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Review Article

TECHNICAL AND PATENT PERSPECTIVE ON FILM FORMING TOPICAL SPRAYS

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ABSTRACT

Film-forming systems were a viable option for topical and transdermal medication administration in the present study. Medication administered via the skin serves two purposes: topical treatment of skin disorders and transdermal drug absorption into the circulation. Apart from the ease of self-administration, the topical route provides a broad and diverse surface and functions as a substitute for oral and hypodermic injection drug delivery routes. Existing dosage forms, such as creams, patches, and ointments, have several drawbacks. In addition to being unsightly, patches can be painful to put on curved surfaces, create discomfort while peeling off, and most often cause skin irritation because of their occlusive qualities, which block sweat ducts and prevent perspiration from evaporating from the skin surface. This review encompasses the mechanism of polymers, such as ethyl cellulose and Eudragit types, plasticizers, and penetration enhancers utilized in film formation. Overall, polymeric film-forming sprays exhibit substantial potential for the convenient administration of antibiotics and antiseptics to treat bacterial, fungal, and viral skin infections. The application of topical medication is thought to result in both local and systemic effects. The physicochemical characteristics of the medication and patient adherence determine how well the topical treatment works. Poor permeability and poor adherence to the skin are some of the disadvantages of conventional pharmaceutical formulations for topical and dermatological administration. The development of medication delivery technologies intended for topical administration to the skin includes the use of topical film-forming systems.

Keywords: Anti-fungal agents, Film-forming agents, Film-forming systems, Patented Formulations, Skin infections, Sustained drug release, Topical drug delivery system, Transdermal sprays

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INTRODUCTION

The skin's intricate structure and characteristics serve as the body's most effective barrier against environmental and external threats while also assisting in maintaining homeostasis. This purpose is primarily served by the stratum corneum, which is the outermost layer of the epidermis. The thickness of the epidermis outer layer, corneocyte size, and superficial lipid content affect the characteristics of the skin and can influence the development of several dermatological illnesses. Anatomical areas with thick epidermis are more resistant to external factors. The condition of the epidermal barrier depends on the amount of serum, hydration, and loss of water. The face, which has a very thin covering, is prone to damage from external sources, but also has a very fast rate of regeneration [1]. The corneocyte size within a layer determines the absorption of material from the skin's surface, and cell size has an inverse relationship with absorption. Skin is a visible organ that interacts with the environment. Additionally, the skin contributes to vitamin D synthesis by activating vitamin D in the body by converting 7-dehydrocholesterol through a 2 hydroxyl group.

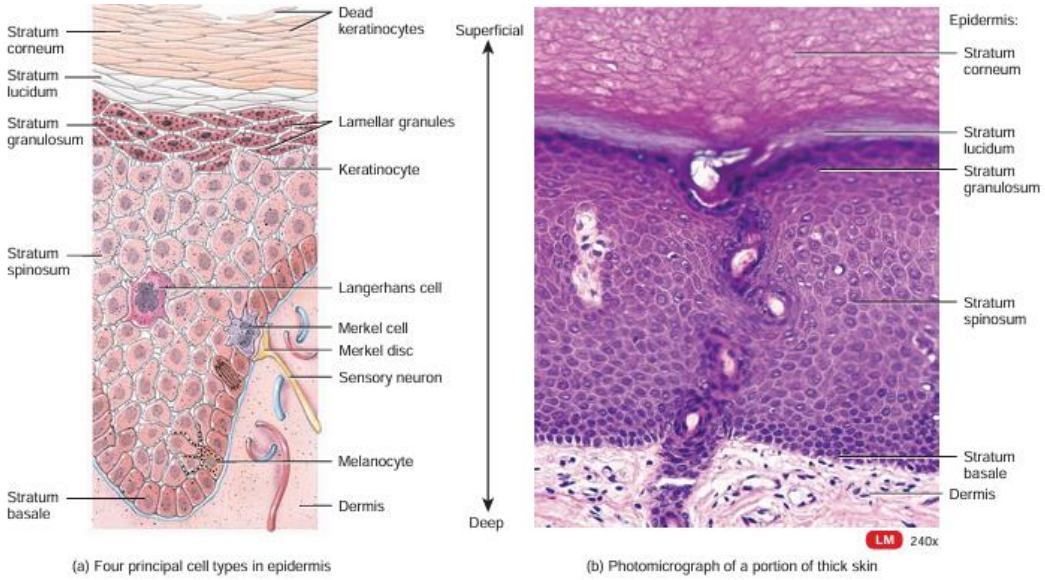

Fig. 1: Layers of epidermis [2]

Various skin infections

Microbes can infiltrate the skin and soft tissue underneath, causing infections of the skin and soft tissues. Their presentations, etiologies, and severities vary. Dermatological infections affect between 7 and 10 percent of hospitalized patients. Skin and tissue infections can produce various clinical symptoms, making the diagnosis challenging. The selection of antimicrobial therapy is based on an understanding of possible microorganisms, point of entry, severity of the disease, and clinical sequelae [3].

Introduction to fungal infections

The recent increase in fungal infections has necessitated immediate intervention. Fungal infections are seldom diagnosed in the initial stages, which can intensify the severity of infections and complicate treatment procedures. Fungal pathogens employ various mechanisms to evade the host immune system and to progress the severity of infections. Fungal infections pose a significant threat to public health. The severity of fungal infections can vary, and they can be superficial, cutaneous, subcutaneous, mucosal, or systemic. Organisms, such as Candida spp., are part of the human microbiota that can cause opportunistic infections in individuals and life-threatening infections (invasive candidiasis) in immunocompromised patients, such as human immunodeficiency virus (HIV) patients, cancer patients receiving chemotherapy, and patients receiving immunosuppressive drugs. The Centers for Disease Control and Prevention (CDC) declared September 20–24, 2021, as a fungal disease awareness week to educate and highlight the importance of early diagnosis of fungal infections to alleviate the debilitating effects (CDC website).

Various fungal infections

- **Candidiasis:** Candida spp., the most common pathogenic cause of invasive mycotic diseases, is the primary cause of all healthcare-associated bloodstream infections in the United States. Despite antifungal therapy, the crude mortality rate of Candida spp. has reached 40% [4, 5]. Invasive candidiasis includes deep-seated infections and bloodstream infections.
- **Cryptococcosis:** The primary causes of Cryptococcosis is C. neoformans and C. gattii, which are invasive fungal illnesses.
- **Dermatophytosis:** Dermatophyte's cause is dermatophytosis, a skin infection that is typically harmless and affects approximately 20% of the world's population. These fungi infect the stratum corneum, along with other keratinized tissues, such as nails and hair, and propagate by secreting enzymes to break down keratin for sustenance.
- **Endemic mycoses:** Endemic mycoses such as Blastomycosis, Coccidioidomycosis, emergomycosis, histoplasmosis, paracoccidioidomycosis, sporotrichosis, and talaromycosis. Historically, these diseases occurred in a limited geographical range and were considered the primary factors contributing to both the incidence rate and mortality in the case of HIV/AIDS, other immunosuppressive diseases, or the use of immunosuppressants.
- **Zygomycosis:** Zygomycosis refers to a group of uncommon but frequently fatal mycoses caused by Zygomycetes that are subdivided into two orders: Mucorales and Entomophthorales [6].
- **Aspergillosis:** Aspergillus spp. cause chronic and invasive infections of the lungs, although they can also disseminate to other organs.

Film forming systems

FFS, a novel film-forming technique, is a viable alternative to the traditional transdermal and topical preparations. This dosage type is described as non-solid and creates a film "in situ," or after delivery, on the skin or any other body surface. Both a solid polymeric substance that serves as a matrix for the delayed release of the drug to the skin and the residual liquid film that is quickly taken up by the stratum corneum are potential results of the procedure. In these systems, the drug is mixed in the vehicle together with film-forming excipients that evaporate the solvent and leave a film behind the excipients and drug when they come into contact with the skin. The resulting film could be a solid polymeric substance that serves as a matrix for continuous drug release. Because they do not have penetration enhancers that might have a systemic impact, local FFSs are used to treat wounds and skin conditions. The ability of film-forming dosage forms to improve pharmacokinetics and provide prolonged release is advantageous for topical treatments. The topical system bypasses first-pass metabolism, and problems related to intravenous therapy, and avoids risks related to absorption, such as gastric emptying time, various enzymes, and pH changes [7].

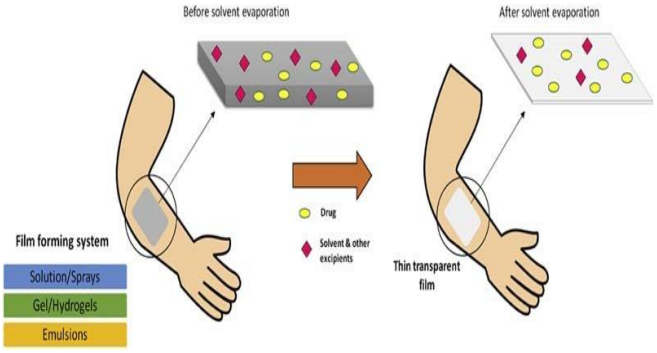

Fig. 2: Film forming system [Error! Bookmark not defined.]

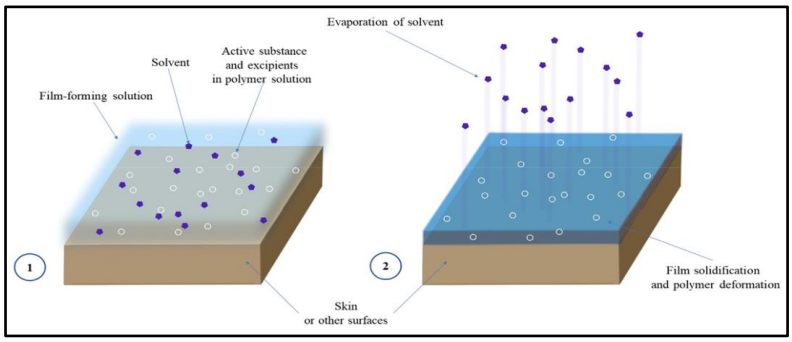

Fig. 3: Mechanism of film forming system [10]

Elements of film-forming sprays

Polymers

The main excipient that influences the characteristics of the film-forming system is the polymer. The viscosity of the formulation and the appearance of the produced film were both influenced by the polymer. In conjunction with a plasticizer, it establishes the pliability and skin adherence of the film. Moreover, the polymer affected the physical stability and solubility of the drug in the film. Ex. ethyl cellulose, chitosan, eudragit E100, carbapol 940, etc.

Crosslinkers

Cross-linkers can affect the glass transition, elasticity, solubility, polymer film stiffness, and viscosity. For example, sodium chloride

Penetration enhancer

Eutectic mixes are frequently used to improve medication absorption. One of the most powerful eutectic mixtures is the combination of menthol and camphor.

Solvents

Despite its rapid evaporation, the solvent is an essential component of the film-forming system and does not end up in the film. The ability of a drug to modify its distribution to the skin in a solvent is limited to solvents with strong solubilizing power. In addition to its indirect effect on penetration, the solvent may also have a direct effect on drug flow. Despite the short skin contact duration, drug transport can be enhanced to varying degrees based on the type of solvent and its ability to enhance skin penetration. Ex. Ethanol, Acetone, etc.

Propellants: Ex. dimethyl ether

Plasticizers

Plasticizers play a key role in facilitating film formation, and the final film is more flexible. Additionally, they can be used to regulate the film's skin adherence to some extent. Plasticizers must have minimal skin permeability and work well with the polymers being utilized. Ex. PEG-200 (Polyethylene Glycol-200), PEG-400 (Polyethylene Glycol-400)

Surfactants: Ex. Tweens 80

Sprays film-forming sprays: an assessment and characterization

pH determination

A digital PH meter was used to calculate the pH.

Viscosity

If the viscosity or concentration is higher, the spreadability decreases. The viscosity of the solution was determined at 25 °C±1 °C using a Brookfield Viscometer.

Tonicity

The spray formed should be isotonic. If it's non-isotonic, then it causes irritancy to the skin.

Bioadhesive strength

The bioadhesive strength was evaluated by attaching the film to mouse skin, and for five minutes, it was permitted to engage with the skin. The total force required to detach the film was then recorded.

$$Fb=\frac{F}{A}$$

Tensile strength

The film can withstand the stress and applied pressure.

Surface morphology of film

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were used to investigate the surface roughness and uniformity of the film.

Film formation time

The drying time of the film was measured when the formulation was sprayed onto the skin to determine how quickly it formed.

Drug content

The mixture was sprayed into a beaker containing 50 ml of methanol. After shaking for 10 min, 100 ml of methanol was added. After adding 10 ml of the solution, filtering it, and measuring the amount of dissolved medication, the concentration was ascertained using a UV spectrophotometer.

Washability

The dried film was used to evaluate its wetting. After cleaning with water, the film was rated on an ordinal scale (i. e., readily, somewhat, and cleaned). If the film-forming solutions come into contact with delicate body parts, such as the mouth and eyes, the convenience of misting them with water will be helpful.

Skin irritancy test

These studies were carried out to evaluate the irritant potential of the developed formulation *in vivo* on rat skin (rats: weight range: 250-300 gm) after its application. The hair on the dorsal side (3 cm × 3 cm) of male and female wistar rats was removed with an electric clipper in the direction of the tail to the head without damaging the skin. Three groups of one rat each were included. One group of rats was treated as a control, the second group received formalin solution, and the third group was treated with an optimized 1% w/w film-forming spray formulation; the formulation should be applied uniformly on the dorsal region. The animals were observed for signs of itching or any change in the skin, such as erythema and edema [11].

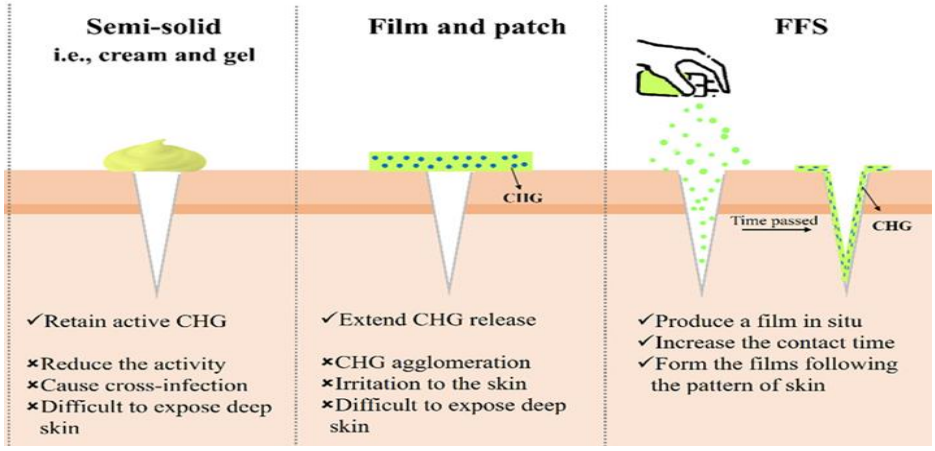

Fig. 4: Graphical comparison between topical dosage forms [Error! Bookmark not defined.]

Table 1: Difference between various topical dosage forms

Characteristics	Semisolid dosage form	Transdermal patches	Film forming spray
Visual appearance	Visible	Highly noticeable	Nearly Invisible
Skin sensation	Occasionally sticky and oily	Non-sticky and greasy	Non-sticky and greasy
Administration	High	Convenient	Convenient
Dose adjustment	High	Low	High
Dosing interval	1 or 2 d	1-7 d	1-2 days
Sustained release	No	Yes	Yes
Occlusive Characteristics	No	Yes	No
Wipe off resistance	No	Yes	Yes
Residual presence	Possible	Possible	No

Table 2: List of patented formulations for film-forming systems

S. No.	Drug/Dosage form/Title	Excipients	Method of preparation/ Evaluation tests	Reference
1.	Glycopyrrolate	Methyl Methacrylate, Eudragit S 100, Copolymer of Dimethylamine, Triethyl Citrate, Propylene Glycol, Acetone, Propane	Solvent casting method	[12]
2.	Flurandrenolide	PVA (Polyvinyl Alcohol), PVP (Polyvinyl Pyrrolidone), Glycerine, Ethyl Alcohol, Benzyl Alcohol, PEG(Polyethylene Glycol), Disodium EDTA, Citric acid	Not Mentioned	[13]
3.	PVP-Iodine (Anti-microbial agent)	PVA (Polyvinyl alcohol), Glycerol Sodium hydroxide, Tartrazine E102, Potassium iodate	Not Mentioned	[14]
4.	Film Forming System	API (Active Pharmaceutical Ingredient), Plastoid B, Eudragit E100 Propylene Glycol, Sodium lauryl sulphate, Acetone, Propellant, Vitamin E, Trancutol	Not Mentioned	[15]
5.	Topical Film Forming System to Treat Cows Teat	Antimicrobial agent, Solvent, Pullulan/ derivative	Not Mentioned	[16]
6.	Water-dispersible film for delivery of API to the epidermis	API(Active Pharmaceutical Ingredient), Plasticizer, Humectant	Viscosity test (5-500cp)	[17]
7.	Water Resistant Film forming composition incorporating Hydrophilic Activities	2-Ethyl Hexyl methacrylate Ascorbic acid, tert-butyl peroxide, Methacrylic acid, Water, Methyl Methacrylate	Not Mentioned	[18]
8.	Topical film delivery system	API, Non-cellulosic Polymer, film-forming agent, Plasticizer, Antioxidant, Hydro alcoholic Solvent	Tensile strength folding endurance thickness	[19]
9.	Minocycline film-forming gel	Minocycline Hcl, Poloxamer 188, Absolute Alcohol, PVA(Polyvinyl Alcohol), Sod. Sulphite, Propyl Gallate, Triethyl citrate, Butyl hydroxyl toluene, Isopropyl myristate, Water	Not Mentioned	[17]
10.	Itraconazole	Itraconazole, Poloxamer 188, Absolute Alcohol, PVA (Polyvinyl Alcohol), Sod. Sulphite, Propyl Gallate, Triethyl citrate, Butyl hydroxyl, toluene, Isopropyl myristate, Water	Not Mentioned	[17]
11.	Topical film-forming spray	Bupivacaine Hcl, Plastoid B, Eudragit EPO, Propylene glycol , Transcutol, Ethanol 95%, Isopropyl Alcohol, Menthol	Solubility Stability Particle size determination	[20]
12.	Picolinic Acid	Polyacrylic acid polymer, Ethanol, Dimethyl phthalate, Benzyl Alcohol	FTIR, SEM	[21]
13.	Film Forming System	PVA(Polyvinyl alcohol), PVP(Polyvinyl Pyrrolidone), Benzyl alcohol, Alpha-tocopherol, Ethylene glycol	Not Mentioned	[17]
14.	Topical Film Forming Spray	Bupivacaine Hcl,Povidone K30, PEG 300, Ethanol 95%, Menthol, Oleyl Alcohol	Solvent Evaporation	[22]
15.	Film-forming composition for spraying on skin	A lipophilic active agent like retinoic acid, Betamethasone polydimethylsiloxane oil, Ethanol, isopropanol	Not Mentioned	[23]
16.	Topical spray comprising a film-forming composition	API, Plastoid B, Eudragit E100, PEG, SLS (Sodium Lauryl Sulphate), Acetone, Isopropyl alcohol, Vitamin E, Transcutol	Not Mentioned	[24]
17.	Film Forming Compositions	Avalure AC118, Avulure UK425, Sodium chloride, Glycerol, Water	Not Mentioned	[25]
18.	Protective film-forming spray for skin surface	PVP, PVA, DME (Dimethyl ether) Propellant, 1.3 Butylene glycol, 95% ethanol, Plascize L53D, Plascize L-53, SH556 FLUID, SH245	Not Mentioned	[26]
19.	Film forming composition for topical use and	Polyurethane-1, HPMC (Hydroxypropyl methylcellulose)	Not Mentioned	[27]

S. No.	Drug/Dosage form/Title	Excipients	Method of preparation/ Evaluation tests	Reference
	delivery of active ingredients	Magnesium Aluminium silicate, Water, alcohol, Iso-paraffin Glycol, Carbomer, AMC (amino methyl propanol), Titanium dioxide, mica pearl, Iron oxide, Dimethicone copolyol and cyclomethicone		
20.	Therapeutic film forming composition and treatment system therefor	Clobetasol propionate, Urea, Dibutyl phthalate, Eudragit RL-100 Ethanol, Water, Acetone	Not Mentioned	[28]
21.	Topical application of enzyme using peelable film (cosmetic application)	FFA (Film Forming agent) + Polyvinyl alcohol, Protease enzyme, Polyol 60-80%, Xanthan gum	Not Mentioned	[29]
22.	Topical composition for covering a skin lesion	PVA, Chitosan, PEG, Glycerol, Benzalkonium chloride, Aloe Vera, Lactic acid, water	Tensile strength, film thickness	[30]
23.	Film Forming silicone acrylate hybrid composition	Ethyl acetate solvent, PSA-1, 2-ethyl hexyl acrylate, methyl methacrylate, Butyl acrylate Methyl butyronitrile	Glass transition temperature by DSC	[31]
24.	Improvement in Therapeutic composition for topical application	Hydroxyethyl cellulose, 2-doxy prednisolone, 17-alpha propionate, Polidene 905 emulsion	Not Mentioned	[32]
25.	Topical Analgesic Composition	Menthol, camphor, HPC(Hydroxypropyl cellulose), Vinyl caprolactum, methacrylate copolymer, Polymide-1, Pentylene glycone, vanillyl butyl, ether, menthoxypropanediol, linseed oil, Vitamin E, Essential oil, ethanol, Isopulegol.	Not Mentioned	[33]
26.	Topical forming composition and use thereof for treatment of mycoses	Nitrocellulose, castor oil, ethanol, ethyl acetate, mixture of glycerol and caprylyl glycol, and glycolic acid.	Not Mentioned	[34]
27.	Film-forming liquid composition	Ethyl acetate, cellulose acetate butyrate, triacetin, benzocaine, menthol, camphor.	Not Mentioned	[35]
28.	Topical pharmaceutical composition, transdermal pharmaceutical composition	Lecithin, Estradiol, vinyl pyrrolidone/ vinyl acetate copolymer, alcohol, silicone, Hexamethyl disiloxane	Not Mentioned	[36]
29.	Non-leaching surface-active film composition for microbial adhesion prevention	N-methyl pyrrolidone, PVP(Kollidon 90), Polyurethane aqueous dispersion Quaternary ammonium compound	Not Mentioned	[37]
30.	Composition for treatment of epistaxis	Phenylephrine HCl, Tranexamic acid, Trimethylsiloxysilicate, Sodium lauryl sulphate, Water	Not Mentioned	[38]
31.	Sprayable film forming preparation for hair	N-Vinyl pyrrolidone, Vinyl monomer, Chloro fluro hydrocarbon	Not Mentioned	[39]
32.	In-situ film-forming composition	Water, glycerine Poly-ethoxyethylmetha acrylate Ethyl acetate, Acetone Ethanol isopropanol Chlorhexidine-diglyconate	Stability Microbiological LC-MS Transparent glass container test	[40]
33.	Testosterone Transdermal Spray with Film	Testosterone, Eudragit RS 100, PEG 400, Octisalate USP Isopropyl alcohol, ethanol	Wash ability crystallization *in vitro* permeation test viscosity	[41]
34.	pH-sensitive mucoadhesive film-forming gel and wax film for topical and mucosal delivery of molecule	Glycerine, Eudragit l 100, Sodium hydroxide, Noveon and carbomer 971	Not Mentioned	[42]
35.	Pharmaceutical emulsion immobilized in a thin polymer matrix and method of making them	Labrasol, Span 80, Propylene glycol, Oleic acid HPMC(Hydroxypropyl methylcellulose), Tween 80, Water	Not Mentioned	[43]
36.	Film forming composition for topical use	Sucrose fatty acid , S1670, OWA1570 , Sodium carboxymethyl cellulose, Mono/diglyceride p-hydroxybenzoic acid, ester and water	Not Mentioned	[44]
37.	Topical film forming monophasic formulation	Hydrofluroalkane, Polyvinylpyrrolidone, Beclomethasone dipropionate, Ethanol, water	Not Mentioned	[45]
38.	Water-resistant film forming Anti-microbial skin preparation	Poly(N-Vinyl pyrrolidone), Iodine, 2-ethylexylacrylamide Polyvinyl alcohol, Polyvinyl acetate	Not Mentioned	[46]
39.	Sprayable film-forming composition for improving the performance of topical preparation	Acrylate/VA copolymer Acrylate, Water Carrageenan and hyaluronic acid, Tocophenyl acetate	Not Mentioned	[47]
40.	Agent for forming a film on the skin	Dimethiconol, Hybrid dimethicone, Surface treated silica Cyclopenta siloxane, 1,2-Hexanediol, Water	Not Mentioned	[48]

Table 3: Different medications formulated as film-forming sprays

S. No.	Drug	Film forming agents	Application	References
1.	Bupivacaine	Eudragit RS 100	To enhance the local anesthetic effect	[49]
2.	Clotrimazole	Not Mentioned	Improve drug transport to achieve antifungal efficacy	[50]
3.	Etodolac	PVP and Ethyl Cellulose	For sustain drug release	[51]
4.	Luliconazole	Eudragit RS 100 and Propylene Glycol	Not Mentioned	[52]
5.	Miconazole nitrate	Eudragit L-100 and Ethyl Cellulose	Not Mentioned	[53]
6.	Mupirocin spray	Eudragit E 100	For bacterial skin infection as well as promote wound healing	[54]
7.	Oxybutynin	Carbopol and Lutrol	To lower the incidence of Anti-cholinergic adverse events	[55]
8.	Chlorhexidine gluconate	Eudragit RS 100	Antiseptic Application	[56]
9.	Voriconazole	Eudragit RS 100	Antifungal Application	[57]
10.	Fluconazole	Eudragit RS100 and Ethyl cellulose	Antifungal Application	[58]
11.	Ketorolac	Not Mentioned	For pain relief	[59]
12.	Silver Sulfadiazine	HPMC E5LV	Not Mentioned	[60]
13.	Ropivacaine	Not Mentioned	Topical efficacy in alleviating pain	[61]
14.	Ketoprofen	Poloxamer	Anti-inflammatory application	[62]
15.	Estradiol	Eudragit RLPO	Not Mentioned	[63]
16.	Itraconazole	Eudragit RL 100	For treatment of dermatophytosis	[64]
17.	Metronidazole	HPMC and Ethyl Cellulose	Use to treat protozoal infection	[65]
18.	Dexketoprofen	Eudragit RL, Kollidone PF12, PVP K30.	Transdermal Drug delivery of Dexketoprofen	[66]
19.	Vitamin D3	Eudragit RS 100, PVP K30	Alternative to oral and Parenteral route of administration	[67]

CONCLUSION

Film-forming sprays create an in-situ film on the skin for topical drug delivery after the solvent evaporates. FFS represents an innovative platform for localized and sustained topical therapies. Multiple drug formulations have been successfully developed and patented to deliver antibacterial, antifungal, analgesic, anti-inflammatory, and hormonal agents. They offer benefits, such as improved drug pharmacokinetics, prolonged release, and avoidance of systemic effects. Commonly used film-forming agents include ethyl cellulose, chitosan, and Eudragit types, and plasticizers such as polyethylene glycol (PEG) improve flexibility. Solvents, such as ethanol, aid in fast drying. Challenges still need attention, including controlling drug crystallization in the film, measurement of residual content, and comparing efficiency to other topical dosage forms. In summary, film-forming sprays show promise for the convenient treatment of skin conditions while avoiding systemic side effects. Further patents and products are expected as research continues to optimize and expand the applications of these convenient and effective dosage forms.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICTS OF INTERESTS

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this manuscript.

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