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FILM-FORMING GELS: A PROMISING ALTERNATIVE FOR ENHANCED DERMAL AND TRANSDERMAL DRUG DELIVERY

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Keywords:

Transdermal delivery systems, Film-forming polymers, Enhanced bioavailability, Skin adhesion improvement, Reduced skin irritation

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ABSTRACT: A new method in this field called film-forming gels may offer an alternative to the common skin dosage forms such ointments, creams, gels, or patches. When applied as a liquid, the polymeric solution evaporates to create a nearly undetectable layer on the skin. Dermal medication delivery and transdermal drug delivery systems compared to traditional pharmaceutical dosage formulations, the approach can offer certain desirable performance, for eliminating first-pass metabolism in the stomach and liver, increasing medication bioavailability, lowering dosage frequency, and stabilizing drug delivery overview. The purpose of this review was to find alternatives to traditional forms that would decrease skin irritation, boost patient acceptability from a cosmetic standpoint, improve skin adhesion qualities, and enhance drug release. The unique rheological nature of polymeric gels makes them advantageous in terms of preparation simplicity. Application simplicity, adherence to the application surface, and broad drug delivery compatibility.

INTRODUCTION: Pharmaceutically active chemicals can be delivered dermal or transdermal through the skin, which is a particularly important route [1]. Polymeric solutions that form films are a novel strategy in this field that could offer a substitute for the typical dosage forms applied topically, like creams, gels, ointments, or patches [2]. The polymer-based remedy is administered as a liquid to the skin, creating an almost by solvent evaporation, an intangible film is created *in-situ* [3]. Transcutaneous drug delivery system (TDDS) can offer a number of advantageous performances compared to standard medicine dosage formulations, including avoiding first-pass hepatic and gut medication bioavailability, enhancing metabolism, and lowering dosage regularity and maintaining stable medication delivery profiles [4].

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There are two main types of drug products that are applied topically to the skin: 1) Local action on the stratum corneum, and 2) Systemic action on the skin's epidermis and dermis. Skin physiology and drug characteristics are the primary determinants of medication release and absorption. The stratum corneum acts as the initial barrier to medication absorption through the skin [4]. FFS is described as non-solid dosages that form a film on the skin as the vehicle evaporates and the excipients in the formulations do the same. This is the drug and film-forming polymer system; the film that is produced serves as a matrix for the drug's continuous release [6].

Skin:

The primary physical barrier that shields us from the outside world is the skin. As seen in Figure 1, it is commonly explained in terms of three tissue layers.

Skin composed of 3 main layers:

1. Epidermis
2. Dermis
3. Subcutaneous [7]

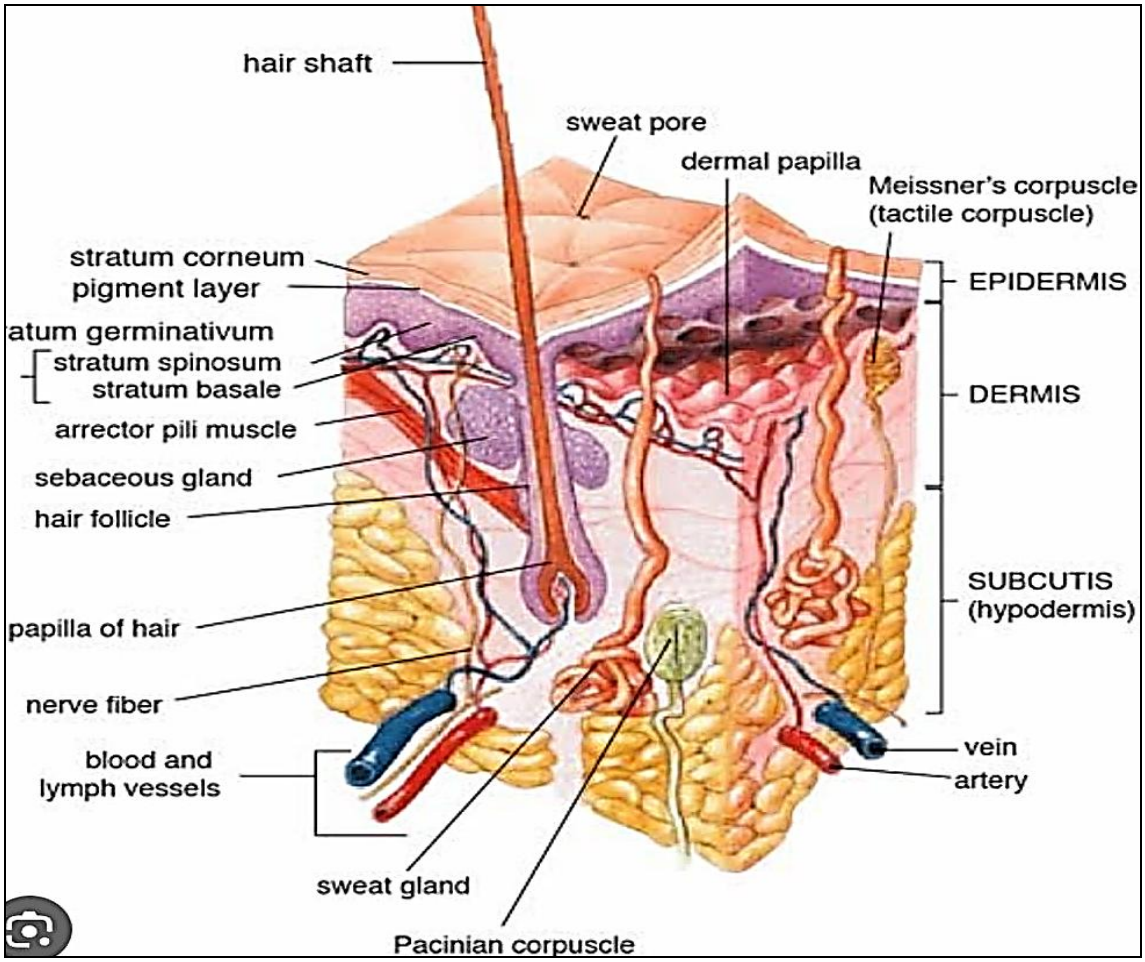

FIG. 1: STRUCTURE OF SKIN

Epidermis: It is the 20–200 μm thick, stratified, keratinized epithelial layer that is squamous. It can generate the pigment melanin, which adds color and absorbs UV light, in the shades of black and yellow.

Two primary components of the epidermis are visible in microscopic sections: the stratum germinativum and the stratum corneum (SC). The outermost Horney layer, known as the stratum corneum, is a very thin layer made up of compressed, flattened, cells that are stratified and dried, keratinized.

It is resistant to skin permeability in excess of 80%. Additionally, it is composed of corneocytes, which are practically impermeable cornified cells. The keratinized layer of skin acts as a natural barrier against infection by preventing the body from absorbing water and other dangerous substances.

- The extra thin layer of keratinized cells underneath the stratum corneum is called the stratum lucidum. Primarily found on the soles of the feet and the palm of the hand.

- The stratum granulosum is the layer that initiates keratinization. Lamellar granules emerge in this layer, fuse with the cell membrane, and release glycophospholipids into the intercellular space, which is what mostly makes up the water permeability barrier.

- Stratum Spinosum, the skin's spinous cell layer made up of keratinocytes that have a distinctive "prickly" appearance because they contain desmosomes, a crucial structural filament known as cytokeratin.

- Stratum Basalei, also known as the basal layer or stratum germinativum, is a continuous single layer made up of columnar epithelial cells. It is made up of Merked cells, Langerhan cells, and Melanocytes.

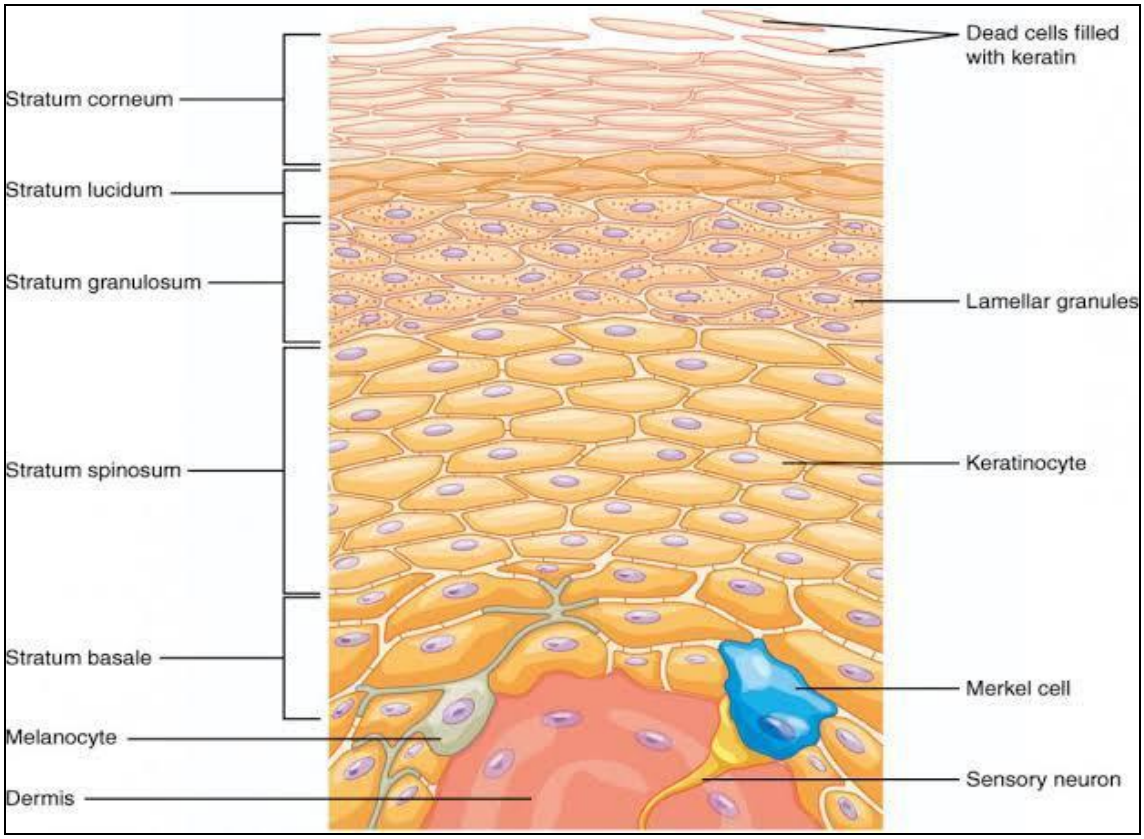

FIG. 2: SECTION OF EPIDERMIS SHOWING MAIN LAYERS

Dermis: It is made up of connective tissues that are firmly bonded by a basement membrane to the epidermis. It is made up of blood vessels, lymphatic vessels, sweat glands, sebaceous glands, and hair follicles. The dermal blood vessel removes waste from its own cells and supplies nourishment. It is in charge of the biological and biochemical deterioration of substances that are transferred through the skin. Under the epidermis, the Fibrous tissue spreads out and unites with the subcutaneous fat-containing tissue.

Subcutaneous: The layer of subcutaneous fat acts as a cushion between the epidermis and dermis. It offers a thermal barrier as well. It is made up of elastin, adipose tissue, and loose connective tissue. It stores fat and regulates temperature, provides mechanical support, nutrition, and shielding. It may contain sensory organs and transports nerves and major blood vessels to the skin [8, 9].

Mechanism of Film Formation: Film forming system is applied directly to the skin and it forms a thin, transparent film in situ upon solvent evaporation as shown in **Fig. 1.** After application of the formulation to the skin, the composition of the film forming system changes significantly due to the loss of the volatile components of the vehicle which results in formation of residual film on the skin surface. In this process the concentration of drug increases, reaching saturation level and with the possibility of reaching super saturation level on the skin surface.

Supersaturation results in the enhanced drug flux through the skin by increasing the thermodynamic activity of the formulation without affecting the skin's barrier, thereby reducing the side effects or irritation [8, 10].

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

$$J = DKCv / h$$

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

From this equation, it is clear that the rate of drug permeation across the skin is proportional to the concentration of the drug. However this is true when the entire drug is dissolved in the vehicle.

Equation describes the modified form of Fick's law of diffusion:

$$J = \alpha D/\gamma h$$

Where a = thermodynamic activity of drug within formulation, γ = thermodynamic activity of drug within membrane.

According to this equation, the flux of the drug is directly proportional to the thermodynamic activity of the system, which is related to saturation. However increasing the super saturation increases thermodynamic instability [11, 12].

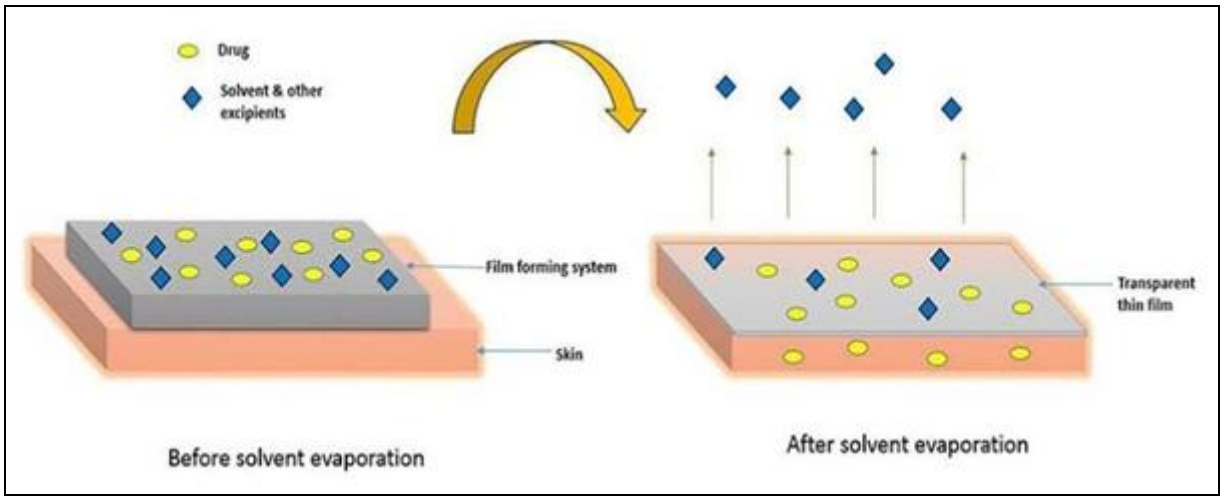

FIG. 3: MECHANISM OF FILM FORMING

Classification of Gels:

There are a variety of ways to classify gels According to source of gelling agent

- ❖ Natural gels
- ❖ Synthetic gels
- ❖ According to the liquid medium entrapped
- ❖ Hydrogels
- ❖ According to their cross linkage
- ❖ Chemical gels
- ❖ Physical gels
- ❖ According to the chemical nature of gelling agent
- ❖ Organic gels
- ❖ Inorganic gels Structure of gels [6]

Properties of Gels:

- For use in pharmaceutical or cosmetic formulations, the gelling agent should ideally be safe, inert, and unable to react with other ingredients.
- When exposed to shear forces, the gelling agent in the formulation should easily break and produce a reasonable solid-like nature during storage. produced by pressing down on the tube, shaking the bottle, or when applying topically
- Under normal use and storage temperature variations, the gel should show minimal viscosity change.
- It should contain suitable anti-microbial to prevent microbial attack.
- The topical gel should not be tacky.
- It should be economical [13].

Uses of Gels: Gels have applications in numerous field, including the food industry, medicine, biotechnology, chemical processing, agriculture, civil engineering and electronics. In the pharmaceutical and cosmetic industry, gels may be enumerated to have the following uses:

- As delivery systems for orally administered drugs.
- To deliver topical drugs applied directly to the skin, mucus membranes or the eye.
- As long acting forms of drugs injected intramuscularly.
- As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquids and suppository bases.
- In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care formulations.

Methods of Preparation of Gels:

Dispersion Method: This method involves dispersing the polymer over water for two hours, until it is fully soaked. After thoroughly mixing and stirring the remaining ingredients, a homogenous mass is acquired**.**

Cold Method: Using a low temperature of roughly 5degree C, all the ingredients are combined to create a homogenous mass in this method. Permeation is combined with the polymer. Enhancer to create solution A, and the medication is combined with solution B by using a solvent. Next, Solution B is added to solution A gradually while thoroughly stirring to create a uniform mass**.**

Chemical Method: In the process of creating sols by precipitation from solution, ingredients interact chemically in the aqueous phase to form a gel structure. An instance of this process creates silica gel, which is produced. Through the reaction of acids and sodium silicate in aqueous answer.

Temperature Effect: The solubility of most lyophilic collloids, including sodium oleate, agar, and gelatin, decreases at lower temperatures. As a result, when a concentrated hot sol cools, it frequently createsa gel. Elevating these sols' temperature will reduce the solubility and break the hydrogen bonding make gelatine.

Flocculation with Salts and Non-solvents: By adding just enough precipitant to create the gel structure state but not enough to cause full precipitation, gels are created using this method. Well, it is vital to guarantee quick mixing in order to prevent high localized concentration of precipitants. Ethyl solutions it is possible to gel cellulose and polystyrene in benzene quickly. Combining with an appropriate volume of a non-solvent, like ether of petroleum.

TABLE 1: MARKETED FORMULATIONS:

Sr. no.	Trade name	Polymers
1	Avalure AC118	Acrylate copolymer
2	Demacryl 79	Acrylate copolymer
3	Hydagen HCMF	Chitosan
4	PVA 7200	Poly vinyl alcohol
5	Klucel LF	Hydroxypropylcellulose
6	Oppanol B100	Polyisobutylene
7	Kollidon 12 PF	Polyvinylpyrrolidone

Component of Film Forming Gel:

Drugs: For medications with the right pharmacology and physical chemistry, the topical route is a very alluring choice. Drugs that target the dermal systems can benefit greatly from go through a lengthy first pass metabolism, medications with limited window of therapeutic opportunity or short half-lives of drugs given that these are the reasons for non-compliance because regular dosage. The potential medication must have a low melting point (less than 200 C) and must have a strong enough that is, useful in a few milligrams daily (ideally less than 25 mg each day). A medication in a saturated aqueous solution ought to be in the range of 5 and 9. The medication must not irritate or cause allergies in people. When applied topically, the medication ought to remain stable. The medication shouldn't cause the skin to become inflamed. The drug's tolerance cannot grow below almost zero dermal delivery system order release profile. It should not get irreversibly bound to the skin. The drug should not get extensively metabolized in the skin.

Characterstics of Drug:

1. Low molecular weight (less than 1000 dalton).
2. Affinity for lipophillic and hydrophillic phases.
3. Low melting point
4. Short half life
5. No irritating

Film Forming Polymer: A polymer's foundation is DDS. When they come into touch with skin, they form a film. They might also manage how the

medication leaves the body. Used polymers ought to both chemically and biocompatible with the medication and additional system elements. Furthermore, they should deliver a medication in a reliable and efficient manner. During the intended shelf life of the product and ought to be thought to be safe for use by humans. The polymers utilized for DDS can be classified as,

- **Natural Polymers:** e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- **Synthetic Polymers:** e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, poly-propylene, polyacrylate, polyamide, polyuria, polyvinylpyrrolidone, polymethylmethacrylate etc.

The polymers like cross-linked polyvinyl alcohol, eudragit, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose can be used as film formers [14, 15].

Solvent: Due to its rapid evaporation, the solvent is not a component of the actual film on skin, but it is still a crucial component in the film-forming solution. The remover has to provide. Adequate solubility for both the medication and the polymer. Just a solvent with a high solubilizing power for the medications permits significant differences in the drug loading to alter the way that drugs are applied topically. The remover can additionally directly impact the drug flux. Based on regarding the solvent's composition and how to improve permeation qualities that may encourage the transportation of drugs to various despite its brief skin contact period, to considerable degrees.

A suitable solvent for a film-forming solution must be highly volatile in addition to having solubilizing qualities for the drug and polymer. Along with the polymer, it should spread evenly on the skin following application to create a short, smooth film drying periods and consequently strong patient adherence. Solvents such as ethanol, isopropanol or ethyl acetate with a higher volatility and a better spreading are to be preferred

Plasticizer: Plasticizers are primarily used in polymeric applications to speed up the formation of films and increase their flexibility. Furthermore, the formulation trials have demonstrated that the film's skin adhesion can be modulated with plasticizer's assistance.

It is imperative to carefully choose the plasticizer in relation to the film former. For it to create a transparent film with minimal visibility on the skin, it must be miscible with the polymer. Considering a plasticizer's effectiveness is dependent on the polymer no there is a general guideline that specifies which plasticizer focus is necessary to create movies with the desired attributes. The individual determination of the adequate plasticizer content is inevitable. An insufficient amount of the excipient leads to brittle films with low skin adhesion. An excessive amount of plasticizer on the other hand results in smooth, but sticky films. Both situations are unacceptable for a reliable drug delivery by the film forming system and a good patient compliance.

Eudragit NE 40D as well as the silicone gum formed adequate films without the help of a plasticizing agent [16].

Evaluation Tests for Film Forming Gels:

Phase Transition Time: Time needed by the gel to get converted into film is the phase transition time. One gram of gel was placed on a petri dish which was spread uniformly on it and kept on a hot plate at 37°C and time needed until gel converts into film was measured.

Film Weight: One gram of the gel was placed on a petridish which was left for drying. After drying the resultant film was weighed on an electronic balance.

Film Thickness: Film thickness was measured by vernier calipers/ screw gauge. The gel was spread on an area of 5 cm^2 demarcated on a petridish. This petridish was left overnight for drying and then the film was peeled off and the thickness was determined from three different points on the film.

Rheological Studies: The Brookfield Viscometer LVDV II was used to determine the rheology of studied gels. Gels were placed under the viscometer using S 64 spindle to determine their viscosity. The viscosity was determined at different RPM of 10, 20, 50, 100 and the corresponding viscosity and torque were noted.

Spreadibility Studies: Minimum quantity of the formulation was placed between two glass plate and the glass plate on the top was gently slided on the bottom glass slide to determine the spreadibility of the formulation Spreadibility was measured on the basis of drag and slip characteristics of gels. A ground glass slide was fixed on this block. An excess of gel (about 2 gm) under study was placed on this ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 80 gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better Spreadability. Spreadibility was calculated using the following formula:

$$\text{Spreadibility} = M \times L / T$$

Where, S = Spreadibility, M = Weight in the pan (tied to the upper slide), L = Length moved by the glass slide and T = Time (in sec.) taken to separate the slide completely each other [17, 18].

Applications:

Wound Care: In the past film forming preparations have been known predominantly from the field of surgery or wound care. Film forming solutions or gels have been used for example as tissue glues for the sealing of operative wounds. The film formers mainly used in this area are fibrin as natural material and cyanoacrylates (octyl- and butylcyanoacrylate) as synthetic polymers

Cyanoacrylates or recently acrylate polymers have also been used for the closure of superficial wounds as liquid bandages. While most film formers are incorporated into the formulations as already polymerised material the cyanoacrylates are often applied as monomers. The polymerisation of the monomers takes place in situ and is catalysed for example by the presence of water on the skin. The velocity of the polymerisation process has to be controlled thoroughly to avoid inconveniences for the patient as the process is exothermic. Wound care preparations can either be drug free or combined with antimicrobial drugs to reduce the risk of infections in the wounds [19].

Ostomy Care: Apart from the wound care film forming preparations are also administered in ostomy care to protect the skin surrounding the ostomy wound from the aggressive bodily fluids [20].

Dermal Therapy: For dermal therapy a few liquid film forming products are approved, mainly for the therapy of warts and calluses. Examples are Clabin Plus (Chefaro, Germany). Furthermore some film forming products for the therapy of nail mycoses are registered such as Loceryl (Galderma GmbH, Germany) or Penlac (Dermik Laboratories, USA) [21].

Transdermal Delivery: The film forming systems that have been described so far are used in the pharmaceutical field but are not designed for the transdermal administration of pharmaceutically active substances. Only very few preparations that aim at a sustained drug delivery over a longer period of time have been described in the literature. Another film forming semisolid preparation was investigated, a transdermal hydrogel on the basis of polyvinyl alcohol and polyisobutylene that solidified into a substantial film in situ on the skin. The formed film was able to provide a sustained release of testosterone over 24 hours. Due to its cohesive structure the formed film was removable by peeling. The fact that the preparation produced a substantial and robust film on the skin, which is the prerequisite for a sustained drug release, distinguishes it from other transdermal gels. In these gels the main purpose of the gelling agents, that can be film forming polymers as well, is not to form films but to increase the viscosity by establishing a gel structure in the preparation. Due to this the gelling agents are not selected for their film forming ability and are often used in low concentrations so that the resulting films (if formed at all) are rather weak and show little persistence on the skin. Therefore, most transdermal gels cannot provide a sustained drug release to the skin and can thus not be considered as film forming preparations in the sense of this work [22].

CONCLUSION: Film forming gels proves to be effective dosage form for the transdermal delivery of drugs. Also, it remains adhered to the effected

part for a longer period without getting rubbed off. It provides sustained effect and better relief than the conventional gels and frequent reapplication is not required. The concept of film forming gels can change to treatment concept of various diseases such as arthritis. A lot of work can be carried out in this field.

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