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HERBAL FILM FORMING SPRAY

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Abstract:

To formulate Spray Bandage to get good protective and therapeutic activities for a longer duration of time and form film which act as a protective barrier for open wound or another tropical disease [5]. It is easy to use and apply by spraying directly on the affected area. It forms film within a few seconds and has good patient compliance. Curcumin is useful in various activities such as anti-tumor, antioxidant, anti-arthritic, anti-amyloid, anti-inflammatory, bacterial infections, wound healing, and tissue repairing. Curcumin has low GI stability hence it is given through a topical drug delivery system for sustained release of the drug. In the formulation.[1]

Conventional formulations for topical and dermatological administration of drugs have certain limitations like poor adherence to skin, poor permeability and compromised patient compliance. For the treatment of diseases of body tissues and wounds, the drug has to be maintained at the site of treatment for an effective period of time. Topical film forming systems are such developing drug delivery systems meant for topical application to the skin, which adhere to the body, forming a thin transparent film and provide delivery of the active ingredients to the body tissue. These are intended for skin application as emollient or protective and for local action or transdermal penetration of medicament for systemic action. Further the various types of film forming systems (sprays/solutions, gels and emulsions) along with their evaluation parameters have also been reviewed.

Key words: Film forming spray, Curcumin/eugenol, Film forming polymers, Gelling agent, Topical drug delivery.

Introduction:

The skin is the most readily accessible organ of the body and acts as a barrier against the micro and macromolecules of the environment because of its low permeability to such substances [1]. The skin of an average adult body has approximately 2 m2 surface area and it receives about one-third of the total blood circulating throughout the body [2].

The goal of drug administration through skin is for topical treatment of skin diseases or for transdermal absorption of drugs in the systemic circulation. The topical route offers a large and varied surface in addition to the ease of application via self-administration and provides an alternative to oral delivery of drugs as well as hypodermic injection [3].

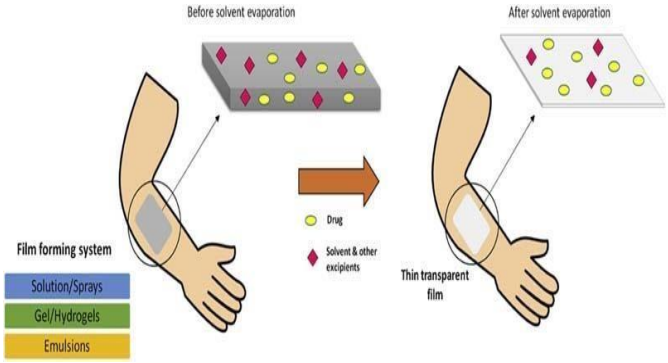
Various drug delivery systems are available for topical application of pharmaceutical formulation such as creams, ointments, lotions, gel, transdermal patches and sprays their use depends on drug pharmacokinetic profile, whether their drug release is immediate or

sustained. Patches have various disadvantages, most commonly skin irritation [4] Hence repeated application is required in case of chronic diseases like athlete's foot, ringworm and candidiasis

Spray bandage or Film Forming System [FFS] is a novel approach that can be used as an alternative to conventional topical and transdermal formulations. It is defined as a non-solid dosage form that produces a film in situ, i.e. after application on the skin or any other body surface. These systems contain the drug and film forming excipients in a vehicle which, upon contact with the skin, leaves behind a film of excipients along with the drug upon solvent evaporation. The formed film can either be a solid polymeric material that acts as a matrix for sustained release of drug to the skin or a residual liquid film that is rapidly absorbed in the stratum corneum

Mechanism of Film forming spray

- After application of the film forming system to the skin, the composition of the film forming system changes significantly due to the loss of the volatile components of the vehicle which results in formation of residual transparent film on the skin surface.



- In this process the concentration of drug increases, reaching saturation level and with the possibility of reaching supersaturation level on the skin surface. Supersaturation results in the enhanced drug flux through the skin by increasing the thermodynamic activity of the formulation without affecting the skin's barrier, thereby reducing the side effects or irritation

- FFS creates supersaturated systems immediately after application to the skin, overcoming the problem of instability. Thus it improves the drug permeation through skin compared to other transdermal dosage forms.

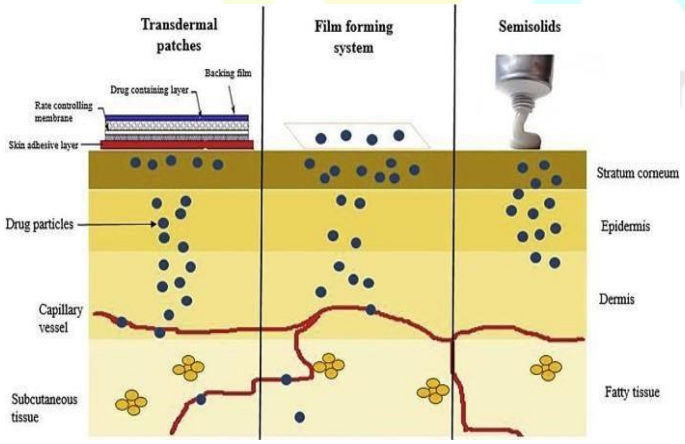
- The concept of supersaturation can be explained by the modified form of Fick's law of diffusion. Fick's law of diffusion is given as:

- $J = \frac{DKCv}{h}$

where,

- J = rate of drug permeation per unit area of skin per unit time (flux)
- D = diffusion coefficient of drug
- Cv = concentration of drug
- h = thickness of barrier to diffusion

- From this equation, it is clear that the rate of drug permeation across the skin is proportional to the concentration of the drug.



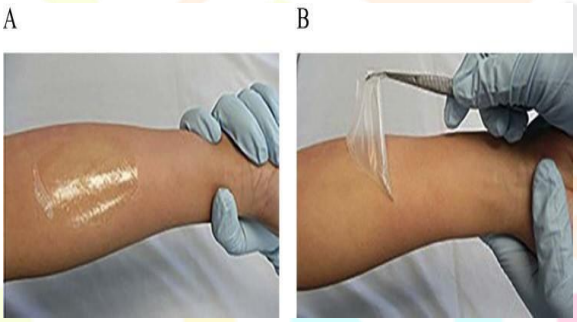
Application of film forming systems

film forming systems were predominantly used in the field of surgery or wound care. Film forming solutions or gels have been used as tissue glues for the closing of operative wounds. The film formers used for this purpose may be natural like fibrin or synthetic like cyanoacrylates. These wound care preparations can be without drugs or with antimicrobial agents to prevent infections in the wounds [6]. It can also be used as transparent peel off mask technologies for skin hydration treatment, acne problems, etc. [7].
Some of the film forming wound care products are as follows; Film forming wound care products (reproduced from Ref. [6], .

Trade names	**Manufacturer**	**Film forming polymer**
Dermabond®	Ethicon GmbH, Germany	Octylcyanoacrylate
EPIGLU® Gewebekleber	Meyer-Haake GmbH, Germany	Ethylcyanoacrylate, Poly(methylmethacrylate)
Flint® Sprühverband	Togal, Germany	Poly(butylmethacrylate, methylmethacrylate)
BandAid® Sprühpflaster	Ethicon GmbH, Germany	Cellulose acetate butanoate
Opsite® Spray	Smith & Nephew GmbH, Austria	Poly(methylacrylate)

Properties of film forming system

The film forming preparation can be applied to the site regardless of shape and area, and can be retained for a long time as compared to conventional semi-solid preparations [A] shows that FFS forms an almost completely transparent fast drying film on application. [B] shows that after drying, a non-tacky, flexible and easily peelable film is formed. There is an excellent adhesion of the formed film to the skin, hence wipe off resistance. Therefore the risk of transfer of active ingredients to other people or clothes is reduced. Hence any medicament or drug can be used is this formulation to form a film forming layer.

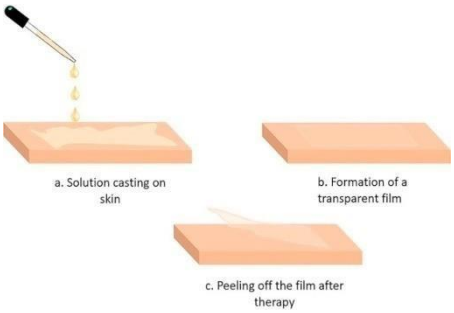


Film forming formulation

Sprays/solutions

Film forming solutions and sprays is an attractive approach in transdermal dosage form. In this the polymeric solution is applied to the skin as a liquid or sprayed on the skin and forms an almost transparent film by solvent evaporation [8].

The film forming sprays/solutions are made up of four main components – drug, solvent systems i.e. volatile and non-volatile vehicles, polymers and penetration enhancers. The non-volatile component present in the solvent system prevents the drug from precipitating in solution when the volatile solvent component evaporates. The non-volatile component is chosen such that it itself partitions rapidly into the stratum corneum and also aids in partitioning of the drug into the stratum corneum.
This type of delivery system creates an invisible depot of drug in the stratum corneum from which the drug can be slowly absorbed into the systemic circulation. Thus a sustained and enhanced permeation of drug across the skin can be achieved following once a day application [09],



• Ammar et al. developed a film forming polymeric solution of ketorolac using Eudragit and polyvinyl pyrrolidone in ethanol as film forming agents [10].

• Gohel and Nagori developed a fluconazole spray containing ethyl cellulose and Eudragit RS 100 as film formers [11].

• Yu et al. developed transdermal film-forming spray containing estradiol and optimized the formulation using different polymers and plasticizers for efficient penetration of estradiol for longer duration of time as compared to gel and patch [12].

Formulation of film forming sprayContents of herbal film forming spary[Curcumin / Eugenol]

1. API
2. Polymers
3. Copolymer
4. Solvents
5. Plasticizers
6. Humectant

API

For transdermal application of film forming systems, the drugs need to have suitable properties which are independent of the dosage form. Generally the drugs which are applicable to these systems are highly potent which permeate the skin rapidly, which cause no skin irritation and which are relatively stable to the enzymes present in the epidermis.
The molecular weight of drug is an important factor in drug permeation as small molecules cross human skin than large molecules.

Ideal properties of drug for transdermal delivery.

Parameter	Properties
Dose	<10 mg/day
Half-life	10 h or less
Molecular weight	<500 Dalton
Partition coefficient Log P (octanol/water)	Between 1 and 3
Skin reaction	Non irritating and non-sensitizing
Oral bioavailability	Low

Polymers

Polymers are the foundation of the FFS and a variety of polymers are available for the preparation of these systems. In order to achieve the desired film properties, these polymers can be used alone or in combination with other film forming polymers [23]. These polymers should form a clear flexible film at skin temperature.

Film forming polymers.

Polymer	Properties
Hydroxypropyl Methylcellulose (HPMC) HPMC (E4M, E15, E50M K4M)	Produce a light, non-greasy uniform film with good texture. Do not interact significantly with other ingredients Surface active agent, therefore adsorbs water providing easy dispersion, lubricity and comfort feel in occlusive state on application to skin
Ethyl cellulose (EC)	Nontoxic, nonirritating, nonallergic material Good film forming properties that form tougher films
Hydroxypropyl cellulose	Nonionic, pH insensitive polymer Water soluble
Polyvinyl pyrrolidine (PVP) (PVP K30, PVP VA64)	Solubility in water and other solvents Adhesive and binding property Acts as a bioavailability enhancer
Polyvinyl alcohol (PVA)	Water soluble Excellent film forming and adhesive properties Nontoxic and biocompatible

Solvents

The solvents form an important component in film formation. The solvent used in film forming systems help in solubilizing the drugs as well as have an impact on drug permeation. Commonly used solvents for topical and transdermal use [24] are listed below in the table. As these solvents are widely used, the safety of these has been established on long term use.

Solvents used in topical systems.

Category	Examples
Glycols	Propylene glycols, polyethylene glycols
Alcohols	Ethanol, butanol, isopropanol, benzyl alcohol, lanolin alcohols, fatty alcohols
Other solvents	Ethyl acetate, oleic acid, isopropyl myristate

Plasticizers

Plasticizers are used in the film forming systems to impart flexibility to the film and improve the tensile strength of the film formed. The plasticizer used should be compatible with the polymers used and should have low skin permeability.
Commonly used plasticizers are glycerine, polyethylene glycol, sorbitol, dibutyl phthalate, propylene glycol, triethyl citrate etc. [13].

Humectant

A humectant is a common moisturizing agent found in lotions, shampoos, and other beauty products used for your hair and skin. They're known for their ability to retain moisture while also preserving the overall properties of the product at hand. Humectants can be good for your skin and hair.
Eg. Glycerol, Sorbitol, Lactic acid, Xylitol, Propylene glycol, hexylene glycol, and butylene glycol etc.

➢ Composition for preparation of curcumin film forming spray for wound healing which forms non staining, miscible and bio-compatible film within few seconds after application on skin/wound, comprises of; API
- Curcumin [0.5-10%]
  Copolymer- Polyvinyl caprolactum, polyvinyl acetate, polyethylene glycol [0.1-90%]
  Solvent- Ethanol, water, Collagen [0.1-1%], Chitosan [0.1-1%], Hyaluronic acid [0.05-1.5%]

Evaluation parameters of spray bandage Film formation and rated as complete and uniform, incomplete or non-uniform, with or without precipitation of the film-forming polymer. The cosmetic aspects of the film are given in terms of transparency or opaque, sticky or dry, peelable or The films are formed in a Petri dish or on an excised pig ear skin. Film-formation is evaluated non-peelable [14].

Film flexibility

Film flexibility is evaluated on the basis of cracking and skin fixation and this is determined by stretching the skin in 2–3 directions. The film is rated flexible if there is no cracking or skin fixation and non-flexible if there is cracking and skin fixation.

Drying time

For the evaluation of the drying **time the formulation is applied to the inner sides of the forearm of a volunteer. After a fixed time period a glass slide is placed on the film without pressure. If no liquid is visible on the glass slide after removal, the film is considered dry [15]. If remains of the liquid are visible on the glass slide the experiment is repeated with an increase in drying time. A good FFS should have a minimum drying time to avoid long waiting time for the patient.**

Stickiness

The stickiness of the film formed is determined by pressing cotton wool on the dry film with low pressure. Depending on the quantity of cotton fibres that are retained by the film, the stickiness is rated high if there is dense accumulation of fibers on the film, medium if there is a thin fiber layer on the film and low if there is an occasional or no adherence of fibers. This evaluation parameter is essential, as the formulation should be non-sticky to avoid adherence to the patients' clothes [16].

Mechanical properties

cut with the help of a scalpel. Film thickness is measured with a digital micrometer. The mechanical properties of the films are determined with a tensile tester.

The tensile strength (σ) is calculated as:

σ=Fmax The polymeric films are produced by solvent evaporation on a Teflon plate. The dry films are /A(N/m2) where,

F_{max} (N) is the maximum force and A (m^2) is the cross-sectional area

Determination of the water vapor permeability

The water vapor permeability is defined as the quantity of water transmitted through a unit area of film in unit time. These water vapor permeation data are important in determining the permeation characteristics of the film as they have influence on skin properties like hydration of stratum corneum, blood flow, and skin temperature [17]. Films are produced with a solvent evaporation technique on a Teflon plate and dried for 72 h at room temperature.

WVP=W/A∗t

Swab studies

Swab test can be performed to evaluate the residence time of film forming system. For adhesion testing, glass was used as a polar, hydrophilic substrate. Glass was chosen as test surface because films adhering strongly to it would also show strong adherence to skin because both materials display a polar surface structure [30].

Dry swab test: This test indicates the behavior of FFS on the skin in dry condition. Dry swab test can be carried out on a glass plate. The glass plate is marked with 6 squares of 1 × 1 cm^2. Developed formulation is applied in this area. Dry cotton swabs of the same volume are taken. Swabbing on the applied film is carried out at 0 min, 30 min, 2 h, 4 h, 6 h and 8 h and checked for drug content after extraction of drug from the swab.

Wet swab test: This test depicts the behavior of FFS when it comes in contact with water or sweat. The procedure for the wet swab test is the same as dry swab test except the swab taken is soaked in water before and then the formulations are swabbed with this wet swab.

Film topography

Atomic force microscopy (AFM) provides information about the topographic and mechanical properties of the polymeric films and helps to match the mechanical properties of the formed films to those of skin. It generates a nanoscale image of the film's homogeneity and roughness and requires no special treatment prior to the measurement [18] **Film homogeneity**

Raman spectroscopy provides information about the chemical composition of the polymeric films. The chemical maps obtained from Raman spectra provide a measure of chemical homogeneity of films. Techniques based on Raman scattering can also be used to track the permeation of topically applied compounds through the skin [19].

***In vitro* diffusion study**

The *in vitro* diffusion studies are used to predict the permeation characteristics of drug *in vivo*. Franz diffusion cell is used to determine the release profile of the drug from the film forming system. The cell is made up of two compartments, the donor and the receiver compartment between which the diffusion membrane is attached (egg membrane or cellophane). The donor compartment is exposed to the atmosphere and the receptor compartment contains the diffusion medium.

***Ex vivo* permeation study**

The *ex vivo* permeation studies are performed to study the effects of skin barrier on the developed film forming system. Franz diffusion cell/Keshary–Chien diffusion cell can be used for permeation study. Rat's skin is mounted between the two compartments, stratum

corneum facing the donor compartment and dermis facing the receptor compartment. The formulation is applied to the skin surface which forms a film after drying. The receptor compartment contains phosphate buffered saline (pH 7.4) maintained at 37 ± 0.5 °C. Aliquots are collected at specific time intervals and analyzed by suitable spectroscopic method [32]

Skin penetration studies The formulation is applied evenly on the skin using a pipette or a spatula. After fixed time intervals (e.g. 15 min, 1 h, 3 h, 6 h, 8 h, etc.) post application, the remaining formulation is removed. The film is wiped off with the help of cotton pads and the amount of drug present in the cotton pads is calculated, which is equivalent to the amount of drug remaining in the film [20].

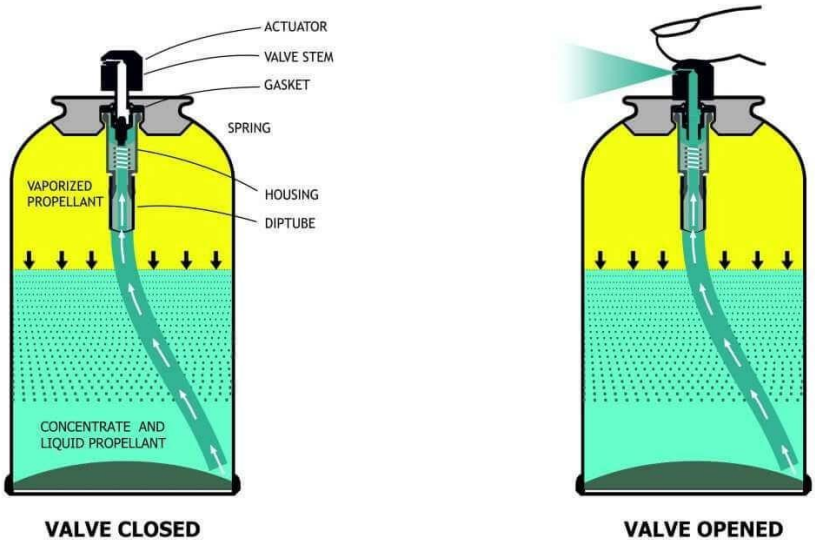
Commercialized film forming products

A number of companies have tried to develop film forming systems as a drug delivery platform and have marketed their products successfully. The companies with their products based on film forming technology are listed below;

Commercialized film forming system.

Product	Drug	Company	Formulation type
Lamisil Once® [21]	Terbinafine hydrochloride	Novartis Consumer Health, Australasia, Pty Ltd	Film forming Solution
Axiron® [22]	Testosterone	Lilly USA, LLC	Film forming spray
Medspray® the Patch-in-aCan® [23]	Terbinafine hydrochloride	MedPharm Ltd, UK	Film forming spray
Liqui-Patch technology [24]	Testosterone hydrocortisone	Epinamics GmbH, Germany	Film forming spray
Durapeel Technology [25]	Ropivacane	Crescita Therapeutics, Inc	Film forming gel
PharmaDur®Technology [26]	Hydroquinone	Polytherapeutics, Inc	Film forming emulsion-gel

Mechanism of spray container or aerosol



1. Pharmaceutical aerosols are products that contain therapeutically active ingredients which are packed under pressure and are released upon activation of an appropriate actuator and valve system. The term "aerosols**" was originally accustomed to describe a liquid or solid fine mists particles with a specific size range. The term "aerosols" now refers to pressurized packed products that contain the active ingredient(s) and excipients that are dispersed in a liquefied or compressed gas known as the** propellant**. Aerosols dosage forms can be topically, orally, nasally, and systemically inhaled**

Advantages of Pharmaceutical aerosol over other doses form

1. Dose removal without contamination of remaining material is possible.
2. Enhance stability of substances which adversely affected by Oxygen and moisture.
3. Maintenance of sterility of product during dispensing dose.
4. Directly delivery of Medicameant to the affected area in a desired form with minimum or no irritation 5. Rapid onset of action
6. Circumvention of first pass metabolism
7. Aerosols are temper proof system so no adulteration is possible

8. Aerosol product can be applied in a thin layer
9. Irritation Produced by the mechanical application of topical medication is reduced or eliminated.nhaled. Disadvantage of aerosols

- Expensive
- Chlorofluorocarbons propellants cause ozone layer depletion
- Toxicity
- Explosive nature of propellant
- Inflammability

Components of Aerosols

Aerosol packages consist of various components including

1. Propellant
2. Containers

Valve and actuator

PROPELLANT USED FOR PHARMACEUTICAL AEROSOLS

Propellants are accountable for generating proper expelling pressure within the container to expel its contents

1. **Liquefied gases propellants**
2. **Compressed gases propellants**

There are mainly two types of **liquefied gases** propellants they are,

A. Fluorinated hydrocarbons [used for oral and inhalation]
B. Hydrocarbons [used for topical application]

VALVE **&** ACTUATOR:

The aerosol valve is a very important part of an aerosol container; it is a vital part responsible for expelling and dispensing the desired dose of the aerosol contents in the desired controlled rate. Valves account for delivering the product concentrate in the preferred form and controlling the flow rate of contents from the container.

The types of the valves are variable; mainly two types are applicable either a continuous spray valve or a metering valve.

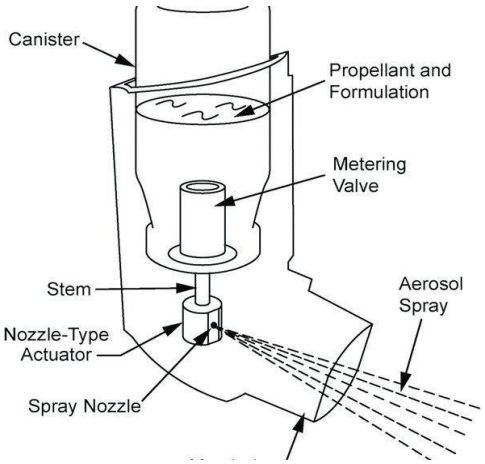
Continuous spray valves

To deliver the product contents constantly in the form of a spray or solid foam stream with or without amount determination. These kinds of valves are the main type used for all categories of pharmaceutical aerosols.

Continuous spray valves

Metering valves or metered valves

To deliver the contents for potent medication, they are dispensing the exact amount of medicament upon each time of activation during application.



Metering valve

Actuator:
It is a Specially designed Button fitted to the valve stem which ensure proper delivery the aerosol product in the desired form (spray, foam or solid stream) or it is a push knob which the user presses to activate or deactivate the assembly of the valve system.
The physical form of the emitted product concentrate is determined by the combination of the type and amount
It further produces a fine particle size, prevents valve clogging with product containing insoluble materials, allows for the product to be satisfactory dispensed with the container in the inverted position, reduces the chilling effect of the propellant on the skin & in the case of hydrocarbons propellant, allows for decrease in flame extension.

Dip tube**:**
It is the part of the valve assembly that extends downstream into the product concentrate aids to transport the contents from the container to the valve.
Dip tubes are made from Polyethylene or polypropylene. Polypropylene tube is usually more rigid/hard. Inner Diameter of dip tube is selected based on desired viscosity & delivery rate (0.050-0.195 inch) Metering

valve
These are used for the dispensing of **Potent medication** with an accuracy of dosage.
50 to 150 mg (10% variation) of liquid material can be dispensed with metering valves.

PRODUCT CONCENTRATE
Product concentrate of an aerosol in which the active drug combined with suitable excipients can be delivered in three forms of liquid form a solution, suspension, an emulsion or in a form similar to semisolid.

Conclusion and future prospects

The film forming system presents a novel platform to deliver drugs to the skin both topical and transdermal. These film forming systems are simple and offer advantages of transparency, non-greasy, lower skin irritation, wipe off resistance, longer retention, greater increased dosage flexibility, improved patient compliance and aesthetic appearance Although considerable work has been done on these systems, not much data are available on its delivery efficiency.

Film forming spray is a noval drug delivery system. As it is a herbal film forming spray (FFS), It contains curcumin & eugenol as an active ingredients (API) These act as antiseptic and analgesic .

Curcumin reduces muscle soreness , pain thus it acts as a muscle relaxant . It also helps to treat inflammatory skin condition . on application the solvent evaporates and a thin film is formed . Polymers . plasticizer helps in the formation of a thin layer or film like structure. Humectant present in the formation helps in the prevention of moisture loss .

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