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FORMULATION, DEVELOPMENT AND CHARACTERIZATION OF FILM FORMING GELS OF EFINACONAZOLE

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ABSTRACT

The overall core of the present study was to formulate and evaluate the film-forming gels of Efinaconazole using the polymeric blend of Eudragit RL-100 and Ethyl cellulose. Polyethylene Glycol-400 is used as a plasticizer. The drug release profile of Efinaconazole was identified to be burst release (18% - 39%) during initial 4 h period, which later sustained its release up to a mark of 24 h. The drug was determined by performing pre-formulation studies, including the solubility test and the melting point test (81°C-86°C), which correlated with the standard values. Three formulations were prepared and named F1, F2 and F3, which were prepared by the solvent dissolution method by altering the concentration of the polymer and the co-polymer and were evaluated for their pH, weight of dry spray, percentage purity and *in vitro* drug release. Physicochemical parameters like drying time (56–57 s), density (0.759-0.885ρ), viscosity (6.75-9.98 cP) and pH of 6 were recorded. Initially, the burst release was found for all three formulations at the starting four hours, which after became a sustained release with over 97% of drug release for 24 hours in F3. From this, it is concluded that F3 showed promising results, and Efinaconazole film-forming gels were prepared successfully using the polymeric blend of Eudragit RL-100 and Ethyl Cellulose.

KEYWORDS: Efinaconazole, Film-Forming System, Onychomycosis, Eudragit RL-100, Ethyl Cellulose, Polyethylene glycol-400.

INTRODUCTION

Film-forming systems are a type of dermal drug delivery system which act as an elevation in the field of pharmacy, which upholds the potential for changing the name of healthcare in a sophisticated manner. Film Forming System, the brainchild of Novel Drug Delivery System, are an important display acting a crucial role in a wide range of sectors, playing an indispensable role in processes ranging from surface coating to pharmaceuticals[1] Essentially, film-forming systems act by the formation of thin, continuous layers (films) of matter which can serve manifold functions, such as protection, decoration, or controlled release. These films are typically made from different types of polymers, resins, or other materials that can undergo an alteration from a slurry liquid phase to a solid film upon drying. The formation of these films is core to many advanced technologies, and implementing how film-forming systems work is the key to optimizing their performance for different applications.[2][3]

Film-forming systems are a critical group of materials that change from a fluid or semi-fluid to a solid or semi-solid thin film upon processing, mainly using solvent evaporation, chemical crosslinking, or phase changes due to temperature. Such systems have widespread use in various industries, ranging from protective coatings and pharmaceutical products to food packaging and electronics. The process of film formation is grounded in material science, polymer chemistry, and surface science, and they provide almost unlimited opportunities for the preparation of functional films with a rich variety of controllable properties.[4][5]

Onychomycosis is a recalcitrant infection which presents as an important cosmetic and medical problem since affected individuals often exhibit nail disfigurement, discomfort due to the thickness of the plate or ridge formation and in some cases secondary bacterial infections. Efinaconazole is a new triazole antifungal experimental agent developed mainly for topical treatment of onychomycosis, which is the most common fungal infection in nails caused largely by dermatophytes as well as some yeasts and molds.[6][7] Efinaconazole inhibits fungal P450-dependent enzyme (14α-demethylase), which is required for the biosynthesis of ergosterol, a constituent of the fungal cell membrane, and its inhibition leads to a decrease in ergosterol production, an essential component of the fungicidal or apoptotic activity. Due to the low solubility of the drug, addition of 3 % Sodium lauryl sulphate was added to increase the solubility of the overall formulation.[8][9] The half-life of Efinaconazole is 29.9 hours. The main objective of the study is to prepare the film-forming gels of

efinaconazole, which helps to overcome the solubility-related bioavailability problem.[10]

MATERIALS AND METHODS

Materials: Efinaconazole was a gift sample from Solara Active Life Sciences, Chennai, India. Eudragit RL-100 (Indian Fine Chemicals, Mumbai), Ethyl Cellulose, Polyethylene Glycol-400(Loba Chemie Pvt Limited, Mumbai), Acetone(BVRH Chemicals, Chennai), Ethanol(Changshu Hongsheng Fine Chemicals Co. Ltd, China) were obtained from commercial sources.

METHODS

Development of standard curve of efinaconazole

Efinaconazole was dissolved in ethanol to prepare a 10 µg/ml concentration. UV scan from 200-400 nm using a UV-visible spectrophotometer (Shimadzu UV-1800) was performed. The maximum absorption wavelength (λ_{max}) was recorded at 210 nm. The stock solution was diluted using pH 7.4 phosphate buffer to obtain various 0.2 to 1 µg/ml concentrations. The absorbance was measured at 210 nm using a Shimadzu UV-1800 UV- Visible spectrophotometer.

Determination of solubility: The solubility of the drug was determined in different solvents.

To conduct the solubility studies 20 ml of solvent was taken in a flask. 10 mg of efinaconazole was put into the conical flak and it was stirred at 37°C using a magnetic stirrer to dissolve it. More drug was added until a saturated solution was obtained. This saturated drug solution was stirred for about 2–3 h until a clear solution was obtained. Absorbance was determined at 210 nm for the determination of the amount of efinaconazole.

Determination of melting point: The melting point of pure efinaconazole was determined by an open capillary method. The capillary was closed at one end by introducing it into a flame. The capillary tube was placed in a melting point apparatus (Maru Electrical Accessories). The temperature was set to automatically increase the temperature. The temperature at which the drug started melting was recorded and compared with the standard.[11]

Preparation of Efinaconazole film-forming systems: The composition of the formulations is given in Table 1. The formulations of efinaconazole film-forming spray solutions were formulated using the solvent dissolution technique in which the ingredients and efinaconazole were homogeneously mixed to form a solution in an ethanol-acetone mixture. The solvents

were prepared in a ratio of 7:3 of ethanol and acetone.

Table 1: Composition of film-forming systems.

Ingredients	F 1	F 2	F 3
Efinaconazole (g)	1.0	1.0	1.0
Eudragit RL 100 (g)	0.35	0.40	0.45
Ethylcellulose (g)	0.15	0.10	0.05
PEG 400 (ml)	0.1	0.1	0.1
Ethanol: Acetone 7:3 (ml) q.s	10	10	10

Evaluation of film-forming gels: Different quality control parameters of all the batches of film-forming gels of efinaconazole were analyzed by adopting the methods as described.

Drying time: The evaporation duration refers to the period required for the spray solution to develop a film through the process of solvent evaporation. This duration was determined by spraying film-forming solutions onto a petridish. The temperature was set at approximately 37 °C± 2. Time was noted until the applied gel was dried completely and a film was formed. The time taken for the film to dry was measured.[12]

pH: The digital pH meter (NMP- 1) was calibrated using standard buffer solutions. The electrode was rinsed with distilled water and dried. The electrode of the calibrated pH meter was dipped into the film-forming solution. The pH was recorded.

Viscosity: The viscosity was measured at room temperature using Brookefield viscometer.

Assay of Efinaconazole: 1 ml of the formulation was dissolved in 100 ml of ethanol. Further dilutions were done with 7.4 phosphate buffer and absorbance was measured at 210 nm using 7.4 phosphate buffer as blank in Shimadzu UV-1800 spectrophotometer.

***In vitro* Drug Release:** An open-ended cylinder equipped with an egg membrane was utilized to facilitate the drug release from the formulation. The membrane was properly positioned and kept intact which served as the donor compartment. 1 ml of the formulation was sprayed on the egg membrane and dried. The receptor section was a beaker filled with 50 ml of phosphate buffer pH 7.4 with 3% sodium lauryl sulphate (SLS) and the temperature was maintained at 37°C ± 0.5. The whole assembly was kept on a magnetic stirrer with an optimal speed of 100 rpm. 5 ml sample was withdrawn from the receptor compartment periodically and the same amount was replaced during every withdrawal with fresh phosphate buffer pH 7.4 to maintain the sink condition. The aliquots were analysed at 210 nm

using a Shimadzu UV-1800 UV- Visible spectrophotometer.[13]

Spray Diameter: A sheet, as the target surface for spray application, was positioned at a distance of 10 cm (L) between the nozzle and the sheet. The spray nozzle was held at the recorded 10 cm distance from the sheet. The formulations were applied to the sheet. The mean diameter of the spray pattern formed was observed and measured.

Amount of Spray Solution Released Per Actuation: The spray container was weighed along with the solution, and the total weight. Following ten actuations, the weight of the formulation along with the container was noted. The weight difference before and after actuation was determined. The volume of the solution delivered per actuation was calculated.

Spray Angle: The spray was directed horizontally onto a filter paper positioned 10 cm away from the nozzle. The height (h) between the paper and nozzle was measured. The radius (r) of the circle created on the paper was measured.[14] The spray angle (θ) was determined using

$$tan\theta = h/r$$

RESULTS AND DISCUSSIONS

Calibration Curve of Efinaconazole

The standard calibration curve of efinaconazole was studied with a pH 7.4 buffer. The λ_{max} was found at 210 nm The results are shown in Table 2 and represented graphically in Fig. 1.

Table 2: Calibration Curve of Efinaconazole.

S.no	Concentration(µg/ml)	Absorbance(nm)
1.	0.2	0.264
2.	0.4	0.517
3.	0.6	0.805
4.	0.8	1.050
5.	1.0	1.252

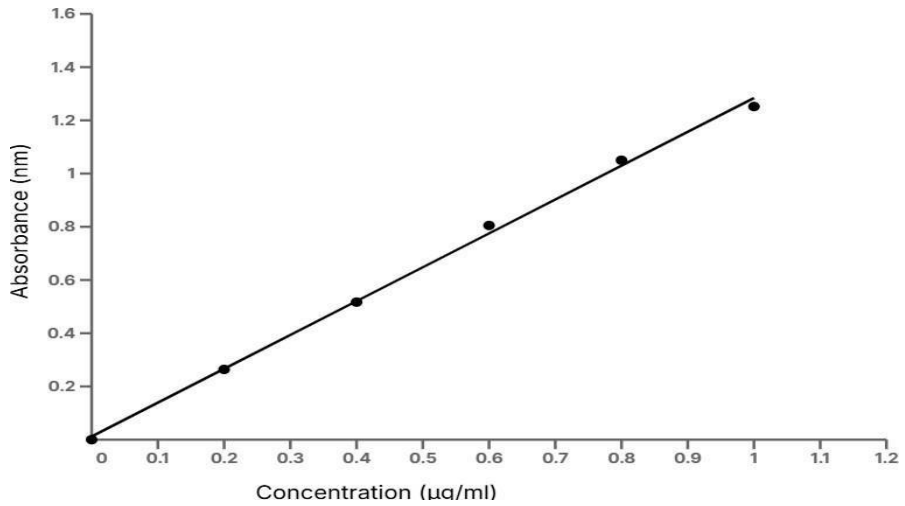

Fig. 1: Calibration Graph of Efinaconazole.

The linearity was found y = 0.254x+0.0119, and R^2 value was found to be 0.9978.

Solubility; The solubility of the drug was found in the given solvents as shown in Table 3.

Table 3: Solubility.

S.no	Solvents	Solubility nature
1	Ethanol	414 mg/ml
2	Acetone	112 mg/ml
3	Methanol	128 mg/ml
4	Water	0.04 mg/ml

Melting point: The melting point of efinaconazole was found to be 82°C. The normal range of the melting point of efinaconazole is between 81°C to 87°C, which shows that the melting point of the drug lies within the range. The melting point indicates the purity of the drug.

Physical appearance and surface texture of films: The physical appearance of the films appears to be flexible, transparent and non-sticky. The surface texture also feels airy without any substantial texture with a smooth, glossy finish after drying. The surface texture remains strong without being heavy on the skin, with a durable nature to penetrate the drug for a long period.

EVALUATION PARAMETERS

Drying time

The average drying time for the formulations F1-F3 were found to be 55-57 s.

The film-forming time, which is the time required for the gel to dry, was found to be

relatively short due to the volatile nature of the solvents used. This is an advantage as the product dries in a short time, as used by the patient.

pH: Considering the fact that highly acidic or alkaline pH may cause irritation to the skin and influence the degree of hydration of the polymer, the surface pH of the fast films was determined to optimize drug permeation. Attempts were made to keep the surface pH between 5-7. The surface pH of all the films was found to be. Since the surface pH of all the film-forming gels was found to be close to pH 6, there will not be any kind of irritation to the skin. The surface pH of all film-forming gels was found to be within the limits 6-7. The standard deviation values calculated for all the film-forming gels are very low, which indicates that the surface pH of all the films was uniform and within the ranges. The prepared film-forming gels of all the formulations were evaluated, and the results are shown in Table 4.

Viscosity: The viscosity of all the formulations from F1 to F3 was found to be in the range of 55-57 cps. Achieving an ideal viscosity is of significance as it is notable that low-viscosity gels have good sprayability and spreadability.

The drying time was found to be between 55-59 s, which was well in the desired range for an ideal film-forming spray formulation. The spray angle of prepared formulations was between 31° to 37°, depicting its uniform delivery on the surface of the skin.

The solution was analyzed for drug concentration spectrophotometrically was reported the highest drug content. The sp was found to be between 97.9 – 99.4 %. Spray diameter and spray content varied slightly as the concentration of the polymers was modulated (Table 4).

***In Vitro* Drug Release Study**

In vitro drug release profile of efinaconazole from different film-forming gel formulations F1, F2 and F3 are shown in Fig,2. Due to the low aqueous solubility of the drug 3 % of Sodium Lauryl Sulphate was added to increase the solubility. Regarding the concentration of polymeric blend, results show that the initial release profile of efinaconazole from formulations incorporating different Eudragit RL 100 and ethyl cellulose concentrations show a difference in release profile. In the initial phase of release upto 8 h formulation F3 showed faster release of 22.0% at 0.5 h and 61.8% at 8 h. In case of F2, 21.3% of drug was released at 0.5 h with 57.9% at 8 h. F1 showed the slowest release with 18.4% drug release

at 0.5 h and 53.7% at 8 h. It was noted that, irrespective of the polymeric blend the cumulative drug release rates for F1-F3 at the end of 24 h were found to be 96.1%, 96.4% and 97.2% respectively.

Initial burst release was seen followed by slow and sustained drug release in all formulations. It was seen that as the concentration of ethyl cellulose decreased there was a marked increase in the percentage of drug released. It was also seen that the concentration of Eudragit RL did not have a significant effect on the percentage of drug release.

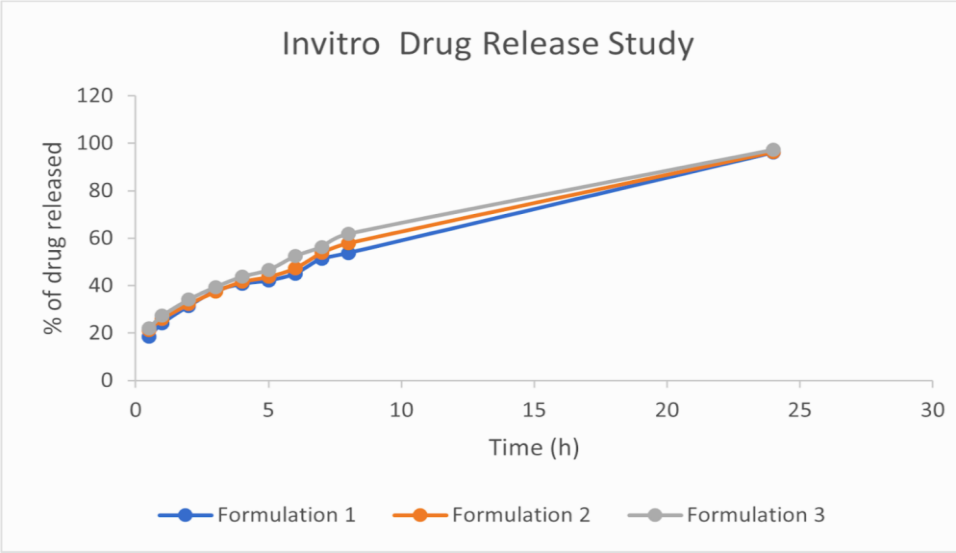

Fig. 2: In Vitro Drug Release Study.

Table 4: Evaluation parameters.

S.No	Parameters	F1 (Mean±S.D)	F2 (Mean±S.D)	F3 (Mean±S.D)
1	pH	6.1±0	6.0±0	6.2±0
2	Drying time (sec)	55±2.16	57±0.816	59±0.708
3	Viscosity(cP)	45.75±0.08	52.98±0.02	54.34±0.02
4	Spray diameter (cm)	11.8±0.08	10.3±0.04	10.2±0.07
5	Spray angle (^{0})	31.45±0.04	32.97±0.02	37.93±0.05
6	Spray content per actuation (mg)	164.8 ±0.2	167.3±0.4	162.1±0.6
7	Assay (% w/v)	99.2±0.02	99.4±0.09	97.9±0.06

CONCLUSION

Film-forming gels of efinaconazole prove to be an effective dosage form for the delivery of drugs. Also, it remains adhered to the affected 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 In vitro drug release studies were

performed for F1, F2, and F3, respectively, along with the addition of 3% Sodium lauryl sulphate due to the low aqueous solubility of the drug. The Burst release of the drug was noted where the drug starts to release in a minimum quantity, but with time, it reaches a high level of drug release. Comparatively, F3 showed a higher drug release percentage compared to the other formulations. In conclusion, the topical treatment of fungal infections proved to be suitable for the efinaconazole film-forming spray formulation. The improved formulation has good spray properties that make it appropriate for topical administration. Longer, continuous medication administration is facilitated by the skin's longer retention period. The efinaconazole film-forming spray is a considerably better alternative to current dosage forms because of its simplicity of administration, retention and action.

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