Study of the Interaction of Some Pharmaceutical Compounds with Different Cellulosic Supports

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The interaction of two pharmaceutical compounds (aspirin and diclofenac) on some cellulosic type supports (cotton fibre, microcrystalline cellulose and fir wood) has been investigated in order to establish in the case of each system the best theoretical adsorption model, as well as their characteristic thermodynamic parameters (enthalpy and entropy). The adsorption process of the pharmaceutical compounds onto the mentioned cellulosic supports was studied by means of spectrophotometry, at three different temperatures (298 K, 308 K and 318 K). The preliminary experiments indicated that absorption equilibrium was attained in a period of time ranging from 150 to 450 minutes, in the case of the investigated systems. The experimental results were fitted to some classical adsorption models such as Freundlich and Langmuir, as well as to some untested ones for these systems type, namely Sips and Jossens isotherm models. The statistical analysis of the obtained results indicated that in all cases, the Sips model described better the adsorption of the model compounds on the investigated supports by comparison to the classical models, as well as to the Jossens' one.

Keywords: pharmaceutic compounds, adsorption isotherms, cellulosic supports

The adsorption process of pharmaceutical compounds on solid substrates such as natural fibres or different excipients used in drug formulations may influence in a great extent the active's substances characteristics, as well as their biodisponibility. As a consequence, one could consider that the adsorption process constitues one of the most important interaction mechanisms which occurs among drugs and excipients or other natural or synthetic supports [1,2]. Thus, adsorption is one of the most relevant factors of which one should be aware when performing pharmaceutical formulations [3].

Nowadays, microcristalline cellulose (MCC) is recognized as an excelent excipient in drug formulations, being used especially as a binder or as a filler, and its presence results in an enhanced compactibility of a great number of formulations [4]. However, few studies regarding drugs adsorption on MCC can be found in litterature, which reffer especially to the adsorption of a limited number of steroids, phenothiazines, antihistaminics and antibiotics on MCC [5-10].

Concerning the adsorption of pharmaceutic substances on natural cellulosic supports such as cotton, hemp, line, or different essential woods, the speciality litterature is extremely poor, although the process presents rich applications in the pharmaceutical industry, as well as in the environmental protection field [11].

The limited number of studies related to this subject, as well as the fact that nowadays the adsorption mechanism of pharmaceutical substances on solid cellulosic type supports is still unclear, constitue two main reasons which prove the actuality of the present study [1,2, 5-10].

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used all over the world and can be ranged among the greatest interest pharmaceutical compounds. Generally, these type of drugs are prescribed in order to reduce inflammation, pain, fever or arthritis. Moreover, some of these drugs, such as aspirin (acetylsalicylic acid) or diclofenac (2-(2,6-dichloranilino) phenylacetic acid, or 2-(2,6-dichlorophenylamino)phenylacetic acid) are very popular and can be purchased over the counter [12, 13].

Aspirin, as well as other NSAIDs drugs have also been investigated as chemopreventive and chemotherapeutic agents in different type of cancers, such as breast, ovarian, lung, colorectal, esophageal and stomach cancers [14-21]. Besides its analgesic, antipyretic, and anti-inflammatory effects, aspirin also exhibit antiplatelet or "anti-clotting" effects. When used in long term low doses, this pharmaceutical compound can prevent heart attacks, strokes, as well as blood clot formation. This drug proved also its applicability in Alzheimer's disease, as well as in the treatment of rheumatoid arthritis [22,23].

Diclofenac is considered among the most used NSAIDs drugs, due to its well known analgesic, anti-inflammatory, antipyretic, antiarthritic and antirheumatic effects in different pharmacological models [24,25]. It was also proved that Diclofenac exhibit antibacterial activity [26], and recently, it has been reported that this compound may be used as potentiometric sensor, with applications in the pharmaceutical analysis, as well as for drug recovery from

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biological fluids [27]. It was estimated that in 2008, the annual consomption of Diclofenac was about 940 tons [28]. The interest for this pharmaceutical compound is very well represented by the great number of studies and reports from speciality literature, many of these also dealing with the impact of the presence of this pharmaceutical compound in the aquatic and terrestrial ecosystem [12, 24, 25, 28-32].

The main purpose of this present work was to perform an experimental study on the adsorption of aspirin and diclofenac onto some cellulosic type supports (namely microcrystalline cellulose, cotton and fir wood), at three different temperatures, in order to obtain new experimental data and thus, more information about the interaction of these pharmaceutical compounds with the mentioned supports. Moreover, the evaluation of the experimental results was performed by considering the classical Langmuir and Freundlich adsorption isotherms, as well as some three parameters models (Sips and Jossens models), which have not been reported yet in the case of these pharmaceutical compounds adsorption on solid supports of cellulosic origin.

Experimental part

Chemicals and Reagents

Aspirin (Acetylsalicylic acid) 99,% (AlfaAesar) and Diclofenac 99 % (2-(2,6-dichloranilino) phenylacetic acid) as its monosodium salt (Aldrich Sigma) were used such as, without further purification.

Microcrystalline cellulose (BCR302-20G) was supplied from Aldrich Sigma, and was used such as, without further purification.

Shavings of fir wood were obtained from a local carpenter workshop and were prepared for the experiments as described in a previous work [33]. The structural characterization of the wood samples was carried-out by scanning electron microscopy (SEM). For this purpose, a scanning microscope of INSPECT-S type was used (in low- vacuum module, at 10 nm, 3 kV resolution).

The samples of cotton (100 %) were purchased from a local store and were preliminary soaked at 80°C, rinsed and air-dried, according to some previous works performed in the field of dyes- cellulosic substrates interactions [34-37].

The UV-Vis spectroscopy study was performed using a CECIL CE 7200 spectrophotometer.

Methods

The working protocol was adapted from previous experiences in a related field of interest [33-37]. The basic steps of the experimental work involved a series of preliminary tests which were run in order to obtain the time necessary to reach the sorption equilibrium in the case of all studied systems, at three different temperatures: 298 K, 308 K and 318 K. Further, based on these results, the sorption studies were carried out for all the test systems, and the mentioned temperatures. In the case of all the experimental work, the initial drug concentrations were from $0.5 \cdot 10^{-5}$ mol/L to $4 \cdot 10^{-3}$ mol/L, and the samples weight of the three cellolosic supports was 0.050 ± 0.001 g.

Preliminary experiments

For both investigated drugs (*Aspirin* and *Diclofenac*), and the three cellulosic substrates (wood, cotton and MCC), several identical experiments were performed, at different periods of time, varying from 1 to 10 h. The sorption experiments were carried-on from aqueous solutions of neutral *p*H (phosphate buffer) at 298, 308 and 318 K, in round flasks (100 mL), and a thermostated shaking bath. After fixed periods of time, the solid supports were separated from the drug's solutions and were rinsed with cold distilled water. Further, the concentrations of the drugs in the remaining solutions were determined by means of UV-Vis spectrophotometery (using a CECIL CE 7200 spectrophotometer) at fixed wavelength (λ_{max} = 225 nm for *Aspirin* and λ_{max}=276 nm in the case of *Diclofenac*), according to their corresponding callibration curves. When it was noticed that no changes occur in the systems with increasing the process's time, it was concluded that the sorption equillibrium was acieved. The obtained results are shown in table 1, and the duration of all the equilibrium experiments was established according to these results.

Sorption equilibrium experiments

The equilibrium sorption process experiments involved the preparation of a series of drug solutions, where the initial concentrations were from $0.5 \cdot 10^{-5}$ mol/L to $4 \cdot 10^{-3}$ mol/L. To theses solutions, the weighed amounts of cellulosic supports were added, and the experiments were runned at the chosen temperatures for different durations of time, according to the results obtained in the preliminary experiments. The drug concentrations from the remaining solutions, as well as those collected from the waters resulting after rinsig the solid supports were estimated by spectrophotometry, thus the concentrations of the adsorbed drugs onto the solid supports was evaluated by difference, according to equation (1):

$$[C]_{ad} = ([C]_i - [C]_s) \cdot V / 1000 \cdot m \qquad (1)$$

where $[C]_{ad}$ is the equilibrium concentration of the drug which was adsorbed by the cellulosic solid support [mmol/g], $[C]_i$ and $[C]_s$ are the initial concentrations, and the equilibrium concentration of the drug in solution [mmol/L], V is the volume of the drug solution [L], and m represents the mass of the solid support used in the experience [g]. The term $[C]_s$, represents the sum of the drug quantities which were present in the final solution, as well as in the washing waters.

In order to attain a greater accuracy, the experiments were performed in triplicate, and the values which were further used in the subsequent analysis of the adsorption processes, represent the average values of those three experiments.

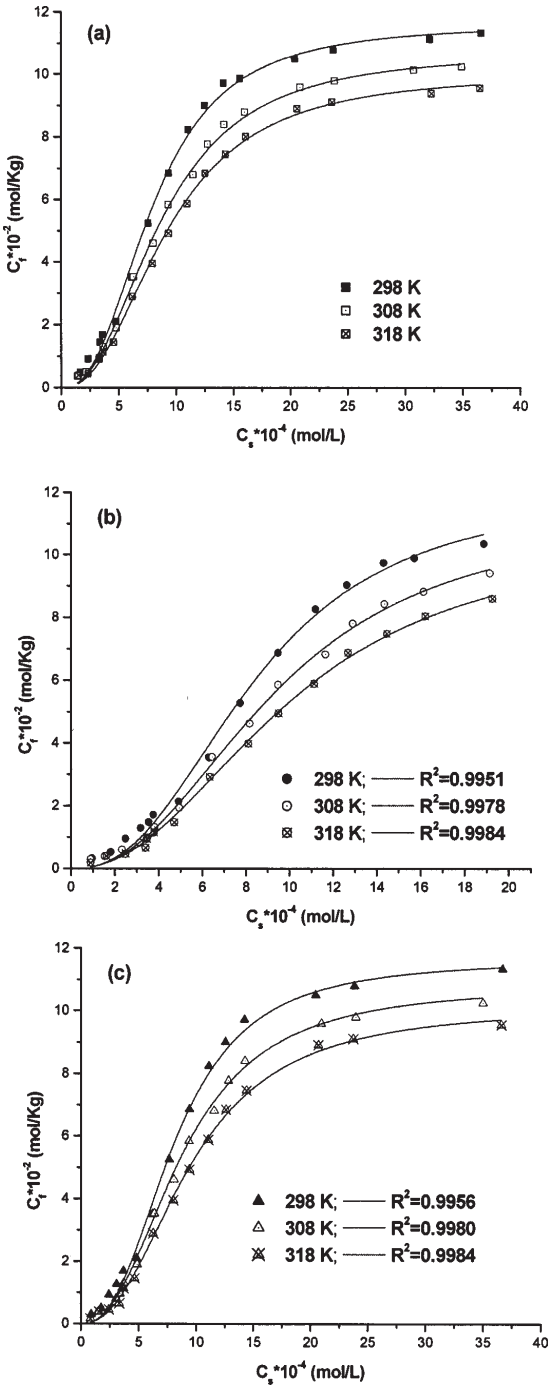
Results and discussions

The interaction of pharmaceutical compounds with cellulosic type supports involves several stages, one of the most important one being the adsorption process. Despite the fact that this complex process was the subject of several studies, its mechanism is still unclear and it is obvious that more experimental data and interpretations are needed in order to obtain some satisfactory explanations on this relevant subject. Most authors found out that Freundlich and Langmuir models should be considered as the adsorption models which fit better with their experimental data, although in the case of other systems, these models do not offer satisfactory explanations about the adsorption process.

Thus, in this present work, the sorption of two popular NSAIDs drugs, namely *Aspirin* and *Diclofenac* on three different cellulosic type supports (wood fibre, cotton and MCC) was studied as a function of drug concentration and temperature. This study was performed in the concentration range of $0.5 \cdot 10^{-5}$ mol/L to $4 \cdot 10^{-3}$ mol/L, at three different

Table 1
EQUILIBRIUM TIME AT 298 K, 308 K AND 318 K FOR THE STUDIED DRUG-CELLULOSIC SUPPORTS SYSTEMS

Drug	Solid support	Time [min] T= 298 K	Time [min] T= 308 K	Time [min] T= 318 K
Aspirin	Wood	380	280	190
	Cotton	320	240	170
	MCC	270	210	150
Diclofenac	Wood	450	345	235
	Cotton	360	290	210
	MCC	315	250	195



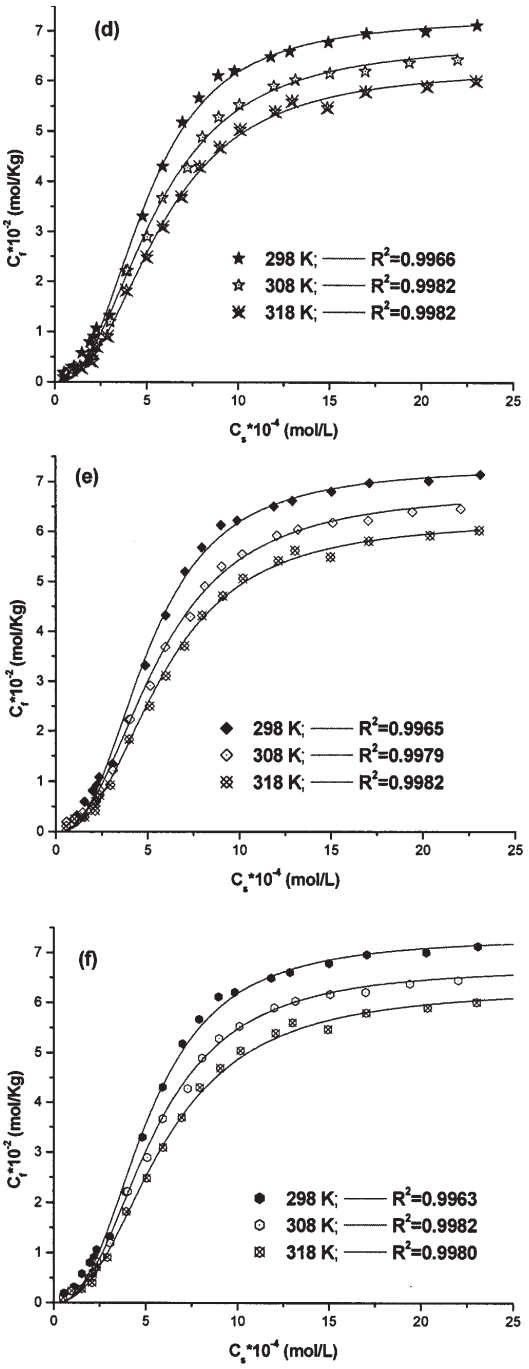


Fig. 1 Effect of temperature on uptake of *Aspirin* on wood fibre (a), cotton (b), MCC (c) and *Diclofenac* on wood fibre (d), cotton (e) and MCC (f)

temperatures: 298 K, 308 K and 318 K. Sorption isotherms see (fig.1) were obtained at the three mentioned temperatures, at the optimised condition of shaking time, which were established through preliminary experiments (table 1).

As shown in figure 1, the uptake of the investigated pharmaceutical substances increased with the increase of their initial concentration and then remained nearly constant after equilibrium time. It can be also noticed that the adsorption on the studied supports occurs quite fast in the initial stages and then gradually decreases with the progress of the adsorption process.

As expected, temperature plays an important role in the adsorption process. This fact is also illustrated in figure 1, which shows that the rise of temperature induced a negative effect onto the sorption of *Aspirin* and *Diclofenac* on fir fibre, cotton and MCC. This behaviour suggests that the increase of temperature generates in the case of all

Investigated Isotherms			
Langmuir	*Freundlich*	*Sips*	*Jossens*
$C_f = \frac{S_f \cdot K_L \cdot C_S}{1+K_L \cdot C_S}$	$C_f = K_F C_S^{1/n}$	$C_f = \frac{S_f \cdot (K_S \cdot C_S)^{1/n}}{1+(K_S \cdot C_S)^{1/n}}$	$Ce = \frac{q_e}{H} exp\left(F \cdot q_e^p\right)$

Table 2
THEORETICAL ADSORPTION ISOTHERM MODELS INVESTIGATED

three solid supports a decrease of their number of accessible sites. Another reason for the sorption decrease with the increase of temperature could be explained by the weakening of bonds among sorbates (the investigated drugs) and the active sites of the solid supports at higher temperatures, or, as in the case of the dye-fibre interactions, by the exothermicity of the sorption process.

The adsorption isotherms are extremely useful in the understanding of the adsorption processes, due to the fact that they provide information about the way in which sorbates interact with sorbents. For a long period of time, the description of the adsorption isotherms onto different excipients was based on classical Langmuir and Freudlich models, which are models with two parameters. However, in different fields of interest (including dyes, and other organic polluants) it was proved that this kind of models (e.g. the two-parameter models) showed in a great extent some limits of application, and thus, more recently, and with the support of computer simulations, models based on more parameters have been developped and used in several studies, due to their accuracy and wide range of applicability [33, 37-41].

The equations corresponding to the adsorption models used in this study are presented in table 2. As it can be seen, Freundlich, Langmuir, Sips and Jossens models have been used.

The Sips model was developed due to the fact that in the case of the Freundlich model the adsorption of sorbate onto sorbents is continually increasing, with the increase of the initial solution concentration, and from physical point of view, this indicates an infinite sorption. The equation proposed by Sips can be considered quite similar to the Freundlich equation form, but the main difference among them is that the Sips equation provides a finite limit in the case of sufficiently high concentrations [39]. This equation was alredy used in some adsorption studies, especially in the case of some dye-fibre systems [33], or in the case of phenolic compounds – activated carbon [38, 40, 41], but to our knowledge, literature does not contain reports concerning its application in the sorption process of drugs onto cellulosic type supports.

As regarding the Jossens model, one could say that this model is essentially based on a distribution of the energy of interactions among adsorbate and adsorbent on adsorption sites. Moreover, the model considers that the adsorbent surface is heterogeneous, as regarding its interactions with the adsorbates [42].

The adsorption equilibrium data for Aspirin and Diclofenac onto the cellulosic type supports were analyzed by non-linear curve fitting analysis, using Origin 6.1 software, in order to fit the experimental data to the considered isotherm models. The principal statistical criteria was the squared multiple regression coefficient (R^2) (table 3 and 4).

The experimental data which were fitted to the theoretical adsorption isotherms Freundlich, Langmuir are depicted in table 3, and those corresponding to the Sips and Jossens models are presented in table 4.

The determination of the parameters which described the theoretical models were assessed by the same software.

By instance, the comparison between experimental data and fit sorption isotherm curves for *Aspirin* and *Diclofenac* adsorption on fir wood fibre at 298 K is presented in figure 2.

The inspection of data presented in tables 3 and 4 indicate that, among the tested equations, the isotherm model which provided a very good representation of the experimental results was the three-parameter model of Sips.

This result indicates that the adsorption process of *Aspirin* and *Diclofenac* is going on after a combined model: Frendlich and Langmuir, which means a diffused adsorption on low dye concentration, and a monomolecular adsorption with a saturation value - at high adsorbate concentrations.

From the Sips sorption isotherm curves (fig. 1e) the maximum adsorption capacity of investigated adsorbents was determined (table 5).

The obtained values allow the following conclusions: adsorption capacity degreases in the order: cotton > MCC > wood, for both investigated drugs. So, one could emphasis that the number of adsorption active centers should decrease in the same order. As expected (adsorption is generally exothermic) the equilibrium constant (K_S)

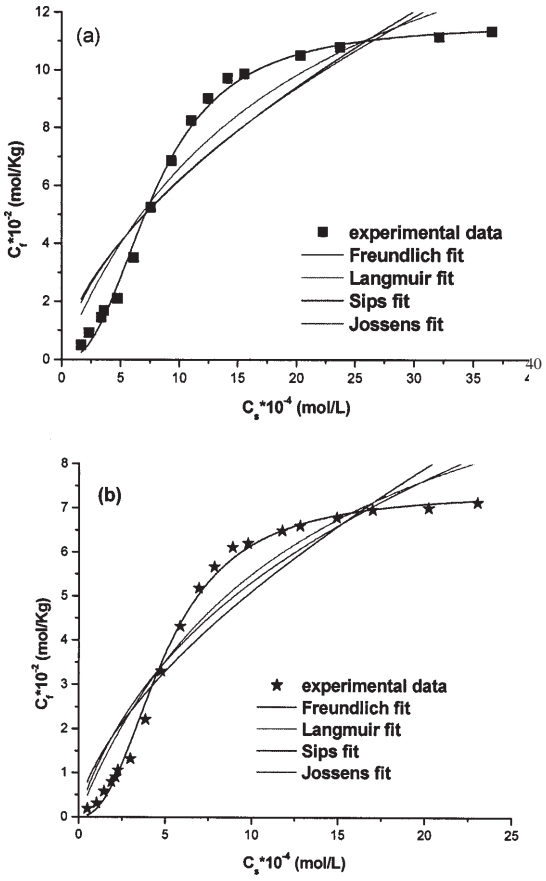


Fig. 2. Correlations between experimental data and different types of adsorption isotherms for *Aspirin* (a) and *Diclofenac* (b) adsorption on wood fibre at 298 K

ASPIRIN	Freundlich			Langmuir		
	298 K	308 K	318 K	298 K	308 K	318 K
wood	0.8486	0.8826	0.8842	0.9161	0.9341	0.9348
cotton	0.9528	0.9644	0.9673	0.9544	0.9621	0.9615
MCC	0.8607	0.8745	0.8892	0.9213	0.9226	0.9344
DICLOFENAC						
wood	0.8759	0.8991	0.8999	0.9321	0.9429	0.9424
cotton	0.8731	0.8983	0.8978	0.9289	0.9411	0.9399
MCC	0.8740	0.8843	0.8985	0.9300	0.9330	0.9406

Table 3
THE SQUARED MULTIPLE REGRESSION COEFFICIENT (R^2) FOR THE CLASSICAL ADSORPTION ISOTHERMS MODELS

	Sips			Jossens		
ASPIRIN	298 K	308 K	318 K	298 K	308 K	318 K
wood	**0.9957**	**0.9982**	**0.9983**	0.8605	0.8605	0.8952
cotton	**0.9951**	**0.9978**	**0.9984**	0.9459	0.9548	0.9571
MCC	**0.9954**	**0.9982**	**0.9984**	0.8815	0.8848	0.8995
DICLOFENAC						
wood	**0.9960**	**0.9985**	**0.9983**	0.9062	0.9159	0.9156
cotton	**0.9965**	**0.9982**	**0.9981**	0.9007	0.9157	0.9095
MCC	**0.9965**	**0.9976**	**0.9982**	0.9023	0.9034	0.9118

Table 4
THE SQUARED MULTIPLE REGRESSION COEFFICIENT (R^2) FOR THE SIPS AND JOSSENS ADSORPTION ISOTHERMS MODELS

Drug	Sorbent	Temp. (K)	S_f (mol/kg)	K_S (L/mol)	n
		298	11.61	0.125	0.396
	Wood	308	10.71	0.114	0.423
		318	10.03	0.108	0.421
Aspirin		298	12.14	0.118	0.404
	Cotton	308	11.39	0.106	0.433
		318	10.73	0.099	0.447
		298	11.62	0.123	0.392
	MCC	308	10.80	0.114	0.419
		318	10.13	0.105	0.427
		298	7.28	0.199	0.399
	Wood	308	6.72	0.181	0.436
		318	6.28	0.171	0.419
		298	7.30	0.197	0.396
Diclofenac	*Cotton*	308	6.83	0.179	0.422
		318	6.23	0.172	0.412
		298	7.30	0.196	0.396
	MCC	308	6.81	0.183	0.412
		318	6.29	0.167	0.424

Table 5
SIPS' EQUATION PARAMETERS

System	T	ΔG^0	ΔH^0	ΔS^0
	(K)	(kJ mol^{-1})	(kJ mol^{-1})	(J mol^{-1} K^{-1})
	298	-5.24		
Aspirin- Wood	308	-5.74	0.61	-15.52
	318	-6.25		
	298	-5.38		
Aspirin-Cotton	308	-5.93	0.73	-15.63
	318	-6.49		
	298	-5.28		
Aspirin-MCC	308	-5.74	0.66	-15.44
	318	-6.33		
	298	-4.08		
Dicofenac- Wood	308	-4.52	0.61	-11.68
	318	-4.96		
	298	-4.09		
Dicofenac -Cotton	308	-4.55	0.56	-11.89
	318	-4.95		
	298	-4.12		
Dicofenac -MCC	308	-4.49	0.64	-11.62
	318	-5.03		

Table 6
THERMODYNAMIC PARAMETERS FOR THE ADSORPTION OF ASPIRIN AND DICLOFENAC ON FIR WOOD, COTTON AND MCC ADSORBENTS.

decreased with increasing temperatures, and this fact could be explained considering that higher temperatures generate the increasing of the stored energy in different types of motion allowed, and weaken the physical binding forces of adsorbed molecules.

Thermodynamic parameters for the adsorption process were calculated in order to evaluate the effect of temperature onto the adsorption process (table 6). The Gibb's free energy (ΔG^0), was calculated according to equation (2):

$$\Delta G^0 = -RT \ln K_S \qquad (2)$$

The corresponding enthalpies (ΔH^0) and entropies (ΔS^0) were computed from van't Hoff equation:

$$\ln K_S = \frac{\Delta S^0}{R} - \frac{\Delta H^0}{RT} \qquad (3)$$

where: R is the universal gas constant (8.314 J K^{-1} mol^{-1}), T the absolute temperature, and K_S represents the Sips equilibrium constant (table 5), obtained from the isotherm plots. ΔH^0 and ΔS^0 values can be calculated from the slope and intercept of the linear plot of lnK versus 1/T.

The obtained negative values of ΔG^0 indicate the spontaneous nature of the adsorption process. The increase of temperature determined an increase of ΔG^0 indicating that adsorption is facilitated by higher temperatures.

Conclusions

In this present work, the interactions of two NSAIDs drugs, namely *Aspirin* and *Diclofenac* with some cellulosic type supports were investigated.

The study involved the experimental evaluation of the effect of initial drug concentrations, temperature and the adsorbent type onto the adsorption process.

The adsorption isotherms of Aspirin and Diclofenac on the three cellulosic supports were studied and modeled using two classical isotherm models: Freundlich and Langmuir, as well as two three –parameter isotherm models, Namely Sips and Jossens, which were not used since present in the case of the investigated drug- cellulosic type supports systems.

The statistical analysis of the obtained results indicate that the Sips model described better the adsorption process in the case of all studied drug-cellulosic supports systems used in this study.

The values of the corresponding thermodynamics parameters of the sorption process indicate that in the case of all the studied systems, the process is spontaneous and exothermic.

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