

PREPARATION AND RELEASE CHARACTERISTICS OF ITRACONAZOLE POLYMERIC FILMS FOR TOPICAL APPLICATION

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ABSTRACT

The objective of this paper was to prepare and evaluate various polymeric films for fungal infection treatment. Different Eudragit polymeric films containing Itraconazole as antifungal drug were prepared by solvent casting technique. The prepared films were tested for their physico-mechanical properties as tensile strength, physical endurance, elasticity, water vapor permeation and water loss. The release of Itraconazole from the prepared medicated films was examined. The results revealed that films prepared with Eudragit RL 100 containing hydroxyl propyl methyl cellulose produced maximum release of Itraconazole both *in vitro* and *in vivo* as compared with other topical dosage forms as ointments and gels. Moreover the films constitute a simple and convenient method for treatment of various fungal infections. As conclusion, the use of antifungal drugs such as Itraconazole which is a broad spectrum antifungal drug used for treatment of dermatophytosis incorporated in polymeric films proved more promising results in the treatment of dermatophytosis.

Keywords: Itraconazole, Eudragit RL 100, Polymeric film, Antifungal drugs.

INTRODUCTION

Medicated polymeric films have found great application in topical therapy, being easily applied and avoid the troubles encountered in oral dosage forms. Fungal infections are so abundant in recent years and require intensive and long time for treatment. Application of medicated substances to the skin is a concept as old as humanity [1,2]. For treatment of skin infections, wide assortments of topical dosage forms are available [3,4]. It comprises powders, lotions, emulsions, ointments, pastes, aerosols, soaps, plasters, shampoos and other preparations[5]. Today, among these preparations, ointment - like preparations, covers about 80%. The application of some ointments to the skin produces systemic actions, which means, that certain degree of absorption occurs. Afterwards, systemic drug administration by the transdermal route was achieved with some cream and ointment preparations for protection and treatment from certain diseases [6]. None of these preparations was satisfactory; the major disadvantage was variable systemic drug absorption due to the absence of specific directions as to the area to be covered. For such reasons medicated topical polymeric films are designed to deliver the drug to the skin surface at a controlled rate [7-10].

The main advantages of such solid dosage forms are: 1) Elimination of variables, which influence G. I. T absorption, 2) Avoidance of influence G. I. T absorption, 3) Avoidance of drug with small therapeutic index, 4) Permits display of only one pharmacological effect show several effects, 5) An alternative route when oral route is not practicable, 6) Elimination of nuisance associated with daily repetitive applications of messy ointments and creams (patient compliance is better), 7) Flexibility of the dose used, it has a definite area. (i.e. increase area leads to increase in dose, 8) Easy to terminate therapy by removing the system. These advantages confirm that drug-containing polymer films are very promising medicinal preparations, Topical dosage forms have been approved for drug delivery for topical medication[11].

Medicated polymeric films constitute one of the most suitable and easily applicable topical preparations since they produce more prolonged effect and are easily and conveniently applied [12]. Itraconazole is a broad spectrum antifungal drug of common use for treatment of various skin infections [13]. The aim of this research article was to prepare and evaluate medicated polymeric films containing itraconazole for topical application.

MATERIALS AND METHODS

Itraconazole was received as a gift sample from Ranbaxy laboratories Ltd., Dewas (India). Eudragit RL100 (Rohm Pharma, Germany).

Carbopol 940, liquid paraffin, white soft paraffin, methanol, hydroxyl propyl methyl cellulose, di butyl phthalate, polyethylene glycol 400 (Sigma Aldrich, USA), All other chemicals were analytical grades.

Methods

Different Itraconazole polymeric films containing 1% of the drug was prepared using Eudragit RL 100 dissolved in acetonitrile and containing various concentrations of hydroxyl propyl methyl cellulose, dibutyl phthalate, and triethyl citrate as plasticizers. The prepared films were tested for their solid-state characteristics, moisture absorption, mechanical properties, such as tensile strength, folding endurance and release characteristics. The *in vitro* release of Itraconazole from the prepared films was determined using Hanson SR8 dissolution test system according to the USP XXVIII apparatus 5 paddle over disk method. The *in vivo* evaluation of the release of Itraconazole from the prepared films was done on healthy volunteers.

Preparation of the polymeric films

Polymeric films were prepared by dissolving various concentrations of Eudragit RL 100 in methyl alcohol. The concentration of Eudragit ranged from 4 to 10 %, the casting technique was used for preparation of the films [14]. The solution mixture was poured on a specifically designed stainless steel spherical assembly consisting of two stainless steel plates of 7.9 cm internal diameter (area 48.99 cm²). The solvent was allowed to evaporate at 37 ± 0.5 °C and relative humidity 40 ± 5%. An inverted funnel was placed over the metallic assembly to prevent rapid evaporation of the solvent. All films were separated from the casting assembly with the help of a sharp blade and then stored in the desiccator till further use. Different plasticizers were employed[15,16]. These are hydroxyl propyl methyl cellulose, dibutyl phthalate and polyethylene glycol 400. The concentration of plasticizers used ranged from 1 to 5%. The drug concentration in all films was 1%.

Preparation of Itraconazole ointment

Itraconazole ointment was prepared by mixing 1% of the medicament with an oleaginous ointment base consisting of 10% liquid paraffin and 90% soft paraffin.

Preparation of Itraconazole gel

The gel was prepared using 5% Carbopol 940 and 1% of Itraconazole in distilled water then the pH of the gel was adjusted to 5.5 by addition of ammonium hydroxide solution. Both ointment and

gel were examined for the *in vitro* and *in vivo* release of Itraconazole in comparison with medicated Eudragit RL 100 films.

Determination of the thickness

The thickness of prepared films was measured using a micrometer (Mitutoyo, Kanagawa, Japan). Each film was measured for its thickness at 5 different points and the mean values were calculated [17].

Folding endurance measurement

This test was carried out to check the brittleness of the prepared films. It was done by repeated folding of the films in the same place until complete break down [18]. The number of folds required to break the films was determined.

Moisture uptake study

The films were put in a desiccator with silica gel for 24 h and weighed (W_i) using Sartorius AG Göttingen electric balance, Germany. The films were then transferred to another desiccator containing saturated NaCl solution (relative humidity 75%) at 25°C until a constant weight was obtained [19]. After equilibrium was attained, the films were taken out and weighed (W_m). Moisture uptake capacity was calculated according to the following equation:

$$\text{Moisture Uptake Capacity} = (W_m - W_i/W_i) \times 100.$$

Moisture Content Study

The prepared films were weighed (W_i) and kept in a desiccator containing silica gel at 25°C until it showed a constant weight (W_d) [19]. The moisture content was calculated according to the following equation:

$$\text{Moisture content (\%)} = W_i - W_d/W_d \times 100$$

Where W_d is the weight of the dried polymer film and W_s denotes the weight after swelling.

Mechanical Properties Study

The mechanical properties were evaluated using Chatillon apparatus for force measurement (greensbro, NC 27409). Rectangular film strips of fixed width and length were fixed between the upper and lower jaws. The lower jaw was driven downward with a speed of 1 mm/s. Load versus displacement curves were recorded until rupture of the film [20]. The mechanical properties were determined as follows:

$$\text{Tensile Strength} = \text{Breaking force/Area of the film.}$$

$$\text{Elongation at break \%} = \text{Difference in length at breaking point} \times 100/\text{Original length.}$$

In vitro Release Studies Using USP Dissolution Tester

The USP 23 apparatus was used to determine the dissolution of the films using 5 dissolution test units, Hanson Research Corp., USA; 1,000 ml of distilled water was used as dissolution medium. The temperature was adjusted at 32 ± 0.5 °C and the speed at 50 rpm.

Films were cut into small strips each 2.5 cm X 2.5 cm which were used for determination of the *in vitro* release of drug contained. Aliquots of 5 ml were withdrawn through sintered glass filter at each time interval and replaced by equivalent amounts of fresh dissolution media. Blank experiments were simultaneously performed [21]. The cumulative amount of drug released after 5 hours was determined by spectrophotometric assay of the methanolic extracts of Itraconazole at 262 nm. This test was also applied for Itraconazole ointment and gel.

In vivo release studies

This study was carried on, in Zagazig University hospital (Zagazig, Egypt). The study involved 25 volunteers suffering from legs fungal infection. Ten of the patients used the films and a follow up study was carried on for 7 days, in comparison with other patients (15 patients) who applied Itraconazole medicated ointments and gels.

RESULTS AND DISCUSSION

The results indicate that as the concentration of the polymer increased there was an increase in the thickness of the film. Moisture absorption is more in films having high amount of the hydrophilic polymer: hydroxyl propylmethylcellulose while low in films having high amount of the hydrophobic polymer; Eudragit RL100. Moisture loss was highest in films having the less concentration of the hydrophobic polymer Eudragit RL100 which offered minimum hindrance for the transfer of moisture, while lowest in films having high amount of the hydrophobic polymer Eudragit RL 100. The presence of plasticizer in the form of HPMC imparts flexibility to the polymer. HPMC forms hydrogen bond with the polymer molecule thereby imparting flexibility to the film strips. This flexibility of the films facilitates their removal from the casting moulds and also makes their application on the skin easier. Polymeric films prepared with HPMC are more flexible than those prepared with either dibutyl phthalate or polyethylene glycol 400. A good relationship between the flexibility of the polymeric films and their efficacy was demonstrated.

The folding endurance test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The folding endurance was found between 83 and 90 folds which is considered satisfactory and reveals good film property.

The *In vitro* release of Itraconazole from the prepared polymeric films and from Itraconazole ointment and gel is illustrated in figure 1. From this figure it is obvious that the amount of drug released for a period of 5 hours was higher from gel than the polymeric films, being 67% of the contained amount in comparison with that released from the film 54%. Itraconazole ointment was the lowest in this concern releasing only 46% of the contained drug, this may be due to the hydrophobic nature of the drug and its solubility in paraffin base do not facilitate its release to the aqueous medium.

Figure 2 illustrates the *In vivo* release of the drug from the polymeric films, it shows that complete healing from fungal infection was achieved within three days of treatment.

Table 1: Composition of the Prepared Films.

Formula I	Formula II	Formula III	Formula IV
Itraconazole 100 mg	Itraconazole 100 mg	Itraconazole 100 mg	Itraconazole 100 mg
Eudragit RL100 400mg	EudragitRL100 500mg	EudragitRL100 750mg	EudragitRL100 1000 mg
HPMC 0.5 ml	HPMC 0.75 ml	HPMC 1.0 ml	HPMC 1.25 ml
Methanol to 10 ml	Methanol to 10 ml	Methanol to 10 ml	Methanol to 10 ml

Table 2: Physico-mechanical Properties of the Prepared Films.

Formula Number	Thickness nm	Tensile Strength (%)	Folding Endurance (Folds)	Moisture Absorption (%)	Water Loss (%)
I	280 ± 1.15	70 ± 1.19	90 ± 1.01	11 ± 1.05	6.8 ± 1.20
II	295 ± 1.13	68 ± 1.11	88 ± 1.15	12 ± 1.12	8 ± 1.30
III	312 ± 1.05	64 ± 1.05	86 ± 0.5	14 ± 1.23	9 ± 1.28
IV	320 ± 0.85	62 ± 1.12	83 ± 1.18	16 ± 1.11	9 ± 1.12

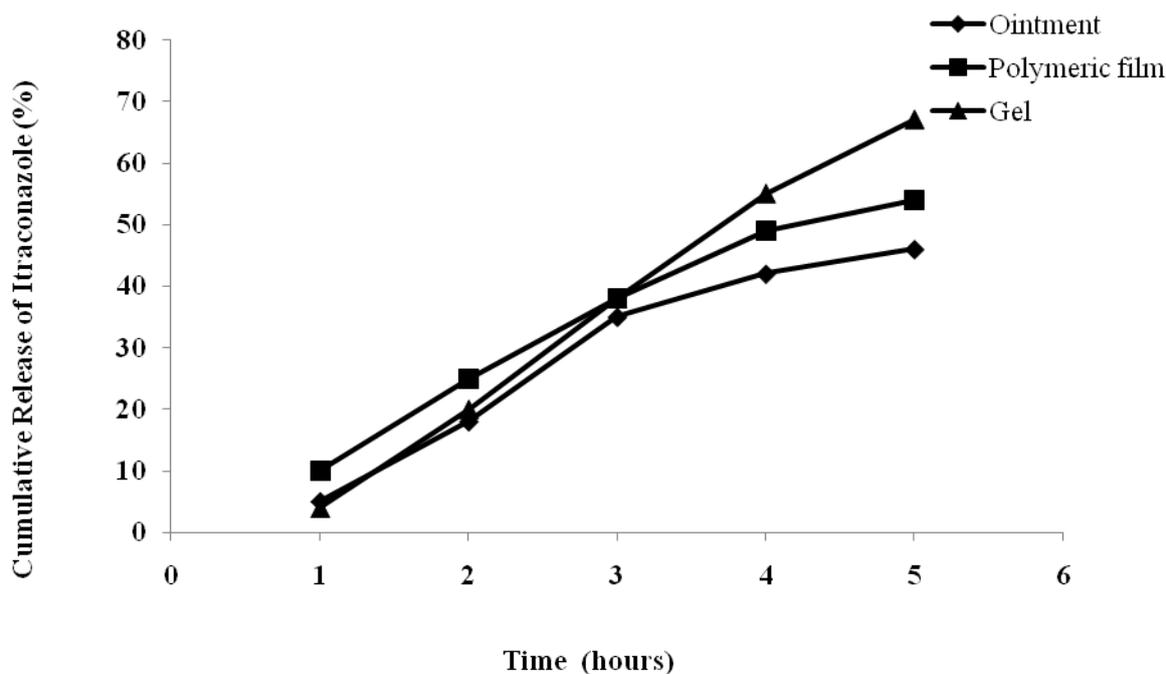


Fig. 1: *In vitro* cumulative drug release from different topical preparations of Itraconazole.



Fig. 2: *In vivo* drug release from medicated polymeric films of Itraconazole on human volunteers.

The *In vitro* release of Itraconazole from the prepared polymeric films and from Itraconazole ointment and gel is illustrated in figure 1. From this figure it is obvious that the amount of drug released for a period of 5 hours was higher from the gel than the polymeric films, being 67% of the contained amount in comparison with that released from the film; 54%. Itraconazole ointment was the lowest in this concern releasing only 46% of the contained drug, this may be due to the hydrophobic nature of the drug and its solubility in paraffin base do not facilitate its release to the aqueous medium. From the obtained results the medicated polymeric films showed good physical and mechanical properties. The *in vitro* release from the different topical preparations illustrated that the amount released ranged from 45 to 56 % of the incorporated amount of drug. Moreover there was no significant variation for all the tested preparations *in vitro*, while the *In vivo* studies were surprisingly higher for the medicated films over other preparations. This indicates the effectiveness of applied polymeric films over other tested topical preparations.

CONCLUSION

Films prepared with Eudragit RL100 containing HPMC as plasticizer proved to be more elastic and flexible, being easily removed from the casting molds and easily applied on the human skin. Furthermore medicated polymeric films proved to be more effective than other topical preparations in treatment of fungal infection, since complete healing occurred within 3 days of treatment.

Moreover the polymeric films are more convenient in application being less adhesive and produce a more prolonged effect.

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