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Review

Emerging Gel Technologies for Effective Transdermal Drug Delivery – A Review

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Abstract

The development of advanced gel systems for transdermal drug delivery has become a significant innovation in pharmaceutical sciences. These gel-based systems offer multiple advantages, including sustained and targeted drug release, enhanced skin permeability, improved drug stability, reduced systemic side effects, and better patient compliance. Various gel types, such as hydrogels, organogels, emulgels, and stimuli-responsive gels, are being actively researched due to their biocompatibility, ease of application, and ability to encapsulate both hydrophilic and hydrophobic drugs. Each type of gel is specifically tailored to match the physicochemical properties of the drug and therapeutic requirements, providing flexible treatment strategies for a wide range of medical and dermatological conditions. Among these, the composition of nanogels tailored to specific therapeutic needs offers promising solutions for effective and patient-friendly treatments in both medical and dermatological fields. Their high surface area, enhanced skin penetration, and controlled release capabilities make them ideal carriers for efficient and site-specific drug delivery. This review focuses on the various types of gels used in transdermal drug delivery and their unique physicochemical characteristics.

Keywords: Hydrogels, Novel gels, Organogels, Stimuli-responsive gels, Emulgels, Transdermal drug delivery.

INTRODUCTION

Gels are transparent or translucent, non-greasy, semisolid preparations widely used in pharmaceutical formulations. They are semisolid systems composed of small or large molecules dispersed in an aqueous medium, transformed into a jelly-like consistency through the incorporation of gelling agents. Common gelling agents include synthetic polymers such as Carbomer 934**,** cellulose derivatives like carboxymethyl cellulose and hydroxypropyl methylcellulose**,** as well as natural gums such as tragacanth**.** The viscosity of gels is largely influenced by the type and concentration of the polymer used. Gels are generally classified into two types: single-phase gels**,** where the gelling agents are completely solubilized, and biphasic gels**,** which contain discrete particles dispersed within the base. Transdermal drug delivery has emerged as a highly effective route of administration due to its ability to bypass the gastrointestinal tract, reduce systemic side effects, enhance patient compliance, and offer sustained drug release. With advancements in drug delivery technologies, the development of novel gel systems has gained momentum to enable localized or systemic delivery in a sustained, controlled, and targeted manner. These advanced formulations, often termed "smart gels"**,** are engineered to respond to specific internal or external stimuli such as pH, temperature, ionic strength, enzymes, antigens, light, magnetic fields, ultrasound, or electric currents. Owing to their unique physicochemical properties, innovative formulations, and controlled drug release capabilities, these systems are collectively referred to as novel gels in modern drug delivery applications. These gels offer a more advanced drug delivery system compared to conventional gels because of their abilities as follows,

- Drug release can be sustained or modified at the targeted site.
- Smart gel systems can respond to natural or external stimuli.
- Therapeutic efficacy is enhanced with minimized adverse effects.
- A high drug load can be incorporated without chemical interaction.
- Nanogels, due to their nanoscale size, can reach even the smallest capillaries.
- They facilitate both active and passive drug targeting.
- These gels are largely biocompatible and biodegradable.

ORGANOGEL

Organogels are non-crystalline, thermoplastic, semi-solid systems characterized by their viscoelastic behaviour and limited mobility of the external apolar (non-polar) phase. This restricted mobility is attributed to the formation of a structured network by low molecular weight compounds known as gelator**s**. These gelators self-assemble through physical interactions to entrap the apolar solvent, resulting in a stable, gel-like matrix. Common gelators include lecithin**,** sterols**,** cholesteryl derivatives**,** and sorbitan monostearate. Organogels are thermodynamically stable**,** primarily due to their rigid, three-dimensional fibrous structures. Among them, lecithin-based organogels are particularly notable for their desirable properties such as moisture insensitivity**,** microbial resistance**,** thermodynamic stability**,** and viscoelasticity**.** These characteristics make organogels highly suitable for pharmaceutical and cosmetic applications. The benefits of organogels include cost-effectiveness**,** ease of preparation**,** enhanced transdermal drug penetration**,** and the avoidance of first-pass metabolism**,** making them ideal for topical and systemic drug delivery [1]. The organogel is formed as shown in Figure 1.

TYPES OF ORGANOGEL

Lecithin organogel

Owing to their superior physicochemical properties, lecithin organogels are primarily employed in cosmetics. These can be used to deliver a variety of hydrophilic and lipophilic specifics transdermally. Lecithin is an organic substance that's safe, stable, and biocompatible. It can be uprooted from a variety of plants and animals. It can transport a variety of bioactive substances. A phosphatidylcholine outgrowth of phospholipids is lecithin. It has been noted that if lecithin contains lower than 95 phospholipids, it will not form gel [3].

Eudragit organogel

Eudragit organogels are made from a admixture of polyols (propylene glycol, glycerol), high concentration (30- 40) of Eudragit (L or S) and polyethylene glycol. To prepare Eudragit organogels, the drug is dissolved in PEG and this mixture is added to Eudragit. Mix this admixture with a mortar and pestle for about a nanosecond. This study showed that the concentration of Eudragit and the quantum of medicine directly affected the viscocity of the gel. The density of gel depends upon Eudragit concentration [4].

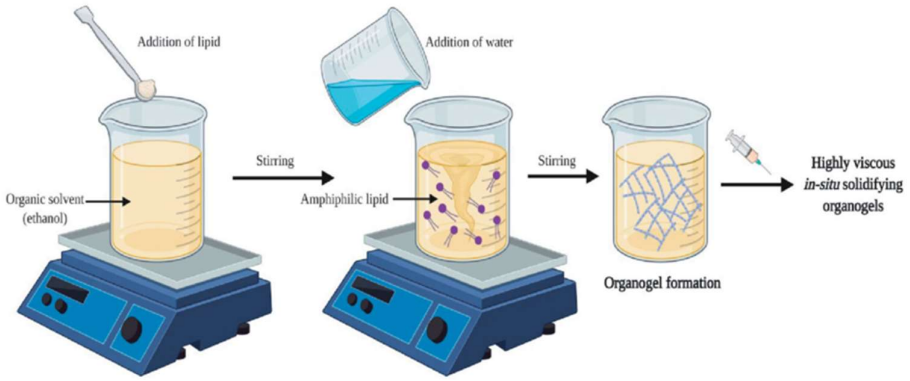

Fig 1: Formation of organ gel [2]

Ideal characteristics of drugs for organogels

- **Log P: Moderate to high Log P (>2)** is preferred, as organogels have a lipid-rich phase.
- **Molecular Weight: Low to moderate molecular weight (<800 Da)** is ideal to facilitate skin permeation (if used for topical/transdermal applications).
- **Lipophilic Nature:** Organ gels are particularly suited for drugs with lipophilic (fat-soluble) properties, as their apolar environment facilitates better drug solubilisation and sustained release.
- **Intended for Topical or Transdermal Delivery:** Drugs designed for localized treatment on or through the skin benefit most from organ gels, which enhance skin penetration and provide controlled release.
- **Instability in Aqueous Environments:** Organ gels protect drugs that are sensitive or unstable in water-based formulations by providing a non-aqueous environment, thereby improving drug stability and shelf-life.

STIMULI RESPONSIVE GELS

Stimuli-responsive gels, also referred to as smart gels or intelligent hydrogels, react to environmental changes (such as temperature, pH, light, enzymes, or even electric fields) to deliver drugs in a controlled or targeted fashion. They are particularly beneficial for site-specific delivery, triggered release, or reducing systemic side effects. Controlled drug delivery via stimuli-responsive materials has been of growing interest to the drug delivery community. Drugs can be easily encapsulated and released with stimuli including temperature, pH, and ionic strength, etc [5]. The creation of ordered nanostructures in the gel phase from colloidal systems can be controlled by other types of external stimuli like temperature, light, ultrasound, electric and magnetic fields, and by the processes of transformation, diffusion, and chemical sensitivity[6]. Physical stimuli: light, temperature, mechanical stress, concentration; Chemical stimuli: ions, pH, Enzymes as shown in Figure 2 and Table 1.

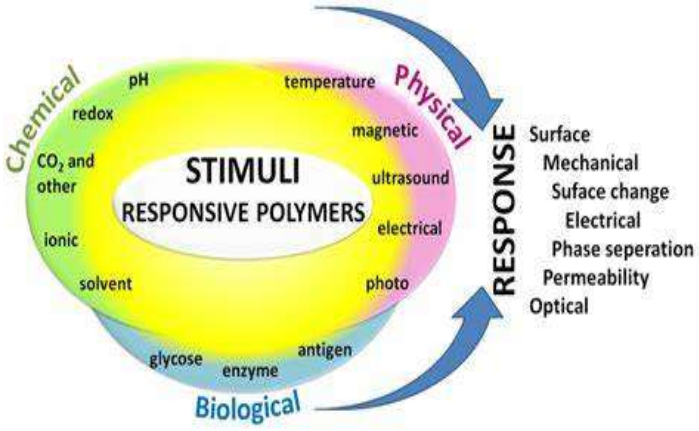

Fig 2: Stimuli responsive gel

Table 1: Types of stimuli-responsive gels [7-9]

STIMULI RESPONSIVE GELS	DEFINITION	POLYMERS USED
Thermo-responsive gels	Gels that transition between sol and gel states at body temperature (~37°C).	Poloxamers (Pluronics), PNIPAM, chitosan/glycerophosphate.
pH responsive gels	Release drugs in response to pH changes (e.g., stomach pH vs. colon pH, tumor acidity).	Carbopol,Eudragit, poly(acrylic acid), alginate.
Enzyme responsive gels	Trigger drug release in the presence of specific enzymes (e.g., overexpressed in diseased tissue).	Peptide-crosslinked hydrogels, gelatin-based matrices.
Light responsive gels	Allow spatial and temporal control using UV, visible, or NIR light.	Azobenzene-functionalized gels, spiropyran, gold-nanoparticle composites
Electro responsive gels	Used in iontophoresis or electrotherapy systems.	Polypyrrole, polyaniline, electroactive hydrogels.

HYDROGELS [10 -16]

A hydrogel is a three-dimensional network of cross-linked, water-swollen polymers formed by polymerizing one or more monomers. It is a polymeric material that does not dissolve in water but can absorb and retain a large amount of water within its structure. The cross-links between polymer chains provide resistance to dissolution, while hydrophilic functional groups enable water absorption. Hydrogels consist mainly of water filling the spaces between polymer chains, with the polymer content being much lower than the water portion. Hydrogels are broadly classified into physical and chemical types based on the nature of the cross-links. Physical hydrogels have non-covalent cross-links such as hydrogen bonds, hydrophobic interactions, or chain entanglements, making them reversible and highly biocompatible. Their gelation can be triggered or reversed by external stimuli like pH, temperature, or ion concentration (e.g., gelatin, alginate). In contrast, chemical hydrogels possess covalent cross-links, forming stronger and often irreversible networks. Some chemical hydrogels, such as thiomer hydrogels cross-linked via disulfide bonds, are non-toxic and widely used in pharmaceutical applications. Hydrogel is formed as shown in Figure 3.

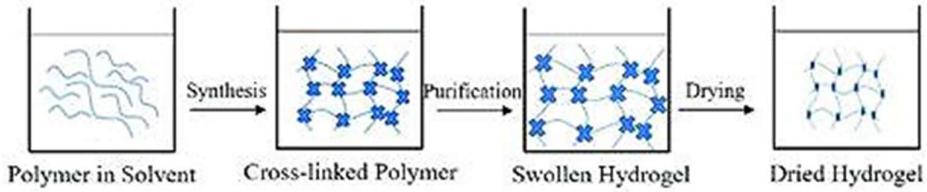

Fig 3: Formation of Hydrogel [17]

Hydrogels formed by physical crosslinks are known as reversible hydrogels, while those with covalent bonds between polymer chains are called permanent hydrogels. Hydrogels are made from various polymers, broadly classified into natural and synthetic origins.Common natural polymers include hyaluronic acid, chitosan, heparin, alginate, gelatin**,** and fibrin, which are generally biocompatible, biodegradable, and may offer additional benefits such as antimicrobial properties and enhanced tissue regeneration. Synthetic polymers frequently used include polyvinyl alcohol, polyethylene glycol, sodium polyacrylate, acrylate polymers, and their copolymers. Although synthetic hydrogels typically provide greater stability and mechanical strength, natural hydrogels are preferred in many medical applications due to their safety and biological advantages. [18-21]

Ideal Characteristics of Drugs for Hydrogel Formulation

- **Molecular Weight:** Low to moderate molecular weight (typically <1000 Da) is preferred for uniform diffusion through the hydrogel matrix.
- **Log P (Partition Coefficient):** Low to moderate log P (0–3) is ideal for good solubility and interaction with hydrophilic hydrogel matrices.
- **Aqueous Stability:** Since hydrogels are water-based systems, the drug must remain stable in an aqueous environment.

- **Controlled Release Potential:** Drugs that require sustained or controlled release are well-suited for hydrogel delivery.
- **Localized Delivery:** Hydrogels are ideal for targeted local administration, such as to wounds, joints, or eyes, making drugs aimed at specific sites preferable.
- **Suitable Molecular Size:** While very large molecules may face diffusion challenges, advanced hydrogels can effectively encapsulate proteins and peptides.
- **Low Irritancy:** For topical or mucosal use, the drug should be non-irritating to ensure patient comfort and safety.

EMULGEL

Emulgels are an emerging and promising system for topical drug delivery, combining the advantages of both emulsions and gels. They consist of two immiscible phases an internal (dispersed) phase and an external (continuous) phase stabilized by emulsifying agents. The drug, usually contained in the internal phase, passes through the external phase and is gradually absorbed into the skin, enabling controlled release.Emulsions can be oil-in-water (O/W) or water-in-oil (W/O), while gels are three-dimensional polymeric networks stabilized by chemical or physical cross-linking, forming solid, transparent materials. Drug release in emulgels is influenced by both the emulsion and gel components. Gels are generally classified as organogels (hydrophobic, based on organic solvents like liquid paraffin) or hydrogels (hydrophilic, water-based). While gels are effective carriers, they have limitations delivering hydrophobic drugs. Emulgels address this by incorporating hydrophobic drugs into emulsions that are then gelled for improved delivery.There are various types of emulgels, including macroemulsion emulgels, microemulsion emulgels, and nanoemulgels, each offering enhanced stability and drug delivery performance [23]. Emulgel formation is shown in Figure 4.

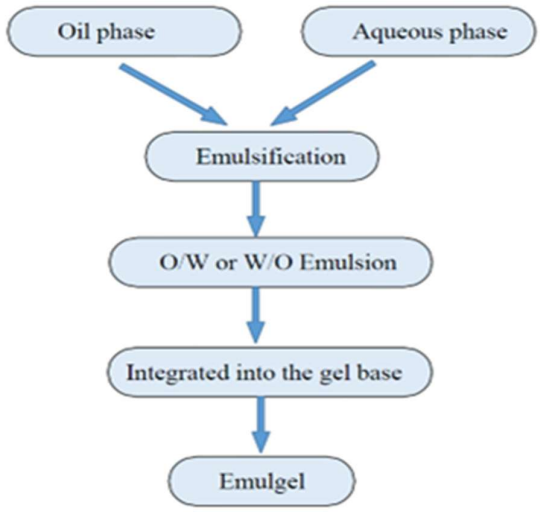

Fig 4: Formation of Emulgel [24]

Ideal characteristics of drugs for emulgel formulation

Poor Aqueous Solubility (Hydrophobic Nature): Emulgels are well-suited for lipophilic drugs with low water solubility, which are incorporated into the oil phase of the emulsion before gelation for easier topical application.
Topical or Transdermal Delivery: Ideal for drugs intended for local action on the skin or systemic absorption through transdermal delivery.
Low Molecular Weight: Drugs with a molecular weight under 500 Da generally penetrate the skin more effectively.
Moderate Lipophilicity: Drugs with a log P (partition coefficient) between 1 and 3 strike a good balance between hydrophilicity and lipophilicity, aiding skin penetration through the stratum corneum.
Non-Irritating and Non-Sensitizing: The drug should be safe for prolonged skin contact without causing irritation or allergic reactions.
Stability in Emulsion and Gel: The active compound must remain chemically stable within both the emulsion and gel components.
Effective at Low Dose: Drugs effective at low concentrations are preferred to maintain emulgel texture and stability without overloading the formulation.

NANOGEL

Nanogels are a type of nanoparticle created by merging a hydrogel with a cross-linked hydrophilic polymer. They have gained attention as effective drug delivery systems for targeting cancer cells due to their ease of formation and customization. Typically, nanogels are sized between 20 and 200 nm. Their classification can be based on several factors, including size, surface area, hygroscopicity, and their behavior under stress or degradation. One of the key advantages of nanogels is their ability to facilitate controlled and sustained release of medications. Their unique three-dimensional structure allows them to effectively encapsulate drugs, polymers, and various liquid phases. Notably, these nanogels can accommodate larger particles or drugs within their pores. Serving as carriers for pharmaceuticals, they are designed to rapidly form biomolecular interactions with active compounds, such as through hydrophobic or hydrogen bonding. Nanogels represent an innovative material that exhibits both solid and liquid properties. According to theoretical models, the effectiveness of the treatment is closely related to the duration of contact between the nanoparticles and the skin following their encapsulation within the nanogel matrix [25].

Ideal characteristics of drugs for nanogel formulation [26-28]

Molecular Weight: Preferably low to moderate (<1000 Da) to allow effective diffusion through the gel network.
Solubility: Drugs with poor water solubility benefit the most, as nanogels can enhance solubility via encapsulation or dispersion.
Lipophilicity (Log P): Moderate lipophilicity (Log P 1–3) is often ideal for balanced loading and release.
Therapeutic Index: Drugs with narrow therapeutic indices benefit from nanogels due to their controlled and targeted delivery.
Targeting Needs: Drugs intended for localized or targeted therapy (e.g., cancer, inflammation, infection) benefit greatly from nanogels.
Short Half-life: Drugs with short half-lives benefit from the sustained release provided by nanogels.
First-pass Metabolism: Ideal for drugs extensively metabolized by the liver, as nanogels can bypass first-pass metabolism (e.g., via transdermal or intranasal delivery).

CONCLUSION

Novel gels are revolutionizing transdermal drug delivery by providing significant advantages over conventional formulations. Their distinctive physicochemical characteristics allow them to encapsulate diverse drugs and respond to environmental stimuli, enabling controlled, sustained, and targeted release. These gels improve drug stability, enhance skin permeability, and reduce side effects, leading to better patient compliance. Advances in materials science and nanotechnology are driving the development of smarter gel systems with improved functionality and precision. As research progresses, novel gels are set to offer more effective and personalized therapeutic solutions across a wide range of medical applications.

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