INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY MEDICINE AND BIOALLIED SCIENCES
An International, Multi-Disciplinary, Peer-Reviewed, Open Access, Indexed, Triannually Published Journal
|www.biomedjournal.com|
ISSN 2348-2109

Formulation, development & evaluations of flexible polymeric topical antifungal film (TAF)

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ORIGINAL RESEARCH ARTICLE

ARTICLE INFORMATION

Article history
Received: 5 December 2015
Revised: 10 December 2015
Accepted: 20 December 2015
Early view: 30 December 2015

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QR Code

ABSTRACT

Aim: The purpose of this study was to formulate and developed a novel topical polymeric film containing the antifungal agents.
Material and methods: Topical antifungal films of clotrimazole were designed with different polymers & permeation enhancers like HPMC-K-100, HEC, CMC, Ethyl-Cellulose, Eudragit S-100 and PVP K-30 etc. incorporated at different concentrations using the casting evaporation technique. Evaluations of these formulae were performed through mechanical characterizations and Fourier Transform Infrared Spectroscopy [FTIR]. In-vitro release studies were performed during 24 h using diffusion cells.
Results: From the preliminary screening of the six polymers based upon the rating system it was observed that the film formulated using polymer PVP K-30 shows the best result. Moreover the film obtained from PVP K-30 was found to be having self-adhesive property.
Conclusion: The polymeric film was found to be non-sticky (from the back) thus preventing adhesion to the clothes of the patient/other physical contact.

Keywords: Topical antifungal film, clotrimazole, formulation and development.

INTRODUCTION

The skin is a very important route for the dermal or transdermal delivery of pharmaceutically active substances. Polymeric film are a novel approach that might present an alternative to the conventional dosage forms used on the skin, such as ointments, creams, gels or patches (Ines Zurdo et al., 2006). Drug-loaded polymeric films are a mechanism to deliver a drug based on application of pharmaceutical technology. Numerous controlled or sustained delivery systems have been described whereby the active ingredient has been dissolved or dispersed within these films (Hadgraft and Guy 1989; Prausnitz et al., 2004).Films are innovative drug delivery systems intended for skin application with the goal of achieving a systemic effect.

Polymer blending is an effective method for providing new materials for a variety of applications. Plasticizing agents are generally essential to overcome the brittleness of the films. Brittleness is an inherent quality attributed to the complex/branched primary structure and weak intermolecular forces of natural polymers. Plasticizers soften the rigidity of the film structure and increase themobility of the polymerchains by reducing the intermolecular forces, thus improving their mechanical properties (Bergo and Sobral, 2007; Padula et al., 2007). Use of polyethylene glycol (PEG) at 0.25% and 0.5% resulted in a reduced tensile strength (TS) and water vapor permeability rate (WVPR) of the film but an increase in percent elongation (%ε) (Srinivasa et al. 2007; Wiles et al. 2000). PEG is a biocompatible polymer with excellent biocompatibility that is non-toxic (Zhang et al. 2002). It is often blended or compounded with other polymers to be used in the field of drug controlled release (Chandy et al. 1998). Glycerol improves film flexibility and reduces film puncture strength (Gontard et al. 1993).

Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery seeks to concentrate the medication in the tissues of interest

while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs exclusively (Gupta and Sharma, 2011).

Topical drug delivery is the term used for localized treatment of dermatological condition where the medication is not targeted for systemic delivery as in transdermal drug delivery.

MATERIALS AND METHODS

Materials

Clotrimazole was given as a gift from Gujarat Pharma Lab. Pvt. Ltd, Ahmedabad, India, Eucalyptus Oil, Eudragit, HPMC and HPC were purchased from Research Lab Fine Chem. Pvt. Ltd, Mumbai, India. Ethyl cellulose, PVP, Polyvinyl Alcohol, CMC, Propylene Glycol, Polyethylene Glycol, Glycerol, Ethanol and Methanol were purchased from Loba Chemicals, Mumbai, India

Preparation of backing membrane (Demiana et al., 2011)

Polyvinyl alcohol (PVA) - 500 mg was dissolved in 15 ml distilled water and heated at 70 °C for 10-15min a clear solution was obtained. The solution was then transferred to the Petri Dish of inner radius 5cm having the effective inner surface area of 78.5cm^2. The solution was then kept for drying in open air. Dried thin film of thickness 0.05mm of PVA was thus obtained which was used as backing membrane.

Preparation of topical polymeric film

For Eudragit, Ethyl cellulose, PVP

1. In a 50ml beaker 15ml ethanol was taken followed by eucalyptus oil, propylene glycol, glycerol and PEG 400 with proper stirring. A clear solution was thus obtained.
2. Drugs were then added in this clear solution, the drug dissolved again giving a clear solution. Polymer was then further added in this solution which get solubilize.
3. The obtained solution was then added in the petri-dish which was then kept in the open air for drying.

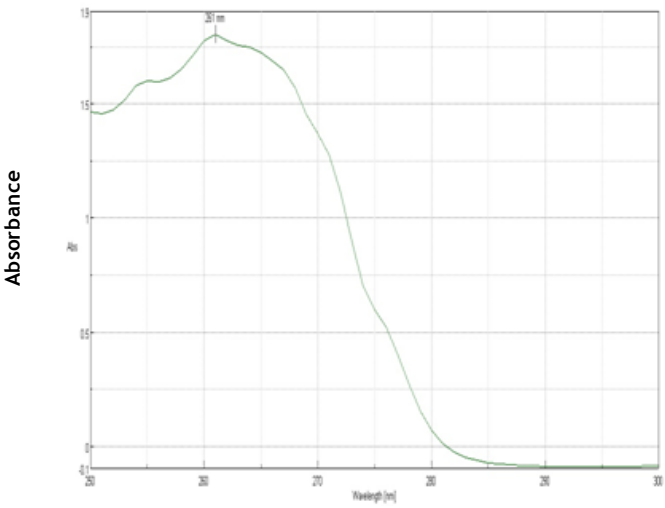
For HPMC, HPC and CMC

1. In a 50 ml beaker 10ml methanol, eucalyptus oil, propylene glycol, glycerol and PEG 400 was taken drugs were then added to this solution with proper stirring. A clear solution was thus obtained.
2. In a second 50ml beaker 15 ml water was taken and the polymer was dissolved in it.
3. Both the solution was then mixed together, and then added in the petri-dish which was then kept in the open air for drying.

Evaluation parameters

Determination of λ max of clotrimazole (Klaus, 2005; Indian Pharmacopoeia, 2010).

UV spectrophotometric method for analysis of Clotrimazole was developed. Clotrimazole solution (20 µg/ml) in methanol was scanned in the wavelength range from 250-400nm for determination of λmax. The reported value is 261nm.



Physical appearance

The physical appearance of the film was observed. The colour, appearance, presence of any clogging/precipitation and texture of the film was evaluated.

Thickness (Chomchan et al., 2005 and Garala, Shinde, 2009)

Thickness of film was measured by digital vernier calipers at three different places and mean value was calculated.

Weight Variation (Gupta, and Mukhrejee, 2003; Shankar et al., 2010)

Weight variation was studied by individually weighing 3 selected film of area 2cm x 2cmfrom each preparation. Such determination was performed for each formulation and mean value was calculated.

Flatness (Arora and Mukherjee, 2002)

Three longitudinal strips were cut out from each film, from the centre, left right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0% constriction equivalent to 100% flatness.

Constriction (%) = $[(L_1-L_2)/ L_2] X 100$

Where, L_1 initial length of each strip, L_2, final length.

Moisture uptake study (Chomchan et al., 2005)

A film of area size 2cm x 2cm was put in a desiccators containing silica gel for 24 h and weighed (*W*s), the films were transferred to another desiccators containing saturated NaCl solution (relative humidity 75%) at 25 ◦C. After equilibrium was attained, the films were taken out and weighed (*W*m). Moisture uptake capacity was calculated according to the following equation:

Moisture uptake capacity (%) = (*W*m – *W*s/*W*s) × 100

Drug content (Shankar et al. 2010 and Agrawal and Munjal, 2007)

For drug content determination a piece of 3.14 cm^2 was cut from the film and added to a beaker containing 100 ml methanol. It was then stirred for 4-5 hrs with the help of a magnetic stirrer. The solution was than analyzed for drug content at 238 nm and 261nm detection wavelength.

Tensile strength (Nguyen et al., 2008)

Tensile strength of the film was determined with the help of Ubique's Digital Tensile Strength Tester, Model-UTT-P. A film of size 25.4mm x 60mm was mounted on the tensile tester with the help of the clamps. The tensile strength was calculated as follow.

Tensile Strength= Load taken to break the wire in Newton's (N)/ Cross sectional area in mm^2X 100.

Adhesive Test (Clarence et al., 2009 and Pramila et al., 2001)

The prepared patches were cut into strips 25.4mm wide and 60mm in length and conditioned for 24 h at 23±2 ◦C and 50±5%RH. The samples were applied to an adherent plate made of stainless steel, smoothened with a 4.5 pound roller five times; the lower end of attached sample was tied with thread. The stainless steel plate on which the sample was adhered was vertically fixed on the lower clamp of the Ubique's Digital Tensile Strength Tester, Model-UTT-P and the thread was tied to the upper clamp and pulled from the substrate at a 180 ◦C angle at a rate of 300 mm/min. The stainless steel plate on which the sample was adhered was fixed on the lower clamp of the Ubique's Digital Tensile Strength Tester, Model-UTT-P and the adhesive test was determined. The peel adhesive test was calculated in g/2.5mm.

Stability studies (Xiao and Brazel, 2001; Prajapati et al., 2009)

Stability studies on the optimized formulated patches (OF1) were carried out as per ICH guidelines. Appearance, drug content and weight variation were used to check the stability of the formulation after predetermined time.

The patches were stored in an aluminum foil and subjected to Elevated temperature and humidity conditions of 40 ± 2^0C/ 75 ± 5 % RH

Samples were withdrawn at the end of 0, 30, 60 and 90 days and evaluated for

- Appearance
- Drug content
- Weight Variation

RESULTS

Physical appearance

Table 1 shows the physical parameters of the topical antifungal film. All the formulated film shows the same results.

Table 1. Physical parameters of film.

Sr. No.	Parameters	Observation
1	Colour	Colourless
2	Appearance	Transparent
3	Clogging/Precipitation	No Clogging/Precipitation
4	Texture	1) Sticky-From site of application. 2) Smooth-From back
5	Odour	Characteristic i.e. Eucalyptus Oil like

Thickness, weight variation, flatness, moisture uptake and drug content of the films

Table 2 shows the thickness, weight variation, flatness, moisture uptake and drug content of the films.

Table 2. Evaluation parameters for formulation F1-F6

Formulation Code	Thickness (mm)	Weight Variation (mg)	% Flatness	Moisture Uptake (%)	Drug Content Clotrimazole (%)
F1	0.23	165.63±1.94	99.45±0.5	5	98.61 ± 0.28
F2	0.25	167.49±2.56	99.24±0.3	3	98.50± 0.49
F3	0.21	158.17±1.45	99.18±0.6	3	97.33 ±0.40
F4	0.22	162.10±0.24	99.33±0.2	6	96.57 ± 0.25
F5	0.22	162.08±2.80	99.27±0.4	5	99.17 ± 1.90
F6	0.22	155.33±1.87	99.36±0.3	2	97.33 ±0.40

Data shows mean (n = 3) ± SD.

From the values obtained for table 2 it was found that the thickness of the film varies from 0.21mm-0.25mm. Weight of the film varies from 155.33mg-167.49mg. Flatness varies from 99.18%-99.45%. Moisture uptake varies from 2%-6% for 4cm^2 area. Drug content varies from 96.57%-99.17% for 3.14cm^2 area.

Stability studies

The stability studies of the optimized OF1 film revealed no significant changes in the physical parameters when

stored at temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH and at room temperature.

No significant reduction in the content of the active drug was observed over a period of three months. However, storage temperature not exceeding 45°C and moisture proof packaging are essential to ensure stability of these formulations.

Table 3: Stability studies of OF1 film during the period of 3 months

Storage time	Appearance	Drug content (%)	Weight variation (mg/4cm^2)
One month	Transparent	98.45 ± 0.96	163.52±0.47
Two month	Transparent	98.22 ± 0.36	161.94±0.73
Three month	Transparent	97.04 ± 0.52	160.13±0.25

Data shows mean (n=3) ± SD.

DISCUSSION

Clotrimazole is selected as active pharmaceutical ingredients (API) for the formulation of Topical Antifungal Film-TAF. In the aim to achieve the desire goal/target six different were selected HPMC-K-100, HEC, CMC, Ethyl-Cellulose, Eudragit S-100 and PVP K-30. From the preliminary screening of the 6 polymers based upon the rating system it was observed that the film formulated using polymer PVP K-30 shows the best result. Moreover the film obtained from PVP K-30 was found to be having self-adhesive property. Hence PVP K-30 was selected as model polymer. Adhesive strength was found to be 500(g/25.4mm). Thus a very thin film (mean thickness=0.23) was obtained. The polymeric film thus prepared meets the desired requirement for the novel Topical Antifungal Film (TAF). The polymeric film was found to be non-sticky (from the back) thus preventing adhesion to the clothes of the patient/other physical contact. Considering the fact that many patients complain about the high visibility of transdermal patches which is considered cosmetically unattractive the polymeric film was found to be transparent.

CONCLUSION

The Novel Topical Antifungal film-TAF thus was successfully formulated, evaluated and optimized. Novel polymeric film containing the antifungal agents which helps to destroy the said infection upon contact with high cosmetic attractiveness. Very thin (0.23mm), very flexible and very light in weight provide a long lasting effect (10hr) against the fungal infection as compared to other topical preparation with minimum irritation to the tissue where so applied and where the film is highly resistance to removal by fluids or other physical contact. Reduce the frequency of application of topical antifungal agents. The polymeric film was found to be self-adhesive (from the site of application) so that it easily adhered to the site of application and also get removed easily. The presence of Eucalyptus Oil in the formulation showed synergistic activity when used in combination with clotrimazole.

CONFLICT OF INTEREST

None declared.

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