RAPID COMMUNICATION

Removal of Amitriptyline from Simulated Gastric and Intestinal Fluids Using Activated Carbons

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ABSTRACT: In this work, the adsorption behavior of a tricyclic antidepressant, amitriptyline hydrochloride, onto several activated carbons (ACs) is reported. The adsorption was done using *in vitro* simulated gastric and intestinal fluid at 37°C to test the performance of the carbons as treatment in overdose cases. The tested materials were one commercial AC (carbomix) and two ACs produced in our laboratory. The highest adsorption capacity was achieved by carbomix, followed by the laboratory-made carbons that still have a very good performance with adsorption capacity up to 120 and 100 mg/g for the gastric and intestinal fluids, respectively. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:5096–5099, 2011

Keywords: nanoparticles; gastrointestinal; elimination; biomaterials; adsorption; activated carbon; amitriptyline; drug overdose

INTRODUCTION

Many legal and illegal drugs are frequently taken in excess, which can constitute a relevant health problem. For the majority of these drugs, the treatment of overdose cases at hospital is done by oral administration of activated carbon (AC) slurry, as there is no specific antidote. Amitriptyline (AMT) is a tricyclic antidepressant (TCA) drug used for the treatment of several mental conditions that is commonly involved in overdose cases leading to severe toxic effects, namely in the cardiovascular system and in the peripheral and central nervous systems.[1] These drugs are among the commonest causes of fatal and nonfatal drug poisoning in the world. Symptoms of an overdose usually develop within an hour of ingestion and may start with rapid heartbeat, dilated pupils, flushed face, and agitation, which can progress to confusion, loss of consciousness, seizures, irregular heart rate, hypotension, and pulmonary edema and ending in respiratory arrest, convulsions, ventricular arrhythmias, coma, and death. The toxic effects are especially acute when young children take the drug, in this case one or two pills can cause acute toxicity.[2,3]

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TCAs are one of the oldest classes of antidepressants but still extensively used worldwide because of its lower price when compared with other more recently developed drugs, namely the selective serotonin reuptake inhibitors (SSRIs). TCAs are comparatively more toxic, in particular at low dosages, with larger side effects than SSRIs.

Several *in vivo* and *in vitro* studies have proven the efficacy of AC to adsorb numerous drugs and decrease their toxic impact.[4–8] The AC provides the elimination of absorbed toxins interrupting the hepatic circulation and promoting the passive diffusion from the capillaries of the mucous intestinal toward the lumen. It is not demonstrated if the gastric wash combined with activated coal is better than the latter only.[9]

The objective of the work here reported is to study the adsorption of AMT onto ACs in order to study the efficiency of using these materials to treat overdose cases.

EXPERIMENTAL

Pharmaceutical Product

Amitriptyline hydrochloride (reference standard, p*K*a 9.42) used in this study was supplied by Sigma–Aldrich (St. Louis, Missouri). The chemical structure is shown in Figure 1 and consists of a central ring that adopts a bent conformation.

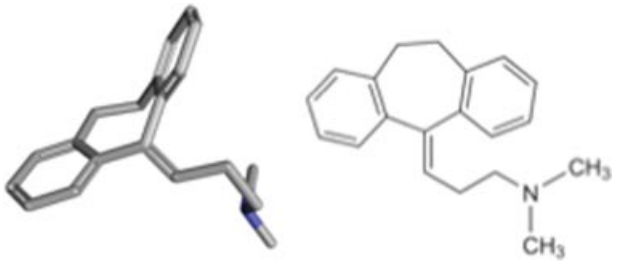

Figure 1. Molecular structure of amitriptyline HCl.

Activated Carbons

Three ACs were used. One sample is commercially available for use in medicinal applications: Carbomix (Norit N.V., the Netherlands), designated carb. Two AC samples were produced in our laboratory using cork (COR849) and eucalyptus pulp (P834) as precursors. The ACs were produced using a horizontal tubular furnace and carbon dioxide as activating agent. Experimental details can be found in Ref.[10].

Materials Characterization

The porosity was evaluated by the analysis of the nitrogen adsorption isotherms at 77 K using suitable methods, namely Brunauer-Emmett-Teller (BET) that provides the BET surface area A_{BET}; and the α_s method that provides the total pore volume, V_S, and the external area, A_{ext}. Nitrogen adsorption isotherms at 77 K were recorded in a Quadrasorb-Tri, Quantachrome Instruments (Boynton Beach, Florida). The point of zero charge (pzc) was determined by mass titrations using 7 wt % suspensions of the ACs in $NaNO_3$ 0.1 M solutions with initial pH adjusted to 3, 6, and 10. The suspensions were placed in a thermostat bath at 25°C and stirred for 48 h, then filtered and the pH measured, details given elsewhere.[11] The pzc value is given by the media of the measured pHs.

AMT Adsorption Study

The adsorption study of AMT was performed in simulated gastric and intestinal conditions at 37°C. A stock solution of AMT (1 g/L) was prepared in simulated gastric fluid pepsin omitted, pH 1.2, which consists of 2.0 g/L NaCl and 7 mL/L of concentrated HCl. Other stock solution of 1 g/L was prepared in simulated intestinal fluid pepsin omitted, pH 7.5, which consists of 50 mL NaH_2PO_4 0.1 M and 42.5 mL NaOH 0.1 M for 1 L of solution.

Batch adsorption experiments were carried out in a series of Erlenmeyer flasks of 100 mL capacity covered with Teflon and inserted in a shaking thermostat bath at 37°C for 72 h using 0.01 g of adsorbent and 25 mL of AMT solutions with variable concentrations up to 255 mg/L.

The determination of AMT concentration was done by ultraviolet absorption at 240 nm using a Nicolet evolution 300 ultraviolet–visible spectrophotometer. The absorbance of the solutions was made in triplicate. The calibration curve obeys the Beer law in all the concentration range tested, 2–255 mg/L, with very good linearity ($r^2 = 0.996$).

RESULTS AND DISCUSSION

Materials Characterization

The results of the materials characterization in terms of porosity and maximum adsorption capacity are reported in Table 1. It can be seen that the AC samples tested are all basic, with pzc always higher than 8.

The sample with the highest surface area and pore volume is carbomix with 1396 m^2/g and 0.70 cm^3/g, respectively. The laboratory-made carbons have less developed porous structure; however, the mesopore volume of sample COR849 is bigger than the values observed for the other carbons. The percentage of pores in the mesopores range (mean pore width between 2 and 50nm) varies with the sample provenience assuming the value of 21%, 31%, and 62% for P834, carbomix, and COR849, respectively.

AMT Adsorption Study

The AMT adsorption study was performed at normal body temperature and in both simulated gastric and intestinal fluids because these are the organs where the drug is absorbed by the human organism when it is ingested. At both pH conditions employed, AMT is mainly found in its protonated form. Figure 2 shows

Table 1. Characterization of the Activated Carbons and Maximum Adsorption Capacity

	Porosity						
	BET	α_s				Maximum Adsorption Capacity (mg/g)	
Sample	A_{BET} (m^2/g)	V_s (cm^3/g)	A_{ext} (m^2/g)	V_{mes}[a] (cm^3/g)	pzc	pH 1.2	pH 7.5
P834	772	0.38	21	0.08	10.26	120	70
COR849	839	0.50	97	0.31	8.65	120	100
Carbomix	1396	0.70	71	0.22	8.01	300	500

[a]The volume of mesopores was taken from the isotherms by subtracting the adsorbed volume at relative pressure of 0.1 (micropore volume) to the total pore volume.

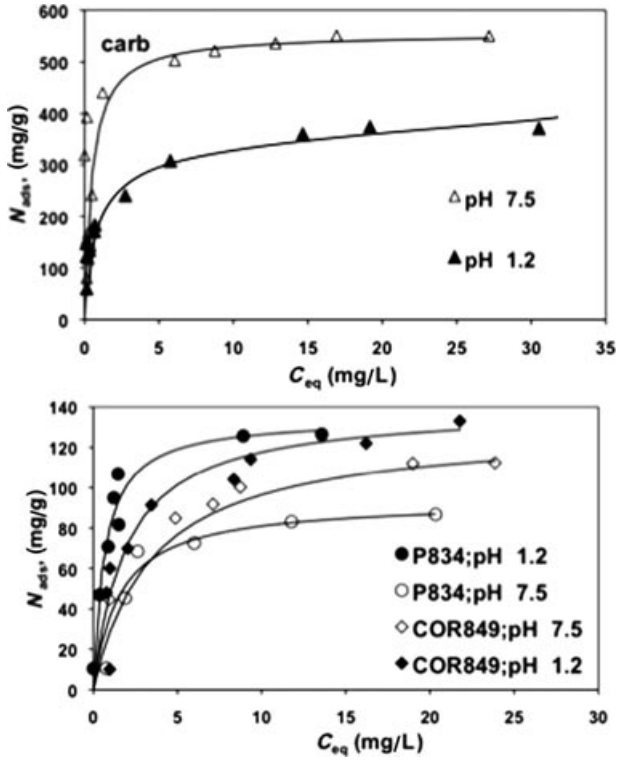

Figure 2. Amitriptyline adsorption isotherms at 37°C.

the milligrams of AMT adsorbed per gram of carbon (N_{ads}) versus the equilibrium concentrations in simulated fluids at 37°C (C_{eq}). From the adsorption isotherms, we can obtain the maximum adsorption capacity that is shown in Table 1.

The maximum adsorption capacity is observed for carbomix that can be due to both its higher pore volume and BET surface area. Also, sample COR849 shows slightly higher adsorption capacity than P834 for the same reasons.

Different carbon types, commercial and laboratory made, have also dissimilar behavior for adsorption at pH 1.2 and 7.5. By one side, carbomix shows higher adsorption capacity at pH 7.5, which is consistent with previous report data on the adsorption of fluoxetine onto the same carbon.[12] This indicates that the adsorption mechanism is determined by the electrostatic interactions between the AMT molecule and the ionized surface of the carbon. At working pH, AMT is protonated acquiring a positive charge that is proportional to the pH decrease. The surface of the ACs achieves a net charge that depends on the ionization of the functional groups determined by the solution pH; when the pH is inferior or superior than the pzc value, the surface became positive or negative. The charge intensity is proportional to the difference between the solution pH and the pzc value. Therefore, at pH 1.2, the electrostatic interactions are more repulsive, leading to lower adsorption capacities. On the contrary, the adsorption mechanism of the laboratory-made carbons is not significantly influenced by the electrostatic interaction as indicated by the fact of showing higher adsorption capacity at pH 1.2. In these cases, it can be hypothesized that the adsorption mechanism is mainly determined by dispersive interactions, or specific chemical interactions, between the delocalized electrons of the carbon basal planes, or the surface functional groups, and the AMT molecular structure that are somehow increased at pH 1.2.

COR849 and P834 samples can be used to prevent the absorption of the drug by the human body in the event of a dug overdose. Usually, the normal dose of AC slurry to treat overdoses involves the use of about 60 g of AC. If we consider the maximum adsorption capacity of each sample, it would mean that the laboratory carbons could adsorb 4–7 g of the drug. This performance is sufficient to treat a person that had ingested a full box of 30 pills of 100 mg dosage of AMT. Therefore, we can state that, despite their lower adsorption capacity, the laboratory-made carbons can constitute an interesting alterative to the commercial product due to their different biochemical structure that is originated by the use of natural biomass as precursor for the ACs production. Also, the use of agricultural and industrial wastes to produce ACs should be underlined, as it constitutes an environmental friendly process.

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