



Quantitative models for predicting adsorption of oxytetracycline, ciprofloxacin and sulfamerazine to swine manures with contrasting properties

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HIGHLIGHTS

- Understanding adsorption of antibiotics to swine manures is important in risk assessment.
- OTC and CIP were more likely to accumulate in swine manures compared with SM1.
- The pH, SOC, and SON determined antibiotic adsorption to swine manures.
- The LgK_d prediction models with high Q^2_{cum} , low SDs and Q^2_{ext} were successfully developed.
- These models improve predictability.

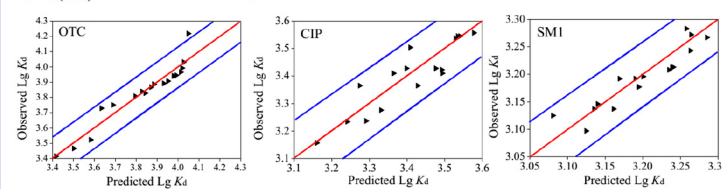
GRAPHICAL ABSTRACT

Quantitative models:

$$LgK_d(OTC) = 5.42 - 2.25 \times 10^{-1} pH - 7.81 \times 10^{-3} SOC + 6.58 \times 10^{-2} SON - 1.90 \times 10^{-3} Ca$$

$$LgK_d(CIP) = 4.39 - 1.28 \times 10^{-1} pH - 6.38 \times 10^{-3} SOC + 1.63 \times 10^{-2} SON$$

$$LgK_d(SM1) = 3.65 - 5.76 \times 10^{-2} pH + 4.42 \times 10^{-3} TON - 3.48 \times 10^{-3} SOC$$



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ABSTRACT

Understanding antibiotic adsorption in livestock manures is crucial to assess the fate and risk of antibiotics in the environment. In this study, three quantitative models developed with swine manure–water distribution coefficients (LgK_d) for oxytetracycline (OTC), ciprofloxacin (CIP) and sulfamerazine (SM1) in swine manures. Physicochemical parameters ($n = 12$) of the swine manure were used as independent variables using partial least-squares (PLSs) analysis. The cumulative cross-validated regression coefficients (Q^2_{cum}) values, standard deviations (SDs) and external validation coefficient (Q^2_{ext}) ranged from 0.761 to 0.868, 0.027 to 0.064, and 0.743 to 0.827 for the three models; as such, internal and external predictability of the models were strong. The pH, soluble organic carbon (SOC) and nitrogen (SON), and Ca were important explanatory variables for the OTC-Model, pH, SOC, and SON for the CIP-model, and pH, total organic nitrogen (TON), and SOC for the SM1-model. The high VIPs (variable importance in the projections) of pH (1.178–1.396), SOC (0.968–1.034), and SON (0.822 and 0.865) established these physicochemical parameters as likely being dominant (associatively) in affecting transport of antibiotics in swine manures.

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1. Introduction

Globally, antibiotics are still extensively used to treat human and animal diseases (Knapp et al., 2010). Antibiotics are also widely used as a

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supplement into animal feed to increase production and reduce diseases, particularly in intensively farmed systems (Ogle, 2013). However, the majority of commonly used antibiotics are not entirely metabolized in the body of livestock. Indeed, about 30–90% of antibiotics used enter the natural environment through application of livestock or poultry manure that containing un-metabolized antibiotics (Sarmah et al., 2006).

The most widely detected antibiotics in manures are tetracycline's (TCs), fluoroquinolones (FQs), and sulfonamides (SAs) (Aust et al., 2008; Dolliver et al., 2008; Hu et al., 2010; Hua et al., 2017; Li et al., 2013). These antibiotics can be transferred into soils following manure application, and eventually into aquatic environments causing surface and ground water pollution (Bailey et al., 2016; Sukul et al., 2008; Zhang et al., 2014). As such, it is crucial to better understand both the adsorption of antibiotics on livestock manure and partitioning of antibiotics between manure and other medium for the purpose of effective mitigation or elimination of residual antibiotics in the environment.

Once entering the soil environment, the adsorption behaviors of antibiotics in manures significantly impact on whether the antibiotics are retained in the manure matrix or mobilized to soils and receiving environments (Sukul et al., 2008), and the degree of partitioning between manure and aqueous phases is often regarded as a key indicator of their environmental fate (Berthod et al., 2016). The partitioning of an antibiotic between these two phases is described by the distribution coefficient (K_d), which is defined as the ratio of the equilibrium concentrations of the substance in the manure and aqueous phases (Gschwend and Wu, 1985):

$$K_d \left(\text{L kg}^{-1} \right) = \frac{C_{\text{manure}}}{C_{\text{aqueous}}} \quad (1.1)$$

The adsorption behaviors of antibiotics in manures depend on not only the chemical structure of antibiotics (Wang and Zhang, 2011) but also the physicochemical characteristics of manures and the interactions that result (Wang et al., 2008; Wei et al., 2010). The K_d values, presented in the literatures strongly suggest that for many antibiotics the tendency to adsorb to soil, sediment and sewage sludge cannot be predicted from their lipophilicity alone (Jia et al., 2012; Srinivasan, 2013; Xu and Li, 2010). This result may be contributed to the specific chemical structure of an antibiotic (i.e., its functional groups) that can bind metal ions and form hydrogen bonds, which has to be considered carefully at the relevant pH value. For example, the chlortetracycline (CTC) and tylosin adsorbed on manure decreased with an increase of pH (Singh, 2016; Wang et al., 2008). Furthermore, the antibiotic adsorption is significantly affected by physicochemical parameters of solid phase (such as organic matter content and metal ion concentrations) (Liu et al., 2012; Vaz, 2016). Loke et al. (2002) found that the adsorption of OTC to swine manure is influenced by ionic binding to divalent metal ions like Mg^{2+} and Ca^{2+} as well as other charged compounds in the matrix. The presence of dissolved organic matter (DOM) also obviously inhibited the adsorption of CTC on swine manure (Wei et al., 2010). Furthermore, the number of effective adsorption sites as well as the specific surface area of the manure influences the degree of adsorption. Despite this knowledge, very little research has been conducted to determine the K_d values of antibiotics in manures. As these analyses are time consuming and expensive, the development of an effective quantitative estimation model that can predict the manure-water K_d of various antibiotics would be of considerable importance.

The current studies of the development of quantitative estimation models to predict the K_d of antibiotics mainly focus on soil-based systems. For instance, multi-species models, such as cationic, neutral/zwiterion and anionic models, were developed to predict the adsorption coefficients of antibiotics, including SAs and TCs, at different pH conditions in soils and other major components of soils, such as clays and goethite (Figuerola et al., 2004; Guo et al., 2016; Lertpaitoonpan et al., 2009; Vithanage et al., 2014). Based on these, effects of organic carbon were also taken into account in the quantitative estimation models for

predicting the K_d of antibiotics in five soils (Lertpaitoonpan et al., 2009). However, these models could not accurately evaluate the adsorption potentials of antibiotics. Subsequently, Gong et al. (2012) successfully constructed three models that incorporated the 14 physicochemical parameters of 23 Chinese soils, which were able to predict the K_d values between soil and water of 3 antibiotics. Hence, it is imperative to include physicochemical parameters in the model development as independent variables to quantify the adsorption potentials of antibiotics in manures.

In this study, it was hypothesized that livestock manures would have strong binding potential with antibiotics, and manures with different physicochemical properties would generate different adsorption potentials. Therefore, the major objectives of this study were: (1) to determine the swine manure-water distribution coefficients (K_d) of three typical veterinary antibiotics (Fig. 1), (2) to develop the quantitative models between the physicochemical properties of swine manures and the $\text{Lg}K_d$ using the PLSs, and (3) to explain the reaction mechanisms between antibiotic and swine manure based on the developed models.

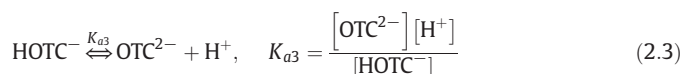
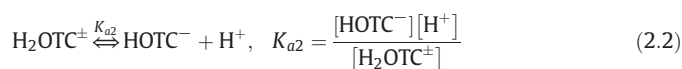
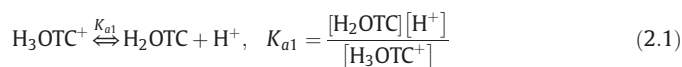
2. Materials and methods

2.1. Reagents and chemicals

OTC, CIP, and SM1 were obtained from Dr. Ehrenstorfer GmbH (Augsburg, Germany). The chemical structures and ionization schemes of these three antibiotics are listed in Fig. 1. The isotope internal standards of norfloxacin-d5, sulfadiazine-d4, and tetracycline-d6 were purchased from WITEGA Laboratories (Berlin, Germany), CDN isotopes (Pointe-Claire, Quebec, Canada) and TRC (Toronto, Canada), respectively. Methanol (MeOH) and acetonitrile (ACN) (HPLC grade) were acquired from Fisher Science Co. Single standard stock solutions of OTC, CIP, or SM1 were prepared in mixed solution of $0.01 \text{ mol L}^{-1} \text{ CaCl}_2$ and $0.01 \text{ mol L}^{-1} \text{ NaN}_3$ (as inhibitors of microbial activity), and stored in the dark at 4°C . The Milli-Q water was used when ultrapure water was required.

2.2. Test model antibiotics

Three antibiotics belonging to three antibiotic classes, including tetracyclines (TCs), sulfonamides (SAs) and fluoroquinolones (FQs), were chosen for our study because of their wide use and the highest detected concentrations from different regions in China reached as high as $10\text{--}354 \text{ mg kg}^{-1}$ in swine manure (Chen et al., 2012; Hou et al., 2015; Wang et al., 2017). The pH of the solution should be considered to be an important factor affecting the adsorbate adsorption process due to its impact on the degree of ionization of pollutant species (Soori et al., 2016). Depending on the solvent pH, three antibiotics exhibit complex ionization patterns because of multiple ionizing groups with different $\text{p}K_a$ values (Eqs. 2.1–2.3) (Fig. 1). For example, three ionic equations that were described as the acid-base dissociation reactions with four species (H_3OTC^+ , H_2OTC^\pm , HOTC^- , OTC^{2-}) of OTC are proposed as follows:



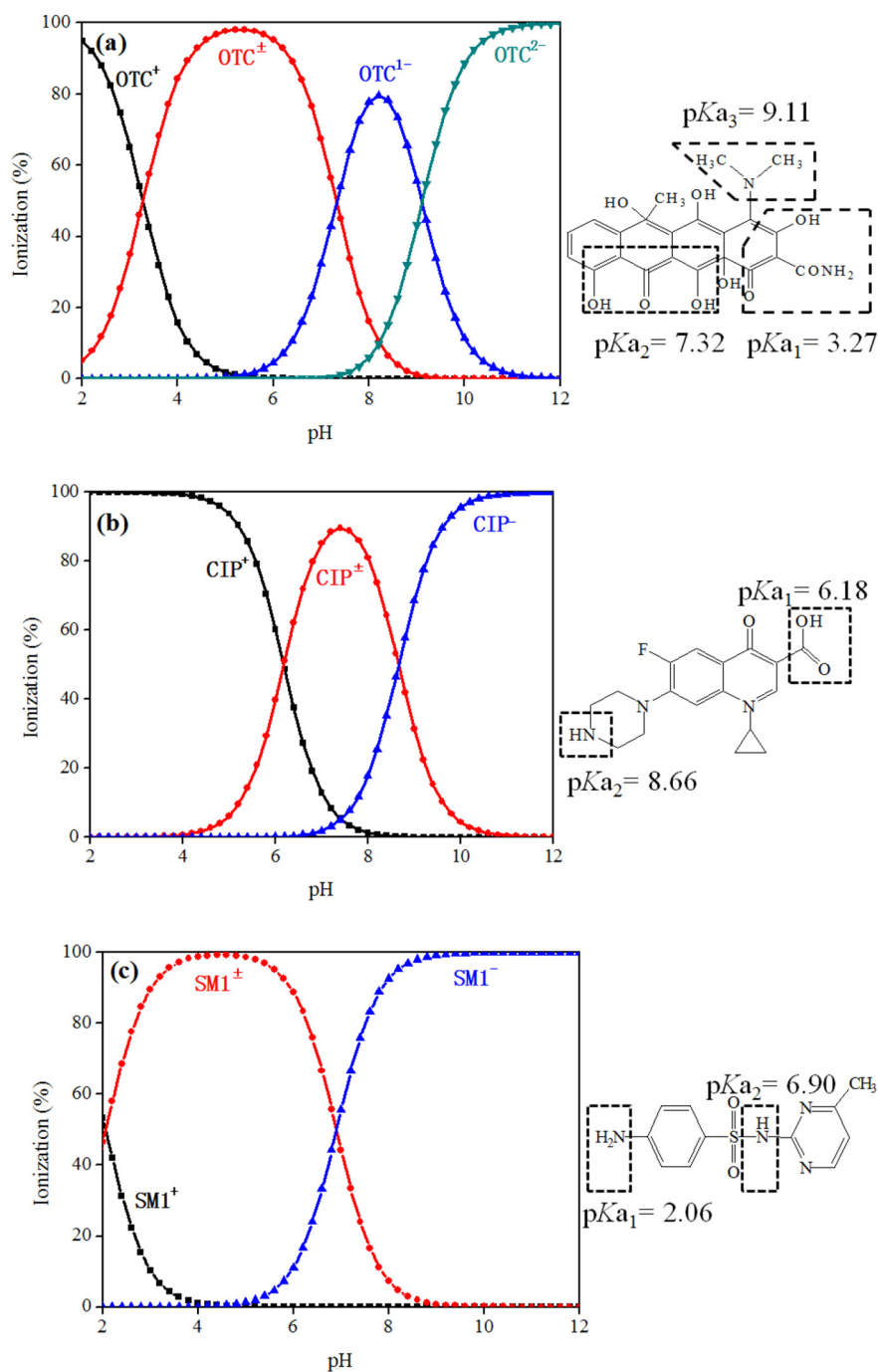


Fig. 1. Structures and ionization schemes of (a) OTC, (b) CIP, and (c) SM1.

The percentage of each ionic species of OTC can be obtained using Eqs. 2.4–2.7 and is presented as follows:

$$\alpha_{[\text{H}_3\text{OTC}^+] }(\%) = \frac{[\text{H}^+]^3}{[\text{H}^+]^3 + K_{a1}[\text{H}^+]^2 + [\text{H}^+]K_{a1}K_{a2} + K_{a1}K_{a2}K_{a3}} \times 100 \quad (2.4)$$

$$\alpha_{[\text{H}_2\text{OTC}^+] }(\%) = \frac{K_{a1}[\text{H}^+]^2}{[\text{H}^+]^3 + K_{a1}[\text{H}^+]^2 + [\text{H}^+]K_{a1}K_{a2} + K_{a1}K_{a2}K_{a3}} \times 100 \quad (2.5)$$

$$\alpha_{[\text{HOTC}^-] }(\%) = \frac{[\text{H}^+]K_{a1}K_{a2}}{[\text{H}^+]^3 + K_{a1}[\text{H}^+]^2 + [\text{H}^+]K_{a1}K_{a2} + K_{a1}K_{a2}K_{a3}} \times 100 \quad (2.6)$$

$$\alpha_{[\text{OTC}^{2-}] }(\%) = \frac{K_{a1}K_{a2}K_{a3}}{[\text{H}^+]^3 + K_{a1}[\text{H}^+]^2 + [\text{H}^+]K_{a1}K_{a2} + K_{a1}K_{a2}K_{a3}} \times 100 \quad (2.7)$$

According to the Eqs. 2.4–2.7, the ionization scheme of OTC as a function of bulk solution pH was drawn (Fig. 1a). In the same way, the ionization schemes of CIP and SM1 were also drawn (Fig. 1b–c). OTC and CIP exist predominantly as cations at pH values < pK_{a1} , zwitterions at pH values between pK_{a1} and pK_{a2} , and as anions at pH values > pK_{a2} .

SM1 speciation changes from cationic $< pK_{a1}$, to neutral between pK_{a1} and pK_{a2} , and anionic $> pK_{a2}$ (Figueroa-Diva, 2012).

2.3. Manure collection and analysis

Twenty-four swine manures representing three different types of pigs (gestation, weaning and fattening pigs) were selected from among many pretested samples that were collected from intensive pig farms in six districts of Beijing; Fangshan, Huairou, Shunyi, Tongzhou, Daxing and Yanqing. The concentrations of OTC, CIP, and SM1 in those 24 swine manure samples were not detected or below the method detection limit (MDL) according to the method of Ho et al. (2013). The fresh manure samples were air-dried (15–20 °C), mixed, crushed, and sieved through a 0.85-mm mesh. The samples were then analyzed for the twelve physicochemical properties (Table S1). The pH of the samples was analyzed in 1:10 (w/v) manure:salt (0.01 mol L⁻¹ CaCl₂) suspension using a pH meter. Total organic carbon (TOC) and nitrogen (TON) were determined using a TOC Analyzer (Shimadzu TOC-VCPH/CPN, Japan) according to Endale et al. (2017). The soluble organic carbon (SOC) and nitrogen (SON) extracted in 1:10 (w/v) manure:water slurry were similarly determined by TOC analyzer. Free iron oxides (DCB-Fe) and aluminum oxides (DCB-Al) were extracted from the swine manure by sodium dithionite-citrate-bicarbonate (DCB) and determined by ICP-OES (Spectro Arcos, Germany) (Townsend, 1971). The concentrations of K, Na, Ca, and Mg in manures were extracted with 0.1 mol L⁻¹ BaCl₂ and analyzed by ICP-OES. The CECs of the swine manure samples (1.0 g) were measured by the BaCl₂ compulsive exchange method (Gillman and Sumpter, 1986).

2.4. Adsorption experiments

The adsorption of antibiotics was studied in batch experiments according to OECD Guideline 106 (OECD, 2000). An aqueous solution containing 0.01 mol L⁻¹ CaCl₂ was used to simulate a natural ionic strength condition of soil solution, while 0.01 mol L⁻¹ NaN₃ was used as an inhibitor of biological activity. The optimum adsorption conditions, such as initial pH, temperature and equilibration times for various manure/solution ratios were determined. Each 50 mL glass centrifuge tube contained 25.0 mL solution. Under optimal conditions, the adsorption isotherms of OTC, CIP, and SM1 were investigated using a series of initial concentrations with a shaking period of 48 h at 250 rpm and 25 ± 2 °C in the dark, which was sufficient to reach the apparent equilibrium. All experiments were determined in duplicate. Two blanks (no swine manure) at each initial concentration were run.

At the end of each shaking operation, the suspension was centrifuged for 10 min at 6000 rpm. The supernatants were filtered through 0.22 µm filter and quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS) for each target antibiotic.

2.5. Determination of antibiotics

Determination of targeted antibiotics in samples was performed using an Agilent 1200 series HPLC, equipped with an Agilent 6410 Triple Quadrupole mass spectrometer and electrospray ionization source (Agilent Technologies, USA). Samples were separated on a Sunfire C18 column (3.5 µm, 150 mm × 4.6 mm, Waters, USA). HPLC conditions were set at 40 °C, 0.4 mL min⁻¹ and 5 µL for the column temperature, flow rate, and injection volume, respectively. The mobile phase consisted of solvent A (0.1% formic acid in ultrapure water) and solvent B (ACN). A linear gradient elution was conducted as follows: 0 min, 8% B; 0–12 min, linear increase to 55% B; 12–13 min, linear decrease to 8% B; 13–16 min, 8% B.

Mass spectrometric detection was performed in the positive ion and multiple reactions monitoring (MRM) mode, and the optimized parameters are listed in Table S2. To determine the concentrations of the target compounds, internal standards were used on the basis of the relative

response factors (RRFs) (Cheng et al., 2017). Norfloxacin-d5, sulfadiazine-d4, and tetracycline-d6 were selected as the internal standards of CIP, SM1, and OTC, respectively. The limit of detection (LOD) was defined as a signal-to-noise (S/N) ratio greater than three.

2.6. Calculations and model development

The concentration of targeted antibiotic in the swine manure was calculated by subtracting the value obtained from the blank and the treatment as described by (Gong et al., 2012):

$$C_{man.} = \frac{(C_b - C_{aq}) \times V_{aq}}{m_{man.}} \quad (2.8)$$

where $C_{man.}$ (mg kg⁻¹) is the antibiotic concentration in manure, C_{aq} (mg L⁻¹) is the equilibrium antibiotic concentration in aqueous solution, C_b (mg L⁻¹) is the equilibrium antibiotic concentration in blank, V_{aq} (L) is the volume of aqueous solution, and $m_{man.}$ (kg) is the dry mass of swine manure.

The pilot experiment results showed that adsorption isotherms of targeted antibiotics fitted best to the Freundlich model (Eq. 2.9), with a broad range of antibiotic concentrations (reached high concentration levels that could not be detected in the actual environment) and presented non-linear isotherms.

$$\text{Lg}C_{man.} = \text{Lg}K_F + \frac{1}{n} \text{Lg}C_{aq} \quad (2.9)$$

where K_F (intercept on Y-axis) is the Freundlich adsorptions coefficient and $1/n$ (slope) is the Freundlich exponent calculated from the linear regression. For $1/n = 1$, the Eq. 2.9 is converted to the linear distribution Eq. 1.1. Appearing a broad range of concentrations in the adsorption isotherm stressed the behavioral trends and multi-mechanisms of adsorption of the selected contaminants. Upon restricting the isotherms to relatively low levels of concentration, the linear equation is obtained within $n \sim 1$, which the isotherms come near to linearity and the K_d values tend towards a constant value (Radian et al., 2015). For this reason, the initial concentrations of antibiotics are fairly lower than the highest initial levels of concentration used in this study, which the isotherms of antibiotic adsorptions mainly fell in the linear ranges (Figs. S1–S3). Therefore, the K_d values determined in the linear isotherm are more suited to the natural situations (Guo et al., 2014).

As shown in Table S1, the entire set of swine manures was randomly divided into two subsets, a training set of 18 samples (75%) and a test set of 6 samples (25%) (Fu et al., 2016). The training set was used to develop models. The test set was used to evaluate the performance of the different models. The PLS method using the Simca 13.0 software (Umetrics, Umea, Sweden) was applied to the regressions for the prediction models of $\text{Lg}K_d$ across the multiple physicochemical parameters (Gong et al., 2012). The variable importance in the projection (VIP) of the PLS is an important parameter that represents the influence of each physicochemical variable of the swine manure (X-axis of the data matrix) on the $\text{Lg}K_d$ (Y-axis of the results matrix) so that those parameters with a larger VIP (>1) have an above average influence on the results of model. Therefore, those parameters also are the closest factors that explain the $\text{Lg}K_d$. The robustness and predictive power of models were mainly evaluated by the following indicators: the cumulative R^2_X up to the specified component ($R^2_{X(cum)}$), the cumulative R^2_Y up to the specified component ($R^2_{Y(cum)}$), the principal component numbers in PLS (A), the number of X variables times R^2_X (Eigenvalue), the cumulative cross-validated regression coefficient (Q^2_{cum}), the standard deviation (SD), the correlation coefficient between observed and predicted values (R^2), and the significance level (P). In general, if Q^2_{cum} larger than 0.5 were obtained, the model was generally accepted. All these indicators could be automatically generated in software except the SD;

this was calculated as:

$$SD = \sqrt{\frac{1}{n_{tr}-A-1} \sum_{i=1}^{n_{tr}} [\text{Lg}K_d(\text{obs.})_i - \text{Lg}K_d(\text{pred.})_i]^2} \quad (2.10)$$

where $K_d(\text{obs.})_i$ was the observed value for i th sample from the training set, $K_d(\text{pred.})_i$ was the predicted value for i th sample from the training set, n_{tr} was the dependent variable number of the training set samples; A was the principal component numbers.

The reliability of models was measured on the test set based on the external validation coefficient (Q^2_{ext}) (Guan and Liu, 2018), which was calculated as follows:

$$Q^2_{ext} = 1 - \frac{\sum_{i=1}^{n_{ext}} [\text{Lg}K_d(\text{obs.})_i - \text{Lg}K_d(\text{pred.})_i]^2}{\sum_{i=1}^{n_{ext}} [\text{Lg}K_d(\text{obs.})_i - \text{Lg}K_d(\text{obs.})_{tr}^{ave}]^2} \quad (2.11)$$

where $K_d(\text{obs.})_i$ was the observed value for i th sample from the test set, $K_d(\text{pred.})_i$ was the predicted value for i th sample from the test set, n_{ext} was the dependent variable number of the test set samples; $\text{Lg}K_d(\text{obs.})_{tr}^{ave}$ was the averaged value of $\text{Lg}K_d(\text{obs.})$ for the entire training set.

3. Results and discussion

3.1. Characteristics of swine manures

The physicochemical properties of different swine manures varied considerably (Table S1). The pH of swine manures ranged from 5.86 to 8.31. Obviously, the TOC and SOC content varied from 35.89 to 44.46% and 8.0 to 31.1%, respectively, confirming that the organic elements were extremely rich in swine manures. These results were caused by the undigested feeds (e.g., forage, lipids, and proteins) for those swine manures (Tsai et al., 2012). On the other hand, the TON and SON contents ranged from 2.51 to 4.13% and 0.46 to 2.54%, respectively, that were relatively higher than those in the crop and forestry residues (Pasangulapati et al., 2012). This may contribute to the high protein content, which are dependent on the dietary feeds, swine species and breeding regions, and so on.

As also shown in Table S1, the main inorganic elements included Ca, Mg, Na and K in the swine manures. This result suggested that the swine manures should be moderately suitable for composting (Tsai et al., 2012). These elements could be present in oxide, carbonate forms or metal complexes with organic matter. These data suggest that swine manures can be directly reused as a soil fertilizer with high macronutrients in N, Ca, K and Mg, and micronutrients in Fe without considering other risk factors (Hillel and Hatfield, 2004).

The composition of swine manure depends on two aspects: the intestinal function and health of animal and the physical, chemical and biological properties of feed (Hanni et al., 2003). For example, manure 9 collected from weaning pig manure was high concentrations of TON, K and Mg, medium concentration of CEC, which could be due to high supplementation rates of crude protein and lysine in the weaner diets (Mendoza-Huaitalla et al., 2011). Conversely, manure 17 collected from fattening pig manure was low concentrations of TON, BCD-Fe, Na, Ca and CEC. Manure 18 collected from gestation pig manure was high concentrations of CEC, BCD-Fe, Na and Ca that could be due to a lot of added trace elements to feed of gestation pig. Moreover, compared with soil, the concentrations of macronutrients, including C, N and K, increased significantly in pig manure samples (Dong et al., 2014; Gong et al., 2012). However, the concentrations of micronutrients such as DCB-Fe and DCB-Al were relatively similar in pig manures (Ngole-Jeme and Ekosse, 2015).

3.2. Manure-water distribution coefficients of three antibiotics

As the adsorption behavior of antibiotics in livestock manure is the primary factor affecting mobilization and transformation into the wider environment, determination of K_d values between the swine manure and water phases are critically important. The observed values of K_d for the three antibiotics in 24 swine manures are summarized in Table 1.

The observed K_d values of three antibiotics in 24 swine manures varied greatly. The K_d values ranged from 2600 to 16,520 L kg⁻¹ for OTC, 1435 to 4550 L kg⁻¹ for CIP, and 1250 to 2193 L kg⁻¹ for SM1 (Table 1). For OTC, these values and ranges were close to reported data (8766–10,642 L kg⁻¹) (Wang and Zhang, 2011). To the best of our knowledge, the K_d values of CIP and SM1 in swine manures have not been reported previously. The relative standard deviations (RSD) of those K_d values for OTC, CIP, and SM1 in swine manures were 38, 30, and 15%, respectively. These results indicated that variation in manure properties had a very significant effect on the antibiotic adsorption.

The gradient disparities in the K_d values of different antibiotics were evident. For example, the K_d values of OTC, CIP, and SM1 in swine manure 4 were 9817 L kg⁻¹, 4111 L kg⁻¹ and 1849 L kg⁻¹, respectively. In swine manure 13, the K_d values of OTC, CIP, and SM1 were 16,520 L kg⁻¹, 4550 L kg⁻¹ and 2193 L kg⁻¹, respectively. This result further proved that the adsorption capacity of a manure varied considerably among the different types of antibiotics, such as OTC, CIP, and SM1. The higher K_d values of OTC and CIP suggested that those two types of antibiotics were highly likely to accumulate on the swine manures. In contrast, SM1 had relatively weak binding potential within the manure. These results also caused the varying degradation rates of these three groups of antibiotics during manure composting (Pan and Chu, 2016; Selvam et al., 2012). Due to the strong adsorption, the bioavailability of OTC and CIP decreased with increasing their contact time with the manure (Pan and Chu, 2016). In addition, the adsorption reactions and diffusion of antibiotics into micro- or even nano-pores of manures that were too narrow for microorganisms temporarily prevented OTC and CIP away from biological degradation or uptake (Förster et al., 2009; Ge et al., 2015; Jechalke et al., 2014). This prolongs the residence of OTC and CIP in the manure through a transient storage form that is not bioavailable. The weak interactions of SMs with manures indicated the relatively high mobility potential of this antibiotic to the soil, and likely groundwater, through use of animal manure as fertilizers (Domínguez et al., 2014).

3.3. PLS models of the $\text{Lg}K_d$ of antibiotics

The development of prediction models in this study utilized observed $\text{Lg}K_d$ values of OTC, CIP, and SM1 along with the 12 physicochemical parameters of the swine manure within a PLS regression framework. During analysis of PLS, the interconnected descriptors introduced in a model could result in inferior prediction. Therefore, it was essential to exclude interconnected descriptors and selected the most superior model. The VIP value was defined to indicate the importance of an independent variable to a model. The variable with the smallest value of VIP was most interconnected to the $\text{Lg}K_d$. Thus, this variable should be deleted during the development of next model. Using this process, many models were generated, but only the edition with the highest $R^2_{y(\text{cum})}$ and Q^2_{cum} was selected as the optimal model. The OTC-, CIP-, and SM1-models were determined as follows:

$$\text{Lg}K_d(\text{OTC}) = 5.42 - 2.25 \times 10^{-1} \text{pH} - 7.81 \times 10^{-3} \text{SOC} + 6.58 \times 10^{-2} \text{SON} - 1.90 \times 10^{-3} \text{Ca} \quad (3.1)$$

$$\text{Lg}K_d(\text{CIP}) = 4.39 - 1.28 \times 10^{-1} \text{pH} - 6.38 \times 10^{-3} \text{SOC} + 1.63 \times 10^{-2} \text{SON} \quad (3.2)$$

Table 1The observed and predicted $\text{Lg}K_d$ of oxytetracycline (OTC), ciprofloxacin (CIP) and sulfamerazine (SM1) in 24 swine manures.

No.	Obs. ^a K_d (L kg^{-1})			$\text{Lg}K_d$ (L kg^{-1})								
	OTC	CIP	SM1	OTC			CIP			SM1		
				Obs.	Pred. ^b	Res. ^c	Obs.	Pred.	Res.	Obs.	Pred.	Res.
1	2924	1714	1250	3.466	3.502	-0.036	3.234	3.241	-0.007	3.097	3.125	-0.028
2	7798	2649	1633	3.892	3.931	-0.039	3.423	3.492	-0.069	3.213	3.240	-0.027
3	2600	1435	1334	3.415	3.416	-0.001	3.157	3.160	-0.003	3.125	3.081	0.044
4	9817	4111	1849	3.992	4.019	-0.027	3.614	3.571	0.043	3.267	3.285	-0.018
5	7691	2679	1614	3.886	3.884	0.002	3.428	3.476	-0.048	3.208	3.235	-0.027
6	6887	2679	1556	3.838	3.828	0.010	3.428	3.398	0.030	3.192	3.190	0.002
7	9247	3508	1871	3.966	4.013	-0.047	3.545	3.541	0.004	3.272	3.264	0.008
8	10,740	3606	2080	4.031	4.027	0.004	3.557	3.577	-0.020	3.318	3.287	0.031
9	6730	3192	1503	3.828	3.843	-0.015	3.504	3.408	0.096	3.177	3.195	-0.018
10	5358	1726	1400	3.729	3.633	0.096	3.237	3.291	-0.054	3.146	3.140	0.006
11	3334	2317	1371	3.523	3.582	-0.059	3.365	3.274	0.091	3.137	3.135	0.002
12	8072	2570	1633	3.907	3.952	-0.045	3.410	3.493	-0.083	3.213	3.239	-0.026
13	16,520	4550	2193	4.218	4.049	0.169	3.658	3.585	0.073	3.341	3.290	0.051
14	5636	1888	1371	3.751	3.689	0.062	3.276	3.330	-0.054	3.137	3.161	-0.024
15	6427	2570	1556	3.808	3.795	0.013	3.410	3.364	0.046	3.192	3.169	0.023
16	8810	3443	1919	3.945	3.992	-0.047	3.537	3.529	0.008	3.283	3.258	0.025
17	8750	3508	1750	3.942	3.978	-0.036	3.545	3.534	0.011	3.243	3.263	-0.020
18	7362	2317	1570	3.867	3.871	-0.004	3.365	3.428	-0.063	3.196	3.200	-0.004
19 ^d	5649	1849	1400	3.752	3.717	0.035	3.267	3.348	-0.081	3.146	3.172	-0.026
20 ^d	7379	4111	1738	3.868	3.869	-0.001	3.614	3.417	0.197	3.24	3.199	0.041
21 ^d	6209	2056	1445	3.793	3.808	-0.015	3.313	3.416	-0.103	3.16	3.206	-0.046
22 ^d	7870	2931	1596	3.896	3.941	-0.045	3.467	3.455	0.012	3.203	3.213	-0.010
23 ^d	8650	3192	1626	3.937	3.964	-0.027	3.504	3.520	-0.016	3.211	3.259	-0.048
24 ^d	7798	2612	1849	3.892	3.948	-0.056	3.417	3.512	-0.095	3.267	3.258	0.009

^a Obs. is the observed value.^b Pred. is the predicted value.^c Res. is the residual value between the observed value and predicted value.^d Test set.

$$\text{Lg}K_{d(\text{SM1})} = 3.65 - 5.76 \times 10^{-2} \text{pH} + 4.42 \times 10^{-3} \text{TON} - 3.48 \times 10^{-3} \text{SOC} \quad (3.3)$$

For the OTC-model (Eq. 3.1), four descriptors including pH, SOC, SON, and Ca were important. However, there were three key descriptors for both the CIP- (i.e. pH, SOC, and SON) (Eq. 3.2) and SM1-models (pH, SOC, and TON) (Eq. 3.3). The VIP values and other model parameters for those three models were listed in Table 2.

In the OTC-model, $R^2_{X(\text{cum})}$ and $R^2_{Y(\text{cum})}$, which represented the cumulative proportion of all the physicochemical parameters and the $\text{Lg}K_d$ values, respectively, could be explained by selected principal components (PCs). As shown in Table 2, three effective PCs were selected in the OTC-model, which can explain the 97.3% and 91.8% variance of X- and Y-axis, respectively. The Q^2_{cum} was 0.868, much higher than 0.5 threshold for a useful model prediction. Similarly, the CIP- and SM1-models were also supported by high Q^2_{cum} values: 0.761 and 0.822, respectively. The three models yielded the low SD values, ranging from

0.027 to 0.064. These results revealed the good internal predictability of the three models. In addition, The Q^2_{ext} of OTC, CIP and SM1 were 0.822, 0.743 and 0.827, respectively, which also indicated a good external predictability of those models (Eqs. 3.1–3.3).

To assess the importance of each physicochemical parameter within each model, VIP values were summarized (Table 2). In PLS analysis, if an independent variable has a large VIP value (especially larger than or close to 1), it will be the most relevant factor to explain variance. The VIP values of pH (1.396), SOC (1.018) and SON (0.865) in the OTC-model were large, suggesting the variance in these three factors across the samples best explaining the model. Likewise, pH and SOC played the most important roles in both the CIP-model and the SM1-model (Table 2).

As shown in Table 1, the values of $\text{Lg}K_d$ for 18 swine manures were predicted on the base of three models. These values were uniform with the corresponding observed $\text{Lg}K_d$ values due to the low residual values that were the difference between the observed and predicted

Table 2

Statistic parameters of OTC-Model, CIP-Model, and SM1-Model.

Model	$R^2_{X(\text{cum})}$ ^a	$R^2_{Y(\text{cum})}$ ^b	A ^c	Eig. ^d	Q^2_{cum} ^e	R^{2f}	SD ^g	P ^h	VIP ⁱ					Q^2_{ext} ^j
									pH	TON	SOC	SON	Ca	
OTC-Model	0.973	0.918	3	2.42/0.935/0.542	0.868	0.912	0.064	4.37E-10	1.396		1.018	0.865	0.515	0.822
CIP-Model	0.964	0.841	2	2.37/0.519	0.761	0.831	0.059	8.67E-8	1.178		0.968	0.822		0.743
SM1-Model	0.964	0.856	2	2.07/0.817	0.822	0.847	0.027	3.79E-8	1.239	0.629	1.034			0.827

^a $R^2_{X(\text{cum})}$ is the cumulative R^2_X up to the specified component.^b $R^2_{Y(\text{cum})}$ is the cumulative R^2_Y up to the specified component.^c A is the number of PLS principal components.^d Eigenvalue is the number of X variables times R^2_X .^e Q^2_{cum} is the cumulative cross-validated regression coefficient.^f R is the correlation coefficient between observed values and fitted values.^g SD is the standard deviation.^h P is the significance level.ⁱ VIP is variable importance in the projection.^j Q^2_{ext} is external validation coefficient.

$\text{Lg}K_d$ values. The variation of residual values ranged from -0.059 to 0.169 , -0.083 to 0.096 and 0.07 to -0.028 to 0.051 for OTC, CIP and SM1, respectively.

Based on the three models, the plots of the observed against predicted $\text{Lg}K_d$ values of OTC, CIP, SM1 in different swine manure samples were generated as Fig. 2. Both observed and predicted values of $\text{Lg}K_d$ for OTC, CIP and SM1 gathered round the 1:1 line, illustrating that the three models were capable of predicting the data for these scenarios fairly well. The high R^2 values ($R^2 \geq 0.831$) and low P values ($P \leq$

$3.79\text{E}-08$) (Table 2) also indicated that three models were accurate and thereby may be used to predict the $\text{Lg}K_d$ values in other swine manures after some validation. As shown in Fig. S4, which include the residual plots for OTC, CIP and SM1 respectively, we found that all the residual values of three models were in the range of ± 2 SD. This also demonstrated that the prediction models of three target compounds were very convenient and precise.

3.4. Adsorption mechanisms of three antibiotics in swine manures

As shown in Table 2, the VIPs of pH for OTC, CIP and SM1 models were 1.396, 1.178 and 1.239, respectively; these were the largest values among all of explanatory variables assessed. These results suggested that pH played a vital role in the distribution of three antibiotics between swine manure and water. The negative coefficient of pH (-2.25×10^{-1} , OTC; -1.28×10^{-1} CIP; -5.76×10^{-2} , SM1) in models (Eqs. 3.1–3.3) indicated that OTC, CIP, and SM1 tended to be enriched into the swine manures at low pH and the adsorption amount of three antibiotics could decrease with the rising of pH in swine manure suspensions.

As seen in Fig. 1a, the predominant species of OTC changed from H_3OTC^+ or H_2OTC^\pm ($pK_{a2} = 7.32 > \text{pH} > pK_{a1} = 3.27$) to HOTC^- ($\text{pH} > pK_{a2} = 7.32$) with increasing pH from 5.86 to 8.31, which decreased the adsorption of OTC in swine manures. Similarly, the predominant species of CIP changed from CIP^+ and CIP^\pm ($6.18 < \text{pH} < 8.66$) to CIP^- ($\text{pH} > 8.66$) with increasing pH from 5.86 to 8.31, while the predominant species of SM1 changed from SM1^\pm ($6.90 > \text{pH} > 2.06$) to SM1^- ($\text{pH} > 6.90$) (Fig. 1b–c). Increased pH also led to a decrease of adsorbed CIP and SM1 in swine manures.

Under alkaline or strong acidic ($\text{pH} \leq 5.5$) conditions, the lower adsorption of antibiotics may be ascribed to the electrostatic repulsion between the anionic species and the colloids of swine manures that were charged more negatively on the surface (Fei et al., 2006; Jian et al., 2016; Sassman and Lee, 2005). With declining pH, the predominant species of antibiotics gradually transition into cations, and electrostatic attraction may be a major influence on antibiotic adsorption. However, throughout the range of pH changes (5.86–8.31), the target compounds (OTC, CIP and SM1) predominantly existed as zwitterions rather than cationic species (Fig. 1). Therefore, the adsorption mechanism of those three antibiotics is more likely to be a surface complexation reaction rather than electrostatic attraction. In addition, the dependence of the antibiotic adsorption on pH also indicates that the adsorption mechanism of antibiotics in swine manures contains cation exchange. This result is consistent with the adsorption of antibiotics in the soil. With the increase of soil pH, the concentration of antibiotics adsorbed in soils decrease (Figueroa et al., 2004; Gong et al., 2012).

The VIPs of SOC in OTC-Model (1.018), CIP-Model (0.968) and SM1-Model (1.034) were close to or >1 (Table 2). This suggests that SOC played a significant role in the adsorption of OTC, CIP, and SM1. The negative sign of SOC coefficients suggested that increase of SOC concentration could inhibit the adsorption of those antibiotics on swine manures and lead to decreased $\text{Lg}K_d$ values. This phenomenon may be contributed to the increase in competitive adsorption from SOC (Fu et al., 2015). In addition, metals such as Cu and Zn are extensively added to feed to promote growth of pigs in intensively farmed systems. These elements are excreted and accumulate in swine manures (Meng et al., 2017) as divalent cations (M^{2+} ; e.g. Cu^{2+} and Zn^{2+}). Antibiotics in the manure undergo cation bridging with M^{2+} , forming SOC- M^{2+} -OTC/CIP/SM1 ternary complexes. That is, M^{2+} may act as a bridge between the negatively charged SOC and antibiotics at pH around 7 (Bo et al., 2012; Mackay and Canterbury, 2005).

The VIPs of SON were 0.865 and 0.822 in the OTC and CIP models, respectively (Table 2). This indicates that SON had a significant effect on the adsorption of OTC and CIP. In general, the main components of SON include ammonium-N, amino acid-N, amino sugar-N, especially for the amino acid-N that occupies a bigger proportion (Bao et al.,

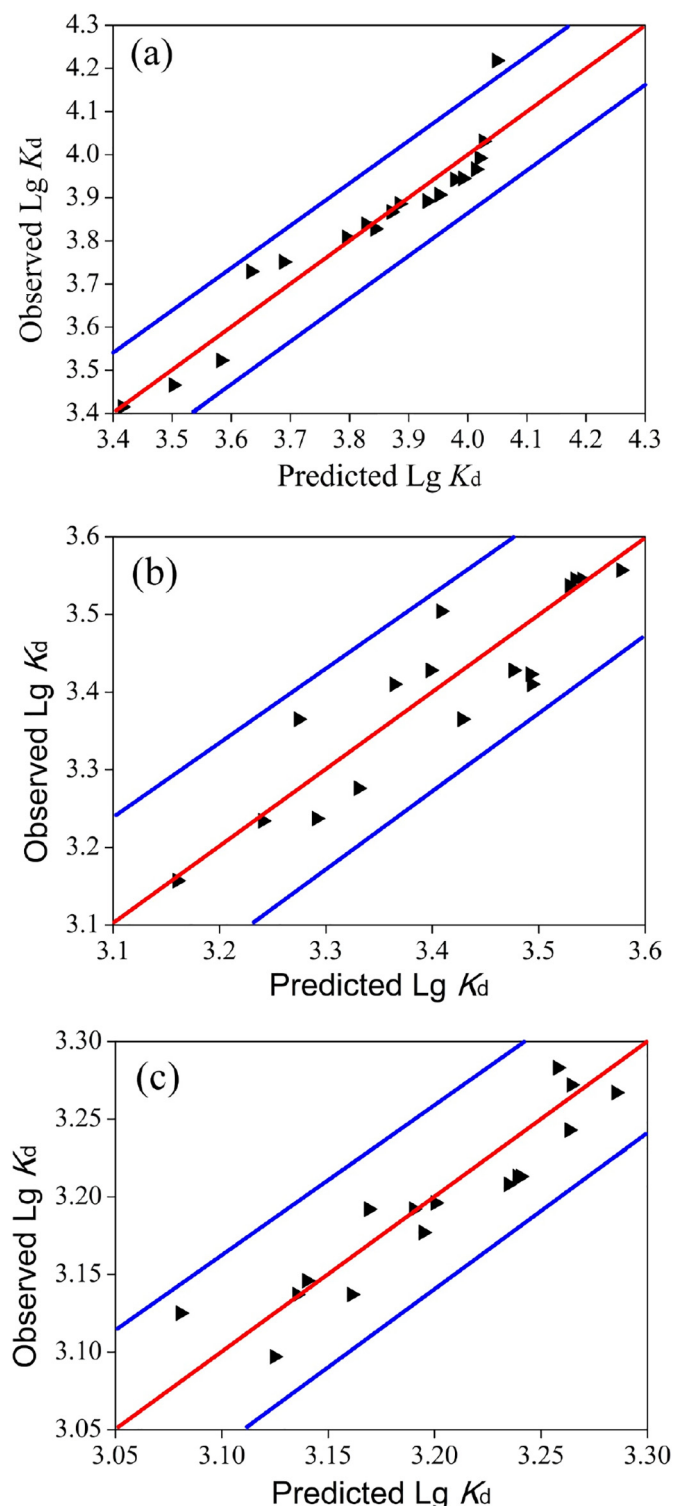


Fig. 2. Plot of the observed vs. predicted $\text{Lg}K_d$ values of (a) OTC, (b) CIP, and (c) SM1.

2008). Many studies have shown that amino acid can adsorb to the cation-exchange sites of solid surfaces and form metal complexes with metal ions, but this binding is weak adsorbability and easy to be attacked by other compounds (Chen et al., 2013; Jones and Darrah, 1994; Jones and Willett, 2006). Therefore, OTC and CIP could competitively adsorb with amino acid and other SON matters that adsorbed on the manures, in which the adsorbed SON was constantly released into the solution with the continuous adsorption of those antibiotics. Further research must be conducted to clarify the specific underlying mechanism about the effect of SON on antibiotics. Furthermore, as the most important components of organic matter of swine manure, TON, including proteins and amino acids, is intimately associated with inorganic mineral components in swine manure and therefore must have larger contribution to the adsorption of various pollutants (Friebele et al., 1980; Li et al., 2017; Shu et al., 2017; Zhang et al., 2018). The VIP value and coefficient of TON in SM1-Model were 0.629 and 4.42×10^{-3} , respectively (Table 2). This indicated that TON content had large influence on the adsorption behavior of SM1 in swine manures. It could be concluded that the LgK_d values of SM1 were proportional to TON content of swine manures due to the “+” coefficient of this one (Eq. 3.3). The increase of TON content in swine manures could enhance the adsorption of SM1 onto swine manures.

Ca also had an important role to play in the adsorption capacity of OTC to swine manures. For the OTC model, the VIP value and coefficient of Ca were 0.515 and -1.90×10^{-3} , respectively. Ca also had an important role to play in the adsorption capacity of OTC to swine manures. For the OTC model, the VIP value and coefficient of Ca were 0.515 and -1.90×10^{-3} , respectively. This result may be due to the binding between OTC and Ca^{2+} that was not bounded to the manure so that the manure reduced the adsorption of OTC. Many studies have demonstrated that OTC easily forms very strong complexes with Ca^{2+} (Loke et al., 2002; Lunestad and Goksøyr, 1990).

4. Conclusions

In this study, important theoretical and empirical information relating to the three antibiotics (OTC, CIP, SM1) present in swine manure were determined. First, three quantitative models for LgK_d values of OTC, CIP and SM1 in swine manures were successfully developed using 12 representative physicochemical parameters though PLSs analysis. The high values of Q^2_{cum} and Q^2_{ext} combined with low values of SDs indicated that the LgK_d of those three antibiotics in swine manures could be predicted accurately. Secondly, the key physicochemical parameters that govern the adsorption behaviors were determined, and the main interaction mechanisms were explained. We suggested that further research must be conducted to clarify the specific underlying mechanism under different conditions, especially for the soluble organic nitrogen (SON).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2018.04.114>.

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