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Film Forming Gels: A Review.

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ABSTRACT

Film forming gels are a novel approach in this area that might present an alternative to the conventional dosage forms used on the skin, such as ointments, creams, gels or patches. The polymeric solution is applied to the skin as a liquid and forms an almost invisible film in situ by solvent evaporation. Transdermal drug delivery system (TDDS) and dermal drug delivery system can provide some desirable performances over conventional pharmaceutical dosage formulations, such as avoiding gut and hepatic first-pass metabolism, improving drug bioavailability, reducing dose frequency and stabilizing drug delivery profiles. The aim of this review was to search for alternatives to the conventional forms in order to reduce skin irritation, improve skin adhesion properties, enhance the drug release and increase the patient acceptability from an aesthetic perspective. Because of their peculiar rheological behavior, polymeric gels are beneficial in terms of ease of preparation, ease of application, adhesion to the application surface and ability to deliver a wide variety of drugs.

Keywords: Film forming gels, transdermal, semi soilds.

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INTRODUCTION

The skin is a very important route for the dermal or transdermal delivery of pharmaceutically active substances. Film forming polymeric solutions are a novel approach in this area that might present an alternative to the conventional dosage forms used on the skin, such as ointments, creams, gels or patches. The polymeric solution is applied to the skin as a liquid and forms an almost invisible film in situ by solvent evaporation. Transdermal drug delivery system (TDDS) can provide some desirable performances over conventional pharmaceutical dosage formulations, such as avoiding gut and hepatic first-pass metabolism, improving drug bioavailability, reducing dose frequency and stabilizing drug delivery profiles [1].

The current dosage formulations used for TDDS are mainly pressure sensitive adhesive patches, ointments and creams [2-3]. However, their performances are currently far from the optimum. For example, the transdermal patches often trigger several questions, such as skin irritation due to their occlusive properties preventing the permeation of water vapour from the skin surface, intense pain when peeled off from skin and difficulties for the preparation [4]. The ointments and creams are usually comfortable to wear but may leave a sticky or greasy feel after application. Therefore, the search for alternatives to the conventional forms is reasonable in order to reduce skin irritation, improve skin adhesion properties, enhance the drug release and increase the patient acceptability from an aesthetic perspective (properties shown in table 1). Because of their peculiar rheological behavior, polymeric gels are beneficial in terms of ease of preparation, ease of application, adhesion to the application surface and ability to deliver a wide variety of drugs [5]. Furthermore, the development of TDDS formulations recently has been focused on employing several polymer gels as a film-forming agent [6-10].Polymer gels administration typically involves coating a dose on the arms, shoulders, abdomen or internal parts of the thighs to fabricate a bioadhesive thin film on the skin surface. Compared with transdermal patches, ointments and creams, the innovative bioadhesive films represent an improvement because they offer more dosage flexibility and ease of use, less irritation potential, better cosmetic appearance and higher simplicity of manufacture, as well as do not leave greasy feeling on application site [11-13].

Film forming preparations are defined as non-solid dosage forms that produce a substantial film in situ after application on the skin or any other body surface. Such compositions can either be liquids or semisolids with a film forming polymer as basic material for the matrix. The formed film is sufficiently substantial to provide a sustained drug release to the skin [14].

Considerations for the composition of film forming polymeric gels

Suitable drugs

The usage of the developed formulations for dermatological indications is theoretically possible as well but cannot be recommended sometimes due to the nature of the solvent in the compositions. Dermatological diseases are often associated with inflamed skin where the administration of ethanolic solutions might be painful for the patient and thus not acceptable.

For a transdermal application suitable drugs have to fulfil certain requirements that are independent of the dosage form [2].Due to the fact that the skin is a very efficient protective barrier for the body, not merely against physical or microbiological noxes but also against drugs, only potent drugs are eligible for this application route with a daily dose of less than 10 mg. The size of the molecule is required to be small in order to provide a sufficient mobility in the skin structures (molecular weight below 500 Da). As the drug has to pass lipophilic as well as hydrophilic areas in the skin on its way into the systemic circulation it is advantageous if the drug is neither very hydrophilic nor extremely lipophilic (log P_{oct} between 1 and 3). Therefore molecules with a pH value between 5 and 9 in aqueous solution are preferred for the transdermal application [5].

Further parameters that are beneficial for the transdermal delivery of a drug are a small number of hydrogen bonding groups (< 2) and a low melting point(less than 200 ^{0}C).

The reservoir size of the dosage form is comparatively small due to the extreme thinness of the films (approximately 5 – 25 µm). With a formulation dose of 10 mg/cm2 and an application area with an acceptable size of for instance 30 cm2 the total applied formulation dose would be 300 mg. In order to reach the limit

daily dose that is assumed for transdermal patches (10 mg/day) more than 30% of the applied dose would have to be absorbed. Such a high absorption was not achieved with the steroidal hormones that were investigated in this work. With these drugs the absorption was clearly below 10% of the applied dose. Taking this into account it seems obvious that the film forming solutions will be mainly attractive for drugs that have

- A high potency (example: the progestin Nestorone)
- A high skin permeability (example: nicotin)
- A high solubility in the solvent (example: ethinylestradiol).

A high potency is beneficial as it results in low required daily doses for the drug. A high skin permeability promotes a high exploitation of the thin reservoir provided a suitable polymeric matrix is given. A high solubility in the formulation, finally, allows high drug loadings and the establishment of a high gradient between formulation and skin. An efficient delivery system, meaning a high exploitation of the drug reservoir throughout the wearing time, is generally desirable for all drugs. If this cannot be achieved the film forming system might not be attractive for expensive drugs due to the considerable portion of drug that is wasted.

It remains subject to further research if the film forming solutions are suitable for drugs with a narrow therapeutic window as the kinetics of the delivery system are not yet known. With respect to the novelty of the film forming systems a thorough and individual evaluation for each new drug candidate is still inevitable until a clearer picture of the capabilities of the film forming solutions in general has been gained.

Appropriate excipients

Polymer

The polymer is required to form films at the skin surface temperature (28°C-32°C) and should have a certain inherent flexibility and affinity to the skin to avoid the usage of excessive amounts of plasticizer. It has to be soluble in a highly volatile, skin friendly solvent. Moreover, strong gelling agents should be avoided as film former as they prevent an application of the formulation by spraying.

In spite of the many requirements the polymer screening experiments have demonstrated that the majority of the tested polymers could be formulated into a film forming composition with suitable macroscopic properties. Only four of the 14 tested polymers (chitosan, polyisobutylene, polyvinyl alcohol, polyvinylpyrrolidone) lacked some of the required properties and were therefore abandoned. The fact that the successfully utilized polymers differed widely in their chemical structure indicates that the formulation of this dosage form is not limited to certain polymer groups. It is highly probable that many more candidates for film forming solutions can be identified among the numerous polymers that are available on the market. Although various polymers yielded films with suitable macroscopic properties, however, the permeation studies have shown that some polymers are superior to others with respect to the drug delivery. The results indicated that the polymers do not only immobilize the drugs in a matrix on the skin, but that they may also have an enhancing (in case of the DynamX® formulation) or a retarding (in case of the Eudragit RL formulation) effect on the drug permeation. These effects can result on the one hand from complex interactions of the polymeric formulation with the skin, on the other hand also from interactions of the polymer with the drug. The extent of the latter is specific for each drug – polymer combination, depending on the physico-chemical properties of the two compounds such as charge or lipophilicity. This should be kept in mind for the selection of a film forming formulation for a new drug candidate [2].

Solvent

The solvent is also a very important compound in the film forming solution although it is not part of the actual film on the skin due to its quick evaporation. The solvent must offer sufficient solubility for the polymer as well as for the drug. Only a high solubilizing power of the solvent for the drug allows substantial variations of the drug loading to modulate the drug delivery to the skin. The solvent can also exert a direct influence on the drug flux. Depending on the nature of the solvent and its permeation enhancing properties it can promote the drug transport to different extents in spite of its short contact time with the skin. This should be kept in mind for a further formulation development.

In addition to its solubilizing properties for the polymer and the drug a suitable solvent for a film forming solution is required to be highly volatile to provide short drying times and thus a good patient compliance. Together with the polymer it is supposed to spread well on the skin after application to produce a smooth film with a uniform thickness on the application site. Both requirements are not met for example by the solvent water. During the formulation experiments an aqueous chitosan formulation displayed unacceptably long drying times and an uneven spreading on the skin due to the high surface tension of the aqueous polymeric formulation. Consequently, water cannot be considered a suitable solvent for the formulation of a film forming polymeric composition. Solvents such as ethanol, isopropanol or ethyl acetate with a higher volatility and a better spreading are to be preferred [6].

Plasticizer

In polymeric applications the main purpose of a plasticizer is to facilitate the film forming and to increase the flexibility of the resulting film. Additionally, the formulation experiments have shown that the skin adhesion of the films can be modulated with the help of plasticizers.

The plasticizer has to be thoroughly selected with regard to the film former. It has to be miscible with the polymer to produce clear films with low visibility on the skin. Since the efficiency of a plasticizer is polymer dependant no general rule can be applied as to which plasticizer concentration is required to produce films with the desired properties. 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.

The plasticizer should preferably have a low skin permeability to prevent leaking from the formed film. A substantial leaking would not only raise safety concerns but would also lead to a deterioration of the film properties. In case of a loss of plasticizer the film becomes brittle and loses part of its adhesive properties. The acrylate polymers poly (ethyl acrylate-co-methyl methacrylate) Eudragit NE 40D as well as the silicone gum formed adequate films without the help of a plasticizing agent.

Further excipients

Apart from the basic compounds of a film forming polymeric solution (polymer, solvent and plasticizer) it can be appropriate to incorporate further excipients into the preparation. For some polymers such as the acrylate Eudragit E 100, it is beneficial to add a crosslinker (succinic acid) to the composition to improve the film stability. For some drugs, a solubilizer or co-solvent can be required in order to increase the drug loading of the formulation and the drug flux. Further examples for supplementary excipients are antioxidants to stabilize oxidation sensitive drugs in the preparation during storage, sun screens for the protection of photosensitive drugs or dyes to facilitate the localisation of the formed film for the patient.

A precondition for the incorporation of further excipients is the compatibility of the materials with all other compounds. Furthermore it has to be kept in mind that every change in the film composition might negatively affect the macroscopic properties of the formed film such as stability, adhesion to the skin or stickiness of the outer surface of the film. Therefore it is advisable to re-evaluate the macroscopic properties of the formed film after any adjustment of the composition.

Applications

Arthritis

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). Transdermal patches or films may be used as an alternative for the oral route for using NSAIDS. In the case of Rheumatoid arthritis, the treatment is carried out by regular usage of NSAIDS. Application of gels is easily wiped off due to clothes on joints and films may provide dryness and irritation after prolonged usage due to adhesive in it. Thus, there is a need to develop novel drug delivery systems for the treatment of rheumatoid

arthritis, which are available in gel form but when applied on skin surface transform into film. These film forming gels (FIFOGE) are a novel approach helpful in providing sustained release of drug indomethacin [13].

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 as showin in table 2 [14].

Cyanoacrylates or recently acrylate polymers have also been used for the closure of superficial wounds as liquid bandages [15]. 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 [12].

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 [16].

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).

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 [17]. 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 [16]. 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.

Mucoitis

Mucositis induced by anti-neoplastic drugs is an important, dose-limiting, and costly side effect of cancer therapy. The ulcerative lesions produced by mucotoxic chemotherapy are painful, restrict oral intake and, importantly, act as sites of secondary infection of oral flora. Pretreatment assessment of oral cavity hygiene and mouthwashes seem to be effective in preventing the onset of oral mucositis. Some therapeutic agents, such as benzydamine, imidazole antibiotic, triazolicantimycotic and povidone iodine have shown some

clinical evidence of their efficacy in reducing oral mucositis. Bioadhesive polymers appear to be particularly attractive for the development of drug delivery systems to improve intraoral administration and reduce the frequency of application and the amount of drug administered. Gels and films may be most suitable for this type of application and they are able to cover a wide area of mucosa for both drug delivery and physical protection.

Film forming gel formulations were prepared using mucoadhesive polymer to produce a physical barrier around the ulcers and form a medicated film for delivery of either diclofenac sodium or ofloxacin to treat the formed ulcer.

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:

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

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.

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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