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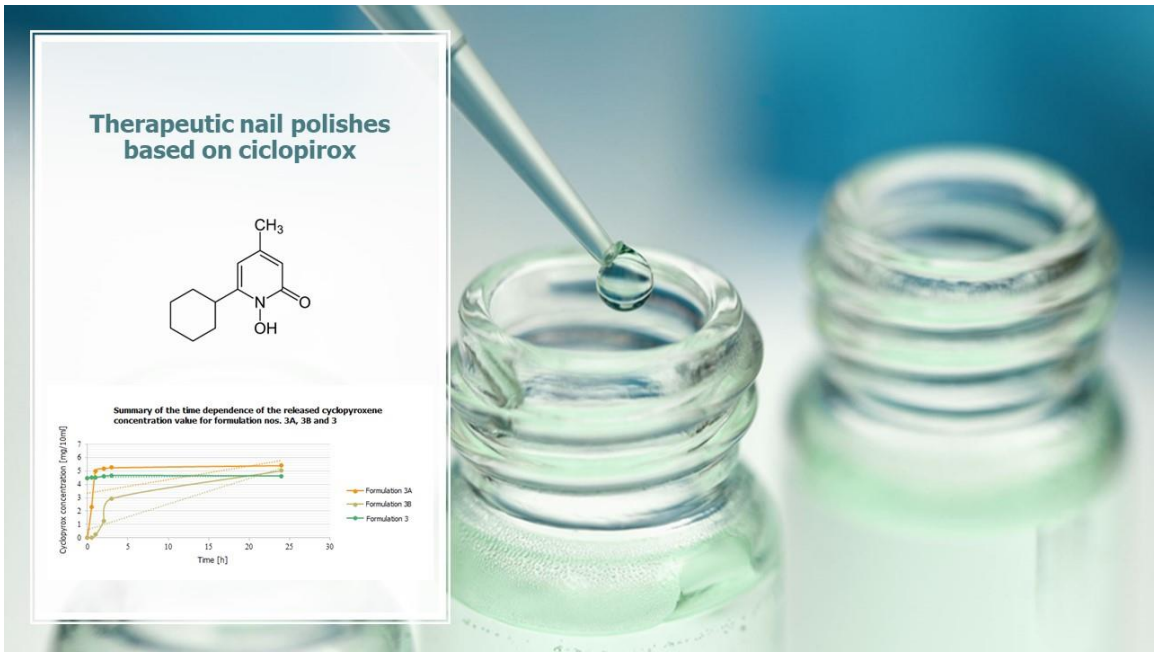
Therapeutic nail polishes based on ciclopirox

Anna K. Drabczyk[(1)], Patrycja Podobińska[(1)], Agnieszka Mamica[(1)], Jolanta Jaśkowska[(1)]✉

[(1)] Department of Organic Chemistry and Technology, Faculty of Chemical and Engineering and Technology, Cracow University of Technology, 24 Warszawska Street, 31-155 Cracow, Poland
✉ Correspondence to: jolanta.jaskowska@pk.edu.pl



Abstract: The aim of the research work was to create a nail polish formulation that would carry the therapeutic substance ciclopirox (ciclopiroxolamine), a drug with an exceptionally broad spectrum of activity, exhibiting antifungal, antibacterial, bacteriostatic and anti-inflammatory activity. The experiments conducted proved that ciclopirox can not only be released from the developed formulations when applied directly to the plate, but can also be applied to nails covered with cosmetic varnish. The amount of released active ingredient reaches the minimum inhibitory concentration for cyclopirox in *Candida spp*. infection. Which suggests that the formulations would be effective for fungal infections. The best results in terms of film formation were obtained for formulations that were based on PVP. The highest released drug concentration

occurred with formulation No. 3 and was 4.47 (mg/10ml) after 24 hours.

Keywords: Therapeutic nail polishes, ciclopirox, *Candida spp*., onychomycosis

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Introduction

The most common nail diseases include: change in nail pigmentation, discoloration, chronic inflammation and fungal infections [1]. The observed conditions are mainly due to disorders arising from the size and shape of the nail plate, ringworm (onychomycosis) and psoriasis [2]. Other nail lesions may be related to genetics, systemic diseases, trauma, nail biting, exposure to water and chemicals, and past infections [1,3]. Onychomycosis is by far the most common nail disorder, accounts for nearly 50% of all nail disorders, and primarily affects the elderly [4-6]. It occurs 4 to 10 times more often in toenails compared to toenail infection and requires a longer treatment period [7]. It is caused mainly by dermatophytes, but also by nondermatophytes and *candida spp*. It is among the most common nail disorders reported in clinical practice with a prevalence of 5.5% worldwide [8]. Almost 70% of these infections are attributed to dermatophytes, mainly Trichophyton rubrum (>50%) and T. mentagrophytes (about 20%). Other etiologic agents causing nail infections include *Epidermophyton floccosum, Microsporum spp., Aspergillus spp., Fusarium spp., Scytalidium spp.* and *Candida spp.* [8, 9]. Patients affected by nail fungus complain of localized pain, discoloration of the nails, delamination, brittleness or thickening. The impact of fungal diseases on aesthetic considerations of the nails makes this problem negatively affect the quality of life [10].

There are basically four methods of treating onychomycosis. These primarily include oral medications, topical medications, combinations of oral and topical medications, and mechanical removal of the nail plate. The latter may be the most effective option for infection of the lateral nail plate. However, it is rarely used since the introduction of newer treatments [12]. Oral systemic treatment with antifungal medications is highly recommended for patients with an infection affecting at least 50% of the distal nail plate, nail matrix or multiple nails, and for patients who have not achieved the expected results after 6 months of topical therapy. The main oral drugs used to treat onychomycosis are terbinafine, itraconazole and fluconazole [13].

Topical monotherapy is indicated for superficial white onychomycosis and is also an interesting alternative in distal subungual onychomycosis affecting less than 50% of the surface without matrix involvement [14]. Nearly 75% of all onychomycoses fall into this category [12]. In addition, it is recommended when several nails are infected and is indicated in children due to its ease of application [11,12]. Currently, the most commonly used topical antifungal drugs are mainly ciclopirox and amorolfine [13]. Patients with onychomycosis may, also, benefit from a combination of oral and topical therapy, as this is an attractive option as it can improve prognosis and help reduce systemic exposure [12].

Nail polish has long served as cosmetics for beautifying and protecting the epidermal creations. They are commonly applied with a brush, but there are other types of application, such as spatulas and sponges. In contrast, medicated nail polishes are a relatively new form of drug delivery. One of the most important features of nails is permeability, allowing topical therapies to be carried out, mainly for the treatment of onychomycosis, a fungal infection of the fingernails and toenails. Topical therapy is highly desirable due to its non-invasiveness, ability to target drugs to the site of action, minimize systemic side effects and improve patient compliance. Recent advances in drug delivery technology have led to the introduction of drug-containing varnishes [15,16], which, when applied to the nail, form a film on it after evaporation of the solvent, from which the drug is released in a sustained manner and reaches the target site - the nail matrix and nail bed. Nail polish with a therapeutic substance mainly contains an active ingredient, a film-forming polymer, a plasticizer and a volatile organic solvent [17]. The advantage of nail polish is the long contact time of the drug with the nail, so that the effective concentration can be reached at the desired site. The drug dispersed in the polymer acts as a matrix controlled release system. After the varnish is applied to the nail plate, a water-insoluble film forms within minutes after the volatile organic solvent evaporates. It will contain a higher concentration of the drug compared to the original nail polish formulation [18]. This will create a concentration gradient that will aid the diffusion of the drug through the nail. Nail polish also has the added benefit of reducing TOWL (Transepidermal Water Loss), a parameter that determines how much water is lost from the body through the nail plate to the external environment. After the nail polish is applied to the nail plate, the TOWL is reduced [19] and thus prevents water loss, leading to over-hydration of the nail plate. As a result of hydration and swelling, the nail will form a network of aqueous pores that further promote diffusion of the active ingredient [20]. Of course, in the case of drugs administered through the nail plate, there may be many obstacles to consider when designing therapeutic formulations such as the size of the diffusing particles, the ability to diffuse depending on

hydrophilic/lipophilic properties, the degree of ionization, the type of carrier and the presence of a back layer [15].

Fungal diseases are often associated with an unsightly aspect so that patients often do not use treatment, but only varnishes to mask the disease. With the above in mind, the aim of the conducted research was to develop a formulation of nail polish as a carrier of therapeutic substances, which could be used both as a typical therapeutic preparation and as a formulation applied to a nail plate previously painted with cosmetic polish. Although ciclopirox-containing lacquers are well known on the market, to date, no tests have been conducted to evaluate the release rate when the product is applied to typical colored nail polish.

Material and methods

Based on the literature review performed, nine formulations of therapeutic nail polishes containing ciclopirox at a concentration of 8% as the active ingredient were prepared (Figure 1).

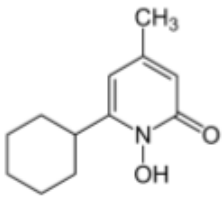


Fig. 1. Cyclopirox (6-cyclohexyl-1-hydroxy-4-methylpyridin-2(1H)-one)

The first step in the preparation of nail polish formulations 1, 2, 3, 4, and 8 was to completely dissolve the selected polymer in a solvent mixture made with alcohol (ethanol or isopropyl alcohol), ethyl acetate, and, in the case of formulation No. 3, also from a permeation enhancer -ethoxydiglycol. Then add the therapeutic substance, or cyclopirox, to the resulting mixture, and mix successively until a homogeneous consistency is obtained. Tables 1-9 provide information on the composition of INCI (International Nomenclature of Cosmetic Ingredients) therapeutic nail polishes and the functions of individual ingredients in the formulation.

Table 1. Formulation formula of nail polish No. 1.

Formulation 1			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Ethyl acetate	Ethyl Acecate	Solvent	33.0
Methocel	Methocel	Film-forming polymer	30.0
Isopropyl alcohol	Isopropyl Alcohol	Solvent	29.0

Table 2. Formulation formula of nail polish No. 2.

Formulation 2			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Ethyl acetate	Ethyl Acecate	Solvent	33.0
Polyvinylpyrrolidone	PVP (Polyvinyl-pyrrolidon	Film-forming polymer	30.0
Isopropyl alcohol	Isopropyl Alcohol	Solvent	29.0

Table 3. Formulation formula of nail polish No. 3.

Formulation 3			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Ethyl acetate	Ethyl Acecate	Solvent	33.0
PVP	PVP (Polyvinyl-pyrrolidon	Film-forming polymer	30.0
Isopropyl alcohol	Isopropyl Alcohol	Solvent	19.0
Ethoxydiglycol	Etoxydiglicol	Permeation enhancing substance	10.0

Table 4. Formulation formula of nail polish No. 4.

Formulation 4			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Polyurethane-62	Polyurethane-62	Film-forming polymer	10.0
Ethyl acetate	Ethyl Acecate	Solvent	18.0
Ethanol	Ethanol	Solvent	64.0

Table 5. Formulation formula of nail polish No. 5.

Formulation 5			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
PVP	PVP (Polyvinyl-pyrrolidone)	Film-forming polymer	10.0
Ethyl acetate	Ethyl Acecate	Solvent	18.0
Ethanol	Ethanol	Solvent	64.0

For formulations 6, 7 and 9, the selected ingredients used to make nail polish were added during mixing according to the order shown in the tables below.

Table 6. Formulation formula of nail polish No. 6.

Formulation 6			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Nitrocellulose	Nitrocellulose	Membrane-forming substance	10.0
Ethyl acetate	Ethyl Acecate	Solvent	18.0
Ethanol	Ethanol	Solvent	64.0

Table 7. Formulation formula of nail polish No. 7.

Formulation 7			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Propylene glycol	Propylene Glycol	Humectant, penetration enhancer	48.8
Urea	Urea	Permeation enhancer, keratolytic agent	17.0
Lactic acid	Lactic acid	Moisturizer, humectant, active ingredientn	10.0
Glycerin	Glycerin	Humectant	6.6
Perhydrol	Perhydrol	Permeation enhancer, keratolytic agent	6.0
10M NaOH	10M Sodium Hydroxid	pH regulator	3.6

Table 8. Formulation formula of nail polish No. 9.

Formulation 9			
Component	INCI	Function	Composition [%]
Cyclopirox	Cyclopirox	Medicinal substance, antifungal drug	8.0
Propylene glycol	Propylene Glycol	Humectant, penetration enhancer	53.4
Urea	Urea	Permeation enhancer, keratolytic agent	20.0
Lactic acid	Lactic acid	Moisturizer, humectant, active ingredientn	10.0
Glycerin	Glycerin	Humectant	5.0
10M NaOH	10M Sodium Hydroxid	pH regulator	3.6

All prepared formulations were left at room temperature for 24 hours before the next step was performed to determine the degree of cyclopirox release from the formulation based on the procedure described in 2021 Aleph by M. S. Souza et al. [21]. Visual observations show that

the best film-forming properties were observed for PVP-based formulations, i.e. for formulations No. 3 and 6 (Table No. 9).

Table 9. Characteristics of the nail polish formulations obtained.

Formulation number	Characteristics/ visual appearance of sample
1	Suspension
2	Transparent, yellow, thick solution
3	Bright yellow dense membrane*
4	Suspension
6	Dense, gel-like brown film*
7	Suspension
8	Suspension
9	Thick, white solution

*-satisfactory formulation

Determination of the calibration curve by analytical method - UV-Vis spectrophotometry

In the first stage of the study, the wavelength range (λ = 400-200 nm) was determined to determine the maximum absorbance wavelength (λ_{max}) from a solution of cyclopirox in methanol (0.1 mg/ml). The solvent itself, i.e. methanol, was used as a blank for the experiments. The experiments were conducted on a UV-Vis spectrophotometer from Thermo Scientific, Spectro-Lab, Evolution 220. The experiment began with a solution of 1.25 mg/10ml of cyclopirox in methanol and further dilutions were made using the successive dilution method. Cyclopirox concentration ranged from 0.0781 to 1,250 mg/10ml. In the range showing adequate linearity, a calibration curve was plotted and used for further calculations (see the supplement for details).

Result and discussion

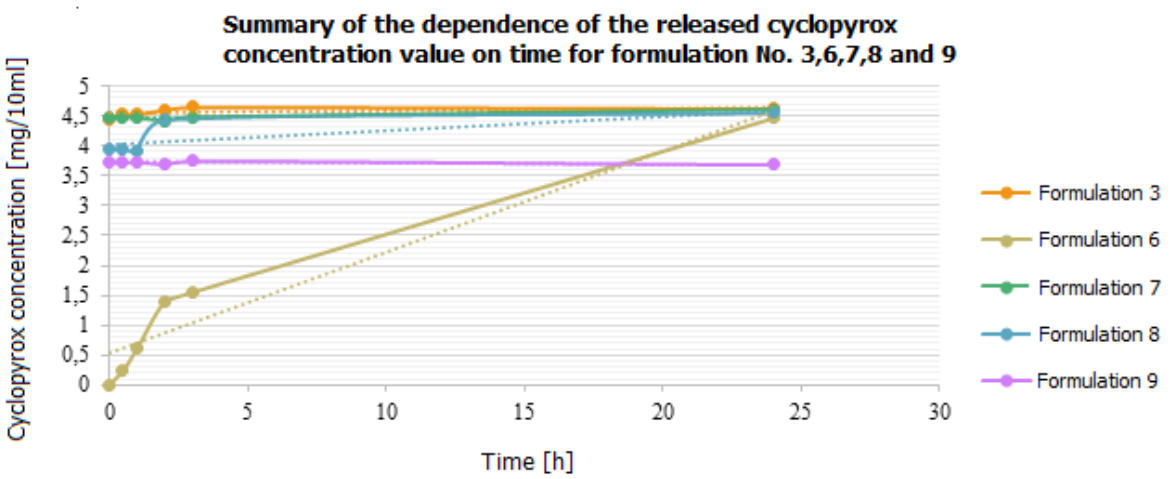
Evaluation of the release rate of cyclopirox from developed nail polish formulations

The purpose of the study was to evaluate the release of the drug from the nail polish and to investigate whether the amount of drug necessary for satisfactory antifungal activity is released from the product. The experiment was conducted based on the procedure described by Aleph M. S. Souza et al. [21], for this purpose, 5g of each of the prepared nail polish formulations that contained ciclopirox (0.08 mg/g) were placed in beakers each time and allowed to dry for 24 hours. Then, 15 ml of release medium (release buffer-concentrate, pH 7.4 (phosphate)) was carefully added to each beaker and placed in an incubator (laboratory thermometer, brand Hartmann BODE), where a temperature of 40°C was maintained to provide the test formulations in the beakers with suitable conditions for cyclopirox release. For

testing, 2 ml of release medium was taken from each beaker at predetermined time intervals (0, 0.5, 1, 2, 3 and 24 h), placed in eppendorf samples and the solution in the beaker was immediately replenished with fresh medium. In addition, a comparison sample (1.46g of a 0.08 mg/ml solution of cyclopirox in ethanol + 15 ml of release medium) was used to measure the amount of antifungal substance released from nail polish containing cyclopirox. The absorbance of the collected samples was then measured by UV-Vis. All experiments were performed in three trials.

Based on literature data and preliminary tests, it was determined that absorbance measurements would be made at a wavelength of 282nm during testing. The linearity of the obtained results was determined using a standard curve for cyclopirox concentration from 0.078 to 1.25 mg/10ml (y =0.738x + 0.3782). The obtained linear correlation coefficient R was 0.9914. Based on the results obtained, it can be concluded that the chosen method of measurement was properly selected.

The drug release study was carried out to evaluate the release of cyclopirox from polymeric nail polish, which will ensure its sufficiency. Release buffer-concentrate, pH 7.4 (phosphate) was used as the medium due to its ability to mimic the properties of human body fluids. The obtained absorbance results of the measured samples are shown in Chart #1. Release level measurements were performed only for formulations that were stable after 24 hours, i.e. 3, 6, 7, 8 and 9.



Graph. 1. Summary of the dependence of the concentration values of the released active substance in solutions on the determined time for the tested samples of formulations No. 3,6,7,8,9, after removal from the laboratory thermometer.

The results presented above showing the concentration of cyclopirox in the tested solutions, after a certain time, indicate that the drug was released in the desired amount for all formulations (the minimum inhibitory concentration, MIC (µg/ml) of cyclopirox on *Candida*

spp. is 1-4 [22]). The highest concentration value of the released drug from the formulation is observed immediately after application for formulations 3, 7, 8 once 9. The data obtained for formulation No. 6 indicate its effect after 0.5 hours. With the passage of time, the concentration of the test drug in solutions with formulations No. 3, 6 and 8 increased. The highest released concentration of the drug occurred with formulation No. 3 and was 4.62 (mg/10ml) after 24 hours. The results obtained show that ciclopirox was released from the varnish layer for all prepared formulations.

Evaluation of the degree of release of cyclopirox from the developed formulations using a barrier of colored nail lacquers available on the cosmetics market

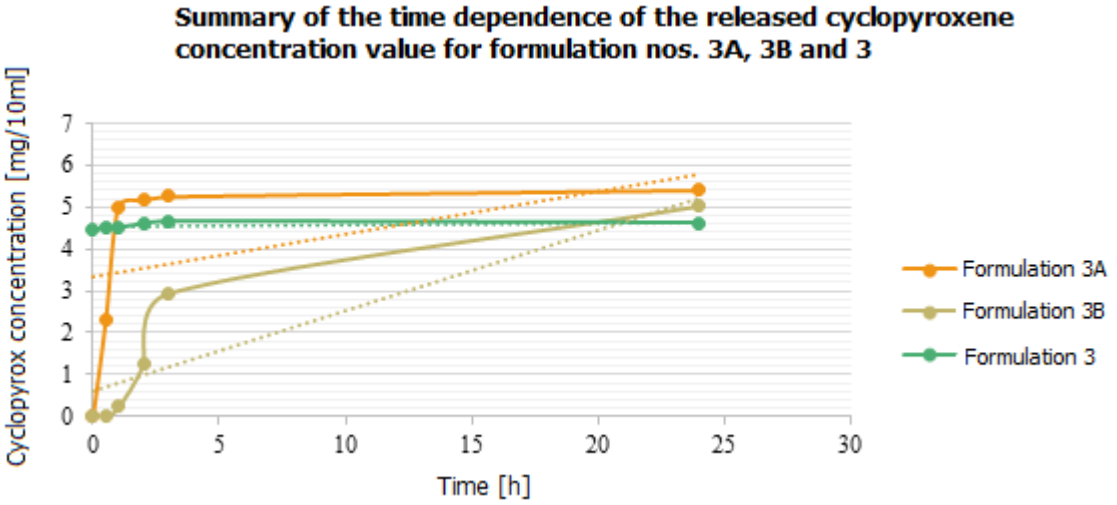
The tests were conducted on a previously prepared nail polish formulation No. 3, which formed the most durable film of all the formulations made. The formulation was placed at the bottom of two beakers and left for 24 hours at room temperature. Layers of color nail polish A and B were then applied (Table 1). Subsequently, the next steps for evaluating the release of the active substance were analogous to the previous measurements. As a medium in this experiment, phosphate release buffer (pH 7.4) was also used. The results are shown in Fig. 2

Table 10. INCI composition of lacquers A and B.

Nail polish	INCI
Nail polish A (OPI, A KISS ON THE CHIC)	Butyl Acetate, Ethyl Acetate, Nitrocellulose, Tosylamide/Epoxy Resin, Isopropyl Alcohol, Acetyl Tributyl Citrate, Mica, Stearalkonium Bentonite, Calcium Aluminum Borosilicate, Benzophenone-1, Silica, Trimethylpentanediyl Dibenzoate, Polyvinyl Butyral, Tin Oxide, Barium Sulfate, [May Contain +/-: Titanium Dioxide (CI 77891), Aluminum Powder (CI 77000), Red 6,7 (CI 15850), Ferric Ammonium Ferrocyanide (CI 77510), Iron Oxides (CI 77491, CI 77492, CI 77499), Manganese Violet (CI 77742), Red 34 (CI 15880), Black 2 [Nano] (CI 77266), Yellow 5 (CI 19140)].
Nail polish B NEONAIL "Lady Ferrari" - lacquer UV-curable	Di-HEMA Trimethylhexyl Dicarbamate, HEMA, Acryloyl Morpholine, Tricyclodecanedimethanol Diacrylate, Hydroxypropyl Methacrylate, Trimethylbenzoyl Diphenylphosphine Oxide, Bis-Trimethylbenzoyl Phenylphosphine Oxide, Silica, BHT, p-Hydroxyanisole, +/- CI 77891, CI 77491, CI 77510, CI 77289, CI 77492, CI 77499, CI 77742, CI 15850, CI 15985, CI 77007, CI 15880, CI 77266, CI 74160, CI 74260, CI 19140

An experiment with cosmetic nail lacquers proved that the concentration of cyclopirox in the tested solutions, after a certain period of time, is greater than the minimum inhibitory concentration (MIC (µg/ml) of cyclopirox on *Candida spp*. which is 1-4 µg/ml [22]). A difference in the level of cyclopirox concentration at the measured intervals was noted compared to previous measurements carried out without the addition of colored varnishes in

Formulation 3 studies. It can be concluded that cosmetic nail polish does not inhibit the release of the test drug substance into the buffer under the conditions of the test conducted. The highest value of the concentration of the released drug from the formulation is observed 1 hour after its application in the case of formulation " nail polish A", while for formulation " nail polish B" after 3 hours. With the passage of time, the concentration of the test drug in solutions with both formulations increased. The quality of color varnishes A and B after application of treatment formulation No. 3, visually maintained a correct appearance until the end of the study.



Graph. 2. Dependence of the concentration values of the released active substance in the solutions on the determined time for the tested samples of formulations nail polish 3A, nail polish 3B and 3 after removal from the laboratory thermometer

Conclusions

The treatment of onychomycosis caused by *Candida spp*. is still a major challenge due to the complex substrate of the disease, which requires a suitable preparation and a potent antifungal drug. In order to create an effective therapeutic nail polish, formulations were made containing ciclopirox as the active ingredient, at a concentration of 8%. The drug has an exceptionally broad spectrum of action, exhibiting antibacterial and anti-inflammatory activity. Using the UV-Vis spectrophotometry method, the absorbance was determined for the adopted cyclopirox solutions, with the specified concentration, and a calibration curve was made. The results obtained showed no interference of excipients in the formulation on the absorbance of cyclopirox at a wavelength of 282 nm.

The drug release study was used to assess the therapeutic suitability of the developed varnishes. From each formulation, the drug ciclopirox had to be released in order to reach the site of infection in the desired concentration and act pharmacologically. Tests conducted show

that the therapeutic substance was released in the desired amount for all formulations (minimum inhibitory concentration, MIC (µg/ml) of cyclopirox on *Candida spp*. is 1-4 [22]) and was properly delivered from the polymeric varnish layer to the substrate, moving through the model nail plate, showing antifungal activity.

The results encourage further research into formulations designed to treat the growing problem of onychomycosis caused by *Candida spp*. In the next stage of research, it would undoubtedly be worthwhile to evaluate the degree of penetration of the active substance through the nail layer.

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