JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

REVIEW ON PREPARATION AND EVALUATION OF HERBAL TRANSDERMAL THIN FILM FORMING SOLUTION

[1]Pranali S. Mali, [2]Trupti P. Lade, [3]Akanksha R. More, [4]Ketaki S. Phalke, [5]Aditi S. Haval.

[1,2,3,4,5]Rajarambapu College of Pharmacy, Kasegaon

Abstract : Thin film forming solutions offer an innovative substitute to conventional topical and transdermal drug delivery systems, addressing several limitations associated with traditional dosage forms. These solutions, applied as liquid or semisolid preparations, transform upon application to the skin, leading to the formation of a residual film after the evaporation of volatile componentsThis approach improves patient adherence because of its fast dissolution, simple administration, and rapid onset of effects.The incorporation of extracts like Piper betel leaves, known for their anti-inflammatory, antifungal, and antioxidant properties, further enhances the therapeutic potential of these films. This review highlights the mechanisms behind thin film formation, outlines their advantages and disadvantages, and discusses possible applications along with key components and limitations.

Index terms : Film forming solution, Transdermal drug delivery system

I. Introduction

Structure of skin

The skin is the human organ that is easiest to access, yet because of its poor permeability, it also serves as a barrier against pathogens. It has a surface area of about 2 square metres. It is crucial in controlling blood pressure and keep the body at the proper temperature. Drug administration through the skin is done to treat skin conditions in tropical climates or to allow for transdermal drug absorption into the bloodstream. It performs several vital roles, including protecting the body from external physical and chemical hazards and preventing excessive water loss.

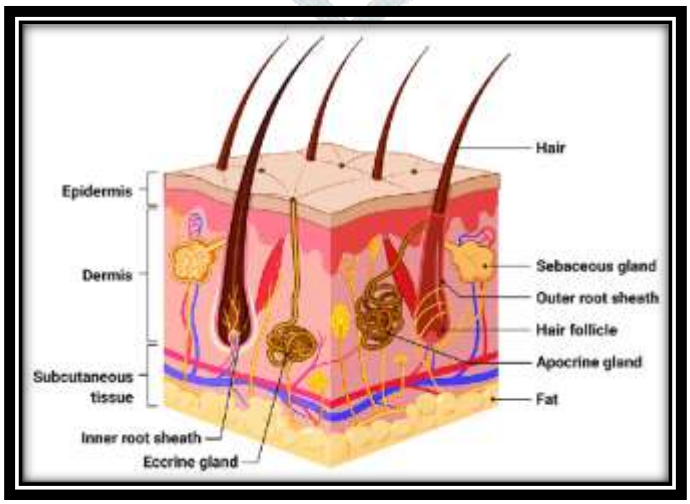

fig. 01 : Structure of skin

Layers of skin

1. Epidermis: The epidermis layer is the outermost cellular layer, which is composed five layers.

1. Stratum corneum (Horny cell layer)

2. Stratum lucidum (Clear layer)

3. Stratum granulosum (Granular layer)

4. Stratum spinosum (Prickly layer)

5. Stratum germinative

2. Dermis : The core layer of the skin, thicker than the epidermis, providing strength and elasticity.
1. Papillary Dermis
2. Reticular Dermis
3. Hypodermis (Subcutaneous Layer) : The underlying layer of the skin, primarily made of fat and connective tissue.

1. Adipose tissue

2. Loose connective tissue

3. Larger Blood Vessels and Nerves

Functions of skin

1. Protection: Skin protects from microbes, chemicals, physical agents.

2. Sensory function: Free nerve endings on the skin are sensitive to pain, touch, heat and cold.

3. Excretion: Skin excretes sodium chloride in sweat, urea when kidney function is impaired.

4. Regulation of body temperature: Skin regulate the body temperature about 36.90 c.

5. Immunity : The skin plays a crucial role in the immune system. Langerhans cells located in the epidermis function as antigen-presenting cells, assisting in the identification and elimination of pathogens.

6. Vitamin D synthesis : It plays important role in synthesis of vitamin D.[22,23]

II. Film forming solution

The topical treatment of skin diseases is the aim of medicine administration through the skin. A vast and diverse surface is provided by the topical approach in addition to its simplicity of use. The delivery mechanism and skin physiology both affect how quickly substances are absorbed. Patches, ointments, creams, and other existing dosing formulations have a number of drawbacks. Patches have a number of drawbacks. Most frequently skin irritation, pain when peeling off, and difficulties applying on curved surfaces are caused by their occlusive qualities, which block sweat ducts and hinder the dehumidification from the skin's surface. Creams and ointments are semisolid preparations that eliminate some of these difficulties but have other restrictions. Ointments, for example, cause irritation and redness. Less stable than solid dose forms are creams. Therefore, it is necessary to produce a dosage form that allows for less frequent administration and long-term close contact with the skin.
An innovative method that can serve as an substitute to conventional topical and transdermal formulations is the film-forming solution. These films consist of flexible, thin layers of polymer, which may or may not contain a plasticizer. A film-forming solution is a liquid prepration that generates a film in situ, meaning it forms a film upon implementation to the skin or another surface of the body.[1,29,32]

III. Mechanism of film formation

When the film-forming solution is placed directly on the skin, it leads to the in-situ creation of a thin, clear film as the solvent evaporates. After the formulation is spread onto the skin, the constitute of the film-forming solution undergoes a change because of the lack of volatile components from the vehicle. This evaporation process results in the formation of a residual film that adheres to the skin’s surface, effectively creating a protective layer. The film's characteristics, such as its clarity and thickness, are influenced by the formulation's specific components and the rate at which the solvent evaporates.[11,23]

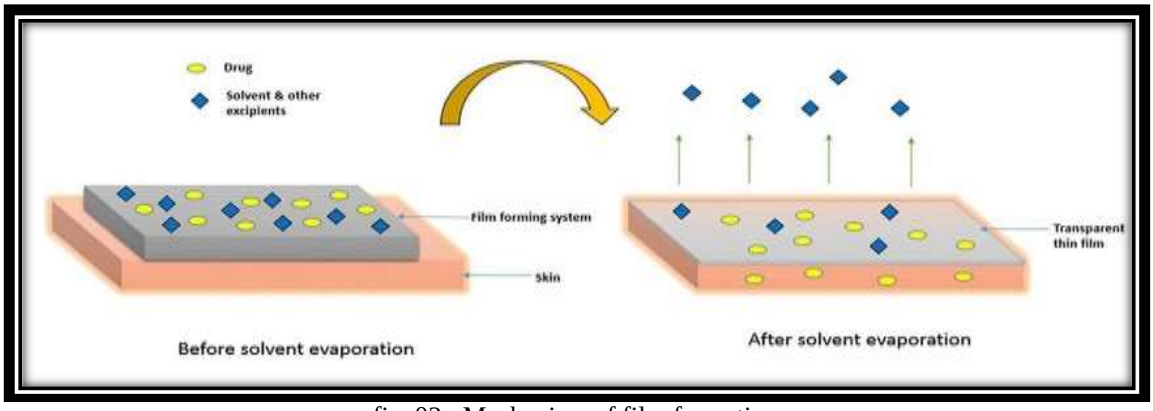

fig. 02 : Mechanism of film formation

IV. Elements of film forming solution [16,35]

A film-forming solution typically comprises several essential components, each contributing significantly to the formulation and effectiveness of the final film.

1. Polymer : Polymersplay a vital role in film-forming solutions, which are used in various applications such as coatings, adhesives, and encapsulants.(Gelatin, alginate, and chitosan, Polyvinyl alcohol , polyvinylpyrrolidone)

2. Solvent : Solvents are used to dissolve the film-forming polymers and facilitate the application of the solution.(ethanol, isopropanol, or acetone).

3. Plasticizer : These compounds are mixed to enhance the flexibility and durability of the film. (Glycerin, polyethylene glycol (PEG), and triethyl citrate.)

4. Additive : Various additives can be incorporated to alter the film's properties or enhance stability. **(**Surfactants, Preservatives, Colorants or Opacifiers)

V.Topical application of a film-forming solution

- To apply a film-forming solution on the skin, first ensure the area is clean and dry to promote optimal adhesion and effectiveness.
- Begin by shaking the film-forming solution container gently to mix the contents thoroughly. Using a clean applicator, cotton swab, or your fingertips, spread a light layer of the solution directly onto the targeted skin area, ensuring complete coverage.
- Avoid rubbing or massaging the solution into the skin, as this can disrupt film formation; instead, allow the solution to spread naturally.
- Once applied, let the solution dry completely, which may take a few minutes depending on the formulation and environmental conditions.
- During this drying period, avoid contact with water or other substances that may disrupt the film.
- Once the film has formed, it will provide a defensive barrier and deliver the active ingredients effectively to the skin.[37]

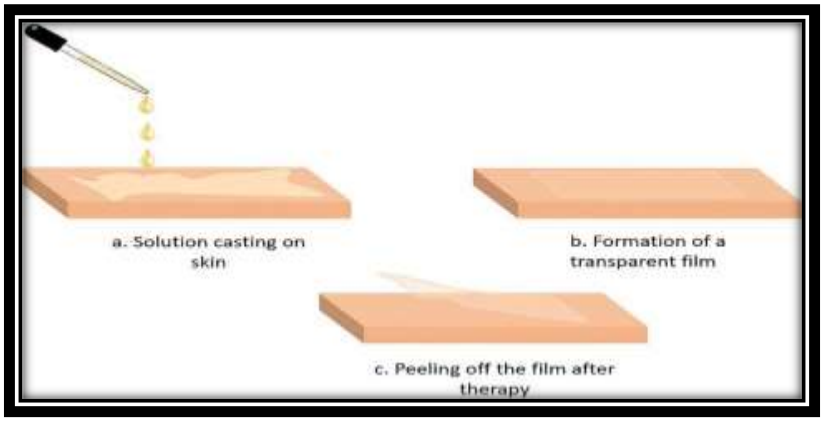

fig. 03 : Topical application of a film-forming solution

VI. Drug release dynamics in topical and transdermal delivery systems

The release profiles of transdermal patches, film-forming systems, and solid dosage forms vary significantly due to their distinct drug delivery mechanisms. Transdermal patches provide a controlled and sustained topical application of active components employing a rate-controlling membrane or matrix system that enables consistent drug absorption over extended periods, typically lasting from hours to days. Similarly, film-forming systems facilitate a localized and sustained release profile by forming a adaptable film on the skin, which gradually releases the drug while protecting the application site; however, their release rate can be influenced by factors such as film thickness and environmental conditions. In contrast, solid dosage forms like tablets and capsules usually exhibit a more immediate release profile, which depends on their specific formulation (whether immediate or extended-release) and disintegration characteristics, resulting in rapid absorption in the gastrointestinal tract.[36]

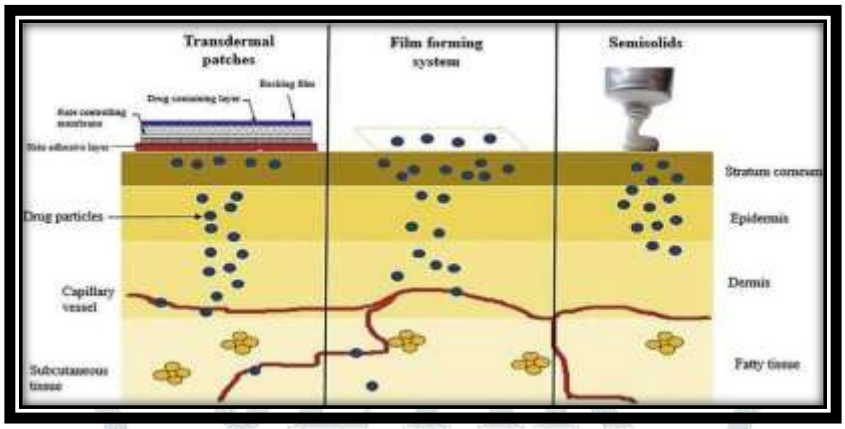

fig. 04 : . Drug release dynamics in topical and transdermal delivery systems

VII. Characterization of film forming solution

Film Formation: Films are produced in Petri dishes, and their formation is evaluated based on three classifications: Consistent and even, and any precipitation of the film-forming polymer. [10,34]

Film Versatality: The versatality of the film is assessed by stretching it in two to three directions to check for cracking. A film is considered flexible if no cracking occurs; if cracking is observed, it is deemed not flexible.

Adhesiveness: The adhesiveness of the dry film is evaluated by compressing cotton wool against it with pressure. If there is a significant accumulation of cotton fibrous partiles on the film, adhesivenes is rated high; if few or no fibers adhere, it is rated low. [34]

Drying Time: To assess drying time, the formulation is applied to a volunteer's inner forearm. After a set duration, a glass slide is gently placed on the film. The film is classified as dry if no liquid remains on the slide when it is removed. If liquid is present, the drying time is extended, and the procedure is repeated. An effective film-forming solution should minimize drying time to reduce waiting for patients. [17]

Skin Permebility Evaluation: The formulation is evenly implemented to the skin using a pipette or spatula. After specific intervals (e.g., 15 minutes, 1 hour, 3 hours, 6 hours), the residual formulation is removed. The amount of drug on the cotton pad indicates the drug remaining in the film. By subtracting this residual amount from the total drug in the formulation, the quantity that has permeated can be calculated. [13]

Water Vapor Permeability Determination: Water vapor permeability measures the volume of water passing through a unit area of film over a defined period. These measurements are crucial for understanding the film's permeation characteristics, which influence skin properties such as blood flow, skin temperature, and moisture in the stratum corneum. Films are created on a Teflon plate using the solvent evaporation method and are dried at room temperature for 72 hours. [14]

VIII. Plant profile

The evergreen, glossy, heart-shaped betel leaf is a member of the piperaceae family and is a creeper. Most of its range is in tropical and subtropical areas. India, Sri Lanka, Malaysia, Indonesia, and East Africa are among the countries that grow piper better. The betel vine comes in more than 90 different types worldwide.[3]

fig.05 : Piper betel

Taxonomical classification of betel leaf

1. Kingdom : Plantae
2. Division :Magnoliophyta
3. Class :Mangolipsida
4. Order :Piperales
5. Family :Piperaceae
6. Genus : Piper
7. Species : Betel

IX. Pharmacological activity

A significant numeral natural products are employed to treat various conditions as conventional healing practices in numerous countries. Piper betel, part of the Piperaceae family, includes over 2,000 species. The leaves of Piper betel have demonstrated effectiveness against several human pathogens. The extraction of Piper betel has been used for the treatment of various ailments for ages, thanks to its essential properties.

•**Wound Healing Activity:** In male albino rats, the application of a mixture containing Piper betel leaves significantly accelerated wound contraction and reduced healing time, likely due to because of faster epithelial healing. The results indicated that this mixture promoted wound healing and repair, particularly evident in the complete coverage of the wound area by a well-organized epidermis. This study suggests that Piper betel may have wound-healing properties.

•**Antifungal Activity:** Piper betel, known for its traditional medicinal uses, exhibits prominent antifungal activity against various fungal pathogens, especially Candida species and dermatophytes. Its antifungal effects are primarily attributed to active compounds such as eugenol and other phenolic compounds, which disrupt fungal cell membranes and inhibit biofilm formation. In vitro studies have demonstrated that extracts of Piper betel can effectively inhibit fungal growth, showing efficacy comparable to conventional antifungal agents. [2]

X. METHODOLOGY :

1. Solvent Casting :

Solvent casting is a widely used and practical technique for film manufacturing, valued for its cost-effectiveness and simplicity. The consistency properties of polymeric mixture play a crucial role, as they affect the drying rate, film thickness, morphology, and content uniformity of the films. To ensure a homogeneous outcome, de-aeration is necessary, since the mixing process can unintentionally introduce air bubbles into the liquid. After casting the solution onto a suitable substrate and allowing it to dry, a polymeric film embedded with the medication remains. Once fully dried, the film is cut into the desired size and shape from the formed strip. Typically, the strip is rolled and held for a specified duration before cutting, a process referred to in the industry as "roll stock." However, care must be taken to avoid prolonged exposure of the film, as it can be susceptible to damage. [8,9,20,30]

2. Hot melt extrusion (HME) :

HME is a flexible process used to create thin films, tablets, granules, and other products. It serves as a solution casting alternative for the purpose of film preparation and is particularly helpful when an organic solvent system is not required. However, there isn't a lot of literature that mentions using hot-melt extrusion to create polymeric thin films. In the HME method, a mixture of excipients, drug ingredient, and polymers are all melted together to form a film. The films are eventually chopped into a specific shape and size. In this process, a mixture of pharmaceutical components is heated to a molten state before being charged through a die to produce homogeneous matrices. This approach is not suited for thermoslabile APIs since they must operate at high temperatures with no solvents at all.

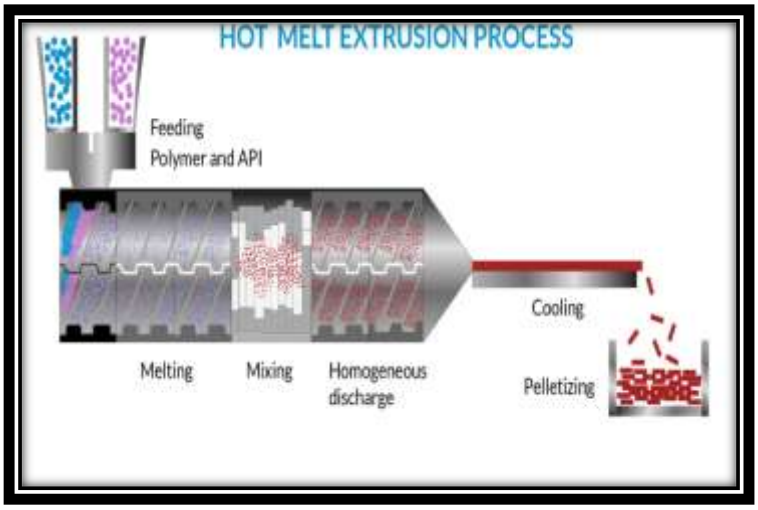

fig. 06 : Hot melt extruder

The practical steps of HME are outlined as follows :
1.Feeding of the components to the extruder through a hopper,
2.Mixing, grinding, and kneading,
3. Flowing the molten and blended mass to the die, and
4. Extruding the mass through the die and further downstream processing .[5,6,7]

3. Solvent evaporation:

Solvent evaporation is a widely used method for producing thin films from water-soluble excipients, polymers, and pharmaceuticals dissolved in deionized water. The process begins by creating a homogeneous mixture through high shear pressures applied by a shear processor. The resulting solution is then subsequently deposited onto a Petri plate, where the solvent evaporates at elevated temperatures, yielding high-quality films. In solvent casting, the film-forming polymer is typically soaked in a suitable solvent overnight. The choice of active pharmaceutical ingredient (API) for the film depends on critical physicochemical properties such as melting temperature, shear sensitivity, and polymorphic form, which also influence the selection of the solvent. It is crucial to assess the compatibility of the drug with the solvent and other additives before finalizing the formulation. Furthermore, the presence of air bubbles during formulation can affect the uniformity of the resulting films.

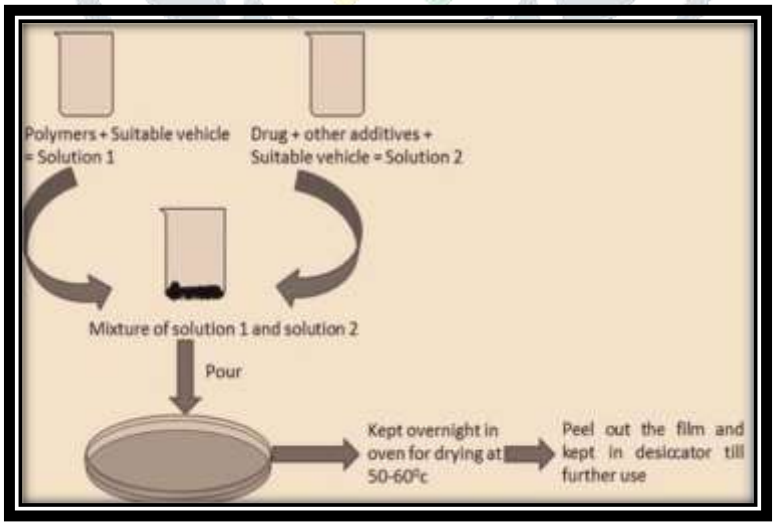

fig. 07 : Solvent evaporation method

XI. Conclusion

The film-forming solution presents an innovative platform for both topical and transdermal drug delivery to the skin. These solutions are easy to use and offer benefits such as transparency, a non-greasy texture, reduced skin irritation, resistance to removal, longer retention, greater dosage flexibility, enhanced patient compliance, and an attractive appearance. Both start-up and

established pharmaceutical companies are actively monitoring this drug delivery platform as they work to develop a range of thin films. Although significant advancements have been made, there is still limited data on their delivery efficiency. The rapid emergence of new technologies for creating thin films suggests a bright future for film technology. The medicinal importance of the herb mentioned earlier clearly shows that betel leaf ranks among the most promising commercial botanicals, according to various research studies. It has shown several therapeutic properties, including anticancer, antifungal, and wound healing effects. Given the recognized therapeutic values of P. betel, comprehensive characterization could be beneficial for long-term drug development research.

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