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Review

Spray Film-Forming systems as promising topical *in situ* Systems: A review

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ABSTRACT

Spray film-forming systems (SFFSs) provide great potential for the treatment of various types of wounds. Such systems afford to prolong the action of active substances, to prevent cross-contamination, and to ensure accelerated wound healing. Spray films are known since the mid-20th century, and nowadays they are widely used to treat minor skin injuries, but numerous clinical cases describe their successful use in the treatment of burns, wounds, bedsores, etc. The current level of polymer development and composite synthesis has greatly expanded the possibilities of creating compositions of spray film-forming systems. Scattered information and lack of standardization of such delivery systems creates difficulties for pharmaceutical development. This review highlights most of the existing requirements and suggestions from studies to standardize the characteristics of SFFSs and classify them based on scientific sources and regulatory documentation, as well as the position of such systems in the pharmaceutical market. The search and evaluation of known characterization methods and their modifications, as well as the approval of their list (separately for development and for standardization) can potentially increase the research interest in the problem of spray film-forming systems development and contribute to the registration of new drugs and medical devices in this promising dosage form, including with its own pharmacological effect.

Contents

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1. Introduction

Currently, the therapy of wound and skin infections is evolving and becoming more effective through timely medication-related care. Rationalization of therapy can be achieved by improving compositions and using local delivery systems. In modern society, scratches, cuts, abrasions, burns and other localized injuries with skin lesions, which can lead to contamination and subsequent infection, are neglected and prevention of skin infections requires adherence to therapy (Gennari et al., 2019; Frederiksen et al., 2016). The current wound healing approaches are based on application of tissue grafts and biocompatible materials, including polymers, and for significant injuries often a complex of systemic and local drug therapy and medical devices (Dreifke et al., 2015). Despite the widespread availability of various ways to prevent infection as a consequence of injury, not all dosage forms and medical devices are able to ensure high patient compliance (Demina, 2013).

There is currently a growing interest in the development of innovative dosage forms (DFs) such as spray film-forming systems (SFFS). SFFSs is a liquid carrier with active substances and excipients, sprayed on the skin using gas (aerosol) or not (spray) and forming a transparent film by evaporation of the solvent directly on the skin (*in situ*) (Frederiksen et al., 2016; Pünnel and Lunter, 2021; Umar et al., 2020; Kathe and Kathpalia, 2017).

The variety of terminology used in relation to these delivery systems adds complexity to the processes of pharmaceutical development, standardization and registration. Thus, in the english-language scientific literature, it is common to use the concept of "film-forming spray", but according to USP-NF less than 1151 > sprays and aerosols should be differed due to their properties (spray containers are not pressurized) (Umar et al., 2020; Kathe and Kathpalia, 2017; Pharmacopeial US, 1151). Along with "film-forming spray" to describe the *in situ* systems, spray system on damaged skin with the subsequent formation of the coating film, it is also used the terms "film-forming aerosol", "film-forming system", "spray patch", "liquid bandage", "plastic dressing", "liquid dressing", "wound dressing", "wound bandage", etc. (Pünnel et al., 2021; Kathe and Kathpalia, 2017; Edwards, et al., 2017; Choy, 1954; Li et al., 2014; Eaglstein et al., 2002; Brandstein et al., 1965; Raigorodsky et al., 2006).

It should be noted at once that all spray film-forming systems can be divided into local (or topical) (Frederiksen et al., 2016; Kathe and Kathpalia, 2017) and transdermal (Pünnel and Lunter, 2021). Local SFFSs are used to treat wounds and skin diseases and do not contain penetration enhancers which can lead to systemic effect (Frederiksen et al., 2016).

Unlike transdermal action, the local action on wound surface requires special *in situ* characteristics of the film: mechanical strength and impermeability to large particles, gas and vapour permeability in some cases, mucoadhesion, a certain pH and isotonicity, etc. (Sritharadol et al., 2017). Thus, to ensure proper quality, it is necessary to understand the differences between the types of SFFSs and differentiate their quality indicators.

The advantage of film-forming dosage forms is the ability to improve pharmacokinetics and provide prolonged release in topical therapy (Frederiksen et al., 2016; Kathe and Kathpalia, 2017). The use of aerosol systems for the delivery of film-forming components eliminates the risks of contamination during subsequent storage that remain when using other types of dressings, as well as special devices for application.

Creating an optimal spray film-forming dosage form is a task that has been worked on for more than 70 years. Currently, medical products are widely represented on the market, often offering

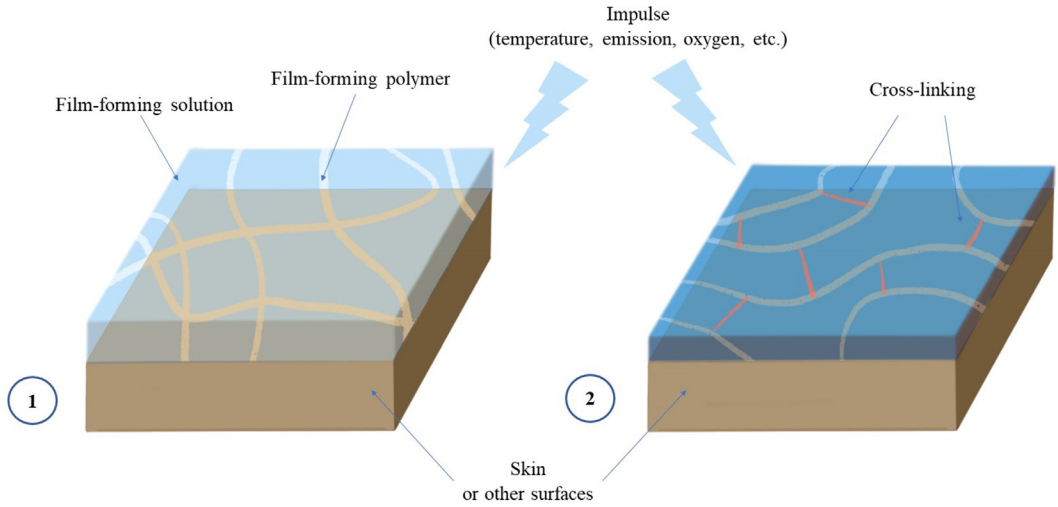

Fig. 1. Cross-linking film formation mechanism.

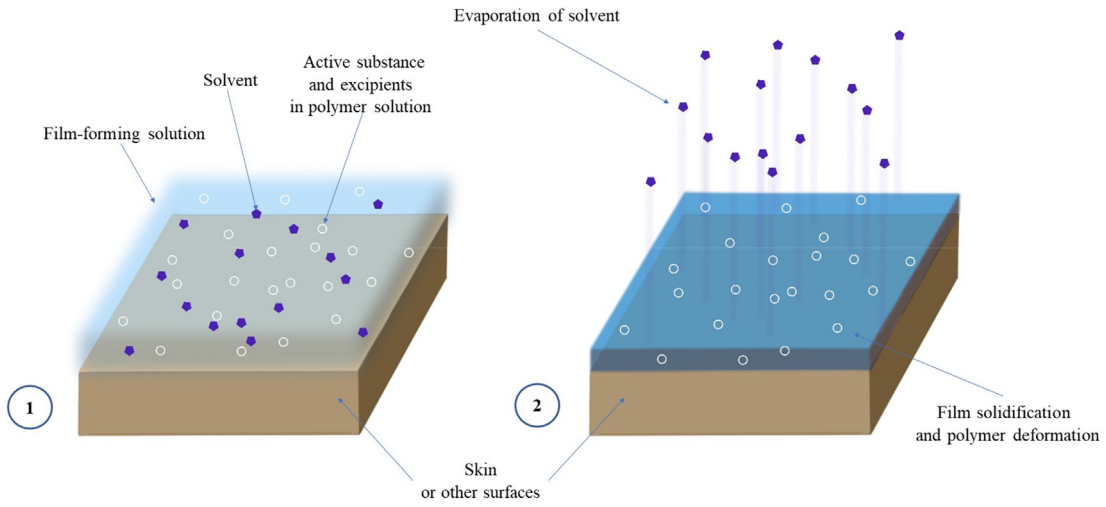

Fig. 2. Evaporation-based film formation mechanism.

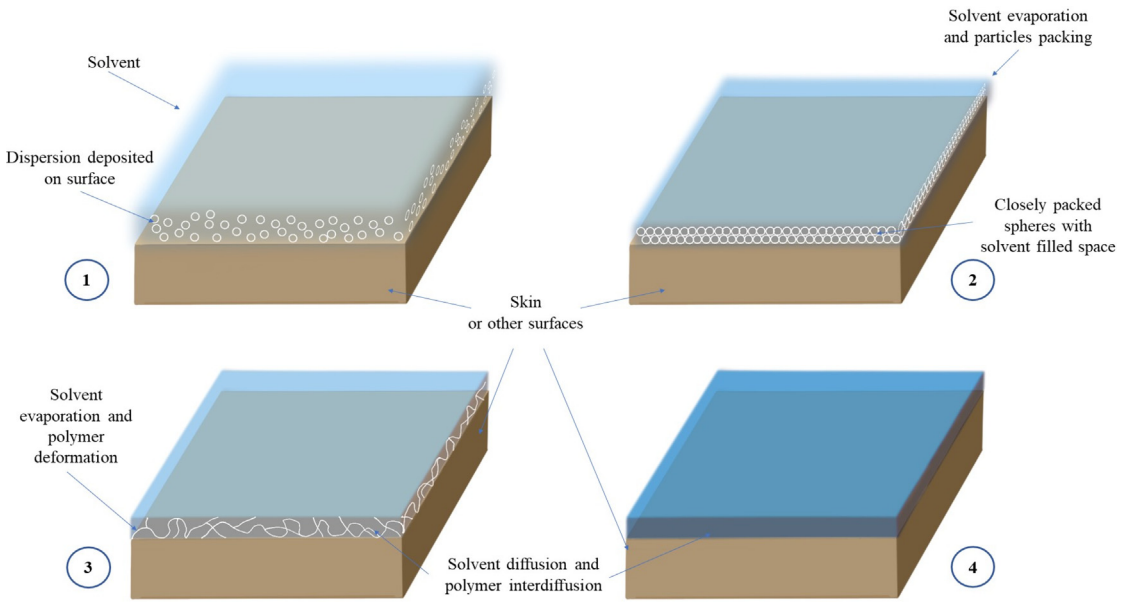

Fig. 3. Coalescence-based film formation mechanism.

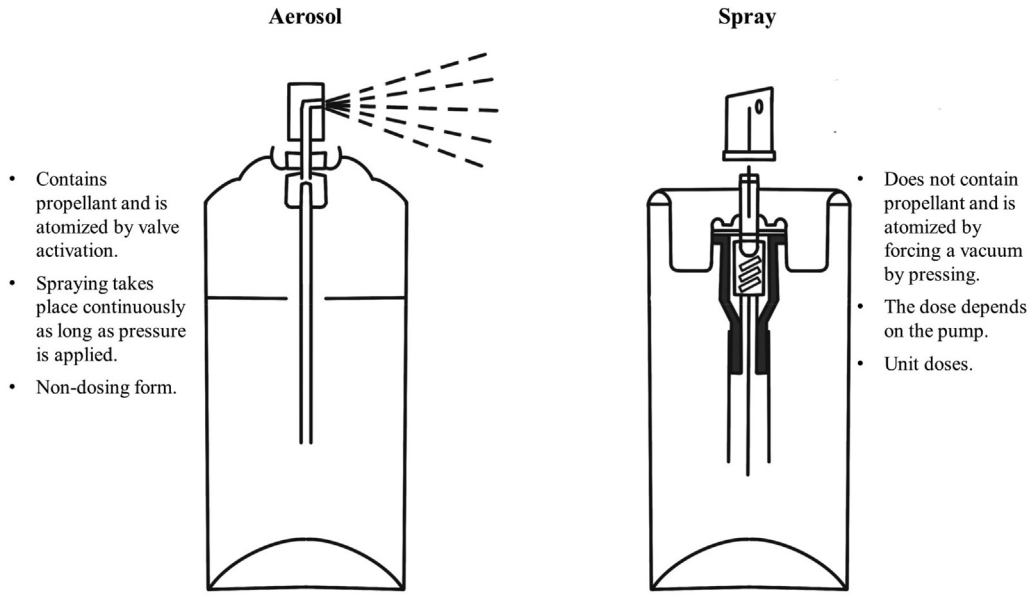

Fig. 4. The differences between sprays and aerosols.

only mechanical protection of the wound surface and containing no active substances (Stepanova et al., 2015; Bromberg et al., 1956; Poulsen et al., 1991; Sukhbir et al., 2013; Nobecutan Sterile Spray Dressing - Dressings / Gauzes And Sutures - Protection And Care Of Wounds In Podiatry - Podiatry Shop, All Kinds Of Podiatric Material - Fisaude Store n.d.). Research is being conducted to develop antibiotic delivery systems in the form of aerosol film-forming systems. However, this measure lags behind the growing threat of antibiotic resistance (Pünnel and Lunter, 2021; Sritharadol et al., 2017; Rob and Eastcott, 1954).

The purpose of this review is to reveal the prospects of pharmaceutical development and the standardization methods of local spray film-forming systems, to clarify the features and to systematize the most valuable information.

2. Film formation mechanisms in SFFSs

There appear to be three film formation mechanisms mentioned in the articles on spray film-forming systems: Cross-linking (Fig. 1), Evaporation-based (Fig. 2) and Coalescence-based (Fig. 3) (Liu et al., 2019; Ahmed et al, 2020; Winnik, 1997; Sanay et al., 2021). Nevertheless, despite the division of these mechanisms, it is clear that they are complementary in some cases, but some take precedence over others. The third mechanism (coalescence-based) is common in tablet coatings. Generally, a water-based dispersion is made and coalescence occurs when the solvent evaporates under the influence of surface-mediated forces. Evaporation-based film formation is associated with high solvent content and low solids content. It is likely that in aerosol spraying the mechanism of film formation relates to coalescence, whereas in spraying via spraying the mechanism is similar to evaporation-based mechanism.

The choice of mechanism, and therefore the spraying system, should ideally depend on the nature of the polymers, but to date this has been little described in the literature, and existing methods are more empirical when it comes to the development of SFFSs.

A different mechanism involves exposure to a stimulus or a third-party substance and cross-linking. It is hardly ever used at the current time in the development of SFFSs, but it is common in other areas and can serve as an alternative to the previous two mechanisms with exclusive coating properties.

Obviously, the films produced from sprays and aerosols have different formation times: a spray contains significantly more solvent, which takes longer to evaporate. The authors indicate different film formation times: sprays have at least 4 min, as a rule (Deshmukh et al., 2022; Wacharalertvanich et al., 2021; Huanbutta et al., 2020), while aerosols have up to 3–4 min (Ranade et al., 2017; Pünnel and Lunter, 2021; Mori et al., 2017) (Fig. 4). Whether this may affect the vapour permeability of the film, which is particularly important for skin breathing and wound surfaces - probably yes. The impact of the propellant is difficult to overestimate.

3. Research retrospective

3.1. The beginning of SFFS development

Historically, revolutionary discoveries in the field of wound therapy are associated with world military conflicts, during which the problem of providing emergency medical care for various types of wounds and burns is particularly acute.

The interest of the scientific community in the creation of atomizing film-forming systems arose worldwide after the end of World War II. The main problem of wound and burn therapy during this period was the prevention of cross-contamination of wound surfaces during surgical procedures using tissue dressings. Different ways to solve the problem have been proposed, both including improvements in dressings and methods of their sterilization, and complete rejection of them, in case of small wound surface treatment. An alternative to reusable dressings were films and adhesives, which, by modern concepts, are *in situ* systems that change their state of matter when applied to the affected area. It has been suggested that film forming liquids to be applied to the wound surface by means of tools such as plastic applicators or brushes made of indifferent material (Rob and Eastcott, 1954; Ellerker, 1955). Derivatives of polyvinyl alcohol, polyacrylates and polyvinyl chlorides were mainly used as film-forming agents (Ellerker, 1955; De Girardier and Aupecle, 1957). Acetone, alcohols, and esters were used as solvents (Ellerker, 1955; Artz, 1960). However, the measures proposed were in some way related to the need for a sterile auxiliary.

3.2. The heyday of aerosol systems

A pioneering approach to therapy of small wound surfaces with film-forming *in situ* systems was proposed in 1954 by Rigler SP and Adams WE. The paper described the use of film-forming aerosol instead of classical medical devices for dressing. This idea, due to the rapid development of aerosol technology around the world, has become extremely popular and timely.

Aerosol systems saw their heyday in the mid-20th century with the invention of the aerosol container in 1927 by Eric Rothheim and the use of the invention by the U.S. Army during World War II for insecticide treatment. After the war, aerosols began to conquer not only the American, but also the European market. The production of paint in aerosol packaging, and then perfumery, cosmetics, and pharmaceutical products has been established since 1949. Aeroplast® film-forming aerosol (USA) had already been developed by 1952, with polyvinyl chloride (PVC) as a film-forming agent and freon as propellant (Choy, 1954). The developed product, a fast-dissolving transparent film-forming dressing, was supposed to be used in the U.S. Army for widespread treatment of burns in natural disasters and emergencies, such as an atomic explosion.

3.3. New solutions and the first trials

In 1964, Hungarian scientists J.Novak et al. described modern approaches to the treatment of burn wounds with a spray preparation, called Plastubol-spray, based on copolymers of methyl methacrylate and butyl acrylate (Novak et al, 1964). The polymer sprayed on the skin surface formed a dense elastic film, tightly adhering to the wound surface. Preclinical studies of the drug were published in 1969 and included 224 cases of experimental animals and clinical patients (horse, cattle, pig, carnivores, and white rat). The studies were carried out on operative wounds, not per primam recovering ones, larger skin discontinuities, burning lesions, artificially infected wound sand such one which had been treated with wound powder. Histopathological analysis has proved that Plastubol-spray does not interfere with the healing and repair of surgical wounds. The product did not show positive results when treating open wounds, large excoriations and burns, further when used together with wound powder, but it was recommended to protect the skin under wounds with extensive excretion, and under fistulas (Kovács et al., 1969).

3.4. New names and new ways

Growing interest in developing spray film-forming systems *in situ* and the lack of timely standardization of the process led to a new term "liquid bandage" appearing in the scientific literature in 1965, describing essentially the previously known film-forming aerosol. Brandstein L. et al. used the term "liquid bandage" to refer to hydrogels that form a film on the wound surface and which viscosity allowed them to be sprayed with an aerosol container (Brandstein et al., 1965). By introducing new terms in the scientific literature describing the rapidly developing spray *in situ* system, it was intended to differentiate preparations according to the strength, elasticity, plasticity of the formed film and, consequently, the degree of protection and cushioning of the wound by the coating. However, a unified system regulating the terminology and characteristics of dosage forms was not approved in a timely manner, which only led to the emergence of new terms and the emergence of difficulties in generalizing the accumulated research results in the future.

Aerosols Lifuzol and Statizol, designed in the 70th in USSR, are similar in their composition to each other (sea buckthorn oil, Nitrofurazone), with identical polymer base polybutylmethylmethacrylate (BMK-5) and containing acetone and freon – 11 and/or –12 as propellants. Films, formed on wound surfaces, provided protection against infection, dryness, they also stimulated tissue regeneration during all phases of wound healing when using in therapy (Raigorodsky et al., 2006).

3.5. New forms and technologies

From the 90th range of delivery means for the film-forming systems began to expand. The trend has gradually shifted from

Table 1
Excipients for spray film-forming systems.

Group of excipients	Requirements	Examples	
Film-forming agents	Low dispersion viscosity for film formation, optimum mechanical properties, uniform, homogeneous and non-sticky film, high adhesion, compatible with all other substances, preferably biodegradable and form a vapour permeable film	• Acrylic acid derivatives (Acrylates copolymers, Eudragit ®); • Cellulose derivatives (carboxymethyl cellulose, hydroxy ethyl cellulose, hydroxypropyl methylcellulose). • Polysaccharides (Gellan gum, chitosan); • PVA, PVP, Lutrols®, Carbomers, Poloxamer®.	Umar et al, 2020; Kathe and Kathpalia, 2017.
Solvents	Non-toxic, fast evaporating, sustainable	• Water, ethanol, isopropanol, etc.	Umar et al, 2020; Kathe and Kathpalia, 2017.
Propellants	Sustainable, disperse if necessary, release the entire composition from the can without losing the dose, compatible with all other substances	• Hydrocarbons (propane, butane, isobutane), • Hydrochlorofluorocarbons and hydrofluorocarbons, • Inert gases (nitrogen, NO2, CO2).	Kar et al., 2019.
Plasticizers	Improves flexibility and tensile strength of a film, but does not result in a significant increase in drying speed or tackiness, compatible with all other substances	Polyethylene glycol 400, glycerin, etc.	Huanbutta et al., 2020
Preservatives	Compatible with all other substances	Benzyl Alcohol, etc.	Kathe and Kathpalia, 2017.
Antioxidants	Compatible with all other substances	Ascorbic acid, EDTA, etc.	Kar et al., 2019.
Permeation enhancers	Do not irreversibly damage the skin, compatible with all other substances,	Propylene glycol, ethanol, etc.	Ranade et al., 2017
Corrigents	Compatible with all other substances	pH corrigents (Buffer solution);Tonicity modifiers (Dextrose, mannitol, etc.)	Kar et al., 2019.

film-forming sprays, popular in the 1970s, to film-forming aerosols and even film-forming foams. The invention of fibrin sealant adhesive systems contributed to the spread of spray systems (Sierra, 1993; Jackson et al., 1996). One such adhesive is currently available as a two-part EVICEL® Fibrin Sealant syringe, which can be attached to a wide range of nozzles. Particularly interesting is the Airless Spray Accessory (ASA) tip, designed for spraying without an external gas source in open surgery, which is controlled by monitoring the pressure and spraying distance (Redl and Schlag, 1986; Evicel - European Medicines Agency. European Medicines Agency n.d). The advantage of this liquid dressing is the high rate of solidification, which is commonly used in surgery.

Meanwhile, *in situ* solidifying Silastic foam dressing was developed and patented, which was prefabricated in a small container of two liquid ingredients and then placed in the wound cavity or on the wound and then solidified (Henn, 1957).

3.6. Towards modern science

To find new solutions for *in situ* spray film-forming systems in wound therapy, modern scientists also turn to retrospective studies. So, in the early 2000s, interest in the Nobecutan drug arose again in Europe, the development of which began in 1953 in Sweden (Ellerker, 1955). The drug was an aerosol for topical use, forming an elastic film after application to the wound. The composition included antibiotics, antiseptics, disinfectants. However, in subsequent studies (Henn, 1957), no antiseptic effect was observed after the film dried, and that, in fact, shows the ineffectiveness of the drug using these active substances *in situ*. The introduction of tetramethylthiuram disulfide (TMTD) into the spray system was proposed as an alternative.

In 2012, the laboratory of INIBSA S.A. (Spain) announced the release of an updated composition based on polymethacrylate in an aerosol package called Nobecutan®. The excipients included acrylic copolymer, ethyl acetate, tetramethylthiouram disulfide, and dimethyl ether (propellant). Thiram was used as the active ingredient, which was previously highly appreciated as an antibacterial agent against Staphylococcus aureus with multiple drug resistance (Long, 2017). The aerosol was used to treat traumatic wounds, mild burns, resorption of sutures and scars.

Nobecutan® was approved as a drug, but today its license has been suspended by the Spanish Agency of Medicines and Medical Devices.

One of the latest solutions that changed the current state of *in situ* film-forming systems development was the discovery of photopolymerization-induced phase transition (Faucher et al., 2010). In this method, polymerized semi-interpenetrating network are applied by spraying and undergo subsequent photopolymerization *in situ* with ultraviolet light at a wavelength of 365 nm using a Clearstone Technologies CF1000 LED controller, which increases the ability of the film to cover a large surface of the body. It does not allow the patient to use these films independently outside the hospital.

4. Excipients for SFFSs

The following groups of excipients can be distinguished: film-forming agents, solvents, propellants, plasticizers, preservatives, permeation enhancers, corrigents if necessary. They are subject to certain requirements in order to achieve an effective and safe dosage form during development. The Table 1 highlights some of the excipients that are used or have the potential to be used and the requirements for them in the creation of SFFSs.

5. In vivo studies

5.1. The 1950s

One of the first clinical studies on the effectiveness of film-forming aerosols was conducted in 1954 in The Third Surgical Division, Bellevue Hospital (New York, USA) for the Aeroplast® (polyvinyl chloride base). The study involved 50 patients with skin lesions of varying severity from the first-degree to the third-degree burns, or with donor areas of skin grafts, which were considered equivalent to second-degree burns, or other types of surgical lesions. All wounds were treated according to routine surgical practice. Aeroplast® was applied by spraying or direct application to the lesion using a piece of gauze on straight forceps or a sterile applicator. In all cases, an area of normal skin from one to two inches was used. The authors made the following observations during the study: Aeroplast® can be applied very quickly; in first and second degree burns there was a pronounced subjective pain relief (after the initial acute tingling sensation passed with the evaporation of ethyl acetate solvent which usually lasted from 30 to 45 s), and Aeroplast® transparency allowed to detect infections at an early stage. The authors emphasized the successful use of Aeroplast® on the abdominal wall, visibly damaged by the ileostomy: the patient quickly noted a relief of discomfort, and after 24 h the abrasions disappeared by 80 % (Choy, 1954).

In 1955, safety studies of Aeroplast® film-forming aerosol in the Chicago Municipal Tuberculosis Sanatorium showed no local irritant effect of the drug (Lees et al., 1955). In the process of the clinical use of Aeroplast®, it was observed that the film has a bacteriostatic effect. Therefore, confirmatory in vitro tests were performed (Choy, 1954). Subsequent in vitro studies not only confirmed the bacteriostatic effect of Aeroplast® and the impermeability of the film, but also noted bactericidal properties in the experiment with bacteria E. coli, B. subtills and B. proteus (Bromberg et al., 1956). However, it was noted that Aeroplast® becomes an obstacle to the recovery of normal skin microflora due to its own bactericidal and bacteriostatic effect.

The need for absorbent action of the wound dressing in some cases led to the practical recommendation of simultaneous use of Aeroplast® with a single-layer sterile gauze containing a cellulose topper (Choy, 1954; Bromberg et al., 1956; Rigler and Adams, 1954). The drug was proposed to be applied to the wounds with a thin layer, and a rectangular piece of gauze was placed on top until the wound exudate was completely absorbed. A multilayer dressing was used for the wound treatment later on, where layers of the film-forming drug were alternated with a single-layer dressing material.

5.2. The 1970s

In the mid-70 s clinical studies of the Plastubol® drug, described earlier, were continued in the USSR in the N.V. Sklifosovsky Research Institute for Emergency Medicine (Moscow). The data obtained showed the advantages of Plastubol® in the treatment of third-degree and fourth-degree burns wounds in comparison with traditional dressings. Depending on the etiology and severity of the wounds, healing lasted about 20–30 days (Vinogradova et al., 1975). Due to the low vapour and gas permeability of polyacrylate and its copolymers compositions, the normal course of oxidation–reduction reactions was disrupted under the film. Besides that, abundant exudation and infection of wounds with sharp slowdown in the process of their epitalization up to 30 and even 40 days were observed. Therefore, not only Plastubol® but also all subsequent aerosol compositions based on polyacrylate

and its copolymers to varying degrees are not devoid of these drawbacks and have not found wide application.

5.3. The 1980s and 1990s

From July 1987 to December 1988, a prospective randomized trial was conducted in the Emergency Department at Esbjerg Central Hospital in Denmark, using a film-forming spray Opsite® (polyurethane) and a gauze dressing Jelonet® impregnated with paraffin (Poulsen et al., 1991). Bandages were applied to burns of various degrees of patients admitted within 6 h of receiving the burn. The wounds were pre-cooled until the pain disappeared and treated accordingly, and then one of the bandages was applied. It was assumed that moisture on the wound should provide improved epithelization. The results showed that satisfaction with both types of dressings was comparable (96 % on polyurethane film and 80 % on gauze), exudate aspiration was performed once in two patients and twice in one patient, but in most cases the exudate seeped out from under the dressings. There was no statistical significance in the seepage of exudate from wounds covered with various dressings in cases where the wounds were less than 1 %. When a wound infection appeared (in 3 patients), none of them developed sepsis as a result. Burns treated with polyurethane film healed in an average of 10 days, whereas when treated with a gauze bandage, on average 7 days ($P > 0.05$). Residual scars were observed in 21 % of patients whose wounds were treated with polyurethane film, and in 8 % of patients treated in the traditional way ($P > 0.05$) (Poulsen et al., 1991).

In the mid-90 s in the Russian Federation (Cherednikov et al., 2016) under the supervision of Cherednikov E.F. and Parkhisenko Y.A. studies were conducted on the effectiveness of *in situ* spray systems with endoscopic application using syringes for Lifusolum, Statisolum, Gastrosolum, biological adhesives MK-6, MK-8 and others. It was shown that the drug injected under pressure with a needle-free injector provided reliable hemostasis due to the formation of hemostatic infiltration in tissues and specific adhesive fillings. Also, as a result of the study, it was demonstrated that such compositions do not have sorption properties, but have a water-repellent effect, film-forming polymers have local hemostatic properties and, in addition, ulcers after treatment form a rough scar, which limits their use in endoscopy.

5.4. The 2000s

In 2000, a study of the barrier film-forming system *in situ* to prevent the formation of pressure sores in patients with spinal cord injury conducted in St. Joseph's Health Centre (Ontario, Canada). 33 patients were included in the study. The film-forming system was applied using an aerosol or a brush. Redness decreased in 96 % of patients of high-risk group. Maceration was prevented in 94 % of patients, and skin removal was prevented in 100 % of patients. Regardless of the method of application, high compliance of patients and medical staff of the therapy was noted. Based on this clinical trial, the feasibility of using a film-forming *in situ* system as a skin protective agent was proved (Campbell et al., 2000).

In 2002, a randomized controlled trial describing a spray film based on octyl-2-cyanoacrylate was published. At the time of the study, it was approved by the FDA, so this study became post-marketing. Earlier, in animal studies, a more flexible composition of octyl-2-cyanoacrylate, suitable for cuts and abrasions, resulted in faster wound healing compared to traditional dressings. The study enrolled 162 patients with recent minor cuts or abrasions and were randomly assigned to treatment with either a spray film-forming system or a control product (Band-Aid brand, clear, 2.5 cm). At day 12th (primary control point), there was no difference between the number of fully healed wounds in the two patient groups ($P = 0.493$), but this result is barely statistically significant. The authors noted that the octyl-2-cyanoacrylate-based spray film provided significant hemostasis ($P = 0.0001$) and pain relief ($P = 0.002$) in patients.

In recent years, clinical studies of liquid *in situ* film-forming systems have continued. In most of the studies conducted, liquid formulations are applied by medical personnel using an applicator or brush, which, however, does not exclude the possibility of using spray dosage forms for non-contact application in the future.

5.5. The 2010s

In 2015, in a study by specialists from Stony Brook University (New York, USA), the use of a cyanoacrylate-based liquid dressing demonstrated efficacy and safety in a single-center prospective incomparable study among adult emergency department (ED) patients with minor nonbleeding skin abrasions and class I and II skin tears (Singer, et al., 2015).

Recently, use of natural ingredients with regenerative effect in the composition has become quite popular. In study conducted by Jin Ju Park et al. (Republic of Korea, 2019) a liquid bandage prepared with cellulose powders from dryed *Styela clava* tunics and *Broussonetia kazinoki* bark showed accelerated healing of surgical wounds in rats by stimulating re-epithelialization and connective tissue formation without any accompanying toxicity (Park et al., 2018).

6. Lack of harmonization in terminology

6.1. Prevalence

As already mentioned, at least ten terms, more often consisting of two words, are currently used to describe the drug delivery system under consideration, according to PubMed.

The first part of the term usually describes the method of application (aerosol; spray) or the primary state of aggregation of the system preceding the phase transition *in situ* (liquid), that is actually describes the dosage form. An exception to this rule is the terms characterizing the structural and mechanical properties of the final film formed *in situ* "plastic dressing" (1.4 %) or the place of application of the dosage form as "wound dressing" and "wound bandage" (8.5 % and 4.2 %, respectively). The terms "wound dressing" (8.5 %), "wound bandage" (4.2 %) are also used by some researchers to describe *in situ* systems, in addition to their direct meaning, classical dressings applied to the wound, which are not dosage forms or drug delivery systems (Ellerker, 1955).

The second part of the term describes the type of system after a phase transition, removing from the primary packaging or application to a wound or burn surface. To describe the final type of delivery system in which it performs a pharmacological effect, the terms "film" (18.3 %), "dressing" (44.4 %), "bandage" (35.2 %), "patch" (1.4 %), as well as "glue" (2.8 %) are used. Each of these terms has its own meaning when used in medical and pharmaceutical literature. However, when using it to describe *in situ* delivery system, the classical generally accepted meaning of the term is distorted.

In some works (Park et al., 2018; Dai et al., 2015; Chen et al., 2020), the use of terminology characteristic of dressings ("bandage", "dressing") is conditioned by the need to emphasize in this way the structural features of the form formed *in situ*. Often such systems have the final appearance of a dense, durable, rigid coating that is applied to the wound surface for a long time (up to 7 days) (Thomas, 1993; Bastos, et al., 2020). However, quite often the term "liquid bandage", for example, does not carry such a semantic load.

Table 2
Some preparations and products for medical and veterinary use in the form of spray films.

	Title	The dosage form, as the manufacturer calls it	Compound	Application
1	BENEV-Silicone-Spray® (BENEV, USA)	Spray	Water (Aqua), Dimethicone, Phenoxyethanol, Methylparaben, Ethylparaben, Propylparaben, Butylparaben.	A means for medical use. Aerosol film dressing for clean, dry, surgical or superficial wounds. It can be used when fixing a skin flap. Protects the skin from chafing. Quick and easy application. Waterproof. Permeable to air and vapour. Adaptable and elastic
2	Akutol™ (Aveflor, Czech Republic)	Spray	Methylal, Butane, Algin, Propane, Calcium Alginate, Stearal-konium Hectorite, Alcohol Denat., Isobutane, PPG-2 Methyl Ether, Simmondsia Chinensis Seed Oil, Hippophae Rhamnoides Fruit Extract, Aloe Ferox Leaf Extract, Calendula Officinalis Flower Extract, Chamomilla Recutita Flower Extract, Menthol.	A means for medical use. Silicone aerosol gel to accelerate the wound treatment and resorption of hypertrophic scars. The gel-like composition is applied to the wound surface using aerosol with the formation of a monomolecular polymer layer on the surface as a protective layer against the penetration of bacteria and fungal infections. The polymer silicone film provides oxygen access to the wound at the same time and retains the necessary moisture. The aerosol is sprayed on the wound repeatedly in thin layers until the desired treatment result is obtained, if possible.
3	3M™ Cavilon™ No Sting Barrier Film (3 M, USA)	Liquid bandage	–	A means for medical use. It is used for the rapid treatment of minor abrasions and superficial wounds. It covers the injury with a flexible film that prevents access of impurities from the environment and is permeable. The waterproof film prevents the evaporation of moisture from the skin, has high adhesion. Suitable for wound surfaces of a large area. Spontaneous, gradual removal by abrasion after 3–4 days. Easy and quick application, drying in 2 min.
4	Afaplast® (Argofarm LLC, Russia)	Barrier film	Polymers, isopropanol, solvent mixture, panthenol, colloidal silver, propellant.	A means for medical use. Spray film, alcohol-free, terpolymer-based, to protect the skin from mechanical damage. Provides adhesion, allows adhesion of tapes, bandages and attachments. Transparent, permeable for air. After application, a thin, non-sticky, elastic coating is formed.
5	No-Sting Liquid Bandage Nexcare™ (3 M, USA)	Liquid patch	Dexpanthenol, colloidal silver, Hexamethyldisiloxane, Acrylate Terpolymer, Polyphenylmethylsiloxane.	A means for medical use. It is used for disinfecting and accelerating wound regeneration. It does not wash off with water, drying time is 30 s, retains elasticity for a long time.
6	LUXPLAST® (FARMAC - ZABBAN S.p.A, Italy)	Liquid patch	Diethyl ether, acetone, PVM/MA butyl ether copolymer, denatured alcohol, PEN-8, propellants, Olet-3, stearalcone chloride.	A means for medical use. It is used for a variety of minor injuries from cuts to large abrasions. The film dries in 30 s and provides waterproof skin protection, contains no alcohol or preservatives.
7	Pharm-X® Second Skin / Vtoraya kozha Super Farm-KH Sprey (Green Life, Russia)	Spray patch	Methylene chloride, propane, dibutyl phthalate, butane, ethyl acetate, activated aluminum powder, BMK 5.	A means for medical use. It forms a protective water-repellent film on the skin, which promotes rapid healing of cuts, scrapes, abrasions, protects the wound from dirt and bacteria. It has an anti-inflammatory effect. It is convenient for use in hard-to-reach places. It dries quickly, does not constrain movement.
8	Hansaplast Spray Plaster (Hansaplast, Germany)	Spray	Acrylic copolymer, polyurethane polymer, ethanol, water, dimethylether.	A product for veterinary use. It is used for wound healing (depending on the composition of the active ingredients has antimicrobial, anti-inflammatory, antihistamine, analgesic properties). It is used for cuts by holding the edges of the wound, thus avoiding the use of staples and sutures (recommended for cosmetic sutures). It is most commonly used as a colorless patch, preventing the dirt entry and the occurrence of cross-contamination. When applied to the affected area of the skin, it forms a dense, elastic, water-soluble film, which has both breathable and drying properties.
9	Pentazol (Valeo Club, Russia)	Spray patch	–	A means for medical use. It covers the wound with a transparent and elastic imperceptible film, having an antiseptic effect due to the ethyl alcohol included in the composition. Waterproof film.
10	Boots Advanced First Aid Spray Plaster (Boots, UK)	Liquid aerosol dressing	–	A means for medical use. As the wound heals, the dressing comes off easily, without damaging the skin, after 1–2 days.
11	Elastoplast Spray Plaster (Beiersdorf, Germany)	Spray patch	Acrylic copolymer, polyurethane polymer, ethanol, water, dimethylether.	A means for medical use. It dries in a minute, forming a breathable, flexible film that protects against water, dirt and microorganisms, reduces the risk of infection and promotes natural healing.

(*continued on next page*)

Table 2 (*continued*)

	Title	The dosage form, as the manufacturer calls it	Compound	Application
12	Medspray® the Patch-in-a-Can®MedPharm ltd, UK	Patch-in-a-Can	–	A novel transdermal and topical drug delivery tool that can be used to deliver drugs in extended-release form via spray-on-films delivered to the skin or other mucosal or topical membranes. This technology allows enhanced drug delivery into or across the membranes via creating a film.
13	Axiron® Lilly USA, LLC	Topical Solution (Pump Actuated Metered-Dose Pump)	Testosterone, ethanol, isopropyl alcohol, octisalate, and povidone.	A means for medical use for transdermal release. Testosterone Topical Solution is applied to the axilla to clean, dry, intact skin. After applying the solution, patient should allow to dry completely prior to dressing. The solution should not be rubbed into the skin with fingers or hand.
14	Liqui-Patch technology, Epinamics GmbH, Germany	Film-forming technology	–	The Liqui-Patch is easy to apply and forms a stable yet flexible film within 90 s. The invisible film adjusts to any physical activity so that the patient can move around freely. The Liqui-Patch is gentle on the skin. In contrast to traditional patches, there are no reddening or allergic responses to be observed. The Liqui-Patch delivers pharmaceutical ingredients conveniently as a liquid by airless pump spray applicator in a 50 µl volume per actuation. Therefore, formulations can be applied onto much smaller skin surface areas, providing flexible dosing.
16	PharmaDur®Technology	Film forming emulsion-gel	For example, Non-steroidal anti-inflammatory drug (NSAID)	the dried transdermal composition functions as a "virtual patch" without the limitations of plastic patches. Typically once/day or twice/day application of the dose of the transdermal composition are utilized. Transdermally administered drug is absorbed continuously over a prolonged period of time in contrast with a relatively rapid absorption through the GI tract. Thus, sustained lower but effective concentrations of the drug are available in the blood circulation by transdermal administration of the drug.

Thus, some publications (Li et al., 2014; Park et al., 2018) describe delivery systems in the form of liquid bandages, which, after application to the skin and drying, form a thin film.

6.2. Documentation

The FDA (FDA, 2022) defines Liquid Bandage (Title 21, Volume 8, §880.5090) as a sterile device that is a liquid, semiliquid, or powder and liquid combination used to cover an opening in the skin or as a dressing for burns. The device is also used as a topical skin protector.

The State Pharmacopoeia of the Russian Federation (XIV edition, 2018) defines the liquid glue (or skin glue, or liquid patch) as a liquid dosage form that is non-aqueous solutions intended for topical use to obtain a film-forming dressing that has the ability to adhere to the skin after evaporation of volatile solvents.

Thus, when analyzing modern research and retrospective, there were no significant differences in most of the terms used to describe the system.

Modern international regulatory documentation also does not clarify the correctness of the use and interchangeability of terminology. We have analyzed some of the global major regulatory documents and pharmacopoeias: FDA - U.S. Food and Drug Administration, United States Pharmacopeia (USP), European Pharmacopoeia, British Pharmacopoeia, Japanese Pharmacopoeia, Chinese Pharmacopoeia, The State Pharmacopoeia of the Russian Federation, the Pharmacopoeia of the EAEU (Eurasian Economic Union).

Each regulatory document describes formulations, one way or another with similar properties of aerosol *in situ* film-forming systems: Aerosols for Cutaneous Application (Section 11–3-1), Tapes (Section 11–7-1) in the Japanese Pharmacopoia; Liquid preparations for cutaneous application (01/2008:0927), Patches, transdermal (01/2008:1011), Pressurised pharmaceutical preparations (01/2008:0523) in the European Pharmacopoia; Topical and Transdermal Drug Products (Chapter 3), Aerosols, nasal sprays, metered-dose inhalers, and powder inhalers (Chapter 601) in USP; Solutions (§1.4.1.0011.18), film-forming aerosols (§1.4.1.0002.15), medical plasters (§1.4.1.0009.18) in the State Pharmacopoeia of the Russian Federation and so on.

However, standardization of spray film-forming systems is practically not represented among national pharmacopoeia articles. Even in national documents where there is a mention of the dosage form (Japanese Pharmacopoia, the State Pharmacopoeia of the Russian Federation), tests for specific characteristics of film-forming systems are not provided, but only general criteria for spray dosage forms (uniformity of dosing, tightness, etc.) are given. Standardization of spray film-forming systems according to several pharmacopoeia's articles (for example, "Aerosols, sprays" and "Films" or "Aerosols for topical use" and "Patches") does not take into account all the features of this dosage form, which excludes the possibility of a qualitative assessment.

Thus, the main obstacle to the progress of pharmaceutical development and production of spray film-forming systems is the lack of harmonization in terminology, definition and, consequently, in the standardization of these systems.

7. Pharmaceutical market

To date, more than a dozen drugs and products related to parapharmaceutical and cosmetic, as well as vet products, in the form of spray systems forming films after application, have been regis-

tered in the world (Table 2) (The information is mostly taken from the packages, as not all formulations are available on the internet).

The registered drugs and remedies for medical use have the following forms of release as indicated in the registration: spray patch (4), spray (2), liquid patch (2), liquid aerosol bandage (1), liquid bandage (1), barrier film (1). They are often used to protect hard-to-reach small wound and burn surfaces from mechanical damage and microbial contamination. Some drugs and products (Afaplast®, Pharm-X® Second Skin) include active ingredients that provide antibacterial, disinfectant, wound-healing effects (Liquid plaster Afaplast®; Pharm-X® Second Skin (Green Life)).

Most modern agents in the form of spray film-forming dressings, once applied to the wound surface, form a strong and elastic membrane that provides air exchange and water resistance to the wound. An aerosol can or other spray system is used to apply the drug, and in some cases (3M™ Cavilon™ No Sting Barrier Film) an applicator or a sterile spatula is additionally used for uniform distribution over the area of the wound (3M™ Cavilon™ No Sting Barrier Film).

8. Classification

It is necessary to conduct a comprehensive study of the modern classification of wound dressings, both clinical and technological, in order to understand the positioning of *in situ* spray film-forming systems, the prospects of their development and indications for their use.

Wound dressings in medicine are dosage forms for the treatment of patients with skin damage. Drugs and medical devices of this group remain in great demand in practical surgery. For example, the technique of treating purulent wounds under the dressing is the main one in clinical practice, as it is the most convenient and cost-effective (Vinnik, et al., 2015).

Practitioners and experts still do not agree on a single classification of wound dressings, but general trends stand out.

The types of dressings can be classified by presence of active substances (medicated and non-medicated), absorption capacity, origin (animal, herbal, synthetic), method of application (primary dressings, which are applied directly on the wound, secondary dressings, which are used to cover the primary dressing), interaction with tissues (passive/inert dressings, interactive/bioactive dressings), presence of advanced characteristics (vapour-permeable films, hydrocolloid dressings, hydrogels or fibrous hydrocolloid dressing, polyurethane matrix hydrocolloid dressing), and type of dosage form (film, membrane, foam, gel, composites, and spray) (Stoica et al., 2020; Ghomi et al., 2019; Vinnik et al., 2015; Swezey, 2011; In Guideline for Prevention of Surgical Site Infection, 2017).

Absorbent dressings have the ability to absorb exudate released from the wound, the amount of which can be significant. The composition of such coatings may vary. Alginate (sorption capacity up to 5000 %), cellulose (sorption capacity up to 3400 %), hydrocolloid and capillary dressings are widely used (Ghomi et al., 2019; Westby and Washington, 2017; Shapovalov, 2005).

Barrier films prevent the penetration of microorganisms on the wound surface, and also limit the evaporation of moisture. The main structural element of such coatings is an elastic polymer film. These dressings are conditionally divided into two groups: coatings applied in finished form; coatings formed directly on the wound surface after solvent evaporation. The general principle of creating such finished coatings is to apply a polymer film with controlled vapour permeability to the outer surface of the coating or to seal the outer surface of the coating by hot pressing (Vinnik, et al., 2015; Westby and Washington, 2017; Swezey, 2011).

Non-adhesive (atraumatic) dressings, unlike classic hydrophilic dressings, do not injure the wound when changing ones, due to the hydrophobization of the polymer layer facing inward. However, due to the loose fit to the wound, such coatings can provoke exudate secretion. A special case of such coatings is ***resorbable*** dressings based on exudate-soluble or biodegradable polymers (sodium salt of carboxymethyl cellulose (CMC), oxyethyl cellulose, amylose, dextran, alginates, chitin, chitosan, hyaluronic acid, etc.) (Vinnik, et al., 2015; Stoica et al., 2020; Westby and Washington, 2017).

The therapeutic effect after the use of wound dressings is due not only to their mechanical and physico-chemical properties, as well as the pharmacological effect of some constituents (ethyl alcohol, chitosan, hyaluronic acid, collagen), but also to the ***active substances***. Iodine, povidone-iodine, chlorhexidine, methyluracil, colloidal silver, medical honey, sea buckthorn oil, etc. are introduced into the composition as active ingredients (Stoica, 2020; Westby and Washington, 2017; Guideline for Prevention of Surgical Site Infection| Infection Control).

It should be noted that while there is a variety of practical and clinical classifications of wound dressing, there is virtually no technological classification that would optimize the processes of developing and standardizing these systems.

Based on the analyzed publications, wound dressings according to the methods of their preparation and technological properties can be divided into *finished (dosage form)* and *formed on the wound in situ*. ***Finished*** wound dressings generally include such dosage forms as films, patches, sponges, tampons, lotions, as well as dressings treated with liquid, soft or solid dosage forms. The dressings ***formed on the wound*** are formed as a result of solvent evaporation. Initially, they are in liquid form and can be applied to the wound surface using a sprayer or applicator (brush, spatula, etc.). The final form of such coatings can be dosage forms of sponge, film, glue or even a bandage.

Thus, the *in situ* spray film-forming systems, that were examined in this review, can play a significant role in modern clinical practice of skin lesion therapy since, depending on the composition and final form, they can perform the functions of all the mentioned above wound dressings (adsorptive, barrier, atraumatic, with active substances).

To differentiate *in situ* spray film-forming systems, according to world practice (as, for example, for soft dosage forms), it can be proposed to use factors of consistency of the final form and the associated functional and purpose of wound dressings. *In situ* spray film-forming system should be divided into three groups: ***dense***, ***plastic*** and ***soft***. Dense film-forming systems are hard and durable (for example, a sponge or bandages), and they are designed to perform a protective, locking, cushioning or adsorbing functions. Plastic film-forming systems, on the other hand, are elastic, flexible and have medium-density (e.g., alginate or chitosan film). Their component compositions allow this type of systems to perform a protective function, self-absorb, carry active substances and perform pharmacological effect. Finally, there are soft film-forming system which are thin with low density and high adhesiveness to the surface. These systems are designed for temporary protection and isolation of minor injuries, scratches and abrasions, including those at the bends.

9. Discussion

Researchers involved in the development and study of film-forming systems note their numerous advantages. Kathe K. and Kathpalia H. emphasize prolonged action, possibility of constant control due to transparency, possible evaluation characteristics of the finished film, as well as numerous options for varying the com-

Table 3
Parameters of standardization of spray film-forming systems.

Parameter	Type of parameter	Phase to control (monitoring phase)	Sources
Drying rate	Obligatory	liquid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Zurdo Schroeder et al., 2007;Gohel and Nagori, 2009;Sangnim et al., 2022; Huanbutta et al., 2020; Mori et al., 2017
pH	Obligatory	liquid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Gohel and Nagori, 2009;Bakkiyaraj et al., 2017;Chamsai et al., 2022
Viscosity / Reology	Obligatory	liquid	Sritharadol et al., 2017;Zurdo Schroeder et al., 2007;Gohel and Nagori, 2009;Ranade et al., 2017;Sangnim et al., 2022;Huanbutta et al., 2020;Chamsai et al., 2022
Density	Obligatory	liquid	Sritharadol et al., 2017;Bakkiyaraj et al., 2017
Surface tension and contact angle	Additional	liquid	Sritharadol et al., 2017
Mucoadhesion	Obligatory	liquid	Gohel and Nagori, 2009
Aerodynamic particle distribution	Obligatory	dispersal	Sritharadol et al., 2017;Bakkiyaraj et al., 2017
Spray structure / spray angle	Obligatory	dispersal	Gohel and Nagori, 2009;Bakkiyaraj et al., 2017;Ranade et al., 2017;Bakshi et al., 2008
Package Tightness / Pump seal efficiency (Leakage Test)	Obligatory	dispersal	Gohel and Nagori, 2009;The State Pharmacopoeia of the Russian Federation. XIV edition, Volume 2, 1.4.1.0011.18 Solutions
Minimum Fill	Obligatory	dispersal	Pharmacopeial US (USP). 1151
Pressure Test	Obligatory	dispersal	Pharmacopeial US (USP). 1151
Moisture content	Additional	solid	Sritharadol et al., 2017
Thickness	Obligatory	solid	Sritharadol et al., 2017;Chamsai et al., 2022
Elasticity	Additional	solid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Ranade et al., 2017
Washability / water resistance	Additional	solid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Ranade et al., 2017
Transparency	Additional	solid	Gohel and Nagori, 2009;
Strength / breaking strain	Obligatory	solid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Sangnim et al., 2022;Huanbutta et al., 2020
Vapour permeability / Gas permeability / Moister permeability	Additional	solid	Umar et al, 2021;Sangnim et al., 2022
Stickiness	Additional	solid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Zurdo Schroeder et al., 2007
Quantitative determination	Obligatory	liquid	Sritharadol et al., 2017
Sterility / Microbiological purity	Obligatory	liquid	European Pharmacopoeia 2.6.1. Sterility; The State Pharmacopoeia of the Russian Federation. XIV edition, Volume 2, 1.4.1.0011.18 Solutions
Dosing Uniformity / content in one dose	Obligatory	liquid, solid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Bakshi et al., 2008
Delivery Rate and Delivered Amount	Obligatory	dispersal	Pharmacopeial US (USP). 1151
Visual uniformity / pattern / integrity on the skin	Obligatory	solid	Sritharadol et al., 2017;Zurdo Schroeder et al., 2007
Local effect on the skin / allergenicity / skin irritation	Obligatory	liquid, solid	Pünnel and Lunter, 2021;Sritharadol et al., 2017;Bakkiyaraj et al., 2017
Aesthetic appearance	Additional	solid	Pünnel and Lunter, 2021;Zurdo Schroeder et al., 2007; Sangnim et al., 2022
Permeability of the stratum corneum, dermis / systemic effect / kinetics of drug transport / transport of active substances / release of active substances	Obligatory	liquid, solid	Frederiksen et al., 2016;Pünnel and Lunter, 2021;Stepanova et al., 2015;Gohel and Nagori, 2009;Ranade et al., 2017
Stability	Obligatory	liquid, solid	Sritharadol et al., 2017;Gohel and Nagori, 2009

position to achieve the desired density, strength, and elasticity of the resulting final form (Kathe and Kathpalia, 2017). Umar et al. noted improved dosing of spray film-forming systems in comparison with other topical and local SFFSs (Umar, et al., 2020).

Clinicians also note that gel film dressing formed directly on the wound surface have many advantages: transparency, tight contact with the wound, preventing the accumulation of exudate, and painless removal. However, as Shapovalov S.G. noted in his work, in practice such coatings are often ineffective due to low mechanical strength, tendency to dry out, low sorption capacity ((Shapovalov, 2005).

The dissatisfaction of some practitioners with spray film-forming systems can be explained by the lack of clear clinical guidelines for the use of these systems as well as skin irritation, product odor, and insufficient or excessive film-skin adhesion. Of course, *soft* and *thin* spray films are not able to cover a large area of the affected surface, to perform cushioning and adsorbing functions, as sponges or dressings. However, they are excellent for application to joint bending areas (finger phalanges, knees), as well as to hard-to-reach areas of the body, without limiting the mobility and functionality of the patient. In this sense, water-resistant and resistant to mild friction film dressings have undeniable advantages over conventional plasters. The simplicity of the technology of introducing the active substances in such systems allows them not to limit their scope of application only to wound therapy, but to be used in local allergic reactions, insect bites, atopic dermatitis, etc.

To solve problems of sorption of a large volume of exudate, mechanical protection and cushioning (for example, in the treatment of bedsores) it is advisable to use dressings ***dense*** and ***plastic*** (medium and high density). After dosing using a spray system, highly adsorptive sponge coatings, aerogels and solid foams can be formed on the wound surface (Thomas, 1993; Brumberg et al., 2021).

As mentioned earlier, the exposure time of the spray film-forming system can vary over a wide range (from a few hours to 7 days), depending on the consistency of the final form, its constituent polymers (Bastos, et al., 2020). Thus, film-forming systems

in general, as a dosage form, can be a versatile solution for clinical practice, providing the ability to choose the density of the formed coating, depending on the purpose.

9.1. Standardization parameters

Standardization parameters of spray film-forming systems should be carried out both before and after the phase transition, which is typical for all *in situ* systems. Most authors describing the development of spray films distinguish mandatory (included in the specification for the dosage form) and additional (screening parameters determined at the development stage for a pool of formulations) standardization parameters distributed between the liquid/spray and solid phases of the delivery system (Table 3).

9.1.1. pH

The pH value of the film-forming liquid is measured and regulated in order to increase the stability of the substances included in the composition, as well as for some additional therapeutic purposes. For example, the optimal acidity of the solution will vary in the range of values from 4 to 6, for diabetic wounds the range will be from 6.5 to 8, but for the treatment of thermal injury the optimal pH value will be lower than 7.32. The pH value can not only affect the healing time of the wound surface, but also improve the properties of permeability through skin barriers during transdermal delivery (Kathe and Kathpalia, 2017; Gohel and Nagori, 2009; Ranade, et al., 2017; Bakshi, et al., 2008; Reish et al., 2009).

9.1.2. Isotonicity

Isotonicity of the solution can be considered an additional characteristic of the film-forming system. It depends on tonicity required on the place and purpose of application to certain affected areas, such as wound surfaces, mucous membranes. Non-isotonic drugs can cause irritation of the mucous membranes and pain. For this reason, the tonicity of drugs can be calculated and adjusted, for example, according to the Kahara method (Umar et al., 2020).

9.1.3. Viscosity, density

The physical properties (viscosity, density) of the film-forming liquid are determined according to accepted pharmacopoeia methods. The rheological parameters of the liquid have a direct effect on the uniformity of dosing, the spray torch of the disperse system, the uniformity of distribution on the skin surface and, as a consequence, the quality of the film formed *in situ* (Pharmacopeial US, 1151).

9.1.4. Surface tension

For the same purpose, the surface tension and the contact angle are determined (Sritharadol et al., 2017; Bakkiyaraj et al., 2017). The determination of the surface tension seems to relate exclusively to the film formation mechanism associated with solvent evaporation; thus this parameter is more necessary for standardisation and description of the properties of sprays than aerosols. The surface tension may affect the distributivity of the solution as well as the evaporation rate of the solvent. It is most popular to surface tension angle with surface tension analyzer or high-level cameras and then calculate in special or general-purpose software (e.g. Digimizer (Digimizer – contact angle tool, 2022), ImageJ, etc.).

9.1.5. Minimum fill or package tightness

Since the delivery systems under consideration are disperse, their standardization parameters have to include characteristic of sprays and aerosols – the package tightness/pump seal efficiency (aerosols), minimum fill, pressure test, delivery rate and delivered amount, the aerodynamic distribution of particles (Pharmacopeial US, 1151; The State Pharmacopoeia of the Russian Federation, 1.4.1.0011.18 Solutions; Gohel and Nagori, 2009; Ranade et al., 2017). The angle of spraying, the shape and distribution of droplets by size, and the spray pattern are described less frequently (Gohel and Nagori, 2009; Ranade et al., 2017; Bakshi et al., 2008).

9.1.6. Mucoadhesion

Mucoadhesion of the film-forming liquid determines the most important indicators of the delivery system, such as the local application ability, duration of exposure, and directly affects the characteristics film formed *in situ* such as thickness, uniformity, film-forming rate. It is important to note that measuring methods for mucoadhesive properties are insufficiently described in studies devoted to the development of spray film-forming systems (Kathe and Kathpalia, 2017; Gohel and Nagori; Bakshi et al., 2008; Kirzhanova et al., 2014; Queen et al., 1987). At the same time, at least a dozen reproducible validated methods for determining this indicator are currently known, including both *in vivo*, *ex vivo*, and in *vitro* methods (Kirzhanova et al., 2014; Palvinskiy et al., 2020). The profitability of *in vivo* studies of mucoadhesion may be high for the motivation of the authors to conduct full-fledged studies in this area. For a comparative study of mucoadhesive properties in a pool of samples during screening, it is advisable to use models with purified mucin (for example, mucin from porcine stomach) and polymer membranes with standardized parameters (moisture content, adsorption capacity, pore size, etc.). Based on these parameters, various models are constructed (to determine the separation force, flow rate, etc.), depending on the intended location and nature of the system application. There is information about the development of reproducible, correlated with *in vivo* methods for determining the mucoadhesive properties by rotational viscometry (Graça et al., 2018; Hombach et al., 2010; Karimunnisa and Atmaram, 2013).

9.1.7. Film formation

The film formation and its evaluation can be performed both in vitro (on glass surfaces, standardized membranes, nonwoven fabrics, etc.), and *in vivo*. Both methods have advantages and disadvantages.

Film formation *in situ* is influenced by parameters such as the place of application, the surface temperature of the skin, its moisture content, the state of the epidermis, humidity and ambient temperature, etc. The authors of most studies, when assessing the drying rate and other characteristics of the film, use different application zones when evaluating *in vivo*, for example, applying a dose to the arms, shoulders, inner thighs or abdomen before the formation of a thin bioadhesive film on the skin (Kathe and Kathpalia, 2017). The variability of these factors take place in the aspect of the use of the drug, however, it is undesirable for the screening method and an objective assessment of the sample pool.

In vitro methods have great simplicity, reproducibility and, as a result, popularity in the evaluation of film formation. Kathe K. and Kathpalia H. describe that films were formed in a Petri dish. In this case, glass was chosen as the test surface, and some authors believe that this material can be comparable to human tissue (Kathe and Kathpalia, 2017). At the same time, it should be noted that the formation of the film *in situ* occurs on a heated (normally up to 32 °C, with pathology up to 35–37 °C) surface having its own moisture level. This adjusts the drying process reproduced on the glass surface. To increase *in vivo*/in vitro correlation, it can be recommended to use a membrane or non-woven coating to cover a glass plate, as well as to perform an experiment with temperature regulating using a thermostat.

None of the considered studies SFFSs were not mentioned studies *ex vivo*, indicating that their low prevalence in this area of

development, in spite of all the advantages of this method such as high representativeness, close to real conditions of application to the mucous membrane or wound surface, no need to appeal to the ethics Committee, which undoubtedly increases the development time and reduces the profitability of production in a sence (Kathe and Kathpalia, 2017; Bromberg et al., 1956; Westby and Washington, 2017; Kirzhanova et al., 2014).

9.1.8. Moisture content

The moisture content of the formed film is evaluated to fix the end of the process of its formation and determine the exact drying time. Pharmacopoeia methods (gravimetry) and available hardware (moisture meters, humidity analyzers) are used to study humidity. A stickiness test can also be considered convenient and cost-effective for determining the end of film formation. Some authors (Kathe and Kathpalia, 2017) recommend a separation test. When drying, if cotton wool is applied to the film, the cotton wool fibers will not remain. This indicates that the film has finally hardened.

With excessive drying of the film, loss of elasticity and injury to the damaged skin by solid particles of the film is possible, therefore, moisture assessment is possible in dynamics.

9.1.9. Thickness

The thickness of the film is determined using special measuring instruments after its separation from the surface. It should be noted that in order to evaluate the parameters of the final state *in situ* of the system, it is necessary to separate the formed film from the surface, which was not achieved by researchers for all compositions being developed. However, in our opinion, these tests are mandatory, especially for films that were formed in vitro (for example, on a glass plate). If it is not possible to separate the formed film from the surface and determine its mechanical and other properties, it is difficult to predict its behavior *in vivo* and the compliance of patients with therapy using it.

9.1.10. Morphology

The morphology of the film can be studied by scanning electron microscopy or transmission electron microscopy. The microscopic shape, surface roughness and uniformity of the film are evaluated (Ranade et al., 2017). The uniformity of the film is characterized exclusively by a visual description of the pattern, gloss, etc. Some studies (Kathe and Kathpalia, 2017; Bakshi et al., 2008) describe *in situ* spray film-forming systems, the film coating of which can hardly be determined visually. For such developments, the described quality indicators concerning the properties of the film are not applicable. In such cases, to prove the effectiveness of the wound surface dressing, it is necessary to develop and implement tests that clearly demonstrate the protective functions of the pharmaceutical composition.

9.1.11. Strength

The strength of the separated film is determined using texture analyzer or in experiments for breaking under the action of the weight of the load (Sritharadol et al., 2017). Along with the strength of the film, it is possible to measure the elongation and elasticity of the film using various techniques (Ranade et al., 2017).

9.1.12. Flexibility

The flexibility of the film correlates with elasticity. The flexibility parameter is usually measured by skin tension. Some authors describe the possibility to determine this characteristic *in vivo* by stretching the skin in 2–3 directions; the film will be considered flexible if there are no cracks in the film or skin fixation disorders (Kathe and Kathpalia, 2017).

9.1.13. Stratum corneum, dermis / systemic effect / kinetics of drug transport / transport of active substances / release of active substances

Although topical systems are discussed, it may be important to establish the presence of transdermal action. In contrast to local action, transdermal action is concerned with the passage of active ingredients through the dermis into the systemic circulation (European pharmacopoeia). There are different mechanisms for dermal passage: both chemical and physical. The active substance molecule must be lipophilic (no more than logP = 1–4), the mass must not exceed 500 Da, and the molecule must be neutral (Frederiksen et al., 2016; Ng, 2018). Obviously, even such strict criteria for the active ingredient molecule are not sufficient for transdermal absorption. Penetration Enhancers are added to the dosage form, affecting the skin through various mechanisms, e.g. down hair follicule, across stratum corneum and down sweat glands (Ng, 2018). In the trans epidermal pathway, low molecular weight substances can pass through and between epidermal cells. The trans follicular pathway allows for the passage of larger molecules, but the number of follicles depends on the individual and they do not cover the entire surface of the skin, which reduces the passage of the active substances (Punnel and Lunter, 2021). However, properties of excipients can also increase permeability. For example, the use of polymers and their application methods that create occlusion can increase skin permeability. In addition, there are other technological techniques that can increase the passage of active ingredients through the skin, such as comminution the active ingredients or creating microemulsions and nanoemulsions (Souto et al., 2022). The safety of the methods depends directly on the skin's ability to restore the natural barrier, e.g., protein denaturation is a destructive method, a priori incapable of being safe.

Local or topical action is intended to either intact or damaged skin, but the aim is not to deliver active substances into the systemic circulation. It is logical, but contentious, that the active substances of such preparations should not enter the systemic circulation, and that their passage into the circulation should be controlled if the skin is damaged. Since the underlying layers of the dermis are less lipophilic, the stratum corneum becomes a reservoir for the active ingredients and they are prolongedly released from this layer (Punnel and Lunter, 2021).

In spite of this, when SFFSs are discussed, it is worth considering both topical and transdermal preparations, as the placebo composition of the excipients may or may not have an effect on enhancing the permeability of the components. Thus, a placebo prototype preparation for topical application could theoretically also serve as a composition for transdermal application. However, the requirements for the final films will differ in terms of physical and chemical properties, so it is rational to consider predominantly topical preparations.

9.1.14. Water washability

Many authors also propose to determine water washability, or erasability with moisture, which can be determined using cotton swabs (Ranade et al., 2017). The ease of wetting the film can be assessed by the dried film. The film is washed with water, and then evaluated using a scale: easily erased, moderately erased and poorly erased (Gohel and Nagori, 2009).

9.1.15. Gas and moisture permeability

Characteristics of gas and moisture permeability are also controversial among the researchers. The presence of these properties in the film, in addition to its hydrogel base, creates a moist environment on the protected surface, which increases regeneration and significantly reduces subsequent scarring of the wound (Reish et al., 2009). The gas permeability of the coating is necessary for tissue regeneration (Li et al., 2014).

The characteristics of the gas and moisture permeability of the coating formed strongly depend on the purpose of the composition. Li Z et al. in 2014 developed a film-forming solution with which tissue oxygenation can be determined *in situ* (Li et al., 2014). Thus, they created a film-forming solution, which is designed not to be gas permeable on its own but serves as a tool for measuring the gas permeability of the wound surface (Li et al., 2014).

Studies of diffusion and moisture permeability in some studies are proposed to be carried out using a Franz or Keshari cell (Kathe and Kathpalia, 2017).

Methods for assessing the transmission of oxygen through films for medical use began to be developed as early as 1987. The study evaluated modern commercially available hydrogel films, and the methodology was based on the evaluation method developed by Keller and Shultis in 1979, which was used in Britain to evaluate the gas permeability of packaging materials (vacuum technique) (Keller and Shultis, 1979; British Standard Method of Measuring the Gas Permeability of Packaging Materials. 1979) as well as a method developed by Wong in 1984 gas-membrane liquid method for evaluating carbon dioxide permeation through membranes for use as a blood-oxidant (Queen et al., 1987; Wong, 1984).

It is noted that the perfect wound dressings should be impermeable to bacteria, but permeable to water vapour (Jonkman et al., 1988). Some papers estimate the permeability to water vapour (Jonkman et al., 1988; Bruin et al., 1990), including using an atmometer developed by Nilsson in 1977 (Nilsson, et al., 1997). Some authors propose to determine the moisture permeability of the film by staining the skin, then applying a dye and then washing off the film (Woo and Chakravarthy, 2014).

9.1.16. Sterility / microbiological purity

The previously mentioned pharmacopoeias provide parameters as microbiological purity for non-sterile products and sterility. The sterility parameter is used for product for injured skin and open wounds. Like other sterile products SFFSs must be manufactured according to GMP requirements in clean rooms. Most composition for film-forming aerosols/sprays can be sterilized by heat, or by filtration (if product viscosity allows). In other cases, e.g. for thermolabile substances (biological products, etc.) the composition may be prepared aseptically. In addition, the spray dosage forms have the unique ability to maintain their sterility after the first and subsequent applications. Spraying creates a spray pressure that avoids microbial contamination of the product.

9.2. Modern approach in pharmaceutical development

Pharmaceutical quality by design (QbD) and the design space. This modern approach to introducing quality at the pharmaceutical development stage is clearly applicable to SFFSs as well. In order to apply it, it is necessary to define the parameters to be brought into the space. And, since there are no normatively fixed optimums, they can be determined on the basis of prototypes available for commercial use. The parameters can be technological, customer-relevant, objectively definable parameters, the methods of determination of which are validated. These parameters can be drying rate, adhesion, elasticity, washability, vapour permeability, etc.

For example, some studies indicate such basic characteristics for the dosage form itself as film formation rate, film elasticity, as well as additional characteristics such as vapour permeability and absence of irritant effect. Characteristics such as the blood coagulation effect mentioned in this study relate to the active ingredient. Which system drying rate, elasticity and vapour permeability values are considered optimal is also up for discussion (Sangnim et al., 2022).

Another example of the determination of optimums is the satisfactory drying time of the film on volunteers in studies (Huanbutta et al., 2020). Such modern approach to find optimums will help R&D teams in development.

Clear examples of factorial design and regression analysis in the articles about spray film-forming systems will also help researchers to start using these methods in their research (Mori et al., 2017).

10. Conclusions

Spray film-forming systems are modern drug delivery systems used for local, topical and transdermal delivery. Many research groups have shown interest in developing in the form of SFFSs, but not all publications uniformly define the tests and have some reasonable and validated range of parameters sought. However, the lack of harmonization in the terminology used in multinational studies, as well as the lack of an existing regulatory framework for the development of spray film-forming systems remains an obstacle to development in this area. Finding, evaluating and validating their differentiated list of characteristics and methodology variations (separately for development and for standardisation) could potentially increase research interest in aerosol film development, aid development using QbD, and facilitate registration of new medicines and medical devices for topical use.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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