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Film-Forming Systems for Topical Drug Delivery: Mechanistic Advances, Nanotechnological Integration and Emerging Clinical Applications

Pandian C.[1*]; Pooja B.[2]; Gowtham A.[2]; Gunaseelan M.[2]; Praveen Kumar D.[2]

[1]Assistant Professor, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai – 625020, Tamil Nadu, India
[2]M. Pharm Scholar, Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Madurai – 625020, Tamil Nadu, India

Corresponding Author: Pandian C.[1*]

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Abstract: Film-forming systems (FFS) are topical semi-solid or liquid formulations that turn into a thin film on the skin surface after solvent evaporation by transforming in situ and containing the drug in a polymer matrix. Unlike conventional semisolid dosage forms and transdermal patches, FFS possesses cosmetic elegance, extends skin residence time, enhances drug permeation through cosmetic supersaturation, and achieves conformability to irregular wound geometries. This review summarizes the formulation science underlying FFS, including the selection of polymers and plasticizers, the design of solvent architecture, strategies to enhance penetration, and the physicochemical basis of in situ film formation and supersaturation. Special focus is given to the use of next-generation platforms for nano-integrated FFS, such as solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and stimuli-responsive matrices. The clinical and experimental evidence from 2020 to 2025 in the wound management, antifungal therapy, psoriasis and atopic dermatitis, and cutaneous leishmaniasis areas is critically appraised, and frameworks for evaluating the evidence based on the principles of Quality-by-Design are described, as are unmet regulatory and translational challenges. The review ends by analyzing new perspectives, such as the combination of 3D printing and FFS, the combination of microneedles and FFS, and the use of artificial intelligence for formulation design, as well as the clearly identified gaps in evidence and manufacturing that need to be overcome before nano-integrated FFS can be routinely translated into clinical practice.

Keywords: *Film-Forming System; Film Formation in Situ; Topical Drug Delivery; Nanostructured Lipid Carrier; Skin Penetration; Spray Forming System; Stimuli-Responsive Polymers; Wound Healing.*

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I. INTRODUCTION

The skin is the body's largest organ, with an area of 1.7-2.0 m2, and it is an even more paradoxical drug-delivery interface, as it is structurally accessible to the body, but physiologically formidable. [1,2] Conventional topical dosage forms include ointments, creams and gels, which tend to be washed off quickly, are poorly dosed, and do not stick to the skin, with all these effects associated with non-compliant skin reactions caused by the adhesive. [3] Passive drug delivery is sustained by transdermal patches, but these are constrained by the inability to adhere to curved surfaces and irregular-shaped skin, the limited drug loading capacity, and adhesive-related skin reactions. [4] Films forming systems (FFS) have been developed as a technological solution to these limitations. [5,6] The field has advanced significantly since its initial introduction in 1998 with the development of multifunctional, thin, flexible and adherent polymeric films produced by spontaneous transformation after topical application of the FFS that are based on a polyvinyl alcohol/polyvinylpyrrolidone matrix dissolved in a volatile solvent, with the development of a sustained drug

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depot that conforms closely to the skin surface; the current state of the art, including advances in polymer chemistry, integration of nanoparticles, and the application of Quality-by-Design (QbD) principles, has seen spray-based FFS formulations find commercial use in wound care, onychomycosis, and dermatitis management and highlighted the potential of nanotechnology in the development of new formulations with novel architectures that are now at a commercial market-ready stage.[8,9]

Despite the growing body of evidence, a critical and integrative synthesis, connecting recent formulation advances with nano-integration technologies, and the published clinical literature from 2020 to 2025 with the technological horizon of FFS has been missing. This review aims to fill this void by offering a formulation-science reference and a translation roadmap for critically evaluating the strength of the evidence presented and doesn't simply list these.

II. REVIEW METHODOLOGY

This is a narrative, critical review, and there was no formal protocol registration. PubMed, Scopus and Web of Science were searched for peer-reviewed literature between January 2015 and mid-2026 with combinations of the following terms: film-forming system, film-forming spray, in situ film, supersaturation, nanostructured lipid carrier, solid lipid nanoparticle, stimuli-responsive, and topical drug delivery, as well as by hand searching the reference lists and tracking citations of relevant articles. For the clinical application parts, studies from 2020 to 2025 were prioritized, and for the mechanistic and formulation-science sections, some of the key landmark studies in the field were used. Evidentiary claims excluded non-peer-reviewed and conference abstracts, which may not have full data, and patents are noted separately where relevant to the commercial context.

III. MECHANISM OF IN SITU FILM FORMATION

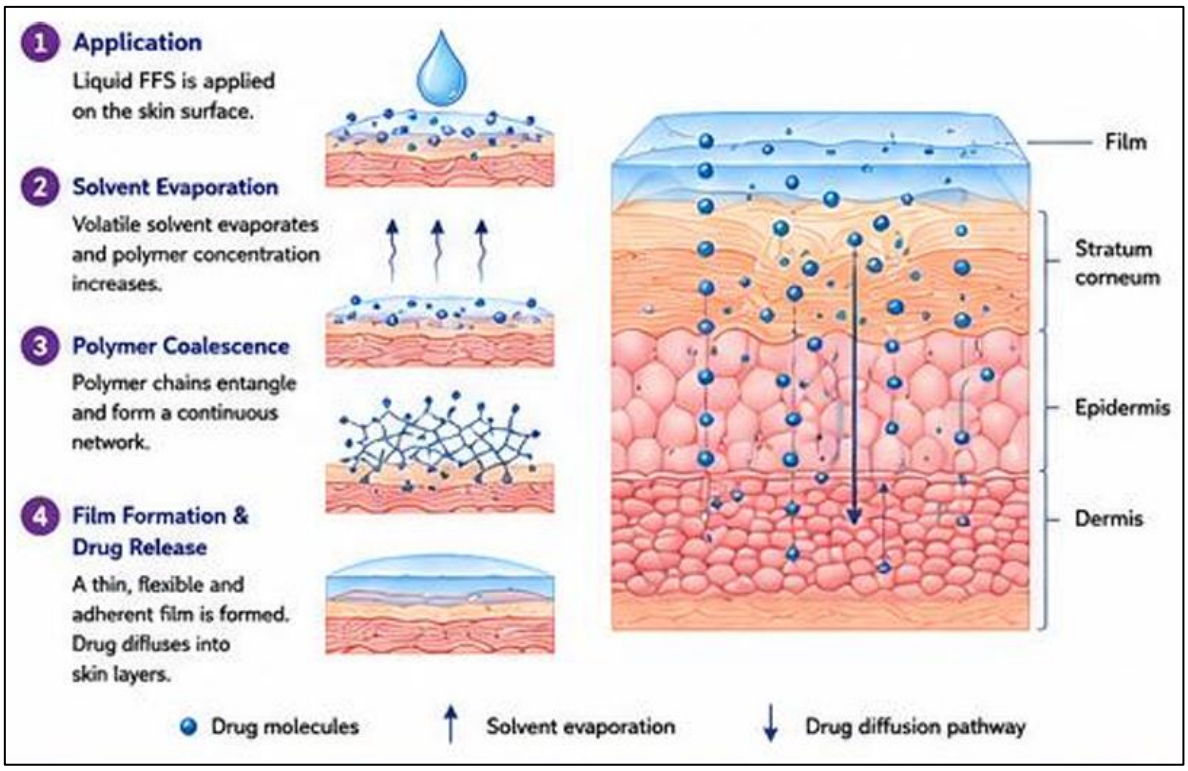

Fig 1 Mechanism of in Situ Film Formation: Sequential Stages of Application, Solvent Evaporation, Polymer Coalescence, and Film Consolidation, Culminating in a Continuous Drug-Loaded Polymeric Film that Governs Directional Drug Diffusion into the Stratum Corneum, Epidermis, and Dermis.

➢ *Physicochemical Basis*

The in situ formation of films is a multi-step process that is not at equilibrium due to polymer chain dynamics, kinetics of solvent evaporation, and drug-polymer interaction.[10] After application to the skin, volatile solvents like ethanol, isopropyl alcohol, and acetone evaporate according to their ambient concentration gradient and result in the increasing concentration of the polymer phase in three major steps: the first step is the dilute phase where the just applied fluid spreads evenly and polymer chains have high mobility and good solvation; the second step is the concentrated phase where the amount of solvent in the polymer solution becomes lower than the polymer overlap concentration (c*); here chain entanglements appear, viscosity increases sharply, and the process of network formation starts; and finally, in the third step, the film formation occurs, as the amount of solvent becomes lower than the glass-transition threshold and chain mobility stops and results in the film formation following the skin's micro-roughness.[11] Film properties like tensile strength, elongation, and flexibility depend on the polymer molecular

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weight, plasticizer concentration, and network formation kinetics. [12]

➢ *Drug Supersaturation as the Thermodynamic Driver*

The main pharmacological effect of FFS usage lies in the formation of the supersaturated state of drugs on the surface of the skin. With evaporation of the solvent, the drug concentration in the residue increases and becomes higher than the solubility equilibrium of the drug in the polymer matrix, leading to a supersaturated state where drug activity becomes greater than one and thus increasing the driving force for distribution into the stratum corneum.[13] Polymers capable of antinucleation effects include polyvinylpyrrolidone, HPMC, and HPC that bind to nascent nuclei of crystallization via hydrogen bonds and steric interactions, thus preventing recrystallization of the drug and maintaining its supersaturated state for a prolonged period.[14] Compatibility of the drug and polymer, described by the Flory-Huggins interaction parameter, is the main factor determining antinucleation properties and needs to be established for each case.[15]

➢ *Biphasic Solvent Strategy*

Another complementary technique employs binary systems comprising volatile and non-volatile solvents. Post-evaporation of the volatile solvent, there will be partitioning of a remaining non-volatile cosolvent, such as propylene glycol, Transcutol, or dimethyl isosorbide, to the stratum corneum, thereby setting up what has been referred to as an "invisible dermal depot." The technique helps in maintaining high drug activity and disrupting the lipid structure of the stratum corneum for long periods. This technique is especially applicable to hydrophilic drugs that do not have any lipophilic character. [5,16]

IV. CLASSIFICATION OF FILM-FORMING SYSTEMS

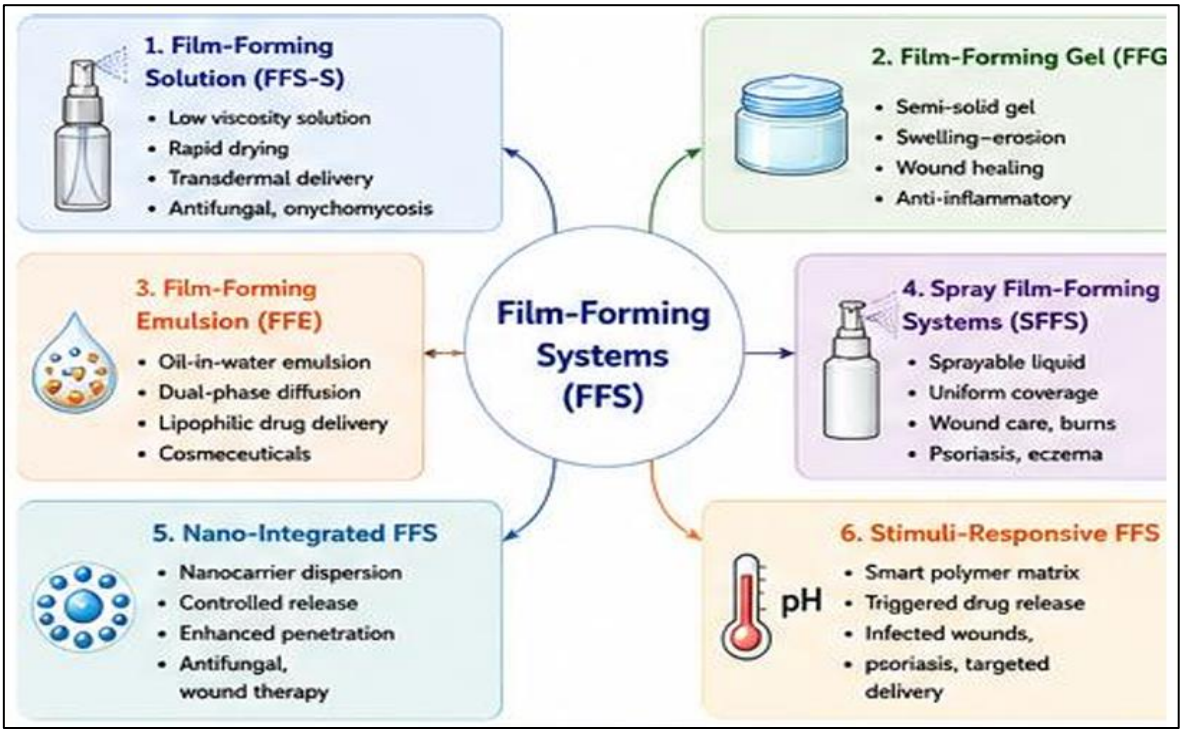

Fig 2 Classification of Film-Forming Systems by Physical Form and Functional Design, Encompassing Solutions, Gels, Emulsions, Sprays, Nano-Integrated, and Stimuli-Responsive Platforms Suited to Distinct Application Methods and Indications.

FFS can be generally categorized based on the physical form before application, the hydrophilic nature of the polymer used, and the aim of administration (see Table 1). Such a categorization goes beyond mere description because it is directly relevant to choosing the type of polymer and solvent, as well as testing procedures.

Table 1 Classification of Film-Forming Systems and their Key Characteristics

Type	Pre-application state	Representative polymers	Predominant release mechanism	Primary applications
Film-forming solution (FFS-S)	Low-viscosity solution	Eudragit RS/RL, ethyl cellulose, HPC	Diffusion; supersaturation	Onychomycosis, antifungal, transdermal delivery
Film-forming gel (FFG)	Semi-solid gel	HPMC, Carbopol, carboxymethyl cellulose	Swelling-erosion; diffusion	Wound healing, anti-inflammatory therapy
Film-forming emulsion (FFE)	Oil-in-water emulsion	PVA with Eudragit NE/RS	Dual-phase diffusion	Lipophilic drug delivery, cosmeceuticals

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Spray film-forming system (SFFS)	Sprayable liquid	Poloxamer, PVP, ethyl cellulose	Supersaturation with diffusion	Wounds, burns, psoriasis, eczema
Nano-integrated FFS	Nanoparticle dispersion in a film-forming vehicle	PLGA, chitosan, lipid nanocarriers	Controlled release from a nano-reservoir	Antifungal, wound, and anti-leishmanial therapy
Stimuli-responsive FFS	Smart polymer matrix	PNIPAM, Eudragit L/S, disulfide-linked polymers	pH-, thermo-, or redox-triggered release	Infected wounds, psoriasis, targeted delivery

V. FORMULATION ARCHITECTURE

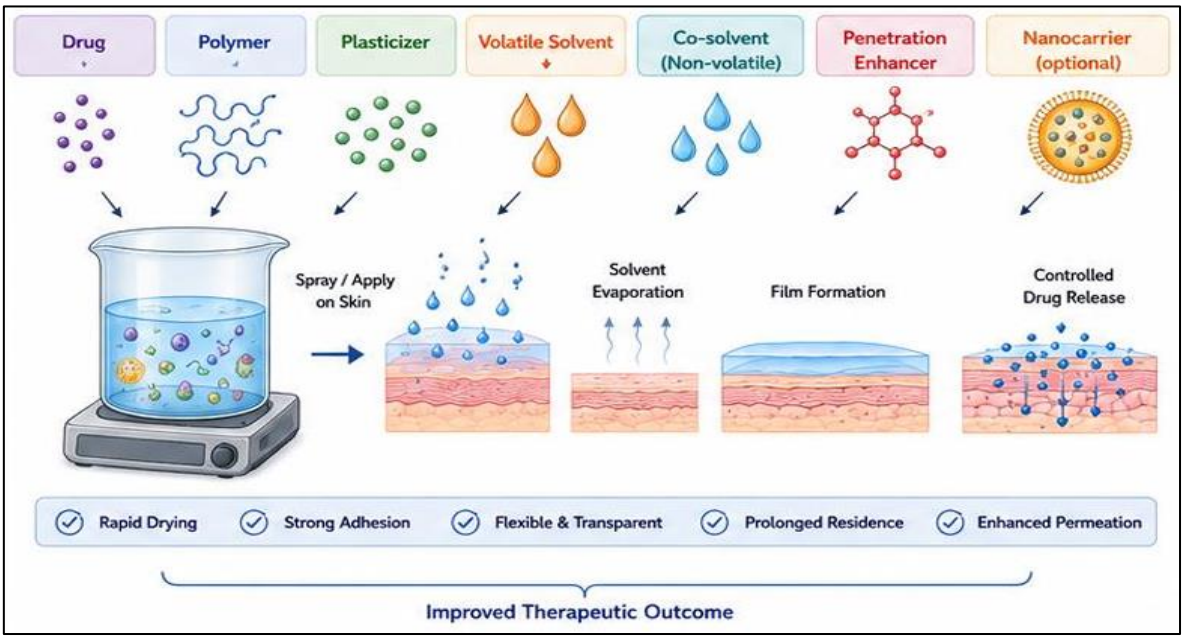

Fig 3 Core Components of an Ideal Film-Forming System—Drug, Polymer, Plasticiser, Volatile Solvent, Co-Solvent, Penetration Enhancer, and Optional Nanocarrier – and their Sequential Contribution to Film Formation and Controlled Drug Release.

➢ *Film-Forming Polymers*

The matrix polymer forms the basis of the structure and functionality of the FFS, and it is responsible for the mechanical strength of the film, release of the drug, adherence to the skin surface, and the aesthetic appearance of the formulation. Table 2 lists some of the commonly used polymers in FFS formulations.

Table 2 Representative Film-Forming Polymers and their Formulation Roles

Polymer	Class	Typical concentration	Notable film property	Drug-release profile
HPMC (K-grades)	Hydrophilic, cellulosic	2-10% w/v	High moisture retention; effective antinucleation	Swelling-controlled; sustained 12-24 h
HPC (e.g., Klucel LF)	Hydrophilic, cellulosic	3-15% w/v	Thermoplastic; flexible at low Tg	Diffusion-controlled; sustained 8-24 h
PVP (K25-K90)	Hydrophilic, synthetic	5-15% w/w	Amorphous stabiliser; glass former	Rapid, transitioning to sustained release
Eudragit RS 100	Hydrophobic, methacrylate	5-15% w/v	Low water permeability; pH-independent	Sustained, rate-controlled over 24-48 h
Eudragit NE 30D	Hydrophobic, methacrylate	10-30% w/v	Flexible without plasticiser (Tg approx. 8°C)	Controlled, water-insoluble matrix
Ethyl cellulose	Hydrophobic, cellulosic	3-15% w/v	Strong barrier; organic solvent-soluble	Sustained; pH-independent
Carbopol 940	Hydrophilic, crosslinked polyacrylic acid	0.05-0.5% w/w	Thixotropic, bioadhesive gel	Swelling-erosion; immediate to sustained
Chitosan	Cationic biopolymer	0.5-3% w/v	Intrinsic antimicrobial activity; bioadhesive	Erosion-controlled; wound-responsive
Poloxamer 407	Amphiphilic block copolymer	15-25% w/v	Thermoresponsive sol-gel transition (32-37°C)	Temperature-triggered release

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➢ *Plasticisers*

The function of plasticizers is to be interposed between the chains of polymers, resulting in a reduction in the glass-transition temperature and making the films less brittle. Lipophilic plasticizers—dibutyl sebacate, tributyl citrate, and triethyl citrate in decreasing order of their effectiveness in enhancing permeability—increase the diffusivity and permeability of drugs across films, whereas hydrophilic plasticizers like PEG 400, propylene glycol, and glycerol help in improving water uptake and are thus more desirable for hydrophilic polymers.[17] An optimum level of plasticizer is around 10-30% of the total polymer weight.

➢ *Solvents and Penetration Enhancers*

Ethanol, between 50-96% concentrations, continues to be the most used solvent in FFS, providing good polymer solubilization, fast solvent evaporation, natural antimicrobial properties and stratum corneum lipid fluidization.[18] An ethanol-water mixture (50:50 to 70:30) is a compromise between the ability of solubilization and skin tolerance. Non-evaporative cosolvents like Transcutol, dimethyl isosorbide and propylene glycol work as penetration enhancers through stratum corneum lipid alteration and drug solubilization.[16] Chemical penetration enhancers comprise oleic acid (1-5%), terpenes such as menthol, eucalyptol, and small amounts of surfactants, such as Tween 80, and poloxamers. The combination of chemical penetration enhancers is called "safe penetration enhancer pairs." [19]

VI. NANO-ENABLED FILM-FORMING SYSTEMS: AN INNOVATION FRONTIER

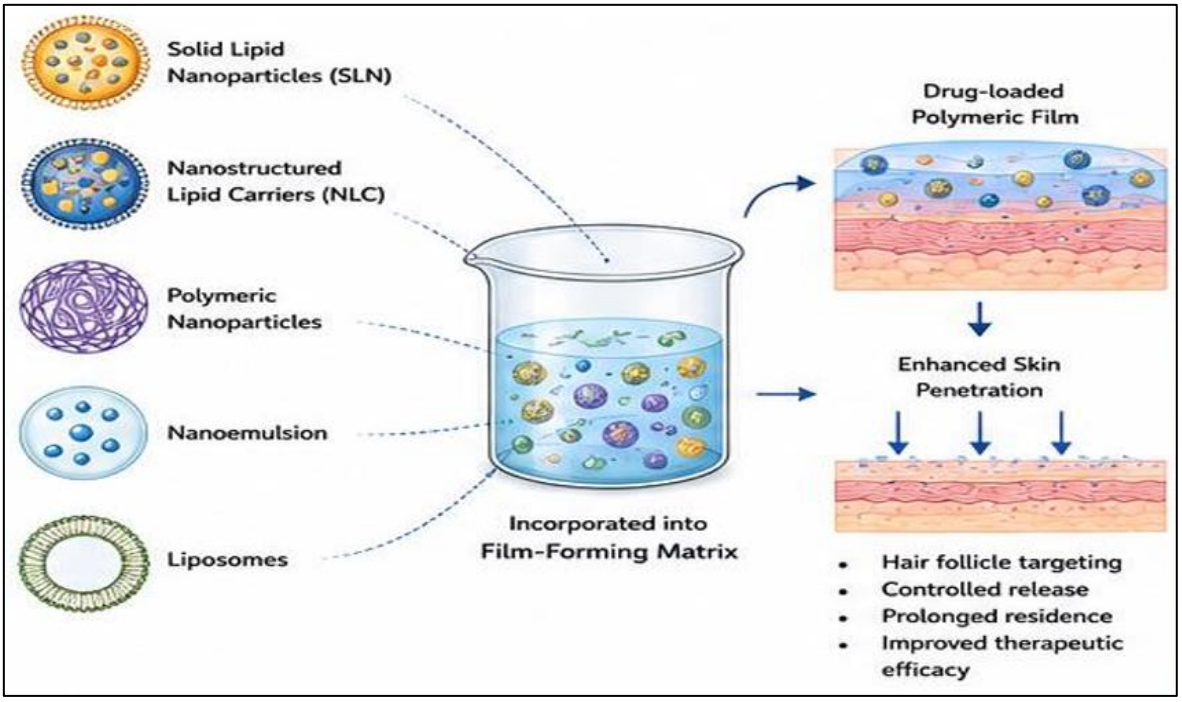

Fig 4 Nano Integration Techniques for Film-Forming Systems: Solid Lipid Nanoparticles, Nanostructured Lipid Carriers, Polymeric Nanoparticles, Nanoemulsions and Liposomes are Added to the Film Matrix for Increased Skin Permeation and Release Control.

➢ *Lipid Nanocarrier-Integrated FFS*

The combination of solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC) within a polymer-based FFS film produces a hierarchical two-step drug delivery system, where the drug is contained within the lipid matrix of the nanoparticles, while the polymer-based film controls the drug delivery to the stratum corneum and thus provides sustained drug delivery, unlike each of the systems individually.[20] NLC, owing to their partially disordered lipid matrix, have been shown to have higher drug loading and a lesser propensity for Ostwald ripening than SLN. It has been observed by Phatale et al. that the film-forming system of NLC loaded with diclofenac sodium showed a 2.3-fold improvement in transdermal flux compared to the plain NLC dispersion system, and was thought to be due to increased occlusion and stratum corneum hydration leading to increased diffusivity of the drug.[21] The SLN and NLC particles have been found to leave behind a residual film-like structure in the stratum corneum after application and result in reduced trans-epidermal water loss.[22]

➢ *Polymeric Nanoparticle FFS*

Nanoparticles of poly(lactic-co-glycolic acid) (PLGA), chitosan, and albumin, having dimensions of 100-400 nm, included in FFS, are of particular interest for utilizing the follicular shunt pathway for the formation of hair-follicle-targeted drug depots with biodegradable controlled-release properties. The study conducted by Dhimmar et al. described the formulation of a voriconazole-loaded chitosan nanoparticle-based film-forming solution, which was composed of an Eudragit RS film-forming matrix and demonstrated 24-hour controlled release of antifungal drugs

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along with a fourfold decrease in minimum inhibitory concentration against Trichophyton rubrum in comparison with a traditional solution.[23] It has been found that the inclusion of chitosan nanoparticles can increase the cross-linking of the polymer matrix, thus increasing its tensile strength and imparting additional antimicrobial properties to it.[24]

➢ *Stimuli-Responsive Smart FFS*

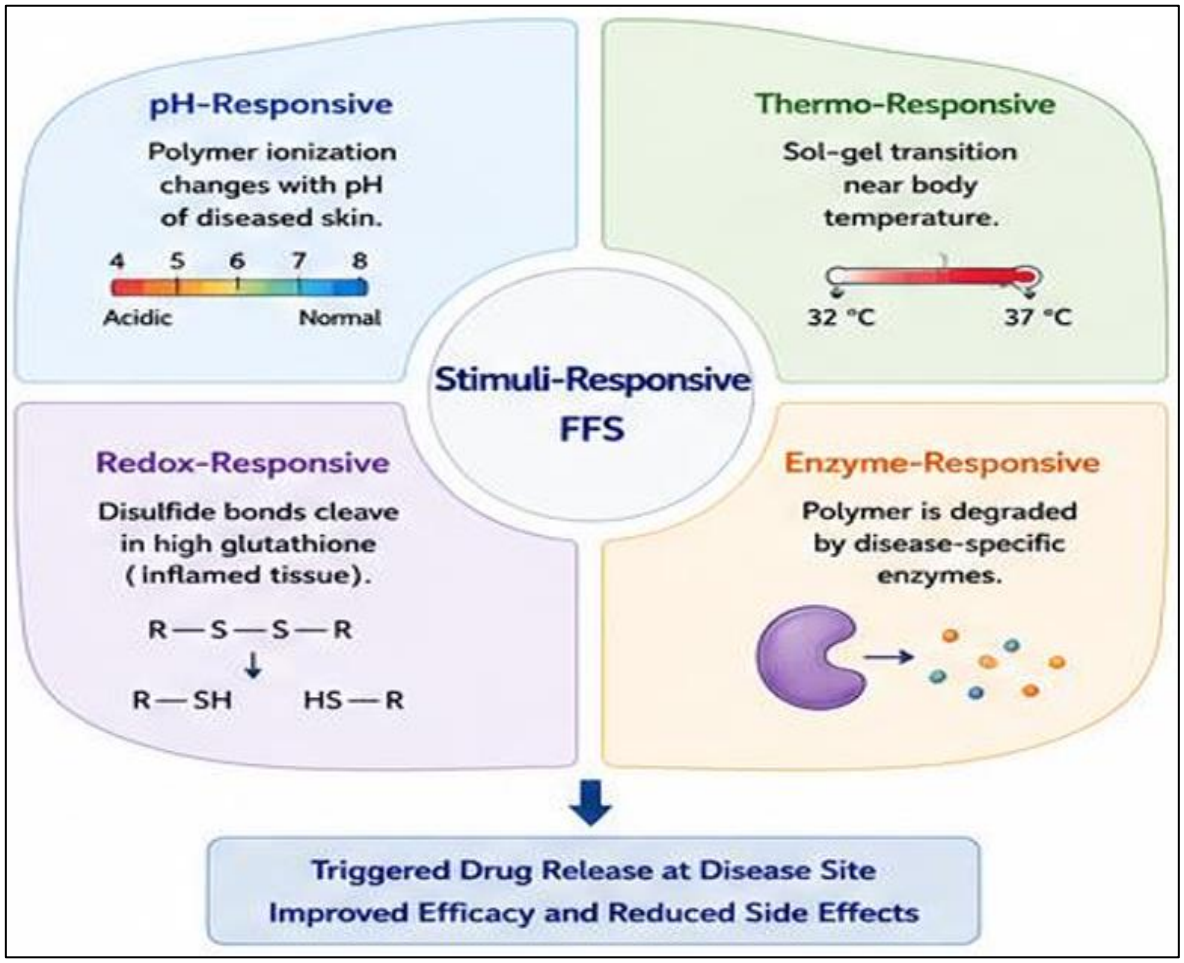

Fig 5 Stimuli-Responsive Film-Forming Systems Designed to Release Drugs Selectively in Response to pH, Temperature, Redox Potential, or Enzymatic Activity Characteristic of Diseased Skin, Enabling Site-Specific, Triggered Drug Release.

- Stimuli-responsive FFS is an evolution of passively released drugs into environmentally activated drug delivery, making use of the difference in the pathophysiology of the microenvironment in the skin [25]
- pH-sensitive FFS: Drug release in FFS based on Eudragit L100 or carbomers is optimized for the mildly acidic pH of diseased skin due to infection, psoriasis, or atopic eczema.[26]
- Thermally sensitive FFS: poly(N-isopropylacrylamide) (PNIPAM) and Poloxamer 407 hydrogels exhibit a coil to globule/sol to gel transition around body temperature, which has been suggested as a means of increasing drug residence times and contact.[27]
- Redox-sensitive FFS: Disulfide-linked polymer chains like Chitosan-SS-PEG are meant to cleave under high levels of glutathione seen in inflammation or hypoxia sites.[28]
- Dual/multi-stimuli-responsive FFS: Polymer interpenetration networks composed of PNIPAM/HPMC and poloxamer/carbomer are among the most advanced FFS reported.[29]
- It is crucial to point out that most of the FFS systems responsive to stimuli are still proof-of-concept in vitro or ex vivo studies; the clinical validation of triggered release in diseased human skin has not been widely investigated yet, and it is an important evidentiary gap mentioned in section 10.

➢ *Nanosuspension and Nanoemulsion FFS*

FFS-based nanosuspensions utilize the relationship between the curvature of the particle and solubility as defined by the Ostwald-Freundlich relationship to dissolve the drug particles of sub-micron size present in the matrix film upon exposure to the stratum corneum, thus creating a high supersaturation level without the need for high polymer concentration.[30] FFS with the incorporation of nanoemulsions (nanoemulgel systems) uses both solubilization of lipophilic drugs via oil droplets and surfactant-induced stratum corneum lipid disruption mechanism.[31]

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VII. EVALUATION AND QUALITY BY DESIGN

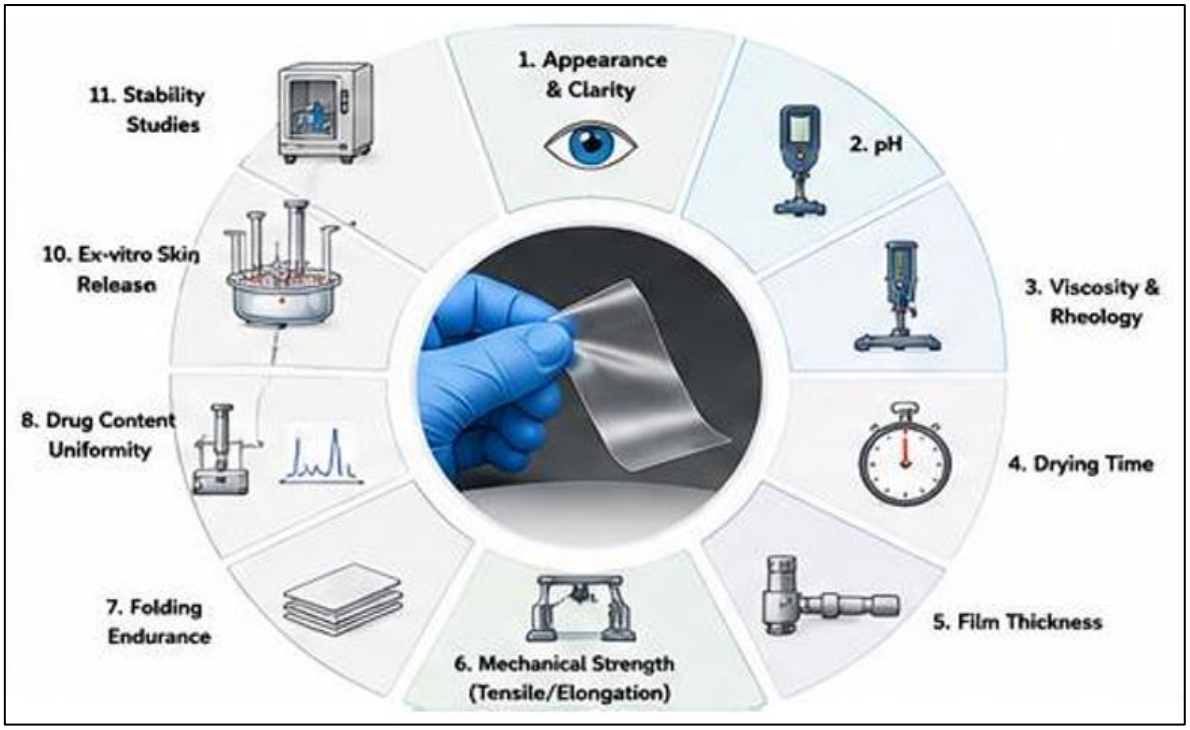

Fig 6 Standardized Evaluation and Characterization Parameters for Film-Forming Systems, Spanning Appearance, pH, Viscosity, Drying Time, Film Thickness, Mechanical Strength, Drug Content Uniformity, Ex Vivo Permeation, and Stability Studies.

➢ *Standardized Evaluation Parameters*

The complete characterization of FFS requires consideration not only of the pre-application solution or gel but also of the properties of the consolidated film. A summary of the characterization matrix for FFS can be found in Table 3.

Table 3 Evaluation Parameters for Topical Film-Forming Systems

Parameter	Typical method	Target/significance
Appearance and clarity	Visual inspection; UV-Vis turbidimetry	Clear, homogeneous solution; absence of phase separation
pH	Calibrated pH meter; skin-surface pH probe	5.5-7.5, for skin compatibility
Viscosity and rheology	Cone-and-plate rheometry (0.01-100 s-1)	Pseudoplastic/thixotropic behaviour appropriate to spray or spread application
Drying time	Touch-dry method; automated timer	30-120 s for sprays; under 5 min for gels
Film thickness	Digital micrometry; profilometry	50-300 micron; uniform across the film
Tensile strength/elongation	Universal testing machine	Tensile strength above 0.5 MPa; elongation above 20%
Folding endurance	Manual fold test	At least 300 folds without cracking
Water vapour transmission rate	Gravimetric cup method (ASTM E96)	200-800 g/m²/24 h, balancing occlusion and breathability
Drug content uniformity	Validated HPLC or UV method	95-105% of label claim; coefficient of variation below 2%
In vitro drug release	Franz diffusion cell with synthetic membrane	Release profile characterized at defined time points up to 24 h
Ex vivo skin permeation	Franz cell with porcine ear or cadaver skin	Flux, permeability coefficient, and lag time
Spray pattern/dose uniformity	Impaction paper; gravimetric assessment	Relative standard deviation below 10% per actuation
Skin adhesion/washability	Cotton-wool tack test; water-wash rating	Non-sticky film; stable to normal washing and light exercise
Stability (ICH Q1A)	25°C/60% RH and 40°C/75% RH storage	No degradation; retained film properties over the proposed shelf life

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➢ *Advanced Analytical Characterization*

In addition to conventional methods, various sophisticated analytical tools have been used to obtain information on molecular-level drug-polymer interaction and film nanostructure. FTIR/ATR spectrometry provides identification of hydrogen bonds, ionic interactions, and the presence of the amorphous state of the drug in the film, which is necessary for establishing the stability of the supersaturation state.[32] DSC and X-ray powder diffraction reveal changes in glass transition temperatures, polymorphism and loss of crystallinity and are indispensable in stability testing of amorphous FFS.[15] AFM provides nano-mapping of surface topography and modulus of elasticity of dried films; Timotijevic et al. employed the combination of AFM, DSC and FTIR to study the redispersion process of betamethasone dipropionate in the film.[15] Raman microspectrometry offers an opportunity for non-destructive chemical mapping of the drug distribution profile throughout the film thickness and in the film/skin contact region and has been applied to visualize drug gradients in emulsions forming a film.[34] CLSM is a technique that allows visualization of the spatial distribution of fluorescently labelled drug or probe penetration into skin layers, allowing differentiation between follicular and transcellular penetration routes.[35]

➢ *Quality-by-Design Framework*

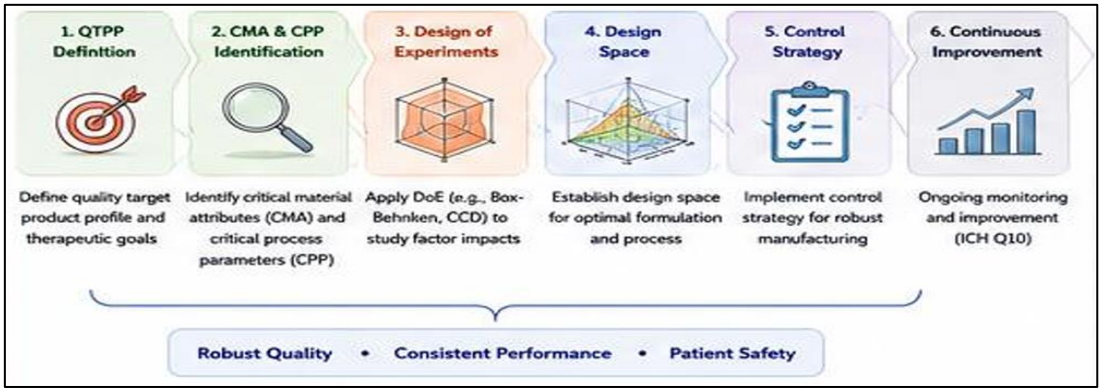

Fig 7 Quality-by-Design Framework for Film-Forming System Development, Progressing from Quality Target Product Profile Definition Through Critical Attribute Identification, Design of Experiments, Design Space, Control Strategy, and Continuous Improvement.

The ICH QbD guideline has often been applied for FFS optimization.[36] This is a typical process: definition of the Quality Target Product Profile (appearance, drug content, rate of delivery and adherence to the skin), identification of Critical Material Attributes (polymer molecular weight and type and level of the plasticizer), Critical Process Parameters (speed of mixing, temperature, and spray pressure), and development of the design space using experimental design, such as D-optimal, Box-Behnken or central composite design. For example, in the study by Patel et al., the quality-by-design strategy was used to optimize the properties of a film-forming spray with simvastatin developed for wound healing by optimizing the tensile strength and drug delivery after 8 hours in vivo.[37]

VIII. THERAPEUTIC APPLICATIONS

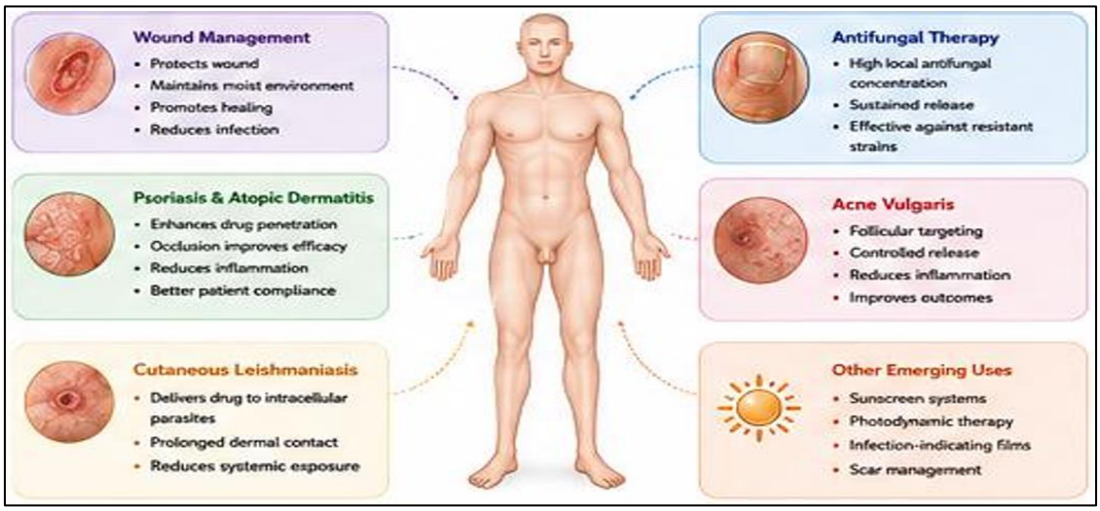

Fig 8 Principal Therapeutic Applications of Film-Forming Systems, Including Wound Management, Antifungal Therapy, Psoriasis and Atopic Dermatitis, Acne Vulgaris, Cutaneous Leishmaniasis, and Emerging Uses Such as Sunscreen and Photodynamic Therapy Delivery.

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➢ *Wound Management*

FFS and spray FFS can be considered a deviation from rigid dressings as they allow a liquid formulation for wound dressing of any shape and the formation of a transparent, breathable, waterproof polymeric dressing in situ.[8] Bakhrushina et al. Summarized different applications of spray-FFS in acute lacerations, surgical wounds, burns, pressure sores, and diabetic foot ulcers with advantages such as no cross-contamination, creation of moisture in the wound, and monitoring of the healing process without removing the dressing.[9] The simvastatin-loaded spray FFS, prepared via the QbD method, can enhance the wound healing process, angiogenesis due to the elevation of VEGF activity, and the deposition of collagen in an animal model of an excisional wound.[37] Nanoparticle silver-chitosan film has demonstrated its capability of degrading the biofilm of MRSA and wound healing of more than 90% within 14 days in diabetes-induced wound animal models.[24]

➢ *Antifungal Therapy*

Onychomycosis, impacting up to 10% of people around the globe, along with the other superficial dermatomycoses, is a condition requiring persistent high concentrations of antifungal drugs at the application site, an area of great fit for FFS. Traditional nail lacquers tend to demonstrate low nail plate permeation rates; however, FFS, made from Eudragit RS favoring nail adhesion along with polymers creating supersaturated solutions, was found to surpass these markers.[38] Dhimmar et al. designed a chitosan nanoparticle-Eudragit RS film-forming composition carrying voriconazole, demonstrating more than a fourfold decrease in minimum inhibitory concentration toward T. rubrum and Candida albicans biofilms and 24-hour release with confirmed follicular drug deposition using confocal microscopy.[23] Mori et al. developed a film-forming transdermal spray containing voriconazole and based on Eudragit RS/ethyl cellulose matrix that demonstrated higher skin retention compared to voriconazole gel.[38] Further development of antifungal FFSs proceeds in the direction of nano-hybrid systems with azoles, echinocandins or antifungal peptides incorporated into the film matrices.

➢ *Psoriasis and Atopic Dermatitis*

Psoriatic plaque surface thickening due to hyperkeratosis of the stratum corneum and impaired barrier function in atopic dermatitis are two challenging drug delivery situations that have been tackled by FFS specifically designed to address them. In the case of psoriasis, occlusion of the plaques through FFS has been suggested as a means of improving the penetration of corticosteroids or calcipotriol by virtue of hydration-induced lipid fluidization of the stratum corneum. Godse et al. performed a prospective, multicenter, open-label study on the spray form of FFS used as a means of occlusion in patients suffering from psoriasis and eczema, and found it to possess good safety, tolerability and cosmetic profile, along with patient satisfaction with the treatment. The use of spray FFS as a means of occlusion has thus been validated for use in inflammatory dermatological conditions.[39] A comparative ex vivo study using human psoriatic skin of the penetration of calcipotriol-betamethasone in an Eudragit RS/HPC matrix FFS vs. a commercial reference cream showed significantly better penetration into the plaques.[40]

➢ *Cutaneous Leishmaniasis*

The drug delivery in cutaneous leishmaniasis needs an intracellular delivery to parasites located in the macrophage phagolysosome in the skin, which is a spatially complex process, but a good target for the protracted contact between drug and target facilitated by FFSs. Van Bocxlaer et al. investigated the film-forming systems for the topical delivery of DNDI-0690, a nitroimidazole compound being developed for treatment of leishmaniasis, finding that Eudragit RS/dibutyl-sebacate and hydroxypropyl cellulose/triethyl-citrate were among the best seven polymer systems investigated, and in an animal model of cutaneous leishmaniasis the film based on Eudragit was more effective than the vehicle only in reducing the parasite load, while no lesion size decrease was observed compared to the systemic treatment in this study.[41] The initial research demonstrates the potential of FFS in the delivery of drugs, decreasing the systemic exposure due to the usual treatment of leishmaniasis, yet the authors themselves prove the ineffectiveness of the investigated formulations.

➢ *Emerging Applications*

The application of FFSs is currently being investigated for an increasing number of indications, ranging from folliculotropic FFSs for the treatment of acne vulgaris based on shunt pathway delivery of pharmaceuticals, including clindamycin, adapalene, and benzoyl peroxide [42], to film-forming sunscreens based on the inclusion of titanium dioxide or zinc oxide nanoparticles, which are supposedly more stable than conventional sunscreen creams.[43] Other potential uses include FFSs containing a pH-sensitive dye for diagnostic and drug delivery applications[44], as well as FFSs for photodynamic therapy of actinic keratosis and superficial basal cell carcinoma using sensitizers like 5-aminolevulinic acid or chlorin e6.[45]

IX. MARKETED FILM-FORMING PRODUCTS

Numerous examples of FFS-based products that have received regulatory approval and entered the market showcase how advanced particular sub-types of FFS have become in terms of their translation into commercial products, especially non-nano spray and lacquer (Table 4).

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Table 4 Selected Commercially Available Film-Forming-System Products

Brand	Active / function	Film-forming polymer	Indication	Manufacturer
Loceryl (R) nail lacquer	Amorolfine 5%	Eudragit RL/RS	Onychomycosis	Galderma
Penlac (R) nail lacquer	Ciclopirox 8%	Ethyl acetate-based solution	Onychomycosis	Dermik Laboratories
Opsite (R) spray	Wound barrier film	Polyurethane	IV-site / wound protection	Smith & Nephew
Cavilon (TM) no-sting barrier film	Skin barrier film	Hexamethyldisiloxane-based	Peristomal / periwound skin protection	3M Healthcare
Nexcare (TM) liquid bandage	Barrier / minor-wound film	Acrylate copolymer	Minor cuts and abrasions	3M
Betadine (R) wound spray	Povidone-iodine 10%	PVP/poloxamer base	Wound antisepsis	Mundipharma
Compeed (R) blister plaster	Hydrocolloid with film backing	Polyurethane film	Blister management	HRA Pharma

X. DISCUSSION: CRITICAL APPRAISAL, TRANSLATIONAL GAPS, AND FUTURE PERSPECTIVES

In summary, three main findings emerge from the current literature. First, the theoretical basis for the FFS mechanism, including the increase in flux as a result of supersaturation, occlusive hydration, and film adhesion, is well-substantiated for simple cases where nanoparticles are not involved, which is clear from the numerous commercially available sprays and lacquers (Section 9). Second, nano-integration (Section 6) is also well justified in terms of its mechanisms and shows consistent positive results in vitro and ex vivo, while most of these results remain preclinical, and there are virtually no controlled clinical trials that would compare FFS with nanoparticle-enhanced FFS or other topicals. Third, the quality of the clinical data greatly varies depending on the indication: the evidence on the psoriasis/eczema occlusion therapy by Godse et al. is a proper prospective clinical trial,[39] while the data on cutaneous leishmaniasis and much of the antifungal nano-FFS evidence are murine or ex vivo and have not yet been confirmed clinically.[23,41] Hence, reviewers and prospective authors should be careful to distinguish between "proof of mechanism" and clinical proof of efficacy.

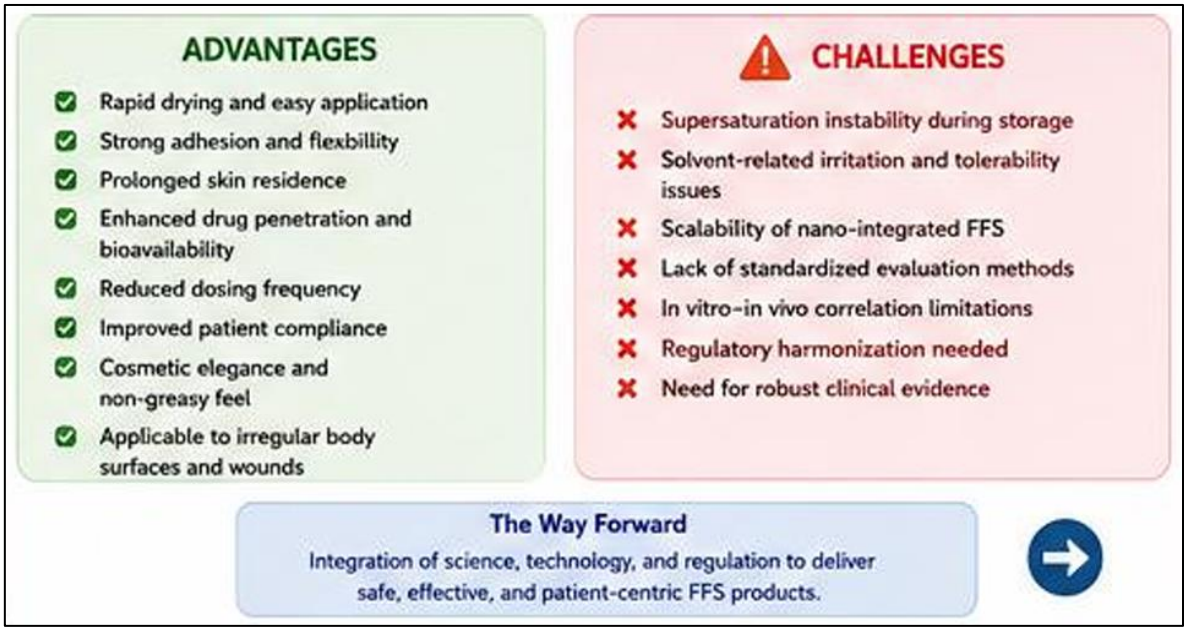

Fig 9 Summary of the Principal Advantages and Unresolved Challenges Associated with Film-Forming Systems, Highlighting the Gap Between Favourable Application Properties and Outstanding Manufacturing and Regulatory Requirements.

Several areas of scientific and regulatory concern inhibit translation progress:

- Instability of supersaturation state: Recrystallization of the amorphous form of the drug during the shelf life continues to be one of the quality issues associated with this type of drug delivery system and requires moisture-proof packaging, inclusion of desiccants or advanced stabilization approaches, which have not been developed yet.
- Irritation of the skin by solvents: Irritation or sensitization of the compromised skin by alcohol- and isopropyl-alcohol-based FFS should be taken into account; hence, further development of aqueous or solvent-free FFS

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prepared by the hot-melt extrusion technique is required.[46]

- Lack of regulatory guidance: Standardized pharmacopoeial monographs on FFS characterization is still missing from the USP, Ph. Eur., and JP, and the in vitro release testing methods allowing generic equivalence studies are still under development by the regulators.[50]
- Limited applicability of IVIVC: Variation in the properties of excised skin models limits the reliability of IVIVC for topical FFS, although biorelevant permeation data obtained from the use of three-dimensional human skin equivalents have been shown to be promising.[51]

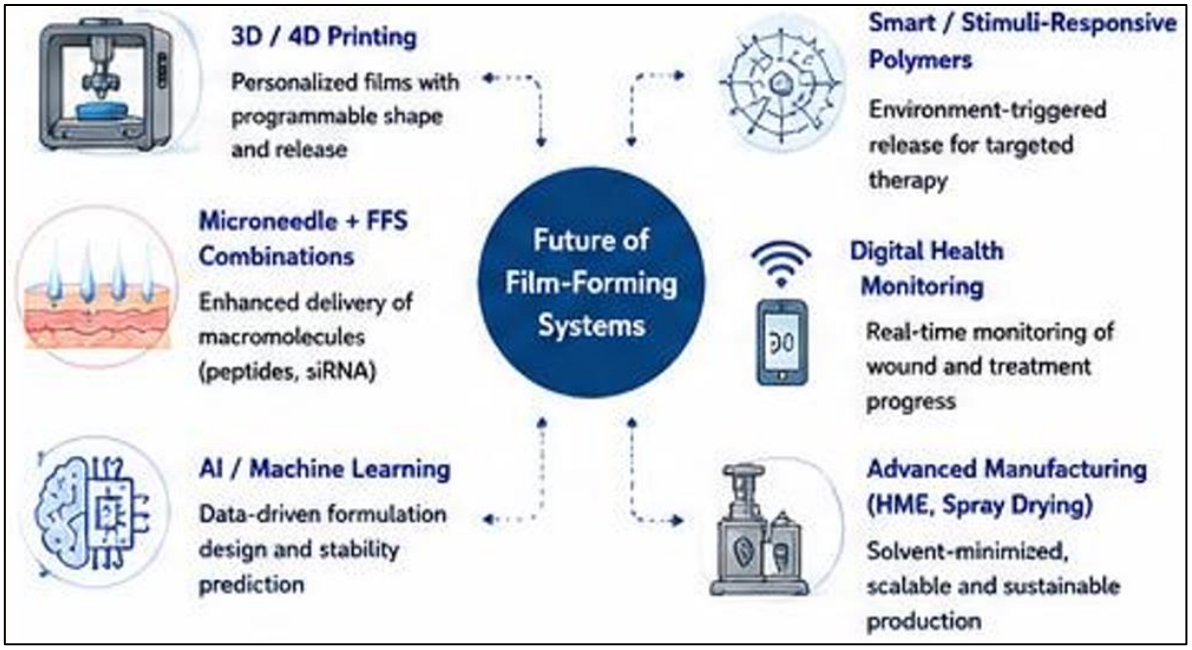

Fig 10 Emerging Technologies Expected to Shape the Next Generation of Film-Forming Systems, Including Three- and Four-Dimensional Printing, Microneedle Combinations, Artificial-Intelligence-Assisted Formulation Design, and Digital Health Monitoring.

In the future, there might be emerging technologies that would assist in the development of FFSs. Among them are 3D/4D printing technologies that will allow the production of personal films with customizable geometry and release properties.[46] The combination of microneedle technology for opening micro-channels through the stratum corneum layer, followed by applying FFS, where the film serves as the mechanism of continuous delivery of the drug via those channels, has been suggested as the technology for delivering macromolecules (proteins/siRNAs) that are not deliverable in a passive delivery manner. [47] Machine learning techniques have already been applied to the design of favorable polymer-plasticizer-drug compositions and prediction of the stability of the film based on a limited amount of data; however, to date, there is no example of prospective validation for FFS, at least.[48] “Smart” films containing biosensors that can track the condition of the wound (for instance, pH or moisture levels), followed by wireless transmission of data to healthcare professionals, may serve as the vision for the future, but that would require considerable research efforts.

XI. CONCLUSION

Film-forming systems constitute an example of a well-studied mechanism-based system which has been successfully translated to the clinic and market, balancing aesthetics and supersaturation-induced enhancement of drug permeation. The modularity offered by lipid and polymeric nanocarriers, as well as stimuli-responsive designs, significantly increases the capabilities of the drug delivery approach, although the scientific support provided for these nano-integrated and 'smart' systems largely stays within the pre-clinical phase, as the transition from promising in vitro and animal experiments to demonstrated clinical effects - especially in the treatment of leishmaniasis and hybrid nano-fungal drugs - has not been fully achieved. For realizing the maximum potential of FFS, concerted efforts towards regulatory standardization, reproducible nano-FFS production processes and comparative clinical trials are required.

ABBREVIATIONS

FFS, film-forming system(s); FFS-S, film-forming solution; FFG, film-forming gel; FFE, film-forming emulsion; SFFS, spray film-forming system(s); SLN, solid lipid nanoparticle; NLC, nanostructured lipid carrier; PLGA, poly(lactic-co-glycolic acid); PNIPAM, poly(N-isopropylacrylamide); PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropyl cellulose; QbD, Quality by Design; QTPP, Quality Target Product Profile; ICH, International Council for Harmonisation; IVRT, in vitro release test; IVIVC, in vitro-in vivo correlation; MNA, microneedle array; AFM, atomic force microscopy; DSC,

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differential scanning calorimetry; XRPD, X-ray powder diffraction; FTIR, Fourier-transform infrared spectroscopy; CLSM, confocal laser scanning microscopy; TEWL, transepidermal water loss; WVTR, water vapour transmission rate; Tg, glass-transition temperature.

➢ *Conflict of Interest*

The authors declare that they have no conflicts of interest.

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