Sorption and Desorption Dynamics of Selected Non-steroidal Anti-inflammatory Drugs Agricultural Systems

by

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ABSTRACT

Non-steroidal, anti-inflammatory drugs (NSAIDs) are widely used pharmaceutical products with analgesic and anti-inflammatory effects that are consistently found in biosolids. Land application of biosolids is a well-established practice worldwide that introduces those NSAIDs into soils, giving rise to potential leaching to groundwater, runoff to surface waters, and accumulation in soil systems. Studies were conducted to investigate individual compound and mixture compound sorption-desorption interactions of four commonly detected NSAIDs (naproxen, ibuprofen, ketoprofen, and diclofenac) in an agricultural loam textured soil and an alkaline treated biosolids-amended soil. Sorption and desorption dynamics of ibuprofen were concentration dependent. Both studies suggest NSAIDs might compete for binding sites but synergistic sorbed to matrices in the mixed compound system. Sorption-desorption dynamics exhibited hysteresis for all NSAIDs in soil and soil-biosolid system.

LIST OF ABBREVIATIONS USED

ANOVA	Analysis of variance
ATB	Alkaline-treated biosolids
BNR	Biological nutrient removal
CAS	Conventional activated sludge system
CEC	Cation exchange capacity
DCF	Diclofenac
DMBs	Dewatered municipal biosolids
EC	Emerging contaminants
EMLs	List of Essential Medicines
ESOC	Emerging substances of concern
GC-MS	Gas Chromatography with Mass Spectrometry
IBF	Ibuprofen
KTF	Ketoprofen
LMBs	Liquid municipal biosolids
LOD	Limits of detection
LOQ	Limits of quantification
MBR	Membrane bioreactor
MTBSTFA	N-tert-butyldimethylsilyl-N-methyltrifluoroacetamide
NPX	Naproxen
NSAIDs	Non-steroidal, anti-inflammatory drugs
OC	Organic carbon
OTC	Over-the-counter
PhACs	Pharmaceutically active compounds
SOM	Soil organic matter
STPs	Sewage treatment plants
SPE	Solid-phase extraction
SIM	Selected ion monitoring
TFB	Tricking filter beds
WWTPs	Wastewater treatment plants

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1 Introduction

1.1 Overview

In recent years, there has been growing attention on the prevalence, fate and ecological impact of pharmaceutically active compounds (PhACs) in the natural environment. These compounds are also known as Emerging Substances of Concern (ESOC) or Emerging Contaminants (EC) (Xu et al., 2010; Chen et al., 2013; Dodgen, 2014; Caracciolo et al., 2015). Large quantities of pharmaceuticals are prescribed as medication or sold as 'over-the-counter' (OTC) drugs without a prescription. In 2014, worldwide distribution of pharmaceutical sales was 44.5% in North America (The United States and Canada), 25.3% in Europe, 8.9% in Japan, 16.6% in Africa and Asia (excluding Japan and Australia), and 7.7% in Latin America (European Federation of Pharmaceutical Industries and Associations, 2015). The global expenditure on pharmaceuticals is expected to reach $ 1.4 trillion in 2020 which is about 30% more than 2015; medicinal use will reach 4.5 trillion doses representing an increase of 24% increase from 2015 (IMS health, 2015).

Non-steroidal, anti-inflammatory drugs (NSAIDs) are chemicals of particular concern because of their widespread use for the treatment of rheumatic disorders, pain and inflammation (Mestre et al., 2007; Margon et al., 2009; Caracciolo et al., 2015). NSAIDs inhibit the cyclooxygenase (COX) enzymes from making prostaglandins, which are associated with inflammatory, analgesic and antipyretic effects (Feng et al., 2013). The NSAIDs used in this study were naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF) and diclofenac (DCF) since they represent the greatestconsumed NSAIDs in the world. McGettigan and Henry (2013) reported on the use of selected NSAIDs in 15 countries and found that DCF accounted for 8.3 to 43.4% of total sales, while IBF ranged from 3.3 to 26.6%, NPX ranged from 0 to 28.2%, and KTF use

accounted for 0.2 to 9.5% of the total sales. NPX had the highest prescription sales in Canada in 2011, but DCF was the most popular NSAIDs in all 15 countries, especially in China (McGettigan and Henry, 2013).

These NSAIDs used in human medical care are excreted via feces and urine, and deposited into municipal sewage systems (Xia et al., 2005; Zhang et al., 2008). Most compounds undergo incomplete or partial degradation in conventional wastewater treatment plants (WWTPs) (Kimura et., 2007; Kasprzyk-Hordern et al., 2009; Feng et al., 2013) but NSAIDs are detected in WWTP effluents or treated sludge at concentrations on the order of ng L^{-1} to µg L^{-1} or ng g dw^{-1} (Tixier et al., 2003; Rabiet et al., 2006; Lishman et al., 2006; Edwards et al., 2009; Gottschall et al., 2012; Loos et al., 2013; Vieno and Sillanpää, 2014). Subsequently, pharmaceutical residues are introduced into the environment through sewage effluent discharge (Feng et al., 2013; Loftus et al., 2015), irrigation using reclaimed wastewater (Chefetz et al., 2008; Gibson et al., 2010; Durán-Álvarez et al., 2012; Durán-Álvarez et al., 2015), biosolids used as a soil amendment in agriculture (Edwards et al., 2009; Gottschall et al., 2012), or leachate from landfills (Eggen et al., 2010). Land application of treated sludge, or biosolids, as a source of crop nutrients and organic matter is a common agricultural practice worldwide, but also results in the introduction of pharmaceuticals into agriculture soils (Topp et al. 2008; Monteiro and Boxall, 2009; Wu et al., 2010; Lapen et al., 2008; Edwards et al., 2009; Gottschall et al., 2012). There they can mobilize and leach into groundwater and drainage networks (Topp et al., 2008; Edwards et al., 2009; Gottschall et al., 2012).

The co-existence of these compounds with different chemical structures may have an impact on the fate of pharmaceuticals (Monteiro and Boxall 2009; Loos et al., 2010; Calderón-Preciado et al., 2011; da Silva et al., 2011; Liu and Wong, 2013), resulting in significant damage

to non-targeted organisms (Cleuvers, 2004; Schnell et al., 2009; Nava-Álvarez et al., 2014). Few studies investigate the fate of pharmaceuticals as a mixture in soil due to the complexity of the chemical interactions with that matrix. This chapter provides an overview of the current body of scientific knowledge on NSAIDs, including their removal in WWTPs, fate in soils as well as their eco-toxicity.

1.2 Literature review

1.2.1 Non-steroidal, Anti-inflammatory Drugs (NSAIDs)

NPX ($C_{14}H_{14}O_3$), is a (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid, of which 95% from any dose is metabolized as a parent compound and their conjugated metabolites, and excreted in urine (https://www.drugs.com/pro/naproxen.html). IBF ($C_{13}H_{18}O_2$) possesses analgesic and antipyretic effects, which is a 2-[4-(2-methylpropyl) phenyl] propanoic acid, 45 to 79% of which was metabolized and excreted in the urine as metabolites and conjugated IBF (https://www.drugs.com/pro/alivio.html). IBF is one of three NSAIDs listed in the WHO model list of Essential Medicines (World Health Organization, 2013). KTF ($C_{16}H_{14}O_3$), an (RS)-2-(3-benzoylphenyl) propanoic acid, is metabolized mainly by the liver and excreted extensively in the urine (85%) (https://www.drugs.com/monograph/ketoprofen.html). DCF ($C_{14}H_{10}C_{l2}NNaO_2$), 2-[2-(2, 6-dichlorophenyl)amino] benzene acetic acid, is commonly used in reducing pain and inflammation. Approximately 65% of the dose is excreted as metabolites and conjugates of unchanged DCF in the urine after administration (https://www.drugs.com/pro/diclofenac.html).

1.2.2 Removal of Non-steroidal, Anti-inflammatory Drugs in WWTPs

Conventional WWTPs use systems of primary treatment, secondary treatment and/or tertiary treatment. Primary treatment is used to remove coarse solids or sediments in wastewater by physical screening or a settling process. Secondary treatment is a biological process which

removes organic contaminants using microorganisms. Tertiary treatment and/or advanced treatment is a biological or chemical process employed to remove nutrients and constituents that cannot be removed by secondary treatment. A variety of removal strategies for NSAIDs are used for different reactor types in secondary treatment; among these are conventional activated sludge systems (CAS), membrane bioreactors (MBR), and tricking filter beds (TFB) (Kasprzyk-Hordern et al., 2009; Sipma et al., 2010). CAS commonly consists of an aeration tank and secondary clarifier to reduce the biochemical oxygen demand and nutrient contents. An MBR uses loose membranes such as microfiltration and ultrafiltration membranes, which reduces excess sludge solids and increases solids retention to achieve higher quality effluent and better biotreatment (Sipma et al., 2010). TFB develop a biofilm (a layer of microbial slime) that supports both oxidative and reductive biological processes. Biological nutrient removal (BNR) is one of the tertiary treatment processes that removes nitrogen and phosphorous. Pharmaceuticals are removed in WWTPs by sorption to sludge, chemical and/or biological degradation. NPX, IBF, KTF, and DCF are highly hydrophilic compounds dependent upon their pKa values ranging from 3.12 to 4.91 (Table 2.2). Although they are mainly eliminated through biological and chemical degradation, they are not adsorbed efficiently into sludge solids. Consequently, they were detected in secondary effluents (Lishman et al., 2006; Rabiet et al., 2006; Li, 2014).

A removal efficiency of 79 to 98% for NPX from wastewater was reported by Lishman et al. (2006) in CAS plants. Jelic et al. (2009) also reported good removal efficiency (>80%) of NPX under CAS systems. Out of the four NSAIDs studied by Kasprzyk-Hordern et al. (2009), NPX was removed in WWTPs using CAS with removal rates 74 to 80%, whereas a lower removal rate of 50 to 58% was observed in treatment using TFB. Higher elimination rates for NPX were exhibited in the MBR treatment than in the CAS treatment (Kimura et al., 2007). The

enhanced elimination of NPX from 70 to 90% by BMR treatment was also observed by Radjenović et al. (2009).

IBF was significantly removed in WWTPs in previous studies regardless of the type of treatment. Lishman et al., (2006) reported a significant reduction of IBF (91 to 98%) using CAS treatment while a good removal efficiency (>80%) was noted by Jelic et al. (2011). Kasprzyk-Hordern et al. (2009) observed an IBF removal efficiency (>80%) during CAS or TFB treatments. IBF was also characterized by a very high removal rate (99%) in CAS and BMR treatments by Radjenović et al. (2009).

In CAS plants, 44% of KTF was removed (Lishman et al., (2006). The CAS treatment (74 to 80% removal) exhibited better elimination of KTF than did the TFB treatment (50 to 58% removal) (Kasprzyk-Hordern et al., 2009). A higher elimination rate for KTF was exhibited in MBR treatment than in the CAS treatment (Kimura et al., 2007), whereas Radjenović et al. (2009) reported that KTF tended to be better removed by CAS treatment (55%) than by BMR treatment (44%).

No removal of DCF was observed during either CAS or TFB treatments (Kasprzyk-Hordern et al., 2009). Low removal of DCF in municipal sewage plants (STPs, Herberer et al., 2002) and in a WWTP with MBR (Quintana et al., 2005) was reported, underscoring the persistence of DCF through wastewater treatment processes. Radjenović et al. (2009) reported 21% and up to 65% removal efficiency of DCF from WWTPs using CAS and MBR respectively. A comparative study of CAS and BMR performance was reported by Kimura et al. (2007), where DCF had greater removal efficiency in BMR treatment due to longer solid retention time and better adaptation of microorganisms, resulting in higher biodegradation.

1.2.3 Land application of biosolids

Biosolids are nutrient-rich organic residues resulting from the treatment of domestic sewage and septage sludge in WWTPs (Wu et al., 2010; Lu et al., 2012). They are often categorized into two groups, Class A and Class B, based on their pathogen and heavy metal content (NSE, 2010; Lu et al., 2012). Municipal biosolids can be stabilized by through various methods. Biosolids can be compost with organic materials to a stable end product. Aerobic or anaerobic is the digestion of organic matter by microorganisms with and without the presence of oxygen. In alkaline stabilization, municipal biosolids are mixed with alkaline materials until a pH of 12 is reached and maintain its value during storage. Deat drying or heat treatment is employed to reduce volatile solids. In pasteurization, heating municipal biosolids are heated to 70°C for 30 minutes to destroy pathogens (NSE, 2010).

The options for managing biosolids include disposal in landfills, energy recovery, agricultural land application, and use for land reclamation and remediation (NSE 2010). Approximately 388,700 dry tons of biosolids are generated in Canada annually, of which 43% of the total are applied to land, with the remainder incinerated, disposed in landfills and used for land reclamation or other uses (Apedaile, 2001). Kinney et al. (2006) estimated that 55% of the total biosolids generated in the United States in 2004 were land applied. Treated biosolids production in the European Union (EU) countries ranged from 9 to 38 kg dw per capita per annum, and Ireland, Finland, and the United Kingdom were estimated to use the highest percentage (>90%) of treated biosolids in agriculture (European Commission, 2001). About 38% of biosolids were applied to agricultural soils in Europe annually (Chang et al., 2002). In the province of Ontario, Canada, the maximum regulatory application rate of municipal biosolids is 22 Mg dw ha^{-1}, in any five-year period (Ministry of the Environment, 2015). It is estimated that

about 120, 000 Mg dw of biosolids are applied to 15, 000 ha^{-1} of agricultural land annually (Lapen et al., 2008). Land application of biosolids is governed by constituent qualities, such as nutrients, metals, pathogens and organic contaminants (CCME, 2010). The use of biosolids as a soil amendment is the preferred method from the perspective of improving crop production and soil properties, and has been practiced in Canada for decades (CCME, 2010; Environmental Canada, 2013; NSE, 2010).

Biosolids amendment has established many benefits for agronomy by improving soil physical-chemical properties (Christie et al., 2001; Copper, 2005; Singh and Agrawal, 2008). Soil organic carbon (OC) content has been improved in soils receiving biosolids (Brown et al., 2011). Microbial activity has increased in long-term biosolid-amended soil (Singh and Agrawal, 2008; Zerzghi et al., 2010). Adding alkaline treated biosolids (ATBs) to soil seems to increase the soil solution pH and the cation exchange capacity (CEC) (Price et al., 2015). Despite the benefits, biosolids containing contaminants, such as heavy metals, pathogens, and ESOC, may accumulate in soils over time and eventually enter waterways by leaching or runoff (Kang et al 2005; Xia et al., 2005; Monteiro et al., 2009; CCME, 2010).

1.2.4 Fate of NSAIDs in soils

The occurrence of NSAIDs is worldwide and at the highest concentration levels up to the μg L^{-1} range occur in terrestrial environments (Lapen et al., 2008; Edwards et al., 2009; Gibson et al., 2010; Monteiro and Boxall, 2010; Chen et al., 2011; Li, 2014). DCF, IBF and NPX accumulated in the 0-20 cm soil layer of a loamy sand soil and sandy loam soil receiving reclaim water irrigation, with concentrations ranging from 1.52 to 6.82 ng g^{-1}, 0.77 to 7.88 ng g^{-1}, and 8.06 to 23.79 ng g^{-1} respectively (Chen et al., 2013). In Spain, Aznar et al. (2014) detected IBF and NPX at concentrations up to 1.5 and 5.9 ng g^{-1} respectively in agriculture fields (Alfisol,

Inceptisol, Psamments, Xerosols, Fluvents, and Fluvaquents). The concentration of pharmaceuticals found in soils in different countries was summarized in the study of Li (2014): the concentration of IBF ranged from 1.51 to 5.03 μg kg^{-1} in China and up to 0.1 μg kg^{-1} in Mexico, and the concentration of DCF ranged from 0.35 to 1.16 μg kg^{-1} in China. When NPX, IBF, KTF and DCF enter into soil compartments through irrigation with reclaimed water or amending with biosolids, sorption and desorption are the primary processes influencing their mobility and availability for biodegradation. A number of studies have investigated the adsorption, transportation, and degradation behavior of these NSAIDs in soils and sediments (Scheytt et al., 2005; Lin and Gan, 2011; González-Naranjo et al., 2013; Vulava et al., 2016).

1.2.4.1 Sorption

NPX, IBF, KTF and DCF are amphiphilic NSAIDs with aliphatic chains (non-polar), aromatic rings (non-polar, π donor/acceptor), carboxylic acid (polar/anionic, pH-dependent) and/or secondary amine functional group (H-bond donor/acceptor). Longer hydrocarbon chains increase non-polar interactions (van der Waals interactions) between NSAID's molecules and soil surface moieties. Aromatic rings of NSAIDs contribute to π-π interactions with aromatic moieties in soil organic matter (SOM) with the presence of potentially strong π-donor/acceptor groups, including protonated aromatic amines, N-heteroaromatic rings and hydroxyl and carboxylic acid functionalities (Schwarzenbach et al., 2005; Zhu et al., 2004). The π-donor ability of organic compounds would increase with their polarizabilities, while the π-acceptor ability of aromatic moieties positively correlates with protonation (Zhu et al., 2004). Carboxylic acid group is highly polar, consisting of strongly polarized carbonyl (C=O) group and hydroxyl (O-H) group (DeRuiter, 2005b), which can involve electrostatic and dipole-dipole interactions (hydrogen bonding and electron donor-accepter interactions) with multiple carboxylic acid and

amines within aromatic moieties of SOM and mineral oxide surfaces (Gibson et al., 2010; Vulava et al., 2016). The metal oxides (Al_2O_3) can ligand-exchange with keto- and carboxylate functional groups of antibiotic ofloxacin (Goyne et al., 2005). The secondary amine contains aromatic groups and a hydrogen (N-C and N-H dipoles), which can be protonated to corresponding ammonium ion and hydrogen bonding with functional groups within SOM (DeRuiter, 2005a; Klepsch et al., 2011). Hydrogen bonding between the amine group of carbamazepine and the silanol surfaces have been reported (Turku et al., 2007). Differences in the sorption behavior of various NSAIDs is a result of the differences in the chemical nature of each NSAID and is reflected in the various coefficients describing their behavior such as the acid dissociation constant (K_d), water solubility (K_{sp})and octanol-water coefficient (log K_{ow}); and the physicochemical properties of soils, such as, soil solution pH, SOM content, CEC and mineral composition (Schwarzenbach et al., 2005).

NPX, IBF, KTF, and DCF are weak acid compounds with pK_a ranging from 4.15 to 4.91 (Table 2.2), therefore, their carboxylic acid groups are deprotonated at soil environmental-relevant pH level from 5 to 8 (Vulava et al., 2016) and occur as anionic species. Studied loam-textured soil solution pH (~5.9) measured was approximately the same as the soil pH (6.1). The surface of soils are predominantly negatively charged in most soils (Schwarzenbach et al., 2005). Negatively charged molecules are repelled by the negative charge soil particles, hence, low sorption coefficients to soils are expected for them (Durán-Álvarez et al., 2012). Despite ionic repulsion, the deprotonated carboxylic acid functional groups of four NSAIDs could adsorb to protonated functional groups on SOM and mineral oxide surfaces, suggesting other polar or non-polar interactions are involved in their sorption to soils, such as hydrogen bonding, and complex interactions with SOM and mineral surfaces (Durán-Álvarez et al., 2012; Vulava et al., 2016).

The abundance of π-accepting sites in humic substances increases when the pH is lowering below neutral, which is enhanced with the protonation of carboxylate, arylamine, and heteroaromatic N functional groups on aromatic rings, and thus is expected to be favorable for strong π-donor compounds (Zhu et al., 2004).

Sorption of NSAIDs into soil has been shown to be highly associated with SOM content (Drillia et al., 2005; Chefetz et al., 2008; Xu et al., 2009a and b; Yu et al., 2009; Durán–Álvarez et al., 2014; Vulava et al., 2016). Sorption coefficients of NPX increased from 3.1 to 356 L kg^{-1} when SOM contents increased from 0.4 to 9% (Vulava et al., 2016). Sorption coefficients in four U.S. soils showed that NPX had the lowest K_d value of 1.36 L kg^{-1} in Hanford loamy sand soil with the lowest SOM (0.58%) and the highest K_d of 16.49 L kg^{-1} in the Palouse silt loam soil with the highest SOM (5.45%) (Xu et al., 2009b). A low K_d value of 0.43 μg kg^{-1} was also reported NPX in a sandy aquifer with low SOM (<0.6%) and predominantly composed of gravels and sand (Teijón et al., 2013). NPX has a diaromatic ring that is absent in IBF and KTF, which may facilitate π-π interactions (nonpolar-nonpolar interactions) between aromatic moieties of NPX and SOM (Chefetz et al., 2008; Lin and Gan, 2011). As SOM content increased (0.4 to 9%), the sorption coefficients of IBF increased (1.72 to 49.5 L kg^{-1}) (Vulava et al., 2016). The K_d value of 3.71 L kg^{-1} recorded for IBF was highest in SOM-rich Palouse silt loam soil (SOM% 5.45) and the lowest of 0.56 L kg^{-1} in SOM-poorer Hanford loamy sand (SOM% 0.58) and Arlington sandy loam soil (SOM% 1.93) (Xu et al., 2009b). The maximum adsorption capacity of 76.6 mg $kg^{-1}$was recorded for IBF in soil with the highest SOM of 3.51% (González-Naranjo et al., 2013). Relatively low distribution coefficient K_d values, ranging from 0.18 to 1.69 L kg^{-1}, have been reported for IBF in natural sediments containing a low fraction of organic carbon (f_{OC}, 0.0013 to 0.002 kg kg^{-1}) (Scheytt et al., 2005). The K_d values for KTF were positively correlated

with SOM content in soils, K_d values increased from 1.26 to 8.24 L kg^{-1} with increased SOM from 0.58 to 5.45% (Xu et al., 2009a). Distribution coefficients (K_d values) varied from 0.55 to 4.66 for DCF in natural sediments with low f_{OC} ranging from 0.0013 to 0.002 kg kg^{-1} (Scheytt et al., 2005). Negligible adsorption was observed for DCF on soils with low OC content (0.16 to 0.33%) (Lin and Gan, 2011). Drillia et al. (2005) studied DCF adsorption in two soils and obtained a low distribution coefficient (0.45 mg L^{-1}) in low OC soils (0.37%), and a high K_d value (164 mg L^{-1}) in soil rich in OC (7.1%). A similar trend for DCF was observed by Xu et al. (2009b) with an adsorption coefficient of 1.21 L kg^{-1} in the low organic matter soil (0.58%) and 17.72 L kg^{-1} in the soil rich in SOM (5.45%). For NPX, a lower distribution coefficient K_d of 2.39 L kg^{-1} in the topsoil (0 to 10 cm, OC 25 mg g^{-1}, pH 8.01) than the K_d of 4.41 L kg^{-1} in the 30 to 40 cm soil (OC 18mg g^{-1}, pH 8.14), suggests SOM quality also affects the sorption of NPX by π-π interactions between aromatic moieties of the compound and rich aromatic molecules in humified OM beneath the top soil (Durán-Álvarez et al., 2012). Batch sorption studies have shown that DCF has higher sorption rates in SOM-rich soil layers, suggesting its interaction with SOM might have been enhanced by the high hydrophobicity (Chefetz et al., 2008; Xu et al., 2009b).

Sorption of NSAIDs in low-SOM soils and sediments (Yu and Bi, 2015; Vulava et al., 2010), indicates that inorganic mineral components of clay, Fe- and Al-oxides also play an important role in retaining NSAIDs in soils. Clays are aluminosilicate minerals that are composed of silica, aluminum, metal oxides and metal ions (i.e. Mg^{2+}, Ca^{2+}, K^{+}, Na^{+}, and $SO4^{2-}$) and acid pharmaceuticals could sorb to clay via ion exchange (Akhtar et al., 2016). Adsorption of IBF (90.0%), KTF (94.3%) and DCF (88.3%) to mesoporous silica SBA-15 by hydrogen bonding was preferred at pH higher than 4.0 and electrostatic repulsion was dominant interaction

between negatively charged silica surface and anionic pharmaceuticals at pH higher than 4.0 (Bui and Choi, 2009). Mesoporous silica MCM-41 incorporated with Nickel (II) was reported to remove NPX by π-complexation with Ni^{2+} (Rivera-Jiménez and Hernández-Maldonado, 2008). In clay, van der Waals Forces play a role in causing migration of compounds between clay sheets (Gibson et al., 2010). The K_d values of NPX to kaolinite, which is a layered structure clay mineral, ranged from 1.30 to1.62 L kg^{-1}; the π-π electron donor-acceptor interaction and hydrogen bonding was found to contribute the sorption of NPX to siloxane surface of kaolinite (Yu and Bi, 2015). As suggested by Martínez-Hernández et al. (2014), NPX was negligibly sorbed to inorganic surfaces in a natural sediment with a pH of 6.65, 1.44% OC and predominantly composed of sand. Negligible sorption for IBF and DCF displayed negligible sorption in sandy and median loam soils characterized: OC content 0.16% to 0.33%, clay content 4% to 25% and soil pH 8.73 to 9.23 (Lin and Gan, 2011), suggesting clay did not play an important role in affecting sorption behavior of IBF and DCF.

An increase of ionic strength has been shown to increase the adsorption of KTF due to a double-layer compression and reduction of the repulsive electrostatic potential, but do not cause a significant impact on adsorption of IBF and DCF (Bui and Choi, 2010). Anions were not found to affect the adsorption of these NSAIDs significantly because of the electrostatic repulsion between anions and negatively charge soil surface (Bui and Choi, 2010). The partition of anions species of organic acids in SOM depends on the extent of Ca^{2+} by reducing the repulsive electrostatic potential of SOM, although Ca^{2+} effect is not comparable to pH-dependent speciation (Tülp et al. 2009). Divalent cations at low concentrations increase adsorption of IBF (Ca^{2+} and Mg^{2+}) and KTF (only Mg^{2+}) significantly by bridging between the negatively charged silica surfaces and anionic pharmaceuticals. The presence of Fe^{3+} only enhanced the adsorption

of KTF; and trivalent cation Al^{3+} impacted the adsorption of IBF, KTF and DCF (Bui and Choi, 2010). The presence of Cu(II) could enhance the sorption of DCF with an acidic soil, due to the potential formation of diclofenac-Cu(II) complex, log K = 6.8 (Agatonović-Kuštrin et al., 1991) and Cu(II)-soil, log K = 5.3 (Rachou and Sauvé, 2008) and thus a ternary diclofenac-Cu(II)-soil complex (Graouer-Bacart et al., 2016).

Pharmaceuticals occur as a mixture in the environment. Bui and Choi (2009) investigated the adsorption of a mixture of pharmaceuticals including IBF, KTF, DCF and carbamazepine, clofibric acid on a mesoporous silica SBA-15. The authors reported a significantly higher removal efficiencies of 77.8% for DCF and 89.3% for KTF in these five-pharmaceutical mixture by adsorption to SBA-15 compared to individual compound (42.4% for DCF and 86.5% for KTF, whereas a smaller removal efficiency for IBF of 75.2% in the mixture than in the single IBF case of 87.6%, indicating that synergistic effect by multilayer co-adsorption as well as competitive adsorption by competing over sorption sites might occur for compounds as a mixture. A stronger adsorption of DCF on activated biochars was observed in the presence of NPX and IBF, whereas a weaker adsorption was shown for IBF in the NSAID-mixture (Jung et al., 2015). The authors addressed competitive sorption of selected NSAIDs on limited sorption sites of sorbents: DCF might exhibit higher binding energy with biochars over IBF, even though IBF has high hydrophobicity. Higher sorption of DCF than NPX indicated that DCF exhibited greater adsorption affinity to an aromatic fraction of biochars because of its higher polarity, π energy, and hydrophobic partitioning. The larger molecular size of DCF occupied the active binding sites preferentially than NPX and IBF, resulting the reduction in adsorption of NPX and IBF in mixtures. IBF was outcompeted by NPX due to lower binding energy, polarity and molecular size and π-effects (Jung et al., 2015). Multilayer co-adsorption implies that compounds that have

higher binding energy will occupy the stronger binding sites on the first layer of sorbent, compounds that have lower binding energy saturate on the relatively weaker binding sites on the first layer and accommodate more molecules through adsorbate-adsorbate interactions on absorbable layers (Liu, 2015) .

1.2.4.2 Desorption

Few studies have related the desorption processes of individual NSAIDs to soil characteristics (Durán-Álvarez et al., 2012; González-Naranjo et al., 2013; Martínez-Hernández et al., 2014), none have included their mixtures. Stronger retention of NSAIDs on soils in desorption processes than in sorption processes are shown when the K_{des} values are higher than K_d values, known as sorption-desorption hysteresis (Huang, 1998; González-Naranjo et al., 2013). The higher the hysteresis index HI values (greater than zero) quantified, the more difficult for compounds to be desorbed from the matrix, HI values that are less than or equal to zero indicating insignificant desorption (Chefetz et al., 2008; Teijón et al., 2013). Significant sorption-desorption hysteresis for DCF showed that DCF might have been entrapped in organic and inorganic matrices, in addition, the HI values of DCF measured were higher with the 15 to 25 cm (0.4% OC) than the 0 to 5 cm (8.13% OC) soil samples, suggesting that the desorption of DCF was not only affected by SOM (Chefetz et al., 2008). Low sorption-desorption hysteresis for NPX suggested that it was easily desorbed from the organic and inorganic matrices, HI values were higher than the SOM-rich soil sample (0 to 5 cm) than for the SOM-poor sample (15 to 25 cm), interpreting a positive relationship between desorption hysteresis and SOM content (Chefetz et al., 2008). Hysteretic desorption for NPX in reclaimed water irrigated soil and a natural sediment was also reported because the HI values were greater than zero (Martínez-Hernández et al., 2014). Low sorption-desorption hysteresis was observed for IBF in wastewater

irrigated and rainfed soils; the HI obtained for IBF in rainfed soil than in the wastewater irrigated one even though wastewater irrigated soil had higher SOM content, which could due to the stronger π-π bonds between aromatic moieties within IBF molecules and humified SOM since high content humified OM had been distinguished with high aromaticity (Durán–Álvarez et al., 2014). Low HI values, ranging from 0.42 to 0.66, were obtained for IBF in soils irrigated with reclaimed water in the study of (González-Naranjo et al., 2013). The author suggested IBF was readily desorbed from soil and subject to leaching downward through percolating water.

Quad-solute desorption could be affected by the different binding energy on soil surfaces. Higher binding energy for DCF aforementioned (Jung et al., 2015) could counteract the desorption of DCF. NPX has aromatic di-rings with enhanced π-π interactions with SOM (Lin and Gan, 2011), comparing to the IBF and KTF, thus be entrapped in soil matrix at a greater extent. When compounds are multi-layer adsorbed, the compounds on absorbable layers can prevent compounds to be desorbed from the soil surface by blocking the sorbed molecules at the first layer of the soil surface (Liu, 2015), might increase the difficulties for first layer molecules to be desorbed.

1.2.4.3 Degradation

Biodegradation has been identified as an important elimination process for these NSAIDs in soils, and microorganisms appear to affect degradation of NSAIDs in soils (Xu et al., 2009a and b; Al-Rajab et al., 2010; Lin and Gan, 2011; Grossberger et al., 2014; Durán-Álvarez et al., 2015). NPX, IBF and DCF were rapidly biodegraded in soils (loamy sand, sandy loam and sandy clay), with half-life t1/2 (day, d) ranging from 0.2 to 0.4 d for DCF, 0.3 to 0.9 d for IBF and 2.0 to 9.5 d for NPX in the spiking level of 50 ng g^{-1} and ranging from 1 to 8 d for DCF, 3 to 16 d for IBF and 9 to 59 d for NPX in the spiking level of 5000 ng g^{-1} (Grossberger et al., 2014). About

50% of ^{14}C-NPX and ^{14}C-DCF were mineralized after 3.04 to 5.44 d and 1.36 to 4.25 d incubation, respectively (Dodgen et al., 2014). Under aerobic conditions, the degradation half-lives t1/2 (d) in sandy loam and medium loam soils for NPX, IBF and DCF were 17.4 to 69.3 d, 10.4 to 15.2 d, and 4.8 to 29.6 d, respectively, at concentration of 40 ng g^{-1} dry soil; NPX and DCF almost remained unchanged under anaerobic conditions or in sterile sandy loam soil under aerobic conditions during 84 d incubation, more than 70% of IBF remained in the medium loam and sterile sandy loam soils, but IBF dissipated in the sandy loam soil with a t1/2 of 49.9 d (Lin and Gan, 2011). IBF had half-lives between 7 to 19 d under aerobic conditions and 207 to 546 d under anaerobic conditions in wetland sediments (Conkle et al., 2012). Al-Rajab et al. (2010) reported that ^{14}C-DCF residues were readily mineralized in agricultural soils receiving 100 ng DCF g^{-1} soil incubated under various temperatures and moisture conditions with half-lives t1/2 (d) ranging from 1 ± 0.2 d (loam), 1.8 ± 1.3 (clay loam) to 3.8 ± 2.7 (sandy loam), it was not amendable in sterile soil. In four nonsterile aerobic U.S. agriculture soils varying widely in textures (loamy sand, sandy loam, silty clay and silt loam) and spiked with 100 ng NSAIDs per g dry soil, the degradation half-lives t1/2 (d) of NPX, IBF, KTF and DCF ranged from 5.68 to 16.82 d, 0.91 to 6.09 d, 4.58 d to 27.61d and 3.07 to 20.44 d (Xu et al., 2009a and b). The authors also reported that in the sterile loamy sand soil, degradation t1/2 (d) values were 38.5 d for NPX, 31.22 d for IBF, 42.51 d for KTF and 70 d for DCF, at the spiking level of 100 ng g^{-1}. Tsekoura et al. (2011) determined the half-lives of 20.7, 18.6 and 7.2 d for NPX, KTF, and DCF, respectively in aerobic dissipation experiments.

The degradation rates of the compound can be related to soil properties, such as SOM, clay content, and biosolids amendment. The degradation rate constants of NSAIDs was negatively associated with soil clay content Xu et al., 2009b). NPX degraded rapidly in soils with

half-lives between 3.1 to 6.9 d, in soil-biosolid mixtures with half-lives between 3.9 to 15.1 d (Monteiro and Boxall, 2009). When NPX was in a compound mixture, the degradation rate was slower in both soils and soil-biosolid mixtures with half-lives ranging from 4.0 to 15.3 d and 10.9 to 19.9 d, respectively (Monteiro and Boxall, 2009). Amendment with biosolids has been reported to increase SOM content and microorganism density: on the one hand, the continuous increase of SOM can facilitate the sorption of NPX, thus hindering its bioavailability and biodegradation (Monteiro and Boxall, 2009). Degradation of KTF was also promoted by increased SOM, however, continuous increased SOM impeded the microbial availability of KTF (Xu et al., 2009a). Topp et al. (2008) reported rapid mineralization of NPX to CO2 in sandy loam, loam and silt loam soils receiving LMB with a half-life of 2d when incubated at 30 ℃ and approximately 15% soil moisture content; no mineralization was observed in autoclaved soils. The addition of the LMBs introduced microorganisms which appeared to enhance the degradation of NPX was also reported by Al-Rajab et al. (2015).

1.2.4.4 Mobility and leaching

Acidic NSAIDs can migrate through soils and reach the adjacent surface and groundwater the following irrigation with reclaimed wastewater or after biosolids application (Topp et al., 2008; Edwards et al., 2009; Gottschall et al., 2012; Chen et al., 2013; González-Naranjo et al., 2013). IBF, KTF, and DCF were measured at maximum concentrations of 395, 2886 and 24 ng L^{-1}, respectively, in ground waters of 23 European countries (Loos et al., 2010). IBF was found in groundwater at concentrations of 25.1 ng L^{-1} in Jasper, Canada (Van Stempvoort et al., 2013). Sui et al. (2015) reviewed the concentrations of some NSAIDs detected in groundwater during 2012 to 2014 in Spain, China, Switzerland, Singapore, Serbia and Germany; and the concentrations of IBF, NPX and DCF reached up to 988, 86.9 and 380 ng L^{-1}

respectively. IBF has been detected in agricultural tile water and groundwater at concentrations of 24 and 10 ng L^{-1} after a high single application of municipal biosolids to a field, applied at a rate of 22 Mg dw ha^{-1} (Gottschall et al., 2012). The maximum 1.05 μg L^{-1} of NPX and 4.12 μg L^{-1} of IBF were detected in tile drainage after nine month land application of liquid municipal biosolids (LMBs) at a rate of 93,500 L ha^{-1} (~ 1 Mg dw ha^{-1}), and NPX and IBF were found at maximum concentrations of 0.03 and 0.07 μg L^{-1}, respectively, after following application of dewatered municipal biosolids (DMBs) (Lapen et al., 2008). Edwards et al. (2009) also found NPX in tile drainage prior land application of DMB, but after nine-month land application of LMB; NPX and IBF peaked at concentrations of 73 and 29 ng L^{-1} respectively, in tile effluent post-application of DMB at a rate of ~ 8 Mg dw ha^{-1}. The amount of NSAIDs mobilized in soil column increased when then loading of biosolids increased (Borgman and Chefetz, 2013).

The amounts of NSAIDs leaching in soil columns varied with texture (silt loam, silty clay and sandy clay), accounted for 6 to 56%, 2 to 18%, 2 to 22% and 6 to 33%, of the overall IBF, NPX, KTF and DCF, respectively (Xu et al., 2010). In a loamy sand soil, concentrations of NPX, IBF, and DCF reached up to 0.21, 0.23 and 0.0042 μg L^{-1}, accounted for 0.97%, 1.4% and 0.17% of the total, respectively, in the drainage water; in the sandy loam soil, concentrations of the same compounds were at negligible levels, <10-5 μg L^{-1}, suggesting that these NSAIDs were more susceptible to leach into the groundwater in the loamy sand soil (Chen et al., 2013). The mobility of NPX might be hindered in soil samples with a higher SOM content resulting from possible π-π interactions between the diaromatic skeleton of naproxen and with aromatic moieties in the SOM (Chefetz et al., 2008, Lin and Gan, 2011). DCF was a slowly-mobile compound in SOM-rich layers, whereas the mobility increased significantly in SOM-poor layers (Chefetz et al., 2008). DCF is more hydrophobic than other NSAIDs, therefore, it is more

retarded in SOM (Borgman and Chefetz, 2013). Low sorption coefficients and desorption hysteresis of IBF at soils irrigated with reclaimed water suggest that IBF could be susceptible to leaching to groundwater (González-Naranjo et al., 2013). The $CaCl_2$ solution had been described to hinder the leaching of NSAIDs in soils (Xu et al., 2010). The leaching of DCF was significantly lower with eluent solutions of 0.01M $CaCl_2$ in arable soil columns (Borgman and Chefetz, 2013). Acidic NSAIDs are sensitive to pH changes in soil, where a higher pH increases carboxylic acid dissociation and solubility, encouraging leaching through the soil (Gibson et al., 2010; Borgman and Chefetz, 2013).

1.2.5 Ecotoxicology

Pharmaceuticals are designed to produce a biological effect on living organisms, which can subsequently present a potential risk to ecosystem health (Ferrari et al., 2003; Fent et al., 2006; Gómez-Oliván et al., 2013; Wu et al., 2015). Renal lesions and alterations of gills were induced for rainbow trout exposed to DCF at the threshold concentrations of 5 μg L^{-1} over 4 weeks (Schwaiger et al., 2004). The cytological effects of DCF in liver, kidney and gills is in agreement with study of Triebskorn et al. (2004). DCF-associated catastrophic population decline in vultures due to acute renal failure was reported in Pakistan (Oaks et al., 2004), and this compound has been attributed to induce acute toxic effects in avian species (Hussain et al., 2008). DCF can cause lethal effects and reproduction reduction on springtail species Folsomia candida after a 4-week exposure (Chen et al., 2015). Lethal toxicity of KTF on Cape Griffon vultures was reported by Naidoo et al. (2010) at doses of 5 mg kg^{-1}. Antioxidant defense system was distresses in mussel Mytilus galloprovincialis gills during two weeks exposure to IBF at concentration of 250 ng L^{-1}, by accessing the oxidative stress biomarkers, such as catalase, glutathione S-transferase-GST, superoxide dismutase, lipid peroxidation and glutathione reductase-GR

(Gonzalez-Rey and Bebianno, 2011). The EC50s were estimated to be 51.4 mg L^{-1} for freshwater cladocerans Daphania magna and 72.6 mg/L for Moina macrocopa when exposed to IBF for 48 h concentration between 1.23 to 100 mg L^{-1} and 3.13 to 50 mg L^{-1}, respectively (Han et al., 2010).

The uptake of NSAIDs from soil into plants has also been documented. NPX and IBF were detected in alfalfa irrigated with reclaimed water at concentrations ranging from <0.011 to 0.061 μg kg^{-1} (Calderón-Preciado et al., 2011). NPX, IBF, and DCF were accumulated in lettuce and spinach at 0.5 μg L^{-1} (Wu et al., 2012). KTF was found at very low level in shoots (Tanoue et al., 2012). NPX an IBF have been taken up into lettuce, carrot, and alfalfa (Carvalho et al., 2014). No NPX, IBF, KTF, and DCF were uptake into soybean and wheat after application of sewage sludge with 22 ng g^{-1} of DCF and 217 ng g^{-1} IBF detected (Cortés et al., 2013). Uptake of DCF and accumulation has been shown in earthworms (Carter et al., 2014a), as well as in radish and ryegrass (Carter et al., 2014b). The bioaccumulation in non-target species and uptake to edible plants poses a secondary poisoning risk through the food chain to top predators.

Toxicity studies related to a mixture of pharmaceutical compounds are scarce (Cleuvers, 2004). Cleuvers (2004) assessed the toxic effects of DCF, IBF, NPX, and acetylsalicylic acid individually and as a mixture of algae and a water flea. In individual compound tests, DCF, IBF, and DCF caused an effect on 50% of the population (half-maximal effective concentration, EC50) on alga at a concentration of 71.9, 342.2 and 625.5 mg L^{-1}; on water flea Daphnia at concentrations of 68.0, 101.2 and 166.3 mg L^{-1}, respectively. For the comparison, mixture toxicity of NSAIDs tested at the EC50 doses were higher: EC50 values were 18.0 mg L^{-1} for DCF, 85.6 mg $L^{-1}$for IBF, 156.4 mg L^{-1} NPX for in the algae test and 17.0 mg L^{-1} for DCF, 25.3 mg L^{-1} for IBF, 41.6 mg L^{-1} NPX for in the algae test (Cleuvers, 2004). Mixture of DCF, IBF and paracetamol had notable cyto-genotoxic effects on freshwater bivalve, Dreissena

polymorpha, Dreissena polymorpha (Parolini and Binelli, 2012), whereas negligible cyto-genotoxic effects of individual DCF (Parolini et al., 2011a) and low to moderated cyto-genotoxic effects of IBF (Parolini et al., 2011b) on this zebra mussel were assessed. It was found that oxidative stress on common carp was induced by DCF and acetaminophen in isolated form and as a mixture (Nava-Álvarez et al., 2014).

1.2.6 Conclusions

The NSAIDs are not eliminated efficiently due to their amphiphilic properties and their characteristics make them biologically persistent in environmental systems. Irrigation with reclaimed wastewater or use of biosolids as soil amendments is common practices in agriculture. The result is a potential loading of bioactive pharmaceutical compounds into terrestrial and aquatic environments. They pose a potential threat to the environment in the long run, even though only trace levels are currently being detected. Moreover, the co-existence of these compounds with different chemical structures as mixtures in the soil environment may have a greater impact on the fate of pharmaceuticals. In this respect, investigating the fate, especially the persistence and sorption-desorption processes, of these trace contaminants in agricultural soils is critical. Thus, the research objective of this project is to evaluate sorption and desorption dynamics of individual and mixed non-steroidal anti-inflammatory drugs (NSAIDs) compound systems in soil and soil-biosolid matrices.

2 Sorption and Desorption of Selected Non-steroidal Anti-inflammatory Drugs in an Agricultural Loam-textured Soil

2.1 Introduction

Concern over the presence and fate of pharmaceutical compounds in the natural environment is increasing (Kolpin et al., 2002; Thiele-Bruhn, 2003; Caracciolo et al., 2015). The potentially negative interaction of pharmaceuticals and other organic compounds originating from consumer products, with biological systems has resulted in them being categorized as emerging contaminants (ECs) or emerging substances of concern (ESOC). Non-steroidal, anti-inflammatory drugs (NSAIDs) are some of the highest consumed over-the-counter medications globally. The global market for NSAIDs reached $11.4 billion in 2014 (BCC research, 2015). This class of medication describes a group of compounds that has antipyretic, analgesic, anti-inflammatory effects in the treatment of rheumatic disorders, pain and inflammation (Mestre et al., 2007). At low doses, NSAIDs are effective at treating symptoms for short periods of time but are subsequently excreted from the body as the undegraded parent substance, or a degraded water-soluble metabolite (Buser et al., 1999). Consequently, a large fraction of NSAIDs makes their way through wastewater treatment plants (WWTPs) or sewage treatment plants (STPs) with only partial degradation. (Metcalfe et al., 2003; Castiglioni et al., 2006; Reemtsma et al., 2006; Kasprzyk-Hordern et al., 2009). Under circumstances where reclaimed wastewater is used for agricultural irrigation or biosolids is land applied, NSAIDs can enter the soil and groundwater systems (Topp et al., 2008; Gottschall et al., 2012).

Previous studies have reported an elimination efficiency of specific NSAIDs in WWTPs to be highly variable. Diclofenac has an estimated degradation range from 20 to 40%, while ibuprofen degrades easily under aerobic conditions (> 90% removal), and naproxen removal has been measured, in the range of 50 to 80% in biological wastewater treatment (Joss et al., 2005).

Nevertheless, residual concentrations of NSAIDs are consistently being detected in aquatic and terrestrial environments (Heberer, 2002; Calderón-Preciado et al., 2011; Gómez-Oliván et al., 2013). NSAIDs are an environmentally relevant group of compounds, due to their potential to negatively affect the physiology of multiple organisms, as well as their high proliferation globally. NSAID-associated acute renal failure in vultures scavenging on livestock carcasses in certain parts of Asia is well documented, particularly with respect to diclofenac, and speaks to a much broader issue of concern (Oaks et al., 2004; Cuthbert et al., 2007). The uptake of diclofenac in soil biological indicators, e.g. earthworms and plants, highlights the need to determine potential threats of NSAIDs in terrestrial systems (Carter et al., 2014a and b). Therefore, understanding the nature of environmental persistence and degradation of NSAIDs is not only of scientific interest but also in the public interest.

Sorption and desorption of chemicals to soil or organic matter are important dynamic processes influencing the transport and biodegradation of ESOCs in the environment (Scheytt et al., 2005; Lorphensri et al., 2006; Chefetz et al., 2008; Lin and Gan, 2011; Mrozik et al., 2014). Solution chemistry and sorbent properties of the solid surface have been shown to largely influence the sorption of ESOCs in soils (Tolls et al., 2001; Drillia et al., 2005; Chefetz et al., 2008). There has been the considerable focus in the scientific literature on the mobility and sorption of individual NSAIDs, such as naproxen, diclofenac, and ibuprofen (Scheytt et al., 2005). However, NSAIDs invariably enter into soil or aquatic ecosystems as mixtures and the co-existence of these compounds in soils can affect their mutual sorption and desorption dynamics (Wu et al. 2009). These phenomena may increase the transport of specific NSAIDs or lead to increased potential risks associated with the presence of low levels of combinations of these compounds (Pomati et al., 2006; Nava-Álvarez et al., 2014). Few studies have examined

the sorption-desorption dynamics of pharmaceuticals in mixed compound systems (Wu et al. 2009; Conkle et al., 2010), and none have focused on NSAIDs.

In an effort to determine how target NSAIDs might distribute in a soil environment, the sorption-desorption dynamics of four highly prevalent NSAID compounds, diclofenac sodium (DCF), naproxen (NPX), ketoprofen (KTF), and ibuprofen (IBF), were studied in single compound and mixed compound systems added to a loam-textured soil. The objective of this study was to determine the individual- and mixed-compound sorption/desorption coefficients of NSAIDs in a loam-textured agricultural soil.

2.2 Materials and Methods

2.2.1 Soils

Soil samples were collected from a private owned agricultural field, located in Mt. Hope, Ontario, (43°15'N, 79°8855'W,). The soil is mapped as a Brantford Series, Gray-Brown Podzol in the Canadian Soil Classification System (CanSIS, 2016). The soil was sampled from the surface to 15 cm depth during the period of October to November 2013. The soil is a loam-textured soil, composed of 42%-41%-18% sand-silt-clay by weight, respectively (Table 2.1). Following collection, soils were air-dried, initially sieved to <4.75 mm to remove large organic debris, and then sieved to a particle size < 2 mm. The soil was analyzed for a range of chemical characteristics by Department of Agricultural Laboratory Services (Truro, NS) which are listed in Table 2.1. Particle size distribution was determined following the hydrometer method as described in Kroetsch and Wang (2008).

Table 2.1 Selected characteristics of a loam textured soil (Mt. Hope, Ontario) matrix used for batch sorption-desorption studies with four non-steroidal anti-inflammatory drugs.

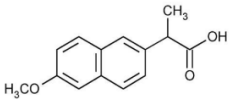
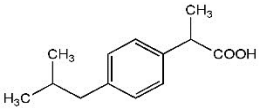
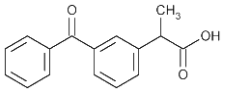
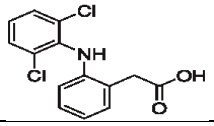
Parameter	Values
Clay (%)	17.7
Silt (%)	40.7
Sand (%)	41.7
pH	6.1
Organic matter (%)	3.8
Calcium (ppm)	2782.5
Magnesium (ppm)	242.5
Aluminum (ppm)	818
Copper (ppm)	4.45
Iron (ppm)	181
Cation exchange capacity (meg/100g)	20.5
Potassium (%)	5.7
Calcium (%)	67.8
Magnesium (%)	9.8
Sodium (%)	0.7
Hydrogen (%)	16.0

2.2.2 Chemicals and reagents

Naproxen (NPX, ≥98% of purity), ibuprofen (IBF, ≥98% of purity), ketoprofen (KTF, ≥98% of purity) and diclofenac sodium salt (DCF, 98.5% of purity) were purchased from Sigma-Aldrich (Oakville, Ontario, Canada). The derivatization reagent N-tert-butyldimethylsilyl-N-methyltrifluoroacetamide (MTBSTFA) was also purchased from Sigma-Aldrich. Other chemicals including ethyl acetate (Optima ® LC-MS grade), methanol (99.9%), calcium chloride dihydrate (104%), and sodium azide (99%) used in this study were purchased from Sigma-Aldrich and Fisher Scientific (Ottawa, Ontario, Canada). Internal standards (±)-ibuprofen-d_3 (99.4%), (±)-naproxen-d_3 (99.9%) and (±)-ketoprofen-d_4 (99.7%) were purchased from CDN Isotopes INC. (Pointe-Claire, Quebec, Canada). Stock solutions of the reference NSAIDs (NPX, IBF, KTF, and DCF) were prepared in ethyl acetate at a concentration of 500 mg L^{-1} and stored

at -18 °C. The chemical properties and molecule structure of the target NSAIDs are shown in Table 2.2.

Table 2.2 Chemical properties and structures of four non-steroidal anti-inflammatory drugs (NSAIDs).

Compound	Molecular weight ($g\ mol^{-1}$)	Structure	Water solubility[a] (K_{sp}, mg/L)	Octanol-water coefficient[a] (Log K_{ow})	Acid dissociation constant[a] (pK_a)
Naproxen (NPX)	230		15.9	3.18	4.15
Ibuprofen (IBF)	206		2.4	3.97	4.91
Ketoprofen (KTF)	254		51	3.12	4.45
Diclofenac (DCF)	296		2.37	4.51	4.15

[a] Data are from SRC's Interactive PhysProp Database.
Accessible at http://esc.syrres.com/fatepointer/search.asp

2.2.3 Batch sorption-desorption experimental design

Batch sorption-desorption equilibrium tests were conducted for each of the selected NSAIDs in the soil following OECD Guideline No. 106 (OECD, 2000). Three grams of soil (dry weight equivalent) were mixed in 15 mL of 0.01 M $CaCl_2$ solution in 50 mL polypropylene centrifuge tubes, a 1:5 (v/v) soil/solution ratio was recommended by the OECD guidelines (OECD, 2000). Sodium azide (5 mg) was added into each centrifuge tube to inhibit microbial activity during the equilibration period (Trevors, 1996). An aliquot of each individual NSAID compound or a mixture of four NSAID compounds (DCF, NPX, IBF, and KTF) was spiked into each centrifuge tube at six different concentrations (0.01, 0.02, 0.05, 0.1, 0.2, and 0.5 mg L^{-1}). The soil suspensions were agitated at 150 rpm at room temperature for 24 hours in the dark. The equilibrium time (24 hours) selected was based on values reported in the literature (Chefetz et al.,

2008; Xu et al., 2009a and b; Lin and Gan, 2011) and on a preliminary test on NPX over a range of concentrations. A soil control in 0.01 M $CaCl_2$ solution (without spiking of NSAIDs) was used to confirm that no compounds originated from the matrix. A positive control, a blank solution of 0.01 M $CaCl_2$ with spiking of NSAIDs (without soil), an i.e. spiked solution without soil, was also included in the study. The spiked solution of NSAID at each concentration level, the soil control, and the positive control was repeated in triplicate and were all analyzed together. After shaking, the treatments were centrifuged for 20 min at 3000 rpm to separate the soil and aqueous phases; subsequently, supernatant (approximately 13 mL) was recovered from each vessel.

Desorption was conducted using the experimental units from the sorption study right after. The desorption isotherms were determined following the procedures listed in OECD 106 (OECD, 2000). Each experimental unit received 13 mL of fresh 0.01 M $CaCl_2$ solution to achieve a volume of 15 mL. The centrifuge tubes were shaken for 24 h, centrifuged, and supernatant (approximately 13 mL) was recovered from each vessel. The liquid phase recovered was analyzed as described in section 2.4 below.

2.2.4 Solid-phase extraction (SPE) and GC-MS analysis

The supernatant recovered for each sorption or desorption concentration treatment was extracted by solid-phase extraction (SPE) using a Phenomenex (Phenomenex Inc., Torrance, CA) reverse phase polymeric sorbent (200 mg, 6mL, Strata-X^{TM}). The cartridges were pre-conditioned by sequentially eluting with 3 mL of ethyl acetate, 3 mL of methanol, and 3 mL of de-ionized water adjusted to a pH 3 with H_2SO_4. The aqueous samples were aspirated through cartridges at a rate of about 1 mL min^{-1}, followed by a 5- min evaporation step in a stream of nitrogen. The cartridges were eluted with two successive 4-mL aliquots of ethyl acetate.

Eluates from the SPE were concentrated to approximately 0.5 mL under a gentle stream of nitrogen in a water bath at 50 °C and then transferred to a 2 mL autolock amber vials. The autolock amber vials were then spiked with 100 µL of 2 mg L^{-1} internal standard (a mixture of (±)-ibuprofen-d_3, (±)-naproxen-d_3 and (±)-ketoprofen-d_4) and then concentrated to dryness. The samples were then derivatized at 70 °C for 60 min by adding 100 µl of MTBSTFA and brought up to a final volume of 200 µL with ethyl acetate.

Derivatized samples were analyzed by gas chromatography-mass spectrometry by injecting 1 µL in a splitless mode using an Agilent 7890 series gas chromatograph (Agilent Technologies, Santa, Clara, CA) interfaced to an Agilent 5975C mass-selective detector in selected ion monitoring (SIM). The carrier gas was helium with a constant flow rate of 1.2 mL min^{-1}. The following GC oven temperature program was used: initial temperature, 70 °C, hold for 1 min; 20 °C min^{-1} to 280 °C, hold for 3 min; and 20 °C min^{-1} to 300°C with a 1-min hold, for a total run time of 16.5 min. Injection port temperature was 250 °C and GC-MS interface temperature was 290 °C.

Table 2.3 NSAIDs included in this study and their characteristic ions (as MTBSTFA derivatives). Bold values are primary ions.

NSAIDs	Retention time (min)	Molecular ion, m/z	Characteristic ions, m/z
Naproxen, NPX	8.49	344	**287**, 185, 288
Ibuprofen, IBF	6.73	328	**263**, 161, 264
Ketoprofen, KTF	9.18	368	**311**, 295, 312
Diclofenac-Na, DCF	9.82	409	**352**, 214, 409

In order to determine the recoveries, seven replicates of three-gram soil matrix were suspended in 15 mL of 0.01 M $CaCl_2$ solution overnight to ensure hydration. The supernatants collected from the soil were spiked at 100 µg L^{-1} with NSAIDs and equilibrated for 24 h prior to the same procedure and determination described above. Average recoveries (n=7) were 103% for NPX, 101% for IBF, 97% for KTF and 99% DCF. The limits of detection (LOD) were expressed

as 3.3 times the standard deviation of responses at the lowest concentration over the slope of the calibration curve. The LOD in this study were 17 µg L^{-1} for NPX; 5 µg L^{-1} for IBF, 7 µg L^{-1} for KTF and DCF. The limits of quantification (LOQ) were expressed as 10 times the standard deviation of responses at the lowest concentration over the slope of the calibration curve. The LOQ in this study were 51 µg L^{-1} for NPX; 16 µg L^{-1} for IBF, 20 µg L^{-1} and KTF; and 22 µg L^{-1} for DCF.

2.2.5 Data analysis

The sorbed amount C_s (mg kg^{-1} dry soil) of NSAIDs to the soil was calculated by subtracting the measured amount in the solution phase after the equilibrium period C_{aq} (mg L^{-1}) from the initial mass added and dividing by the soil mass. The sorption and desorption data were fitted to the Freundlich adsorption isotherm model. The Freundlich adsorption isotherm is described by the equation,

$$\mathrm{Cs} = K_F \times C_{aq}^{n} \qquad [1]$$

Where K_F ($mg^{1-1/n}$ $L^{1/n}$ kg^{-1}) is the Freundlich isotherm constant and n, is the linearity parameter. Average sorption coefficients (K_d, L kg^{-1}) were calculated for all measured paired data using the equation:

$$K_d = \frac{\mathrm{Cs}}{\mathrm{Caq}} \qquad [2]$$

The desorption coefficient (K_{des}, L kg^{-1}) is calculated by the equation,

$$K_{des} = \frac{(m_s^{sor} - m_{aq}^{des}) \times V}{m_{aq}^{des} \times m_{soil}} \qquad [3]$$

Where m_s^{sor} (kg) is the calculated mass of the test NSAIDs adsorbed on the soil at sorption equilibrium; m_{aq}^{des} (kg) is the total mass of test NSAIDs desorbed from the soil, V (L) is total

volume of aqueous phase in contact with soil, m_{soil} (kg) is the mass of soil. The sorption-desorption hysteresis index (HI) was quantified for each NSAIDs, defined by (Huang et al., 1998):

$$HI = \left[\frac{C_s^{des} - C_s^{sor}}{C_s^{sor}}\right]_{average} \quad [4]$$

Where the C_s^{des} (mg kg^{-1}) and C_s^{sor} (mg kg^{-1}) are solid-phase solute concentrations for desorption and sorption processes, respectively.

Standard calibration curves were fitted by linear regression analysis in Minitab 17 (Minitab Inc., State College, USA). One-way analysis of variance (ANOVA) with Tukey's test was used to determine the difference between mean K_d values among four NSAIDs. The difference between K_d values in the individual and mixed compound treatments were analyzed using the general linear model of ANOVA with two factors of interest: concentrations, and individual vs. mixed compound treatments. The probability level of significance was used to express the strength of the relationship between variables at $p<0.05$. If significance was found on the effects ($p <005$), One-way analysis of variance (ANOVA) with Tukey's test to completed the multiple means comparison and generate the latter groups using a 5% level of significance. SigmaPlot software 12.0 (Systat Software Inc., San Jose, CA) was used for all model fitting and estimating Freundlich isotherm constant K_F and linearity parameter n in this study.

2.3 Results and discussion

2.3.1 Sorption of NSAIDs to an agricultural loam soil

Graphical representations of the sorption isotherms of selected NSAIDs in the loam soil for individual and mixed compound systems are shown in Fig. 1. The sorption isotherms did not reach sorption maxima, indicating unsaturated sorption sites on the soil at the concentrations in

the study. Sorption equilibrium data of the four NSAIDs were fitted well using the Freundlich model ($R^2 > 0.99$) (Table 2.4). Freundlich isotherms were used in this study since it is based upon as assumption of cooperative multilayer adsorption, which takes compound-compound and compound-soil components interactions into consideration (Liu, 2015). Values for the linearity parameter, n, were not close to 1, indicating non-linear sorption. This parameter is a measurement of adsorption intensity and soil surface heterogeneity. The Freundlich isotherm constant, K_F, represent the sorption affinity of NSAIDs to the soil were n-dependent and therefore not comparable when the n values are different (Martínez-Hernández et al., 2014). Experimental average K_d values were calculated for all the measured data to allow comparison the sorption distributions between soil and solutions among NSAIDs (Xu et al., 2009a and b; Martínez-Hernández et al., 2014). The discrepancy between K_F and K_d is due to the non-linearity of the isotherm (Scheytt et al., 2005).

2.3.1.1 Individual-compound and mixed-compound sorption

Based on observation of the Freundlich isotherm constant (K_F), the sorption affinity of the NSAIDs in the individual-compound system to the loam soil followed the order: IBF > NPX > DCF > KTF; in the mixed-compound system, the order was IBF > DCF > NPX > KTF. The higher the K_F values, the greater sorption affinity of the compound to the soil. The differences between K_F and K_d values were due to the non-linearity of isotherms, especially for IBF. Comparing the K_d values obtained in the individual compound batch sorption experiments, the order of the degree to which the target NSAIDs were sorbed (K_d) to the soil was: DCF > NPX > KTF > IBF, the average percentage of compound sorbed to the soil (m) was 71% for DCF, 59% for NPX, 52% for KTF and 43% for IBF (Table 2.4). Analysis of variance indicated significant differences in K_d values between the NSAIDs. The K_d values for all concentrations in the mixed-

Table 2.4 Sorption and desorption parameters of four NSAIDs in a loam-textured soil (Mt. Hope, Ontario) in individual-compound and mixed-compound systems ((Mean ± SD, n=18). Number subscripted by HI show the initial concentration of the tested compound

Compound	Sorption					Desorption					
	m^a	$K_F{}^b$	n^c	R^2	$K_d{}^d$	m^e	$K_{Fdes}{}^f$	n^c	R^2	$K_{des}{}^g$	HI^h
Individual-compound system											
Naproxen	0.6±0.1	16.2±1.8	1.4±0.1	0.998	6.5±1.4	0.3±0.1	212.3±70.7	1.8±0.1	0.996	12.3±8.1	0.8
Ibuprofen	0.4±0.1	19.0±3.0	1.8±0.0	0.996	3.4±1.3	0.4±0.1	223.1±71.6	2.1±0.1	0.997	6.7±3.9	0.7
Ketoprofen	0.5±0.0	6.5±0.5	1.2±0.0	0.998	4.8±0.7	0.3±0.0	18.4±2.7	1.2±0.1	0.997	11.1±1.7	0.7
Diclofenac	0.7±0.0	8.3±0.3	0.9±0.0	0.999	10.9±2.1	0.1±0.1	10.5±1.9	0.8±0.1	0.992	55.3±52.2	0.9
Mixed-compound system											
Naproxen	0.6±0.1	7.2±0.2	1.1±0.0	1.000	5.6±1.5	0.2±0.1	18.1±3.2	0.9±0.1	0.994	33.8±18.7	0.9
Ibuprofen	0.4±0.1	33.5±9.5	2.0±0.0	0.993	3.7±1.6	0.3±0.1	244.6±103.3	1.9±0.2	0.995	9.6±4.6	0.8
Ketoprofen	0.5±0.0	4.6±0.1	1.0±0.0	1.000	4.4±0.4	0.2±0.0	10.3±0.5	0.9±0.0	1.000	13.2±1.8	0.7
Diclofenac	0.7±0.0	7.5±0.5	0.9±0.0	0.998	11.8±2.8	0.1±0.0	15.3±1.0	0.7±0.0	0.999	60.2±25.1	0.9

in liquid soil solution (mg L^{-1})**.**

[a] Proportion of amount of compound sorbed of total amount added in the loam-textured soil
[b] Freundlich isotherm constant ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)
[c] The linearity parameter
[d] Sorption coefficient ($L\ Kg^{-1}$)
[e] Proportion of amount of compound desorbed from sorbed amount of compound
[f] Freundlich desorption coefficient ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)
[g] Desorption coefficient($L\ Kg^{-1}$)
[h] Sorption-desorption hysteresis index

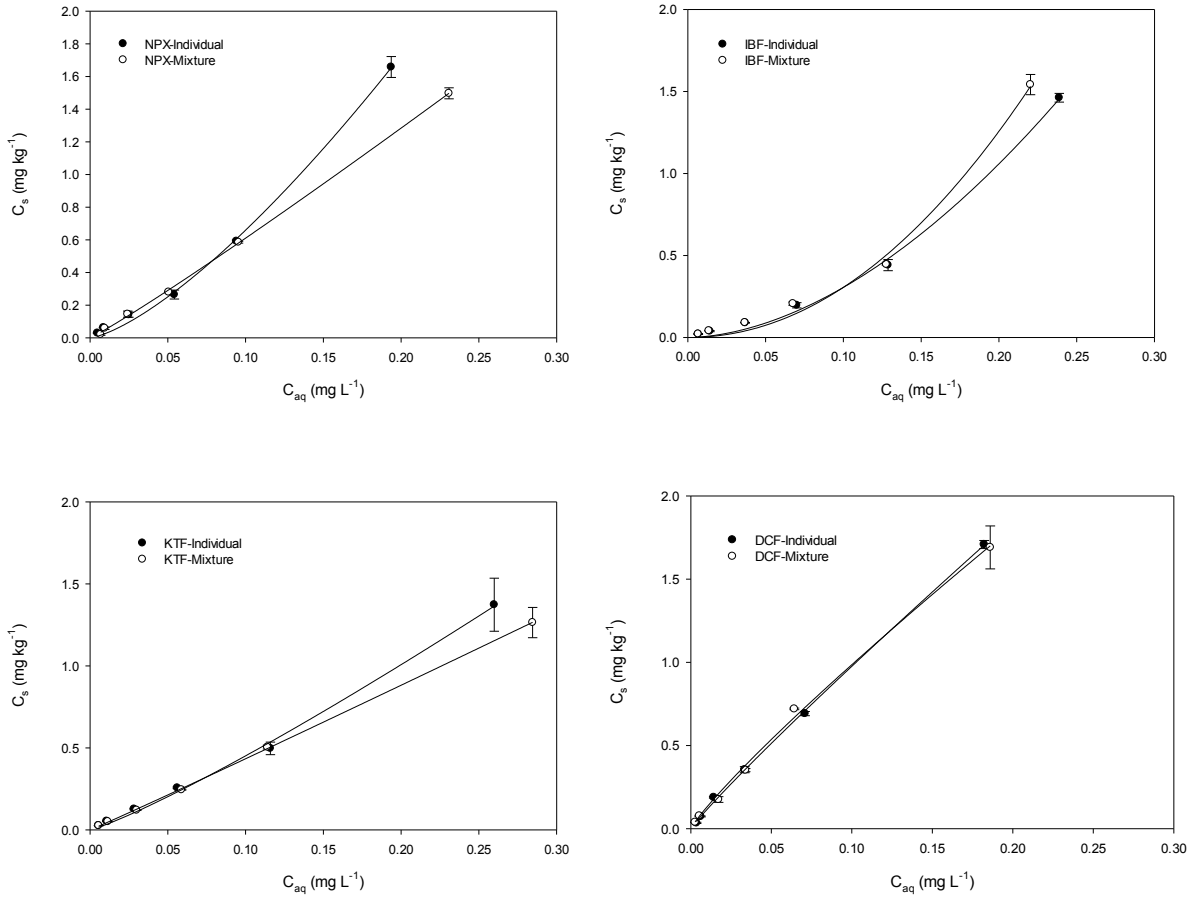


Figure 2.1 Freundlich sorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in the individual compound and mixed compound systems.

compound system yielded the same trend as in individual compound sorption: DCF > NPX > KTF > IBF, and the fraction sorbed to the soil was 72%, 55%, 50% and 45%, respectively (Table 2.4). The K_d value of DCF was statistically different from other three NSAIDs, whereas there was no significant difference among NPX, IBF, and KTF.

The sorption isotherms of NSAIDs in individual- and mixed-compound systems did not exhibit sorption maxima, which suggests unsaturated sorption sites for compounds at the concentrations studied. The isotherms of DCF concaved downward, indicating weaker binding energies associated with soil components when the concentration of DCF increased. In contrast,

isotherms of NPX, IBF and KTF concaved upward, suggesting that these three compounds were bond to soil components with higher binding energy when their concentrations increased.

2.3.1.2 Sorption mechanisms

The surface of the soil is predominantly negatively charged at typical environmental pH (Schwarzenbach et al., 2005). The four NSAIDs, NPX, IBF, KTF, and DCF are weakly acidic, with pKa values ranging from 4.15 to 4.91 (Table 2.2), which are lower than the pH of soil which was 6.1 (Table 2.1). These chemicals are mostly deprotonated and the degree of deprotonation can be calculated according to equations in Martínez-Hernández et al. (2014). The majority of the NSAID molecules were present in anionic forms under the experimental conditions in this study and the degree deprotonation was calculated to be 97% for NPX and DCF, 86% for IBF, and 95% for KTF (Martínez-Hernández et al., 2014). Ionized NSAIDs are repelled by the negatively charged soil particles, therefore, they would be expected to exhibit low affinity to the soil. Sorption of ESOCs to soil particles can be attributable to partition to soil organic matter (SOM), surface complexation with mineral surfaces, ionic interaction, and bonding to different surface moieties (Schwarzenbach et al., 2003; Schaffer et al., 2012). In many cases, sorption of ESOCs has been shown to be correlated with SOM content (Huang et al., 2003; Chefetz et al., 2008; Xu et al., 2009b; Maoz and Chefetz, 2010; Martínez-Hernández et al., 2014). In particular, Xu et al. (2009a and b) reported an increase in NSAID's sorption coefficients as SOM increased.

In both individual and mixed compound systems, IBF had the lowest K_d values (3.4 and 3.7 L kg^{-1}), compared to the other compounds, whereas DCF exhibited the highest sorption (K_d=10.9 and 11.8 L kg^{-1}) to soil. IBF has higher hydrophobicity compared to KTF, which would result in greater partitioning into SOM (Tülp et al. 2009; Yamamoto et al., 2009). The presence

of Al^{3+}, Ca^{2+} and Mg^{2+} at acidic and neutral conditions may have enhanced the sorption of IBF. These cations might lower the negative potential of the soil surface by the complexation with soil surfaces (Bui and Choi, 2010). Simple ligand exchange between positive charged Fe oxides and can also affect the sorption of IBF (Vulava et al., 2016).Greater than 86% of IBF molecules were dissociated, resulting in an anionic molecule, hydrogen bonding can be formed between the 14% cationic acid moieties that were not dissociated and soil surface moieties (Chefetz et al., 2008). However, the repulsive forces between the carboxylic acid moieties within the ionized IBF molecule and the negatively charged particles within the soil hinder sorption (Scheytt et al., 2005; Xu et al., 2009b; Lin and Gan, 2011; Durán-Álvarez et al., 2014). Other authors determined K_d and/or K_F values from 0.02 to 0.1 mg L^{-1} in sediments (Yamamoto et al., 2009), from 0.002-0.04 mg L^{-1} in wastewater irrigated soils (Lin and Gan, 2011), from 0.5 to 10 mg L^{-1} in agricultural soils (Xu et al., 2009a; González-Naranjo et al., 2013), and from 0.01 to 10.0 µg L^{-1} in wastewater irrigated and rainfed agricultural. They all exhibited lower sorption coefficients and/or sorption affinity to soil than in this study no matter at what concentrations. These might be explained by the higher acidity and richer SOM of the loam soil studied than many of the soils reported on in the literature. Negligible sorption of IBF to mineral surfaces (clays) was reported by Lin and Gan (2011), suggesting that clay content was not a major factor affecting adsorption. The non-linearity of the individual compound sorption isotherms (Fig. 1) for IBF implies that the intensity of IBF sorption to the soil surface in our study was not the same across the range of soil solution concentrations, being higher when concentrations increased. This suggested that positive compound-compound interactions may be involved in IBF sorption. In addition, IBF exhibited more linear isotherms (Figure B1 in Appendix B) and lower K_F in both individual- and mixed-compound systems at environmentally relevant concentrations ranging between 0.01 to 0.2 mg L^{-}

[1] (Table B1 in Appendix B) than at concentrations ranged between 0.01 to 0.5 mg L^{-1} (Table 2.4), indicating than the K_F was largely affected by the highest concentration of 0.5 mg L^{-1}. High concentration of solute may cause swelling and disordering of the SOM, resulting in an increase of sorption sites (Wu et al. 2009). Compared to IBF, KTF had a numerically greater and significantly different sorption coefficient, K_d of 4.8 L kg^{-1}, in the individual compound system but not in the mixed compound system, K_d of 4.4 L kg^{-1}. Xu et al. (2009a) observed weak to moderate sorption of KTF with average values of K_d ranging from 1.50 to 8.24 L kg^{-1} in four U.S. soils with pHs around 7. As with IBF, KTF molecules were highly dissociated under experimental pH, as noted above, because of a pK_a value of 4.45; therefore, electrostatic attraction to negatively charged surfaces of OM and mineral would not contribute to sorption (Xu et al., 2009a). The polar anionic forms of KTF decrease the tendency to absorb to SOM. The hydrophobicity of the four NSAIDs followed the order: DCF > IBF > NPX > KTF (Table 2.4). Tülp et al. (2009) suggested sorption of anionic species to soil OM was positively associated with their hydrophobicity. Therefore, KTF may not form considerable association with SOM due to its low hydrophobicity. However, the carboxylate and keto groups of KTF can complex with surface metal species (Al and Fe), metal cations (Al^{3+} and Fe^{3+}) or metal hydrous oxides in the aqueous solution (Gu and Karthikeyan, 2005; Bui and Choi, 2010), lowering the negative potential of the soil surface by forming inner-sphere complexes on soil surfaces. In addition, divalent dissolved cation Mg^{2+} at acidic and neutral conditions can also bridge between anionic KTF and negatively charged soil surface, thus enhancing the sorption of KTF to the soil (Bui and Choi, 2010).

Like KTF and IBF, NPX is also negatively charged at neutral pH and repelled by negatively charged soil particles (Chefetz et al., 2008; Martínez-Hernández et al., 2014).

Negligible electrochemical interactions and sorption onto inorganic surfaces have been suggested by Martínez-Hernández et al. (2014), while sorption to SOM is viewed as the predominant process. The low log K_{ow} of NPX (3.18) suggests it has a limited hydrophobic effect. In previous studies, NPX predominantly partitioned to SOM by π–π interactions between the conjugated π clouds of the aromatic di-ring of NPX and the aromatic moieties of the SOM (Chefetz et al., 2008; Lin and Gan, 2011). At acidic and neutral conditions, Fe oxides and Fe hydroxides have positive charge which enable simple ligand exchange with NPX (Vulava et al., 2016).

The highest sorption coefficient in our study was measured with DCF. The ionization of DCF is expected to be similar to the other NSAIDs, i.e. negatively charged, and expected to exhibit a low sorption affinity to the soil (Scheytt et al., 2005; Chefetz et al., 2008; Lin and Gan, 2011; Graouer-Bacart et al., 2016). However, the high sorption observed can be explained via the formation of complexes between carboxylate groups of DCN and the trivalent cation Al^{3+} and surface metal species Al. At acidic conditions, Al mainly occurs as Al^{3+}, and this cation acts as a bridge between the negatively charged pharmaceutical functional groups and negatively charged sites on soil surfaces (Bui and Choi, 2010). DCF can also sorbed to the amphoteric Al oxides surfaces. The adsorption of DCF was not significantly affected by the divalent cations (Ca^{2+} and Mg^{2}) (Bui and Choi, 2010), therefore, the use of 0.01 $CaCl_2$ solution was expected to have negligible impacts on DCF adsorption. Previous studies presented the formation constants of diclofenac-Cu(II) complexes, log K = 6.8 (Agatonović-Kuštrin et al., 1991) and Cu(II)-soil, log K = 5.3 (Rachou and Sauvé, 2008), suggesting a potential formation of diclofenac-Cu(II)-soil complex of DCF in an acidic soil and thus enhancing the sorption of DCF. Klepsch et al. (2011) reported moderate to strong hydrogen binding of aromatic amines onto the SOM. DCF can, therefore, interact with SOM non-covalently by forming weak to strong hydrogen bonds, cationic

amino moieties can complex with the carboxyl and hydroxyl groups on SOM by either donating or accepting a proton. The highest hydrophobicity of DCF facilitates a partitioning with SOM (Chefetz et al., 2008; Tülp et al. 2009). Drillia et al., (2005) also found a strong distribution coefficient, (K_d =164.5 L kg^{-1}), for DCF in soil with a high organic carbon (OC) content (7.1%), whereas a very low K_d (0.45 L kg^{-1}) was observed in soil with a low OC content (0.37%). The loam soil in our study contained a high level organic matter content (OM = 4.1%, OC ~ 2.3%), which would provide more binding sites for NSAIDs, resulting in K_d = 18.56 5 L kg^{-1} (Table 2.4).

DCF had greater K_d values compared to the other three NSAID compounds. As with the single compound studies, electrostatic interactions were likely negligible due to the repulsive forces of negatively charged soil particles. According to Liu (2015), isotherms of four NSAIDs can be expressed by multilayer cooperative adsorption, which can be both chemisorption (chemical bonding) and/or physical sorption (van der Waals forces). Chemisorption may have occurred for DCF by occupying unique monolayer sites on soil surfaces due to the linearity parameter n being below one. This explains the non-significant differences between individual DCF K_d and mixed NSAID K_d for DCF. The physical sorption of NPX, IBF and KTF can be achieved by adsorbate-adsorbate-adsorbent interactions where values for n were above one, suggesting that the interaction between compounds and soil particles were synergistic and multi-layered (Liu, 2015). In addition, the most hydrophobic partitioning effect of DCF, a stronger surface complexation with Al^{3+} or Al oxides and cationic amine exchange with soil surface, might have resulted a stronger sorption of DCF to the soil. The K_d values for NPX, IBF and KTF were not significantly different. Although there was also no significant difference between the K_d values for individual and mixed compound K_d values for any of the four compounds studied

(NPX, p = 0.108; IBF, p = 0.175, KTF, p = 0.220 and DCF, p = 0.232). Our study points to potential cooperative sorption occurring between NSAID compounds in association with an agricultural loam-textured soil. Cooperative adsorption implies the effect of adsorbed molecules on the adsorption of new adsorbate molecules (Liu, 2015). When exposed to a mixture of compounds, K_d values of NPX and KTF tended to be greater than when the solution contained only the individual compound, whereas DCF and IBF tended to have lower K_d values (Fig.1, Table 2.4) suggesting more hydrophobic compounds are more strongly competitive in partitioning into SOM. The presence of Ca^{2+} at concentration of 0.01 M only significantly increased IBF sorption on Ca-saturated soil components, suggested byBui and Choi (2010).

2.3.2 Desorption tests

Sorption-desorption hysteresis is a common phenomenon and is indicated when the ratio of values of the Freundlich desorption coefficient (K_{Fdes}) are higher than the Freundlich isotherm constant s (K_d) (Huang et al., 1998). This hysteretic effect indicates a stronger retention of NSAIDs during desorption processes compared to initial sorption processes (González-Naranjo et al., 2013). The higher the hysteresis index (HI) values are, the more difficult for sorbed compounds

to be desorb from the matrix (Drillia et al., 2005; Chefetz et al., 2008). Pignatello and Xing (1995) determined that desorption equilibrium may require weeks to months in order to be fully achieved. A potential limitation of our study was that the focus was only on the short-term (24 h) desorption from the loam-textured soil.

2.3.2.1 Individual-compound and mixed-compound desorption estimates

Desorption isotherms of the four NSAIDs studied with the loam-textured soil as individual compounds or mixed compound systems are presented in Figure 2.2. The desorption

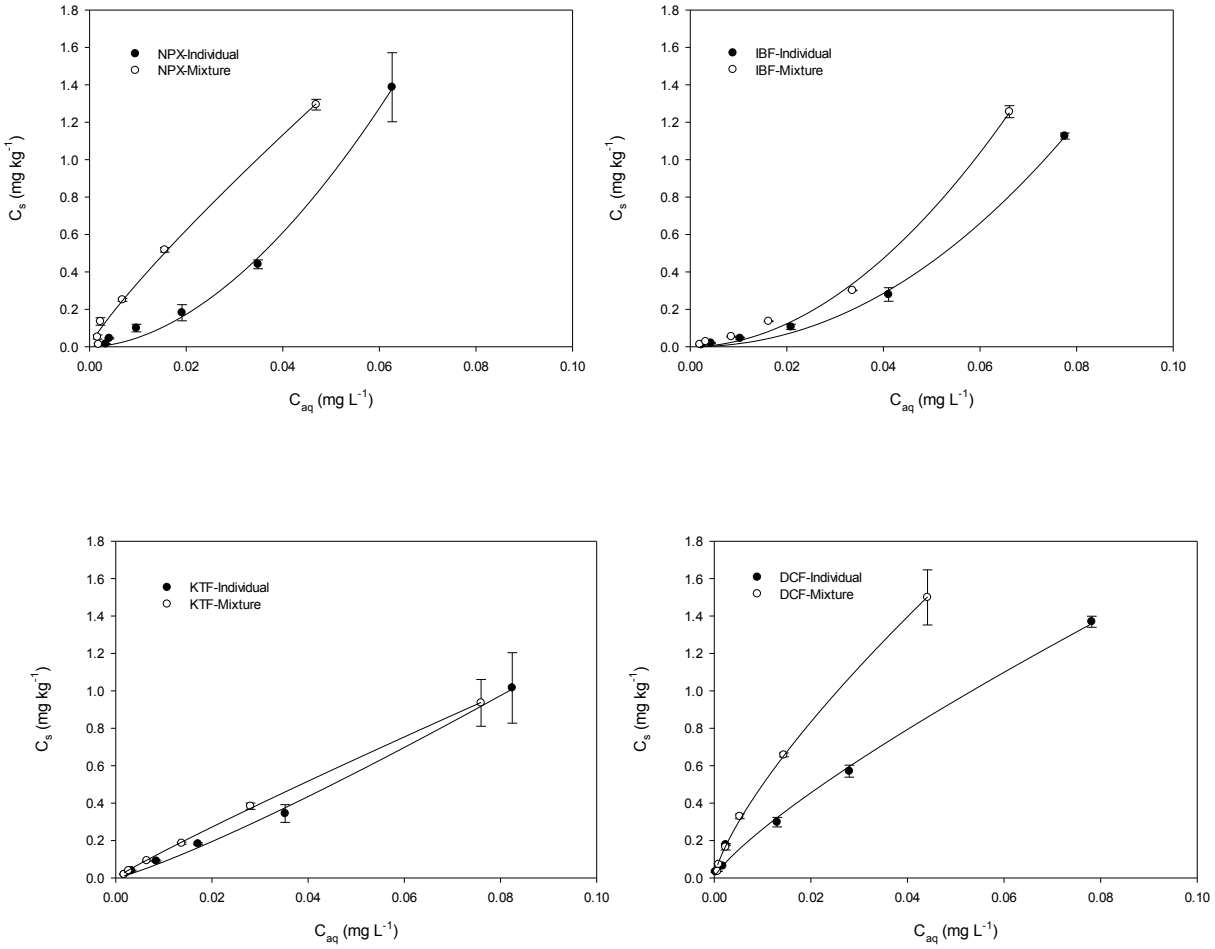


Figure 2.2 Freundlich desorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in the individual compound and mixed compound systems.

processes were non-linear as indicated by the deviation of the linearity parameter (n) from 1.0 (Table 2.4). The order in which the target NSAIDs were desorbed from the soil was: DCF < NPX< KTF < IBF. The decrease in K_{des} values for DCF and increasing K_{des} values for IBF as a function of residual aqueous solution concentration were observed. The Freundlich desorption coefficients, K_{Fdes}, of the four individual-compound NSAIDs in this study were higher than K_d

values obtained during the sorption phase, showing stronger retention of compounds during desorption than in sorption, similar to previous studies (Drillia et al., 2005; Durán–Álvarez et al., 2012; González-Naranjo et al., 2013). Sorption-desorption hysteresis was demonstrated by HI values that were greater than zero (Martínez-Hernández et al., 2014). HI values followed a descending order numerically: DCF > NPX > KTF ≈ IBF.

In individual compound systems, the average percentage of desorbed NSAIDs that desorbed was 13% for DCF, 28% for KTF, 30% for NPX, and 43% for IBF. The K_{des} values for DCF were greater and statistically different than the other three compounds, but the differences between KTF, IBF and NPX were not significant. In regards to the mixed compound system, the average percentage of total sorbed NSAIDs that desorbed for DCF, NPX, KTF and IBF were 8%, 16%, 25% and 33%, respectively. The K_{des} values of the four NSAIDs were significantly different from each other, except between KTF and IBF. Significant differences were observed in the K_{des} values of NSAIDs between the individual compound and mixed compound systems, except for DCF (NPX, $p = 0.001$; IBF, $p = 0.000$, KTF, $p = 0.005$ and DCF, $p = 0.837$).

2.3.2.2 Desorption mechanisms

A high sorption between the soil and DCF was observed in our study, with only 8 to 13% of the sorbed DCF becoming desorbed. Higher HIs for DCF compared to the other three NSAID compounds indicated stronger desorption hysteresis between DCF molecules and soil particles. Non-linear desorption processes, as indicated by n values ranging from 0.9 to 2, suggest that adsorption site energies were differentially distributed (González-Naranjo et al., 2013). These NSAID compounds can interact with soil components covalently or non-covalently in order to maximize their binding affinity, which prevents dissociation from the binding sites. Through multilayer cooperative adsorption, DCF was chemically absorbed to the limited binding sites on

soil surfaces, whereas IBF, NPX and KTF saturated synergistically on the relatively weaker binding sites on the first layer of soil surfaces and formed absorbable layers to accommodate more molecules. Outer layers were less attractive to these molecules but also can prevent compounds from being desorbed from the soil surface. This would explain the non-significant change in desorption coefficients of DCF between the individual compound and mixed compound systems, but a significant increase in K_{des} values of the other NSAIDs in mixed compound systems. Chemical bonding (ionic bonds and covalent bonds) is stronger than van der Waals forces of physical sorption requiring more energy to break, which in turn is stronger than other dipole-dipole interactions enhancing the difficulty of sorbed DCF to be desorbed. Chefetz et al. (2008) reported significant sorption-desorption hysteresis of DCF in soils; higher HIs in the low-SOM content soil than the high-SOM content soil suggest a strong entrapment of DCF in both organic and inorganic soil components. Ligand exchange surface complexation with Al oxides might have occurred other than hydrophobic partitioning into SOM (Bui and Choi, 2010). Ligand exchange bonds are stronger than non-covalent bonds facilitated by other three NSAIDs such as π-π interactions and van der Waals Forces (weak attraction between nonpolar groups), which would result in pronounced hysteresis of DCF than the other NSAIDs.

Low HI values of IBF, ranging from 0.42 to 0.66 for soils (OC%, 0.87^{-1}.7 and pH, 7.63-8.01) were reported by González-Naranjo et al., (2013). Chefetz et al. (2008) also reported lower HIs (0.07-0.16) of NPX than of DCF (0.09-0.62) in soils (OC%, 0.40-8.13; pH, 7.4-7.7). Therefore, the adsorption of NPX and IBF were suggested to be readily desorbed from soil organic and mineral surfaces. Higher sorption-desorption hysteresis for NPX, IBF and KTF were observed in this study, likely due to stronger π–π interactions between carboxyl moieties within

these compound molecules and SOM (Zhu et al., 2004; Lin and Gan, 2011, Martínez-Hernández, et al., 2014).

2.3.3 Conclusions

The sorption of four NSAIDs in a loam-textured soil was found to be dependent on the chemical structures of the compounds. Naproxen, ibuprofen, ketoprofen and diclofenac all exhibited weak to moderate sorption affinity to the soil in our study. In particular, the NSAID mixed compound system displayed synergistic sorption and desorption interactions and higher sorption capacity. This was strongly illustrated with NPX, IBF and KTF by significantly varied desorption coefficients between the individual compound and mixed compound systems during the desorption phase of the study. DCF exhibited strongest binding energy to soil components with the highest sorption and desorption coefficients, and the sorption and desorption dynamics were not affected by other sorbed NSAIDs by insignificant differences in sorption and desorption coefficients between individual- and mixed compound systems. A hysteretic desorption phenomenon was also observed with the selected NSAIDs in this study. Ion interactions and hydrophobic interactions may play an important role in the retention of emerging substances of concern, especially NSAIDs, in the soil. On the basis of this study, the sorption coefficients of NSAIDs exposed to a high organic matter (3.8%) loam soil followed a descending order of: DCF > NPX > KTF > IBF. Cooperative sorption of four NSAIDs in this study demonstrates the need to further investigate sorption and desorption behavior of mixtures of ESOCs across different soil textures and types.

3 Competitive Sorption and Desorption for Non-steroidal Anti-inflammatory Drugs in a Biosolids Amended Agricultural Soil

3.1 Introduction

Organic contaminants, including emerging substances of concern (ESOC), can be introduced into terrestrial environments through reuse of wastewater for irrigation of agricultural land (Kinney et al., 2006a; Gibson et al., 2010; Durán-Álvarez et al., 2012; Durán-Álvarez et al., 2015) and from amending soils with biosolids (Kinney et al., 2006b; McClellan and Halden, 2010). Municipal wastewater treatment plants (WWTPs) are major routes transferring ESOC into the environment. Variable removal efficiencies of ESOC during treatment in WWTPs limits the elimination of these compounds from aquatic or terrestrial environments (Lishman et al., 2006; Kasprzyk-Hordern et al., 2009). Highly hydrophobic compounds partition into sewage sludge, and are present even after treatment into biosolids, while hydrophilic compounds remain in treated wastewater that is discharged from these facilities. The land application of biosolids has been practiced for decades and is still the most common method of disposal. In the United States and Europe, millions of dry tons of biosolids are generated every year with over 50% reused (Chang et al., 2002; Kinney et al. 2006; McClellan and Halden, 2010). Approximately 388,700 dry tonnes of biosolids are generated in Canada annually, and about 43% of the total were land applied, with the remainder incinerated, disposed in landfills and used for land reclamation or other uses (Apedaile 2001). About 120 thousand dry tons of sewage biosolids are applied to agricultural fields annually in Ontario, Canada (Sabourin et al., 2012). Residual ESOC parent compounds are found at medium concentrations from μg kg^{-1} to mg kg^{-1}in biosolids (Xia et al., 2005; CCME, 2010; McClellan and Halden, 2010) and in biosolids amended agricultural soils (Edwards et al., 2009; Chen et al., 013; Aznar et al., 2014; Li, 2014). Some ESOC has been

detected at low concentrations in tile drainage and runoff after application of liquid municipal sewage to soils in Ontario, Canada (Lapen et al., 2008; Topp et al., 2008).

Alkaline treated biosolids (ATBs) are the product of an alkaline stabilization process in which sufficient lime or other alkaline materials are added to the municipal biosolids to bring the material up to a pH of 12 after two hours mixing (NSE, 2010). Addition of ATBs to soil can be agronomical beneficial (Christie et al., 2001; Singh and Agrawal, 2008), as well as improving many soil properties such as the soil solution pH, the cation exchange capacity (CEC), and soil organic carbon (OC) content (Brown et al., 2011; Price et al., 2015). The use of ATBs is prevalent in many parts of North America due to the ease of transporting and applying the material in agricultural soils. While the quality of the material varies based on the geographic location, many ATBs in Canada are categorized as Class A biosolids that can be applied to soils with few restrictions (CCME, 2010).

Non-steroidal Anti-inflammatory Drugs (NSAIDs), including naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF) and diclofenac-Na (DCF), are extensively used as medications and have antipyretic, analgesic, anti-inflammatory effects in the treatment of rheumatic disorders, pain, and inflammation (Mestre et al., 2007). IBF is one of the World Health Organization's (WHO) essential medicines, while NPX was listed on 27 and DCF on 74 of the List of Essential Medicines (EMLs) of 100 countries (McGettigan and Henry, 2013). The market share of DCF is larger than that of other three NSIADs (McGettigan and Henry, 2013). NSAIDs are reported to have adverse effects on non-target organisms, even at trace levels (Cleuvers, 2004; Schnell et al., 2009; Nava-Álvarez et al., 2014). Therefore, their fate in soils is attracting increasing attention, particularly with respect to their persistence and degradation (Topp et al., 2008; Xu et al., 2009a and b; Lin and Gan, 2011), transport into groundwater (Tsekoura et al., 2011; Borgman and

Chefetz, 2013), and uptake by plants (Sabourin et al., 2012; Carter et al., 2014a and b; Wu et al., 2015), especially in the context of land application of biosolids. NPX and IBF have been detected in biosolids at concentrations of 98.1 and 522 ng g^{-1} total solid dewatered, respectively, and concentrations in the ATBs (N-Viro) were 178 and 522 ng g^{-1} total solid dewatered, respectively (CCME, 2010). The pH-dependent sorption of acidic NSAIDs to soil organic matter has been reported by Tülp et al. (2009). As soil pH increases, acidic compounds tend to be more ionized and water soluble, leading to lower electrostatic interactions and partitioning into natural organic matter (Gibson et al., 2010; Borgman and Chefetz, 2013). SOM has been shown to promote the sorption of NSAIDs to soils (Drillia et al. 2005; Chefetz et al., 2008; Xu et al., 2009b). Hence, evaluating the effect of ATBs amendment on desorption and desorption of NSAIDs in soils is particularly important.

There are various possible outcomes for NSAIDs once they enter into soils that depend on their sorption and desorption capacities, biodegradation potential, and solubility that depends on how they interact with surfaces, and with each other, when present in mixture. Compounds with strong sorption properties are recalcitrant to degradation and remain on the soil surface. Some potential for subsequent plant uptake and bioaccumulation in soil organisms exists, whereas compounds that are less sorbed will have greater leaching potential. Sorption-desorption studies for ESOC, including NSAIDs, often consider individual compounds although in reality they enter as mixtures in the environment (Scheytt et al.,2005; Xu et al., 2009a and b; Durán-Álvarez et al., 2012; Durán–Álvarez et al., 2014; Estevez et al., 2014). Measurements of sorption and desorption coefficients for mixture-NSAIDs in soils are not common in the scientific literature, perhaps due to the complexity of the interacting mechanisms. Nevertheless, understanding of the mechanisms driving sorption and desorption behavior of NSAID mixtures

in the soil provides better insight to determine their fate, and possible eco-toxicity, notably in agricultural soils that can serve as sinks for these compounds. In these situations, the contaminants may compete for soil surfaces, or act synergistically to enhance retention over time.

The objective of this study was to determine the sorption and desorption dynamics of selected NSAIDs (NPX, IBF, KTF, and DCF) in an agricultural loam-textured soil receiving an amendment of ATBs. The behavior of NSAIDs were compared as individual and mixture compound systems in the soil-biosolid matrix.

3.2 Materials and Methods

3.2.1 Soils and biosolids

Soil samples were collected from a privately owned agricultural field, located in Mt. Hope, Ontario, (43°15'N, 79°8855'W). The soil is mapped as a Brantford Series, Gray-Brown Podzol in the Canadian Soil Classification System (CanSIS, 2016). The soil was sampled from the surface to 15 cm depth during the period of October to November, 2013. Following collection, soils were air-dried, initially sieved to <4.75 mm to remove large organic debris, and then sieved to a particle size < 2 mm. A number of chemical properties were analyzed by Department of Agricultural Laboratory Services (Truro, NS) that are presented in Table 3.1. Particle size distribution was determined separately at the Faculty of Agriculture, Dalhousie University following the hydrometer method as described in Kroetsch and Wang (2008).

An alkaline treated biosolids (ATBs) was obtained from the Halifax Biosolids Facility operated by N-VIRO Systems Canada Ltd., owned by the Walker Group, in Halifax, Nova Scotia, Canada. The ATBs properties are presented in Table 3.1. Soil-biosolid matrix was achieved by mixing 2.957 g of soil with 0.043 g of ATBs to achieved a rate equivalent to the field

application rate of 28 Mg ha^{-1} (wet weight equivalent). Soil-biosolid matrix properties were listed in Table 3.1.

Table 3.1 Selected characteristics of an alkaline treated biosolids (ATB) (wet basis) and a soil-biosolid matrix applied for batch sorption-desorption studies with four non-steroidal anti-inflammatory drugs.

Parameter	Biosolids	Soil-biosolid
pH	10.42	7.0
Organic matter (%)	15.9	3.7
Dry matter	67.5	N/A
Calcium (ppm)	78187	2848
Magnesium (ppm)	1323.5	246.8
Aluminum (ppm)	727.5	769
Copper (ppm)	44.5	3.9
Iron (ppm)	286	207.5
Cation exchange capacity (meg/100g)	235.6	18.5
Potassium (%)	13.2	4.0
Calcium (%)	83.1	76.8
Magnesium (%)	2.4	11.1
Sodium (%)	1.4	0.6
Hydrogen (%)	0	7.6

N/A: not applicable.

3.2.2 Chemicals and reagents

The analytes naproxen (≥98% of purity), ibuprofen (≥98% of purity), ketoprofen (≥98% of purity) and diclofenac sodium salt (98.5% of purity), as well as the derivatization reagent N-tert-butyldimethylsilyl-N-methyltrifluoroacetamide (MTBSTFA) were all purchased from Sigma-Aldrich (Oakville, Ontario, Canada). Other chemical solvents obtained, including ethyl acetate (Optima ® LC-MS grade), methanol (99.9%), calcium chloride dihydrate (104%), and sodium azide (99%) for this study were purchased from Sigma-Aldrich and Fisher Scientific (Ottawa, Ontario, Canada). Internal standards (±)-ibuprofen-d_3 (99.4%), (±)-naproxen-d_3 (99.9%) and (±)-ketoprofen-d_4 (99.7%) were purchased from CDN Isotopes INC. (Pointe-Claire, Quebec,

Canada), Stock solutions of the reference NSAIDs (NPX, IBF, KTF and DCF) were prepared in ethyl acetate at concentration of 500 mg L^{-1}, and stored at $^{-1}8$ °C. Working solutions were obtained by diluting from stock standard solutions. The chemical properties and molecule structure of the target NSAIDs are shown in Table 2.2.

3.2.3 Batch sorption-desorption experimental design

Batch sorption-desorption equilibrium tests were conducted for each of the selected NSAIDs in the soil-biosolid matrix following OECD Guideline No. 106 (OECD, 2000). A three gram sample (soil-biosolid matrix) was mixed with 15 mL of 0.01 M $CaCl_2$ solution to achieve a solid to solution ratio of 1:5 (v/v) in 50 mL polypropylene centrifuge tubes. Sodium azide (5 mg) was added into each centrifuge tube to inhibit microbial activity during the equilibration period (Trevors, 1996). An aliquot of individual NSAID compound or a mixture of four NSAID compounds (DCF, NPX, KTF, and IBF) was spiked into each centrifuge tube at six different concentrations (0.01, 0.02, 0.05, 0.1, 0.2, and 0.5 mg L^{-1}). The soil-biosolid suspensions were shaken at 150 rpm at room temperature for 24 hours in the dark. The equilibrium time (24 hours) selected was based on values in soils reported in the literature (Chefetz et al., 2008; Xu et al., 2009a and b; Lin and Gan, 2011) and on a preliminary test on NPX in the loam-textured soil over a range of concentrations. A soil-biosolid control in an unspiked 0.01 M $CaCl_2$ solution was used to confirm that no NSAIDs desorbed from the matrix. In addition, an unspiked, unamended (blank) solution of 0.01 M $CaCl_2$ was also included in the study. The treatments in the study, i.e. solution spiked with NSAID at each concentration level, the control, and the blank solution, were repeated in triplicate and were all analyzed together. After shaking, the treatments were centrifuged for 20 min at 3000 rpm to separate the solid and aqueous phases; subsequently, the supernatant was recovered from each vessel (approximately 13 mL). Desorption was conducted

using the experimental units from the sorption study. The desorption isotherms were determined following the procedures listed in OECD 106 (OECD, 2000). Each experimental unit received fresh 13 mL of 0.01 M $CaCl_2$ solution (without NSAIDs) to achieve a volume of 15 mL. The centrifuge tubes were shaken for 24 h, centrifuged, and decanted as described above. The supernatant recovered (approximately 13 mL) was analyzed as described in section 2.4 below.

3.2.4 Solid-phase extraction (SPE) and GC-MS analysis

The supernatant recovered for each sorption or desorption concentration treatment was cleanup solid-phase extraction (SPE) using a Phenomenex (Phenomenex Inc., Torrance, CA) reverse phase polymeric sorbent (200 mg, 6mL, Strata-X^{TM}). The cartridges were sequentially pre-conditioned with 3 mL of ethyl acetate, 3 mL of methanol, and 3 mL of de-ionized water adjusted to a pH 3 with H_2SO_4. The aqueous samples were loaded to cartridges at a rate of about 1 mL min^{-1}, after which the cartridges were dried under vacuum for 5 minutes. The cartridges were eluted with two successive 4 mL aliquots of ethyl acetate and then further dried under vacuum for 15 minutes.

Eluates from the SPE were concentrated to approximately 0.5 mL under a gentle stream of nitrogen in a water bath at 50 °C and then transferred to a 2 mL autolock amber vials The autolock amber vials were then spiked with 100 µL of 2 mg L^{-1} internal standard (a mixture of (±)-ibuprofen-d_3, (±)-naproxen-d_3 and (±)-ketoprofen-d_4) and further condensed to dryness. The sample was then derivatized at 70 °C for 60 min by adding 100 µl of MTBSTFA and brought up to a final volume of 200 µL with ethyl acetate.

Derivatized samples were analyzed using gas chromatography-mass spectrometry by injecting 1 µL of sample in a splitless mode using an Agilent 7890 series gas chromatograph (Agilent Technologies, Santa, Clara, CA) interfaced to an Agilent 5975C mass-selective detector

in selected ion monitoring (SIM). The carrier gas was helium with a constant flow rate of 1.2 mL min^{-1}. The following GC oven temperature program was used: initial temperature, 70 °C, hold for 1 min; 20 °C min^{-1} to 280 °C, hold for 3 min; and 20 °C min^{-1} to 300°C with a 1-min hold, for a total run time of 16.5 min. Injection port temperature was 250 °C and GC-MS interface temperature was 290 °C.

In order to determine the recoveries, seven replicates of three-gram soil-biosolid matrix were suspended in 15 mL of 0.01 M $CaCl_2$ solution overnight to ensure hydration. The soil-biosolid solution was spiked at 100 µg L^{-1} with NSAIDs and equilibrate for 24 h prior to the same procedure and determination described above. Average recoveries (n=7) were 97% for NPX, 96% for IBF, 84% for KTF and 92% DCF. According to the validation of analytical procedures of Guideline, I. H. T. (2005), the limit of detection (LOD) may be expressed as 3.3 × (the standard deviation of response at low concentration/the slope of the calibration curve); were 18 µg L^{-1} for NPX; 8 µg L^{-1} for IBF, 15 µg L^{-1} for KTF and 2 µg L^{-1} DCF. The limit of quantification (LOQ) may be expressed as 10 × (the standard deviation of response at low concentration/the slope of the calibration curve); were 54 µg L^{-1} for NPX; 25 µg L^{-1} for IBF, 46 µg L^{-1} and KTF; and 6 µg L^{-1} for DCF.

3.2.5 Data analysis

The sorbed amount of C_s (mg kg^{-1} dry soil) of NSAIDs to the soil-biosolid matrix was calculated by subtracting the measured liquid phase solute concentration, C_{aq} (mg L^{-1}), from the initial mass added and dividing by the soil mass. The sorption and desorption data were fitted to Freundlich isotherm models, but the Freundlich model provided the best fits and is described by the equation,

$$\mathrm{Cs} = K_F \times C_{aq}^{n} \qquad [1]$$

Where K_F ($mg^{1-1/n}$ $L^{1/n}$ kg^{-1}) is the Freundlich isotherm constant and n, is the linearity parameter. Average sorption coefficients (K_d, L kg^{-1}) were calculated for all measured paired data using the equation:

$$K_d = \frac{\mathrm{Cs}}{\mathrm{Caq}} \quad [2]$$

The desorption coefficient (K_{des}, L kg^{-1}) is calculated by the equation,

$$K_{des} = \frac{(m_s^{sor} - m_{aq}^{des}) \times V}{m_{aq}^{des} \times m_{soil}} \quad [3]$$

Where m_s^{sor} (kg) mass of the test NSAIDs adsorbed on the soil at sorption equilibrium; m_{aq}^{des} (kg) is the total mass of test NSAIDs desorbed form the soil, V (L) is the total volume of the aqueous phase in contact with soil, m_{soil} (kg) is the mass of soil. The sorption-desorption hysteresis index (HI) was quantified for each NSAIDs, defined by (Huang et al., 1998):

$$HI = \left[\frac{C_s^{des} - C_s^{sor}}{C_s^{sor}}\right]_{average} \quad [4]$$

Where the C_s^{des} (mg kg^{-1}) and C_s^{sor} (mg kg^{-1}) are solid-phase solute concentrations for desorption and sorption processes, respectively.

Standard calibration curves were fitted by linear regression analysis in Minitab 17 (Minitab Inc., State College, USA). Differences between K_d values in the individual- and mixed-compound treatments were analyzed using a general linear model ANOVA with two factors and two-factor interaction of interest: concentrations and individual- and mixed-compound treatments. The probability level of significance used to express the strength of the relationship between variables was set at $p<0.05$. If significance was found on the effects ($p < 0.05$), One-way analysis of variance (ANOVA) with Tukey's test to completed the multiple means

comparison and generate the latter groups using a 5% level of significance. SigmaPlot software 12.0 (Systat Software Inc., San Jose, CA) was used for all model fitting in this study.

3.3 Results and Discussion

The sorption and desorption isotherms of individual-compound and mixed-compound systems for target NSAIDs in the soil-biosolid matrix are shown in Fig. 3.1 and 3.2. The sorption isotherms did not reach sorption maxima, indicating unsaturated sorption sites on the soil-biosolid matrix at the concentrations studies. Sorption equilibrium data of the four NSAIDs were fitted by the Freundlich model (R^2 > 0.99) (Table 3.2). Freundlich isotherms are preferred because they can be applied to multi-layer heterogeneous adsorption, which takes compound intermolecular interactions and competition into consideration. In contrast, Langmuir isotherms are better suited to homogenous adsorption, assuming all sites possess an equal affinity for the compound molecules and adsorbed molecules do not have an effect on unoccupied binding sites (Liu, 2015). Values for the linearity parameter, n, were not close to 1 indicating a non-linearity of sorption. This parameter is a measurement of adsorption intensity and soil surface heterogeneity. The Freundlich isotherm constant, K_F values, which represent the sorption affinity of NSAIDs to the soil were n-dependent and not comparable when the n values were different. Instead, a sorption coefficient, K_d, was calculated for all the measured data and compared to those previously reported in the literature (Xu et al., 2009a and b; Martínez-Hernández et al., 2014). The average K_d values were used to compare differences between individual-compounds and mixed-compounds (Table 3.2). Hysteresis (HI) is evident by desorption K_{des} > sorption K_d (Huang et al., 1998), where the hysteresis index implies an increased difficulty of NSAIDs to be desorbed form the soil-biosolid matrix (González -Naranjo et al., 2013). The discrepancy between K_F and K_d is due to the non-linearity of the isotherm (Scheytt et al., 2005).

Table 3.2 Sorption and desorption parameters of four NSAIDs in a loam soil-biosolid matrix in individual-compound and mixed-compound systems (Mean ± SD, n=18). Number subscripted by HI show the initial concentration of the tested compound in liquid soil solution (mg L^{-1}).

[a] Proportion of amount of compound sorbed of total amount added in the loam soil-biosolid matrix

Compound	Sorption					Desorption					Sorption-desorption hysteresis
	m^a	$K_F{}^b$	n^c	R^2	$K_d{}^d$	m^e	$K_{Fdes}{}^f$	n^c	R^2	$K_{des}{}^g$	HI^h
Individual-compound system											
Naproxen	0.5±0.1	7.8±0.8	1.3±0.1	0.996	4.5±1.7	0.5±0.2	16.9±1.8	1.3±0.0	0.998	6.4±3.6	0.7
Ibuprofen	0.3±0.2	32.0±8.3	2.8±0.2	0.995	2.8±3.6	0.7±0.2	118.9±48.7	2.1±0.2	0.996	4.9±4.5	0.6
Ketoprofen	0.4±0.1	3.3±0.4	1.1±0.1	0.991	3.1±0.7	0.5±0.2	9.3±1.6	1.2±0.1	0.994	5.8±2.0	0.6
Diclofenac	0.5±0.1	3.2±0.2	0.9±0.0	0.997	5.5±2.1	0.3±0.1	4.2±0.4	0.8±0.0	0.996	10.6±5.4	0.6
Mixed-compound system											
Naproxen	0.5±0.1	5.7±0.5	1.1±0.1	0.996	4.7±1.0	0.3±0.1	11.0±1.2	1.1±0.0	0.997	10.1±2.4	0.7
Ibuprofen	0.3±0.1	14.0±2.4	2.1±0.1	0.995	1.9±1.2	0.7±0.2	103.8±33.3	2.0±0.1	0.997	5.0±3.4	0.6
Ketoprofen	0.4±0.1	2.4±0.1	1.0±0.1	0.997	2.5±0.7	0.5±0.2	5.6±1.0	1.0±0.1	0.991	5.9±2.8	0.6
Diclofenac	0.5±0.1	3.7±0.3	0.9±0.1	0.994	5.4±1.6	0.3±0.1	6.8±1.0	0.9±0.1	0.992	12.7±5.3	0.7

[b] Freundlich isotherm constant ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)

[c] The linearity parameter

[d] Sorption coefficient ($L\ Kg^{-1}$)

[e] Proportion of amount of compound desorbed from sorbed amount of compound

[f] Freundlich desorption coefficient ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)

[g] Desorption coefficient ($L\ Kg^{-1}$)

[h] Sorption-desorption hysteresis index

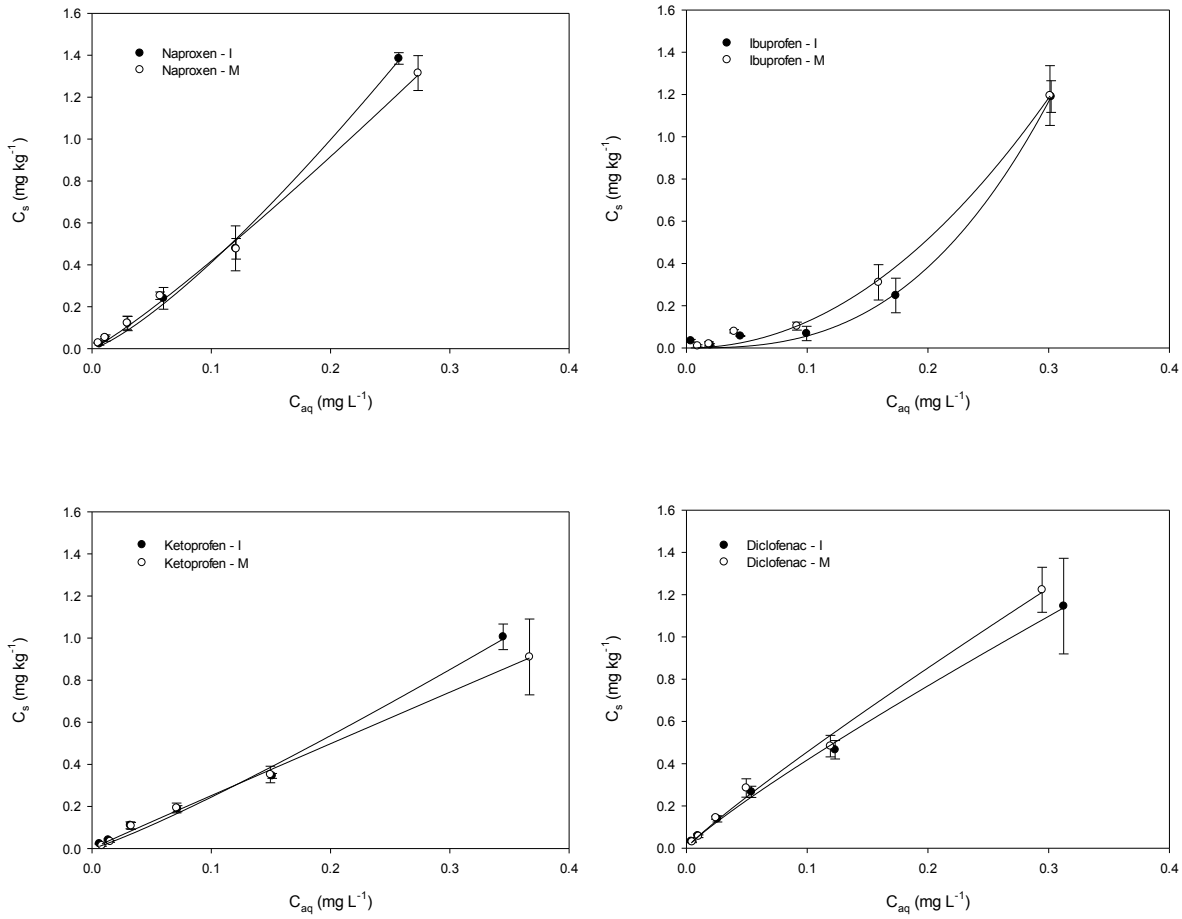


Figure 3.1 Freundlich sorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in individual-compound and mixed-compound systems in a biosolids-amended soil.

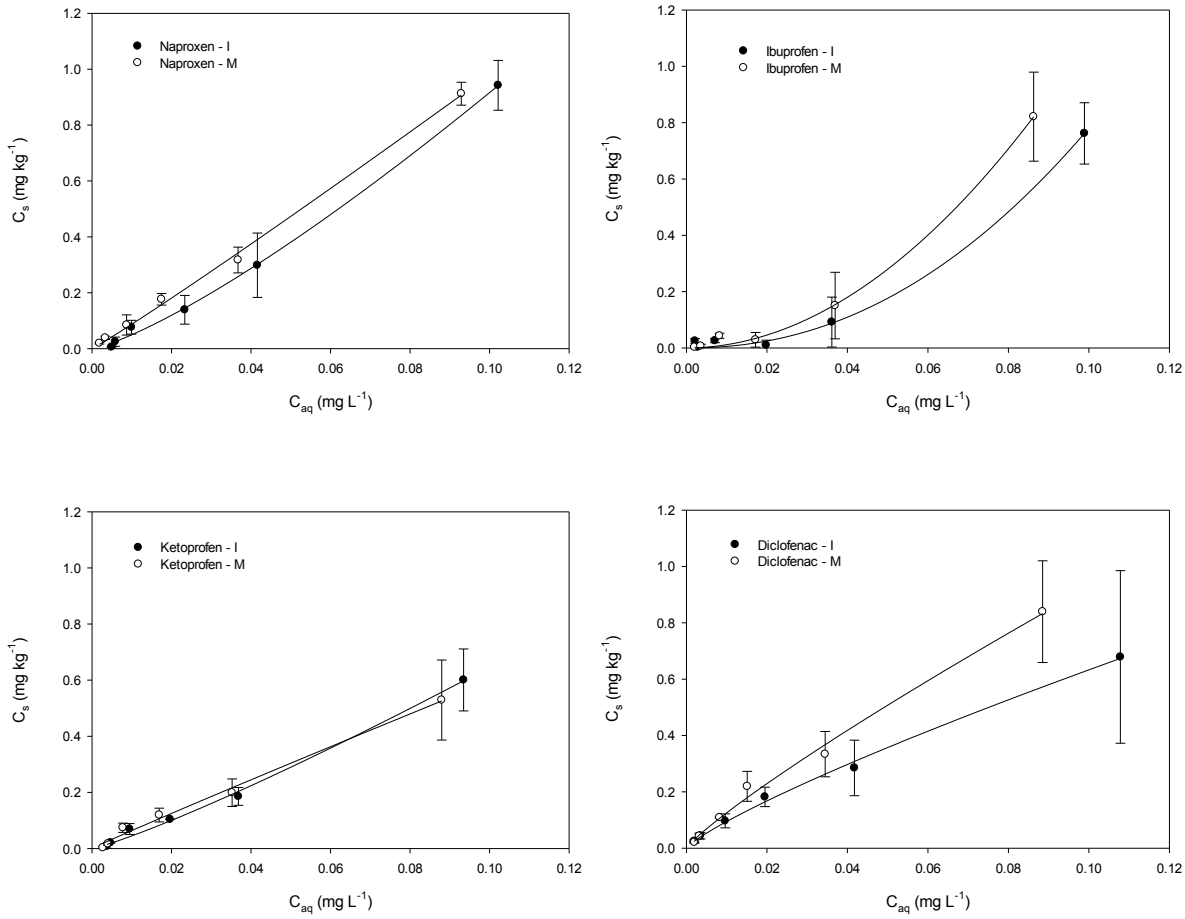


Figure 3.2 Freundlich desorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in individual-compound and mixed-compound systems in a biosolids-amended soil.

3.3.1 Individual compound sorption and desorption

The four target NSAIDs in our study had weak to moderate sorption in the soil-biosolid matrix examined. An average of 49% NPX, 30% IBF, 41% KTF and 54% DCF of initial NSAIDs added in solution were sorbed to soil-biosolid matrix after 24 h. Referring to Freundlich isotherm constant s (K_F), IBF had highest sorption affinity to the soil-biosolid matrix, followed by NPX, KTF and DCF over the concentration range between 0.01 to 0.5 mg L^{-1}. Lower K_F values (Table B2 in Appendix B) estimated for NSAIDs at the environmentally relevant concentrations from 0.01 to 0.2 mg L^{-1}, suggesting that their sorption affinity might be

overestimated when the high initial concentration was included, IBF isotherms, especially, were more linear at environmentally relevant concentrations (Figure B2 in Appendix B). The sorption coefficients of NSAIDs to the loam textured soil amended with biosolids followed in the order of: DCF (5.5 L kg^{-1}) > NPX (4.5 L kg^{-1}) > KTF (3.1 L kg^{-1}) > IBF (2.8 L kg^{-1}). One-way ANOVA indicated K_d values of DCF was not significantly different with of NPX, but significantly varying from KTF and IBF. There were not significant statistical differences in K_d values among NPX, IBF, and KTF. Sorption of IBF and DCF were concentration dependent ($p < 0.05$); IBF was preferentially sorbed to the soil-biosolid matrix at the higher concentrations. Concaved upward isotherms of NPX, IBF and KTF showed higher binding energies were positively associated their concentrations, in contrast, the concaved downward isotherms of DCF indicated weaker binding energies at low concentrations.

In terms of desorption, the percentage desorbed of total NSAID sorbed was 45% for NPX, 73% for IBF, 50% for KTF and 33% for DCF. The K_{des} values for DCF were statistically different compared with the other three compounds', the differences between IBF, KTF and NPX were not significant. The average K_{des} (L kg^{-1}) values for all concentrations yielded the following desorption order: DCF (10.6) > KTF (6.4) > NPX (5.8) > IBF (4.9). The desorption of IBF was significantly affected by concentrations ($p < 0.05$), and the desorption isotherms (Fig. 2) suggest that IBF desorbed in fewer quantities as concentrations increased. The K_{des} of the other NSAIDs were not concentration dependent ($p > 0.05$).

The degree of sorption-desorption of NSAIDs depends on the soil properties and the properties of each compound. In our study, the soil-biosolid matrix contained 5696 kg ha^{-1} Ca, 769 mg kg^{-1} Al, 207 mg kg^{-1} Fe, 3.91 mg kg^{-1} Cu, an organic matter content of 3.7 %, and a cation exchange capacity (CEC) of 18.5 cmol kg^{-1} (Table 3.1). Cations such as Ca^{2+}, Mg^{2+}, $Al^{3+,}$

and Fe^{3+} have been suggested to complex with NSAIDs on ionized matrix surfaces (Bui and Choi, 2010). Soil OM content has also been shown to positively correlate with sorption coefficients for NSAIDs (Huang et al., 2003; Xu et al., 2009a and b; Maoz and Chefetz, 2010). Cation exchange is an important mechanism regulating the sorption of NSAIDs in soils (Bui and Choi, 2010).

The four target NSAIDs in our study were weakly acidic with pKa values ranging from 4.15 to 4.19 (Table 2.2). The acidic NSAIDs in this study have either carboxylic functional groups that are capable of electrostatic attraction to oppositely charged surface sites (hydroxyl and carboxylic acid functionalities). The degree of protonation and deprotonation of compounds can be calculated according to equations in Martínez-Hernández et al. (2014). Under most environmental conditions, NSAIDs are negatively charged in most soils at pH between 5 to 9 (Margon et al., 2009), and are repelled by the negatively charged surface sites (Krascsenits et al., 2008). The pH of the soil-biosolid matrix solution in our study was 6.8, implying that the majority of NSAIDs (>99%) would be in an anionic form, whereas the remaining fractions would be cationic. Anionic NSAID molecules are repelled by negatively charged soil particles, and therefore are expected to exhibit low sorption to these surfaces. In the study, the highest sorption coefficient was recorded for DCF (5.5 L kg^{-1}). Hydrogen bonding between the amine group of carbamazepine and the silanol surfaces have been reported (Turku et al., 2007). DCF possesses a secondary cationic amine which can be hydrogen bonding with functional groups within SOM. This electrostatic attraction is unlikely to be affected by the repulsion between the anionic carboxylic group and the negatively charged surface since amine group is several bond lengths away from the anionic moiety ($-COO^-$). Carrasquillo et al. (2008) demonstrated that the aromatic amine delocalized the positive charge to the aromatic rings, increasing the electronic

effect within the rings, hence, enhancing attraction to the negatively charged aluminosilicate surface. Hydrophobic forces may also have been one of the predominant processes for the sorption of DCF (log K_{ow}, 4.51) and IBF (log K_{ow}, 3.97), whereas in the sorption of NPX (log K_{ow}, 3.18) and KTF (log K_{ow}, 3.12) hydrophobic forces may not have played a relatively minor role (Yamamoto et al., 2009).

The soil-biosolid matrix would be expected to contain higher organic matter content implying more potential binding sites available for sorption. Higher sorption of NSAIDs in soils rich in organic matter have been previously documented (Drillia et al., 2005; Xu et al., 2009a and b; Lin and Gan, 2011; Durán–Álvarez et al.; 2014). Martínez-Hernández et al. (2014) reported that the partitioning into SOM was the predominant mechanism for NPX, and negligible sorption to inorganic surfaces was observed. The π–π interactions between the aromatic ring of NSAIDs and the aromatic moieties of the SOM may also play an important role in the sorption of NSAIDs (Zhu et al., 2004; Chefetz et al., 2008). In particular, NPX has the conjugated π clouds in diaromatic ring that is absent in other three NSAIDs, and may have contributed to the sorption of NPX to the soil-biosolid matrix (Lin and Gan, 2011; Durán-Álvarez et al., 2012). In addition, weak van der Waals attractions (dipole-dipole interactions), as well as the electron donor-acceptor interaction, could be formed when NSAID molecules migrate through the mineral surface of the clay sheets (Sparks, 2003; Gibson et al., 2010; Yu and Bi, 2015). KTF has greater polarity than NPX and IBF molecule (KTF 28.0, NPX, 26.4 and IBF 23.6), which may have facilitated weak van-der-Waals interaction with the soil-biosolid matrix.

Mg and Ca occur as divalent cations at acidic and neutral conditions. Thesecations are suggested to contribute to the adsorption of IBF (both $Ca^{2+}$and Mg^{2+}) and KTF (only Mg^{2+}); they can bridge between the negatively charged IBF and KTF and the negatively charged silica

surface due to the reduction of surface potentials (Bui and Choi, 2010). Trivalent cations Al^{3+} and Al oxides complexe with carboxylate groups of NSAIDs (DCF, IBF, and KTF), then form the ternary surface complex, and thus enhance the sorption of these compounds (Bui and Choi, 2010). Deprotonated NPX and IBF were likely sorbed to amphoteric Fe oxide surfaces and simple ligand exchanged with positive changed Fe oxides (Vulava et al., 2016). Fe and Fe hydrous oxide can play a role in increasing sorption of KTF by the complexation between carboxylate and keto groups of KTF (Gu and Karthikeyan, 2005). To a limited extent, sorption of DCF can be due to surface complexation to soil metal oxides or aluminosilicates because of the lacking carboxyl or hydroxyl groups adjacent to DCF carboxylic groups.

In our study, the sorption of anion NSAIDs was reversible, with evidence of desorption K_{Fdes} > sorption K_F. The most polarized and hydrophobic compound, DCF, was retained in the OM, potentially entrapped in the organic and inorganic matrices (Chefetz et al., 2008). Hydrogen bonding between amine groups of DCF and hydroxyl and carboxyl moieties can provide strong intermolecular forces. Increased attractive forces hold molecules together, and therefore, requires more energy to pull apart from each other. The electrostatic interactions between the cationic amine and the negatively charged sites are stronger than the non-covalent π–π interactions. These would explain the pronounced hysteresis of DCF than that of other NSAIDs.

Due to the high water solubility of NPX and KTF, their molecules might escape the SOM into solution. Sorption-desorption hysteresis for NPX implies that SOM quality may have affected the π-π interactions between aromatic moieties of the NPX and rich aromatic molecules in humified OM beneath the topsoil (Durán-Álvarez et al., 2012). Low desorption hysteresis of NPX reported by Chefetz et al. (2008) suggests that NPX molecules were mainly sorbed to organic and inorganic surfaces of soil matrix and readily desorbed. Sorption coefficients

increased as the equilibrium concentrations increased suggested that at lower concentrations IBF might have higher affinity to water.

3.3.2 Mixed-compound system sorption and desorption

In order to identify the potential competition between NSAIDs in the mixed-compound system for sorption sites in the soil-biosolid matrix all four compounds were spiked in solution simultaneously over a concentration range. Whether the NSAIDs were in a mixture system or in solution individually did not cause any significant changes in the sorption of NSAIDs in the soil-biosolid matrix ($p > 0.05$). Freundlich sorption coefficents of K_F at concentrations between 0.01 to 0.5 mg L^{-1} were higher than K_F values at environmentally relevant concentrations between 0.01 to 0.2 mg L^{-1} (Table B2 in Appendix B), suggesting that sorption affinities of NSAIDs to soil-bisolid matrix were overestimated when a high concentration of 0.5 mg L^{-1} was encountered. The percentage of initial NSAIDs added sorbed was 51% for NPX, 28% for IBF, 36% for KTF and 55% for DCF after a 24 h equilibrium period. The mixed-compound sorption comparison showed that NPX and DCF had statistically greater K_d values compared to IBF and KTF, with a general trend of DCF (6.8 L kg^{-1}) > NPX (4.7 L kg^{-1}) > KTF (2.5 L kg^{-1}) > IBF (1.9 L kg^{-1}). The sorption of IBF was concentration dependent ($p < 0.05$), and the preferential sorption of IBF occurred at the higher concentrations (Fig. 2). Four NSAIDs had numerically lower K_d values in the mixed-compound system than in the individual-compound system, but the differences were not significant except for KTF (NPX, $p = 0.684$; IBF, $p = 0.342$, KTF, $p = 0.026$ and DCF, $p = 0.889$). In the case of desorption, the order in which the target NSAIDs were desorbed from the soil was: DCF < NPX< KTF < IBF. The percentage of total NSAIDs originally orbed that desorbed after 24 h was 31% for NPX, 71% for IBF, 49% for KTF and 28% for DCF. The K_{des} values of IBF were concentration-dependent ($p < 0.05$), and decreased desorption was observed

over the range of concentrations in the isotherm (Fig. 2). No significant differences were observed in the desorption of NSAIDs between the individual-compound and the mixed-compound systems, except for NPX (NPX, $p = 0.001$; IBF, $p = 0.924$, KTF, $p = 0.984$ and DCF, $p = 0.245$)

Numerically, yet significantly lower $K_{d\ values}$ and higher K_{des} values for NSAIDs in the mixed-compound system, indicating synergistic effect by multilayer co-adsorption as well as competitive sorption might occur for compounds as a mixture. At the soil-biosolid solution pH measured (6.8) in our study, all four anionic NSAID molecules were expected to experience repulsion forces with the negatively charged matrix surface, exhibiting low sorption affinity of NSAIDs to the soil-biosolid matrix. The differential structures of NSAIDs with functionalities enable them to interact with soil-biosolid components by various mechanisms, such as hydrogen bonding, surface complextion, cation exchange and hydrophobic forces. The sorption processes for NSAIDs were non-linear, suggesting that binding site energies were not uniformly distributed. Differential distribution of site energies and affinities occur over the heterogeneous matrix surfaces for multi-layer adsorption was described by Liu (2015). DCF might have adsorbed to the stronger binding sites by chemisorption (chemical bonding) on the first layer of soil-biosolid matrix due to the linearity parameter n being below one, whereas NPX, IBF and KTF can interact with sorbent surfaces and sorbates by physical sorption (van der Waals forces) where values for n were above one (Liu, 2015). DCF had highest K_d values (5.4 L kg^{-1}), suggested that DCF exhibited higher binding energy (larger molecular size, higher hydrophobicity and polarity) to the soil-biosolid matrix and outcompeted other three compounds in terms of the total surface sorption sites. The non-significant different K_d values of DCF between DCF-individual and in the NSAID-mixture indicated that sorption of DCF was not affected by the presence of other

sorbed molecules. A numerically stronger sorption of NPX on the soil-biosolid matrix was observed in the presence of other three NSAIDs, whereas weaker sorption was shown for IBF and KTF in the NSAID-mixture. The two defused benzene rings for NPX employed higher π-π interactions as well was van der Waals force with SOM, enhancing the sorption capacity of NPX. The ligand-exchange with keto- and carboxylate acid structure of KTF on Fe oxide surfaces could overcome the binding deficiency derived from its low hydrophobicity. Smallest structure of IBF might partition into small binding sites on the soil-biosolid matrix with its relatively high log K_{ow} of 3.97, however, the lacking of π energy from the single benzene ring and lowest polarity might explained the lower competitive ability of IBF in the sorption to a solid matrix in the NSAID-mixture. Nevertheless, NPX, IBF and KTF can form a lower energy adsorbate-adsorbate layer above the first layer of solid surface, and adsorb more molecules upon the completion of sorption processes (Liu, 2015).

Apparent sorption-desorption hysteresis for NSAIDs was shown by the HI values (0.5 to 0.7) in the soil-biosolid maritx. DCF had higher K_{des} values than the other three compounds, but not statistically higher than K_{des} values of NPX. The highest K_{des} of DCF indicated that DCF was more likely to bind to higher quality sites strengthening sorption to the matrices, in turn increasing the difficulty of sorbed DCF to be desorbed, this is in fair agreement with high HI values calculated for DCF. The hydrogen bonding, hydrophobic and π interaction dominated by DCF with organic and inorganic soil-biosolid matrix are stronger than van der Waals force, requiring more energy to break. The significantly increase in K_{des} of NPX suggested advanced affinity of NPX to the soil-biosolid matrix by synergistic effects induced by mixture NSAIDs. When compounds are multi-layer adsorbed, the compounds on absorbable layers can prevent compounds to be desorbed from the soil surface by blocking the sorbed molecules at the first

layer of the soil surface (Liu, 2015), might increase the difficulties for first layer molecules to be desorbed. For KTF and IBF, mixture K_{des} values were numerically greater (not significant) than their respective individual K_{des} values, demonstrates that these two compounds might have cooperatively sorbed to the binding sites in the soil-biosolid matrix.

3.4 Conclusions

Four NSAIDs exhibited weak to moderate sorption coefficients to the soil-biosolid matrix with a descending order of: DCF >NPX > KTF > IBF. Competition over the binding sites as well as cooperative sorption appeared to be involved in the sorption of NSAIDs when they existed as a mixture. In this way, these compounds strengthened the bonding to soil-biosolid components and between each other, subsequently counteract the desorption processes. Most selected NSAIDs were numerically lower in sorption coefficients and higher in desorption coefficients in the mixed-compound system. Non-specific interactions, such as van der Waals forces, hydrophobic interactions and π effects, can play a more dominant role in the sorption mechanisms of acidic NSAIDs in this study. A one-time application of alkaline-treated biosolids in our study increased the soil pH, but did not appear to have a significant effect on other soil properties, such as cation exchange capacity and soil organic matter. Further investigations are needed to understand the impacts of long-term application of biosolids on multi-NSAIDs sorption and desorption dynamics in soils.

4 Conclusion

Overall, this study shows that the sorption coefficients of four individual NSAIDs and their mixture to the soil and soil-biosolid matrix follow the order: DCF > NPX > KTF > IBF. The order in which the target NSAIDs were desorbed from the soil and soil-biosolid matrix was: DCF < NPX< KTF < IBF. DCF has statistically the highest sorption capacity in the soil and soil-biosolid matrix and is the most difficult compound to be desorbed from these two solid matrices, therefore, giving rise to higher potential accumulation in soil systems. In contrast, the other three NSAIDs have low to moderate sorption and desorption coefficients, especially for IBF, and are susceptible to potential leaching into groundwater and runoff to surface waters. In the mixed-compound system, some NSAIDs exhibited lower K_d values, whereas others showed higher K_d values, these results suggested that NSAIDs that has higher sorption capacity might outcompete other compounds for the higher energy binding sites on soil and soil-biosolid matrix. The higher K_{des} values for most of NSAIDs in mixed-compound system indicated that compounds might cooperatively sorb to soil and soil-biosolid matrix, resulting in lower desorption rates.

In a loam-textured soil, sorption coefficients of individual NSAID compounds varied significantly, suggesting that the sorption behavior of these compounds were dominated by different sorption mechanism due to their diverse chemical structures and functional groups. When they appeared in a mixture, DCF had the largest sorption coefficient, whereas the other three NSAIDs were not significantly different from each other. The sorption coefficients of the four NSAIDs were not significantly different when they occurred individually or as a mixture, but desorption coefficients of these NSAIDs were significantly different between the individual compound and mixed compound system, except for DCF. These suggested that the existence of a mixture of compounds might have influenced their sorption dynamics, in the term, affecting their

desorption dynamics. The numerical increase in desorption coefficients and hysteresis in mixed compound system suggested the NSAID compounds might be synergistic sorbed during sorption and impeditive desorbed.

In the soil-biosolid matrix, DCF also exhibited the highest sorption and desorption coefficients in both individual compound and mixed compound systems. Individual NPX sorption coefficients were statistically larger than that of KTF and IBF. Insignificant statistical differences in mixed compound sorption coefficients indicated mixed-compound effects among four compounds. The differences were not significant for NSAIDs in sorption coefficients except for KTF; in the desorption coefficients except for NPX, between the individual-compound and the mixed-compound systems. Numerically lower sorption coefficients and higher desorption values for NSAIDs in the mixed-compound system, indicating competitive sorption and desorption in terms of total binding sites occurred in a mixture.

The addition of biosolids lowered the sorption and desorptionof NSIADs and the desorption hysteresis is weaker following biosolids addtion. The soil-biosolid matrix pH is about one unit higher than soil pH, resulting greater repulsive forces between pharmaceuticals and soil-biosolid surfaces. The pH may be the predominant factor reducing the sorption capacity of compounds to the solids. Besides electrostatic interactions, long-term application of biosolids might change the soil composition and properties which could collaborately influence the sorption and desorption dynamics of NSAIDs. These results show how alkaline treated biosolids, used as agriculture lime amendments, in turn, play an important role influencing in the sorption and desorption processes for selected NSAIDs. Therefore, further investigation is needed to determine the impacts of long-term biosolids application, such as soil chemistry

properties, soil organic matter quality, and mineral components, on multi-NSAID sorption and desorption dynamics.

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Appendix A Standard Operating Procedures

A1 Preparation of Solvent

A1.1 0.01 M Calcium Chloride Solution

Mass 5.840 g calcium chloride, and transfer to 4 L volumetric flask. Bring to volume with de-ionized water.

A1.2 Preparation of Stock and Working Solutions

This stock solution contains enough of each target compound to perform all of the experiments in the validation study. The stock solutions are prepared in ethyl acetate to be used in both spiking and preparation of calibration standards. Read MSDS sheets before working with the target compounds. Always wear protective gears, including a clean lab coat, gloves, and glasses.

A1.3 Stock Solution in Ethyl Acetate

Accurately mass 0.05 g of each target compound onto a piece of aluminum foil using a four decimal point balance. Quantitatively transfer to 100 mL volumetric flask by rinsing with ethyl acetate. Bring to volume with ethyl acetate, cap and mix thoroughly achieve a concentration of 500 mg L^{-1}.

A1.4 Working Solutions in Ethyl Acetate

Pipette required volume of stock solution and transfer to 25 mL volumetric flask to achieve concentrations of 2, 4, 10, 20, 40, 100 mg L^{-1}. Bring to volume with ethyl acetate.

A1.5 Stock Internal Standards in Ethyl Acetate

This method uses internal standards labeled with deuterium added before the evaporation step to account for differences in solvent volumes. Accurately mass 0.0050 g of naproxen_d_3, ibuprofen_d_3, ketoprofen_d_4 into 50 mL beakers using a four decimal point balance.

Quantitatively transfer to 50 mL volumetric flask by rinsing with ethyl acetate. Bring to volume with ethyl acetate, cap and mix thoroughly to achieve a concentration of 50 mg L^{-1}.

A1.6 Working Internal Standards in Ethyl Acetate

Transfer 1000 µL of 50 µg mL^{-1} Internal Standard to 25 mL volumetric flask. Bring to volume with ethyl acetate to achieve a concentration of 2 mg L^{-1}.

A2 Preparation of Standards

Calculate required volume of working solution for the desired calibration range 0.1 to 20 mg L^{-1}.

A3 Internal Standard Calculations

$$\left(\frac{S_A}{S_{IS}}\right)_{standard} = K \times \left(\frac{C_A}{C_{IS}}\right)$$

Where S_A is the instrument signal of analyte, S_{IS} is instrument signal of internal standard, C_A is the concentration of analyte in a standard, C_{IS} is the concentration of an internal standard, K is the response factor.

The equation can be plotted by S_A/ S_{IS} versus C_A/ C_{IS}, to estimate a slope K with regression. Concentration in the sample can be calculated by the equation:

$$C_A = \left(\frac{C_{IS}}{K \times S_{IS}}\right) \times S_A$$

A4 GC-MS Operating Parameters

These instructions are for operating Agilent 7890 series gas chromatograph (Agilent Technologies, Santa, Clara, CA) interfaced to an Agilent 5975C mass-selective detector in selected ion monitoring (SIM).

Carrier gas	Helium (at a rate of 1.2 mL min-1)
Injection port temperature	250 °C

GC-MS interface temperature	290 °C
GC oven temperature program	Initial temperature, 70 °C, hold for 1 min; First ramp: 20 °C min^{-1} to 280 °C, hold for 3 min; Second ramp: 20 °C min^{-1} to 300°C with a 1-min hold, for a total run time of 16.7 min.

Appendix B Supplemental Data

Table B1 Sorption and desorption parameters of four NSAIDs in a loam-textured soil (Mt. Hope, Ontario) in individual-compound and mixed-compound systems (Mean ± SD, n=18).

Compound	Sorption				Desorption			
	K_F[a]	N[b]	R^2	K_d[c]	K_{Fdes}[d]	N[b]	R^2	K_{des}[e]
Individual-compound system								
Naproxen	9.3±3.3	1.2±0.1	0.986	6.1±1.0	32.3±12.6	1.3±0.1	0.992	9.7±3.5
Ibuprofen	5.8±0.8	1.3±0.1	0.998	2.9±0.5	20.7±4.3	1.4±0.1	0.998	5.0±1.1
Ketoprofen	3.8±0.2	0.9±0.0	1.000	4.6±0.4	7.5±0.5	0.9±0.0	0.999	10.8±1.1
Diclofenac	7.0±0.7	0.9±0.0	0.998	11.2±2.2	5.5±2.4	0.6±0.1	0.963	64.1±54.5
Mixed-compound system								
Naproxen	7.4±1.0	1.1±0.1	0.997	5.5±1.6	26.2±17.6	0.9±0.2	0.962	35.0±20.4
Ibuprofen	5.3±0.7	1.2±0.1	0.998	3.1±0.4	14.4±2.8	1.1±0.1	0.997	7.8±1.4
Ketoprofen	5.0±0.3	1.1±0.0	0.999	4.3±0.3	13.6±1.1	1.0±0.0	1.000	13.3±1.6
Diclofenac	12.7±2.1	1.0±0.1	0.997	12.3±2.7	17.6±3.8	0.8±0.0	0.994	65.4±24.2

[a] Freundlich isotherm constant ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)
[b] The linearity parameter
[c] Sorption coefficient ($L\ Kg^{-1}$)
[d] Freundlich desorption coefficient ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)
[e] Desorption coefficient($L\ Kg^{-1}$)

Table B2 Sorption and desorption parameters of four NSAIDs in a loam soil-biosolid matrix in individual-compound and mixed-compound systems (Mean ± SD, n=18).

Compound	Sorption				Desorption			
	K_F[a]	N[b]	R^2	K_d[c]	K_{Fdes}[d]	N[b]	R^2	K_{des}[e]
Individual-compound system								
Naproxen	3.9±0.1	1.0±0.0	1.000	4.3±1.8	13.6±6.6	1.2±0.1	0.983	5.6±3.5
Ibuprofen	5.3±5.4	1.8±0.6	0.916	2.5±4.0	N/A	N/A	N/A	4.1±4.7
Ketoprofen	1.6±0.1	0.8±0.0	0.997	3.1±0.8	4.0±1.8	0.9±0.1	0.974	5.6±2.0
Diclofenac	2.3±0.2	0.8±0.0	0.997	5.9±2.0	2.9±0.5	0.7±0.0	0.993	11.4±5.4
Mixed-compound system								
Naproxen	3.3±0.2	0.9±0.0	0.998	4.7±1.1	5.8±0.8	0.9±0.0	0.997	10.2±2.7
Ibuprofen	4.3±2.8	1.4±0.3	0.955	1.5±0.7	19.3±29.0	1.5±0.4	0.925	3.8±2.5
Ketoprofen	1.7±0.3	0.9±0.1	0.991	2.5±0.8	3.5±1.9	0.8±0.1	0.957	5.9±3.0
Diclofenac	2.4±0.4	0.8±0.1	0.989	5.7±1.6	4.4±1.7	0.8±0.1	0.972	13.2±5.4

N/A: not applicable.
[a] Freundlich isotherm constant ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)
[b] The linearity parameter
[c] Sorption coefficient ($L\ Kg^{-1}$)
[d] Freundlich desorption coefficient ($mg^{1-1/n}\ L^{1/n}\ kg^{-1}$)
[e] Desorption coefficient($L\ Kg^{-1}$)

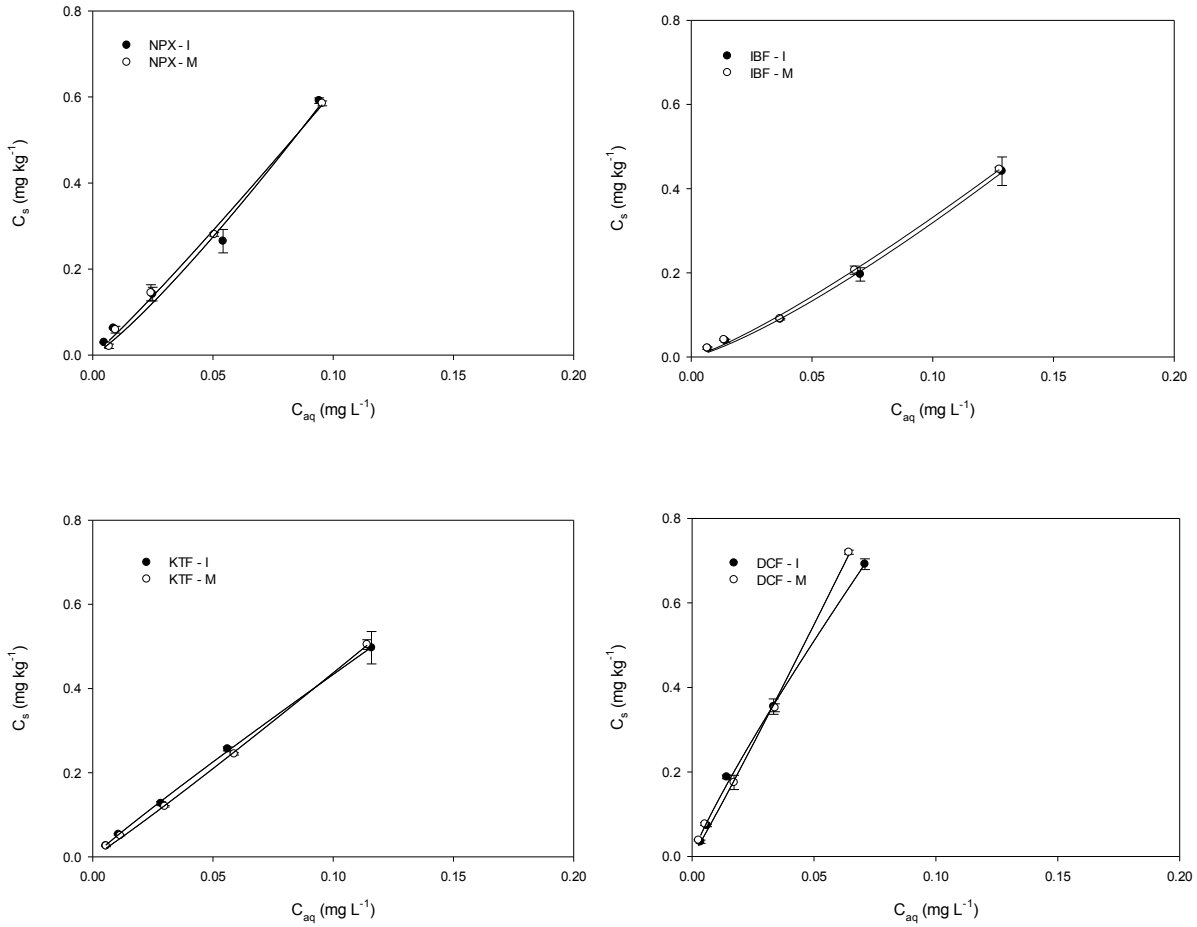

Figure B1 Freundlich sorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in the individual compound and mixed compound systems in a loam-textured soil.

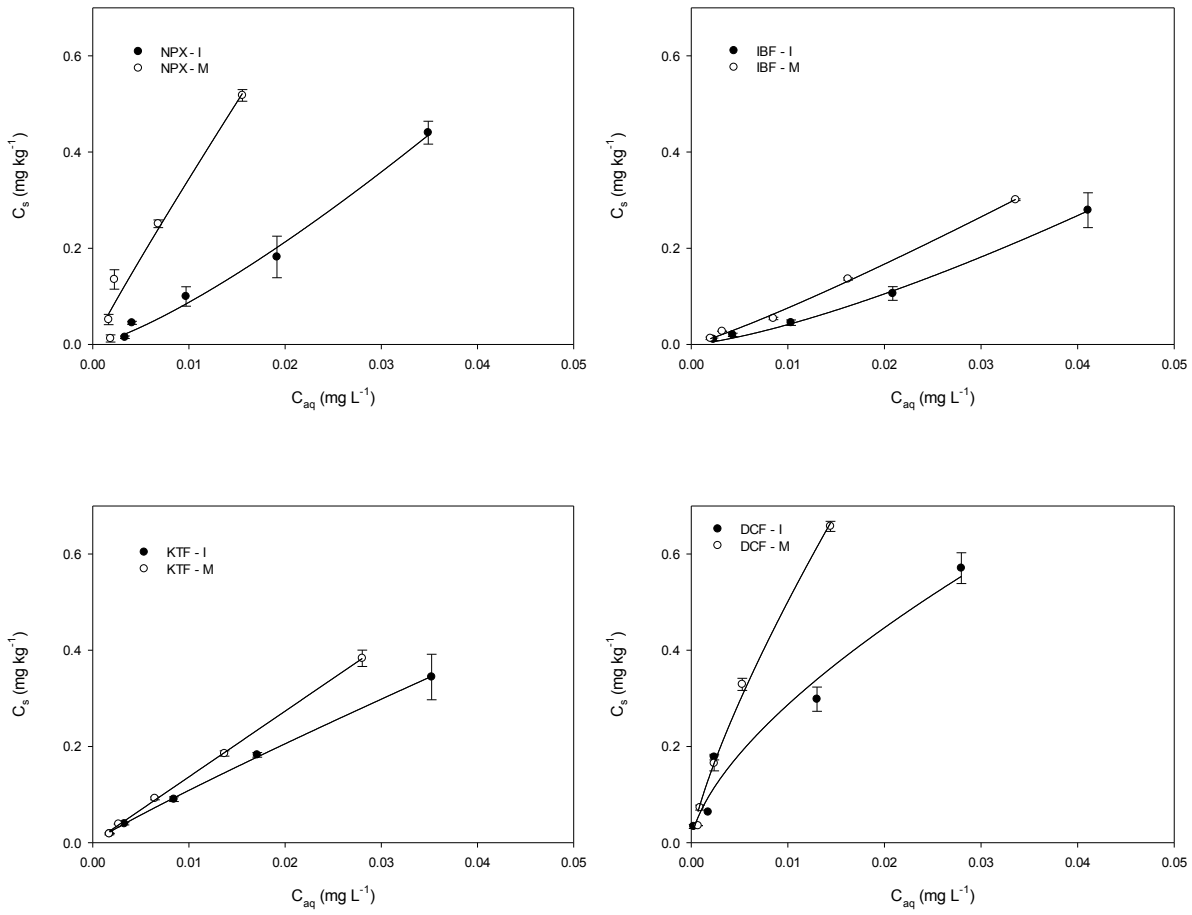

Figure B2 Freundlich desorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in the individual compound and mixed compound systems in a loam-textured soil.

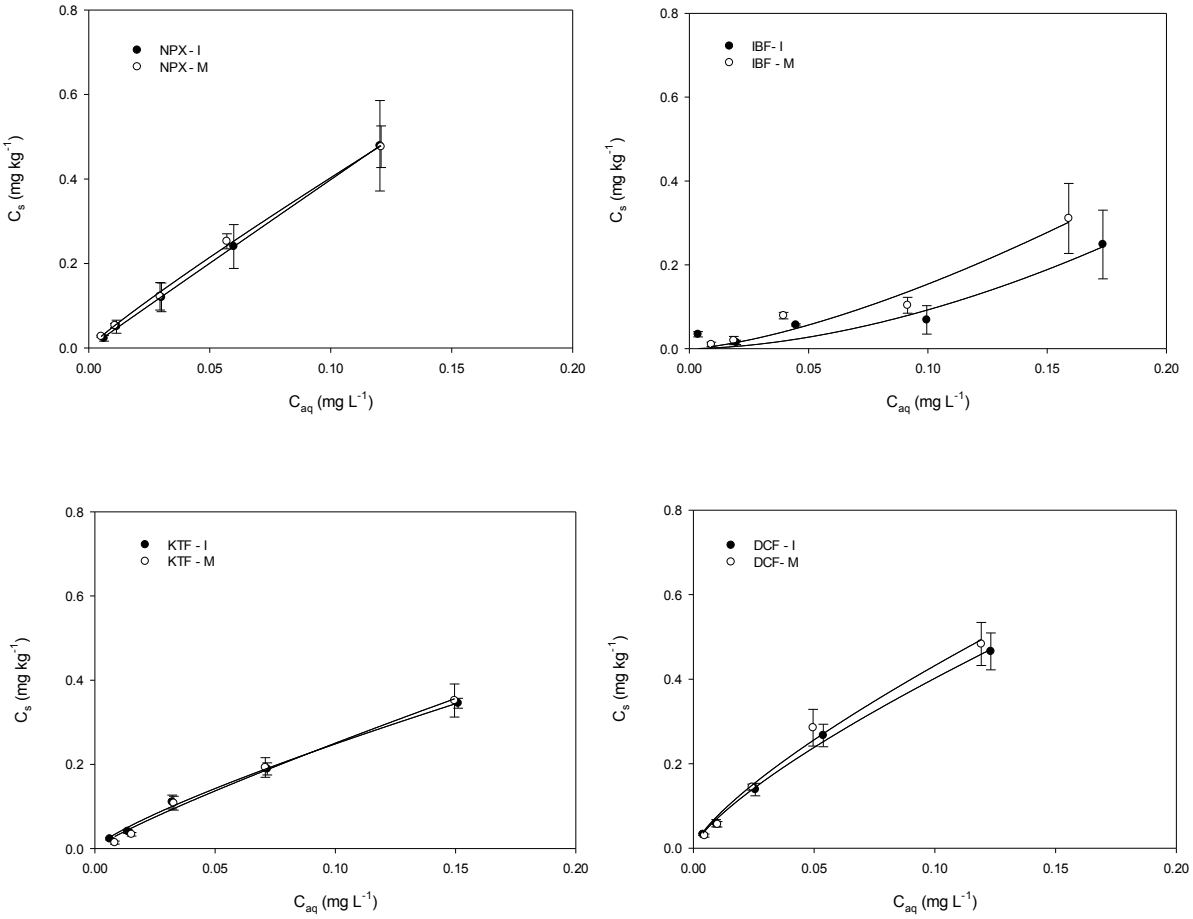

Figure B3 Freundlich sorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in individual-compound and mixed-compound systems in a biosolids-amended soil.

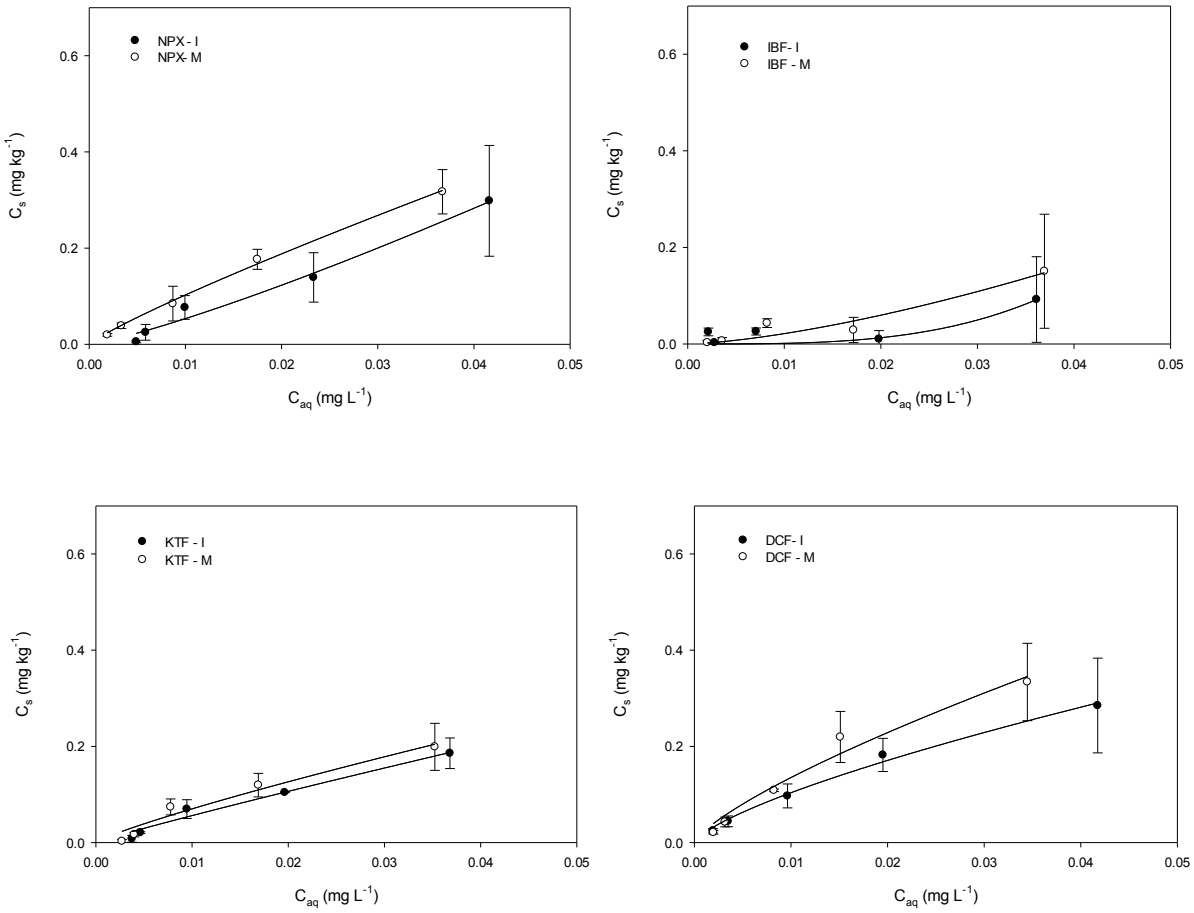

Figure B4 Freundlich desorption isotherms of naproxen (NPX), ibuprofen (IBF), ketoprofen (KTF), and diclofenac (DCF) in individual-compound and mixed-compound systems in a biosolids-amended soil.