EXPERIMENTAL STUDY OF THE INTERACTION OF ONE LOCAL ANESTHETIC WITH A CELLULOSE TYPE SUPPORT

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ABSTRACT

The extent of the adsorption of a local anesthetic (Bupivacaine) on a pharmaceutical adsorbent, namely microcrystalline cellulose (MCC) suspended in aqueous solution was investigated spectrophotometrically at three different temperatures. The equilibrium adsorption contact times were determined for all the temperatures and were found around 90 minutes. Adsorption isotherms have been analyzed by the Freundlich and Langmuir models. The obtained results indicated that the Freundlich isotherms presented the highest correlation coefficients, and thus they describe better the adsorption of the studied drug on MCC.

INTRODUCTION

Adsorption is one of the most important mechanisms of interaction between drugs and excipients due to the fact that the adsorption of a drug onto solid dosage form excipients may influence its characteristics, analytical testing and bioavailability. This matter of fact is of a particularly interest especially for drugs which are normally used in low doses and it is obvious that drug interactions are one of the most important factors that should be considered in any preformulation study [1].

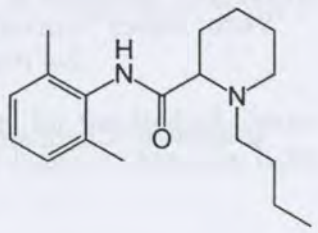
Bupivacaine (*RS*)-1-butyl-*N*-(2,6-dimethylphenyl) piperidine-2-carboxamide) is a local anaesthetic drug belonging to the amino-amide group and is commonly marketed under various trade names, including Marcain, Marcaine, Sensorcaine and Vivacaine [2]. Bupivacaine blocks the generation and conduction of nerve impulses. It is commonly used for analgesia by infiltration of surgical incisions. Preemptive use of analgesics (including local anaesthetics used to control post-operative pain), before tissue injury, is recommended to block central sensitization, thus preventing pain or making pain easier to control [3]. Bupivacaine has a longer duration of action than lidocaine, to which it is chemically related - approx. 6-8 hours as opposed to 1-2 hours for lidocaine. Duration of action is affected by the concentration of Bupivacaine used and the volume injected. Concentration affects the time for local anaesthesia to occur and the density of the block. Volume determines the area that is infiltrated and therefore anesthetized [4].

Microcrystalline cellulose (MCC) is considered to be as an excellent excipient in the preparation of direct-compressed tablets and, is extensively used in the field of drug formulations [5]. However, few studies were carried-on in order to obtain information about its interaction with drugs. In this area of interest, one could only refer to the adsorption on MCC of some few steroids, phenothiazines, antihistaminics and antibiotics, but the adsorption mechanism is still unclear and of great actuality [6-10]. The aim of this present work was to

study the adsorption of Bupivacaine on MCC suspended in aqueous solution, at severeal temperatures, in order to obtain more information concerning the interaction of this specific drug with this type of excipient. The basic idea was to find out if the experimental results could be fitted into the classical Langmuir and/or Freundlich adsorption isotherms.

MATERIALS and METHODS

Bupivacaine hydrochloride (99%) was provided by Fluka, and Microcrystalline cellulose (BCR302-20G) was supplied from Aldrich Sigma. Both reagents were used such as, without further purification. The UV-VIS spectroscopy study was performed using a CECIL CE 7200 spectrophotometer. The analytical wavelenght [nm] used in the spectrophotometric determinations of bupivacaine was 271 nm



Adsorption studies

A series of stock solutions containing Bupivacaine hydrochloride were prepared in distilled water. The absorbance of the drug solutions was measured at 271 nm in order to obtain a calibration curve, according to Lambert-Beer law. In the first stage, we investigate the time necessary to reach the equilibrium. Further, based on the results from the preliminary experiments, we investigate the extent of adsorption of the drug on MCC. In the case of the preliminary experiments, 10 mL of an initially bupivacaine solution (8×10^{-5} M) was added into 25 ml volumetric flasks containing 0,2 g (±0,0001) of MCC. were placed. Similarly, 12.5 ml of distilled water was added to equal graded amounts to adsorbents in 25 ml volumetric flask (without drug used as blanks for the absorbance measurements). The mixtures were put in a shaker bath set at different temperatures (ranging from 25, 35 and 40°C (± 1°C)) and were shaken for 12-60 h. At the end, the solutions were filtered by using double filter papers. The final concentrations of the free drug in solution were obtained spectrophotometrically, using the Lambert Beer's plot previously obtained. The preliminary studies indicate that the adsorption equilibrium of Bupivacaine on MCC was attained within 90 mintes.

In order to obtain the adsorption isotherms of the studied drug, solutions of different concentrations of Bupivacaine were prepared by serial dilutions in the range of $1x10^{-5}$ to $3,2x10^{-4}$ mol/L. Adsorbent surface samples of 0.20 g each were weighed and placed in a screw cap bottle, to which 10 mL of the drug solutions were added. The mixtures were shaked in the thermostated shaker at the same temperatures and times as in the preliminary experiments. At the end of the adsorption period, the solutions were filtered and the clear supernatants were analysed spectrophotometrically after appropriate dilutions. The adsorbed amount of the drug was calculated from the concentration in solutions before and after adsorption according to the equation (1):

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

where $[D]_{ad}$ is the equilibrium drug concentration on MCC (mmol/g), $[D]_i$ and $[D]_s$ are the initial and equilibrium concentrations of drug solution(mmol/L), V is the volume of drug solution (L), and m is the amount of MCC sample used (g).

Control experiments, in which no drug was added, were performed in parallel, and the filtrate was used as a reference solution.

RESULTS

In the thermodynamic studies, the results of experimental sorption measurements are usually expressed in the form of equilibrium sorption isotherms. In this, present study, two types of isotherms have been investigated, namely the Langmuir and Freundlich isotherms [11].

The Langmuir equation assumes that there is no interaction between the adsorbed molecules and that the sorption is localized in a monolayer. This model also assume that once a drug molecule occupies a site, no further sorption can take place at this site. Theoretically, therefore, a saturation value is reached, beyond which no further adsorption can take place. The Freundlich equation is an empirical relationship describing the adsorption of solutes from a liquid to a solid surface. The equations for the two types of sorption isotherms are given by equations (2) and (3).

$$[D]_{ad} = K_F \cdot [D]_s^x \quad (2)$$

$$[D]_{ad} = \frac{S_f \cdot K_L \cdot [D]_s}{1 + K_L \cdot [D]_s} \quad (3)$$

where $[D]_{ad}$ and $[D]_s$ are the equilibrium concentration of adsorbed drug, respectively in solution (mmol/L), K_F and K_L are the Freundlich and Langmuir equilibrium constants, S_f is the saturation value and x is a subunitary power.

In order to decide which type of isotherms fits better the sorption experimental data, equations (2) and (3) were linearised giving equations (4) and (5). Further, we plotted the quantities log $[D]_{ad}$ *Versus* log$[D]_s$ for the Freundlich isotherm and $[D]_{ad}^{-1}$ *Versus* $[D]_s^{-1}$ in the case of Langmuir model.

$$\log[D]_{ad} = \log K_F + x \log[D]_s \quad (4)$$

$$\frac{1}{[D]_{ad}} = \frac{1}{S_f \cdot [D]_s \cdot K_L} + \frac{1}{S_f} \quad (5)$$

The choice of the model which fitted the best with the experimental data was based on the values of the squared regression coefficient (r^2), the standard deviation (SE) and the Fisher test (F) which were used as statistical criterions and were computed by linear regression analysis. These results are presented in table 1.

Table 1. Statistical results of the adsorbtion of Bupivacaine on MCC at 25, 35 and 40 °C

	25°C		35°C		40°C	
	Freundlich	Langmuir	Freundlich	Langmuir	Freundlich	Langmuir
r^2	0,989	0,653	0,978	0,546	0,986	0,628
SE	0,004	0,069	0.007	0,102	0,005	0,087
F	1529.108	45,463	1169,453	38,765	1347,629	41,613

As it can be seen from the results presented in table 1, the Freundlich isotherm fits better with the experimental results, at all the studied temperatures.

The inspection of the experimental results clearly indicate that the adsorption of Bupivacaine on MCC decreased with increasing temperature, showing thus an exothermic nature of the process. In figure 1 is given the adsorption isotherm of Bupivacaine on MCC at 25°C.

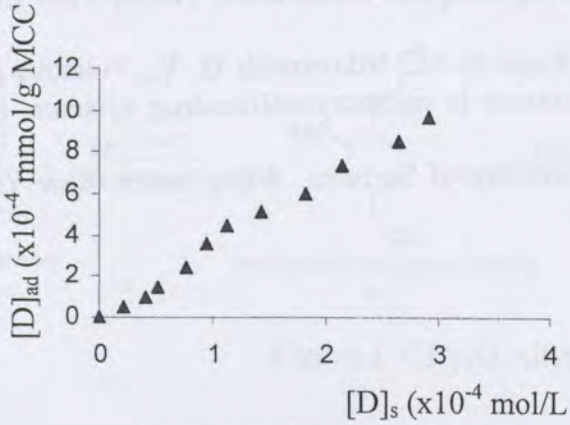


Figure 1. Adsorption isotherm of Bupivacaine on MCC at 25°C

The general shapes of the drug's adsorption on MCC at the others studied temperatures are very similar. One could consider that the extent to which the studied drug's adsorption capacity decreases with increasing temperature might be attributed to the change in the surface properties of the adsorbent, as well as to the solubility of the adsorbate species.

CONCLUSIONS

- The adsorption of Bupivacaine hydrochloride on MCC from aqueous solutions is a function of initial drug concentration, temperature and contact time.
- Adsorption isotherm of the drug under study on MCC obeyed Freundlich isotherm as the adsorption increases with increasing the concentration at equilibrium. This result indicated the surface heterogeneity leading to different adsorption force from site and different affinities toward drug molecule.

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