INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 6, June 2026 | ISSN: 2456-4184 | IJNRD.ORG

A Comprehensive Review on Hydrogel Matrix Systems in Transdermal Drug Delivery: Contemporary Formulation Strategies and Advanced Optimization Technologies

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ABSTRACT

Transdermal drug delivery systems are a new technology of pharmaceutical delivery that represents a significant improvement over traditional patches due to excellent biocompatibility, regulable drug delivery, and skin permeation. This is a literature review of modern development techniques of formulations and his progressive technologies of optimization of hydrogel matrices to use in transdermal development. Essential details such as hydrogel chemistry, classification systems, physicochemical characterization, drug release, and skin penetration enhancement are coherently presented. The modern formulation techniques include the rational choice of polymers, crosslinking techniques, nanotechnology, prodrug technologies, chemical and physical increase of permeability, stimuli-responsive intelligent systems and nanocomposite hydrogels. Highly sophisticated optimization tools such as Quality by Design (QbD) concepts, Design of Experiments (DoE) methods, Response Surface Methodology (RSM), and artificial intelligence/machine learning systems have been widely tested and are proven to be transformative in the systematic formulation development. A variety of clinical applications such as pain control, cardiovascular treatment, hormone replacement, neurological and dermatological utilize therapeutic versatility. Issues related to manufacturing, scale-up, regulatory and quality control plans are covered. The existing constraints such as drug candidate constraints, skin variability, and safety considerations are reviewed critically. The future outlook suggests the integration of personalized medicine, the use of smart wearables, IoT connectivity, sustainable materials, and the new application in gene therapy and vaccine delivery. The review gives pharmaceutical scientists and researchers in depth information that will bridge the basic concepts with the latest optimization technologies to develop rational hydrogel transdermal patches.

Keywords: Hydrogel matrix, Transdermal drug delivery, Quality by Design, Response Surface Methodology, Artificial Intelligence, Smart hydrogels.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) have transformed pharmaceutical therapy as it provides a non-invasive method of administration as opposed to other modes of drug delivery. The field has been experiencing exponential growth since first transdermal patch of scopolamine was approved in 1979 and since that time a lot of products have gained commercial success [1]. The transdermal route bypasses the first-pass hepatic metabolism, provides stable plasma drug levels during long-term use, decreases the dosing frequency, increases patient adherence, and provides controlled release of drugs with the added benefit of easy discontinuation through removal of the patches. Although they have these benefits, the stratum corneum, which comprises of corneocytes embedded in lipid matrix, poses a daunting obstacle to the penetration of drugs. This uppermost layer of the epidermis actually restricts TDDS applications to molecules that fulfill particular physicochemical requirements: the molecular weight must be less than 500 Da, the lipophilicity

must be sufficient (log P 1-3), the potency must be sufficient to permit therapeutic dosages with patch sizes that are realistically achievable, and the melting points must be favourable. These are hard requirements which have previously limited transdermal delivery to a few drug candidates [2].

Mats of hydrogel have become advanced systems eliminating most of shortcomings by traditional transdermal patches. Hydrogels are crosslinked networks of polymer, which are able to take up large amounts of water or biological fluids and still retain their structure. Their special features such as, high level of biocompatibility, tunable mechanical properties, swelling behavior and high water content, which mimics biological tissues, high drug loading capacity, and easy application make them perfect candidates to be used in transdermal applications. Hydrophilic properties of hydrogels with ease leads to stratum corneum hydration, which temporarily breaks its organized lipid structure and increases drug permeation in a variety of mechanisms [3]. The rubber like nature ensures that there is ease of wear and good ability to conform to body shape. The hydrogels can entrap lipophilic drugs as well as hydrophilic drugs by making relevant changes in their formulations. The transparent or translucent nature will give the opportunity to see the application site visually. These strengths make hydrogels the better choice compared to traditional pressure sensitive adhesive matrices [4].

Due to recent developments in the field of polymer chemistry, nanotechnology, material science, and pharmaceutical engineering, it is now possible to generate advanced hydrogel systems with stimuli-responsiveness, improved mechanical strength, regulated release properties, and bi-/trivalent functions. Implementation of nanomaterials, creation of interpenetrating polymer networks, and design of intelligent responsive systems are all important technological advances [5]. At the same time, the principles of Quality by Design (QbD) and high-level optimization technologies adopted by the pharmaceutical industry has shifted the development of hydrogel formulations out of the trial and error methods to the systematic and science-based ones. Design of Experiments (DoE), Response Surface Methodology (RSM), artificial intelligence, machine learning, and computational modeling allow exploring formulation space effectively, finding optimal formulations, and creating robust formulations whose performance is predictable [6].

This review provides an in-depth analysis of modern strategies in formulation that are used in the development of hydrogel matrices to deliver drugs through transdermal deposition, and special attention is given to sophisticated optimization methods that have transformed the process over the last few years. We are critical of polymer selection strategies, crosslinking mechanisms, drug incorporation strategies, permeation enhancement strategies and smart Hydrogel Systems. The incorporation of systematic optimization techniques such as DoE and RSM as well as artificial intelligence and computational modeling of formulating optimal hydrogel formulations is widely explained. The aspects of manufacturing, scale-up issues, clinical use in the various therapeutic areas, regulatory issues, current restrictions, and future outlook are discussed to give a full picture on this fast-evolving field that integrates the basic pharmaceutical sciences to the innovative technology.

2. FUNDAMENTALS OF HYDROGEL MATRIX SYSTEMS

2.1 Hydrogel Chemistry and Classification

Hydrogels are a special category of substances that can be defined as crosslinked polymeric networks that are hydrophilic and are stable in three dimensions and remain stable in aqueous conditions. The name of the hgel is based on their capacity to absorb water without becoming dissolved owing to crosslinkages between them. This water-solubility capacity is due to the hydrophilic functional groups such as hydroxyl, carboxyl, amide and sulfonate groups that are bound on the polymer backbone [7]. The schemes of classification offer guidelines into hydrogel diversity. Hydrogels are either classified as physical or chemical based on the nature of crosslinking. The reversible non-covalent interactions in which physical hydrogels are created are hydrogen bonding, ionic interactions, hydrophobic associations, crystallization, and chain entanglements [8]. Such

systems show reversible gel-sol changes to environmental stimuli like changes in temperature, pH or ionic strength. The self-healing and injectability are made possible by the reversibility. In chemical hydrogels, crosslinking via a chemical reaction with crosslinking agents, crosslinking via radiation-induced polymerization, or enzymatic crosslinking is achieved and a permanent set of networks with superior mechanical stability and dissolution resistance are formed [9].

Hydrogels are either natural, synthetic or semi-synthetic polymers based on the source material. Natural polymers that are used in transdermal hydrogels are chitosan which is a derivative of chitin that is extracted to form algae, gelatin which is a derivative of collagen that has been hydrolyzed, hyaluronic acid which is extracted in the connective tissues, and different derivatives of cellulose [10]. Such biopolymers have superb biocompatibility, biodegradation by enzymatic or hydrolytic means, low immunogenicity, and biologically recognisable signals. They, however, can be susceptible to batch-to-batch variation, low level of mechanical strength, possible contamination by pathogens, and high degradation rates necessitating stabilization through a chemical modification [11]. Synthetic polymers, including polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyacrylic acid (PAA), poly(N- isopropylacrylamide) (PNIPAAm), and carbomers are better reproducible, can be tuned accurately by molecular design, have better mechanical properties, degrade at controlled rates, and they are not immunogenic. Nevertheless, synthetic polymers can contain no biological recognition cues and can pose biocompatibility challenges that should be carefully studied. Semi-synthetic polymers (especially cellulose derivatives, such as hydroxypropyl methylcellulose cellulose (HPMC), hydroxyethyl cellulose (HEC) and sodium carboxymethylcellulose (Na-CMC) are a blend of the benefits of either category with natural origin characteristics, and chemically modified characteristics. Interpenetrating polymer networks (IPNs) are also a more sophisticated type of architecture, in which two or more polymer networks are entangled at a molecular scale, but are not connected to each other through covalent bonds [12]. IPNs may be simultaneous in which all networks are created simultaneously, or sequential in which a network is created in an already existing network. Semi-IPNs have one crosslinked structure and one linear polymer. The dual network structure provides IPNs with synergistic property, improved mechanical strength, thermal stability and controlled swelling behavior to avoid excessive uptake of water, and optimized drug release profiles as a result of property combinations [13].

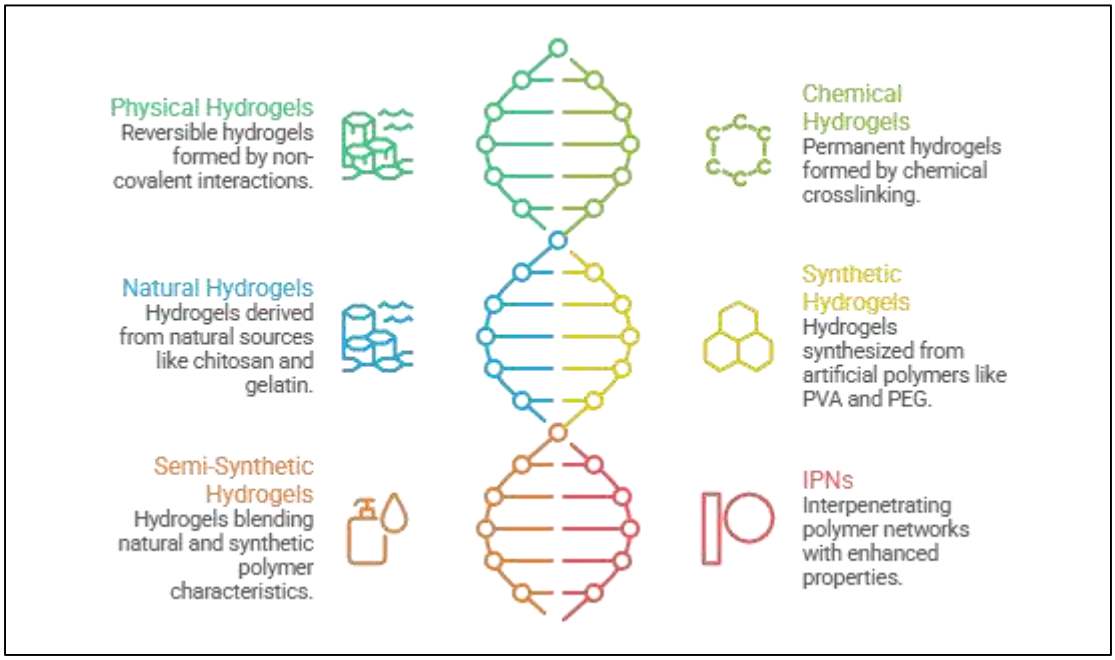

Figure 1: Classification of hydrogels

2.2 Physicochemical Properties and Characterization

Knowledge of the basic physicochemical characteristics allows rational designing of hydrogel. The behavior of swelling is an important feature that defines drug loading capacity, release kinetics, and mechanical properties. Swelling occurs when the networks of polymer are filled with water, leading to an increase in the volume of the polymer network until a balance is reached between the forces of osmotic pressure bringing water into the polymer and the forces of elastic recoil of the polymer network [14]. The balance swelling ratio is determined by the hydrophilicity of the polymer, crosslinking concentration, ionic nature and environmental factors such as pH, temperature and ionic rise. The crosslinked insoluble fraction is measured by gel fraction. Measurements are done by taking soluble fractions using suitable solvents and calculating the residual insoluble crosslinked network. An increase in gel fractions means that it is more crosslinked and better structurally stable [15]. Porosity characterization The methods such as mercury intrusion porosimetry, gas adsorption analysis, or a microscopic analysis can be used to characterize porosity size distribution, which influence the rate of water uptake and diffusion of drugs [16]. Tensile strength, compressive strength, elongation at break, and elastic modulus are some of the mechanical properties that dictate the handling properties, durability when used, and comfort to patients. Oscillatory measurements used to characterize rheology give data on the viscoelastic behavior, the strength of the gel after deformation, and the structural recovery. Storage modulus (G(prime) which is a measure of elastic character and loss modulus (G(second) which is a measure of viscous character are measured as functions of frequency or temperature or strain amplitude. Intersection of G’ and G is a crossover point of sol-gel [17].

The property of bioadhesion to biological surfaces is a very important characteristic of transdermal patches because it determines intimate contact during the entire application time. The forces of bioadhesion are created due to mechanical interlocking, electrostatic attraction, diffusion and interpenetration of the polymer chains into the mucus or tissue, and creation of weak chemical bonds [18]. Tensile testing, which measures the detachment force, shear testing, which tests the resistance to the tangential forces, and adhesion work, which is determined by the force-displacement curves, are all measurement methods. Bio compatibility testing is a measure of safety during extended skin contacts [19]. Preliminary screening is done through in vitro cytotoxicity using fibroblast or keratinocyte cell lines. Primary skin irritation tests are performed according to standardized guidelines which measure erythema and edema of the rabbit or guinea pig skin after application of the patches. Sensitization studies measure allergic potential by means of repeated exposures. Microscopic modification of the skin biopsies can be seen through the histopathology with either inflammatory infiltration, necrosis or architectural variations [20].

2.3 Drug Release Mechanisms from Hydrogel Matrices

Knowledge of drug release will allow rational controlled delivery system design. Drug release out of hydrogel matrices are based on diffusion-controlled, swelling-controlled or erosion-controlled processes, which tend to work in combination where one process takes preeminence over the other based on system characteristics. In diffusion-controlled systems, the drugs dissolved or dispersed in the matrix are diffused through the water-filled pores or polymer network according to the laws of diffusion that have been provided by Fick. In the case of reservoir systems where the cores with the drug are encircled with rate-controlling membranes, diffusion across the membrane controls release, frequently giving zero-order kinetics. In the case of matrix system with drugs evenly dispersed throughout it, release is determined by the drug solubility in the matrix, diffusion coefficient of the drug across the swollen gel, geometry of the matrix and the initial drug loading. The diffusion rate tends to decrease with time as diffusion length path and the gradient of drug concentration reduces and is usually in the form of square root of time as represented by Higuchi equation [21].

Swelling-controlled release entails relaxation of polymer chains and expansion of the polymer matrix through initial interaction of water with the polymer resulting in relaxation and expansion of the polymer and diffusion of the drug through the swollen network. The process is especially applicable in glassy polymers that

experience glass transition when they get hydrated. The release kinetics are dependent on the rate of water penetration, rate of polymer relaxation with regard to the rate of drug diffusion and the interaction between the two processes [22]. In the case where the polymer relaxation is slower than the diffusion of the drug, classical Fickian diffusion takes place. In the case of significantly similar relaxation and diffusion rates, anomalous transport is obtained. In situations where diffusion is not only slow compared to relaxation but also zero-order release is caused by Case-II transport. In biodegradable hydrogels, erosion-controlled release is achieved in which the hydrolysis or enzyme cleavage degradation of the matrix controls liberation of the drug. Surface erosion, in which the degradation takes place mainly at the matrix surface and the interior is not affected, causes the surfaces to maintain constant surface area and release kinetics of zero order ideal in maintaining sustained delivery. Bulk erosion, where erosion is found all through the matrix volume, gives more complicated release profiles [23]. The rate of erosion relies on the polymer chemistry, crosslinking density, the rate kinetics of degradation, the environment such as the pH and the enzyme concentration. Mathematical modeling can give information on the mechanics of releases and can be used to predict release profiles. Zero-order kinetics is the model of a steady release rate that is not dependent on drug concentration. First-order kinetics is used when the rate of release is proportional to the amount of drug left. The Higuchi model describes diffusion-controlled release from planar matrix systems yielding square root of time relationship. The Korsmeyer-Peppas model distinguishes between Fickian diffusion (release exponent $n=0.5$ for slabs), anomalous transport ($0.5<n<1.0$), Case-II transport ($n=1.0$ representing zero-order release), and super Case-II transport ($n>1.0$). The Hixson-Crowell model accounts for surface area changes during dissolution. The Weibull model offers empirical fitting for complex release profiles [24].

2.4 Skin Penetration Enhancement Mechanisms

Hydrogels contribute to transdermal drug delivery in various synergistic ways other than merely loading and releasing drugs. The hydration of matrices plays a significant role in raising the level of water content in the stratum corneum by the process of occlusion that inhibits transepidermal water loss [25]. The hydration has the effects of swelling intercellular lipid domains, raising lipid fluidity, diffusional resistance, and establishing aqueous pathways that enable hydrophilic drug permeation. Under occlusion the stratum corneum water content may rise to 50 percent or more than the normal level of 15-20 percent. Drugs permeate faster in the moist, hydrated environment due to the increased thermodynamic activity of drugs in the moist environment based on the thermodynamic principles [26]. Higher thermodynamic activity of drugs reaches their saturation limits, which gives maximum driving force to permeate. The stratum corneum lipids may be interacted with by hydrogel components such as polymers, plasticizers and excipients in a number of ways. Lipid components are extracted or solubilized leaving behind defects in the barrier. Lipid bilayers are fluidized making the diffusion of drugs easier. Intercalation that disrupts the organization of lipid packing lowers barrier function [27].

Hydrogel patches are the occlusive effect of hydrogel patches and inhibits evaporation of the skin surface to retain water and enhance permeation during the application time. This maintained occlusion is the difference between patches and topical formulations in which evaporation quickly reduces the effects of hydration [28] . There are some intrinsic properties of hydrogel polymers that have integration of penetration enhancement. Cell membranes that have a negative charge are bound to chitosan due to its cationic property, which temporarily destabilizes tight junctions and increases paracellular transport. The hyaluronic acid regulates cell-cell and cell-matrix interactions that affect permeability. Hydrogel formulations influence the ionization of drugs and the skin permeability depending on the pH. The preservation of a pH that biases the union of the lipophilic form is usually beneficial in increasing permeation across the lipid-enriched stratum corneum. But in the case of some ionizable drugs optimum flux is obtained by maximizing the total drug concentration with a given concentration of lipophilic form by optimization of pH. The charged drugs form neutral lipophilic complexes with oppositely charged excipients over which ion-pairing takes place, resulting in greater permeation [29].

3. CONTEMPORARY FORMULATION STRATEGIES

3.1 Rational Polymer Selection and Design

Rational selection of polymers is a core of the effective formulation development of hydrogel which needs to be evaluated in terms of many aspects. Biocompatibility is the most important requirement, whereby, polymers are not toxic, irritating, sensitising, or inflammatory after long-term contact with the skin. Status of regulatory approval and well-established safety profiles is used to select well-characterized materials [30]. The characteristics of swelling should be in line with the needs of the application. Swelling that is excessive impairs mechanical integrity and adhesion and swelling that is insufficient impairs loading of drugs and can hamper drug diffusion. The ratios of target swelling normally vary between 200 and 1000 percent when it is used in certain applications. Mechanical properties such as tensile strength, elongation, and elastic modulus should offer sufficient handling strength, ability to turn to any body shape and movement, and serviceability within the desired time of activity usually a few hours to days [31].

Drug compatibility includes physical stability which helps avoid drug-polymer incompatibilities, chemical stability to avoid degradative reactions and solubility of the drug in the matrix. The interactions between the drug and polymer can be advantageous in increasing the release duration by ionic or hydrogen bonds, but too many interactions can negatively affect the availability of the drug [32]. Some manufacturing issues, such as the solubility of polymers in pharmaceutically acceptable solvents, processing temperature compatibility with drug stability, reproducible gelation or crosslinking kinetics that allow repetitive production, and cost-effectiveness considerations are relevant to manufacturing. Single polymer systems provide the simplicity in formulation and characterization and do not provide the ideal combinations of properties. An individual polymer does not offer the best swelling, mechanical, drug release, and bioadhesion properties. Polymer blends allow synergistic benefits of individual components to be gained, which allows properties to be optimized by varying composition [33]. As an example, a combination of brittle polymers which offer structural properties and flexible polymers which offer elasticity results in balanced mechanical properties systems. The biphasic release profiles in the combination of rapidly swelling polymers to burst and slowly swelling polymers to sustain release have been realized [34].

The concept of crosslinking strategies has a tremendous effect on the nature of hydrogel, including network structure, swelling ability, mechanical strength, and degradation. Reverse networks through ionic interactions, hydrogen bonding, hydrophobic associations or crystalline domain formations form reversible networks that are susceptible to stimuli-responsive behavior and self-healing. Rapidly, polysaccharide polymers (polyelectrolytes, such as alginate or chitosan, and divalent ions) are ionically crosslinked with divalent cations (calcium, zinc) or polyanions respectively. Temperature-reversible networks are formed by hydrogen bonding of complementary groups. Amphiphilic block copolymer contains hydrophobic associations which are physically crosslinked by forming micelles [35]. The crosslinking of polymer chains is done by the use of chemical crosslinking agents which are bifunctional or multifunctional and provide covalent bond between the chains of polymer to form permanent network that is more mechanically stable and resistant to dissolution. Examples of common crosslinker are glutaraldehyde with amines, genipin with biocompatible crosslinking and reduced cytotoxicity than glutaraldehyde, ethylene glycol diglycidyl ether with hydroxyl bearing polymers, and N,N'-methylenebisacrylamide with free radical crosslinking systems. Crosslinking with radiation, which may be provided with gamma rays or electron beams, produces free radicals that trigger crosslinking without the need of any chemical additives, which is useful to implantable systems where sterility is required. Enzymatic crosslinking which uses transglutaminase catalyzing acyl transfer reactions between glutamine and lysine residues or horseradish peroxidase oxidizing phenolic residues provides mild reaction conditions which maintain drug and polymer integrity [36].

The molecular weight optimization tempers the mechanical properties, drug release characteristics and biological interactions. Polymers that possess a higher molecular weight offer better mechanical strength by

increasing the concentration of the chain entanglements and the concentration of chain overlaps at the expense of slowing down the diffusion of drugs due to denser networks and increasing viscosity. Reduced size polymers are both easy to diffuse and penetrate, but are mechanically weak. The best molecular weights vary according to each of the polymers and its application. The concentration of the polymer is an important factor that influences the strength of gel, ability to swell, rate of drug release, and the bi-adhesion and must be carefully controlled by means of systematic research assessing the concentration effects on each of the important quality properties [37].

Table 1: Classification and Characteristics of Polymers Used in Hydrogel Transdermal Patches [38–41].

Polymer Category	Specific Polymers	Advantages	Limitations	Typical Applications
Natural Polymers	Chitosan	Excellent biocompatibility; Biodegradable; Mucoadhesive; Antimicrobial properties; Wound healing promotion	Batch variability; Limited mechanical strength; pH-dependent solubility; Poor solubility at neutral pH	Wound dressings; Anti-inflammatory drug delivery; Antimicrobial patches
	Alginate	Biocompatible; Rapid gelation with divalent cations; Cost-effective; Easy processing	Poor mechanical strength; Uncontrolled degradation; Lack of cell adhesion sites	Wound healing; Anti-inflammatory applications
	Gelatin	Excellent biocompatibility; Biodegradable; Cell adhesion promotion; Low cost	Poor mechanical properties; Rapid degradation; Temperature sensitivity; Risk of disease transmission	Wound healing; Growth factor delivery
	Hyaluronic Acid	Outstanding biocompatibility; Excellent hydration; Cell signaling capabilities; Non-immunogenic	High cost; Rapid enzymatic degradation; Weak mechanical properties	Anti-aging formulations; Wound healing; Anti-inflammatory delivery
Synthetic Polymers	Polyvinyl Alcohol (PVA)	Excellent mechanical strength; High water retention; Biocompatible; Chemical stability; Reproducible properties	Non-biodegradable; Requires crosslinking; Limited bioadhesion	Controlled release patches; Mechanical support matrices
	Polyvinylpyrrolidone (PVP)	Excellent biocompatibility;	Non-biodegradable;	Immediate release systems;

		High water solubility; Non-toxic; Forms clear films	Weak mechanical properties; High swelling; Rapid drug release	Solubilization enhancement
	Polyethylene Glycol (PEG)	Biocompatible; Non-immunogenic; Protein resistance; Tunable molecular weight	Non-biodegradable; Weak mechanical properties; Requires blending with other polymers	Drug conjugation; Permeation enhancement; Network modifier
	Carbomer (Polyacrylic Acid)	Excellent bioadhesion; pH-responsive; High viscosity; Thixotropic; Sustained release	Non-biodegradable; pH-dependent gelation; Potential skin irritation at high concentrations	Bioadhesive patches; pH-responsive systems
Semi-Synthetic Polymers	Hydroxypropyl Methylcellulose (HPMC)	Good biocompatibility; Controlled swelling; Film-forming; Moderate adhesion; Reproducible	Limited mechanical strength; Temperature-dependent properties; Moderate cost	Sustained release matrices; Matrix-type patches
	Hydroxyethyl Cellulose (HEC)	Good biocompatibility; Excellent thickening; Transparent gels; Non-ionic; Broad pH stability	Limited mechanical strength; Non-biodegradable; Moderate adhesion	Gel-based patches; Viscosity modifiers
	Sodium Carboxymethyl Cellulose (Na-CMC)	Biocompatible; Excellent water retention; Good adhesion; Cost-effective	Limited mechanical strength; Anionic charge limitations; Protein binding	Bioadhesive systems; Wound dressings
Interpenetrating Networks (IPNs)	PVA-Chitosan IPN	Synergistic mechanical strength; Enhanced biocompatibility; Tunable properties; Improved stability	Complex preparation; Optimization required; Higher cost	Advanced controlled release; Multi-drug delivery
	Alginate-PVA IPN	Improved mechanical properties; Controlled degradation; Enhanced stability;	Preparation complexity; Potential brittleness; Requires optimization	Wound healing; Sustained delivery systems

		Good biocompatibility		

3.2 Advanced Drug Incorporation and Loading Strategies

The drug incorporation strategies have a strong influence on the distribution uniformity, loading performance, chemical stability, and release behavior. The direct mixing method entails solubilization or dispersion of drugs in polymer solutions, followed by gelation by crosslinking or evaporation. The latter basic strategy fits well with stable drugs that can be formulated in suitable conditions, yet can lead to premature drug-polymer interactions that could result in loading efficiency or release kinetics. In poorly soluble drugs, uniform distribution is achieved by the use of solubilization methods such as the use of cosolvents, surfactants or by complexation with cyclodextrins. In-situ polymerization includes drugs in the formation of the network using either free radical method of polymerization, condensation reaction, or enzymatic polymerization [42]. This system may have an increased ability to entrap drugs by physically encapsulating them in forming networks or chemically bonding to active groups and needs the drug to be compatible with polymerization parameters such as temperature, pH levels, initiator systems, and possible exposure to free radicals. Close consideration of drug stability during polymerization is obligatory. Post loading methods involve the exposure of pre-shaped hydrogels to high-descending drug solutions that allow the drug to diffuse and partition through the swollen net. This technique is especially applicable to thermolabile or polymerization-sensitive drugs and may lead to non-uniform distribution with surface enrichment, reduced loading efficiency relative to direct mixing and longer loading times especially with large hydrogel sizes. The loading efficiency is affected by the drug solubility in loading medium and hydrogel, partition coefficient in favor of hydrogel phase and equilibration time [43].

3.3 Nanotechnology Integration

Introduction of drug-loaded nanoparticles, liposomes, niosomes, solid lipid nanoparticles or polymeric micelles into hydrogel matrices form highly complex hybrid systems with synergistic benefits. Nanocarrier encapsulation prevents degradation of labile drugs, solubilizes poorly soluble drugs, delivers multiple drugs with independent release profiles, allows dual controlled release in which initial release of drugs occurs through nanocarriers followed by diffusion through the hydrogel network. The systems of nanoparticles in hydrogel have longer release times than direct drug loading. PLGA, chitosan or albumin polymeric nanoparticles release drugs to days and weeks by erosion or diffusion. Phospholipids or non-ionic surfactants create liposomes and niosomes which have bilayer structures that accommodate both hydrophilic drugs in aqueous cores and lipophilic drugs in lipid bilayers. SLNs are solid lipid matrixes which are stabilized by a surfactant which results in controlled release and enhanced physical stability over liposomes [44].

The process of preparing nanocarriers needs to be done so that the macromolecules remain intact during the formation of the gel. Nanocarrier structure is maintained at mild gelation conditions such as ionic crosslinking, physical crosslinking at physiological temperature and pH or low-temperature solvent evaporation. Characterization involves the distribution of nanocarrier sizes, zeta potential, encapsulation efficiency, the release of nanocarriers by itself or nanocarrier-loaded hydrogels, and morphological analysis that ensures that nanocarriers are distributed uniformly without aggregation [45].

3.4 Prodrug Approaches

Prodrug strategies temporarily modify physicochemical properties through reversible chemical derivatization, enhancing drug loading and permeation characteristics. Esterification of carboxylic acid groups increases lipophilicity and reduces ionization, facilitating incorporation into hydrogel matrices and permeation through stratum corneum lipids. Subsequent hydrolysis by cutaneous esterases regenerates active drugs. Careful

selection of ester moieties controls hydrolysis rates balancing permeation enhancement with adequate skin retention [46].

3.5 Permeation Enhancement Strategies

The penetration enhancers are temporary, chemical, reducing the stratum corneum barrier activity by a variety of mechanisms. The selection will be based on enhancer mechanisms, the physicochemical characteristics of drugs, concentrationeffect interactions, reversibility to allow barrier recovery following debridement of patches, and long-term and safety profiles. Intercellular lipids are fluidized by the insertion of fatty acids and esters such as oleic acid, linoleic acid, lauric acid, isopropyl myristate and ethyl oleate, making them more disordered and more mobile. Mechanisms can include the separation of phases to form domains with a different arrangement of lipids, the formation of distinct fluid domains in the structured lipid matrix, as well as the isolation of lipid components into enhancer pools. The best concentrations are usually between 1-10 percent balancing effectiveness and skin acceptability [47].

Surfactants such as sodium lauryl sulfate, polysorbates, Brij series and Pluronic interfere with the organization of the lipids by solubilization and micellar formation. Keratin proteins are attracted by anionic surfactants by the electrostatic force. The non-ionic surfactants invade the lipid domains by means of hydrophobic interaction. The factors that need to be taken into serious concerns are concentration in relation to critical micelle concentration, equilibrium between permeation increase and irritation risk, and the selection of mild surfactants in sensitive applications [48].

Alcohols and glycoses like ethanol, propylene glycol and polyethylene glycol dissolve and destabilize the lipid and keratin proteins respectively. Ethanol of 30-70 percent concentration is effective in increasing permeation though it can lead to skin drying with long exposure. Propylene glycol 5-20% is hydrating with moderate improvement that is better tolerated. Menthol, limonene, eucalyptol, carvone and pinene, are terpenes which provide natural alternatives with excellent safety profiles and good sensory properties. The mechanisms are lipid fluidization by intercalation, temporary destabilization of lipid packing, and augmented drug partitioning into lipid domains. A large number of terpenes also offer cooling effects that are useful in pain management. Data concentrations in the range of 1-5 percent are normally practical. Azone (1-dodecylazacycloheptan-2-one) is a strong synthetic disruptor of lipid organization and is an augmenter of drug partitioning. Even low concentrations of 0.1-1% show a great improvement. Sulfoxides such as dimethyl sulfoxide (DMSO) and decylmethyl sulfoxide enter the skin and form drug-binding polar pathways and react with lipid and protein domains. Nevertheless, DMSO can absorb lipid and protein in skin when left to act over a long period so it is not applicable in long-term usage [49].

3.6 Physical Enhancement Methods Integration

The iontophoresis requires the application of low electrical current (usually 0.1-0.5 mA/cm 2) that pushes charged agents of drugs through the skin through the process of electrorepulsion of ions of the same charge and electroosmotic flow of solvents. Hydrogels are ideal electrolyte reservoirs that offer excellent electrical conductivity, homogenous current distribution and conformability to electrodes. The drugs that are added as solutions or suspensions in hydrogel touch the skin under electrodes. The factors of enhancement of 10-100 fold are possible. They have been used as local anesthesia in the form of lidocaine, pain management in the form of fentanyl, and anti-inflammatory in the form of methotrexate. Sonophoresis makes use of low-frequency ultrasound (20-100 kHz) that forms temporary aqueous pores due to cavitation effects [50]. The formation of oscillating microbubbles in coupling media breaks stratum corneum organization by the action of mechanical stress, shock wave, and the formation of microjets. Hydrogels give attachment between ultrasound transducers and skin. Optimization is necessary on duty cycles, frequencies and intensities to balance between enhancement and safety. Microneedle arrays form microscale channels (50-900 ほ 50-900 μm deep) in the stratum corneum without going through the nerve ending, which causes no pain but drastically

decreases barrier resistance. Hydrogel patches can be used as reservoirs of drugs on microneedle-treated sites. The dissolution of the microneedles produced using hydrogel forming materials combine penetration enhancement with regulated drug delivery because the microneedles become inert once the drug is inserted. This dual method attains synergistic enhancement of permeation with microneedles opening a pathway and hydrogel releasing it overtime [51].

3.7 Smart and Stimuli-Responsive Hydrogel Systems

Smart hydrogels are responsive to changes in the environmental conditions by conformational deformation, phase deformation or swelling/deswelling transition of drug release kinetics. It is possible to achieve triggered release, on-demand delivery, or self-regulated release in response to physiological conditions using these systems in which ionizable groups are incorporated into hydrogels that respond to environmental pH by either performing protonation or deprotonation. Polymers containing weakly acidic functionalities such as carboxylic acids (polyacrylic acid, alginate) are in collapsed protonated forms at low pH, and swell at high pH by being ionized and to avoid electrostatic repulsion. On the other hand, polymers with weakly basic molecules such as amines (chitosan, polyethylenimine) swell when at low pH and collapse when at higher pH via protonation and deprotonation respectively. The above changes in pH between healthy tissue (pH 4.5-6.5), inflamed tissue (pH 5.5-7.5), and wound conditions (pH 7.0-8.5) allow the pH-mediated release to be condition specific [52].

Hydrogel temperature responsive Hydrogel temperature-responsive hydrogels exhibit volume phase changes at critical solution temperatures. Poly(N-isopropylacrylamide) (PNIPAAm)-based systems have their critical solution temperature (LCST) of approximately 32 o C below which polymers are hydrophilic and above which they are hydrophobic and collapse. The LCST could be copolymerized by increasing LCST with hydrophilic monomers, or decreasing LCST with hydrophobic monomers. The patches result in deswelling and drug release due to temperature (37 degree C) of the body. On the other hand, polymers possessing high critical solution temperature (UCST) act with converse behaviours as they swell beyond transition temperatures. Enzyme-cleavable sequences such as peptide substrates of the matrix metalloproteinases, hyaluronic acid that is cleaved by hyaluronidase or polysaccharides that are cleaved by glycosidase are incorporated in enzyme-responsive hydrogels. They tend to increase such enzymes in pathological processes such as inflammation, infection and cancer. Release is done at disease specific tissues having a high enzyme activity and to deliver disease-specifically [53]. Photochromic molecules such as azobenzene or spiropyran that undergo reversible changes in their conformational state in response to the light are used in light-responsive systems. The trans-cisomerization of azobenzene groups modifies the hydrophilicity of polymer and network structure. Spiropyran is able to alternate between hydrophilic and hydrophobic zwitterions. Light-induced release provides control of the spatiotemporal resolution, but the depth of light-induced skin penetrations limits usage. Multi/dual-responsive hydrogels with more than one stimulus measure can give enhanced control. pH and temperature dual-responsive systems, pH and enzyme dual-responsive systems, temperature and redox dual-responsive systems can give Boolean logic gates on controlled release that demand the concomitant fulfilment of multiple conditions [54].

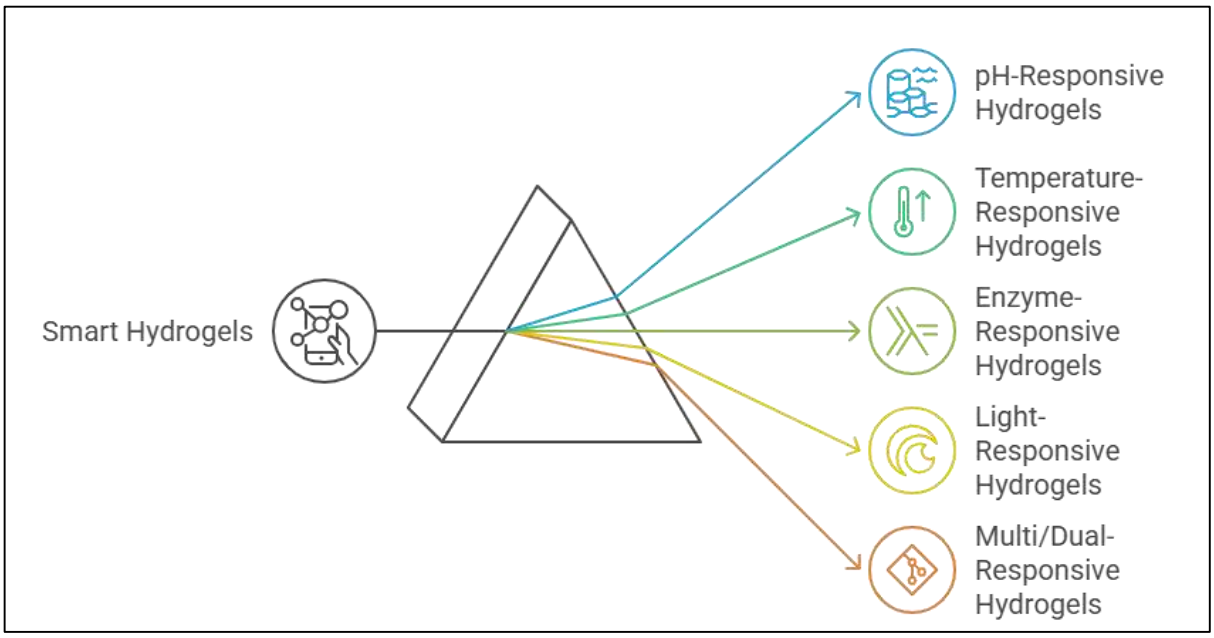

Figure 2: Classification of Stimuli Responsive Hydrogel

3.8 Composite and Hybrid Hydrogel Systems

Nanocomposite hydrogel entails the use of nanomaterials that increase the mechanical strength, electrical conductivity, antimicrobial activity, or gives other functional properties. Hydrogel reinforced with graphene oxide has a better tensile strength of load transfer between the polymer matrix and the high-strength sheets of graphene, electrical conductivity that is useful in iontophoretic applications, and antimicrobial properties owing to the presence of edges of graphene oxide that destroy bacteria membranes. Hydrogels loaded with metal nanoparticles such as silver, gold or copper nanoparticles have broad spectrum antimicrobial properties that are useful in wound healing practice. Silver nanoparticles give out silver ions that interfere with respiration and replication of bacterial cells. Antimicrobial efficacy, but no cytotoxicity, is normally achieved with concentrations of 0.01-0.5%. Carbon nanotube-containing systems increase mechanical behaviors by nanotube reinforcement, electro-responsively release drugs by electrical conductivity, and have the potential to enter the skin by nanotube-mediated skin penetration. Hydrophilization increases the dispersion in hydrogel matrixes. Bioactive Glass-hydrogel composites facilitate wound healing by facilitating the release of therapeutic cations such as calcium, phosphate and silicate that trigger osteogenesis and angiogenesis [55].

4. ADVANCED OPTIMIZATION TECHNOLOGIES

4.1 Quality by Design (QbD) Principles and Implementation

Quality by Design is the shift of quality by testing to quality by design, the focus on systematic product and process knowledge. Guidelines of ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality System) can be used to implement QbD in pharmaceutical development. The QbD process begins with the Quality Target Product Profile (QTPP), a perceived outline of quality attributes that are going to be attained to guarantee the required quality, safety, and effectiveness. In the case of transdermal hydrogel patches, the QTPP elements that might be considered are route of administration, pharmacokinetic profiles, dosage form, therapeutic indication, adhesion properties, wear time, and stability characteristics. The QTPP is a decision guide that is used in development and the basis of quality [56].

Critical Quality Attributes (CQAs) refer to physical, chemical, biological, or microbiological characteristics or properties that need to be within proper limits, ranges or distributions to assure desirable quality of products. Hydrogel patch CQAs typically comprise drug content and uniformity, dissolution / release characteristics, adhesive characteristics, mechanical characteristics, water content, pH, microbial limits and appearance characteristics. Identification of CQA is the risk assessment which correlates the characteristics of the products

with safety and efficacy. Risk assessment uses such tools as Failure Mode and Effects Analysis (FMEA) methodically analyzing possible failure modes, causes, verses, and detectability. Risks are prioritized using risk priority numbers (RPN) that are based on the severity, occurrence and detectability scores. The cause-effect relationships are visualized in Ishikawa fishbone diagrams. Hazard Analysis and Critical Control point (HACCP) determines critical control points that should be monitored. The Risk assessment determines Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) that could affect CQAs. CMAs are features of input materials such as polymer molecular weight, degree of substitution, moisture content, size of drug particle and purity that may impact CQAs. CPPs are process parameters such as mixing time and speed, crosslinking conditions, drying temperature and time and casting thickness, which must be controlled in order to achieve a consistent material meeting CQAs. CMAs/CPPs to CQAs The relationships are determined by systematic experimentation which normally uses Design of Experiments [57].

The design space is a multidimensional combination and interaction of input variables (CMAs and CPPs) shown to guarantee quality. The regulatory authorities view working within the design space as not being a change and movement outside the design space as a regulatory change, which must be evaluated and approved. The establishment of design space involves intensive research to show the limit of control to assure that the CQAs do not go out of the boundaries. The control strategies help that the processes do not move outside the design space, but they also generate quality products all the time. Some of the elements are material specifications that regulate CMA variability, process parameter specifications that define the CPP operating ranges, in-process controls that monitors the critical operations, finished product specifications which assures the CQA acceptance, monitoring and feedback systems that detects trends and change management procedures. Process Analytical Technology (PAT) is a technology that facilitates real-time monitoring and control that assists in the implementation of the control strategy [58].

4.2 Design of Experiments (DoE) Methodologies

Design of Experiments uses the statistical principles to investigate the relations between several factors at the same time in a systematic way. DoE vastly simplifies experimental load relative to one-factor-at-a-time (OFAT) designs and offers much more valuable information such as interaction effects that cannot be observed in the OFAT designs. Screening designs are used to detect meaningful factors among the large number of candidates under situations of limited prior knowledge. A type of two-level fractional factorial design is called Plackett-Burman designs and is efficient at screening a large number of factors, with minimum runs, based on the Hadamard matrices. These designs assume that there are no interaction effects in question, but only main effects. In the case of k factors Plackett-Burman designs will need k + 1 runs (to the nearest multiple of 4), which is significantly less than 2 k in the case of full factorial designs [59].

Fractional factorial designs test partial combinations of full factorial combinations in cases where lower-order interactions are deemed to be less significant. In design III, main effects are estimated, but confound main effects with two-factor interactions. The designs of Resolution IV plans estimate the main effects that are free of two-factor interaction, but the plans confound the two-factor interactions that the main effects have amongst themselves. The main effects and two-factor interactions are clearly estimated in resolution V designs. The design choice strikes equilibrium between the information requirements and the available resources. The Taguchi designs focus on robustness by reducing the variation of performance to uncontrollable noise factors based on orthogonal arrays. Controllable factors are added to designs as inner arrays and noise factors are added in outer arrays. Signal-to-noise ratios are measures of robustness, where larger-the-better, smaller-the-better or nominal-the-best may be, depending on the nature of responses. Sensitivity to noise is minimized by identifying the factor levels that are analyzed [60].

The optimisation designs determine the relationship between factors and responses in a quantitative manner that allows predicting and optimisation. Full factorial designs test all combinations of factors, which is appropriate when the interactions are vital but resource-consuming. In the case of k factors at n levels, n k runs

are necessary. Compared to full factorials, Central Composite Designs (CCD) are more efficient in estimating quadrants with less runs. CCDs consist of factorial points at corners of the design space, and axial points in estimation of curvature along factor axes and center points in estimation of pure error and curvature. Rotatable CCDs offer even predicted variance of prediction across all equidistant points relative to the design center. Face-centered CCDs put axial points at the cube faces, which is beneficial in cases where factor ranges cannot be expanded past original boundaries. Spherical CCDs strike a tradeoff between face-centered designs and rotatability. CCDs normally demand 2^k + center point replicates on k factors. Box-Behnken Designs (BBD) are three-level designs which do not need the runs that CCDs do, nor do they need to test extreme combinations of factors which might fall out of the safe or practical operating range. BBDs locate design points in the middle of the edges of the multidimensional cube, on the center points. BBD needs 13-15 runs in comparison to 20 with CCD because of three reasons. BBDs are better than existing estimators and do not need as many extreme settings to estimate second-order models [61].

D-optimal designs select experimental points on a case-by-case basis, depending on a set of desired constraints, such as irregular design space, mixture constraints or categorical factors. The D-optimality criterion is used to maximize the determinant of information matrix in order to minimize the variance of parameter estimates. Optimal combinations of points are chosen by computer algorithms on candidate sets. D-optimal designs are used when the classical designs are inadequate in addressing complicated situations. Mixture designs are the best to maximize the proportions of components in case total composition is 100 percent, especially in optimization of polymer blends. Simplex designs such as simplex-lattice and simplex-centroid designs efficiently search the mixture space. Augmented designs include interior points that enhance prediction. Mixture models use special forms of polynomials taking into consideration the constraint that components add to one [62,63].

4.3 Response Surface Methodology (RSM) and Mathematical Modeling

Response Surface Methodology develops empirical mathematical relationships between independent variables (factors) and dependent variables (responses) through polynomial equations fitted to experimental data. The methodology enables visualization of response surfaces, prediction of responses at untested factor combinations, and optimization identifying factor settings producing desired response values. Second-order polynomial models typically describe relationships adequately:

$$Y = \beta_0 + \Sigma\beta_i X_i + \Sigma\beta_{ii} X_i^2 + \Sigma\Sigma\beta_{ij} X_i X_j + \varepsilon$$

Where Y represents response variable, β_0 is intercept, β_i are linear coefficients, β_{ii} are quadratic coefficients, β_{ij} are interaction coefficients, X_i represents factors, and ε represents experimental error. Multiple linear regression estimates coefficients minimizing sum of squared residuals between observed and predicted values. Model adequacy assessment employs Analysis of Variance (ANOVA) partitioning total variability into contributions from model terms and residual error. F-statistics test model significance and individual term significance. P-values below 0.05 indicate statistical significance at 95% confidence. R^2 values quantify variability explained by the model, with values above 0.90 generally considered good fits. Adjusted R^2 accounts for the number of terms, penalizing overly complex models. Predicted R^2 estimates prediction capability for new observations, calculated from PRESS (predicted residual sum of squares). Adequate precision measures signal-to-noise ratio, with values above 4 indicating adequate discrimination [64].

Residual analysis evaluates model assumptions including normality, independence, and constant variance. Normal probability plots assess normality of residuals, with random scatter around the straight line indicating normal distribution. Residuals versus predicted values plots detect non-constant variance (heteroscedasticity) or systematic patterns indicating model inadequacy. Residuals versus run order plots identify time-dependent effects or measurement drift. Three-dimensional response surface plots visualize relationships between two factors and one response, facilitating intuitive understanding of factor effects and interactions. Peaks, valleys,

and saddle points indicate optimal regions. Two-dimensional contour plots display response levels as contour lines in factor space, enabling quick identification of combinations producing target responses. Overlay plots superimpose multiple response contours, identifying regions satisfying multiple criteria simultaneously. Optimization identifies factor settings producing desired response values. Single response optimization employs calculus-based methods or numerical algorithms finding maxima, minima, or target values. Constraints restrict factor ranges and response limits. Multiple response optimization requires balancing competing objectives. Desirability function approach transforms individual responses to dimensionless desirability scales from 0 (completely undesirable) to 1 (completely desirable or ideal). For responses to be maximized, desirability functions assign 0 for values below minimum acceptable levels, increase to 1 at target values, and remain at 1 above target. For responses to be minimized, functions assign 1 below target, decrease to 0 at maximum acceptable levels. For target values, functions peak at 1 at target values and decrease toward boundaries. Shape parameters control function linearity, enabling different emphasis on approaching targets [65].

Individual desirability values are combined into overall desirability using geometric mean: $D = (d_1 \times d_2 \times ... \times d_n)^{(1/n)}$, where d_i represents individual desirability and n represents number of responses. Importance weights modify contributions: $D = (d_1^{w_1} \times d_2^{w_2} \times ... \times d_n^{w_n})^{(1/\Sigma w)}$. Optimization algorithms maximize overall desirability, identifying factor combinations providing best compromise across all responses. Multiple solutions may exist; evaluating several high-desirability solutions ensures robust selection [66].

4.4 Artificial Intelligence and Machine Learning Applications

The new technologies of Artificial Intelligence and Machine Learning transform pharmaceutical development by using pattern recognition, predictive modeling, and optimization that are especially useful where the relationships between formulation parameters and performance are strong nonlinearities or have complex interactions. Artificial Neural Networks (ANNs) are based on biological neural networks, where processing units (neurons) are connected in layers. The feed-forward networks are made up of input, hidden and output layers that receive formulation parameters, do nonlinear transformations, and make predictions respectively [67]. The connections have adjustable weights. The input-output pairs are introduced in training, and the weights are changed by input-output pairs to minimize the error in prediction. Activation functions such as sigmoid, hyperbolic tangent or rectified linear units add nonlinearity that allows the learning of complicated relationships. ANNs are highly competent to address nonlinear relations, multiple interacting variables and extensive datasets. Its applications in this area are to predict drug release characteristics of polymer type, concentration, crosslinking density, and drug characteristics, to find optimum polymer blend compositions with desired mechanical and release properties, to predict skin permeation of drug based on physicochemical properties and formulation composition, and to classify formulation stability based on accelerated stability data [68].

The network architecture choice is made with regard to numbers of hidden layers and number of neurons per layer. Single hidden layers may be sufficient in case of simple problems, whereas multiple layers (deep learning) are effective with complex problems. The number of neurons is too small to learn (underfitting) and too large to overfit to the training data in a poor generalization to novel data. Architecture optimization and performance measurement is made possible by the cross-validation methods which separate data into testing, validation, and training sets. Support Vector Machines (SVM) is a classification or regression method which identifies the best hyperplanes that give the maximum margins across classes or the least amount of errors in prediction [69]. In non-linearly separable data, the use of kernel functions (polynomial, radial basis, sigmoid) implicitly transforms data into higher dimensional feature spaces in which it is possible to separate. SVMs are able to work with high-dimensional data, can work well with small-sized training data, and they are able to offer global optima and not suffer the problem of local minima that neural networks suffer. It has been used to classify formulations as acceptable or not depending on quality attributes and predict continuous response such

as drug release rates. Random Forest algorithms are based on ensemble learning (a combination of the predictions of several decision trees). Trees are trained on random subsets of training data and features, which lowers overfitting and enhances generalization. Predictions Final predictions are averaged predictions (regression) or majority votes (classification) of all trees. Random Forests are good predictors, can process mixed data, automatically rank the importance of features, and can tolerate missing data. Most influential formulation parameters are determined with the help of feature importance rankings [70].

Deep Learning models are based on multi-layered neural networks that derive hierarchical features of complicated data. Convolutional neural networks (CNNs) are very effective in the analysis of images, and they can be applied to microscopy images depicting the morphology of hydrogel, pore structure, and location of drug crystals. RNNs and LSTM networks process sequential data, which are appropriate to process time-series of drug release, or stability data. Transfer learning utilizes experience on a large set of pre-trained models and applies them to smaller pharmaceutical sets. Such a solution fills gaps in the data in the pharmaceutical research. The off-the-shelf models on general chemical or biological are fined tuned using particular formulation data, and prediction performance is significantly enhanced using few experiments. The use of big data analytics combines the literature data with experimental results, patent records, and clinical outcomes, which allows drawing knowledge and hypotheses and identifying potentially effective formulation approaches. Information is extracted out of scientific publications using natural language processing. Data mining detects just patterns, correlations and trends of big data. Meta-analysis is the combination of data provided by several researches that enhances statistical power [71].

5. CLINICAL APPLICATIONS AND THERAPEUTIC AREAS

Hydrogel transdermal patches serve diverse therapeutic applications leveraging controlled delivery, non-invasiveness, and patient compliance advantages.

Pain Management: NSAIDs including diclofenac, ketoprofen, and ibuprofen deliver localized anti-inflammatory and analgesic effects for musculoskeletal pain, arthritis, and sports injuries. Hydrogel matrices maintain therapeutic drug concentrations at target sites while minimizing systemic exposure and gastrointestinal side effects. Opioid patches containing fentanyl manage chronic severe pain in cancer patients and chronic pain conditions. Local anaesthetics like lidocaine provide topical anaesthesia for minor procedures and neuropathic pain management [72].

Cardiovascular Therapeutics: Nitroglycerin patches treat angina pectoris by providing sustained nitric oxide release causing vasodilation. Clonidine patches manage hypertension. Antiplatelet agents administered transdermally reduce cardiovascular events.

Hormone Replacement Therapy: Estradiol patches provide hormone replacement in menopausal women alleviating symptoms and preventing osteoporosis. Testosterone patches treat hypogonadism in men. Contraceptive patches delivering combined estrogen-progestin provide convenient birth control with weekly application [73].

Neurological Disorders: Rotigotine patches deliver dopamine agonists for Parkinson's disease management, avoiding gastric complications and providing consistent plasma levels. Donepezil patches treat Alzheimer's disease with improved gastrointestinal tolerability compared to oral formulations. Methylphenidate patches manage attention deficit hyperactivity disorder in children and adults with once-daily application.

Dermatological Applications: Anti-inflammatory corticosteroids treat localized inflammatory skin conditions. Antifungal agents manage dermal mycoses. Growth factors and antimicrobials incorporated into hydrogel dressings promote wound healing in chronic wounds, burns, and diabetic ulcers.

Smoking Cessation: Nicotine replacement therapy patches reduce withdrawal symptoms and cravings facilitating smoking cessation. Various dosage strengths enable stepwise reduction [74].

6. MANUFACTURING, SCALE-UP, AND REGULATORY CONSIDERATIONS

The manufacturing processes should be able to produce reproducible, quality and cost effective manufacturing techniques. The most prevalent is solvent casting which consists of dissolving polymers and drugs in the right solvents and pouring solutions into molds or onto supporting materials and the evaporation of solvents under controlled temperature and humidity. The optimization is needed to achieve uniform casting thickness, full removal of the solvent and the prevention of drug crystallization. In hot-melt extrusion, the polymers are not dissolved and they are thermoplastic, which is desirable in drugs that are susceptible to moisture. Drug-polymer mixtures are heated and subjected to heat above the glass transition temperatures, pressed out of dies and allowed to cool. Scale-up is favored by continuous processing and solvent-free manufacturing but high temperatures can restrict the use of thermolabile drugs [75].

The freeze-drying forms porous structures of hydrogel that are of improved quality. Hydrogels are frozen, ice is sublimated in a vacuum, which forms very porous materials with high surface areas, high swelling speed, and high drug loading. Nonetheless, lyophilization is energy intensive and time consuming which restricts through put. Three-dimensional printing permits individualized patches with complicated structures, different drug doses distributed spatially, and on demand production. Bio printing Extrusion-based bioprinting places hydrogel-drug formulations in layers. Inkjet printing lays down accurate sizes of droplets. The photopolymerization of hydrogels can be carried out with Uv-crosslinking, allowing them to gel rapidly. Despite these prospects, 3D printing has been struggling with such issues as a lack of material options, a slower pace of production, and increased price [76].

The difficulties with scale ups are the consistency of batch to batch in high volumes, similar mixing and crosslinking in scaled equipment, scaling of the drying conditions and confirming that the scaled processes give equal products. Evidence that the processes always generate specifications of product is obtained through process validation according to the principles of the FDA. The equipment and processes are tested using installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). Patches need to be waterproof, lightproof, airtight and contamination-free. Multi-layer laminates which contain aluminum foil, polyethylene and polyester give moisture barriers. Cross-contamination is avoided by placing individual sealed packets. Shelf-life is determined by stability testing (according to ICH principles long-term at 25o C/60 per cent RH, accelerated tests at 40o C/75 per cent RH, stressed conditions). Regulatory issues are in line with FDA regulations regarding transdermal systems in terms of chemistry, manufacturing and controls; bioequivalence; labeling; and post-market surveillance. Generic drugs need to have pharmaceutical equivalent (identical active ingredient, dosage form, route) and bio equivalent (equivalent rate and extent of drug delivery) based on comparative in-vitro release testing and clinical pharmacokinetic examination in humans where necessary [77].

7. CHALLENGES AND FUTURE PERSPECTIVES

There are present-day restrictions in the way it can be used broadly. Many therapeutic agents are excluded by the drug candidate restrictions following Lipinski-like rules (MW less than 500 Da, log P 1-3, strong enough to be delivered into-cell within a 10-40 cm 2 patch). The variability of skin between different people, different ages, different locations and pathologies influences the reproducibility of permeation. The long-term safety of new polymers, nanomaterials and enhancers need a comprehensive assessment. High level of technologies in manufacturing and quality control add to the cost that may restrain commercialization. The regulatory ways of new delivery systems might be ambiguous and necessary dialogue with the authorities will need a lot of dialog. The future promises some revolutionary changes. Individualized transdermal patches, based on patient specifics (skins properties, metabolism of drugs, disease condition) through on-order manufacturing technologies will streamline treatment. Dose individualization may be informed by pharmacogenomic information. Smart wearable patches are sensor-based patches with microelectronics and wireless connectivity to allow real-time therapeutic drug monitoring, physiological parameters monitoring (glucose, lactate, pH) and

closed-loop delivery systems automatically varying doses. The IoT integration is linked to patches and links the smartphones, cloud databases, and healthcare providers supporting telemedicine and remote patient monitoring [78].

The synergy of combination approaches improves delivery. Microneedle- hydrogel combinations combine the microneedle -created pathways and hydrogel sustained release. Ionized hydrogel patches are incorporating electrical driving force as well as release release controlled by matrices. Combination therapies are provided by the use of multi-drug delivery systems with independent release kinetics in which different drugs are incorporated. Green packaging made of renewable and biodegradable materials (cellulose, starch, protein) is in line with environmental awareness. The principles of green chemistry reduce the use of organic solvents and toxic reagents. Life cycle assessment is used to assess the environmental impacts in order to guide sustainable development. Frontier applications are in gene therapy and vaccine delivery. Delivery of plasmid DNA, siRNA or mRNA by transdermal routes would be groundbreaking in the treatment of genetic diseases and cancer. Vaccine patches provide immune responses without needles with increased immunity rates by antigen presenting cells abundant in skin, which are especially important in preparedness to pandemics [79].

8. CONCLUSION

Hydrogel matrix systems are advanced systems of transdermal drug delivery, which are synergistic with biocompatibility, release control, permeation promotion, and patient compliance benefits. The current formulation techniques include rational polymer choice, intelligent stimuli-responsive, nanocomposite incorporation, and systematic permeation increase to create personalized delivery systems that meet targeted therapeutic requirements in the case of different medical disorders. The formulation development has undergone a paradigm shift, where advanced optimization methods such as Quality by Design, Design of Experiments, Response Surface Methodology, as well as artificial intelligence have taken the place of empirical development of the formulation through trial and error research. Computational modeling, chemometric and Process Analytical Technology integration enable quick efficient development with better understanding of the formulation-performance relationship which saves development time and costs, and improves product quality and consistency. The fact that many hydrogel transdermal patches have been successfully translated into clinical applications in the field of pain management, cardiovascular therapy, hormone replacement, neurological disorders, and other therapeutic applications proves the maturity and clinical utility of the technology. Further developments in materials science, nanotechnology, manufacturing technologies, and data science will continue to increase opportunities and fields of application. The interdisciplinary approach to current challenges, new materials, new technologies, and new regulatory structures will widen the scope of the hydrogel transdermal patch application to new areas of therapeutic relevance and patient groups. The future is seen in the personalized, intelligent, and sustainable hydrogel patches, as well as the digital health ecosystems that are smoothly embedded into the personal clothes, that will transform on-demand medication delivery and patient care by offering precision medicine treatment, real-time tracking, and therapy optimization. Further investigation towards the basis of knowledge of skin-hydrogel-drug interactions, the creation of new responsive polymers and nanocomposites, the optimization of methods of manufacture and design, and strict clinical translation research will make the hydrogel matrix systems the inseparable foundations of the novel transdermal therapeutics, eventually leading to more successful patient outcomes and quality of life in a wide range of medical issues.

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