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Review Article

FIFOGE: A NOVEL DOSAGE FORM

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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) 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.

KEY WORDS: FIFOGE, transdermal, gels.

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 (Langer,2004; Prausnitz, Langer,2008). The current dosage formulations used for TDDS are mainly pressure sensitive adhesive patches, ointments and creams (Kalia, Guy, 2001; Thomas, Finnin, 2004). 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 (Zhai, Maibach, 2002). The ointments and creams are usually comfortable to wear but may leave a sticky or greasy feel after application (Thomas, Finnin, 2004). 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. 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 (Alberti *et al*., 2005). Furthermore, the development of TDDS formulations recently has been focused on employing several polymer gels as a film-forming agent (Lee, Park, Robinson, 2000; Patel, Patel, Patel, 2009; Stamatialis *et al.,* 2008; Baboota, Shakeel, Kohli, 2006; Tas, Ozkan, Baykara 2003; Shin *et al*., 2005) .Whose 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 (Schroeder *et al*., 2007; Schroeder et al., 2007; Jones, Woolfson, Brown, 1997).Films must have a bioadhesive charactertics. Bioadhesion is defined as the ability of biological or synthetic material to stick to the human epidermis or a mucous membrane. Bioadhesion of films is based on belief that inter-atomic or inter-molecular forces are established at the interface of adhesive –skin assembly. Surface free energies of both adhesive and substrate determine the magnitude of adhesive forces. For an adhesive to adhere on substrate, the measured surface energy of adhesive must be equivalent to less than substrate i.e. human epidermis (Venkataraman , Gale, 1998) There are numerous other mechanism which may lead to bioadhesion are Hydrogen bonding, Surface energy and contact angle consideration (Helfand , Tagami, 1972; Lehar *et al*., 1992) Swelling rate of polymer interacting with skin and mucin, Polymer chain intepenetration (Kaelbe , Moacanin, 1977)Surface properties influences polymer-substrate interaction such as force of adhesion, elongation at adhesive failure and adhesive toughness.(Felton, Forbes , Moore, 2000).

Film forming agents

Phaseolus vulgaris

Is an annual herbaceous plant belonging to family Leguminosae. It is a common bean; most widely cultivated of all beans in temperate regions and widely cultivated in semitropical regions. In temperate regions the green immature pods are cooked and consumed. The plant is herbaceous, erect and bushy, 20–60 cm tall with a taproot and nitrogenous nodules. The leaves are alternate, green or purple, trifoliate, stipulate and petiolate. Flowers are white, pink or purplish, zygomorphic and variegated. Seeds or beans can be white, red, tan, purple, grey or black, often variegated, reniform, oblong or globose, up to 1.5 cm long, endosperm is absent. Phaseolus vulgaris seedscan be associated with a decreased risk for a wide variety of chronic diseases like cancer, obesity, cardiovascular diseases and diabetes (Kouakou *et al*., 2010). Phytochemical screening showed that Phaseolus vulgaris seeds have some bioactive components such as alkaloids, anthocyanin, carbohydrate, catechin, fibers, flavonoids, phasine, phytic acid, quercetin, saponins, steroids, tannins and terpenoids (Celleno, Tolaini, Damore, 2007). The biopolymer was isolated from the Phaseolus vulgaris beans using an economical process (Ojha, Madhav, 2012). First of all Phaseolus vulgarisbeans were taken & soaked in water. The outer covering of beans was removed &inner portion was collected. It was mashed with distilled water & filtered. Acetone was added to the filtrate. The filtrate

was kept overnight & centrifuged. Bio material was collected & dried in dessicator

Chitosan

Chitosan is a tough natural biopolymer for developing films due to their non-toxicity, biocompatibility, biodegradability, film forming ability inherent antimicrobial properties along with permeation enhancing and good adhesive properties. Chitosan can be dissolved in very many dilute organic acids such as acetic, lactic, malic, citric, ascorbic, benzoic and succinic acids and hold general antimicrobial activity can be used for this purpose.

Gelatin

Gelatin is a protein of animal origin, resulting from the acid or basic hydrolysis of collagen coming from bones, bovine and porcine skins, and from connective tissues. This macromolecule has been used in films production, most probably due to its outstanding filmogenic properties and its high production volumes at competitive prices. Gelatin has the capacity to form physical gels, i.e., thermoreversible gels. At a molecular level, gelatin gel formation involves a structural re-arrangement of the protein, implying the change from a disordered stage to a more ordered one, formed by triple helix structures (Sobral, *et al*., 2001;Gilsenan, Rose-Murphy, 2000).

Giant squid (Dosidicus gigas)

Squid gelatin, together with other marine gelatins, is offered asan alternative to mammalian gelatin source due to the sociocultural and safety considerations associated with the latter. Production of gelatin from pig skins is not acceptable for Judaism and Islam and beef gelatin is acceptable only if it has been processed in accordance with religious requirements. Furthermore, bovine spongiform encephalopathy (BSE) and other food safety problems are perceived by some consumers as a concern and provide an opportunity to market alternative materials the functional properties of the gelatin are greatly influenced by the amino acid composition and the molecular weight distribution. The melting temperature of gelatin prepared from the skins of warm-blooded animals and warm-water fish is generally higher than that of gelatin from the skin of fish living in cold-water, owing to the greater imino acid content and increased degree of proline hydroxylation. However, it is possible to enhance the gel properties of these gelatins by mixing with high quality gelatins from warm-water fishes or mammal or by means of chemical and enzymatic modifications. On the other hand, the type of chemical pretreatment and extraction conditions used in the extraction procedure may influence the molecular weight distribution and, as a result, the functional properties of the resulting gelatin. It is well accepted that the more severe treatment conditions are detrimental to the gelatin's physical properties. Nevertheless, extreme heating conditions are commonly used to increase the yield in commercial gelatins (Gilsenan, Rose- Murphy, 2000).

Polysaccharides

Polysaccharides are known for their film-forming properties which have been intensively investigated for food and non-food applications. It has been shown that a wide range of film properties can be obtained owing to the diversity of available polysaccharides. Starch, an abundant natural polysaccharide, has been widely studied to achieve renewable and biodegradable films thanks to its wide availability, its low cost, and its functional diversity. Mechanical properties of starch films are highly dependent on the amylose/amylopectin ratio, the two main macromolecular components of starch. Amylose, the linear component, favours good film properties compared to amylopectin, the highly branched macromolecule. Starch films contain residual water which also plays a significant role for their mechanical properties by reducing the glass transition temperature.

However, the industrial application of starch films for non-food uses is limited due to their brittleness and their hydrophilic nature. Plasticizers such as glycerol can be used to overcome these limitations by improving the processing and the flexibility of starch films. Another way to reduce these drawbacks is the use of modified starch or the incorporation of another biopolymer. Studies have been carried out to develop modified starches to improve the processing and extend their film-forming ability. These modifications, which can be chemical, physical or enzymatic, enable to change the physico-chemical properties of the dispersions and of the films (Bemiller, 1997).

Evaluation (Singh, Kukreti, Singh, 2013).

Phase transition time

Time taken by the gel to get converted into film is the phase transition time. 1 gram of gel was taken on a petri dish which was spread uniformly on it and kept on a hot plate at 37˚C and time taken was noted until gel converts into film.

Film Weight

1 gram of the gel was taken on a petridish which was left for drying after drying the resultant film was weighed on an electronic balance.

Film thickness

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

Rheological Studies

Using Brookfield Viscometer LVDV II+ model. Carefully prepared gels were placed under the viscometer to determine the viscosity of the formulation. Carefully prepared gels were placed under the viscometer using S 64 spindle to determine the viscosity of the formulation. 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. (Kumar,Verma, 2010). Spreadibility was measured on the basis of drag and slip characteristics of gels. The gel was kept in between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A one kg weigh was placed on the top of the two slides for 5 minutes in order to expel the air and to provide a uniform film of the gel between the slides. Excess of the gel was removed from the edges. The top plate was then subjected to pull of 100 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 spreadibility. Spreadibility was calculated using the following formula:

Spreadibility = M x 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.

Applications

Arthritis

Gels are most commonly used topical preparations used for the treatment of various disease. Gels proved a replacement of those formulations which seems to be uncomfortable by another route such as oral route, which may lead to peptic ulcers in excessive usage of NSAIDS. Transdermal patch or films may be used as an alternate of oral route for using NSAIDS. In case of Rheumatoid arthritis, 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 is available in gel form but when applied on skin surface transform into film. These film forming gels (FIFOGE) are novel approach helpful in providing sustained release (Singh, Kukreti, Singh, 2013).

Surgery

Presently, film forming polymeric solutions are well known from the field of surgery, wound care or skin protection. In surgery, film forming preparations are for example used as tissue glue for the thread-free closing of incisions or as disinfectants for the preoperative skin preparation. Film forming polymeric solutions are also utilized with or without antimicrobials active substances for the non-surgical care of minor cuts and abrasions or in ostomy care for the protection of the skin surrounding the ostomy wound against the aggressive bodily fluids. In contrast to this, only very few authors have described the use of film forming systems for the delivery of drugs to the skin. (Donkerwolcke, Burny , Muster, 1998;Hall, Bailes, 2005; Ritterband *et al*. 2005;Foroutan, Ettehadi, Torabi, 2002;Eaglstein, Sullivan *et al*., 2002; Campbell *et al*., 2000;Misra *et al*., 1996;Misra *et al*., 1997).

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, actas sites of secondary infection of oral flora (Sonis, Clark, 1991). 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 particulary 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 (Scully, Epstein, Sonis, 2003).

CONCLUSION

FIFOGE proves to effective dosage form for the topical 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 pain relief than the conventional gels and frequent reapplication is not required. FIFOGE concept can change to treatment concept of various diseases. A lot of work can be carried out in this field.

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