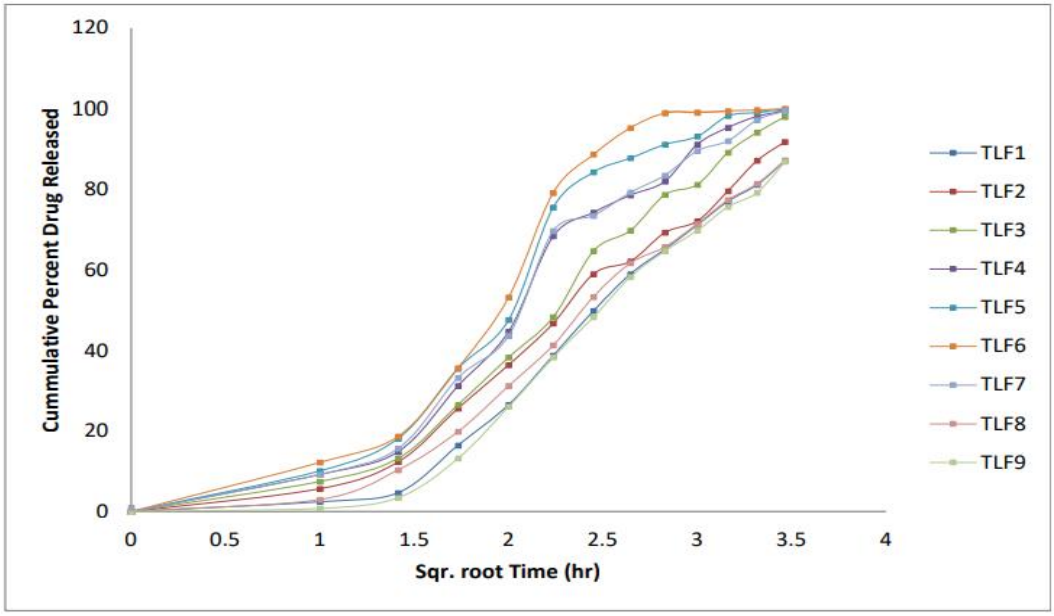

Fig. 14 In vitro drug release profile (Higuchi-plot) of transdermal film (TLF1 – TLF9)

Table 16 in-vitro drug release kinetic profile of transdermal film (TLF1–TLF9)

Formulation Code	Zero Order		First Order		Higuchi Equation		Korsmeyer Equation	Peppas
	r^2	K_0	r2	k	r^2	KH	r^2	n
TLF1	0.95	3.0	0.92	0.081	0.98	18.2	0.82	2.20
TLF2	0.95	3.5	0.92	0.082	0.99	18.5	0.81	2.01
TLF3	0.96	3.0	0.93	0.080	0.991	19.0	0.82	2.11
TLF4	0.95	3.1	0.93	0.084	0.98	19.1	0.81	2.20
TLF5	0.92	3.3	0.94	0.081	0.98	19.2	0.82	2.11
TLF6	0.92	3.0	0.94	0.081	0.98	19.1	0.81	2.01

TLF7	0.92	3.1	0.92	0.081	0.99	19.8	0.81	2.22
TLF8	0.95	3.6	0.91	0.080	0.96	19.2	0.83	2.14
TLF9	0.95	3.0	0.93	0.080	0.97	19.1	0.81	2.36

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Chapter 4

Results and discussions

The absorption maximum (λ-max) of capsaicin (10 µg/ml) in a pH 7.4 phosphate buffer was observed at 221 nm, as shown in the spectrum graph of absorbance versus wavelength (refer to Fig.). Capsaicin quantification was performed in vitro using optimized UV spectrophotometric methods tailored for laboratory conditions. These methods were utilized for drug estimation in a dissolution medium with pH 7.4 phosphate buffer. Calibration curves, plotted by correlating absorbance with known capsaicin concentrations, exhibited excellent linearity with correlation coefficients exceeding 0.99, demonstrating rectilinear behavior within a concentration range of 10–50 µg/ml. Organoleptic analysis identified capsaicin as a white, odorless, slightly bitter crystalline substance. Its bulk and tapped densities were measured at 0.618 g/cm³ and 0.676 g/cm³, respectively, with an average particle size of 82 µm. Flow property assessments revealed a Carr's index of 8.57 ± 0.038%, a Hausner's ratio of 1.09 ± 0.012, and an angle of repose (θ) of 24.5° ± 0.111, categorizing it as having good to passable flowability. Solubility studies indicated capsaicin's solubility as 1.323 mg/ml in water, 1.786 mg/ml in 0.1 N HCl, 0.821 mg/ml in pH 4.5 buffer, 3.122 mg/ml in pH 6.8 buffer, and 1.061 mg/ml in pH 7.4 buffer. The partition coefficient was calculated to be 1.93, while the melting point was determined to be 123°C.

FTIR spectral analysis of pure capsaicin showed distinct peaks at 1193 cm^{-1} (C-N stretch), 1024 cm^{-1} (C–C stretch), 1541 cm^{-1} (C=C stretch), 1396 cm^{-1} (carboxylate anion stretch), 1735 cm^{-1} (C=O stretch), 3279 cm^{-1} (N–H stretch), and 2879–2941 cm^{-1} (C–H stretch). These peaks were unaltered in the physical mixture spectra, confirming no interaction between the drug and polymers. Transdermal films (TLF1–TLF9) prepared with capsaicin exhibited flexible, smooth, opaque, and non-sticky characteristics. Film thickness ranged from 0.22–0.29 mm, and weight variation was between 110.33–119.23 mg. Folding endurance values ranged from 75–97, percentage elongation varied from 93.74–119.11%, tensile strength ranged from 3.66–7.79 N/mm^2, swelling ratios varied from 16.63–23.97%, and surface pH values were within 5.5–5.8. Drug content ranged from 93.99–99.74%. These films were assessed for various parameters, including optical properties, smoothness, transparency, thickness, mass uniformity, surface pH, tensile strength, cracking resistance, moisture absorption, and swelling ratio. In vitro drug release studies showed a release of 58.34–95.37%, indicating that hydrophilic polymers like guar gum enhanced the dispersibility and spreadability of water-soluble capsaicin. The hydrated

polymeric layer facilitated matrix loosening, allowing for over 95.5% drug release within 6–7 hours, suitable for immediate-release formulations. The TLF6 film was selected as the optimized formulation based on its superior physical attributes, tensile strength, elongation, folding endurance, swelling ratio, moisture content, and drug release profile. Release kinetic studies confirmed that the prepared film followed diffusion-controlled kinetics within the specified time frame.

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Chapter 5

Summary and Conclusion

The proposed model drug, capsaicin, is an ethyl ester prodrug of capsaicinat, a non-sulfhydryl ACE inhibitor. The transdermal drug delivery devices (TDDs) in these cardiac arrhythmia treatments address short biological half-life, limited oral bioavailability, dosage, and molecular weight restrictions to improve drug bioavailability. A slow-release calcium channel blocker and a prolonged, controlled-release capsaicin are in the proposed transdermal patch. The capsaicin film was tested for optical properties (color, transparency, and smoothness), flexibility, polymeric film thickness, mass uniformity, texture consistency, surface pH, tensile strength, crack resistance, water absorption, swelling ratio, moisture content, and in-vitro drug release. The hydrophilic polymer chitosan improved the spreadability and dispersibility of water-soluble capsaicin, providing over 95.5% controlled drug release over 12 hours. The polymeric film formulation TLF6 was chosen for its outstanding tensile strength, percentage elongation, folding endurance, swelling ratio, moisture content, moisture uptake, drug content, and in-vitro drug release performance. Studies showed that the produced film followed diffusion-based kinetics, releasing immediately within a specified duration. The release mechanism followed a super case-II transport mechanism, allowing sustained release. A significant linear association was found in regression analysis, with r^2 values verifying the release profile consistency. Slope values were calculated from graphical data.

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