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# Adsorption, partition and release balances of terbinafine hydrochloride, part I

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In this study the adsorption, partition and releasing balances of terbinafine hydrochloride have been studied. The adsorption isotherms of antifugal drug terbinafine hydrochloride (terbinafine), on the base of its adsorption from aqueous solutions on the surface of activated charcoal, were obtained in the temperature range of 25 to 45 °C used UV VIS spectrophotometric method. The experimental data have been analyzed by Freundlich and Langmuir equations to obtain parameters describing properly this adsorption process. The thermodynamic parameters (average change molar Gibbs energy – $\Delta_{ad}G^0$, enthalpy – $\Delta_{ad}H^0$ and entropy – $\Delta_{ad}S^0$) were calculated and compared. The partition coefficient of terbinafine hydrochloride in the system organic phase/water phase with different organic phases (n-butyalcohol, n-hexylalcohol and n-octylalcohol) using the "shake flask" method have been studied. The experimental partition coefficient of terbinafine increased from butylalcohol to octylacohol in the partitioning system. The influence of the concentration of polymer – hydroxy ethyl cellulose (HEC) (2–3%) used for preparation of the hydrogel (terbinafine-HEC-water), on terbinafine release has been studied. Both the concentrations of polymer and the drug had influence on the release process.

## 1. Introduction

Topical antifugal drugs have an important role in the modern management of onychomycosis (Baran and Kaoukhor 2005, Neubert et al. 2006). The studied drug – terbinafine hydrochloride (TB) effects is effective against *Trichophyton mentagrophytes* and *Trichophyton rubrum*, both *in vivo* and *in vitro* and is topically used as a cream.

Adsorption, partition and releasing balances of a drug are important properties which have to be known in the development of dosage forms.

Investigations of the temperature dependence of a drug adsorption on hydrophylic or hydrophobic surfaces is often used to obtain information about the adsorption and adhesive mechanisms, which are directly related to its physicochemical properties.

To study partition balances is useful for understanding of the behaviour of drugs in the organism.

For drugs used in hydrogel forms (composition – drug-polymer-water) it is very important to study the influence of polymers and drug concentration on release.

In this paper, the effect of the temperature on adsorption of terbinafine on activated charcoal at different temperature was studied in order to find out which isotherm describes more appropriate the experimental adsorption process. The thermodynamic parameters of this process are also described.

The effect of length of alcohol on the partition process of TB in system o/w was studied, as well as the influence of the concentration of polymer – hydroxyethyl cellulose (HEC) used for preparation of the hydrogel on the release of TB.

## 2. Investigations, results and discussion

The absorption spectrum of TB had three maximums at the wavelengths $\lambda_{max} = 232$, 284 and 318 nm (Fig. 1). Determination of the calibration curve and all measurements for adsorption, partition and release balances were carried out 284 nm.

From the plot of absorbance (A) at $\lambda_{max} = 284$ nm vs concentration [concentration range $(0.5–4.0) \times 10^{-4}$ mol/L] (Fig. 2) and temperature 25 °C parameters of linear regression – slopes ($b = 5468.8$ L/mol$^{-1}$) and coefficient of correlation ($r = 0.999$) were calculated.

### 2.1. Adsorption balances

The effect of the temperature on adsorption and thermodynamics of TB adsorption from aqueous non-buffered solutions on activated charcoal at different temperature (25, 35 and 45 °C) was studied. The purpose of this study was to elucidate which isotherm is more appropriate for experimental adsorption and thermodynamics of this process. Adsorption isotherms of TB onto activated charcoal (AC) at 25, 35 and 45 °C were measured in water. From the measured values (absorbance – A) values amount of solute adsorbed per gram of AC – a [mol g$^{-1}$] at all tem-

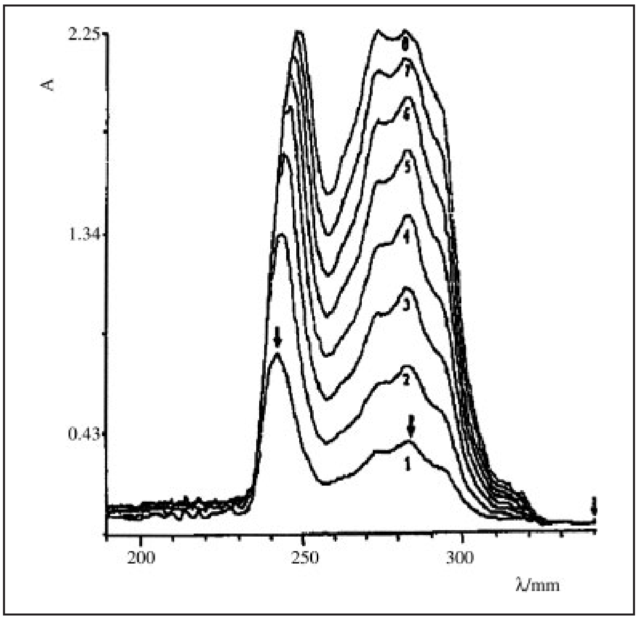

Fig. 1: Measured spectral curves of TB in solution at different concentration

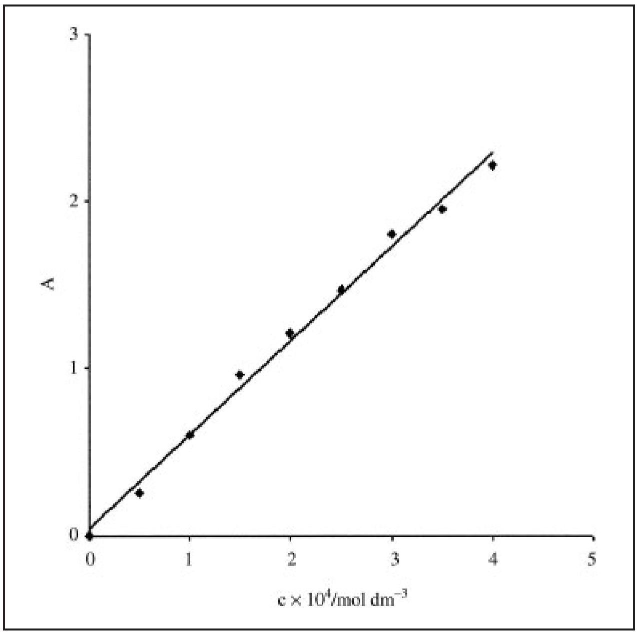

Fig. 2: Calibration curve of TB at 25 °C in aqueous solution ($\lambda_{max} = 284$ nm)

peratures were calculated and are shown in Fig. 3. As it was expected, the adsorbed amount of TB was lower at high temperature than that at low temperature under the present experimental condition.

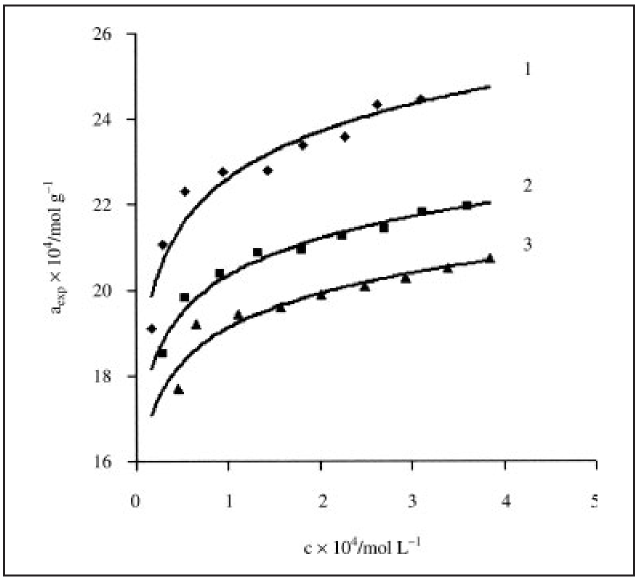

Fig. 3: Experimental adsorption isotherms of TB on activated charcoal (AC) at 25 °C curve (1), 35 °C (2), 45 °C (3)

Experimental adsorption isotherms were expressed by the Freundlich – FI – Eq. (1) and Langmuir – LI – Eq. (2) models of adsorption.

$$a_{FI} = k_{FI} c^{\frac{1}{n}} \qquad (1)$$

$$a_{LI} = \frac{A_{max} k_{LI} c}{1 + k_{LI} c} \qquad (2)$$

where c is molar concentration of TB in solution at equilibrium [mol/L], a is the number of moles of the TB per gram of AC [mol $g^{-1}$], $k_{FI}$ is Freundlich parameter depended on character of the adsorbent and adsorbed substance, and n is Freundlich parameter depended on temperature, $A_{max}$ is amount of maximum monolayer adsorption [mol $g^{-1}$], $k_{LI}$ is an adsorption coefficient, representing the affinity (the ratio of the rate constants of adsorption and desorption).

Logarithmic transformations of the Freundlich (Eq. (1)) – [ln $a_{exp} = f(\ln c)$] for TB and different temperatures are linear (Fig. 4a) and provided n and $k_{FI}$ values which are collected in Table 1. The values n increased with temperature of solutions and plot n vs temperature was not found linear, (polynomical). Plot $k_{FI} = f(t)$ was found to be nearly linear and decreased with increasing of the temperature.

Langmuir adsorption isotherm (Eq. (2)) was transformed to a linear form [$c/a = f(c)$] and these plots are shown for TB and for each temperature in Fig. 4b. All the Langmuir plots for different temperatures gave $A_{max}$ and $k_{LI}$ values which are listed in Table 1. The values $A_{max}$ and $k_{LI}$ decreased with increasing temperature of solutions.

The values the number of moles of the TB adsorbed per gram of AC – $a_{FI}$ were calculated by Eq. (1) and $a_{LI}$ by Eq. (2), are shown in Fig. 5.

**Table 1: Adsorption parameters for the Freundlich and Langmuir adsorption isotherms of TB at different temperatures**

| t/°C | Freundlich n | Adsorption $k_{FI}$** | Isotherm r**** | Langmuir $k_{LI}$*** | Adsorption $A_{max} \times 10^4$* | Isotherm r**** |
|---|---|---|---|---|---|---|
| 25 | 17.70 | 0.0038 | 0.988 | 139589 | 24.70 | 0.999 |
| 35 | 19.34 | 0.0033 | 0.997 | 121376 | 22.27 | 0.999 |
| 45 | 23.04 | 0.0029 | 0.989 | 105555 | 21.05 | 0.999 |

* $A_{max} \Rightarrow$ (mol $g^{-1}$); ** $k_{FI} \Rightarrow$ ($dm^3\ g^{-1}$); *** $k_{LI} \Rightarrow$ (L $mol^{-1}$); **** coefficient of correlation

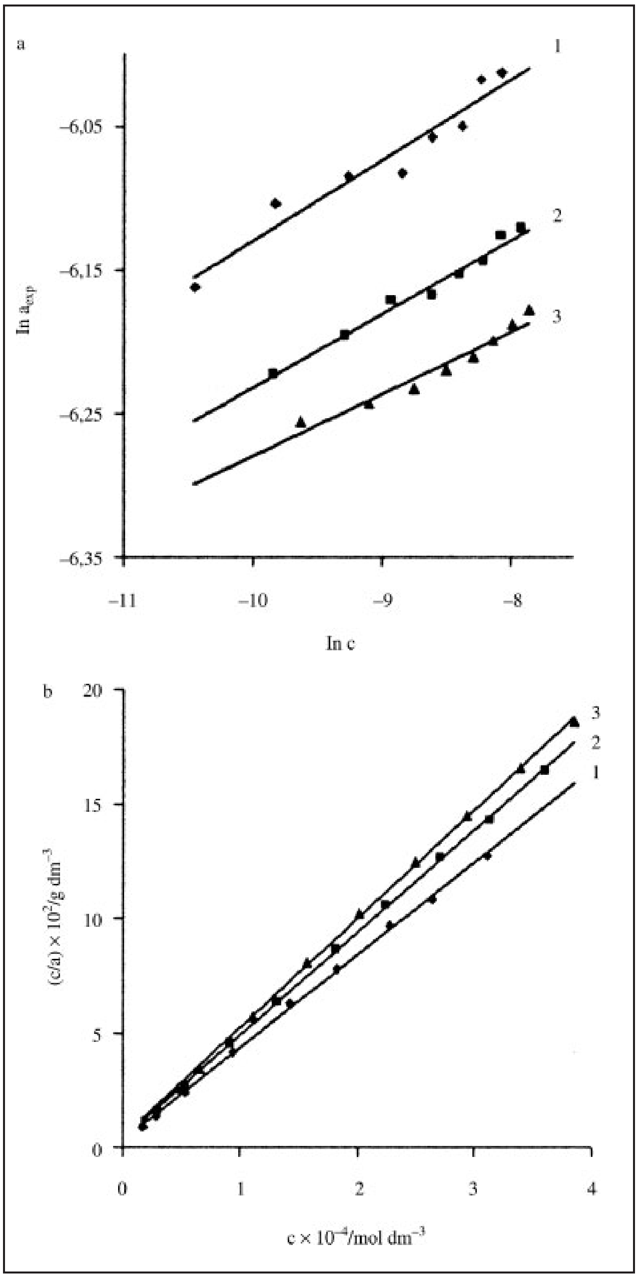

Fig. 4: a: Plots ln $a_{exp} = f(\ln c)$ for calculation of paramereters for Freundlich adsorption isotherms of TB on activated charcoal (AC) – Eq. (1) at 25 °C curve (1), 35 °C (2), 45 °C (3).
b: Plots $c/a = f(c)$ for calculation of paramereters for Langmuir adsorption isotherms of terbinafine (TB) on activated charcoal (AC) – Eq. (2) at 25 °C curve (1), 35 °C (2), 45 °C (3)

The process of adsorption of terbinafine on activated charcoal at different temperatures conveniently described both models of adsorption.

Calculated values – $a_{exp}$, $A_{max}$ and $k_{LI}$ measured at various temperatures were used to calculate the thermodynamic parameters of adsorption:

- the change of standard molar Gibbs energy of adsorption according to Skrylev et al. (1980) – Eq. (3):

$$\Delta_{ad}G^0 = -RT \ln k_{LI} \tag{3}$$

and according to Dai et al. (1999) – Eq. (4):

$$\Delta_{ad}G^0 = RT \ln c \left( \frac{A_{max}}{a_{exp}} - 1 \right) \tag{4}$$

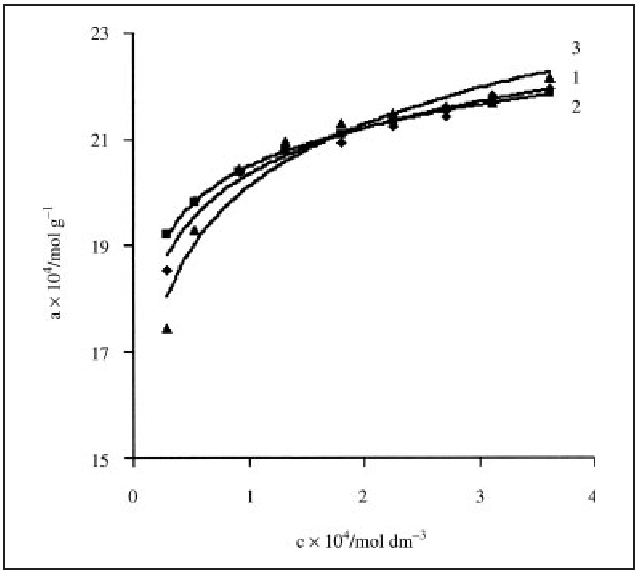

Fig. 5: The number of moles of adsorbate per gram of adsorbent (a) vs molar concentration of adsorbate at equilibrium at 35 °C; curve (1) experimental; 3 – (FI); Freundlich; 2 – (LI) – Langmuir adsorption isotherms

Values $\Delta_{ad}G^0$ calculated according Eq. (3) and average values $\Delta_{ad}\bar{G}^0$calculated according Eq. (4) for adsorption TB are summarized in Table 2. The values of the standard molar Gibbs energies of adsorption calculated by Eq. (3) and Eq. (4) was found to be the same and negative for all temperatures i.e., the process of adsorption is thermodynamically favoured and spontaneous.

The standard molar enthalpy of adsorption ($\Delta_{ad}H^0$) (Skrylev et al. 1980) – Eq. (5):

$$\Delta_{ad}H^0 = RT^2 \left[ \frac{\partial \ln k_{LI}}{\partial T} \right] \tag{5}$$

**Table 2: Change of standard molar Gibbs energy, enthalpy and entropy of adsorption of TB at different temperatures**

| T/K | 298.15 | 308.15 | 318.15 |
|---|---|---|---|
| $\Delta_{ad}G^0$/kJ $mol^{-1}$ Eq. 3 | −29.36 | −29.99 | −30.59 |
| $\Delta_{ad}\bar{G}^0$/kJ $mol^{-1}$ Eq. 4 | −29.62 | −30.00 | −30.66 |
| ±s*/kJ $mol^{-1}$ | 0.33 | 0.29 | 0.21 |
| $\Delta_{ad}H^0$/kJ $mol^{-1}$ | −10.32 | −11.03 | −11.76 |
| $\Delta^{ad}S^0$/J $K^{-1}$ $mol^{-1}$ | 63.96 | 61.53 | 59.19 |

* is standard deviation calculated using the following equation

$$s = \sqrt{\frac{\sum (\Delta_{ad}G_i - \Delta_{ad}\bar{G})^2}{n - 1}}$$

where: $\Delta^{ad}G_i$ are values of molar Gibbs energy of adsorption at equilibrium concentration ($c_i$); n – number of measurements (n = 8)
Parameters of Eq. (7) for calculation of change of standard molar enthalpy of adsorption of TB at different temperatures A = 16.01263; B = −0.01397; C = 0; r = 0.9999

**Table 3: Partition coefficients for TB**

| organic phase | $\bar{P}'$ | log $\bar{P}'$ | ±s (log $\bar{P}'$)* |
|---|---|---|---|
| n-Butylalcohol | 7.709 | 0.887 | 0.012 |
| n-Hexylalcohol | 111.042 | 2.047 | 0.023 |
| n-Octylalcohol | 262.422 | 2.419 | 0.002 |

* is standard deviation

Eq. (5) could be also expressed in the form Eq. (6):

$$\Delta_{ad}H^0 = RT^2(B + 2CT) \qquad (6)$$

where B, C are parameters of second polynomial Eq. (7):

$$\ln k_{LI} = f(T) = A + BT + CT^2 \qquad (7)$$

Calculated parameters of Eq. (7) and $\Delta_{ad}H^0$ values for different temperatures are given in Table 2. The variation in the standard molar enhalpy of adsorption are more expressive. The negative values of $\Delta_{ad}H^0$ indicate that the process of adsorption of TB is exothermic.
The changes of the standard molar entropy of adsorption ($\Delta_{ad}S^0$) (Skrylev et al. 1980) – Eq. (8) can also be seen from Table 2:

$$\Delta_{ad}S^0 = \frac{\Delta_{ad}H^0 - \Delta_{ad}G^0}{T} \qquad (8)$$

The changes in the standard molar entropy of adsorption are positive and decreasing.

### *2.2. Partition balances*

Parameters of the calibration curve from adsorption balances were used for determination of the experimental partition coefficients in the partition system o/w. the relative concentrations of TB in the aqueous phase after partitioning were determined from the adsorption band at 284 nm. The experimental partition coefficients (P′) were calculated form the Eq. (9):

$$P' = \frac{m - V_{water} \cdot c_{water} \cdot M}{V_{alcohol} \cdot c_{water} \cdot M} \qquad (9)$$

where:
m – is weight of substance TB [kg], $c_{water}$ – is molar concentration of TB in the aqueous phase after partitioning [mol/L$^{-1}$], $V_{water}$ – is volume of aqueous phase [$15 \times 10^{-6}$ m$^3$], $V_{alcohol}$ – is volume of organic phase [$0.5 \times 10^{-6}$ m$^3$], M – molar weight of TB [kg · mol$^{-1}$].
The calculated experimental partition coefficients for TB are listed in Table 3. Values for log P′ increased from butylalcohol to octylalcohol. The partition coefficient of a compound between octylalcohol and water is a physicochemical property with widespread application in the assessment of its distribution, fate and toxicity in the environment.

### *2.3. Release balances*

#### *2.3.1. Hydrogels containing 2 and 3% HEC and 1% of terbinafine*

Influence of the polymer concentration on amount of the drug released from hydrogels is not statistically significant. From hydrogels containing 2% (m/m) HEC 50.1% of the drug was released and from hydrogels containing 3% HEC the amount was 54.5% at though the apparent viscosity of the 3% (m/m) HEC was higher (0.69 Pa.s) then that of the 2% HEC (0.31 Pa.s). In both cases the presence of the drug had not any influence on the hydrogel viscosity. Apparent viscosity was measured and counted at a share rate 644.4 s$^{-1}$. The evaluated hydrogels are non-Newtonian systems and exhibit plastic flux.

#### *2.3.2. Influence of TB concentrations on its release and rheological properties of hydrogel with 3% (m/m) HEC*

The influence of terbinafine concentrations (1% m/m and 0.1% m/m) on its release and rheological properties of hydrogels with 3% of HEC was evaluated. The concentration decrease of terbinafine from 1% to 0.1% caused increases in drug release from 54.5 to 65.5%. The 0.1% concentration of terbinafine had also impact on rheological properties of hydrogel, namely the plastic flux (Fig. 6a) has changed on tixotropic (Fig. 6b), which is advantageous from a practical point of view.

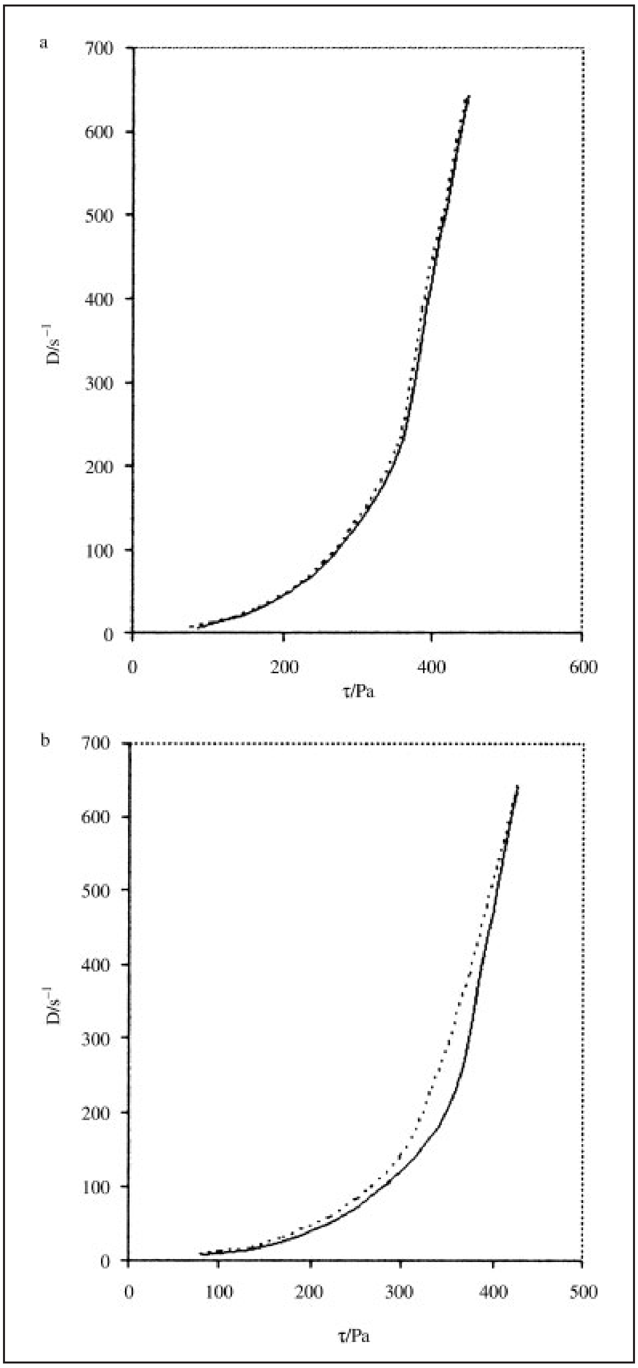

Fig. 6: a: Rheogram of hydrogel with 1% (m/m) of drug;
b: Rheogram of hydrogel with 0.1% (m/m) of drug
——— ascending curve, — — — descending curve

### *2.4. Conclusions*

The process of adsorption of TB on activated charcoal at different temperatures conveniently described both models of adsorption. Adsorption data obtained experimentally, using a wide range of adsorbate concentration fit well the

**Table 4: Influence of polymer and drug concentrations on the drug release**

| time (min) | released Amount (%) | | |
|---|---|---|---|
| | 3% HEC | | 2% HEC |
| | Terbinafine hydrochloride | | |
| | 0.1% | 1% | 1% |
| 15 | 30.7 | 24.5 | 23.3 |
| 30 | 38.1 | 30.9 | 29.6 |
| 45 | 44.0 | 35.8 | 33.3 |
| 60 | 51.4 | 40.0 | 38.0 |
| 90 | 58.4 | 45.2 | 38.9 |
| 120 | 62.2 | 47.8 | 45.8 |
| 180 | 65.5 | 54.5 | 50.1 |

Langmuir and Freundlich isotherms. Increased temperature of solution decreased the amount of terbinafine adsorbed on activated charcoal. The calculated thermodynamic parameters indicate that the process of adsorption of terbinafine on activated charcoal is spontaneous, thermodynamically favoured (negative values of $\Delta_{ad}G^0$), exothermic (negative values of $\Delta_{ad}H^0$). Activated charcoal seems to be an excellent adsorbent for terbinafine as a drug.

Experimentally determined partition coefficients increased with the length of alcohol in the partitioning system.

Based on the results obtained, it could be concluded that a 3% (m/m) concentration of HEC with 0.1% of terbinafine is more suitable than 1%. This is because a greater amount of the drug is released (Table 4).

## 3. Experimental

### 3.1. Materials

Terbinafine hydrochloride (TB) – [*N*-(2E)-(6,6-dimethyl-2-hept-2-en-4-ynyl-*N*-methyl-(1-naphtylmethyl)amine hydrochloride obtained from Slovakofarma Hlohovec (SR) was used without purifing.

Activated charcoal (AC) – powdered activated charcoal type KOLOREX K was used. Properties: grain size $\leq 0.10$ nm; surface area 1000 $m^2\,g^{-1}$. The AC was washed twice with hot distilled water and dried at 110 °C two days and then was kept in a dessicator containing silica gel. Hydroxyethyl cellulose – HEC, (Natrosol) obtained from Zentiva (SR). Water used for experiments was purified by double distillation in a silica glass apparatus. The specific conductivity was $\kappa \leq 2\ \mu S\ cm^{-1}$.

### 3.2. Analytical assays

#### 3.2.1. UV spectrophotometry

Absorbances of the solutions (for calibration, study of stability TB in solution and adsorption curves and adsorption measurements) were measured with an UV VIS spectrophotometer Hewlett-Packard 8452A (diode aray) in thermostatized and stoppered 10-mm quartz cuvettes at 25 °C in the wavelength range 190–340 nm. Absorption spectrum of TB has three bands at 232, 284 and 318 nm (Fig. 1). The amounts of solute adsorbed per gram of AC (a) from the measurement of the absorbance (A) at $\lambda_{max} = 284$ nm and calibration curve were determined spectrophotometrically for each solution.

#### 3.2.2. Adsorption isotherms

Adsorption isotherms of aqueous solutions of TB on AC were obtained by adding 5 mg AC and 25 ml of the solution of a known solute concentration [in the range of 4.0 to $8.0 \times 10^{-4}$ $mol/L^{-1}$] to the sample tube and tightly capped. The tubes were shaken in a water bath maintained at 25, 35 and 45 °C for 60 min. After equilibration, the sample was taken out from each tube and was filtered through a membrane to remove completely AC. The content of TB in the filtrate was measured at 284 nm as $A_{284}$. The amount of solute adsorbed on the charcoal at equilibrium was calculated as a difference between the original and the filtrate concentrations according to Eq. (10):

$$a_{exp} = \frac{(c_0 - c)\,V}{g}\ (\text{mol g}^{-1}) \qquad (10)$$

where $a_{exp}$ is the experimental amount of solute adsorbed per gram of AC [mol $g^{-1}$], $c_0$ is initial (original) concentration of adsorbate [$mol/L^{-1}$], c is concentration of adsorbate in the filtrate [$mol/L^{-1}$] at the equilibrium, V is volume of solution [L], g is weight of AC [g].

#### 3.2.3. Partition coefficient

The partition coefficient (P′) was determined in the system alcohol/water (alcohol – n-butylalcohol, n-hexylalcohol and n-octylalcohol) at 25 °C by the “shake flask” method. The samples were left to stay 24 h after 1 h shake.

#### 3.2.4. Composition of hydrogel bases

In the prepared systems as a gelling agent was used HEC (2 and 3%) and hydrogel samples contained 1% and 0.1% TB. Blank samples were prepared in a similar way. All hydrogel samples were left to stay for 48 h after their preparation.

#### 3.2.5. Determination of the release

A series of permeation cells was used. Into the donator part of chambers 3.0 g of the hydrogel were added and 20 ml of isotonic NaCl solution were inserted into the acceptor part. The acceptor phase was mixed with a magnetic stirrer. The drug was left to permeate at 37 °C through a hydrophilic membrane (19.6 $cm^2$) (Nephrophan, Filmfabrik Wolfen Germany) into isotonic NaCl solution. Amounts of the drug released were determined by spectrophotometry at 284 nm, after 15, 30, 45, 60, 90, 120 and 180 min. The results were evaluated from released cumulative amounts of the drug and they represented averages of 6 measurements determined from two parallel systems.

#### 3.2.6. Determination of rheological properties

Rheological properties were measured by a Viscotester VT 500 (Haake Mess-Technik GmbH u.Co., Germany) at 20 °C, carrying out three parallel measurements 48 h after hydrogel preparation.

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