Section A-Research paper
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Design of Film Forming Spray solution for Antimicrobial Agents

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Abstract:
Conventional formulations for topical administration of drugs have certain drawbacks like poor adherence to skin, poor permeability and compromised patient compliance. 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 substances to the body tissue for longer duration. The objective of the present research work was to formulate and evaluate spray-based film forming systems for fungal and bacterial infections. The formulation was prepared by addition of film-forming polymers to the solvent system followed by addition of plasticizer and drug. Two different Film forming spray solutions were prepared of Clotrimazole and Mupirocin calcium along with ethyl cellulose and eudragit RS 100 as film formers, PEG 400 and PEG 5000 as plasticizer and ethanol, acetone as the solvent mixture. Optimization was done by 3^2 factorial design using Design expert 13 software. The optimized formulations were evaluated for various parameters like viscosity, drying time, spray angle, film formation time, drug release, anti-microbial activity, pH and water washability. Film forming systems will provide a better platform for topical delivery against various skin infections with benefits like controlled release, reduced dosing, water resistance, curbing further infection, reduced risk of wiping out, contact free application, etc as compared to the conventional semisolid dosage forms.
Keywords: film forming spray, infections, spray-based, topical, controlled release, dosing.

INTRODUCTION:

Bacterial skin infections occur secondarily in conditions involving a vulnerable skin barrier such as atopic eczema, as well as primarily such as impetigo. They are mainly caused by *Staphylococcus aureus* and *Streptococci*. Recently, the prevalence of methicillin-resistant *S. aureus* has been increasing.[1]

Fungal skin infections are the most common global issue for skin health. Fungal infections are often treated by topical or systemic anti-fungal therapy. Topical fungal therapy is usually preferred because of their targeted therapy and fewer side effects. Advanced topical carriers because of their distinct structural and functional features, overcome biopharmaceutical challenges associated with conventional drug delivery systems like poor retention and low bioavailability.[2]

Hence, topical dosage forms are used widely for treating Bacterial and Fungal Skin infections. Topical drug delivery system can be defined as a direct effect of drug containing medication to the skin to get the effect of drug or to cure disorders. Creams and ointments and patches are used as topical dosage form in conventional dosage forms. Film forming solutions is a Novel topical dosage form.

Topical routes of drug delivery aim for systemic or local effects and offer various advantages, including avoiding first-pass metabolism and the effect of low pH and enzymes in the gastrointestinal tract, as well as a large available surface area. To improve therapeutic efficiency or pharmacokinetic profiles, drugs administered via the topical route are generally made in a dosage system, such as a patch, gel, lotion, cream, ointment, or spray.

Advantages of Topical Drug Delivery are Avoidance of first pass metabolism, Convenient and easy to apply, Achievement of efficacy with lower total daily dosage of drug due to continuous drug input, Avoidance of gastro-intestinal incompatibility, Improve patient compliance. Limitations of Topical Drug Delivery are that Skin irritation and contact dermatitis may occur due to the drug and/or excipients, can be used only for drugs which require very small plasma concentration for action, Drugs of larger molecular size are not easy.

Cream- Advantages: Convenient and easy to apply, Easy termination of medications when needed, Avoid alteration of drug levels inter-and intra- patent variations. Disadvantages: Skin irritation, some drugs show low penetrable through skin, Possibility of allergic reactions, small plasma concentration, larger particle size drug is showing the poor effect to be absorbed by the skin.[3]

Disadvantages of an ointment: Application with finger tip may contaminate the formulation or cause irritation when applied.[4]

Patches may cause skin irritation and hence may not be preferred.
In recent decades, various innovations have continued to be developed to obtain efficient and effective spray preparations. One of them is a film-forming spray (FFS) which has been applied in multiple fields, such as the food industry, cosmetics, pharmaceuticals, plantations, etc. FFS generally consists of active substances, enhancers, and polymers that are dissolved in organic solvents. A thin, non-sticky film forms that can increase the contact time and permeability of the drug, resulting in continuous drug release, and can prevent crystallisation so that more drug is available to provide therapeutic effects compared to other conventional topical preparations. [14]

The type of nozzle, the size of the aperture, the pressure of spray applied, and the nature of the liquid strongly influence the sprayability of FFS. The viscoelastic, in situ gel, pH and thermal-sensitive properties of FFS are essential to study to determine what aspects need to be considered in selecting polymers, solvents, and other excipients. Therefore, this review explores the types of polymers, excipients, and sprayers commonly used in FFS and the evaluation standards needed to determine the quality of FFS for better development.

Film-forming sprays offer many advantages compared to conventional topical preparations because they can provide uniform drug distribution and dose, increased bioavailability, lower incidence of irritation, continuous drug release, and accelerated wound healing through moisture control. Film-forming sprays consist of polymers and excipients that improve the characteristics of preparations and enhance the stability of active substances. Each type of polymer and excipient will produce films with different features. Therefore, the various types of polymers and excipients and their evaluation standards need to be examined for the development of a more optimal form of film-forming spray. It includes information on polymers as film-forming matrices and the application of these sprays for medical purposes or for potential medical use. This report discusses the types and concentrations of polymers and excipients, sprayer types, evaluations, and critical parameters in determining the

sprayability and film characteristics. It can be concluded that both natural and synthetic polymers that have in situ film or viscoelastic properties can be used to optimize topical drug delivery.[4]

Definition: An FFS is a drug delivery system in the form of a sprayed solution that will form a film when it contacts the target therapeutic site by utilizing the polymer as a matrix for film formation.

After forming the film, the drug release process is similar to a patch, in which the polymer matrix containing the drug will release it in a sustained fashion. However, in contrast to topical patches and other topical preparations, films form following the pattern of the skin or wound since deep indentations can be exposed to small droplets of the film-forming solution. Of course, this greatly facilitates drug access to the target tissue. In a film-forming spray, drug dosages can also be adjusted based on the volume of solution per spray so that systemic or local effects can be controlled. An FFS also provides an even distribution of drugs and spreads well. Ease of use can also increase patient compliance.

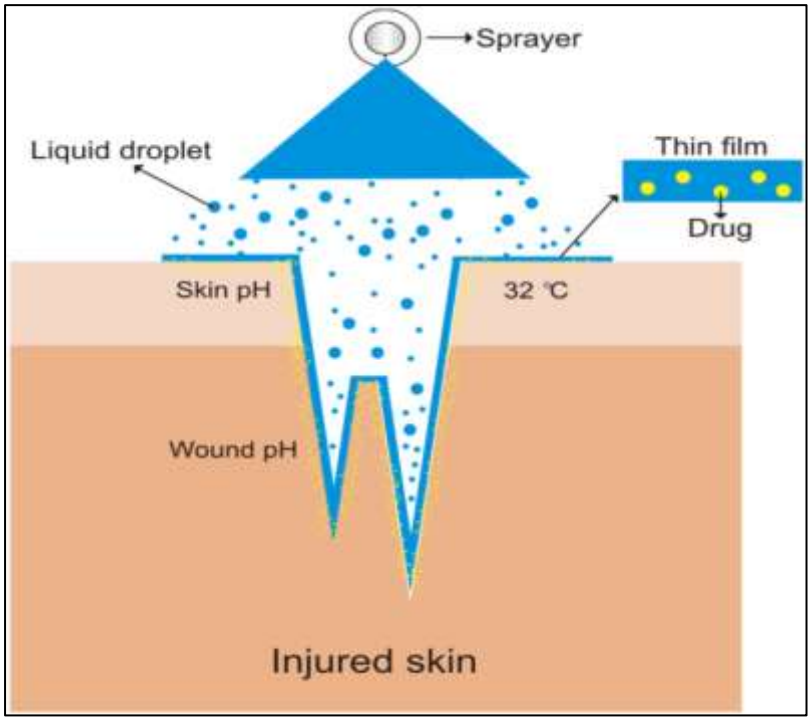

Figure 1 – Mechanism of FFS

The thin film is easy to wash away with water. This thin and non-sticky film also increases patient comfort during activities compared to using patches, ointments, gels, etc., because these have a rough and sticky texture when applied. The thin film also facilitates the permeation of wound moisture so that the balance can be maintained. Inappropriate wound humidity can cause infection or irritation, as happens with the use of patch preparations.

In formation of droplets, the film-forming solution is sprayed using any kind of sprayer. Each sprayer has different specifications and intended uses, but has specific potential in medical applications. [15]

Polymers used in FFS:

Polymers play a significant role in the success of FFS preparations. Aside from being a drug release controller, polymers also act as the film-forming base. Polymers can also prevent the

transformation of molecules, such as the formation of unexpected crystals. General considerations in the selection of polymers are its ease of being washed away by water, stability, biodegradability, and non-irritating properties. Polymers used in FFS can be natural or synthetic as long as they have in situ gel or viscoelastic properties.

Polymers that have thermo-sensitive properties will form a solution at room temperature and turn into a gel when they are exposed to the body temperature, while those that have pH-sensitive properties will form a solution at a certain pH and turn into a gel if the pH of the system changes. Viscoelastic polymers start at a thick consistency but can become elastic when placed under pressure (sprayed) and return to a thick consistency after the pressure is removed.

Cellulose - Ethylcellulose forms films that are easily washed away with water. The concentration of ethyl cellulose that produces films with excellent characteristics is 5.02–5.25% and is generally combined with Eudragit. Hydroxypropylmethylcellulose (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.[16]

Eudragit - Eudragit is available in various types with different purposes for use. Generally, these synthetic polymers are used as additives to tablets for modifying drug release. However, Eudragit is also known to increase drug permeation in the skin, 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.

Eudragit *RS* 100 has been reported to have good sprayability, adhesiveness, and flexibility. However, use above a concentration of 15% can reduce the ability to wash with water.
Besides polymers, other excipients are also added for the purpose of improving the quality of the preparation and its therapeutic efficiency.

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.

Permeation Enhancers –
Eutectic blends are often used as enhancers to drug permeation. One of the most potent eutectic blends is a mixture of camphor and menthol. Camphor and menthol form a hydrophobic mixture, so it is suitable as a penetration enhancer for drugs that are also hydrophobic. However, camphor and menthol can cause leaching and the formation of pores in the skin. A warm feeling followed by a cold feeling that builds slowly is characteristic of a mixture of camphor and menthol. The eutectic mixture of camphor and menthol significantly increases the permeation of the antifungals, fluconazole, clotrimazole, and voriconazole in a Franz diffusion cell using nylon membranes. Because it has hydrophobic properties, camphor and menthol can increase drug permeation through interactions with the lipids of the stratum corneum.

Research conducted by Lu et al showed that the order of permeation enhancers that is the best for increasing testosterone permeation is azone > isopropyl myristate (IPM) > propylene glycol (PG) > N-methyl-2-pyrrolidone (NMP). Furthermore, the results of a study by Lu et al showed that dexketoprofen permeation was better using lauryl lactate (LA) > IPM > azone > PG as permeation enhancers.

This indicates that the penetration enhancing ability of these compounds varies for each drug. However, azone is very suitable for highly hydrophilic drugs. The combination between azone and PG improves the penetration ability of azone.

Plasticisers and Stabilising Agents –

In the film formation, the plasticiser maintains elasticity and prevents cracking of the film. Plasticisers can also maintain the stability of active substances and increase the permeation of drugs. Polyethylene glycol (PEG) and propylene glycol (PG) are reported to have a role in increasing the permeation of antifungal drugs. Apart from being a plasticiser, PG also has a role as a solubiliser, which is also useful in carrying drugs through the skin. PG has a significant effect on the viscosity of the film-forming solution, so the concentration needs to be considered The use of PG in a mixture with water and ethanol does not have a good effect as a mixed solvent in preventing the crystallisation of testosterone. The effective PG concentration for increasing drug permeation is below 5 %.

PEG 400 can also increase the volume per spray of a 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.

Solvents –

The solvents used in the FFS system include both volatile and non-volatile solvents. The aim is to balance the film drying rate. Films that dry out too quickly and form a hard film make it difficult for drugs to escape and penetrate. The active substance is usually dissolved to saturation in the solvent to facilitate the film drying process.

FFS can be a promising drug delivery system with various benefits. 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 substance. Sprayers help form droplets with better and more uniform distribution and dosage of drugs. Each sprayer also has critical and specific testing specifications and parameters.

MATERIAL AND METHODS

Material:

Drugs were selected from anti-fungal and antibiotic class viz. clotrimazole and mupirocin calcium respectively and it was received as gift sample from Cipla Ltd, Vikroli. Solvents like ethanol, ethyl acetate, propylene glycol, poly ethylene glycol, isopropanol were purchased from Dolphin Pharmacy Instruments Pvt. Ltd. Mumbai, Maharashtra. Eudragit RS 100 was obtained as a gift sample from Evonik Pvt Ltd.

Methodology:

PREFORMULATION:

- Drug M – Anti-bacterial drug (Mupirocin Calcium)
- Drug C – Anti-fungal drug (Clotrimazole)

- Solvent used as per the solubility of the Anti-bacterial and Anti-fungal drugs: Ethyl alcohol, iso-propyl alcohol, Acetone.
- Film forming polymers used: Eudragit S-100, Eudragit RS-100, Ethyl cellulose.
- Plasticizer used: PEG 400, PEG 5000

Table 1 – Pre-formulation batches

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	0.75	-	-	0.75	-	-
Ethyl cellulose	-	0.75	-	-	0.75	-
Eudragit S100	-	-	0.75	-	-	0.75
PEG 400	0.05	0.05	0.05	0.05	0.05	0.05
Iso-propyl alcohol:Acetone (8:2)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%

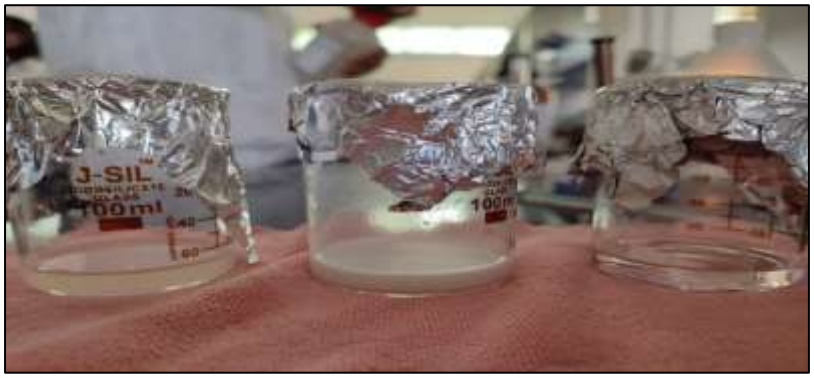

Figure 2 – Pre-formulation trials

Table 2 – Pre-formulation batches

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	1	-	0.5	1	-	0.5
Ethyl cellulose	-	1	0.5	-	1	0.5
PEG 400	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol:Acetone (8:2)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%

Table 3 – Preformulation batches

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	1	-	0.5	1	-	0.5
Ethyl cellulose	-	1	0.5	-	1	0.5
PEG 5000	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol:Acetone (8:2)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%

FORMULATION:

- After conducting various developmental trials, screening of excipients was done which were preferred for developing the film forming topical sprays.
- Design expert 13 software was used for optimization purposes.
- 3^2 factorial design was used for optimization of the batches.

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	-	0.25	0.5	-	0.25	0.5
Ethyl cellulose	1	0.75	0.5	1	0.75	0.5
PEG 5000	0.3	0.3	0.3	0.3	0.3	0.3
Ethanol:Acetone (7:3)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%

- The concentration of Eudragit RS100 and Ethyl cellulose were selected as independent variables and their three levels were chosen as +1, 0, -1 respectively.
- Parameters like appearance, pH, drug content, film drying time, viscosity, volume of the solution delivered upon actuation and spray angle were taken as the dependent variables.
- After screening of excipients, it was found that Eudragit RS100 and Ethyl cellulose were suitable as film formers and PEG 5000 was suited as a plasticizer.
- The optimized batches are mentioned in the tables below:

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	0.25	0.75	0.5	0.25	0.75	0.5
Ethyl cellulose	0.75	0.25	0.5	0.75	0.25	0.5
PEG 5000	0.2	0.2	0.2	0.2	0.2	0.2
Ethanol:Acetone (7:3)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%

Table 4 – Formulation batches

Table 5 – Formulation batches

Formulation Preparation:

Quantity- 10 ml
Batches- 3 batches each
Drug M - Anti bacterial drug
Drug C - Anti fungal drug

Table 6 – Formulation content

Ingredient	Used as
Ethyl Cellulose	Film forming agent
Eudragit RS100	Film forming agent
PEG 5000	Plasticizer
Ethyl Alcohol	Solvent
Acetone	Co-solvent
Ethyl alcohol	q.s. 100%

Table 7 – Formulation batches of Drug M

Drug M	M1	M2	M3
Ethyl cellulose	1g	0.75g	0.5g
Eudragit RS100	0g	0.25g	0.5g
PEG 5000	0.3g	0.3g	0.3g
Ethanol	7ml	7ml	7ml
Acetone	3ml	3ml	3ml

Table 8 – Formulation batches of Drug C

Drug C	C1	C2	C3
Ethyl cellulose	1g	0.75g	0.5g
Eudragit RS100	0g	0.25g	0.5g
PEG 5000	0.3g	0.3g	0.3g
Ethanol	7ml	7ml	7ml
Acetone	3ml	3ml	3ml

Procedure-

Mix Ethanol and Acetone in a beaker

↓

Dissolve Film forming agents completely and then add drug

↓

Lastly add PEG 5000 and dissolve completely

↓

Transfer this FFS into a Spray bottle (container)

Figure 1 – Formulation batches

EVALUATION PARAMETERS:

1. **Organoleptic evaluation –**
   The FFS was studied for physical characteristics such as colour, and appearance by visual inspection and testing.
2. **pH -**
   The pH value is measured and adjusted to improve the stability of the active substance or make it suitable for the area of application. For skin pH ranging from 4–6, the pH of diabetic wounds ranges from 6.5–8, whereas faster healing time for burns occurs below pH 7.32. The pH adjustment of the preparation aims to prevent irritation and changes in

the physiological condition of the wound in the healing process. Besides, the pH value of the dosage can also affect drug permeation through the skin based on the degree of ionization.

Procedure:

a) Put the meter into calibration mode.

b) Decide on the calibration type and collect the buffers.
c) Decant the buffers into suitable containers.
d) Perform the first point of the calibration.
e) Rinse the electrode
f) Perform the next point of the calibration and rinse again.
g) Put the meter into measurement mode
h) Measure your sample
i) Rinse the electrode
j) Store the electrode properly.

3. **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 FFS. Increasing the concentration of the film-forming solution can reduce the coverage area of the spray**.**[8]

Brookfield viscometer was used to measure the viscosity by using small volume adaptor with a thermos stated water jacket and ULA-S00 spindle. A total of 20 mL of the sample was taken in a cylinder and the spindle was rotated at 10 rpm speed at 25 ± 1 °C. The samples were equilibrated for 10 min before the measurement; moreover, the instrument was equipped with a temperature control unit. An average of three readings was taken for all the formulations.

4. **Film formation time –**

The film forming time of the film is measured to determine how quickly the film forms after the solution are sprayed.

5. **Drying time** –

The solution is sprayed on the surface of the tiles and then allowed to dry at room temperature. Drying time can also be observed directly by applying a film-forming solution to the skin. To find out if the film has dried, a glass plate is placed against the film without being pressed. If there is no water adhesion to the glass, the film is said to have dried.[9]

Procedure: The time taken by the polymeric solution to dry on a glass slide or the hand arm is referred to as drying time. The drying time was recorded by using a digital stopwatch.

6. **Water Washability –**

The ease of film wetting is assessed in the dried film. The film is washed with water and assessed in ordinal scale, i.e easily washed, moderately washed, and poorly washed. 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.[9]

7. **Spray angle** –
   The method of impingement of spray on a piece of paper was used for the study.
   Sudan red (10 mg) was dissolved in formulation to facilitate visualization. The sprays were actuated in horizontal direction onto a white paper mounted at a distance of 15 cm from the nozzle. The radius of the circle, formed on the paper, was recorded in triplicate from different directions. Spray angle (θ) was calculated by eq Spray angle (ð)= tan-1(l/r), where l is the distance of paper from the nozzle, and r is the average radius of the circle.[4]

8. **Microbiological Evaluation** [10]–

Microbiological evaluation is done to check the intensity and the anti-microbial activity of the formulation and to determine its efficacy in treating a particular disease.

Inoculation media:

- For Anti-Bacterial testing – Nutrient agar is used
  2.8 gram of nutrient agar is dissolved in 100 ml in a conical flask. The mouth of conical flask is then sealed by using cotton and aluminium foil.
  It is then sterilized by keeping it in Autoclave for 20 mins at 15 atm pressure.

- For Anti-fungal testing – Sabouraud dextrose agar is used
  6.5 gram of Sabouraud dextrose agar is dissolved in 100 ml water and the process for sterilization is same as mentioned above.

- This sterilized agar is then poured into hot air oven sterilized petri dishes, upto 1/3rd of the petri dish is filled with agar medium.

- It is then allowed to set and then afterwards it is inoculated with bacteria or fungus by using spread plate technique.
  Bacterial species used: *Staphylococcus aureus, Bacillus subtilis*
  As fungal species were not available for anti-microbial testing, fungus was inoculated in the agar medium by keeping it in the contaminated open environment for 5-10 mins.

- And then, Microbiological assay is performed by using either Cup plate technique or Disk diffusion method.

- Zone of inhibition is calculated to determine the efficacy of the formulation and it's ability to inhibit microbes.

Culturing Techniques-

1. Spread Plate Technique:[11]

The spread plate method is a microbiological laboratory technique for isolating and counting the viable microorganisms present in a liquid sample by spreading a certain volume of the sample over an appropriate solidified culture media. Following the incubation, in a successful spread plate, there will be the formation of evenly distributed discrete colonies all over the surface of the culture media.

Objectives of Spread plate technique-

- To isolate the microorganisms from the liquid specimen (or suspension)
- To calculate viable microbial load by counting colony formation unit (CFU) per mL

- To isolate the pure culture of microorganisms from a mixed population
- To isolate microorganisms in discrete colonies in order to study their colony characters
- To obtain sufficient growth for conducting antimicrobial sensitivity testing and biochemical studies.

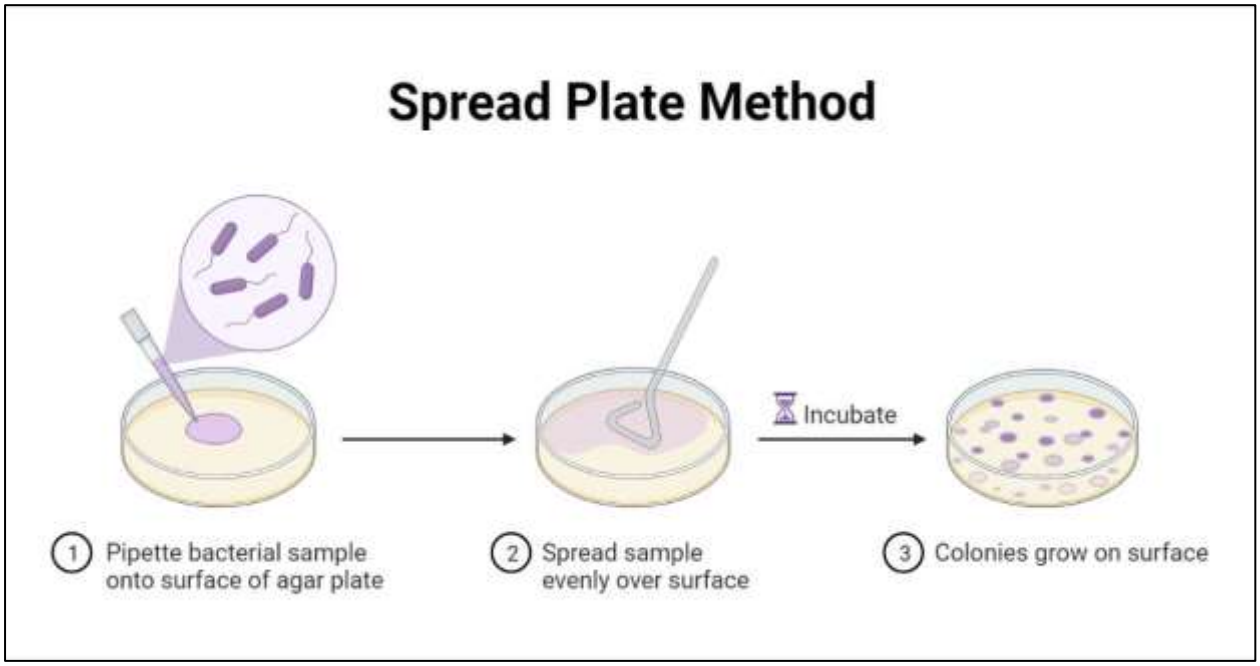

Figure 2 – Spread plate technique for inoculation of bacteria

Microbiological Assay Methods[12]-The microbiological assay of antibiotics is done by comparing the zone of inhibition formed by the microorganisms to a specific concentration of antibiotics having a known activity. There are different types of methods for microbiological assay of antibiotics like cup plate method and disc diffusion method.

1. Cup Plate Method: Prepare nutrient agar plate inoculated with test organism, with a depth of 4-5mm and then allow it to solidify. Divide the NA plate into four equal portions. Then with the help of a sterile borer make four cavities one in each portion. Then fill three cavities with antibiotic solution and in one fill the standard solution. Then slowly incubate the plates at 37^0C for 24 hours. After incubation measure the zone of inhibition.

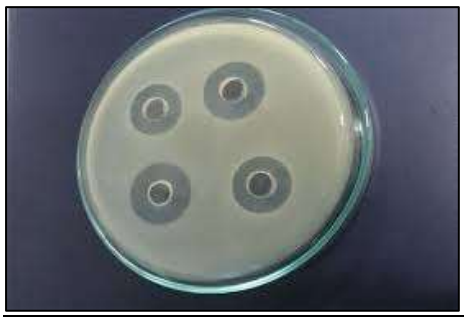

Figure 3 – cup plate method

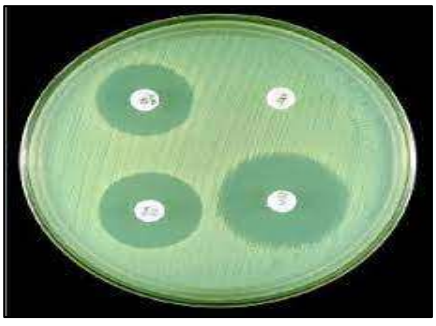

Figure 6 – disk diffusion method

2. Disk Diffusion Method:_It is also known as Kirby Bauer method. Prepare nutrient agar plates and with the help of a cotton swab spread the broth solution containing the test microorganism uniformly. Then with the help of a sterile forceps put the required

antibiotic disc slowly above the plate. Then incubate the plate at 37^0C for 24 hours. Measure the one of inhibition formed.

Zone of Inhibition studies[13]-

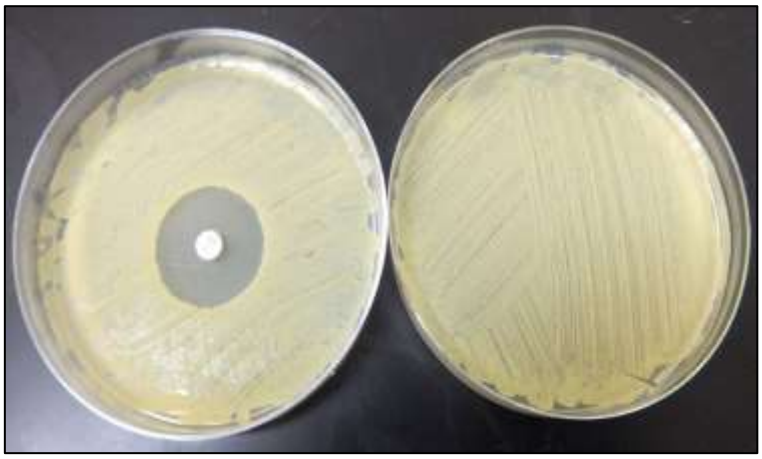

Figure 7 – zone of inhibition

A Zone of Inhibition Test, also called a Kirby-Bauer Test, is a qualitative method used clinically to measure antibiotic resistance and industrially to test the ability of solids and textiles to inhibit microbial growth.

Researchers who develop antimicrobial textiles, surfaces, and liquids use this test as a quick and easy way to measure and compare levels of inhibitory activity.
With this method, approximately one million cells from a single strain are spread over an agar plate using a sterile swab, then incubated in the presence of the antimicrobial object (ex: an oxacillin disk, pictured below). If the bacterial or fungal strain is susceptible to the antimicrobial agent, then a zone of inhibition appears on the agar plate, such as on the agar plate on the left-hand side of the photo below. If it is resistant to the antimicrobial agent, then no zone is evident, such as on the agar plate on the right-hand side of the photo above.

9. **Diffusion studies[4] –**

Franz Diffusion Cell:

Drug permeation can be tested on the abdominal skin of mice or rabbits using Franz diffusion cells. The skin is cleaned of all attached fat tissue still using a cotton swab that has been soaked in propanol or isopropanol, then washed with normal saline solution. Diffusion media include phosphate buffer pH 6.8. On the receptor compartment side, medium flow is achieved using flow-through cells connected to silica tubes at speeds of 0.3 mL-0.6 mL/hr. After the compartment system is ready, the film-forming solution is placed in the donor compartment. Aliquots are then taken from the receptor compartment at specific time intervals, and then the drug levels are measured using an instrument. New diffusion medium is added at the same time, replacing aliquots that are taken to maintain sink conditions.

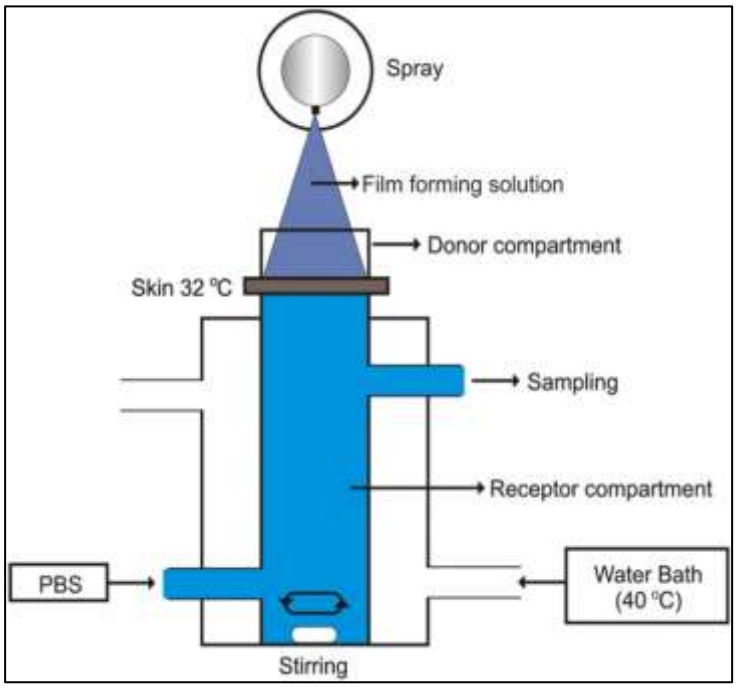

Figure 8 – Franz diffusion cell

In vitro drug diffusion studies on Franz diffusion cell using dialysis membrane of pore size 0.45 microns at 32^{o} C, should be done. These studies are yet to be performed.

RESULT:

Preformulation –

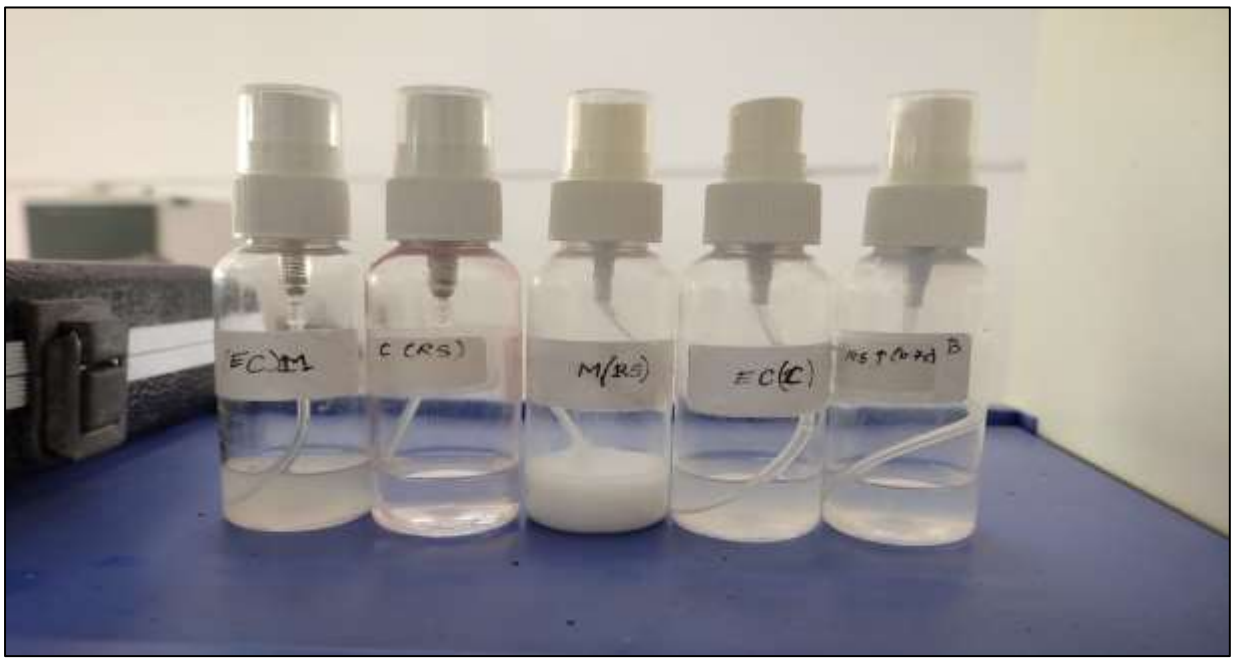

Figure 9 – pre-formulation batches

Table 9 – Pre-formulation table 1 with observations

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	0.75	-	-	0.75	-	-
Ethyl cellulose	-	0.75	-	-	0.75	-

Eudragit S100	-	-	0.75	-	-	0.75
PEG 400	0.05	0.05	0.05	0.05	0.05	0.05
Iso-propyl alcohol:Acetone (8:2)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%
Observation	Opaque and turbid	Translucent	Turbid	Translucent	Turbid	Slight hazy
Inference: Iso-propyl alcohol and S100 were discontinued as they were not suitable for FFS formulation due to solubility reasons and PEG 400 concentration needs to be increased.						

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	1	-	0.5	1	-	0.5
Ethyl cellulose	-	1	0.5	-	1	0.5
PEG 400	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol:Acetone (8:2)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%
Observation	Opaque and turbid	Translucent	Turbid	Clear and transparent	Clear	Slight opaque

Table 10 – Pre-formulation table 2 with observations

Inference: Iso-propyl alcohol was replaced with ethyl alcohol; PEG 400 was not able to form a firm film even after increasing its concentration.

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	1	-	0.5	1	-	0.5
Ethyl cellulose	-	1	0.5	-	1	0.5
PEG 5000	0.1	0.1	0.1	0.1	0.1	0.1
Ethanol:Acetone (8:2)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%
Observation	Film formed	Flexible film	Film formed	Rigid Film	Flexible film	Film formed

Table 11 - Pre-formulation table 3 with observations

Inference: Ethanol was found to be as a suitable solvent as solubility of film forming agents was achieved. PEG 5000 was able to produce good films. Eudragit RS100 showed good results

Formulation –

Figure 10 – Final batches of formulation

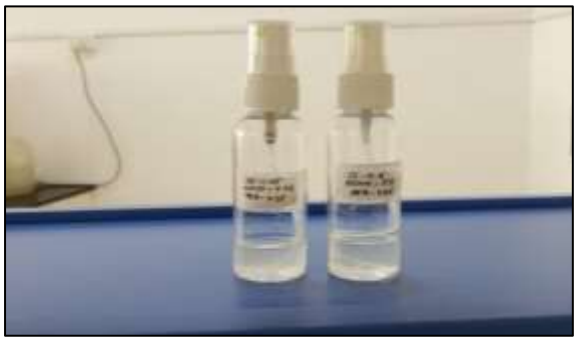

Figure 11- PEG 5000 batches

Figure 12 – varied concentration of PEG 5000

Table 12 – Formulation batches 1 with observations

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	0.25	0.75	0.5	0.25	0.75	0.5
Ethyl cellulose	0.75	0.25	0.5	0.75	0.25	0.5
PEG 5000	0.2	0.2	0.2	0.2	0.2	0.2
Ethanol:Acetone (7:3)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%
Observation	Clear, flexible film	Clear film	Clear film	Clear and Flexible film	Clear film	Clear film

Inference: Batch M2 and C2 were not able to form a flexible film and did not show good washability.

Table 13 – Formulation batches 2 with observations

Ingredients	M1	M2	M3	C1	C2	C3
Drug	2%	2%	2%	1%	1%	1%
Eudragit RS100	-	0.25	0.5	-	0.25	0.5

Ethyl cellulose	1	0.75	0.5	1	0.75	0.5
PEG 5000	0.3	0.3	0.3	0.3	0.3	0.3
Ethanol:Acetone (7:3)	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%	q.s 100%
Observation	Clear Film formed	Flexible, clear film Washable film	Clear and washable film formed	Clear film formed	Flexible, clear and washable film	Clear film formed

Inference: M2 and C2 formulation showed the best results.

Evaluation Results:

The evaluation result of the optimized formulation are as follows:

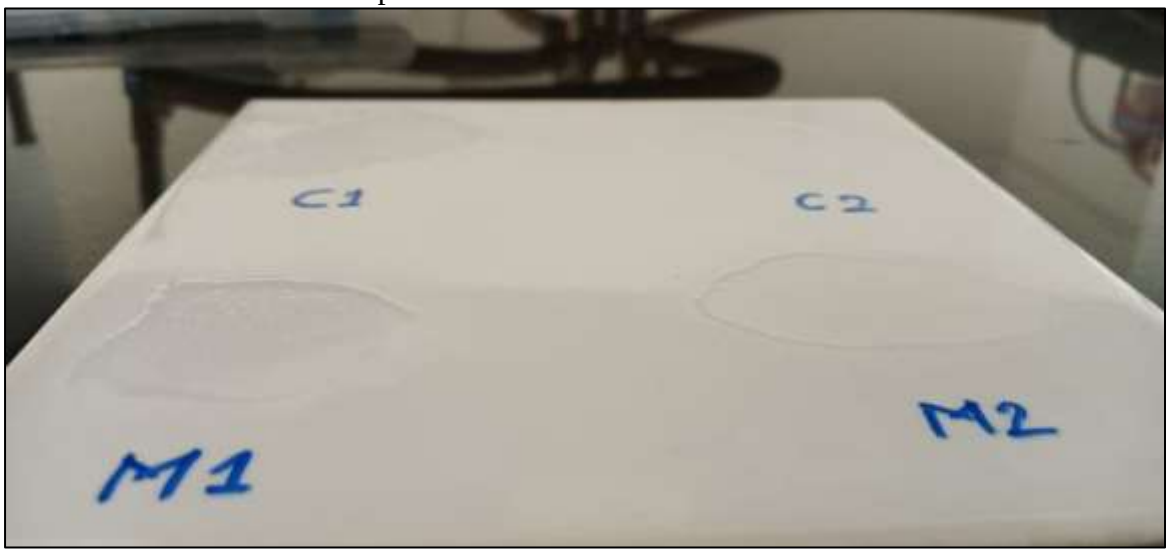

Figure 13 – Film formation of FFS spray

Table 14 – Evaluation results

Evaluation parameters	For Batches of M	For Batches of C
Organoleptic properties	Shiny and Translucent	Shiny and Transparent
pH	5.6±0.2	5.5±0.3

Viscosity	81±2cps	75±2.5cps
Film formation time	23±2 secs	30±3 secs
Drying time	240±5 secs	190±2 secs
Water Washability	Good	Good
Spray Angle	67.52±0.5°	69.18±0.5°
Zone of Inhibition	25±0.24 mm	30±0.54 mm

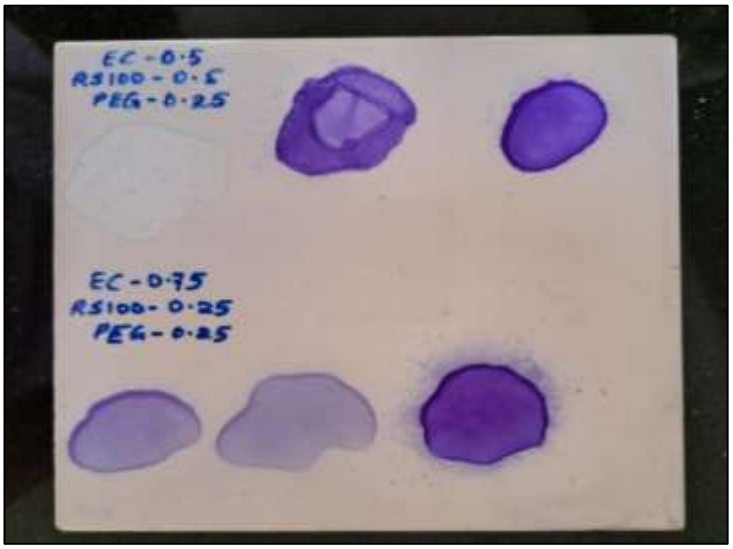

Figure 14 – Drying time and film forming

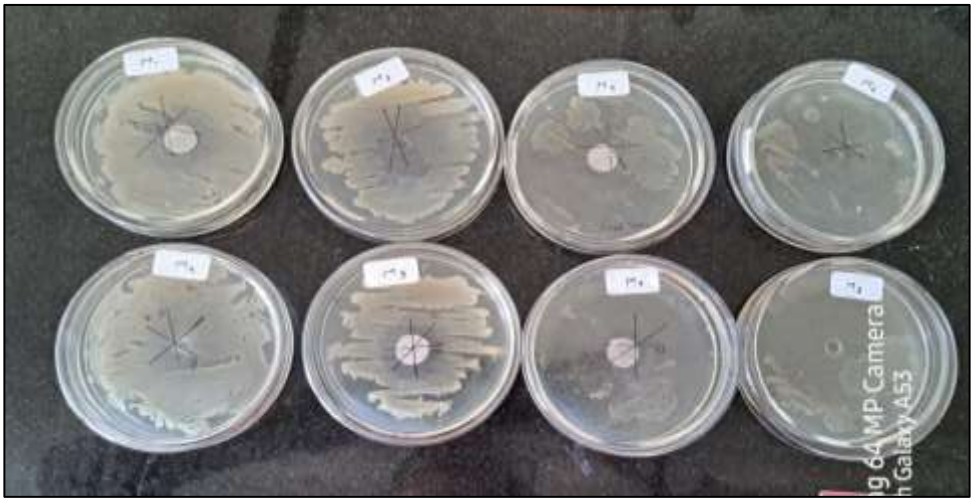

Figure 15 – Anti-microbial activity result of Drug M with zone of inhibition

Figure 16- Anti-microbial activity of Drug C

Figure 17- Zone of inhibition of Drug C

OUTCOME:

- Film forming systems will provide a better platform for topical delivery against various fungal and bacterial infections.
- It will give various benefits over other dosage forms (creams, ointments, patches) like controlled release, reduced dosing, water resistance, curbing further spread of infection, reduced risk of wiping out and contact free application.

Applications-

- The prepared FFS formulation can be used to treat topical fungal and bacterial diseases such as Athlete's foot, Candidiasis, Ringworm, Cellulitis, Impetigo.

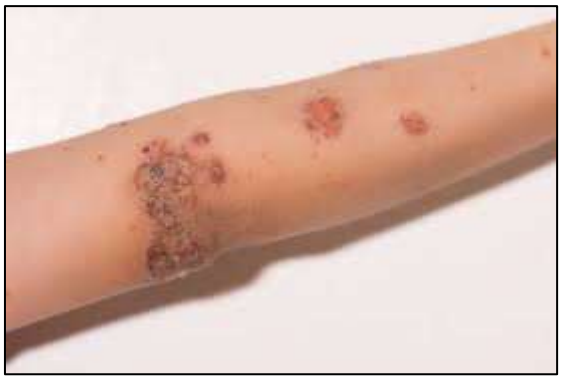

Figure 18- Athlete's foot

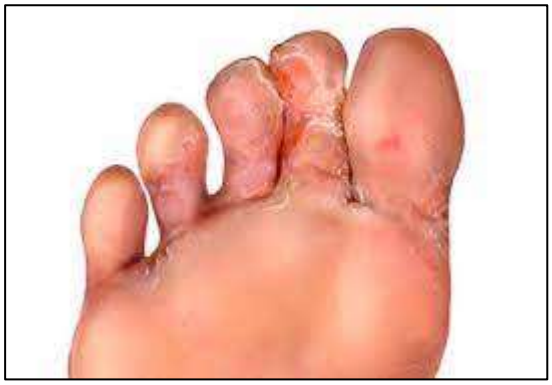

Figure 19- Impetigo

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