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Review Article

Film Forming gel - A Novel Drug Delivery System: a mini review

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Abstract

In this era, as an alternative of other conventional drug delivery systems such as patches, gels, creams or ointments it might be considerable to use film forming gels as novel drug delivery system. The film forming gels are the liquid polymeric solutions which after topical application result in the formation of a transparent thin film on the surface of skin as a result of evaporation of solvent. As compared to other conventional drug delivery systems, certain advantages are presented by the transdermal drug delivery systems as they improve bioavailability of drug, cause reduction of dosing frequency as well as help to avoid the first pass effect. The purpose of this research was to find out any substitute for other conventional drug delivery systems for the improvement of adhesion characteristics of dosage form, reduction of irritation of skin, enhancement of aesthetic properties and to improve the patient compliance. Consequently, the film forming gel formulations are able to cause delivery of numerous active pharmaceuticals, can be prepared easily, applied conveniently and adhered to the surface of skin hence, FFG might be advantageous over other conventional topical dosage forms.

Keywords: Conventional drug delivery systems, Film Forming Gel

Introduction

In recent years, a considerable influence in pharmaceutical field has been developed through the development of drug delivery systems that release drug in a controlled manner. The low therapeutic effects caused by inadequate delivery of drug or multiple dosing has fascinated the researchers particularly towards transdermal drug delivery system (Tran and Tran, 2019).For the transdermal or dermal delivery of drug skin is considered as an important route (Bajaj *et al.*, 2016).

In human body the largest organ is skin and in Latin skin is known as Cutis (McLafferty *et al.*, 2012). The average surface area of skin in a healthy adult is 1.8 squares meter comprising eleven percent of total mass of body (Alany, 2017). There are approximately ten to seventy hair follicles and two hundred and fifty sweat glands in each square cm of skin. The average weight of skin is 5 kg as twice the mass of brain while its width is approximately two millimeter (Kim *et al.*, 2015b). Skin plays a major role in providing protection against foreign substances, radiations and infections, regulation of body temperature. Skin also serves as a pathway for the permeation of pharmaceutical agents to facilitate the topical delivery of active ingredients (Menon, 2002). It enhances patient comfort by reduction of dosing frequency through provision of sustained delivery of drug into central compartment of body (Bolzinger *et al.*, 2012). In topical drug delivery the drug is diffused into central compartment either by permeation through hair foolicles, stratum corneum or intracellelar junction (Alvarez-Román *et al.*, 2004). Stratum corneum is mainly involved in percutaneous absorption of active pharmaceutical ingredient through skin. Stratum corneum acts as a barrier to the permeability of drug as it is composed of dead eoidermal keratinized cells making the diffusion of drugs difficult (Michaels *et al.*, 1975). The topical delivery may be opted either for local or systemic effects as it makes self administration possible for the patient (Prausnitz *et al.*, 2012). The physico chemical properties of active pharmaceutical ingredient and doasge form as well as

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physiology of skin affects the rate and extent of absorption of active agent. Various limitations are presented by other conventional drug delivery systems such as creams, ointments, transdermal patches etc. The transdermal patches have many limitations as they have poor asthetic properties as well as they obstruct sweat ducts and prevent the escape of moisture causing irritation of skin thus reducing patient compliance (Dhiman *et al.*, 2011). As concerned with semisolid drug delivery systems including creams and ointments they are greasy and sticky (Tan *et al.*, 2012)and require repeated application in some chronic conditions. Moreover they are simply wiped from surface of skin by clothes of patient causing patient incompliance (Devaux *et al.*, 2012). Hence in order to enhance patient comliance it is required to formulate a drug delivery system which permits contact of dosage form for extended period of time thus reducing the dosing frequency.

In this era, polymeric solutions which form film after topical application may be presented as an alternate to various conventional topical drug delivery systems like patches. Gels, ointments or creams (Bajaj *et al.*, 2016). In comparison to other drug delivery systems, a number of advantages including improved bioavailability of active ingredient, reduced dosing frequency and avoidance of first pass effect are presented by transdermal drug delivery system (Taksande *et al.*, 2016). The film obtained after evaporation of solvent may be either a liquid film which is then readily absorbed into the stratum corneum or polymeric material in solid state which acts as a matrix system which releases drug in a sustained manner (McAuley and Caserta, 2015). The transdermal film forming gels are preferred to the other conventional drug delivery systems in various aspects as following:

- The active pharmaceutical ingredient is released in a controlled manner from the topical film forming gel (Singh *et al.*, 2013).
- Film forming gels lack stickiness adhered to the site of application through film formation and provide prolonged drug release.
- The film forming gels have enhanced attraction due to their aesthetic properties so the patient compliance is enhanced(Khasraghi and Thomas, 2019).
- In comparison to the other conventional topical dosage forms such as gels and ointments, film forming gels are not easily wiped with clothes from the site of application (Saravanan *et al.*, 2018).

Film formation and transdermal permeation of drug

When the film forming gel formulation is applied to the skin then the solvent is evaporated and a thin transparent film is formed on the surface of skin. After this process of film formation, the amount of drug is increased and then the drug saturation is achieved which might proceed to super saturation causing an increase in the flux of drug across the skin barrier and reduction of local irritation (Zurdo Schröder, 2007). The modified Fick's law of diffusion might be used to explain the process of super saturation which explains the direct relationship of the drug saturation and the thermodynamics of the system (Kathe and Kathpalia, 2017).

Formulation of topical film forming gel system

The film forming gels are formulated by incorporating drug and the film forming agent with other excipients and solvent which evaporates after topical application so as to form a transparent film after topical application (Bhalani *et al.*, 2018). So various considerations like the physicochemical characteristics of active agent, type and concentration of polymeric and plasticizing agents and the evaporation of solvent will play a major role in the extent of release of drug from the topical film forming system (Frederiksen *et al.*, 2015).

Choice of suitable drug

It might be possible to use the topical film forming gel formulations in treating certain skin conditions. However due to the nature of the solvent it might not be suggested to use these topical formulations. Mostly the skin disorders cause the inflammation of the skin. So if the formulations containing ethanol as a solvent are applied topically then it might cause discomfort to the patient thus making him non compliant. The drug must be chosen on the basis of certain requirements which are not dependent on the drug deli very system (Schroeder *et al.*, 2007). In choice of the suitable drug, certain factors must be considered. The potent active ingredients having a dose of less than ten milligram are suitable for the topical delivery. For provision of adequate permeation through skin the drug should be preferably of low molecular weight of approximately less than 500 Dalton. The partition coefficient of the drug should be between 1 and 3. In aqueous solution the pH of the drug should be between 5-9 (Alberti *et al.*, 2005). While choosing the drug suitable for the formulation of the film forming system following points must be considered

- The drug should be highly potent
- The permeation of the drug through skin should be maximum
- The drug should be highly soluble in the solvent (BORNARE *et al.*, 2018)

It was suggested in a research study to dissolve the drug of choice in castor oil then loaded on the silica particles after which it was incorporated into the film forming polymeric solution in order to achieve the sustain release of the drug (Heck *et al.*, 2016). The result of this study in healthy persons showed that controlled release of drug was achieved without causing any irritation of skin (Heck *et al.*, 2017).

Choice of suitable excipients

Film forming polymers: For the formation of film at the surface of skin a suitable polymeric agent and in order to prevent the use of large amount of plasticizing agent the polymeric agent should be adequately flexible and adherence to the skin surface (Kathe and Kathpalia, 2017). It should be soluble in a solvent which should not b irritant to the skin and have a high volatility (Naik *et al.*, 2000). A number of polymeric agents have ability to form film such as chitosan, polyvinyl alcohol, polyvinyl pyrrolidone and certain cellulose derivatives. In the development of film forming systems, cellulose derivatives particularly ethyl cellulose and hydroxpropyl cellulose might be used (TD Tran and HL Tran, 2017). Ethyl cellulose is not soluble in water while hydroxypropyl cellulose dissolves and swells in aqueous medium to form hydro gel. However organic solvents might be used to solubilize ethyl cellulose to form gel (Shin *et al.*, 2018). In order to develop a controlled drug release system both ethyl

cellulose and hydroxypropyl cellulose are often used in combination (Andersson *et al.*, 2013). Polyvinyl pyrrolidone might be used as a film forming agent as it is soluble in both aqueous and organic solvents (Borges *et al.*, 2015). Chitosan also have film forming properties which is a linear polysaccharide derived from chitin (Abou-Aiad *et al.*, 2006). It can be easily grafted with oleic acid which enhances the properties of film like tensile strength and elongation at break (Oh *et al.*, 2017).

Plasticizing agent: In order to enhance the flexibility of the film, plasticizing agents might be used in the film forming systems. To enhance the aesthetic appeal of the gel formulation and to produce transparent film the plasticizing agent should have miscibility with the polymeric agent (Ngo *et al.*, 2019). The plasticizing agent should be used in adequate amount as if it is used in large amount then the formed film will be sticky while in case of lesser amount the film will be brittle (Zhai and Maibach, 2002). The plasticizing agents might improve the release of drug as they might enhance the chain mobility and the free volume of the polymeric agents (Frederiksen *et al.*, 2015).

Physicochemical characterization of film forming gel systems

Measurement of viscosity: The viscosity of the topical film forming gels was determined by using Brookfield viscometer by rotating the spindle of the specific viscometer at 0.5 revolutions per minute into the formulation at room temperature i.e. 25-27˚C. The process was repeated in a triplicate.

pH Determination: pH of topical film forming gel was determined by inserting the tip of the electrode of pH meter in to the jar holding the film forming gel formulation. pH value showed on the display of the pH meter was noted. The process was repeated at room temperature in a triplicate.

Drying time test: It is also known as the phase transition time and it was the time period during which the gel formulation changes into film (Taksande *et al.*, 2016). A petri dish was properly cleaned and dried. Approximately 1 gram of formulation was evenly distributed on it and placed on a hot plate at 37˚C and time was noted until a film was formed (Kim *et al.*, 2015a).

Determination of weight of film: One gram of the film forming gel formulation was placed on a petri dish and left for drying. After some time interval the film would be formed which is then weighed on a balance.

Determination of thickness of film: A circle of 5 cm^2 was marked on a petri dish and the formulation was placed on it. After 24 hours the film was peeled off and a screw gauge or Vernier Caliper was used to determine the thickness of the film at 3 different points (Taksande *et al.*, 2016).

Homogeneity: The film forming gel formulations were allowed to set in the container and then visually examined for homogeneity and uniformity of the formulations (Gupta *et al.*, 2010).

Rheological evaluation: A rheometer was used for the rheological evaluation of the sample of about one gram at 25˚C. The viscosity of the formulation was estimated at various rates of shear through plot of rate of shear versus viscosity for generation of flow curve for the identification of flow properties of each formulation (Silva-Weiss *et al.*, 2013).

Spreadability test: Approximately one gram of film forming gel formation was pressed between two clean dried glass plates to determine the spreadability of the

formulation (Khasraghi and Thomas, 2019). A weight of about one kg was applied and it was left for about one minute then the upper slide was removed and the diameter of spread formulation was determined in centimeters (Maru and Lahoti, 2018). Then following formula was used to determine the spreadability:

Spreadability = M × L/T

Where S = Spreadability, M = weight applied, L = Length by which the glass slide has moved,

T = Time taken by glass slides to separate in seconds.

Fourier Transform Infra-Red (FTIR) Spectrophotometry: Fourier transform spectrophotometry might be conducted to determined the drug-drug and drug-polymer compatibility based on their different functional groups (Attia and El Badawy, 2010).

Evaluation of invitro release of drug and its topical permeation

In Vitro Drug Release Study

A dissolution apparatus with paddle and basket is used to determine the in vitro release of the drug through the film forming gel formulation while using 900 ml of PBS pH 6.8 as a release medium. A part of cellophane membrane is kept in PBS pH 6.8 for 24 hours after which it is filled with approximately 2 grams of the formulation and fastened with thread on both ends and placed basket assembly of dissolution apparatus which is then operated at 100 revolutions per minute at 37˚C. Then aliquots of 5ml are collected at predetermined intervals and replaced with fresh PBS pH 6.8. In vitro drug release is determined by taking absorbance of the aliquots at specific absorbance. The process is repeated in a triplicate.

Ex Vivo Drug Release study

A Franz diffusion cell is used to determine the ex vivo release of the film forming gel. The skin of albino mice was shaved and pealed carefully without any cuts, after sacrificing the mice. The skin was cleaned with normal saline and dried between the filter paper and kept in PBS pH 6.8 for 24 hours. In order to avoid leakage high pressure grease was used to fix a small piece of skin on receptor compartment of the Franz cell. A clamp was used to fix the donor and receptor compartments. The release medium in receptor compartment was degassed to remove any air bubbles. Franz cell assembly was placed on a hot plate and skin was charged for one hour at 37˚C. Then formulation was placed in donor compartment and samples were drawn from receptor compartment after regular intervals and absorbance was determined. The process was repeated in a triplicate (Oh *et al.*, 2017).

Advancements

(Khasraghi and Thomas, 2019) developed topical film forming gel containing Lornoxicam for the treatment of rheumatoid arthritis with increased patient acceptability. For the formulation of film forming gel containing Lornoxicam along with ethanol, water and PEG, a gravimetric mixture of PVA and PVP was used in different ratios. Afterwards the formulation was characterized for homogeneity, texture, spreadability and drug release kinetics. A chitosan based film forming gel containing Ketoprofen was effectively developed by (Oh *et al.*, 2017) in which various permeability enhancers like oleic acid and tween 80 were used as permeability enhancers. The formulation was evaluated for its physicochemical properties and drug release by using Franz diffusion cell. To

assess in vivo effectiveness of the film forming gel, rheumatoid arthritis was induced in animal model. Through results the analgesic and anti inflammatory effectiveness of chitosan based film forming gel containing Ketoprofen was proved.

(Jay *et al.*, 2017) worked for the development of the transdermal film forming gel in which Bifonazole was used as an active pharmaceutical ingredient which is a broad spectrum anti fungal agent. In order to treat superficial mycosis, antifungal agent should remain on the site of infection for prolong duration. Hence FFG was designed to provide the extended release of Bifonazole through film formation. Since the dosing frequency was reduced through these film forming systems so the patient compliance was enhanced. The aim of (Kim *et al.*, 2015b) was the development of chitosan based film forming gel containing tyrothricin for the treatment of wounds like cuts, broils, injuries and burns etc. Various bruises in animal models were effectively covered and protected by these chitosan based film forming gels formulations having tyrothiricin. By this study it was suggested that film forming gels containing tyrothricin might be effective to heal various burns, cuts and lesions etc.

Conclusion

For the transdermal delivery of drugs, topical film forming gel systems might be effective as compared to the other conventional topical dosage form in various aspects. Since FFG lack stickiness and might not be easily wiped off so remained on the skin surface for desired extended time period and drug released from the film forming systems (FFS) in a controlled manner as compared to other conventional topical drug delivery systems. Through this novel drug delivery system, the dosing frequency would be reduced and the enhanced patient compliance. In FFS, an immense research work might be desirable in future.

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