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NEWER TRENDS IN FILM FORMING SYSTEMS FOR TOPICAL AND TRANSDERMAL DRUG DELIVERY

Anuroop U. P.[1]*, Sruthy S. Nair[1] and Ajith Babu T. K.[2]

[1]Department of Pharmaceutics, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

[2]Department of Pharmaceutical Chemistry, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

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***Corresponding Author**
Prof. Anuroop U. P.
Department of Pharmaceutics, Malik Deenar College of Pharmacy, Kasaragod, Kerala.

ABSTRACT

Skin is one of the important routes of drug administration. There is a variety of dosage forms are available now a day's such as transdermal patches, creams, ointments and implants. The drugs are absorbed through the skin based on the different physicochemical properties of the drug and other ingredients. Conventional formulations for topical administration of drugs have certain limitations like poor adherence to skin, poor permeability and compromised patient compliance. For the treatment of wounds, burns and other skin diseases the drug has to be maintained at the site of treatment for an effective period of time. Topical film forming systems are such developing drug delivery systems meant for topical application to the skin, which adhere to the body, forming a thin transparent film and provide delivery of the active ingredients to the body tissue. These are developed for skin application as emollient or protective and for local action or transdermal penetration of medicament for systemic applications. The transparency is an appreciable feature of this polymeric system which greatly influences the patient acceptance. In this review, the film forming systems are referred as a promising choice for topical and transdermal drug delivery. The various formulation available, various film forming agents, advantages and evaluation of transdermal drug delivery systems have also been reviewed.

KEYWORDS: Polymers, Transdermal Drug delivery, Film forming agents.

1. INTRODUCTION

Transdermal drug delivery system (TDDS) is the integral part of novel drug delivery system. It is defined as self – contained discrete dosage form which when applied transdermally provides systemic circulation at controlled rate.[1] Transdermal drug delivery is a new approach to provide prolonged action of the drug with low toxicity and better patient compliance and thus reduces the side effect caused by oral route.[2] The primary objective of controlled drug delivery is to ensure safety and efficacy of the drugs as well as patients compliance. TDDS is one of the systems lying under the category of controlled drug delivery; in which the aim is to deliver the drug through skin in a predetermined and controlled rate.[3] TDDS increase the patient compliance and reduces the loads as compared to oral route. Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below minimum efficacy concentration nor exceed the maximum effective concentration.[4,5]

The skin of an average adult body has appropriately 2m2 surface area and it receives one - third of the total blood circulating throughout the body.[6] Film forming system is a novel approach which can be used as an alternative to conventional topical and transdermal formulations. It is defined as non – solid dosage form that produces a film in situ, i.e., after application on the skin or any other body surface. These systems contain the drug and film forming excipients in a vehicle which upon contact with the skin, leaves behind a film of excipients along with the drug upon solvent evaporation. The formed film can either be a solid polymeric material that acts as matrix for sustained release of drug to the skin or a residual liquid film which is rapidly absorbed in the stratum corneum.[7,8] Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network.[9]

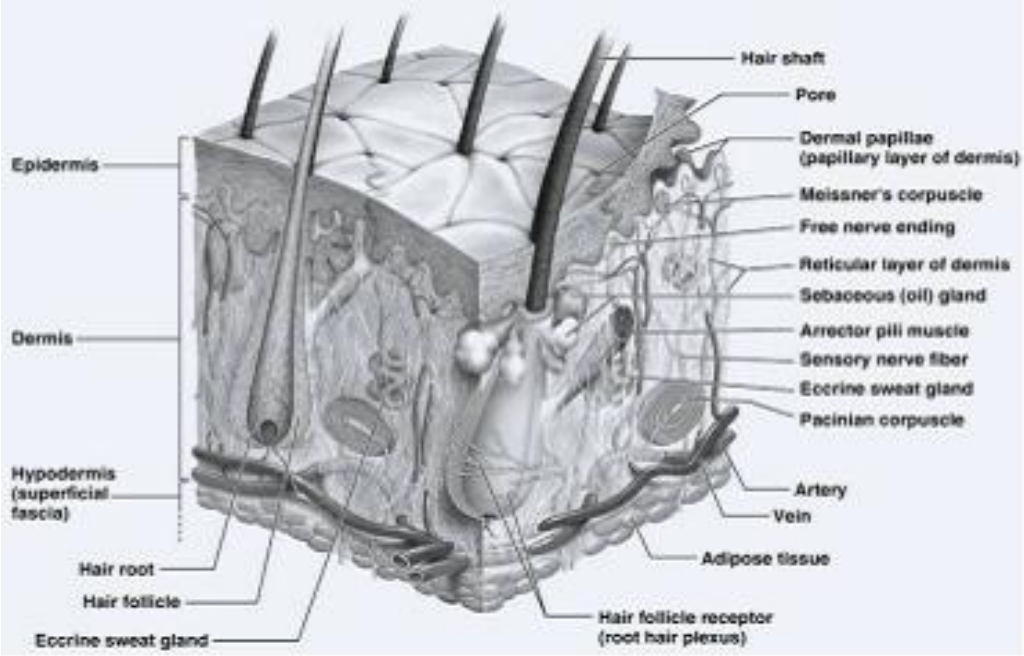

Fig. 1: Structure of Skin.

1.1 Transdermal permeation

Earlier skin was considered as an impermeable protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration.[9,10] The various steps involved in transport of drug from patch to systemic circulation are as follows.

- Diffusion drug from drug reservoir to the rate controlling membrane.
- Diffusion of drug from rate controlling membrane to stratum corneum.
- Sorption by stratum corneum and penetration through viable epidermis.
- Uptake of drug by capillary network in the dermal papillary layer.

1.2 Mechanism of film formation and permeation

Film forming system is applied directly to the skin and it forms a thin, transparent film in-situ upon solvent evaporation. 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 results in the enhanced drug flux through the skin by increasing the thermodynamic activity of the formation without affecting the skin's barrier, thereby reducing the side effects or irritation.[11]

1.3 Applications of film forming systems

Film forming systems were predominantly used in the field of surgery or wound healing. Solutions or gels, which have the capacity of film forming, have been used as tissue glues for the closing of operative wounds. The film forming agents used for this purpose are obtained from either natural or synthetic source. These preparations are mainly without drugs or with antimicrobial agents to prevent infections in the wounds.[12] It can be also used in the cosmetic field for preparing cosmetic creams, ointments and transparent peel off mask, for various skin disorders.[13] The film forming technology also has potential application as a substrate for various barrier membranes used in the industry to protect workers from detergents, acids, bases and other hazardous chemicals, infra – red heat, U V exposure etc.[14]

2. Film forming formulations

2.1 Sprays and solutions

Film forming solutions and sprays are now available and is an attractive approach in transdermal dosage form. On the application of solution or sprays to the skin it will immediately forms a transparent film by solvent evaporation.[15]

2.2 Gels

Gels are defined as semisolid dosage form containing both solid and liquid components. Gels are most commonly used topical preparations for the treatment of various diseases. Gels proved to be a good replacement for those formulations which seems to be uncomfortable when applied by another route such as oral route, as it may lead to peptic ulcers (in excessive usage of NSAIDS). Hydrogels are the aqueous gels containing hydrophilic polymers that form three dimensional networks in water.[16]

2.3 Emulsions

Emulsions are semisolid or liquid preparations having the ability to solubilize both lipophilic and hydrophilic drugs. Pharmaceutical emulsions consist of mixtures of aqueous phase and oily phases stabilized by suitable emulsifying agents.[17]

3. Components of film forming systems

3.1. Drug

For transdermal application of film forming systems, the drugs need to have suitable properties which are independent of the dosage form. Generally the drugs which are applicable to these systems are highly potent which permeate the skin rapidly, which cause

no skin irritation and which are relatively stable to the enzymes present in the epidermis. Other properties of the drug like partition coefficient dictate the pathway a drug will follow through the skin. Second, the molecular weight of drug is an important factor in drug permeation as small molecules cross human skin than large molecules.

3.2. Polymers

Polymers are the foundation of the FFS and a variety of polymers are available for the preparation of these systems. In order to achieve the desired film properties, these polymers can be used alone or in combination with other film forming polymers. These polymers should form a clear flexible film at skin temperature.[18] The list of polymers and its properties listed in Table 1.

Table 1: List of polymers.

Polymer	Properties
Hydroxypropyl Methylcellulose (HPMC) HPMC (E4M, E15, E50M K4M)	• Produce a light, non-greasy uniform film with good texture • Do not interact significantly with other ingredients • Surface active agent, therefore adsorbs water providing easy dispersion, lubricity and comfort feel in occlusive state on application to skin.[19]
Ethyl cellulose (EC)	• Nontoxic, nonirritating, nonallergic material • Good film forming properties that form tougher films.[20]
Hydroxypropyl cellulose	• Nonionic, pH insensitive polymer • Water soluble.[21]
Polyvinyl pyrrolidine (PVP) (PVP K30, PVP VA64)	• Solubility in water and other solvents • Adhesive and binding property • Acts as a bioavailability enhancer.[22]
Polyvinyl alcohol (PVA)	• Water soluble • Excellent film forming and adhesive properties • Nontoxic and biocompatible.[23]
Chitosan	• Excellent film forming ability • Opens the tight junctions of mucosal membrane, thereby enhancing the paracellular permeability and penetration of drug[24] • Controls drug release
Eudragit (polymethacrylates copolymer) Eudragit RS 100, RL 100, NE, RS 30D, S 100	• Transparent, elastic, self-adhesive • Good adhesion to the skin[25]
Silicones Polydimethylsiloxane (PDMS)	• Water vapor permeable film • Adequate substantivity and durable film[26]
Acrylates copolymer Avalure® AC 118, AC 120	• Tough, breathable, abrasion resistant films

3.3. Solvents

The solvents form an important component in film formation. The solvent used in film forming systems help in solubilizing the drugs as well as have an impact on drug permeation. Commonly used solvents for topical and transdermal use[27] are listed in Table 2.

Table 2: List of solvents used in topical delivery.

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

4. Evaluation of transdermal films

4.1 Interaction studies

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.[28,29]

4.2. Thickness of patch

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.[30]

4.3. Weight uniformity

The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.[30]

4.4. Folding endurance

A strip of specific are is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.[30]

4.5. Percentage moisture content

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula.[30]

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100.

4.6. Percentage moisture uptake

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.[31]

Percentage moisture uptake = [Final weight- Initial weight/ initial weight] ×100.

4.7. Water vapour permeability evaluation

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula

WVP=W/A

Where, WVP is expressed in gm/m^2 per 24hrs,

W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m^2[32]

4.8. Drug content

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique). Each value represents average of three different samples.[32]

4.9. Uniformity of dosage test

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2cm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.[33]

4.10. Shear adhesion test

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.[33]

4.11. Peel adhesion test

In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180º angle, and the force required for tape removed is measured.[33]

4.12. Thumb stack test

It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.[33]

4.13. Flatness test

Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.[34]

4.14. Rolling ball tack test

This test measures the softness of a polymer that relates to talk. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.[35]

4.15. Quick stick (peel-tack) test

In this test, the tape is pulled away from the substrate at 90ºC at a speed of 12 inches/min. The peel force required breaking the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.[35]

4.16. Probe tack test

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.[35]

4.17. Percentage elongation break test

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula

$$\text{Elongation percentage} = \frac{L1-L2}{L2} \times 100$$

Where, L1is the final length of each strip and L2 is the initial length of each strip.[36]

4.18. In vitro drug release studies

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5-mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.[28]

4.19. In vitro skin permeation studies

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats weighing 200 to 250g. Hair from the abdominal region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at 32 ± 0.5°C using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm-2) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm-2).[28]

4.20. Skin irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50cm2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.[33]

4.21. Stability studies

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 75±5% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.[28]

4. CONCLUSION

Transdermal drug delivery system is useful for topical and local action of the drug. The drugs which shows hepatic first pass effect and unstable in GI conditions are the suitable candidate for TDDS. Transdermal drug delivery system may be ideal for many injected as well as orally

given drugs, but many drugs cannot penetrate the skin membrane effectively because of low permeability of skin barrier. The film forming system presents a novel platform to deliver drugs to the skin both topical and transdermal. These film forming systems are simple and offer advantages of transparency, non-greasy, lower skin irritation, wipe off resistance, longer retention, greater increased dosage flexibility, improved patient compliance and aesthetic appearance Although considerable work has been done on these systems, not much data are available on its delivery efficiency. Hence the marketed products available are less. Additional research is necessary to prove the relevance of film forming system as transdermal dosage form, but the obtained results are encouraging for further development of this novel topical drug delivering technology.

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