AMERICAN JOURNAL OF PHARMTECH RESEARCH

**Journal home page:** http://www.ajptr.com/

# Review on Anti-Fungal Film Forming Hydrogel

**Linsha Paul T[1]*, K. Krishnakumar[2], Dineshkumar B[2], Smitha K Nair[2], Sandhya S[1]***

*1.Dept. of Pharmaceutics, St James College of Pharmaceutical Sciences, Chalakudy, Kerala*

*2. St James Hospital Trust Pharmaceutical Research Centre (DSIR Recognized), Chalakudy, Kerala*

## ABSTRACT

Anti-fungal agents like flucanazole, itraconazole, ketoconazole, clotrimazole etc. are used to treat various superficial and systemic fungal infections. Oral and parenteral administration of the antifungal drugs are associated with various side effects including headache, nausea, vomiting, abdominal pain, gastric ulceration and bleeding. Hepatic and renal toxicity was also observed in patients on high and prolonged use of drugs. Film forming hydrogels are the dosage form for the topical delivery of drugs and it can bypass the side effects related to the conventional dosage forms and can provide effective topical release of the drugs. These film forming gels are novel approach for providing sustained release with increased residence time, therapeutic effect and patient comfort.

**Keywords**: Antifungal agents, film forming hydrogel, topical drug delivery.

*Corresponding Author Email: stjamespharmacyproject@gmail.com

Received 12 December 2016, Accepted 22 January 2017

Please cite this article as: Paul LT *et al*., Review on Anti-Fungal Film Forming Hydrogel . American Journal of PharmTech Research 2017.

## INTRODUCTION

Fungal infections are one of the most common disease that affects our body, mainly skin. It has been estimated that about 40 million people are suffering from fungal infection around the world [1]. The pathogens responsible for superficial infections include dermatophytes, yeasts, and molds. Dermatophytes are the most frequently encountered causative agents of SFIs, which are generally classified according to the body site affected. Superficial and subcutaneous fungal infections affect the skin, keratinous tissues and mucous membranes[2]. A wide range of antifungal agents are utilizing for effective management of various dermatological infections including both superficial and deep fungal infections. Treatment approaches include topical and oral antifungal agents. There are various types of formulations like tablets, creams, shampoos and gels are available on market to treat the fungal infections.

Topical administration of antifungal agents are superior over systemic therapy due to its advantages such as targeting of drugs to the site of infection and reduction of the risk of systemic side effects. In topical administration, the drug absorption into the systemic circulation is prevented or minimized. Thus, the systemic side effects of drugs are avoided. Besides, topical preparations have better patient compliance due to their non-invasiveness . Topical agents that are conventionally used for the treatment of skin fungal infections are usually formulated as creams, lotions or gels. Depending upon the agent being delivered they either act as fungicidal or fungistatic. Another advantage of topical formulation is that it avoids drug-drug interactions, which are more common in case of oral administration[3]. For the localized treatment of an anti fungal agent to be effective, it should remain at the site of application for prolonged period of time. But it will not be adhered to the applied part due to sweat, movements, clothing, etc. that have limited the effectiveness and residence time of conventional topical formulations for treatment of fungal infections of skin. Hence, a composition that adheres to skin surface infected and provides localized delivery of an antifungal agent is needed.

The film-forming hydrogel (FFH) is a dosage form which transform from the hydrogel into film-type after application to the infected site by solvent evaporation. These are hydrophilic polymeric networks that may retain large amount of water and exhibit a semi-solid morphology. This formulation has the advantages of both hydrogel and film types. Film forming hydrogels proves to be effective dosage form for the topical delivery of drugs and it can bypass the side effects related to the conventional systems like gastric ulceration and bleeding. They preserve the active drug for a long time, and are biocompatible in nature [4]. They also prolong the drug release from the

formulation and reduce frequency of drug administration which will results in improved patient compliance.

## MECHANISM OF ACTION OF ANTIFUNGAL AGENTS

Fungal diseases are called mycosis and they can be divided into five groups[5] based on the level of penetration into the body tissues:-

### Superficial mycosis

These are caused by fungi that grow only on the surface of the skin or hair. Superficial mycoses are limited to the outermost layers of the skin and hair.

### Cutaneous mycosis or dermatomycosis

This includes infections such as athlete's foot and ringworm. Cutaneous mycoses extend deeper into the epidermis, and also include invasive hair and nail diseases.

### Subcutaneous mycosis

It penetrates below the skin to infect the subcutaneous, connective, muscle and fascia. These infections are chronic and can be initiated by piercing trauma to the skin which allows the fungi to enter. Its treatment is difficult and at some times may require surgical interventions.

### Systemic mycoses due to primary pathogens

It originates primarily in the lungs and may spread in to other organ systems.

### Systemic mycoses due to opportunistic pathogens

These are infections of patients with immune deficiencies who would otherwise not be infected. Examples include AIDS, immunosuppressive therapy, and metastatic cancer etc.

Antifungal drugs are used to treat mycoses. Depending on the nature of the infection, a topical or systemic agent may be used. A broad classification of antifungal drugs based on mechanism is given in Table 1.

**Table 1: Classification of antifungal drugs [6]**

| Anti fungal drug class | Examples | Mechanism of action |
|---|---|---|
| Polyenes | Amphotericin B, Nystatin | Interacts with sterols in cell membranes forming channels that leak cellular contents |
| Antibiotic | Griseofulvin | Inhibits mitosis (sliding of microtubules) in fungi |
| Azoles | Fluconazole, Ketoconazole, Itraconazole Etc. | Inhibits ergosterol biosynthesis at the level of C 14 -demethylase |
| Allylamines | Terbinafine | Inhibit ergosterol biosynthesis at the level of squalene epoxidase |
| Thiocarbamate | Tolnaftate | Inhibit ergosterol biosynthesis at the level of squalene epoxidase |
| Antimetabolite | Flucytosine | Inhibit DNA and RNA synthesis |

| | | |
|---|---|---|
| | | via conversion of 5-fluorocytosine to 5-fluoricil |
| Profens | Flurbiprofen, Ibuprofen | Direct damage to fungal cytoplasmic membrane |

**Topical Delivery of Antifungals via Skin**

The skin is a well organized membrane which covering an area of about 2 $m^2$ of average human adult body with an average thickness of 0.5 mm having three main layers, which are *epidermis, dermis, hypodermis*. *Stratum corneum* is the outermost layer of the skin formed by dead and keratinized cells which forms the principle barrier for the permeation of drugs through skin[7].

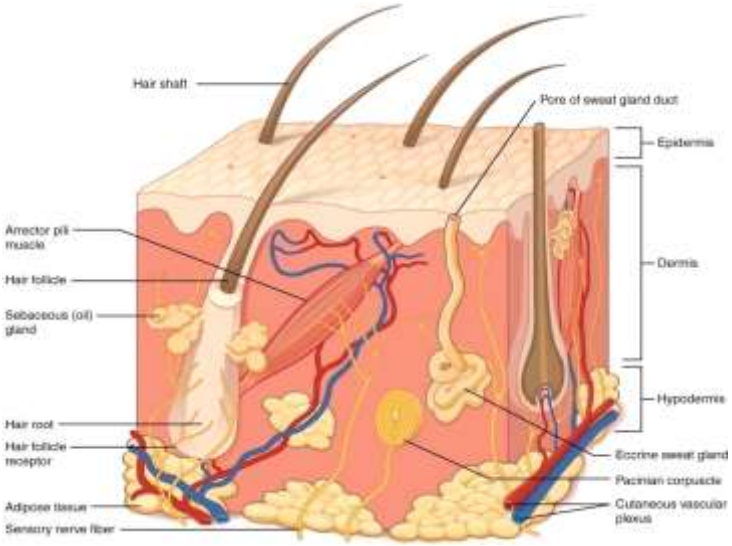


**Figure 1: Structure of skin[8]**

Following topical administration drugs should penetrate into the skin layers to ensure effective drug concentrations. Types of the formulations as well as the physico-chemical characteristics of drug molecules are the main factors affecting topical drug delivery. In topical administration, the entry of drugs into systemic circulation is prevented or minimized. Thus, the systemic adverse effects of drugs are avoided. Besides, topical preparations have better patient compliance due to their non- invasiveness and, they can be self-administered. The greatest challenge in case of dermal drug delivery is *stratum corneum*, and in order to improve its permeability, new formulation approaches have to be investigated[9].

**Film Forming Hydrogel**

The film-forming hydrogel (FFH) is a dosage form which transform from the hydrogel to film-type after application to the site by solvent evaporation. This formulation has the advantages of both hydrogel and film types[10]. The term hydrogel describes three-dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant

amount of water [11]. The formulation on contact with the skin will form a semi occlusive film over the skin, thereby concentrating the active ingredient of the formulation in a matrix of the polymer. The film-forming polymers used for topical administration include polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), HydroxyPropyl cellulose (HPC), HydroxyPropyl Methyl cellulose (HPMC), eudragit etc [12].

Hydrogel materials possess many specific properties like ability to contain water, stability in aqueous media and softness etc. that make them attractive for a wide range of applications such as tissue engineering, wound healing, controlled drug release, contact lenses etc[13]. Hydrogels, due to their high water content possess a degree of flexibility similar to natural tissue [14].

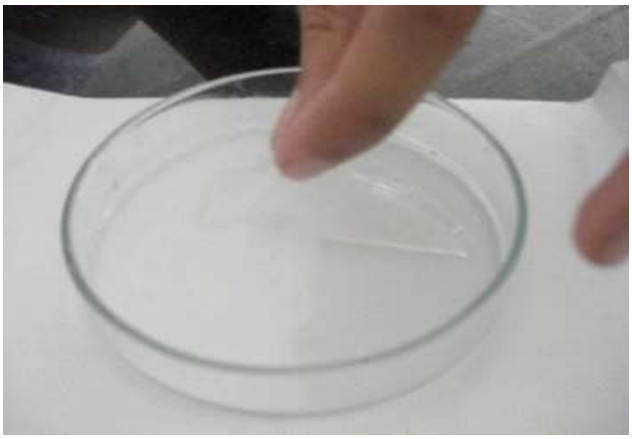

**Figure 2: Transformation of gel into film**

Liu X et al designed transparent film forming hydrogel of tolterodine using carbopol 980, Hydroxy propyl cellulose, HPMC and tween 80 as matrices and evaluated their effects on stratum corneum[15]. They showed sustained release over 24 hrs. An et al. [16] investigated a transdermal hydrogel on the basis of polyvinyl alcohol and polyisobutylene that solidified into a substantial film on the skin. The formed film was able to provide a sustained release of testosterone over 24 hours.

**Film Forming Hydogel in Topical Drug Delivery**

Usually topical formulations are more convenient for treating the skin infections. But the applied medicament may wiped off, due to clothes or any other reason. Thus there is a need to develop to novel drug delivery system which is in a gel form in a tube or container, but when applied to skin surface converts or transform into a film. Initially, gels provide a immediate drug release and after transformation into film prolonged drug release can be maintained [17].

**Figure 3: Formation of Film(courtesy: Google images)**

hydrogel adhere to skin because of hydration of skin and presence of hair follicles and sweat gland contain aqueous channels increases the skin surface hydration[18].

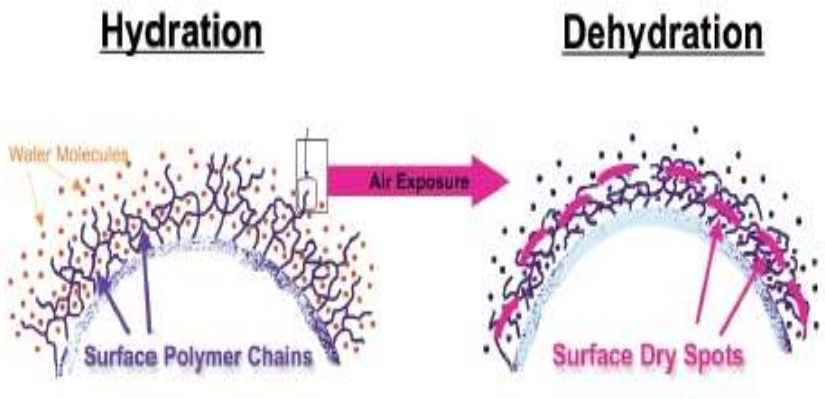


**Figure 4: formation of film on skin**

These film forming hydrogels are novel approach helpful in providing sustained release with increased residence time, therapeutic effect and patient comfort. This new drug delivery system has many advantages over the conventional formulations in terms of many biopharmaceutical parameters.

**CHARACTERISTICS OF HYDROGEL[19]**

The most important characteristic features of hydrogel include its water holding capacity and permeability. Firstly polar hydrophilic groups gets hydrated upon contact with water which leads to the formation of primary bound water. As a result the network swells and it exposes the hydrophobic groups which are also capable of interacting with the water molecules which leads to the formation of hydrophobically-bound water('secondary bound water'). Primary and secondary bound water are often combined and called 'total bound water'. Then this network will absorb additional water (free/bulk water) and this additional swelling is opposed by the covalent or physical cross-links, which leads to an elastic network retraction force. Thus, the hydrogel will reach an equilibrium swelling level. The additionally absorbed water will fill the spaces between

the network chains. Depending on the nature and composition of the hydrogel the next step is the disintegration/dissolution( if the network chain or cross-links are degradable).

**Biocompatibility**[20] is the third most important characteristic property required by the hydrogel. Hydrogel as well as its metabolites formed upon degradation will be compatible with the immune system and will be non toxic in nature.

**ANTIFUNGAL FILM FORMING HYDROGELS**

Topical therapy is an attractive choice for the treatment of the superficial infections due to its advantages such as targeting of drugs to the site of infection and reduction of the risk of systemic adverse effects. Systemic therapy is usually reserved for infections of the nails, extensive cutaneous infections or those which have not responded to topical therapy. Systemic treatment has the side effects like gastric irritation, diarrhea, nausea, vomiting and stomach pain, headache, fever, renal impairment and anemia [21].

Conventional topical formulations like gel, cream etc. are unable to retain the drug over the skin for a prolonged period and hence necessitate longer treatment duration or have to be supplemented by oral therapy. For effective topical delivery of an antifungal agent that is applied to the surface of the skin, it must get partitioned firstly from the vehicle into the stratum corneum, and then into the local tissues including the viable epidermis, dermis, subcutaneous tissue and appendages. This is problematic since antifungal compounds are generally hydrophobic and a new method is needed to perform this partitioning to deliver therapeutically effective concentrations of active agent in situ. For effective delivery of drugs via dermal route, much effort has been invested in providing chemical enhancers for drug penetration, such as DMSO. Many of these substances cause irritation and are not desirable due to their toxicity. Hence, there is a need for improved formulations for topical delivery of antifungal agents that would minimize the systemic exposure of the medicament. The need for multiple applications a day is frequently associated with poor patient compliance. Thus, prolonging the contact time of active substances to the skin and thereby reducing the application frequency is subject of intensive research.

The concepts of film forming formulations are novel. Film forming formulations may be solutions, gels or emulsions. Film forming formulations are defined as non-solid dosage forms which produce a 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 can provide a sustained drug release to the skin. Incorporation of the drug in a film forming gel would facilitate prolonged contact of the drug on the skin and the film formed on drying can improve its skin retention ability, thereby improving the topical treatment of

fungal skin infections. This approach not only sustain the release of drug , but also helps for drug targeting to the skin, thereby improving patient compliance by reducing application frequency .

Vij NN et al, developed and evaluated film forming gel containing anti fungal agent terbinafin hydrochloride for prolonged dermal delivery using polymers eudragit and hydroxyl propyl cellulose . The optimized formulation showed drug release of 99.84% and antifungal activity in terms of efficacy as 99.44% [22].

**METHOD OF PREPARATION**

The general methods [23] to produce physical and chemical gels are described below.

**Physical cross-linking**

There has been an increased interest in physical or reversible gels due to its ease of production and the advantage of not using any cross-linking agents. The various methods to obtain physically cross-linked hydrogels are:

**Heating/cooling a polymer solution:**

The gel formation is due to helix-formation, association of the helices, and forming junction zones. Carrageenan in hot solution above the melting transition temperature is present as random coil conformation which upon cooling transforms into rigid helical rods. In presence of salt (K+, Na+, etc.), due to screening of repulsion of sulphonic group (SO–3), double helices further aggregate to form stable gels Some of the examples are polyethylene oxide-polypropylene oxide, polyethylene glycol-polylactic acid hydrogel.

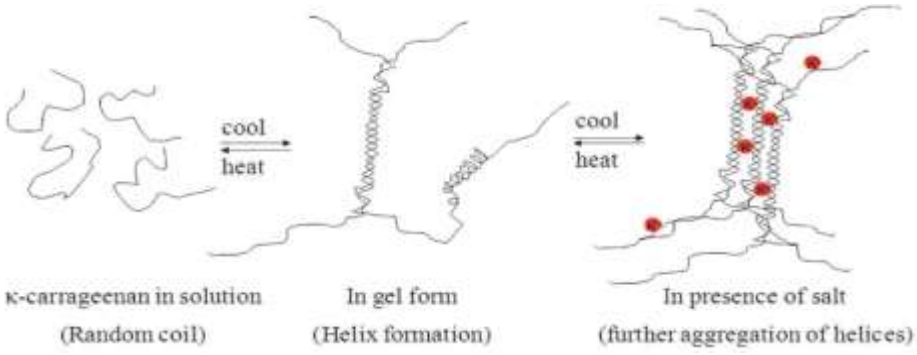


**Figure 5: Gel formation due to aggregation of helix upon cooling a hot solution of Carrageenan.**

**Complex Coacervation:**

Complex coacervate gels can be formed by mixing of a poly anion with a poly cation. The principle behind this method is that polymers with opposite charges stick together to form soluble and insoluble complexes depending upon the pH and concentration of the respective solutions. One such example is coacervating poly anionic xanthan with poly cationic chitosan.

**Chemical cross-linking**

Chemical cross-linking involves the use of a cross-linking agent to link two polymer chains. Natural and synthetic polymers can be cross linked through the reaction of their functional groups (OH, COOH, and NH2) with cross-linkers (e.g. glutaraldehyde, adipic acid dihydrazide).

**Chemical cross-linkers:** Glutaraldehyde, epichlorohydrin etc have been widely used to obtain the cross linked hydrogel. Example is hydrogel prepared by cross-linking of corn starch and polyvinyl alcohol using glutaraldehyde as a cross-linker.

**Grafting cross linking**

To improve the mechanical properties of a hydrogel, it can be grafted on surface coated onto a stronger support. In this technique free radicals are generated onto a stronger support surface and then monomers are polymerized directly onto it and as a result a chain of monomers are covalently bonded to the support. A variety of polymeric supports can be used for the synthesis of hydrogel by using grafting techniques. Starch grafted with acrylic acid by using N-vinyl-2-pyrrolidone is an example of this kind of process.

**Radiation cross-linking**

Radiation cross-linking is a widely used technique as it does not involve the use of chemical additives. It can retain the biocompatibility of the biopolymer and also the modification and sterilization can be achieved in single step .Hence it is a cost effective process to modify biopolymers having their end-use specifically in biomedical application. The technique mainly depends on producing free radicals in the polymer following the exposure to the high energy source such as gamma ray, x-ray or electron beam.

## CONCLUSION

The prevalence of fungal infections are increasing rapidly. Conventional topical formulations are not able to provide prolonged drug release and are also associated with various side effects including gastric ulceration, bleeding etc. Film forming hydrogels are effective dosage form for the topical delivery of drugs and it can bypass the side effects related to the conventional antifungal agents. Also it remains adhered to the effected part for a longer period without getting rubbed off .Thus it can provide sustained drug release and improve patient compliance.

## REFERENCES

1. Ameen M. Epidemiology of superficial fungal infections. Clinical Dermatology. 2010; 28(2):197- 201.

2. Narasimhalu CR,. Kalyani M, Somendar S. A cross-sectional, clinico-mycological research study of prevalence, aetiology, speciation and sensitivity of superficial fungal infection in indian patients. Journal of Clinical Experimental and Dermatology Research. 2016; 7(1): 324-334.
3. Bhowmik B, Ram AA, Gowda DV, Singh A, Srivastava A, Ali RM. Recent trends and advances in fungal drug delivery, Journal of Chemical and Pharmaceutical Research. 2016, 8(4):169-178.
4. Meshram I, Mishra DK, Jain DK. Formulation and evaluation of ketoconazole loaded hydrogel for topical fungal infections. Asian Journal of Biomaterial Research *2016; 2(3): 94-98.*
5. Wikipedia contributors. Mycosis internet. Wikipedia, the free Encyclopedia; 2017 Jan 17, 22.50 UTC cited 2017 Feb 13. Available from https: // en.wikipedia.org / w/ index.php?title= Mycosis & oldid = 760589544.
6. Spann M, Fedde KN. Topical cosmetics. Isw groups Inc., assignee. Patent WO2008030359A2. 13 Mar. 2008. print
7. Williams A. Transdermal and topical drug delivery: from theory to clinical practice. Pharmacy Education. 2004; 4(1):49–50.
8. Samuel SM, Saudagar RB. Transformed topical drug delivery: film forming lotions. International Journal of Universal Pharmacy and Bio Sciences. 2015 ;4(6):146-156.
9. Gungor S, Erdal MS, Aksu B. New formulation strategies in topical antifungal therapy. Journal of Cosmetics. Dermatological Sciences and Applications, 2013; 3:56-65.
10. Kima DW, Kima KS, Seob YG, Leec BG, Parkc YJ, Yound YS, Kimb JO, Yongb CS, Jina SG, Choia HG. Novel sodium fusidate-loaded film-forming hydrogel with easy application and excellent wound healing. International Journal of Pharmaceutics. 2015; 495: 67–74.
11. Hennink WE, Nostrum CF. Novel cross linking methods to design hydrogels. Advanced Drug Delivery Reviews 2002; 54:13–36.
12. Ranade S, Bajaj A, Londhe V, Kao D, Babul N. Fabrication of polymeric film forming topical gels. International Journal of Pharmaceutical Science Review and Research. 2014; 26(2):306-313
13. Mohamed SM, Masoud AME, Elgadir MD, Mahdy MA. Preparation and release characteristics of itraconazole polymeric films for topical application. International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(3):167-70.

14. Mateescu A, Wang Y, Dostalek J, Jonas U. Thin hydrogel films for optical biosensor applications. Membranes. 2012; 2:40-69.
15. Liu X, Fu L, Dai W, Liu W,Zhao J,Wu Y,Teng L, Sun F,Li Y. Design of transparent film forming hydrogel of tolterodine and their effects on stratum corneum. International Journal of Pharmaceutics. 2014; 471(1-2):322-331.
16. An NM, Kim DD, Shin YH, Lee CH. Development of a novel soft hydrogel for the transdermal delivery of testosterone. Drug Development and Industrial Pharmacy. 2003; 29: 99-105.
17. Gulrez SKH, Al-Assaf S, Phillips GO. Hydrogels: Methods of Preparation, Characterisation and Applications, Progress in Molecular and Environmental Bioengineering - From Analysis and Modeling to Technology Applications, Prof. Angelo Carpi(Ed.), ISBN: 978-953-307-268-5, InTech, Available from: http://www.intechopen.com/books/progress in molecular and environmental bioengineering from analysis and modeling to technology applications / hydrogels methods of preparation characterization and applications
18. Prashant PK, Vivek BR, Deepashree ND, Pranav PP. Hydrogels as drug delivery system and applications: a review. International Journal of Pharm Pharm Sciences. 2012; 4:1-7.
19. Das N. Preparation methods and properties of hydrogel: a review. International Journal of Pharmacy & Pharmaceutical Sciences. 2013; 5( 3):112-117
20. Nakusha D, Prakash K, Vishal P. Emerging trends in topical antifungal therapy: a review. Inventi Rapid: NDDS. 2015; (2):1-5.
21. Vij NN, Saudagar RB. Formulation, development and evaluation of film-forming gel for prolonged dermal delivery of terbinafine hydrochloride. International Journal of Pharmaceutical Sciences and Research. 2014; 5(5):537-554.
22. Li X, Zhang R, Liang R, Liua W, Wanga C, Su Z, Sun F, Li Y. Preparation and characterization of sustained-release rotigotine film-forming gel. International Journal of Pharmaceutics. 2014; 460(1):273-79.