

Review Article

## Film Forming Gels: A Review

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### ABSTRACT

Film forming gels are a novel approach in this area that might present at an alternative to the conventional dosage form 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 and dermal drug delivery system can provide some desirable performance over conventional pharmaceutical dosage formulations, such as avoiding gut and hepatic first-pass metabolism, improving drug bioavailability, reducing dose frequency and stabilizing drug delivery profile. The aim of this review was to search for alternative to 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 gel, transdermal, semi-solid.

### 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<sup>1</sup>.

The current dosage formulations used for TDDS are mainly pressure sensitive adhesive patches, ointments and creams<sup>2,3</sup>. 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<sup>4</sup>. 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<sup>5</sup>. Furthermore, the development of TDDS formulations recently has been focused on employing several polymer gels as a film-forming agent<sup>6-10</sup>. 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<sup>11-13</sup>.

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<sup>14</sup>.

*Gels for prolonged dermal delivery of drug*<sup>15-17</sup>

The term "gel" represents a physical state with properties intermediate between those solids liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity. A gel consists of a polymer which swells in the presence of fluid and perhaps it within its structure. The rigidity of the gel is determined by the amount of fluid it entraps. These gels are wet and soft and look like a solid material. These are capable of

undergoing large deformation in their physical state i.e. from solid to liquid.

#### *Classification of gels*<sup>17</sup>

There are a variety of ways to classify gels

According to source of gelling agent

- Natural gels
- Synthetic gels
- According to the liquid medium entrapped
- Hydrogels
- Organogels
- According to their cross linkage
- Chemical gels
- Physical gels
- According to the chemical nature of gelling agent
- Organic gels
- Inorganic gels

#### *Structure of gels*<sup>16,17</sup>

Gels should, in general, be considered to be composed of heterogeneous structures in different orders from a few angstroms to several micrometers (structure hierarchy).

In gels with good solvents, as in aqueous gels, the long chains of organic gel formers are extended. This is due to hydrogen bond formation between water and hydroxyl groups of gelling agent. In a poor solvent, the gel molecules will be tightly coiled. The viscosity and structure of organic gels is thus dependent upon molecular entanglement by solvent molecules.

#### *Properties of gels*<sup>15,16</sup>

Gels should possess following properties:

- Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe and should not react with other formulation components.
- The gelling agent included in the formulation should produce a reasonable solid-like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
- The gel should exhibit little viscosity change under the temperature variations of normal use and storage.
- It should contain suitable anti-microbial to prevent microbial attack.
- The topical gel should not be tacky.
- It should be economical

#### *Uses of gels*<sup>15,16</sup>

Gels have applications in numerous field, including the food industry, medicine, biotechnology, chemical processing, agriculture, civil engineering and electronics.

In the pharmaceutical and cosmetic industry, gels may be enumerated to have the following uses:

- As delivery systems for orally administered drugs.
- To deliver topical drugs applied directly to the skin, mucus membranes or the eye.
- As long acting forms of drugs injected intramuscularly.
- As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquids and suppository bases.
- In cosmetics like shampoos, fragrance products, dentifrices, skin and hair care formulations.

- The bulk property of swelling is of particular interest for swelling implants, which can be implanted in small dehydrated state via a small incision and which then swell to fill a body cavity and / or exert a controlled pressure.

#### *Methods of preparation of gels*<sup>18,19</sup>

##### *Dispersion method*

In this method, the polymer is dispersed over water for 2 hours till it is completely soaked. The remaining ingredients are mixed and stirred well until a homogeneous mass is obtained.

##### *Cold method*

In this method all the ingredients are mixed together to form a homogeneous mass, under low temperature of about 5<sup>o</sup> C. The polymer is mixed with permeation enhancer to form solution A whereas drug is mixed with solvent to form solution B. Solution B is then poured into solution A slowly with complete stirring to form a homogeneous mass.

##### *Chemical method*

the formulation of sols by precipitation from solution involves chemical reaction where the ingredients interact in aqueous phase to form a gel structure. An example of gel formed by this method is silica gel which is produced by interaction of sodium silicate and acids in aqueous solution.

##### *Temperature effect*

At lower temperatures the solubility of most lyophilic colloids like gelatin, agar, and sodium -oleate is reduced. Hence on cooling a concentrated hot sol, it will often produce a gel. Increasing the temperature of these sols will break the hydrogen bonding and the reduced solubility will produce gelatin.

##### *Flocculation with salts and non-solvents*

in this method, gels are produced by adding just sufficient precipitant to produce the gel structure state but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid high concentration of precipitants locally. Solutions of ethyl cellulose and polystyrene in benzene can be gelled by rapid mixing with suitable amount of a non-solvent such as petroleum ether.

#### *Component of film forming gel*<sup>20,21</sup>

##### *Drug*

The dermal route is an extremely attractive option for the the drugs with appropriate pharmacology and physical chemistry. Dermal systems offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half- life since these are the causes of non- compliance due to frequent dosing. The drug candidate must have a low melting point (less than 200 C) and is required to be potent i.e. effective in few milligrams per day (ideally less than 25 mg /day). A saturated aqueous solution of the drug should have a pH value between 5 to 9. The drug should be non-irritant and non-allergic to human skin. The drug should be stable when in contact with skin. The drug should not stimulate an immune reaction to the skin. Tolerance to the drug must not develop under near zero order release profile of dermal delivery system. The drug

Sr.no.	Trade name	Polymer
1	Avalure AC118	Acrylates copolymer
2	Dermacryl 79	Acrylate /octylacrylamide copolymer
3	DynamX	Polyurethane-14 and AMP- acrylates copolymer
4	Eudragit E 100	Poly(butyl methacrylate,(dimethylaminoethyl) methacrylate, methylmethacrylate) 1:2:1
5	Eudragit NE 40D	Poly(ethyl acrylate, methyl methacrylate) 2:1
6	Eudragit RL PO	Poly(ethyl acrylate, (2- trimethylaminoethyl) methacrylate, methyl methacrylate) 1:0:2:2 chloride
7	Eudragit S 100	Poly(methacrylic acid, methyl methacrylate) 1:2
8	Hydagen HCMF	Chitosan
9	Kollidon 12 PF	Polyvinylpyrrolidone
10	Kollidon VA 64	Polyvinylpyrrolidone-vinyl acetate copolymer
11	Klucel LF	Hydroxypropylcellulose
12	Oppanol B100 /10SFN	Polyisobutylene
13	PVA 7200	Polyvinyl alcohol

should not get irreversibly bound to the skin. the drug should not get extensively metabolized in the skin.

#### Film Forming Polymer

Polymers are the backbone of DDS. They form a film on contact with the skin. They may also control the release of the drug from the system. Polymers used should be biocompatible and chemically compatible with the drug and other components of the system. Additionally, they should provide consistent and effective delivery of a drug throughout the product intended shelf life and should be regarded as safe for human use. The polymers utilized for DDS can be classified as,

- Natural polymers: e.g. cellulose derivatives, zein, gelatin, shellac, waxes, gums, natural rubber and chitosan etc.
- Synthetic polymers: e.g. polyvinyl alcohol, polyvinylchloride, polyethylene, polypropylene, polyacrylate, polyamide, polyuria, polyvinylpyrrolidone, polymethylmethacrylate etc.

The polymers like cross-linked polyvinyl alcohol, eudragit, ethyl cellulose, polyvinylpyrrolidone and hydroxypropylmethylcellulose can be used as film formers.

#### Solvent

Solvent is also very important compound in film forming solution although it is not a part of the actual film on 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 drugs 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 be promote the drug transport to different extents in spite of its short contact time with the skin. This should be kept in mind for 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 Together with the polymer it is supposed to spread well on the skin after application to produce a smooth film short drying times and thus a good patient compliance. 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<sup>6</sup>.

#### Plasticizer

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

The plasticizer has to be thoroughly selected with regard to the film former. It has to be miscible with the polymer to produce clear film 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 desired properties. The individuals 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 plasticizer the film becomes brittle and loses part of its adhesive properties. The acrylate polymers poly (ethyl acrylate-co-methacrylate)

Eudragit NE 40D as well as the silicone gum formed adequate films without the help of a plasticizing agent.

#### 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<sup>2</sup> 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.

#### Spreadability studies

Minimum quantity of the formulation was placed between two glass plate and the glass plate on the top was gently slid on the bottom glass slide to determine the spreadability of the formulation. Spreadability 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. Spreadability was calculated using the following formula:

$$\text{Spreadability} = M \times L / T$$

Where, S = Spreadability, 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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