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In Situ Film Forming Systems

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Reshma N. Mirajkar*, Ashwini R. Madgulkar, Abhishek G. Harne, Shyamsundar L. Dhage

AISSMS College of Pharmacy, Kennedy Road, Near RTO, Pune-411001, India

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ABSTRACT

Patient compliance and drug targeting at the desired concentration are still concerns for effective treatments, even after the many available approaches for topical drug delivery. A film-forming system is a novel approach that has great potential for surpassing the disadvantages of the other dosage forms (hydrogels and films). As an additional advantage, it has controlled drug-releasing properties. To control drug release through the skin, diverse strategies have been employed, including changes to film-forming polymers, plasticizers, additives, and even model drugs in formulations. The types and concentrations of polymers and excipients, sprayer types, evaluations, and critical parameters in determining spray ability and film characteristics are all covered in this article.

INTRODUCTION:

The topical route of drug delivery is one of the widely accepted route for drug delivery for superficial, cutaneous as well as systemic drug delivery as it offers many advantages over oral drug delivery. Avoidance of some disadvantages of the oral route like first-pass metabolism, low pH effect, and enzyme hindrance makes topical drug delivery a better option. To improve therapeutic efficiency or pharmacokinetic profiles, topical drugs are delivered via lotion, creams, ointments, sprays, solutions, gels, and also with the help of bioadhesive pre-formulated films known as patch.[1] These formulations mentioned above are having some drawbacks like stickiness, multiple dosing frequency, less bioavailability of the drug. However, though the patch is a better formulation with lesser drawbacks, the patch has disadvantages too. Patch preparations are also often associated with hypersensitivity, irritation, and blistering.

The recent innovation of the film-forming system has come along with much-reduced disadvantages in the topical drug delivery and has low chances for skin irritation hypersensitivity and provides controlled release of the drug. A film-forming system can be delivered via film-forming gels, solutions, or spray.

Principles and working of film-forming systems:

FFSs can be in the form of a solution or dispersion in which the drug and film-forming excipients are dissolved/dispersed in a volatile solvent or solvents. The solubility of the drug/excipients or dispersions of encapsulated drug microparticles/nanoparticles in solvents determines the liquid state of the FFS. When the solvents come into contact with the skin, they evaporate and form a film with the excipients.[2]

The drug release process is similar to that of a patch after the film is formed, in that the polymer matrix containing the drug releases it over time.[3] Drug dosages in a film-forming formulation can also be adjusted depending on the volume of solution per spray to control systemic or local effects. An FFS also ensures that drugs are distributed evenly and effectively. Patient compliance can also be enhanced by ease of use.[4-6] The principle is demonstrated in Fig. 1.

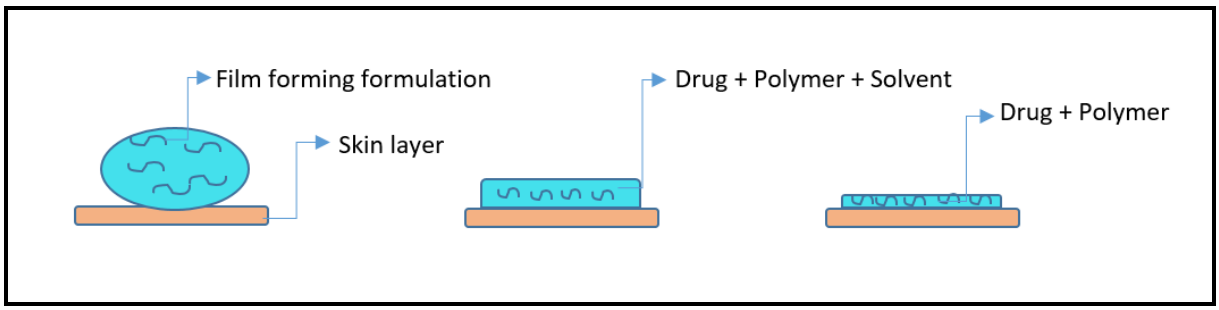


Figure No. 1: Principle of film forming systems

Components of Film Forming System:

1. Active pharmaceutical ingredients
2. Film-forming polymers
3. Plasticizers
4. Volatile solvents

1. Active pharmaceutical ingredients

As the drug is to be applied to the skin the drug must pass through the upper layer of the skin which is the stratum corneum. The stratum corneum is the skin's first barrier which is lipophilic. So the drug with high lipophilicity can penetrate the stratum corneum more easily than the hydrophilic drug. Log P [7-8]. Thus the drug with a log P of more than 2 is most suitable and needs very less or no penetration enhancer.[9]

Certain other factors than lipophilicity play an important role in the drug transfer into the skin such as the drug molecular weight and size. Size less than 500 Dalton is a suitable drug transferer through the skin.[10]

The drug solubility in the non-volatile solvent in sufficient quantity is also required as the drug should not crystallize when the volatile solvent gets evaporated. Studies show that a formulation containing the dissolved API should have a pH value of 5 to 10.[7]Since the pH of the skin is around 5, the formulation's pH should be in the same range to avoid skin irritation during application.[11-12]

2. Film-forming polymers

Film-forming polymers are very important for film formation. The selection of film-forming polymer has the greatest impact on the formulation's substantivity. Individually or combined, polymers can be used. It's important that they can establish a flexible, thin, clear, and long-lasting film. Essentially, there are 2 kinds of film formers.

1. water-soluble and
2. Water-insoluble.[13]

Characteristics of water-soluble polymers.[14]

a. Water-soluble polymers have a hydrophilic nature, and while many of them are not suitable for enhancing substantivity in conventional skin-surface formulations.

b. They are ideal for formulations in which the drug rapidly penetrates the stratum corneum to form a drug reservoir.

c. Water-soluble polymers must be used with water-insoluble polymers to achieve a drug reservoir.

Characteristics of water-insoluble polymers.[14]

a. Water-insoluble polymers have higher drug substantivity.

b. They are often brittle and rigid making formulation crumble.

c. Plasticizers are usually added to the formulation to improve the film's uniformity and flexibility, or the polymer is combined with a water-soluble polymer.

Some of the well-known polymers used in the film-forming system are as follows.

Polyvinyl Pyrrolidone (PVP):

Due to its solubility in both organic solvents and water, the use of PVP allows for a more flexible solvent selection for FFSs.[15]High hygroscopicity, good biocompatibility, and the ability to increase bioadhesive strength. As a result, PVP was investigated in several wound dressing studies. In some cases, polyvinylpyrrolidone-vinyl acetate copolymers are used instead of PVP.[16]

Polyvinyl Alcohol (PVA):

Because of its low hydrophilic nature, rigid film generation, and insufficient elasticity, PVA in FFSs is a source of concern and constraint .[16-17]As a result, a limited fraction of PVP (0.5–5%) in a PVP-PVA mixture has been preferred for stable hydrogels.[18].

Chitosan: [22-23]

Chitosan is obtained from chitin. It has specific biological activity and is also biocompatible. It is generally applied fabrication of wound dressing. The combination of chitosan and PVP has antibacterial activity.[19-21] Its mucoadhesive nature makes it advantageous for the film-forming system. Chitosan is soluble in an acidic medium and not soluble in water and organic solvents.

Polymethacrylates:[1, 4, 24]

Polymethacrylates are widely used in film-forming systems. Eudragit comes in a variety of forms, each with its own characteristics. These synthetic polymers are commonly used as tablet additives to modify drug release. Eudragit, on the other hand, is known to increase drug permeation through the skin.

Some of the popular Eudragits are as follows:

Table No. 1: Film forming Eudragits

Sr. no	Eudragits	Properties
1	Eudragit RL-100	Water-insoluble has good tensile strength, forms a transparent film
2	Eudragit RS-100	Water-insoluble has good tensile strength, forms a transparent film
3	Eudragit RSPO	Water-insoluble, Does not produce a transparent and shiny film
4	Eudragit RLPO	Water-insoluble, Does not produce a transparent and shiny film
5	Eudragit S100	Water-soluble, Does not cause skin irritation
6	Eudragit E100	Water-insoluble forms a transparent film
7	Eudragit L30D-55	Water-dispersible at pH 2–3
8	Eudragit EPO	Water-insoluble forms a transparent film

Carbopol:

It is a water-soluble and pH-sensitive polymer. Carbopol forms an amorphous hydrogel that can absorb wound fluids, making it ideal for open wounds. From the studies, it is shown that combining Carbopol and Poloxamer is superior to utilizing Carbopol alone. The polymer combination forms a film with good sprayability at a concentration of 0.05 percent.[27]

Carbopol® 940 and Carbopol® 971P is used in the formulation of Ketoprofen, oxybutynin, and Beta-1,3/1,6-glucan which are present in the market. As it is viscoelastic it increases the diffusion coefficient of the drug.[25]

Hydroxypropyl cellulose:

It is a hydrophilic polymer. It gets swollen when added to the water. The amount of hydroxypropyl cellulose in the films affects drug release and water permeability the more hydroxypropyl cellulose in the films, the better is the drug release and permeability.[28] It is generally incorporated with the corbopol to give sustained release.[29]

Hydroxypropyl methylcellulose: [29-30]

It is a water-soluble and non-ionic polymer used in the preparation of the hydrogel-based film. It gives sustained release of the drug but has limitations due to slow drying time.

3. Plasticizers

Plasticizers are a very important component of the film-forming formulation. They are to be added in a minute amount in the formulation to provide the necessary flexibility to the film and to enhance the water permeation through the film.[31]Some plasticizers also act as drug diffusion enhancers along with providing plasticity to the film. They act by the mechanism by decreasing the glass transition temperature of the film.[32]Plasticizers can also help to keep API stable.[23, 33]

Plasticizers enhance the following characters of the film:

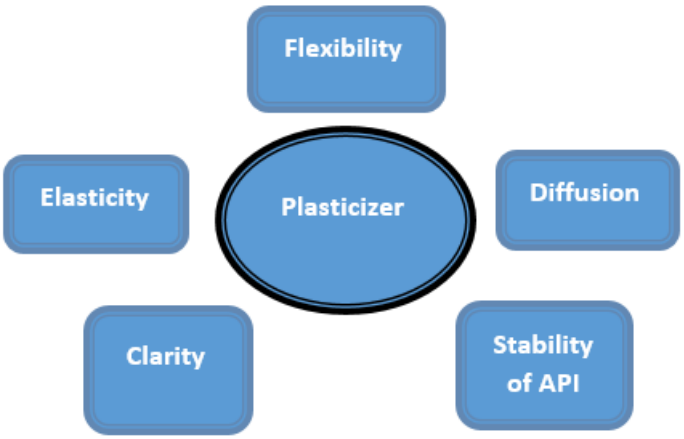


Figure No. 2: Plasticizers enhance the above characteristics of the film characters of the film

Some examples of plasticizers are as follows.

Table No. 2: Plasticizers used in the film forming system.[32,34]

Sr. no	Plasticizers	Properties
1	Dibutyl phthalate	Plasticizer
2	Triacetin	Versatile water or oil miscible solvent. plasticizer
3	Polysorbate 80	Non-ionic solubilizer, plasticizer, emulsifier, co-emulsifier
4	Propylene glycol	Polymeric solubilizer, plasticizer
5	Triacetin	Versatile water or oil miscible solvent. plasticizer
6	PEG 400	Plasticizer
7	Sorbitol	Plasticizer, Versatile water or oil miscible
8	Glycerol	Stabilizing agent and plasticizer

4. Solvents

Both volatile and non-volatile solvents can be used in the FFS system, to achieve the goal of balancing the drying rate of the film. Drugs have a difficulty in escaping and penetrating films that dry out too quickly and form a hard film. Mostly the solvents are used in combination to get required and sufficient effect on the drying time, film formation, and drug release.[35]

The solvent must be compatible with the skin. Even if the skin barrier is damaged during the evaporation process, it also shouldn't irritate the skin. The dispersion or dissolution of the

film-forming polymer is required.[3-4]There should be lesser time for the formation of film. It should be not that quick that will affect the film formation.[35]For film-forming formulations, ethanol and isopropanol are particularly suitable solvents. Isopropyl myristate and propylene glycol have additional penetration-enhancing properties, but they do not evaporate. [3,4, 35]

Some of common volatile solvents used in the film-forming system are as follows.

Table No. 3: Volatile solvents used in the film forming system.[3,36]

Sr. No	Solvents	Nature
1	Ethanol	volatile
2	Isopropyl alcohol	volatile
3	Isopropanol	volatile
4	Butanol	volatile
5	Water	Non volatile
6	Acetone	volatile
7	Isopropyl myristate	Non volatile
8	Propylene glycol	Non volatile

Different types of film forming formulations:

1. Film Forming Solutions
2. Film Forming Gels
3. Film forming Emulsions

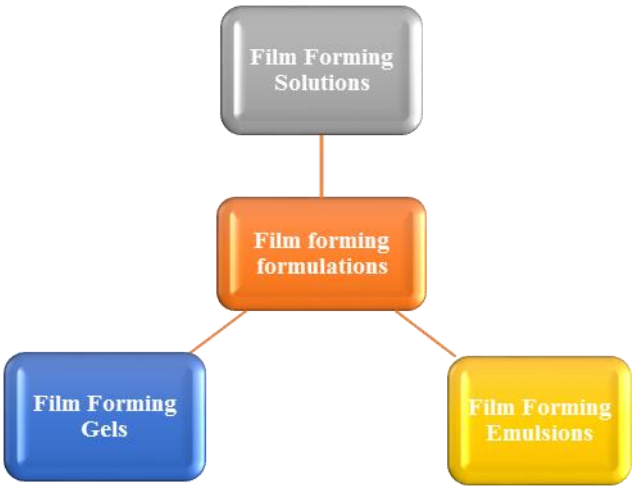


Figure No. 3: Different types of film-forming formulations

Film Forming Solutions:

Film-forming solutions can be given via metered-dose spray. Many film-forming solutions are marketed widely. Axiron® is one of the film-forming formulations containing testosterone marketed by Eli Lilly which gives a prolonged release of the hormone via skin. It was made using polymer polyvinylpyrrolidone. Ethanol and isopropyl alcohol were used as a solvent.[39-40]

There is another film-forming antifungal formulation of Terbinafine HCL marketed by company GlaxoSmithKline Consumer Healthcare named as Lamisil Once®. It is a solution given via metered-dose spray. Polymer used for the preparation was Poly (acrylamide-coisooctylacrylat), Hydroxypropylcellulose, and Ethanol as a solvent.[41]

Hansaplast® Sprühpflaster is a film-forming spray marketed by company Beiersdorf. Hansaplast Wound Spray is an easy-to-use spray for the antiseptic cleansing of minor acute wounds such as cuts, abrasions, first and minor second-degree burns, and open blisters, by mechanical irritation.[42]The polymers used were Acrylic copolymer, polyurethane polymer. Ethanol, water, dimethyl ether were used as solvents.

Liqui-Patch® by EpinamicsMedSpray® by MedPharm, are the other film-forming spray available in the market.[43-44] CareFusion created a film-forming iodophor preoperative skin preparation. Povidone-iodine, a complex of polyvinylpyrrolidone and triiodide, is dissolved in isopropyl alcohol to make Prevail-FX®.[43]

Film Forming Gels:

Gels are generally colorless, transparent preparations and are easily applicable on the skin with more accurate dosing. The advantage of using film-forming gel preparations instead of film-forming solutions is that the formulation is easier to apply due to its semi-solid nature of the formulation. The polymer matrix is more viscous than comparable liquid preparations due to the added gelling agent, which can be advantageous in the development of sustained-release dosage form.[7]

Kin et al. prepared film-forming hydrogels using film-forming polymers such as polyvinyl alcohol and polyvinylpyrrolidone, as well as propylene glycol, ethanol, and water. The gel

adhered well to the skin and protected the wound well from outside influences. The gel can also be used as a base for drug application on the skin.[19]

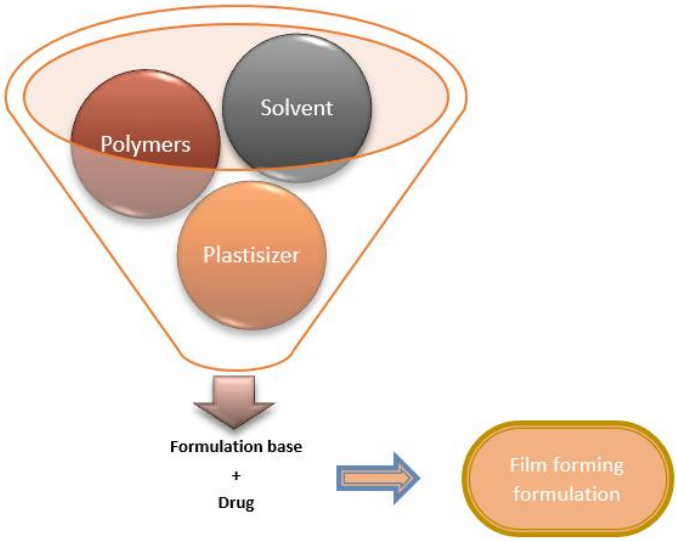
The team led by Li et al. was successful in developing film-forming hydrogels for the transdermal application of tolterodine to treat overactive bladder. One or a combination of film-forming polymers such as poloxamer, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and methylcellulose were added as a gelling agent after the drug and triethanolamine were dissolved in water and ethanol. The permeation and penetration experiments revealed that tolterodine penetrated quickly into the stratum corneum, where it formed a depot. When compared to oral bioavailability, the bioavailability was sufficient for transdermal action. The researchers were able to demonstrate that active substances can be applied transdermally using film-forming gels in general.[46]

Film-forming Emulsions:

Emulsions are widely used as cosmetic and pharmaceutical formulations because of their excellent solubilizing capacities for lipophilic and hydrophilic active ingredients and application acceptability. Emulsions are liquid preparations that are usually made up of two phases: oil and water. Because they are thermodynamically unstable, they are usually stabilized using an emulsifier. It has the advantage that both hydrophilic and lipophilic drugs can be added into the two-phase or multi-phase system.[47] The emulsion is usually preferred by patients due to its lower viscosity so has great importance in aesthetic preparations.[48]

The polymer is dissolved or dispersed in the volatile solvent and forms the continuous phase in this type of emulsion. The viscosity of the polymer phase increases as the solvent evaporates, stabilizing the inner phase. The active ingredient is found in the dispersed phase's droplets and diffuses into the skin via the polymer matrix.[47] By developing a film-forming emulsion, Lunter et al. were able to achieve a sustained release of the active ingredient nonivamide. The dispersed phase of the emulsion was formed by dissolving nonivamide in medium-chain triglycerides.[82-83]

Formulation of film-forming systems



1, 7

Figure No. 4: Formulation of film-forming systems

FFS formulations typically include a drug, excipients (polymers and plasticizers, as well as additives like penetration enhancers), and volatile solvents that can turn a liquid or semi-solid into a film on the skin's surface after application. As a result, several factors, such as the physicochemical environment, the properties of drugs, the types and concentrations of polymer and plasticizer, and the role of additives must be considered. The rate of drug release through the skin will be determined by the formulation and the solvent evaporation by drug saturation modulation.

Evaluations of the Film Forming System:

1. PH:

For the normal skin pH ranging from 4–6.[63] Diabetic wound's pH ranges from 6.5–8, whereas a faster healing period for burns occurs below pH 7.32.[64-65]The preparation's pH adjustment aims to prevent irritation and changes in the wound's physiological condition during the healing process. Furthermore, depending on the degree of ionization, the pH value of the dosage can affect the permeation of drugs through the skin.[66]

2. Viscosity:

Viscosity is a very important parameter for the spreadability of the film-forming solution. For good spraydability, the viscosity must be optimum. The coverage area of spray can be reduced by increasing viscosity.[69-70]The concentration of film-forming polymers in the formulation is responsible for the viscosity. In case of gel, lower the viscosity better is the drying time.[24]

3. Film's tensile strength:[71]

The film's tensile strength (TS) is its ability to withstand applied pressure. The goal of TS testing is to see if the resulting film is abrasion-resistant and flexible enough to follow the movement of the skin without cracking. It can be calculated by the formula below.

$$TS = \frac{Fm}{LxW}$$

Where, Fm is the maximum pressure that can be held by the film before tearing,

L is the thickness of the film, and

W is the initial width of the film.

After stretching elongation which describes the elasticity of the film can be can found by formula given below.

$$EB = \frac{lmax - lo}{lo} * 100\%$$

Where, l_{max} is the length of the film before the film is torn when pulled andL_0 is the initial length of the film.

4. Surface Morphology of the Film:

Using scanning electron microscopy (SEM) or transmission electron microscopy, this test is carried out to determine the microscopic shape, surface roughness, and homogeneity of the film (TEM). [24, 72]

5. Drying time:

To determine how quickly the film forms after the solution is sprayed, the drying time of the film is measured. The solution is sprayed on the glass surface and then allowed to dry at room temperature. Drying time can be measured by using a paper or using a glass slide. [1, 73-75]

6. Spray Angle, Pattern, and Droplet Size Distribution[74]

Paper that has been soaked in indicator reagents are used to make spray pattern visualize. The pattern and spray droplet size distribution will be clarified by using solvent-sensitive paper. The area covered and the spray angle are then determined by measuring the pattern's diameter.

7. Drug Content per Spray and Uniformity

Each spray's dose uniformity is determined by weighing or measuring its volume, which is then used to calculate the amount of active substance based on its concentration in the film-forming solution. Collecting the sprayed solution and measuring it instrumentally can also be used to determine the active substance level[74].

The film-forming solution is used to determine how much spray volume comes out.The weight of the film-forming solution remaining in the sprayer should be determined rather than the weight of the liquid coming out of the nozzle. Because the spray droplets are so small and easily carried by the wind, it is unlikely that all of it will be collected and weighed. The spray volume is calculated using the equation below[74].

8. In vitro Drug Release Study.[1, 75, 76, 77]

Using Franz diffusion cells, cellulose membranes with a pore size of 0.45 m, nylon membranes with a pore size of 0.22 mm, or silicone membranes are used as compartment separators. Phosphate buffer pH 7.4 was used as a medium. The film-forming solution is placed in the donor compartment after the compartment system is ready. The solution that diffuses through the cells is collected at regular intervals and then measured with an instrument. After collecting samples, the same volume of fluid is replaced.

9. *Ex-vivo* Skin Permeation Study.[78]

Franz diffusion cells can be used to test drug permeation on the abdominal skin of mice or rabbits. Using a cotton swab soaked in propanol or isopropanol, the skin is cleaned of all

attached fat tissue and then washed with normal saline solution. Phosphate buffer pH 7.4 or acetate pH 6.0 are used as diffusion media. Medium flow is achieved in the receptor compartment using flow-through cells connected to silica tubes at speeds of 0.3 mL-0.6 mL/hr. The film-forming solution is placed in the donor compartment once the compartment system is ready. The drug levels are then measured using an instrument after aliquots are taken from the receptor compartment at specific time intervals. At the same time, a new diffusion medium is added to replace the old one.

CONCLUSION:

FFSs have been shown to have therapeutic potential in a number of studies. The efforts to design controlled drug release FFSs are expected to show effective system for modulating drug release. Both natural and synthetic polymers can be useg to prepare the film-forming formulations. There is wide variety of options of the film-forming formulations like solvent, gel and emulsions too. Metered-dose sprays give more accurate dose with more ease for application. Patient compliance is expected to increase with the help of this concept.

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REFERENCES:

1. Paradkar M, Thakkar V, Soni T, Gandhi T, Gohel M. Formulation and evaluation of clotrimazole transdermal spray. Drug Dev Ind Pharm. 2015;41(10):1718-25.
2. Leichtnam ML, Rolland H, Wuthrich P, Guy RH. Formulation and evaluation of a testosterone transdermal spray. J Pharm Sci. 2006 Aug; 95(8):1693-702.
3. Kathe K, Kathpalia H. Film forming systems for topical and transdermal drug delivery. Asian J Pharm Sci. 2017; 12(6):487–497.
4. Ranade S, Bajaj A, Londhe V, Babul N, Kao D. Fabrication of topicalmetered dose film forming sprays for pain management. Eur J Pharm Sci. 2017;100: 132–141
5. Geh KJ, Stelzl A, Gröne A, Wagner L, Förster B, Winter G. Development of a sprayable hydrogel formulation for the skin application of therapeutic antibodies. Eur J Pharm Biopharm. 2019;142 (November2018):123–132
6. Lu W, Luo H, Wu Y, Zhu Z, Wang H. Preparation and characterization of a metered dose transdermal spray for testosterone. Acta Pharm Sin B. 2013;3(6):392–399.

7. Alberti, I.; Grenier, A.; Kraus, H.; Carrara, D.N. Pharmaceutical development and clinical effectiveness of a novel gel technology for transdermal drug delivery. Expert Opin. Drug Deliv. 2005, 2, 935–950.
8. Kalia, Y.; Merino, V.; Guy, R.H. Transdermal Drug Delivery: Clinical Aspects. Dermatol. Clin. 1998, 16, 289–299.
9. Ditzinger F, Price D, Ilie A, Köhl N, Jankovic S, Tsakiridou G et al. Lipophilicity and hydrophobicity considerations in bio-enabling oral formulations approaches – a PEARRL review. Journal of Pharmacy and Pharmacology. 2018;71(4):464-482.
10. Ita K. Transdermal Drug Delivery: Progress and Challenges. *J. Drug Deliv. Sci. Technol.* 2014; 24:245–250.
11. Matousek, J.L.; Campbell, K.L.; Kakoma, I.; Solter, P.F.; Schaeffer, D. Evaluation of the effect of pH on in vitro growth of Malassezia pachydermatis. Can. J. Vet. Res. Rev. Can. Rech. V*été*rinaire2003, 67, 56–59
12. Bucher, K.E.;Walz, D. Irritant actions of unphysiological pH values. A controlled procedure to test for topical irritancy. Agents Actions 1979, 9, 124–132.
13. Karki, S.; Kim, H.; Na, S.-J.; Shin, D.; Jo, K.; Lee, J. Thin films as an emerging platform for drug delivery. Asian J. Pharm. Sci. 2016,11, 559–574.
14. de Oliveira, F.F.D.; Menezes, L.; Tavares, M.I.B. Film-Forming Systems in Topically Administered Pharmaceutical Formulations.Mater. Sci. Appl. 2020, 11, 576–590.
15. Borges, A.F.; Silva, C.; Coelho, J.F.J.; Simões, S. Oral films: Current status and future perspectives: I—Galenical development and quality attributes. J. Control. Release 2015, 206, 1–19.
16. Tran, T.T.D.; Tran, P.H.L.; Choi, H.G.; Han, H.K.; Lee, B.J. The roles of acidifiers in solid dispersions and physical mixtures. Int. J. Pharm. 2010, 384, 60–66.
17. Teodorescu, M.; Bercea, M.; Morariu, S. Biomaterials of PVA and PVP in medical and pharmaceutical applications: Perspectives and challenges. Biotechnol. Adv. 2019, 37, 109–131.
18. Kamoun, E.A.; Chen, X.; MohyEldin, M.S.; Kenawy, E.-R.S. Crosslinked poly(vinyl alcohol) hydrogels for wound dressing applications: A review of remarkably blended polymers. Arab. J. Chem. 2015, 8, 1–14.
19. Kim, D.W.; z, K.S.; Seo, Y.G.; Lee, B.-J.; Park, Y.J.; Youn, Y.S.; Kim, J.O.; Yong, C.S.; Jin, S.G.; Choi, H.-G. Novel sodium fusidate-loaded film-forming hydrogel with easy application and excellent wound healing.Int. J. Pharm. 2015, 495, 67–74.
20. Abou-Aiad, T.H.M.; Abd-El-Nour, K.N.; Hakim, I.K.; Elsabee, M.Z. Dielectric and interaction behavior of chitosan/polyvinyl alcohol and chitosan/polyvinyl pyrrolidone blends with some antimicrobial activities. Polymer 2006, 47, 379–389.
21. La_eur, F. Mucoadhesive polymers for buccal drug delivery. Drug Dev. Ind. Pharm. 2014, 40, 591–598.
22. Archana D, Singh BK, Dutta J, Dutta PK. Chitosan-PVP-nano silver oxide wound dressing: in vitro and in vivo evaluation. Int J BiolMacromol. 2015 Feb; 73:49-57. Zhuang C, Zhong Y, Zhao Y. Effect of deacetylation degree on properties of Chitosan films using electrostatic spraying technique. Food Control. 2019; 97:231.
23. Zhong Y, Zhuang C, GuW, Zhao Y. Effect of molecular weight on the properties of chitosan films prepared using electrostatic spraying technique. CarbohydrPolym. 2019; 212(May2018):197–205.
24. Gohel MC, Nagori SA. Fabrication of modified transport fluconazole transdermal spray containing ethyl cellulose and eudragit® RS100 as film formers. AAPS PharmSciTech. 2009; 10 (2):684–691.
25. Rajab NA. Preparation and evaluation of ketoprofen as dermalspray film. Kerbala J Pharm Sci. 2013; 6:1–8.
26. Larsson, M.; Hjärtstam, J.; Berndtsson, J.; Stading, M.; Larsson, A. E_ect of ethanol on the water permeability of controlled release films composed of ethyl cellulose and hydroxypropyl cellulose. Eur. J. Pharm. Biopharm. 2010, 76, 428–432.
27. Li, X.; Zhang, R.; Liang, R.; Liu, W.; Wang, C.; Su, Z.; Sun, F.; Li, Y. Preparation and characterization of sustained-release rotigotine film-forming gel. Int. J. Pharm. 2014, 460, 273–279.
28. Rowe, R.C. The effect of the molecular weight of ethyl cellulose on the drug release properties of mixed films of ethyl cellulose and hydroxypropylmethylcellulose. Int. J. Pharm. 1986, 29, 37–41.
29. Saingam W, Chankana N, Madaka F, Sueree L, Homchuam S. Formulation development of topical film formimg spray from Piper nigrum L. Thai J Pharm Sci. 2018;42(supplement):93–97.
30. Frederiksen, K.; Guy, R.H.; Petersson, K. Formulation considerations in the design of topical, polymeric film-forming systems for sustained drug delivery to the skin. Eur. J. Pharm. Biopharm. 2015, 91, 9–15.
31. Güngör, S.; Erdal, M.; Özsoy, Y. Plasticizers in Transdermal Drug Delivery Systems. Recent Adv. Plast. 2012, 1, 91–92.

32. Grip J, Engstad RE, Skjæveland I, Škalko-Basnet N, Holsæter AM. Sprayable Carbopol hydrogel with soluble beta-1,3/1,6-glucan as an active ingredient for wound healing - Development and in-vivo evaluation. Eur J Pharm Sci. 2017 Sep 30; 107:24-31.
33. Felton, L.A. Film Coating of Oral Solid Dosage Forms. In Encyclopedia of Pharmaceutical Technology; Swarbrick, J., Ed.; Inform Healthcare: New York, NY, USA, 2007; pp. 1729–1747.
34. Bornare, S.S.; Aher, S.S.; Saudagar, R.B. A Review: Film Forming Gel Novel Drug Delivery System. Int. J. Curr. Pharm. Res. 2018, 10, 25–28
35. Gennari, C.G.; Selmin, F.; Franzè, S.; Musazzi, U.M.; Quaroni, G.M.; Casiraghi, A.; Cilurzo, F. A glimpse in critical attributes to design cutaneous film-forming systems based on ammonium methacrylate. J. Drug Deliv. Sci. Technol. 2017, 41, 157–16
36. Misra, A.; Raghuvanshi, R.S.; Ganga, S.; Diwan, M.; Talwar, G.P.; Singh, O. Formulation of a transdermal system for biphasic delivery of testosterone. J. Control. Release 1996, 39, 1–7.
37. Misra, A.; Pal, R.; Majumdar, S.S.; Talwar, G.P.; Singh, O. Biphasic Testosterone Delivery Profile Observed with Two Derent Transdermal Formulations. Pharm. Res. 1997, 14, 1264–1268.
38. Axiron. Available online: https://www.drugs.com/dosage/axiron.html (accessed on 16 April 2022).
39. Axiron. Available online: https://beipackzetteln.de/axiron-30mg15ml (accessed on 16 April 2022).
40. GlaxoSmithKline Consumer Healthcare. Available online: https://www.medicines.org.uk/emc/product/6481/smpc (accessed on 16 April 2022).
41. HansaplastSprühpflaster. Available online: https://www.hansaplast.de/produkte/wundversorgung/sprueh-pflaster (accessed on 16 April 2022).
42. Liqui-patch. Available online: https://www.aescuvest.de/projekte/liqui-patch/ (accessed on 16 April 2022).
43. MedSpray. Available online: https://www.medpharm.com/en/discovery/delivery-technology/ (accessed on 16 April 2022).
44. PREVAIL-FX ONE STEP: Povidone-Iodine and Isopropyl Alcohol Solution CareFusion 2200 Inc. Available online: https: dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=39195cf1-3c59-498e-9403-f1889a39e44e&audience=consumer (accessed on 17 April 2022).
45. Liu, X.; Fu, L.; Dai,W.; Liu,W.; Zhao, J.;Wu, Y.; Teng, L.; Sun, F.; Li, Y. Design of transparent film-forming hydrogels of tolterodine and their effects on stratum corneum. Int. J. Pharm. 2014, 471, 322–331
46. Otto, A.; Du Plessis, J.; Wiechers, J.W. Formulation effects of topical emulsions on transdermal and dermal delivery. Int. J. Cosmet. Sci. 2009, 31, 1–19.
47. Daniels, R. Compliance messen und verbessern. Pharm. Ztg. 2005, 150, 20–25
48. Schroeder, I.Z.; Franke, P.; Schaefer, U.F.; Lehr, C.-M. Delivery of ethinylestradiol from film forming polymeric solutions across human epidermis in vitro and in vivo in pigs. J. Control. Release 2007, 118, 196–203.
49. Potts, R.O.; Guy, R.H. Predicting Skin Permeability. Pharm. Res. 1992, 9, 663–669.
50. Ito, Y.; Yoshimura, M.; Tanaka, T.; Takada, K. E
ect of Lipophilicity on the Bioavailability of Drugs After Percutaneous Administration by Dissolving Microneedles. J. Pharm. Sci. 2012, 101, 1145–1156.
51. Padula, C.; Nicoli, S.; Colombo, P.; Santi, P. Single-layer transdermal film containing lidocaine: Modulatio of drug release. Eur. J. Pharm. Biopharm. 2007, 66, 422–428.
52. Benita, S.; Dor, P.; Aronhime, M.; Marom, G. Permeability and mechanical properties of a new polymer: Cellulose hydrogen phthalate. Int. J. Pharm. 1986, 33, 71–80
53. Lecomte, F.; Siepmann, J.; Walther, M.; MacRae, R.J.; Bodmeier, R. Polymer blends used for the aqueous coating of solid dosage forms: Importance of the type of plasticizer. J. Control. Release 2004, 99, 1–13.
54. Lecomte, F.; Siepmann, J.; Walther, M.; MacRae, R.J.; Bodmeier, R. Polymer blends used for the aqueous coating of solid dosage forms: Importance of the type of plasticizer. J. Control. Release 2004, 99, 1–13.
55. Williams, A.C.; Barry, B.W. Penetration enhancers. Adv. Drug Deliv. Rev. 2012, 64, 128–137
56. Davis, A.F.; Hadgraft, J. ect of supersaturation on membrane transport: 1. Hydrocortisone acetate Int. J. Pharm. 1991, 76, 1–8.
57. Moser, K.; Kriwet, K.; Froehlich, C.; Kalia, Y.N.; Guy, R.H. Supersaturation: Enhancement of Skin Penetration and Permeation of a Lipophilic Drug. Pharm. Res. 2001, 18, 1006–1011

58. Edwards, A.; Qi, S.; Liu, F.; Brown, M.B.; McAuley, W.J. Rationalising polymer selection for supersaturated film forming systems produced by an aerosol spray for the transdermal delivery of methylphenidate. Eur. J.Pharm. Biopharm. 2017, 114, 164–174.
59. Marie-Alexandrine Bolzinger; StéphanieBriançon; Jocelyne Pelletier; Yves Chevalier (2012). Penetration of drugs through skin, a complex rate-controlling membrane. , 17(3), 156–165.
60. Alberti, I.; Grenier, A.; Kraus, H.; Carrara, D.N. Pharmaceutical development and clinical effectiveness of a novel gel technology for transdermal drug delivery. Expert Opin. Drug Deliv. 2005, 2, 935–950
61. Matousek, J.L.; Campbell, K.L.; Kakoma, I.; Solter, P.F.; Schaeffer, D. Evaluation of the effect of pH on in vitro growth of Malassezia pachydermatis. Can. J. Vet. Res. Rev. Can. Rech. Vétérinaire 2003, 67, 56–59
62. Ali S, Yosipovitch G. Skin pH: from basic science to basic skin care. Acta DermVenereol. 2013;93(3):261–267
63. Mcardle C, Lagan K, Spence S, Mcdowell D. Diabetic foot ulcerwound fluid: the effects of pH on DFU bacteria and infection. J foot ankle res. 2015;8
64. Sharpe JR, Booth S, Jubin K, Jordan NR, Lawrence-Watt DJ, Dheansa BS. Progression of wound pH during the course of healingin burns. J Burn Care Res. 2013;34(3):e201–e208. D
65. Woodall R, Arnold JJ, McKay D, Asbill CS. Effect of formulation
66. pH on transdermal penetration of antiemetics formulated in poloxamer
67. Lecithin organogel. Int J Pharm Compd. 2013;17(3):247–253
68. Pennington AK, Ratcliffe JH, Wilson CG, Hardy JG. The influence of solution viscosity on nasal spray deposition and clearance. Int J Pharm. 1988;43(3):221–224.
69. Liu X, Doub WH, Guo C. Assessment of the Influence factors on nasal spray droplet velocity using phase-doppler anemometry (PDA). AAPS PharmSciTech. 2011;12(1):337–343.
70. Reid ML, Benaouda F, Khengar R, Jones SA, Brown MB. Topical corticosteroid delivery into human skin using hydrofluoroalkane metered dose aerosol sprays. Int J Pharm. 2013;452(1–2):157–165
71. Saudagar R, Gangurde P. Formulation, development and evaluation of film-forming gel for prolonged dermal delivery of miconaole nitrate. Research Journal of Topical and Cosmetic Sciences. 2017; 8(1):19.
72. Gohli T, Shah P. Formulation and development of transdermal spray of ibandronate sodium. 2019;1.
73. Bakshi A, Bajaj A, Malhotra G, Madan M, Amrutiya N. A novel metered dose transdermal spray formulation for oxybutynin. Indian J Pharm Sci. 2008;70(6):733–739.
74. Edwards A, Qi S, Liu F, Brown MB, McAuley WJ. Rationalisingpolymer selection for supersaturated film forming systems produced by an aerosol spray for the transdermal delivery of methylphenidate. Eur J Pharm Biopharm. 2017; 114:164–174.
75. Nnamani O. Characterization and controlled release of gentamicin from novel hydrogels based on Poloxamer 407 and polyacrylic acids. Afr J Pharm Pharmacol. 2013;7(36):2540–2552.
76. Mori NM, Patel P, Sheth NR, Rathod LV, Ashara KC. Fabrication and characterization of film-forming voriconazole transdermal spray for the treatment of fungal infection. Bull Fac Pharmacy Cairo Univ. 2017;55(1):41–51.
77. Leichtnam M-L, Rolland H, Wüthrich P, Guy RH. Impact of antinucleants on transdermal delivery of testosterone from a spray. J Pharm Sci. 2007;96(1):84–92
78. Lunter, D.; Daniels, R. In vitro skin permeation and penetration of nonivamide from novel film-forming emulsions. Skin Pharm. Physiol. 2013, 26, 139–146.