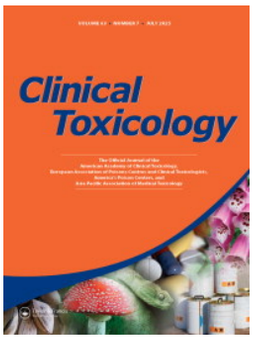

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Adsorption of antidepressant and cardiovascular drugs to activated charcoal: amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine

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BASIC RESEARCH

Adsorption of antidepressant and cardiovascular drugs to activated charcoal: amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine

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ABSTRACT

Background: Overdoses involving antidepressant and cardiovascular drugs account for 21.9% of non-opioid overdose-related fatalities in the United States. Activated charcoal is commonly used for gastrointestinal decontamination, but data regarding its adsorption efficacy for several clinically relevant drugs remain limited.

Objective: We aimed to evaluate the adsorption of amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine to activated charcoal by fitting adsorption isotherm data.

Methods: Kinetics and adsorption isotherm experiments were conducted using simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8). Freundlich and Langmuir isotherm equations were fitted to experimental data to model adsorption behavior. Drug-specific activated charcoal-to-drug ratios required to achieve ≥95% adsorption were identified.

Results: All five drugs were adsorbed effectively to activated charcoal although adsorption efficiencies varied by pH. Maximal adsorption capacities of all drugs were higher in simulated intestinal fluid compared to simulated gastric fluid. In simulated intestinal fluid, ≥95% of bupropion was adsorbed at a 10:1 activated charcoal-to-drug ratio, while this level was not reached in simulated gastric fluid even at a 12:1 ratio. Amitriptyline and propranolol reached ≥95% adsorption at ratios below 10:1. Venlafaxine and minoxidil required higher ratios of activated charcoal ratios to reach maximal adsorption. Activated charcoal had a higher drug-binding capacity in simulated intestinal fluid, but binding was stronger in simulated gastric fluid. Bupropion was adsorbed more in simulated intestinal fluid overall, though efficiency decreased at higher concentrations.

Discussion: A single 50 g dose of activated charcoal at 10:1 ratio may be inadequate for clinically significant overdoses of bupropion, minoxidil, and venlafaxine, especially for immediate release bupropion for which gastric adsorption may be important.

Conclusions: This study supports the use of activated charcoal for gastrointestinal decontamination in overdoses involving amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine. However, drug-specific differences in adsorption behavior suggest a need for refined dosing strategies, particularly in cases involving drugs with lower binding efficiencies.

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Activated charcoal; adsorption; bupropion; Freundlich; Langmuir; minoxidil; propranolol; venlafaxine

Introduction

Antidepressant and cardiovascular drug overdoses are a significant cause of morbidity and mortality [1]. In 2022, these drug classes accounted for 21.9% of nonopioid overdose-related deaths reported to the America's Poison Centers® National Poison Data System® [2]. Furthermore, antidepressants were involved in 5.58% and cardiovascular drugs in 4.97% of all human exposure cases in 2023 [1]. In many cases, treatment was limited to supportive care. Bupropion, a cardiac myocyte gap junction inhibitor, presents a particularly difficult case in overdose [3,4]. Unlike other cardiotoxic drugs, it does not respond well to standard interventions such as sodium bicarbonate [5]. This highlights the need for decontamination strategies.

Gastrointestinal decontamination is often recommended in overdose management to prevent drug absorption, which may decrease systemic toxicity [6]. Decontamination is critical in the management of overdoses, such as bupropion, for which antidotes and other treatment options are limited once the drugs have entered systemic circulation. Activated charcoal is widely used for gastrointestinal decontamination, but

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its effectiveness depends on the chemical properties of the drug and timing of administration. Adsorption onto activated charcoal occurs primarily through its high surface area, porosity, and interactions with electron-rich aromatic rings [7]. Aromatic drugs bind via π-stacking, while molecules with lone electron pairs interact through nonbonding forces [7,15,16].

While activated charcoal is generally safe, its use is not without risk [8]. Pulmonary aspiration can occur, especially following emesis, leading to severe respiratory distress and in rare cases, death [9,10]. Gastrointestinal complications, such as bowel obstruction and bezoar formation, have also been reported [11–13]. Due to these potential risks, the benefits of activated charcoal must be carefully weighed, particularly when data on its effectiveness for specific drugs remain incomplete.

Furthermore, optimal dosing for activated charcoal is not well-established. An initial dose of 1 g/kg up to 50 g is typically administered in emergency departments after acute overdoses [14]. Past studies have shown that an adsorbent-to-drug ratio of 10:1 may be optimal for some drugs [14]. However, the adsorption kinetics and binding capacities of activated charcoal for many drugs remain poorly characterized. This is particularly true for bupropion, minoxidil, propranolol, and venlafaxine, which limits the ability to optimize activated charcoal dosing. This study aims to fill this gap by determining the maximum adsorption capacities and binding affinities of amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine to activated charcoal. Since prior studies have characterized amitriptyline adsorption to activated charcoal under controlled conditions, its inclusion in this study serves as an internal control to ensure experimental procedures work as expected [17]. Further, revisiting or refining past studies can provide clinically actionable insights for modern toxicology and emergency care.

Methods

Materials

Activated charcoal (DARCO® – 100 mesh particle size powder, surface area: 905.4 m^2/g, pore volume: 0.04 cm^3/g, pore size: 16.4027 Å) was purchased from Sigma-Aldrich. Amitriptyline hydrochloride, bupropion hydrochloride, minoxidil, and venlafaxine hydrochloride were purchased from Chem-Impex. Propranolol hydrochloride was purchased from Tokyo Chemistry Industry Chemicals. Simulated intestinal fluid was prepared according to United States Pharmacopeia (USP) guidelines (6.8 g KH_2PO_4, 0.896 g NaOH, 1 L deionized water, pH 6.8). Simulated gastric fluid was prepared according to USP guidelines (2.0 g NaCl, 7.0 mL of concentrated HCl, 1 L deionized water, pH 1.2).

Kinetics

Adsorbent/adsorbate mixtures (10:1 ratio) were prepared in 1.8 mL Eppendorf tubes, vortexed briefly, and incubated at 37 °C with rotational shaking. At selected time points ranging from 30 sec to 10 min, samples were centrifuged and the supernatant absorbance was analyzed using a Tecan Spark® plate reader. Adsorption equilibrium was defined as the time point at which adsorbate adsorption plateaued. Full experimental details are provided in the Supplemental Material.

Adsorption isotherm

Adsorbate solutions (20–250 mg/L) were combined with adsorbent dispersions to achieve ratios ranging from 1:1 to 12:1 in a final volume of 450 µL. Samples were incubated at 37 °C until adsorption equilibrium had been achieved (20 min), centrifuged, and the supernatant absorbance was analyzed via plate reader. Further details are available in the Supplemental Material.

Model fitting

To determine fit parameters from the adsorption isotherm experiments, the experimental data was plotted ($Q_{e,exp}$ versus C_e) and was modelled to the non-linear form of the Langmuir and Freundlich isotherm equations (Figure 1). Here, $Q_{e,exp}$ (mg/g) represents the experimentally determined equilibrium adsorption capacity—how much of the substance has been adsorbed onto the surface of the adsorbent at equilibrium. These values are plotted against C_e (mg/L), which represents the equilibrium concentration of the drug. These isotherm models make different assumptions regarding the adsorption process. As a result, their equations vary and allow the determination of different parameters of the system—such as Q_m and K_L (Langmuir isotherm) and K_F and n (Freundlich isotherm).

In the Langmuir isotherm, larger Q_m values indicate a greater maximal adsorption capacity, and that the adsorbent can hold more drug at saturation. Meanwhile, larger values of K_L indicate a strong binding affinity of the adsorbate to the adsorbent. In the Freundlich isotherm, larger K_F values signify greater relative adsorption capacity for the adsorbate at a given concentration. In this model, larger n values (typically >1) indicate a favorable adsorption process, such that adsorption is stronger at lower concentrations but does not increase excessively at higher concentrations. Using experimental C_e values

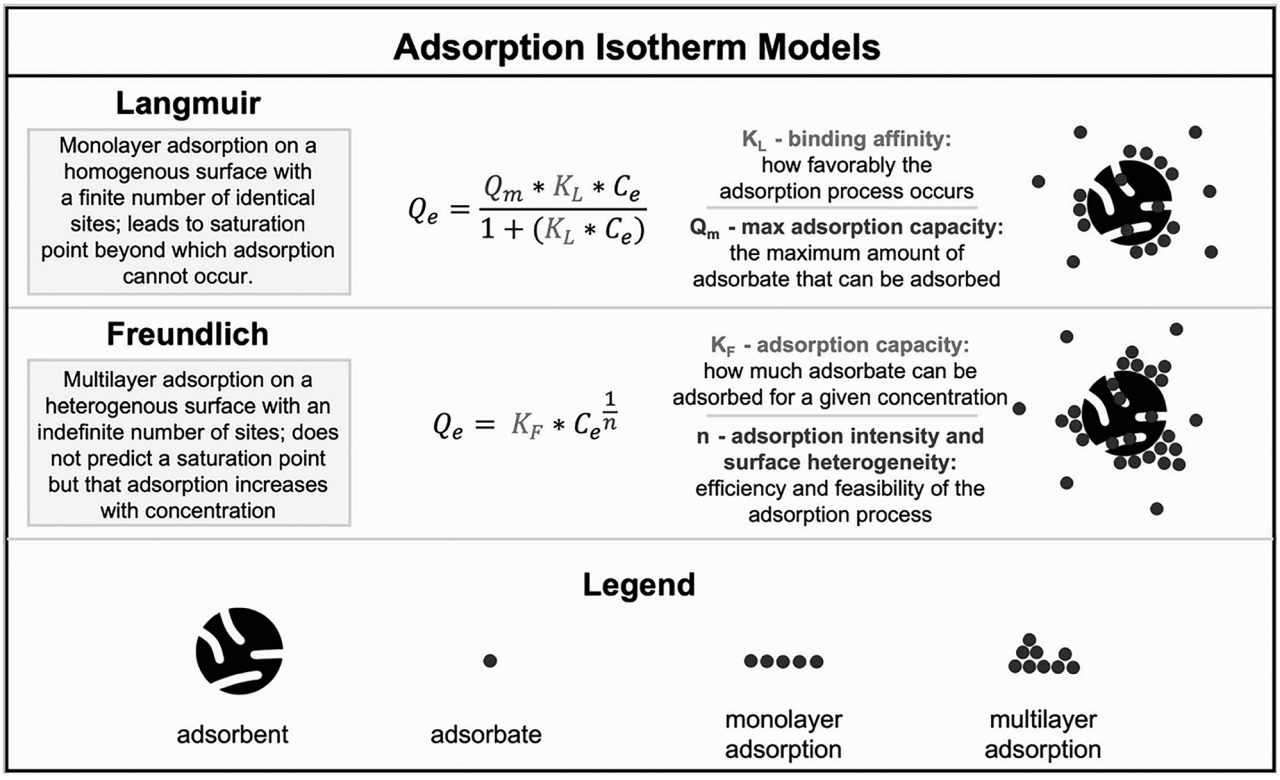

Figure 1. Langmuir and Freundlich isotherm models. Physical constants are defined to the right of each equation.

$$Root\ mean\ square\ error = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(Q_e^{exp} - Q_e^{calc}\right)^2}$$

Figure 2. Root mean square error used to quantify the difference between experimental and calculated equilibrium adsorption capacities ($Q_{e,exp}$ and $Q_{e,calc}$, respectively).

and estimates for the isotherm fitting constants, a theoretical set of Q_e values ($Q_{e,calc}$) was calculated. Root mean squared error was calculated to quantify the deviation between the $Q_{e,calc}$ values and experimental Q_e ($Q_{e,exp}$) values according to Figure 2. Next, using the Solver add-in in Microsoft Excel, the estimate values for unknown variables were optimized until a minimum root mean squared error value was reached. Error bars for the experimentally determined values represent the standard deviation of triplicate measurements in the amount of drug adsorbed per weight of adsorbent ($Q_{e,exp}$, y axis). Grubbs tests were performed to ensure no statistical outliers were present between triplicate measurements.

Results

Kinetics

Kinetics experiments determined the time required to reach equilibrium of ≥95% drug adsorption to activated charcoal (Figures 3–7(B)) under most conditions was within 10 min. In some cases, adsorption plateaus were observed at lower drug removal efficiencies. In simulated gastric fluid, adsorption to activated charcoal was less efficient for bupropion (69.5% removed), minoxidil (70.9% removed), and venlafaxine (70.0% removed). In simulated intestinal fluid, adsorption to activated charcoal was more efficient, with ≥95% adsorption observed for all drugs except venlafaxine (90.8%).

Adsorption isotherm

Adsorption isotherm experiments determined drug adsorption to activated charcoal was typically greater in simulated intestinal fluid (Figures 3–7(D)) than in simulated gastric fluid (Figures 3–7(C)). Using these data, the percentage of drug adsorbed was quantified in both simulated gastric and intestinal fluids, and the "optimal" doses to administer based on the ratio of activated charcoal-to-drug were determined (Figures 3–7(A)). Langmuir maximal adsorption capacities (Q_m) were consistently higher in

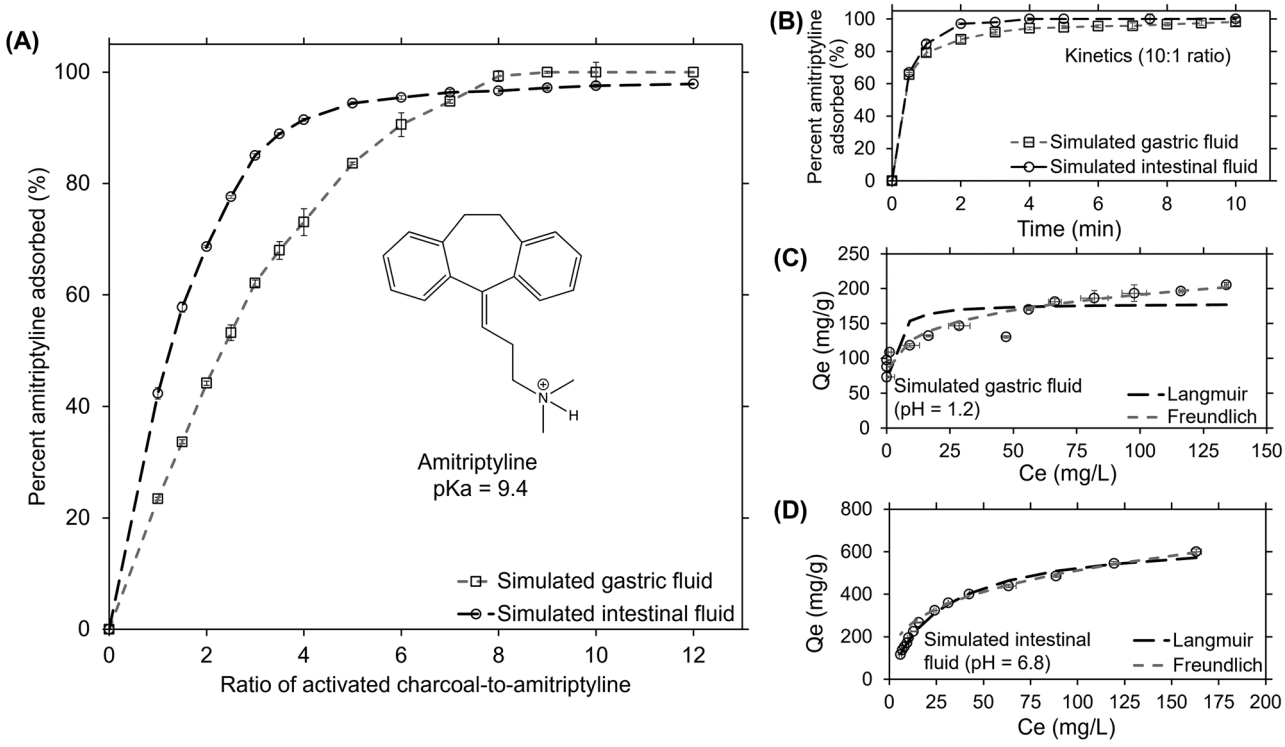

Figure 3. Capacity (A, C, and D) and kinetics (B) data for adsorption of amitriptyline to activated charcoal.

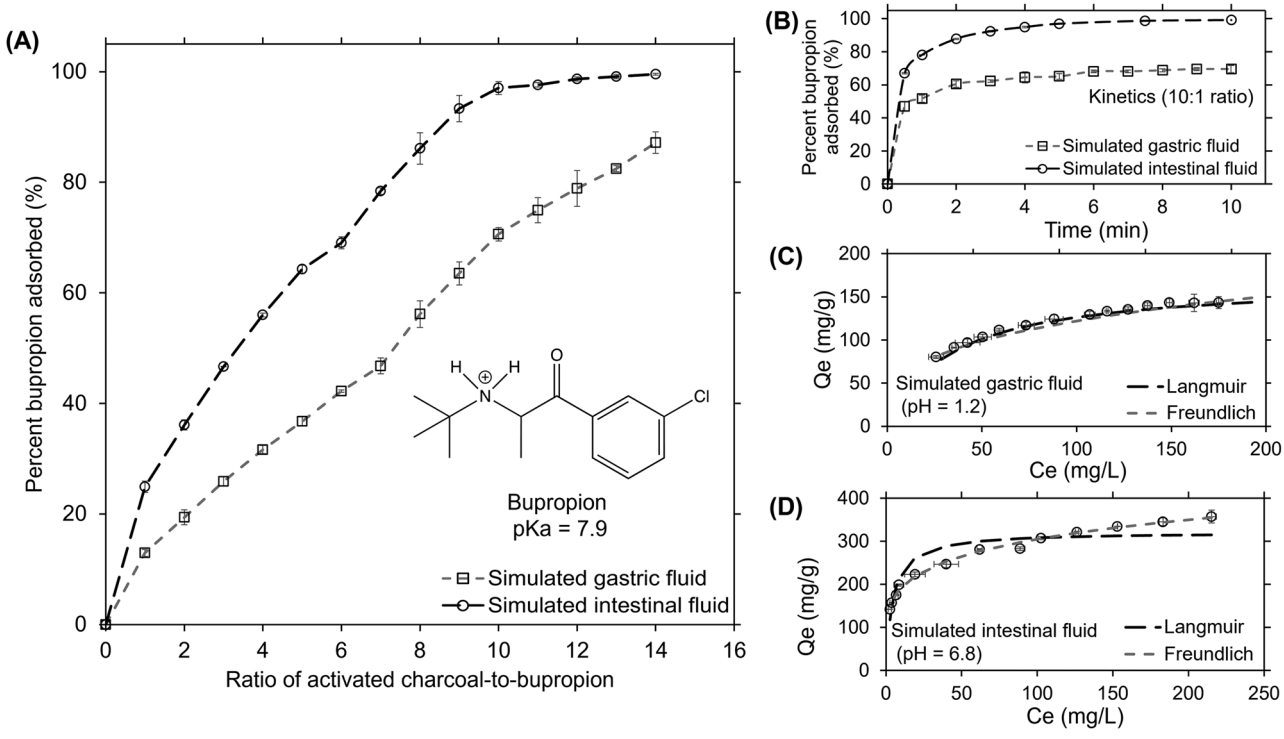

Figure 4. Capacity (A, C, and D) and kinetics (B) data for adsorption of bupropion to activated charcoal.

simulated intestinal fluid than in simulated gastric fluid across all drugs (Table 1). Higher K_L is seen in simulated intestinal fluid for amitriptyline, venlafaxine, and propranolol; drug structure and activated charcoal surface chemistry influence these values. Freundlich relative adsorption capacities (K_F) were generally greater in simulated intestinal fluid (Table 2). Alternatively, Freundlich n values—which describe favorability of adsorption with

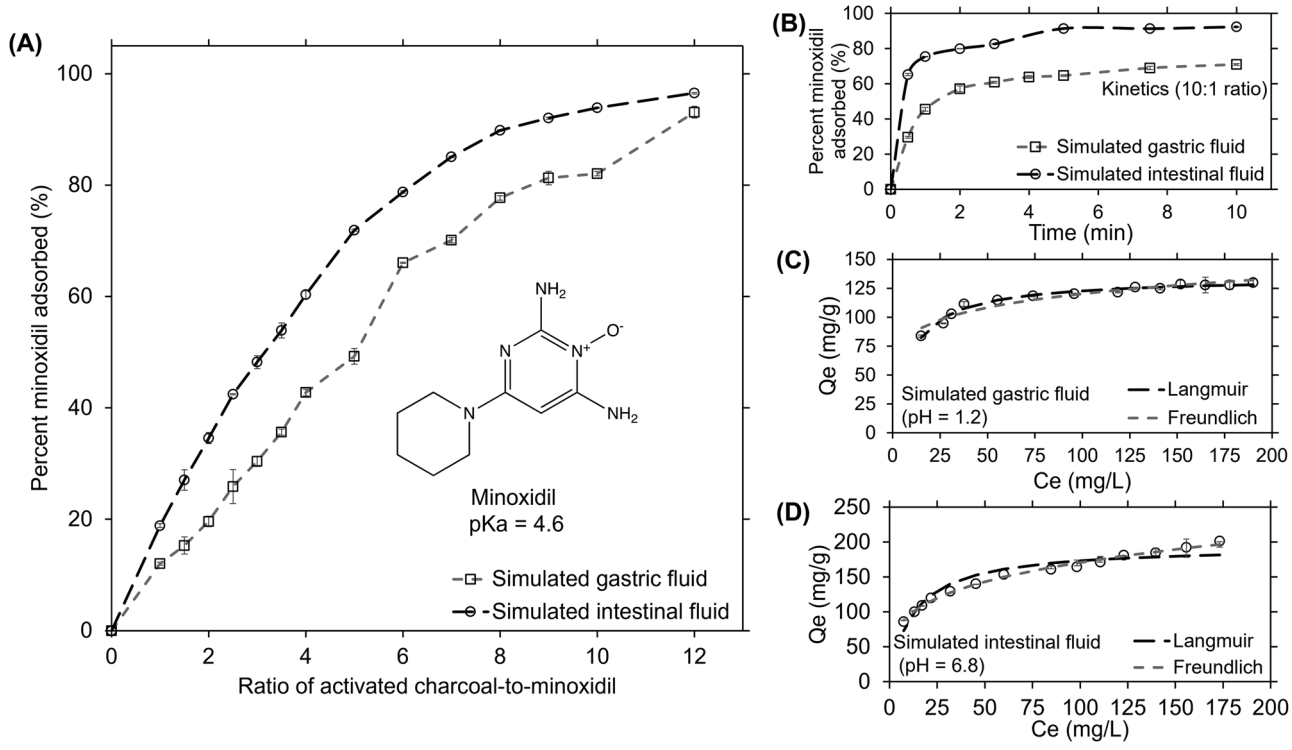

Figure 5. Capacity (A, C, and D) and kinetics (B) data for adsorption of minoxidil to activated charcoal.

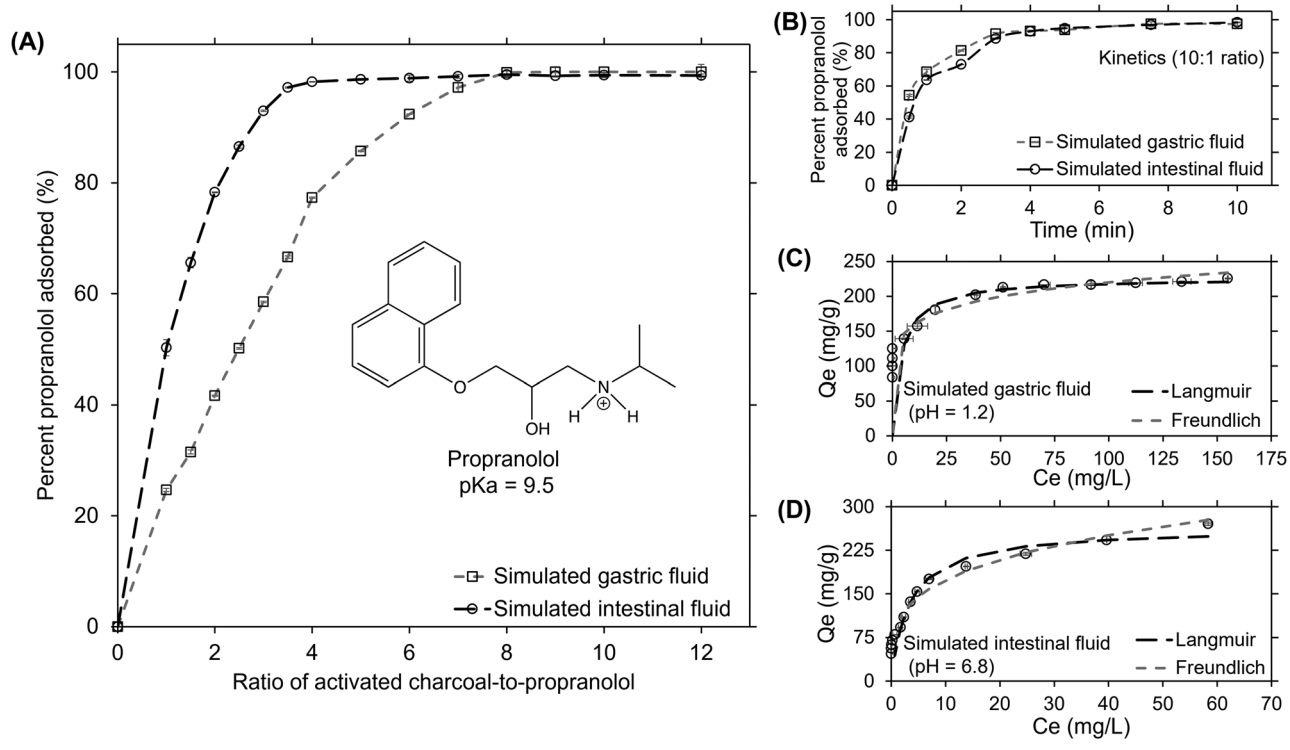

Figure 6. Capacity (A, C, and D) and kinetics (B) data for adsorption of propranolol to activated charcoal.

changing drug concentration—were typically higher in simulated gastric fluid, consistent with theoretical expectations (Table 2).

Adsorption was more efficient in simulated intestinal fluid than simulated gastric fluid, with most drugs achieving ≥95% adsorption at a 10:1 activated

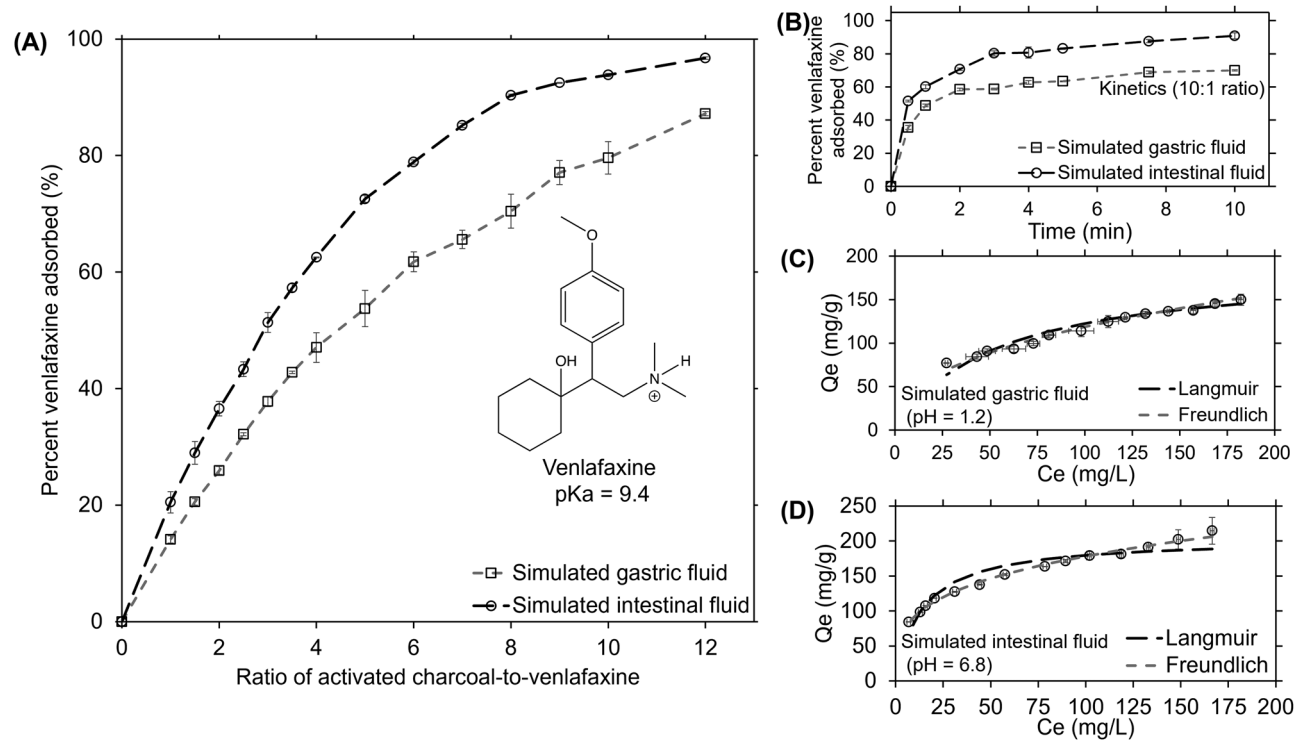

Figure 7. Capacity (A, C, and D) and kinetics (B) data for adsorption of venlafaxine to activated charcoal.

Table 1. Freundlich isotherm fitting constants determined from adsorption isotherm curves in both simulated gastric fluid and simulated intestinal fluid.

	Freundlich isotherm fitting constants			
	n		$K_F\left(\frac{mg}{g}\right)\left(\frac{L}{mg}\right)^{\frac{1}{n}}$	
Drug	Gastric	Intestinal	Gastric	Intestinal
Amitriptyline	5.91	11.15	88.7	338.6
Bupropion	10.11	4.76	89.4	113.1
Minoxidil	8.61	0.25	63.7	54.1
Propranolol	6.48	3.33	103.4	87.2
Venlafaxine	2.44	3.86	18.0	51.8

The favorability of adsorption based on drug concentration is represented by n. The relative adsorption capacity is defined as K_F. Values are derived from experimental data in Figures 3–7 using plots C and D.

Table 2. Langmuir isotherm fitting constants determined from adsorption isotherm curves in both simulated gastric fluid and simulated intestinal fluid. Q_m represents the maximal adsorption capacity. K_L represents the binding affinity of the drug to activated charcoal.

	Langmuir isotherm fitting constants			
	$Q_m\left(\frac{mg}{g}\right)$		$K_L\left(\frac{L}{mg}\right)$	
Drug	Gastric	Intestinal	Gastric	Intestinal
Amitriptyline	175.1	492.6	1.02	5.31
Bupropion	150.9	318.6	0.23	0.17
Minoxidil	118.4	192.6	0.14	0.08
Propranolol	214.9	251.9	0.26	0.50
Venlafaxine	187.1	192.9	0.02	0.08

Values are derived from experimental data in Figures 3–7 using plots C and D.

Table 3. Ratios (weight/weight) of activated charcoal-to-drug to administer for gastrointestinal decontamination determined from adsorption isotherm studies in simulated gastric fluid and simulated intestinal fluid.

	Optimal activated charcoal-to-drug ratios	
	Ratio for ≥95% adsorption	
Drug	Gastric	Intestinal
Amitriptyline	7:1	7:1
Bupropion	>12:1	10:1
Minoxidil	12:1	10:1
Propranolol	7:1	4:1
Venlafaxine	>12:1	12:1

Values are derived from experimental data in Figures 3–7 using plot A.

charcoal-to-drug ratio (Table 3). Exceptions included amitriptyline (≥95% in both media at 7:1), propranolol (≥95% in simulated gastric fluid at 7:1; simulated intestinal fluid at 4:1), minoxidil (≥95% in simulated gastric fluid at 12:1), and venlafaxine (≥95% in simulated intestinal fluid at 12:1, but not in simulated gastric fluid).

Discussion

Our study demonstrates that amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine adsorb effectively to activated charcoal at varying capacities in simulated gastric fluid and simulated intestinal fluid. This confirms prior reports that activated charcoal can reduce systemic absorption of amitriptyline [17]. Our data extends this to bupropion, propranolol, minoxidil,

and venlafaxine, all of which lacked comprehensive data regarding adsorption to activated charcoal. These data are especially important considering the increasing incidence of bupropion overdoses [18,19].

The maximal adsorption capacity of amitriptyline is similar to those reported in past studies, thus validating the methods of our *in vitro* experiments [17,20,21]. One study found the maximal adsorption capacity of activated charcoal to amitriptyline incubated at 37 °C for 15 min in pH 1.3 was 133 mg/g, which was similar to our finding of 175.1 mg/g at pH 1.2 with 20 min of incubation at 37 °C [21]. Another study described higher maximal adsorption capacities using two formulations of activated charcoal with higher surface areas incubated at 37 °C for 60 min. At pH 1.2, the maximal adsorption capacities were 450 mg/g and 660 mg/g, and at pH 7.2, the maximal adsorption capacities were 490 mg/g and 700 mg/g [22]. Longer incubation times, differences in activated charcoal formulation, pH, and differences in the ratios of activated charcoal to amitriptyline likely contributed to the observed differences in maximal adsorption capacities [17]. Our study used 10:1 activated charcoal-to-amitriptyline ratio for our adsorption isotherm studies. Through kinetics studies, we determined that activated charcoal at a 10:1 ratio adsorbed most drugs in simulated gastric fluid and simulated intestinal fluid at ≥95% within 10 min. At lower activated charcoal-to-drug ratios and for certain drugs, longer incubation times may increase experimental maximal adsorption capacities. Clinically, contact time between activated charcoal and drug will be difficult to determine. Drugs that slow gastrointestinal transit time or have propensity to form bezoars may have increased adsorption to activated charcoal [23]. Unfortunately, those clinical situations also increase the risk of activated charcoal harms [14].

Adsorption efficiencies varied across media, with higher maximal adsorption capacities observed in simulated intestinal fluid compared to simulated gastric fluid. The ionization state of a drug is dictated by pKa and local pH and therefore may influence absorption and activated charcoal efficacy. In the stomach (pH 1.2), basic drugs like amitriptyline (pKa ~9.4), bupropion (pKa ~7.9), propranolol (pKa ~9.5), and venlafaxine (pKa ~9.4) are highly ionized and less able to cross biological membranes for systemic absorption [24]. In contrast, in the intestine (pH ~6.8), these drugs become less ionized and are more readily absorbed [24]. The matching of maximal adsorption capacity with drug absorption is important for the therapeutic efficacy of activated charcoal and appears to be true for these basic drugs to decrease systemic absorption. However, the matching of bupropion maximal adsorption capacity with activated charcoal is less optimal. Bupropion has a lower pKa and worse maximal adsorption capacity in simulated gastric fluid. Minoxidil (pKa ~4.6) is similarly mismatched. Thus, larger doses of activated charcoal may be necessary for overdoses of immediate release bupropion and minoxidil to prevent gastric adsorption than the typical 10:1 ratio. Extended-release formulations of medications such as bupropion, venlafaxine, and propranolol may target drug release and absorption in the intestines, where adsorption by activated charcoal is enhanced. Thus, determining optimal activated charcoal dosing strategies for drugs with these characteristics is challenging.

We found that several drugs—including amitriptyline, propranolol, and minoxidil in simulated intestinal fluid—achieved ≥95% adsorption at activated charcoal-to-drug ratios below the conventional 10:1 benchmark. This suggests that standard dosing practices may overestimate the activated charcoal requirement and refining these strategies could reduce the risk of complications such as non-selective adsorption, aspiration, and poor tolerability. However, a 10:1 ratio was not sufficient for all conditions. For example, minoxidil in simulated gastric fluid and venlafaxine in simulated intestinal fluid required a 12:1 ratio for ≥95% adsorption, while venlafaxine and bupropion in simulated gastric fluid did not reach that threshold even at this level, indicating that bupropion and venlafaxine may require higher or additional dosing in certain settings. Yet, our findings are conducted in ideal experimental conditions and may not account for real-world clinical scenarios of polypharmacy overdoses or the presence of other gastric content. Thus, the ideal activated charcoal-to-drug ratio may be an underestimation of the optimal activated charcoal dose.

A single initial 50 g dose of activated charcoal, commonly used in emergency settings, may reduce systemic drug concentrations if administered early. However, overdoses often exceed the adsorptive capacity of the single 50 g dose. Case reports document ingestions as high as 6 g of amitriptyline [25], 28.2 g of bupropion [26], 3 g of minoxidil [27], 8 g of propranolol [28], and 17.5 g of venlafaxine [29]. In these cases, our results show that amitriptyline and propranolol would still be effectively treated with 50 g of activated charcoal, requiring a smaller excess of activated charcoal for complete adsorption. In contrast, a 50 g dose would be insufficient for bupropion, minoxidil, and venlafaxine at higher ingested amounts, as ingested drug amounts exceeded the reported minimum toxic dose. Notably, bupropion required higher activated charcoal-to-drug

ratios to approach full adsorption, especially in both simulated gastric fluid and simulated intestinal fluid. In these situations, additional doses of activated charcoal (ADAC) or other medical interventions may be required to improve patient outcomes [30].

Conclusions

This study provides a detailed evaluation of the adsorption characteristics of activated charcoal for five drugs commonly involved in overdose scenarios. Our findings confirm that amitriptyline, bupropion, minoxidil, propranolol, and venlafaxine are effectively adsorbed by activated charcoal, although maximal adsorption capacities vary between gastric and intestinal conditions based on pH and drug pKa. Importantly, several drugs required higher activated charcoal-to-drug ratios to achieve near-complete adsorption, indicating that conventional dosing guidelines may be insufficient in certain clinical situations. These results emphasize the importance of tailoring activated charcoal administration based on the pharmacologic properties of the ingested drug. Future clinical studies are warranted to further define dosing strategies and evaluate real-world outcomes associated with activated charcoal use in overdose management.

Authors contributions

Hunter Wood was involved with conceptualization, methodology, investigation and writing of the manuscript. Stella Trickett and Joe Dosch were both involved with investigation and writing of the manuscript. Dazhe James Cao and Stefanie Sydlik were both involved with conceptualization, methodology, and writing of the manuscript.

Disclosure statement

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Data availability statement

Data is available upon reasonable request to the corresponding author.

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