ISSN No:-2456-2165

Film Forming Spray: A Comprehensive Review

Priyanka Mohite*, Harshil Patel, Mansi Patel, Chainesh Shah, Umesh Upadhyay
Sigma Institute of Pharmacy, Bakrol, Vadodara- 390019

Abstract:- In comparison to traditional topical preparations, film-forming sprays have a number of benefits, including uniform drug distribution and dose, enhanced bioavailability, decreased incidence of irritation, continuous drug release, and quicker wound healing through moisture control. Polymers and excipients used in film-forming sprays work to increase the properties of preparations and the stability of active ingredients. Different excipient and polymer combinations will result in films with various characteristics. The potential for developing compositions of spray film-forming systems has substantially increased thanks to the current state of polymer development and composite synthesis. Therefore, in order to create a film-forming spray that is more effective, it is necessary to evaluate the various types of polymers and excipients and their assessment criteria.

Keywords:- *film-forming spray, film-forming polymer, topical drug delivery.*

I. DEFINITION AND MECHANISM OF A FILM-FORMING SPRAY [1-4]

An FFS is a drug delivery system that sprays a solution at a specific therapeutic site, where it contacts the site and uses the polymer as a matrix for film formation to build a film. 20,25,30 The drug will be released from the polymer matrix housing the drug over time after the film has been formed, much like a patch. However, unlike topical patches and other topical medicines, films adhere to the contours of the skin or wound because minute droplets of the film-forming solution can enter deep indentations. Naturally, this makes it much easier for drugs to reach their target tissues. Drug dosages can also be changed in a film-forming spray depending on the amount of solution per spray to control any local or systemic symptoms. Additionally, an FFS offers a good spread and an even distribution of medications. Patient compliance may also rise with simplicity of usage. It is simple to remove the thin film with water. Comparing this thin, non-sticky film to patches, ointments, gels, etc., which have a rough, sticky texture when applied, boosts patient comfort during activities. 35,36 To keep the equilibrium, the thin film also makes it easier for wound moisture to permeate. The use of patch preparations can result in inappropriate wound humidity, which can lead to infection or irritation.

The film-forming fluid is sprayed using any type of sprayer to create droplets. Each sprayer has unique features and purposes, but they all have potential for usage in medical settings. The potential uses of several sprayer types as medication delivery mechanisms in film-forming systems are described below.

II. FILM-FORMING SPRAYERS [5-9]

A. Ordinal Spray

The ordinal spray is a form of spray that typically uses a plastic or aluminium container with a dip tube diameter of 1.2 mm and an aperture size of 0.3 mm. This sort of spray does not require any special technology during the spraying process. The spray produced has an average angle of 78.69-87.39°, 0.11-0.35 g or - mL of film-forming solution can often be sprayed. An ordinary spray container has an average leakage rate of 0.01–0.03%. 34 An ordinal spray may be vertical or horizontal. It has been claimed that the 3 K® Horizontal Spray Nozzle can keep the film-forming fluid sterile while being stored and used. The type and concentration of the polymer utilised affects the ordinal spray's spray force as well. 31 The preparation of extracts can also be done with the ordinal spray.

B. Metered Dose Spray

The metered dose spray (MDS) is a spraying tool that has a variable spray output. This device is typically used to provide medications via the transdermal or transmucosal route to the systemic compartment. Because it is related to the medication dose, the spray volume must be taken into account when evaluating a film-forming spray. The amount of MDS that can be sprayed can be affected by the bottle's capacity, how evenly the particles are dispersed, and where the container is placed while being used. 45 The typical volume of FFS that can be sprayed is between 90 and 102 mL. 30,32,33 MDS has an 83.51° spray angle on average. 20 An MDS container has an average leakage rate of 0.01 to 0.02%. 30.

C. Electrostatic Spray

A common technique for applying pesticides in agriculture is electrostatic spray (ES). ES can improve loss from drift, droplet formation speed, cover-age uniformity, and deposition efficiency. 46 The effectiveness of ES depends on the viscosity, surface tension, and electrical resistivity of the solution. The conductivity of a solution must be between 108 and 105 S/m in order to be sprayed with ES. The droplets produced by ES have an average diameter of 6.3 to 26 m.

D. Ultrasonic Spray

Excellent potential exists for film-forming solutions to be delivered by ultrasonic spray. The resulting droplet has thin-film properties and can approach the nano scale. The ultrasonic spray nozzle can operate at both low and high pressures, generating consistent droplets with less than 10 m in diameter. The droplet diameter of the ultrasonic spray is 1–10 m, and the nozzle is 0.5 mm in diameter. The electrode being used has a resonance frequency of 10 MHz. Layer-by-layer (LBL) coating films can be produced using an ultrasonic spray for medical applications that have greater particle size uniformity. Specifications for each type of

sprayer correspond to particular polymers. The FFS system has utilised a variety of polymers, both natural and manufactured.

III. STANDARDIZATION PARAMETERS [10-19]

It is important to standardise spray film-forming system parameters both before and after the phase shift, which occurs in all in situ systems. The majority of authors who discuss the development of spray films distinguish between mandatory standardisation parameters that are distributed between the liquid/spray and solid phases of the delivery system (included in the specification for the dosage form) and additional standardisation parameters that are determined during the development stage for a pool of mulations.

A. pH

To strengthen the stability of the ingredients in the composition and for extra therapeutic purposes, the pH value of the film-forming liquid is tested and regularly adjusted. For the treatment of heat injury, the ideal pH value will be lower than 7.32, whilst 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, and so on. The pH level can influence not only how quickly the wound surface heals, but it can also influence how well a substance can pass through skin barriers when delivered transdermally.

B. Isotonicity

Another trait of the film-forming system that might be evaluated is the solution's isotonicity. It relies on the level of tonicity needed for the application's location and intended use on specific afflicted areas, like wound surfaces and mucous membranes. Non-isotonic medications might irritate and hurt the mucous membranes. Because of this, it is possible to determine and modify the tonicity of medications, for instance using the Kahara method.

C. Viscosity, density

One more characteristic of the film-forming system is that the solution isotonicity. It depends on the level of tonicity needed for the application and the afflicted areas in question, such as mucosal membranes and wound surfaces. Non-isotonic medications might irritate mucous membranes and hurt. Due to this, the tonicity of medications can be determined and modified, for instance using the Kahara method (Umar et al., 2020).

D. Surface tension

The surface tension and contact angle are calculated for the same reason. This characteristic is more important for standardisation and description of the properties of sprays than aerosols since it appears to be solely related to the film generation mechanism linked to solvent evaporation. Both the solution's distributivity and the solvent's rate of evaporation may be impacted by surface tension. The most common method is to measure the surface tension angle using a surface tension analyzer or high-resolution cameras, and then to compute it using specialised or general-purpose software.

E. Minimum fill or package tightness

Given that the delivery systems under consideration are disperse, the characteristics of sprays and aerosols, such as package tightness/pump seal efficiency (aerosols), minimum fill, pressure test, delivery rate and delivered amount, and aerodynamic distribution of particles, must be included in the standardisation parameters. Less frequently mentioned are the spraying angle, the form and distribution of droplets by size, and the spray pattern.

F. Mucoadhesion

The mucoadhesion of the film-forming liquid defines the most crucial delivery system indicators, such as the capability of local application and exposure time, and directly influences the characteristics of the in situ film formed, such as thickness, uniformity, and rate. It is significant to highlight that studies devoted to the creation of spray film-forming systems do not fully define measuring methodologies for mucoadhesive characteristics. At least a dozen reliable, proven approaches, including in vivo, ex vivo, and in vitro techniques, are now known for determining this indication.

The authors' drive to carry out comprehensive studies in this field may be fueled by the profitability of in vivo studies of mucoadhesion. It is recommended to employ models with purified mucin (such as mucin from the porcine stomach) and polymer membranes with specified parameters for a comparative evaluation of mucoadhesive capabilities in a pool of samples during screening (moisture content, adsorption capacity, pore size, etc.). Various models are built based on these characteristics, depending on the planned location and type of system application (to estimate the separation force, flow rate, etc.). For assessing the mucoadhesive qualities by rotational viscometry, there is information on the creation of reliable, correlated with in vivo procedures.

G. Film formation

The production of the film and its evaluation can be carried out in vivo as well as in vitro (on glass surfaces, standardised membranes, nonwoven textiles, etc.). Both approaches have benefits and drawbacks.

The location of application, the skin's surface temperature, its moisture content, the condition of the epidermis, humidity, ambient temperature, and other factors can all affect film development in situ. When analysing in vivo for the drying rate and other properties of the film, the authors of the majority of research use diverse application zones, such as delivering a dosage to the arms, shoulders, inner thighs, or abdomen before the creation of a thin bioadhesive film on the skin. The utilisation of these factors varies depending on how these elements are different. The substance is undesired for the screening procedure and a dispassionate evaluation of the sample pool, nevertheless. The evaluation of film formation is quite popular due to the high simplicity, reproducibility, and ease of use of in vitro methods. According to Kathe K. and Kathpalia H., the films developed in a Petri dish. Glass was used as the test surface in this instance because some scientists think that it can be compared to human tissue. In addition, it should be

emphasised that the film forms in situ on a surface with its own moisture content that is heated (typically to 32 °C, with pathologies reaching 35–37 °C). By doing this, the drying process replicated on the glass surface is adjusted. It may be advised to cover a glass plate with a membrane or non-woven covering to boost the in vivo/in vitro correlation and to conduct an experiment in which the temperature is controlled by a thermostat.

None of the researches considered Studies ex-vivo did not mention SFFSs, indicating their low prevalence in this field of development despite all the benefits of this approach, such as high representativeness, close applicability to real conditions on the mucous membrane or wound surface, and absence of the need to consult an ethics committee, which undoubtedly lengthens development time and negatively affects production profitability.

H. Moisture content

To fix the conclusion of the process of its construction and pinpoint the precise drying period, the moisture content of the produced film is assessed. Humidity is studied using pharmacopoeial techniques (gravimetry) and readily available equipment (moisture metres, humidity analyzers). The end of film formation can also be determined by a stickiness test, which is practical and affordable. A separation test is advised by certain writers. If cotton wool is put to the film before drying, the cotton wool fibres will disappear. This shows that the film has at last dried out.

Due to the risk of elasticity loss and skin harm from solid film particles, severe drying of the film makes moisture assessment in dynamics conceivable.

I. Thickness

After the film has been removed from the surface, its thickness is measured using specialised equipment. It should be highlighted that separating the formed film from the surface, which was not accomplished by researchers for all compositions being created, is required in order to analyse the parameters of the system's ultimate state in situ. However, in our opinion, these examinations are necessary, particularly for in vitro films (for example, on a glass plate). It is challenging to predict the behaviour of the produced film in vivo and the adherence of patients to therapy utilising it if it is not possible to separate the film from the surface and measure its mechanical and other properties.

J. Morphology

Transmission or scanning electron microscopy can be used to examine the morphology of the film. The film's homogeneity, surface roughness, and microscopic shape are assessed. A visual description of the pattern, gloss, etc. serves as the sole indicator of the film's uniformity. In situ spray film-forming systems, whose film coating is rarely visible, are described in several investigations. The quality indicators for the film's properties that were described are not appropriate for such developments. In these situations, it is vital to create and use tests that unequivocally show the protective properties of the pharmaceutical composition in order to demonstrate the efficacy of the wound surface dressing.

K. 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. Along with the strength of the film, it is possible to measure the elongation and elasticity of the film using various techniques.

L. 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.

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

Although topical systems are mentioned, it might be crucial to prove that transdermal action exists. Transdermal action, as opposed to local action, is concerned with the delivery of active substances via the dermis into the bloodstream (Euro- pean pharmacopoeia). Dermal transit can occur through a variety of chemical and physical routes. The molecule of the active drug must be lipophilic (logP = 1-4 or less), have a mass of no more than 500 Da, and be neutral. There is no doubt that even such stringent criteria for the active component molecule are insufficient for transdermal absorption. When Penetration Enhancers are added to the dosage form, the skin is affected in a variety of ways, including across the stratum corneum and below the hair follicle. and down sweat glands. Low molecular weight compounds can move through and among epidermal cells in the trans epidermal pathway. Larger molecules can pass via the trans follicular channel, but because each person's follicle count varies and they don't cover the full skin surface, the amount of active chemicals that can pass through is reduced. However, excipient properties can also make a difference in permeability. For instance, the use of polymers and the methods for applying them that result in occlusion can make the skin more permeable. Other technical methods, such comminuting active substances or producing microemulsions and nanoemulsions, can improve the flow of active chemicals through the skin. The direct relationship between the methods' safety. Affecting the skin's capacity to reestablish the natural barrier, for instance, protein denaturation is a destructive technique that is by definition unsafe. The goal of local or topical action is not to transport active ingredients into the systemic circulation, but rather to treat either healthy or injured skin. The idea that the active ingredients in these preparations shouldn't reach the systemic circulation and that their release into the bloodstream should be regulated if the skin is damaged is rational yet disputed. The stratum corneum acts as a reservoir for the active substances since the dermis' deeper layers are less lipophilic, and their release from this layer is prolonged.

Despite this, it is important to take into account both topical and transdermal preparations when SFFSs are discussed because the excipients' placebo effect may or may not increase the permeability of the components. Therefore,

a placebo prototype preparation intended for topical use may conceivably also double as a transdermal composition. It makes sense to focus primarily on topical preparations because the demands for the final films will vary in terms of their physical and chemical properties.

N. Water washability

Many authors also recommend using cotton swabs to determine the water washability, also known as the moisture erasability, which can be done. The dry film can be used to gauge how easily the film was moistened. After washing the film with water, it is rated on a scale from readily erased to moderately erased to poorly erased.

O. 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 wound. The gas permeability of the coating is necessary for tissue regeneration.

P. 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 thermo- labile 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 sub- sequent applications. Spraying creates a spray pressure that avoids microbial contamination of the product.

IV. POLYMERS USED IN FILM FORMING SPRAY

A. NATURAL AND SEMISYNTHETIC POLYMERS [20-24]

Cellulose & Ethyl cellulose forms films that are easily washed away with water.34 The concentration of ethyl cellulose that produces films with excellent characteristics is 5.- 02–5.25% and is generally combined with Eudragit. HPMC is reported to have a slow drying time. The optimal concentration to get excellent film characteristics is 2%. At these concentrations, HPMC produces clear, thin, and smooth films.

Na-CMC is known to have a thixotropic flow rate that allows it to become thinner when under pressure so that it is easy to pass through the nozzle and return to initial consistency after being sprayed. The maximum limit of Na-CMC concentration that can be sprayed is 2.5 %. The optimal level of Na-CMC that produces films with excellent sticking properties and a constant dose in each spray is 1.5%. Na-CMC has also been reported to maintain stability and release the drug in a controlled manner, thereby increasing its therapeutic efficacy.

a) Chitosan

Aside from being a filmmaker, chitosan also has antimicrobial, antioxidant, and mucoadhesive activity, making it suitable for use in topical drug delivery. Chitosan has a relatively high surface tension. The surface tension of chitosan increases with increasing concentration and molecular weight, but these properties make chitosan difficult to dissolve in water. Surfactants are usually used to improve the solubility of chitosan.

In making FFS from chitosan, Tween 80 can be used to reduce the surface tension. The decrease in surface tension of chitosan goes hand in hand with an increase in the degree of deacetylation and its concentration, but the trend is not very significant. The use of PEG 400 can also increase the stability and solubility of drugs in chitosan. Chitosan also has good conductivity with an increase in molecular weight so that it can be delivered using a electrostatic spray. Chitosan viscosity also decreases with increasing degrees of deacetylation. With these properties, chitosan can form films with denser droplet densities with smaller droplet diameters, ranging from 4–27 μm. Chitosan is also more hydrophilic at higher degrees (30–40 °C) such as on the skin and eyes.

b) Xanthan Gum

Based on research conducted, the spray- ability of xanthan gum was strongly influenced by its viscosity. The addition of surfactants in the xanthan gum solution decreased the surface tension and reduced the size of the droplet. Interestingly, the viscosity and flow proper- ties were not significantly changed. In addition, the spray angle and coverage area of the xanthan gum solution decreased with increasing xanthan gum concentration.

B. SYNTHETIC POLYMERS [25-29]

a) Carbopol

Carbopol also has thixotropy flow properties. Carbopol itself forms an amorphous hydrogel that is good for open wounds because it can donate or absorb wound moisture. The viscoelastic nature of carbopol allows of deacetylation. However, its hydrophilic nature does not correlate with its permeability to water vapour. The tensile strength of chitosan will also increase with increasing degrees of deacetylation, contrary to its elongation.

b) Cyclodextrin

Cyclodextrin is known to maintain drug stability from crystal deformation. Cyclodextrin is also reported to have a small impact on increasing the viscosity of the film- forming solution, so it is easy to spray.

c) Gellan Gum

Gellan gum (GG) has viscoelastic properties so that it is easily delivered using a spray system. The viscoelastic nature allows GG to melt in consistency

ISSN No:-2456-2165

when sprayed and return to its original texture after being on the sur- face of the skin. In a spray system, GG is also reported to be able to encapsulate cells and deliver them via gel droplets in situ.

GG has thermosensitive properties that are very beneficial in spray systems. Its thermosensitive nature makes it easy to change shape from solution to gel when contacting surfaces with temperatures higher than room temperature increase in the diffusion coefficient of the drug. The combination of Carbopol and Poloxamer is said to be better than using Carbopol alone. At a concentration of 0.05 %, the polymer combination produces a film with good spray ability (spray angle, drying time, and uniform content per spray) with an acceptable release of the drug. Carbopol is also known to produce gels with characteristics that are more resistant to heating.

d) Eudragit
Eudragit is available in various types with different pur- poses for use. Generally, these synthetic polymers are used as additives to tablets for modifying drug release.85 However, Eudragit is also known to increase drug permea- tion in the skin,34,86,87 so that its application in topical preparations is widely developed.

Eudragit EPO, Eudragit E 100, Eudragit S 100, Eudragit RL 100, and Eudragit RS 100 produce transparent and shiny films while Eudragit RSPO and RLPO do not. Films produced by Eudragit EPO, Eudragit E 100, Eudragit RL 100, and Eudragit RS 100 cannot be washed away with water. In contrast, Eudragit S100 provides film that can be removed with water after being applied to the skin. This is because Eudragit S100 can dissolve above pH 7. Eudragit S100 also does not cause any skin irritation.

Eudragit RS 100 has been reported to have good spray ability, adhesiveness, and flexibility. However, use above a concentration of 15% can reduce the ability to wash with water, whereas Eudragit RLPO produces better films at a level of 10.05% in a mixture with ethyl cellulose 5.02 %.

e) Lutrol
Lutrol F-127 has film characteristics and spray patterns similar to Carbopol 940 but produces a more uniform dose of the drug in each spray, with a smaller standard deviation. Lutrol F-127 also produces films with better drug release compared to Carbopol 940. No skin irritation has been reported.

f) Plasdone
Research conducted by Lu et al32 shows that Plasdone can increase testosterone permeation better than other polymers. The best testosterone permeation sequence was Plasdone > Eudragit EPO > PVP K30 > Eudragit RL. This was due to the nature of the polymer, which can inhibit the crystallisation of testosterone, thereby increasing its flux.88,89.

g) Kollidon
Kollidon is a synthetic polymer that is also widely used in the pharmaceutical world. There are several types of Kollidon with different characteristics appropriate for solid, semisolid, and liquid preparations. In liquid and semisolid forms, Kollidon can increase solubility and permeability, and control drug release.

Kollidon® 30 has been reported to form transparent, thin, and well-dispersed films. During 28 days of storage, the pH of Kollidon® 30 remained stable without significant changes.43 Kollidon® 30 and Kollidon® VA64 have the ability to act as antinucleants that can inhibit testosterone crystallisation. Drug permeation in the skin has also been reported to be increased with the use of Kollidon® 30 films.

C. EXCIPIENTS USED IN FILM-FORMING SPRAYS [30-34]

Besides polymers, other excipients are also added for the purpose of improving the quality of the preparation and its therapeutic efficiency. The following is a list of excipients (Table 3) commonly used in film-forming spray systems.

a) Crosslinkers
The use of crosslinkers can affect the elasticity, viscosity, solubility, glass transition, and film stiffness of the polymer. The use of NaCl as a crosslinker in gellan gum also affects the gel's sensitivity to temperature, so that film formation is better and faster. NaCl also increases cell encapsulation in gellan gum.

b) Permeation Enhancers
Eutectic mixes are frequently used to increase the penetration of drugs. A mixture of menthol and camphor is one of the strongest eutectic mixtures. It is appropriate to use camphor and menthol as a penetration enhancer for medications that are also hydrophobic since they combine to generate a hydrophobic combination. However, menthol and camphor might promote skin peeling and the development of pores. A blend of camphor and menthol is characterised by a warm feeling that develops into a cold feeling that comes on gradually.

In a Franz diffusion cell with nylon membranes, the eutectic mixture of camphor and menthol significantly improves the penetration of the antifungals fluconazole, clotrimazole, and voriconazole. Camphor and menthol can improve medication penetration by interacting with the lipids in the stratum corneum since they have hydrophobic characteristics.

c) Plasticisers and Stabilising Agents
The plasticizer keeps the film elastic during film formation and stops it from cracking. Plasticizers can also improve the penetration of medicines and keep active molecules stable. According to reports,

ISSN No:-2456-2165

PEG and PG play a part in enhancing the penetration of antifungal medications. In addition to its function as a plasticizer, PG also serves as a solubilizer, which is helpful in delivering medications through the skin. Because PG has a sizable impact on the viscosity of the film-forming solution, the concentration must be taken into account. The use of PG as a mixed solvent to stop the crystallisation of testosterone does not work well when combined with water or ethanol. 68 Less than 5% of PG is necessary to increase medication penetration.

PEG 400 can also increase the volume per spray of film-forming solution. The amount per spray increases with increasing PEG 400 concentrations. The covered spray area also increases with increasing PEG 400 levels. This is associated with a decrease in vapour pressure due to the presence of PEG as a non-volatile solvent.

d) Solvents
Both volatile and non-volatile solvents are utilised in the FFS system. The goal is to balance the pace of film drying. Drugs find it difficult to enter and escape from films that dry out too soon and produce a hard film. To speed up the drying of the film, the active ingredient is typically dissolved in the solvent until it reaches saturation.

D. EVALUATION TESTS [35-42]

a) pH
To increase the stability of the active ingredient or make it acceptable for the application location, the pH value is tested and modified. The pH of diabetic wounds ranges from 6.5-8 for skin pH of 4-6, while burns heal more quickly below pH 7.32. The preparation's pH adjustment attempts to stop inflammation and modifications in the physiological state of the wound during the healing process. In addition, the degree of ionisation in the dosage can influence how much of the medicine permeates the skin.

b) Viscosity
Each type and concentration variation of the polymer will result in a different viscosity. The viscosity of the film forming solution will affect its sprayability, so this is an important parameter, especially in MDS. Increasing the concentration of the film-forming solution can reduce the coverage area of the spray.

c) Tonicity
The application of film-forming solution to certain parts of the body such as wound and eye mucosa requires the tonicity adjustment of the film-forming solution. Non- isotonic preparations can cause mucosal irritation and eye pain. For this reason, the tonicity of the preparations needs to be calculated and adjusted using the Kahar method. The following equation is used to determine the isotonic concentration of the materials.

d) Rheological Properties
To ascertain if a substance is thixotropic or not, flow testing is used. If a mixture possesses certain flow characteristics, it can readily pass repeatedly through the sprayer nozzle. The film-forming solution can be thinned by this flowing property as it moves past the nozzle and becomes strained before returning to its normal viscosity after being sprayed (stress is lost). Thixotropic behaviour is characterised by the hysteresis circle, which is the region that is covered by the ascending and descending curves.

e) Bioadhesive Strength of the Film
By sticking a film to the surface of the mouse skin, the bioadhesive strength of the film can be measured (2 x 5 cm). After that, 0.5 mL of distilled water is used to moisturise the skin. Five minutes are given for the film and tissue surface to interact. The overall force (F) required to separate the film from the skin's surface is noted.

f) Tensile Strength and Elongation of the Film
Tensile strength (TS) is the ability of the film to resist applied pressure.117 TS testing aims to determine whether the film formed is resistant to abrasion and flexible so that it can follow the movement of the skin without cracking.

g) Water Washability
The ease of film wetting is assessed in the dried film. The film is washed with water and assessed in ordinal scale, ie easily washed, moderately washed, and poorly washed.34,40 The ease of sprinkling with water will be useful if the film-forming solutions contact with sensitive areas in the body such as eyes and mouth.

h) Fluid Affinity
This test is carried out to see how the ability of the film formed to absorb moisture from the wound or provide moisture to the wound. An adequate supply of moisture to the injury will speed healing, but excess moisture can cause erosion of the wound tissue.

i) Occlusion Potential or Water Vapor Permeability of the Film

It's crucial to establish the film's permeability to wound fluid because it influences the wetness of the wound. Infection will result from too much dampness, which will promote the growth of microorganisms. For this test, filter paper is placed over the mouth of a glass beaker holding 50 mL of water. A film-forming solution is sprayed on one of the papers, and then the film is allowed to develop. Following that, the beaker is kept at ambient temperature and humidity. Based on the decreased water weight in the beaker, the film's water permeability is calculated.

ISSN No:-2456-2165

j) Surface Morphology of the Film
This test is carried out to determine the microscopic shape, surface roughness, and homogeneity of the film using scanning electron microscopy (SEM) or transmission electron microscopy (TEM).

k) Film Formation/Drying/Evaporation Time
How rapidly the film forms once the solution is sprayed is determined by the drying time of the film. In some cases, the glass's surface is coated with the solution, which is then left to air dry at room temperature. In other research, the surface of the glass plate is coated with a mixture of activated silica gel and dye to provide absorption.

Applying a film-forming solution to the skin allows for the direct observation of drying time. A glass plate is put against the film without being touched to determine whether the film has dried. The film is considered to have dried if there is no sign of water adherence to the glass. The drying time may differ from using glass plates in the film drying time test since this approach is more accurate because the skin contains pores and body heat.

Cotton wool is used to gently press the dry film. The quantity of cotton wool fibres adhered to the film serves as a gauge for the viscosity of the material. The film's adhesiveness is rated as high if there is a thick connected fibre, medium if there is a thin attached fibre, and low if there is little to no attached fibre. It requires attention when in motion since stickiness is evaluated to determine whether the film will easily attach to clothing or other items.

l) Spraying Force
This test is carried out to find out how much pressure is needed to spray the film-forming solution. The tool that can be used is Plus texture analyser (Stable Micro Systems)

m) Potential Drug Aggregation
Changes in particle size will undoubtedly affect sprayabil- ity. Some methods to determine the potential for of a drug are zeta potential and size exclusion chromatography (SEC).

n) In vitro Drug Penetration/Release Study
Franz diffusion cells are typically employed in this test as compartment separators together with cellulose membranes (pore size 0.45 m), nylon membranes (pore size 0.22 mm), or silicone membranes. The medium is phosphate buffer with a pH of 7.4. The film-forming solution is added to the donor compartment once the compartment system is prepared. At specific time intervals, a sample of the solution that diffuses through the cells is obtained, and the equipment is then used to measure it. Following the collection of samples, the same amount of fluid is replaced.

o) In vivo Skin Irritation Test
The film-forming solution is applied to the skin of test animals such as mice and rabbits after being shaved. Irritation, inflammation, erythema, oedema, papule forma- tion, flakiness, and dryness are observed 24 hours – 7 days after application.

p) Stability Study
Changes in particle size, chemical and 3D structures, levels, and therapeutic action of active compounds after storage under various settings are characteristics that are frequently investigated. Thermal analysis is occasionally used to determine whether or not meta- stable active compounds recrystallize. The medicine can be kept in its original crystalline form thanks to the antinucleon polymer that is being used. The drug's dosage per spray and its spray pattern as a metered-dose spray will be retested in a number of studies. During the storage term, the dose must be ensured.

V. CONCLUSION

FFS can be a promising drug delivery system with various benefits. Spray film-forming systems are modern drug delivery systems used for local, topical and transdermal delivery. Natural or synthetic polymers can be used as drug matrices and film formers following the need for increased stability and therapeutic effectiveness of the active sub-stance. Sprayers help form droplets with better and more uniform distribution and dosage of drugs.

REFERENCES

[1.] Sharadha M, Gowda DV, Vishal Gupta N, Akhila AR. An overview on topical drug delivery system – updated review. Int J Res Pharm Sci. 2020;11(1):368–385. doi:10.26452/ijrps.v11i1.1831
[2.] Kaur J, Kaur J, Jaiswal S, Gupta G. Recent advances in topical drug delivery system. Pharm Res. 2016;6(7).
[3.] Leppert W, Malec–Milewska M, Zajaczkowska R, Wordliczek J. Transdermal and topical drug administration in the treatment of pain. Molecules. 2018;23(3):681. doi:10.3390/molecules23030681
[4.] Dayan N. Delivery system design in topically applied formulations: an overview. In: Delivery System Handbook for Personal Care and Cosmetic Products. Elsevier; 2005:101–118. doi:10.1016/B978-081551504-3.50009-2
[5.] Ruela ALM, Perissinato AG. Evaluation of skin absorption of drugs from topical and transdermal formulations. Brazilian J Pharm Sci. 2016;52(3):527–544. doi:10.1590/s1984-82502016000300018
[6.] Garg T, Rath G, Goyal AK. Comprehensive review on additives of topical dosage forms for drug delivery. Drug Deliv. 2015;22 (8):969–987. doi:10.3109/10717544.2013.879355
[7.] Chang R-K, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products: formulation development, process development, and

testing of topical dermatologic products. AAPS J. 2013;15(1):41–52. doi:10.1208/s12248-012-9411-0
[8.] Radhakrishnan A, Kuppusamy G, Karri VVSR. Spray bandage strategy in topical drug delivery. J Drug Deliv Sci Technol. 2018;43:113–121. doi:10.1016/j.jddst.2017.09.018
[9.] Ibrahim SA. Spray-on transdermal drug delivery systems. Expert Opin Drug Deliv. 2015;12(2):195–205. doi:10.1517/17425247.2015. 961419
[10.] Algin-Yapar E, Önal Ö. Transdermal spray in hormone delivery. Trop J Pharm Res. 2014;13(3):469–474. doi:10.4314/tjpr.v13i3.23
[11.] Variankaval NE, Jacob KI, Dinh SM. Crystallization of estradiol in an acrylic transdermal drug delivery system. J Biomed Mater Res. 1999;44(4):397–406. doi:10.1002/(SICI)1097-4636(19990315) 44:4<397, AID-JBM5>3.0.CO;2-Q
[12.] Mandal UK, Chatterjee B, Husna F, Pauzi B. A review on trans- dermal spray: formulation aspect mathews journal of pharmaceu- tical science a review on transdermal spray: formulation aspect. Mathews J Pharm Sci. 2016;1(March):006.
[13.] Chavan P, Bajaj A, Parab A. Topical sprays: novel drug delivery system. Int J Pharm Chem Res. 2016;2(2):102–111.
[14.] Parmar K, Patel MB. A review on sublingual spray: novel drug delivery system. Int J Pharm Sci Res. 2017;8(11):4533–4539. doi:10.13040/IJPSR.0975-8232.8(11).4533-39
[15.] Aravindhanthan V, Anjali PB, Radhakrishnan A. Sublingual spray: a new technology oriented formulation with multiple benefits. Int J Res Pharm Sci. 2019;10(4):2875–2885. doi:10.26452/ijrps.v10i4.1567
[16.] Algin-Yapar E, Inal Ö. Transdermal spray in hormone delivery. Trop J Pharm Res. 2014;13(3):469. doi:10.4314/tjpr.v13i3.23
[17.] Kumar Mandal U, Chatterjee B, Husna F, Pauzi B. A review on transdermal spray: formulation aspect. Rev Transdermal Spray Formul Asp M J Pharma. 2016;1(1):6.
[18.] Ranade S, Bajaj A, Londhe V, Babul N, Kao D. Fabrication of topical metered dose film forming sprays for pain management. Eur J Pharm Sci. 2017;100:132–141. doi:10.1016/j.ejps.2017.01.004
[19.] Kathe K, Kathpalia H. Film forming systems for topical and trans- dermal drug delivery. Asian J Pharm Sci. 2017;12(6):487–497. doi:10.1016/j.ajps.2017.07.004
[20.] Frederiksen K, Guy RH, Petersson K. The potential of polymeric film-forming systems as sustained delivery platforms for topical drugs. Expert Opin Drug Deliv. 2016;13(3):349–360. doi:10. 1517/17425247.2016.1124412
[21.] Kim DS, Kim JS, Lee MC. Thin film forming technique based on hybrid spray coating using electrostatic force and air pressure. Jpn J Appl Phys. 2014;53(5S3):05HC08. doi:10.7567/JJAP.53.05HC08
[22.] Urkan E, Guler H, Komekci F. A review of electrostatic spraying for agricultural applications. Tarim Makinalari Bilim Derg. 2016;12 (4):229–233.
[23.] Zhuang C, Zhong Y, Zhao Y. Effect of deacetylation degree on properties of Chitosan films using electrostatic spraying technique. Food Control. 2019;97:25–31. doi:10.1016/j.foodcont.2018.10.014
[24.] Zhong Y, Zhuang C, Gu W, Zhao Y. Effect of molecular weight on the properties of chitosan films prepared using electrostatic spraying technique. Carbohydrate Polymer. 2019;212(May2018):197–205. doi:10.1016/j.carbpol.2019.02.048
[25.] Tran TTD, Tran PHL. Controlled release film forming systems in drug delivery: the potential for efficient drug delivery. Pharmaceutics. 2019;11(6):290. doi:10.3390/pharmaceutics11060290
[26.] Baio FHR, Antuniassi UR, Castilho BR, Teodoro PE, Silva EE. Correction: factors affecting aerial spray drift in the Brazilian Cerrado. PLoS One. 2019;14(6):e0217957. doi:10.1371/journal.pone.0217957
[27.] Gaytan I, Nicolas B, Gouriou F, Leru JP, Mallarach J. Effect of working pressure, fluid temperature, nozzle type and nozzle orifice size, on spray characteristics using viscous feed additive DL-2-hydroxy-4-(methylthio)-butanoic-acid. Powder Technol. 2018;336(2017):383–392. doi:10.1016/j.powtec.2018.05.045
[28.] Bakshi A, Bajaj A, Malhotra G, Madan M, Amrutiya N. A novel metered dose transdermal spray formulation for oxybutynin. Indian J Pharm Sci. 2008;70(6):733–739. doi:10.4103/0250-474X.49094
[29.] Geh KJ, Stelzl A, Gröne A, Wagner L, Förster B, Winter G., Development of a sprayable hydrogel formulation for the skin application of therapeutic antibodies. Eur J Pharm Biopharm. 2019;142 (November2018):123–132. doi:10.1016/j.ejpb.2019.06.015
[30.] Lu W, Luo H, Wu Y, Zhu Z, Wang H. Preparation and characterization of a metered dose transdermal spray for testosterone. Acta Pharm Sin B. 2013;3(6):392–399. doi:10.1016/j.apsb.2013.10.003
[31.] Lu W, Luo H, Zhu Z, Wu Y, Luo J, Wang H. Preparation and the biopharmaceutical evaluation for the metered dose transdermal spray of dexketoprofen. J Drug Deliv. 2014;2014:1–12. doi:10.1155/2014/697434
[32.] Paradkar M, Thakkar V, Soni T, Gandhi T, Gohel M. Formulation and evaluation of clotrimazole transdermal spray. Drug Dev Ind Pharm. 2015;41(10):1718–1725. doi:10.3109/03639045.2014.1002408
[33.] Dhiman S, Singh TG, Rehni AK. Transdermal patches: a recent approach to new drug delivery system. Int J Pharm Pharm Sci. 2011;3(SUPPL. 5):26–34.
[34.] Bishop SM, Walker M, Rogers AA, Chen WYJ. Importance of moisture balance at the wound-dressing interface. J Wound Care. 2003;12(4):125–128. doi:10.12968/jowc.2003.12.4.26484
[35.] Gohel MC, Nagori SA. Fabrication of modified transport fluconazole transdermal spray containing ethyl cellulose and eudragit® RS100 as film formers. AAPS PharmSciTech. 2009;10 (2):684–691. doi:10.1208/s12249-009-9256-8

[36.] Mori NM, Patel P, Sheth NR, Rathod LV, Ashara KC. Fabrication and characterization of film-forming voriconazole transdermal spray for the treatment of fungal infection. Bull Fac Pharmacy Cairo Univ. 2017;55(1):41–51. doi:10.1016/j. bfopcu.2017.01.001
[37.] Rajab NA. Preparation and evaluation of ketoprofen as dermal spray film. Kerbala J Pharm Sci. 2013;6:1–8.
[38.] Saingam W, Chankana N, Madaka F, Sueree L, Homchuam S. Formulation development of topical film formimg spray from Piper nigrum L. Thai J Pharm Sci. 2018;42(supplement):93–97. doi:10.1134/S0965545X11100087
[39.] Sukhbir K, Navneet K, Sharma AK, Kapil K. Development of modified transdermal spray formulation of psoralen extract. Der Pharm Lett. 2013;5(2):85–94.
[40.] Hakim M, Walia H, Rafiq M, Grannell T, Cartabuke RS, Tobias JD. Oxymetazoline metered dose spray: factors affecting delivery volume. J Pediatr Pharmacol Ther. 2016;21(3):247–251. doi:10.5863/1551-6776-21.3.247
[41.] Ru Y, Gan Y, Zheng J, Zhou H. Design and experiments on droplet charging device for high-range electrostatic sprayer, 2008; 1:561–571. doi:10.5772/18546
[42.] Kwon S-I, Kyung K-H, Park J-Y, et al. Uniform anti-reflective films fabricated by layer-by-layer ultrasonic spray method. Colloids Surf a Physicochem Eng Asp. 2019;580((August):123785):123785. doi:10.1016/j.colsurfa.2019.123785