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FILM FORMING SYSTEM: A NOVEL DRUG DELIVERY

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Abstract:
Film forming systems (FFS) are novel platform for the delivery of drug through the skin. These systems can form a thin film upon application over the skin after evaporation of solvent. These films can form drug release over an extended period of time. Here drug, film forming solvents and other excipient are dissolved in suitable solvent. Film forming system upon application can form a thin film that will adhere on the applied site with improved flexibility. It can be used as the alternative for topical and transdermal formulation by overcome several disadvantageous of existing formulation such as cream and patches. This review includes advantages, disadvantages, evaluations and applications of film forming system-based drug delivery.
Key words: Film forming systems (FFS), Skin, solvent.

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INTRODUCTION:

Skin is the largest organs of the body with an approximate area of 1.5-2 m2. Skin consist of superficial layer called epidermis and a deeper layer called dermis, which act as a barrier for most of the macromolecules enter into the body [1,2].

Film forming systems (FFS) are novel platform for the delivery of drug through the skin. It can overcome the several disadvantageous of existing formulation like cream and patches. Patches are associated with disadvantages like skin irritation and it can also result in the obstruction of sweat duct which resulting in the poor patient acceptance. Creams are associated with poor wipe off resistance. Which lead to poor contact time of drug at the site of application.

FFS can be used as the alternative for topical and transdermal formulation. Here the drug and film forming polymers are dissolved in a suitable solvent. These are the system which can form a thin film upon application over the skin and can cause drug release over an extended period of time. It possesses the advantageous of both creams and patches [3,4].

ADVANTAGES

- Improved adherence
- For those who are unable to take systemic medication.
- Film forming systems are simple and offer advantages of transparency, non-greasy and lower skin irritation.
- Greater increased dosage flexibility, improved patient compliance and aesthetic appearance.
- Preferred in early patients/patients receiving multiple medication to avoid drug interaction.
- The film forming gel formulation has prolonged contact time with the applied nail surface and has a controlled release of drug.

DISADVANTAGES

- Formed film may detach from the applied site if it is not protected properly.
- These formulations are having local side effects such as periungual erythema and proximal nail fold erythema.
- The therapy is longer, it takes longer time to cure disease of nail.

MECHANISM OF FILM FORMATION

Film forming gel upon application leaves a thin film on evaporation of the volatile solvent. After application of gel to the surface of skin there is a significant change in the composition of the gel which resulting in the formation of flexible film on the surface of the skin. In this process there is an increase in the concentration of the drug at the site, saturation of drug at the site and with the possibility of reaching super saturation level on the skin surface. Super saturation of drug at the site result in increased thermodynamic activity and increased dug diffusion through the skin surface.

The concept of super saturation can be explained by the modified form of Fick's law of diffusion. Fick's law of diffusion is given by,

$$J=\frac{DKCv}{h} \qquad (1)$$

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 equation (1) it is clear that the rate of drug permeation across the skin is proportional to the concentration of the drug. The modified form of Fick's law of diffusion is given by,

$$J=\frac{\alpha D}{\gamma h} \qquad (2)$$

α=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 [4,5,6].

COMPONENTS OF FILM FORMING SYSTEMS [3,4]

DRUG

Drug selected for film forming system should not cause skin irritation and should relatively stable to enzyme present in the skin conditions. Factors influencing the release of drug through film forming system include partition coefficient, molecular weight etc.

FILM FORMING POLYMER

Film forming polymers are the building blocks of film forming gel. In order to achieve the desired film forming properties polymers can be used along or in combination with other film forming polymers. These film forming polymers will form a clear flexible film upon evaporation of the volatile solvent. Several polymers are used as film forming agent along with gelling agents.

E.g.: Ethyl cellulose, Hydroxyl propyl cellulose, Hydroxyl propyl Methyl cellulose etc.

SOLVENTS

Solvents are important components of film forming system. The solvents used in film forming system

helps in solubilizing drug as well as have an impact on drug permeation. These are volatile organic solvents that combine with other ingredients and forms homogeneous viscous preparations. These volatile solvents evaporate leaving behind thin film on application.
E.g.: Ethanol, Butanol, Ethyl cellulose etc.

PLASTICIZER
Plasticizers in film forming gel impart the required flexibility, adhesion to skin. Plasticizers should be nonvolatile and miscible with film formers, solvents and other constituents.
E.g.: Glycerol, propylene glycol etc.
The characteristics of the Film formed by FFS are found to be,

- It should be of even thickness for which viscosity should be proper and satisfactory.
- Non-sticky, non-greasy skin feel on application
- Wipe-off resistant.
- Almost invisible film upon application and evaporation of solvents.
- Good adhesion to the skin.
- Satisfactory flexibility to avoid brittleness and cracking.
- It should form a non-tacky surface.
- Quick drying character.
- Long maintenance of the film character.
- Product should be stable on storage.
- It must be easy and convenient to apply.
- It should not be harmful or toxic to the skin or adjacent skin surface.

EVALUATION
Physical characterization
The physical characterization assessed by checking for the colour, appearance and the feel on application [3,4].
Homogeneity
The developed formulations are allowed to get set in the container and tested for their appearance and presence of any lumps, flocculates or aggregates.
Film formation
Film formation was evaluated by observing with naked eye after applying a small amount of FFS on a microscopic slide. Film formed should not sticky and non- uniform with the precipitation of polymers [3,4,5].
Drying time
Drying time was measured by the time in seconds taken by the FFS to form a dry film upon evaporation of the solvent. Complete dryness is ensured by placing a cotton/ glass slide over the surface of the film, if no liquid is visible in the cotton/ glass slide indicate complete dryness [8].
Stickiness
Stickiness of the FFS was measured by pressing the formulation with a cotton wool with low pressure. Depending on the quantity of cotton fibers remained by the film, the stickiness is noted high if there is higher accumulation of fibers on the film, medium if there is a thin fiber layer on the film and low if there is no adherence of fibers[3,4].
Swab studies
Dry swab test: This test indicates the behavior of FFS on the skin in dry condition. It is done on a glass plate. Developed formulation is applied in this area. Dry cotton swabs placed over the applied film. Swabbing was carried out at 0 min, 30 min, 2 h,4 h,6 h and 8 h and calculate the drug content.
Wet swab test: This test helps to predict the behavior of FFS under wet condition. The procedure for the wet swab test is the same as dry swab test except the swab taken is soaked in water before and then the formulations are swabbed [4].
Adhesive strength
Adhesive strength of FFS was measured by preparing an agar plate containing 1.5%w/v of agar in phosphate buffer solution of pH 7.2. Place weighed quantity of the formulation on the center of the agar plate. Plate is slanted at an angle of 30°C and measure the distance travelled by the gel [14,15].
***In-vitro* drug release study**
In-vitro release study is carried out in Franz diffusion cell containing 25 ml of phosphate buffer with pH 7.4 as receptor medium which is kept at 37 ± 2°C and stirred by magnetic stirrer. The formulation is uniformly spread on the cellophane membrane. The samples are withdrawn at fixed time interval and sink condition is maintained throughout the release study. Samples of 1 ml were collected at predetermined time intervals and analyzed spectrophotometrically at specific wave length [3,7,16].

APPLICATION
Nitin Merubhai Moria et al., in 2017 formulated and characterized film-forming voriconazole transdermal spray for the treatment of fungal infection. Here transdermal spray was formulated by using Eutragit RLPO and ethyl cellulose at a ratio of 1:2. Eutetic camphor: menthol (1:1) mixture used as a penetration enhancer in the film forming transdermal spray. The optimized formula is determined by using 32 factorial designs by selecting the concentration of Eudragit RLPO (X1) and EC (X2) as independent variables, Viscosity (Centi Poise: cP) as (Y1) and the time required to transport 50% of the drug (t50%, Y2) as dependent variables. The transdermal spray was subjected to evaluate parameters related to formulation and containers. From the study it was concluded that the optimized transdermal formulation was suitable for fungal infection[6].

Vij N.N, Dr. Saudagar R et al., in 2014 formulated developed and evaluated film forming gel for prolonged dermal delivery of terbinafine hydrochloride here Eutragit RSPO and hydroxyl propyl cellulose used to provide matrix film that provide prolonged release of antifungal agents. The gels are evaluated in terms of drying time, drug release, antifungal activity, skin irritation and stability studies. Bio adhesion and permeability are also tested. Different formulations are developed by changing the ration of Eutragit RSPO and hydroxyl propyl cellulose. All the formulation results are found to be in the acceptable range and the optimized formulations shows drug release of 99.84% and antifungal activity in terms of efficacy as 99.44%[7].

Dong Wuk Kima et al., 2015 formulated novel sodium fusidate loaded film forming hydrogel for excellent would healing activity. Here film forming hydrogel of sodium fusidate is prepared with drug, polyvinyl alcohol, polyvinyl pyrrolidine, propylene glycol, ethanol and water. It will form a thin film within 4 min of application. The developed film forming hydrogel of sodium fusidate shows appropriate hardness and adhesive strength and formed film has excellent flexibility, elasticity and high rate of drug release. Upon evaluating film forming hydrogel was stable at 45°C for at least 6 months and it possess improved wound healing activity when compare with sodium fusidate commercially available product [9].

Mukesh C et al**.,** in 2009 formulated fluconazole transdermal spray containing Ethyl Cellulose and Eudragit® RS100 as Film Formers. Optimized formulation was selected by using 32 full factorial designs. Eudragit® RS100 (X1) and ethyl cellulose (X2) were selected as independent variables and drug transport in first hour (Y1) and the time required for 50% drug transport (Y2) were selected as dependent variables. Eutectic blend of camphor and menthol was used as permeation enhancer and solvent for film-forming polymers. The formulations are subjected for pH, viscosity, volume of solution delivered upon each actuation, spray angle, ex–in vivo physical evaluation and in vitro drug transport. From the study it was found that the film of optimized batch was flexible and dermal-adhesive [10].

Dominique Jasmin Lunter et al**.,**in 2012 developed film forming emulsion containing Eudragit®NE and/or RS 30D for sustained dermal delivery of Nonivamide. Here the film forming emulsion prepared with polysorbate 80 as surfactant also helps to reduce flocculation during the preparation. Hydroxypropylmethylcellulose added as thickener in the film forming emulsion. The film formed by film forming emulsion evaluated for the mechanical property and water resistance. From the in-vitro drug release study it was found that an increase in the concentration of NE in the film forming emulsion increases the drug release. From the study it was concluded that sustained delivery of the drug can effectively achieved by the combination of water soluble and water insoluble polymers [11].

Amit Misra et al., 1996 formulated transdermal film for the biphasic delivery of testosterone. Here film was prepared by dissolving drug in isopropanol along with blend of film forming polymers like polyvinyl pyrrolidine and polyvinyl alcohol in different amount. Film was designed to possess sufficient adhesive strength to stick on the skin. The physical properties, drug content, stability and in-vitro drug permeation of the films are evaluated. In-vitro drug permeation was evaluated in wistar rat found that polymeric film delivers the drug with biphasic kinetics. It provides an initial burst release of the drug by creating a dehydrated channel through the application of isopropanol on wistar rat skin and later it provide a slow release by the polymeric matrix [12].

Edwards et al., in 2017 formulated and a supersaturated film forming system by an aerosol spray for the transdermal delivery of Methylphenidate. Supersaturated film forming systems are suitable for improving the drug absorption and bioavailability at the site of application. Here Differential scanning calorimetry (DSC) to measure the solubility of methylphenidate both as the free base and as the hydrochloride salt in two polymethacrylate copolymers, Eudragit RS and Eudragit E. Quantitative analysis are performed by using High performance liquid chromatography. The calibration curve was produced was linear at a range of 1-1000µg/ml. From the study it was found that Eudragit RS provide greater drug delivery than Eudragit E due to the lower solubility of Methylphenidate in Eudragit RS provide better saturation of drug at the membrane model. The rate of drug transport across the membrane depends on the solubility of the in the polymer and the degree of super saturation [13]. Saudagar et al., in 2017 formulated and evaluated Film-forming gel for Prolonged Dermal Delivery of Miconazole Nitrate. Here Eudragit RS PO and hydroxyl propyl cellulose were used as film forming polymer. the combination of Eudragit RS PO and hydroxyl propyl cellulose provide a matrix film that would permit the release of the medication for an extended period of time. The optimized formulations were prepared using 32 full factorial designs. Drug content, drying time, effective dosage volume, skin irritation and stability studies of the developed formulation are evaluated. From the study it was concluded that the

optimized formulation of film forming gel shows better bio adhesive property and improve the bioavaibility of Miconazole Nitrate [16].

CONCLUSION:

Film forming systems are the drug delivery system which can overcome several disadvantages of existing formulation such as cream and patches. It can form a thin film upon application over the skin there by provide drug release over an extended period of time. Film forming systems containing vesicular system are still under development. These FFSs are expected to provide an efficient drug delivery.

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