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Absorption, Distribution and Elimination Behaviours of Cadmium Treated by *in vitro* DIN from WLP Residue using SAAM II Modeling

(Proses Penyerapan, Pengedaran dan Perkumuhan bagi Kadmium yang Dirawat dengan *in vitro* DIN daripada Residu WLP dengan Menggunakan Pemodelan SAAM II)

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ABSTRACT

Mathematically, the human alimentary tract organs were simplified in the model structure as separate compartments with pathways of transfer that are kinetically homogenous and equally distributed. The development of gastro-compartment model follows the first order kinetics of differential equations to describe cadmium absorption, distribution and elimination in the human digestive system. With the aid of in vitro *DIN assay, an artificial gastric and gastrointestinal fluid were prepared using water leach purification (WLP) residue as a sample that contained toxic metals cadmium. The Simulation, Analysis and Modelling II (SAAM II) V2.1 software is employed to design models easily, simulate experiments quickly and analyze data accurately. Based on the experimental inputs and fractional transfer rates parameter incorporated to the gastro-compartment model, the concentration of cadmium against time profile curves were plotted as the model output. The curve presented concentration of cadmium in both gastric and gastrointestinal fluid where initially absorption phase (first hour) occurred followed by the distribution phase (second to third hours) and elimination process (third to fifth hours). The concentration of cadmium obtained from the simulated model structures was in good agreement with the fitted model predicted measurements as statistical t-test conducted showed the values were not significantly different. Therefore, modeling approach with SAAM II software gave realistic and better estimation of cadmium dissolution into the human gastrointestinal tract.*

Keywords: Cadmium; compartmental model; in vitro *DIN; SAAM II*

ABSTRAK

Dengan kaedah matematik, organ saluran pencernaan manusia boleh dipermudahkan dengan menggunakan struktur model sebagai ruang berasingan dilengkapi dengan laluan pemindahan yang bersifat homogen dan diedarkan secara sama rata. Pembangunan model gastro-ruang dibina dengan kaedah persamaan pembezaan kinetik tertib pertama bagi menghuraikan proses penyerapan kadmium, pengedaran dan perkumuhan dalam sistem pencernaan manusia. Dengan bantuan teknik cerakin in vitro *DIN, cecair gastrik dan gastrousus tiruan telah disediakan menggunakan sisa pemurnian larut lesap air (WLP) sebagai sampel yang mengandungi logam bertoksik kadmium. Perisian Simulasi, Analisis dan Pemodelan II (SAAM II) V2.1 digunakan bagi mereka bentuk model dengan lebih mudah, mensimulasi uji kaji dengan cepat dan menganalisis data secara tepat. Berdasarkan input uji kaji dan parameter kadar pemindahan pecahan yang dimasukkan ke dalam model gastro-ruang, lengkungan kepekatan kadmium terhadap profil masa telah dilakarkan sebagai output model. Lengkungan menunjukkan kepekatan kadmium dalam kedua-dua cecair gastrik dan gastrousus dimulai dengan fasa penyerapan (jam pertama) dan diikuti dengan proses pengedaran (jam kedua hingga ketiga) dan perkumuhan (jam ketiga hingga kelima). Kepekatan kadmium yang diperoleh daripada struktur model simulasi adalah selari dengan lengkungan suaian model anggaran dengan ujian statistik t-test yang dijalankan menunjukkan nilai tersebut tidak mempunyai perbezaan yang signifikan. Oleh itu, pendekatan pemodelan dengan perisian SAAM II dapat memberikan anggaran yang realistik dan lebih baik bagi proses pelarutan kadmium ke dalam saluran penghadaman manusia.*

Kata kunci: in vitro *DIN; kadmium; kompartmen; model; SAAM II*

INTRODUCTION

Since 1979, the International Commission on Radiological Protection (ICRP) has developed the gastrointestinal tract model that has been used to describe the transport and kinetic behavior of heavy metals throughout the human body (ICRP 1989). Mathematically, all the human organs and tissues are represented with separate compartments with each of them connected via fractional transfer rates. In general, modeling plays vital role to analyze dynamic systems of the human body in relation to transfer of substances as it undergoes absorption, distribution and excretion in the biological systems (Kjeldsen & Ottesen 2014). Simulation, Analysis and Modelling II (SAAM II) Version 2.1 software was developed by the University of Washington, Seattle in aid for kinetic analysis as well as to empower understanding of physiology and

pathophysiology (Clifford & Muller 1998). Several other purposes include the identification of the system structure, estimation of immeasureable quantities, prediction of physiologic variables and diagnosis to improve reliability and accuracy of the system studied (Bronzino 2000). Compartment models are created based on the differential equations incorporated to the model structures which are unique for every system studied. Thus, a complex physiologic system can be viewed as a finite number of compartments with pathways that are well mixed and homogenous (Clifford & Muller 1998).

The exposure of cadmium in the environment has long been recognized as health hazards due to its tendency to concentrate in critical organs such as bone and liver that bound to metallothionein, a sulfur-rich intracellular protein (Akesson et al. 2014). Cadmium is a trace element from Group 12 that is known as an ecotoxic metals that exhibit adverse impacts to the environment and the quality of food (Kabata-Pendias & Mukherjee 2013). Cadmium existed naturally in the range of 0.1 - 0.5 ppm concentrations in the earth crust. The soluble forms of cadmium can be transported to surface and groundwater whereas the unsoluble forms remained to sediment as a result of adsorption process (ATSDR 2012). Meanwhile during weathering process, cadmium tends to form mobile compunds such as $Cd(OH)_2$, $CdCl_2$, CdO and CdF_2. The emission of cadmium either in the particulate forms or leachate will expose humans via food chains, inhalation, skin wound and direct contact with contaminated soils. The toxicity impact may be acute or chronic depends on the amount of cadmium ingested and accumulated in the biological tissues (ATSDR 2012).

The absorption efficiency of cadmium depends on the solubility behaviour, exposure concentration and route of the cadmium compounds. Based on previous study of (Goyer 1991), cadmium deposition has been estimated to be 50 to 70% in the kidneys and livers. The contents of cadmium in soft tissues of humans range from 0.03 to 14 mg kg^{-1}, being the highest in kidneys and lowest in the muscles. Concurrently, the average content of cadmium for the 'reference man' is 0.17 mg kg^{-1}. The estimated intake of Cd in the diet is 20-50 μg d^{-1} where it may retained in the body for a relatively long time up to 30 years (Kabata-Pendias & Mukherjee 2013).

In this study, a gastro-compartment model was developed to simulate the oral intake of cadmium released from water leach purification (WLP) residue samples with the aid of *in vitro* DIN assay; to compare concentrations obtained between experimental and predicted measurements; and to deepen understanding of cadmium absorption, distribution and elimination into the gastrointestinal tract using mathematical model SAAM II approach.

Materials and Methods

Sample Preparation

Water leach purification (WLP) residue samples were collected from Lynas Advanced Materials Plant (LAMP), Gebeng Industrial Estate (GIE), Kuantan, Pahang with the Global Positioning System (GPS) coordinate of E 103º 22' 34", N 4º 0' 21" as shown in Figure 1. The samples were kept in the clean polyvinyl plastic container during transportation to avoid any contamination. The samples were oven dried at 80ºC for 24 h, grounded with a mortar and sieved with 0.5 mm mesh siever to produce a homogenized samples (Al-areqi 2014; Mohd et al. 2017).

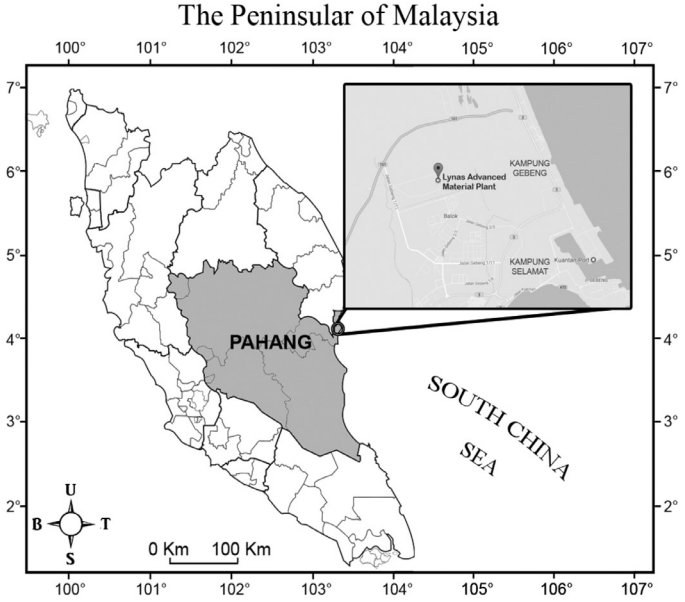

FIGURE 1. Location of sampling area in Gebeng Industrial Estate (GIE), Kuantan, Pahang, Malaysia

ANALYTICAL PROCEDURE

WLP residue samples collected from the study area were analyzed with Wavelength Dispersive X-ray Fluorescence (WDXRF) and Inductively Coupled Plasma Mass Spectrometer (ICP-MS) for both prior and after digestion of samples, respectively. To obtain the total concentrations of cadmium contained in WLP, the residue samples were sent to analyze using Bruker S8 Tiger at Centre for Research and Instrumentation (CRIM), Universiti Kebangsaan Malaysia (UKM). The result obtained was used to represent the input data incorporated to the gastrointestinal tract compartmental model (Clifford & Muller 1998). A reference standard soil International Atomic Energy Agency (IAEA 2004) - 7 was employed to ensure the accuracy of the analytical instrument (Pszonicki et al. 2000). Subsequently, the samples and blank solution were digested for further analysis using ICP-MS Perkin Elmer ELAN 6000 at Malaysian Nuclear Agency (MNA). The National Institute of Standards and Technology (NIST), United States (US) standard reference material was included for quality assurance (QA) and quality control (QC) of the instrument measurements (Kamunda et al. 2016). The samples were digested via *in vitro* Deutsches Institut für Normung (DIN) (Höllriegl et al. 2010), respectively, depending on the digestion method. Subsequently, the committed effective doses from intake of (238; Mohd et al. 2017). The assay was developed by the German Institute to aid in digestion of samples that resemble human digestive system. The samples were digested to produce both gastric and gastrointestinal fluids.

GASTRIC PHASE

About 2.0 g of WLP residue samples were mixed with 0.29 g NaCl, 0.07 g KCl, 0.027 g KH_2PO_4, 0.1 g pepsin, 0.3 g mucin, and HCl (30%) to form synthetic gastric fluids. The samples were prepared in triplicate with solid to liquid ratio of 1:50. The mixed solutions were subjected for 2 h of incubation with pH of 2.0 ± 0.3 that follows the human residence time (1-3 h) and pH of the stomach (pH 1.5 - 4). The temperature of the water bath used throughout the incubation phase was maintained at 37ºC to simulate normal human body temperature. After incubation ended, the gastric fluids were extracted (10 mL) and centrifuged at 3500 rpm for 15 min. Finally, the gastric fluids were filtrated with 0.45 µm filter paper using Rocker 400 laboratory vacuum gas pump. The filtrated synthetic gastric fluids were analyzed for 5 h of interval time with ICP-MS (Höllriegl et al. 2010), respectively depending on the digestion method. Subsequently, the committed effective doses from intake of (238; Mohd et al. 2017; Rashid et al. 2015; Wragg & Cave 2002).

GASTROINTESTINAL PHASE

The gastrointestinal assay was prepared by mixing the remaining volume of the synthetic gastric fluids with 0.03 g KCl, 0.05 g $CaCl_2 \times 2H_2O$, 0.02 g $MgCl_2 \times 6H_2O$, 0.03 g trypsin, 0.9 g pancreatin, 0.9 g bile bovine, 0.03 g urea and $NaHCO_3$ solid (solid to liquid ratio 1:100). The synthetic gastrointestinal fluids prepared were incubated for 6 h with pH of 7.5 ± 0.3 and 37ºC of water bath temperature. The normal human residence time for intestinal digestion is 1 - 6 h with pH 5.5 - 7.5 (Versantvoort et al. 2004). About 10 mL of the fluids were extracted and subjected for centrifugation at 3500 rpm for 15 min. These process were followed by the filtration process of gastrointestinal fluids before further analysis with ICP-MS (Höllriegl et al. 2010), respectively, depending on the digestion method. Subsequently, the committed effective doses from intake of (238; Mohd et al. 2017; Rashid et al. 2015; Wragg & Cave 2002).

BIOKINETIC MODEL DEVELOPMENT

An integrated software of SAAM II was employed to construct and develop gastrointestinal tract compartment model that is used to describe the kinetic dissolution of cadmium from WLP residue samples in the human digestive system. The model in Figure 2 described the *i*th compartment of an *n*-compartment model and the general (1) used to express the compartmental model is as follows (Bronzino 2000).

$$q_i = \sum_{j \neq i} k_{ij} - \sum_{j \neq i} k_{ji} - k_0 i + u_i \quad (1)$$

where q_i is the *i*th compartment; u_i is the exogenous input; k_{ij} is the fractional transfer rates from compartment *j* to *I;* k_{ji} is the fractional transfer rates from compartment *i* to *j;* k_{0i} is the fractional loss rates from compartment *i*.

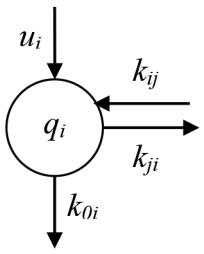

FIGURE 2. The basic *i*th compartment model development with fractional transfer of flow in and out of the compartment and exogenous input incorporation where q_i is the *i*th compartment, u_i is the exogenous input, k_{ij} is the fractional transfer rates from compartment *j* to *i*, k_{ji} is the fractional transfer rates from compartment *i* to *j* and k_{0i} is the fractional loss rates from compartment *i*

Based on ICRP Pub 30, four compartments with default transference coefficient (λ) that involved following ingestion were stomach (24 d^{-1}), small intestine (6 d^{-1}), upper large intestine (1.8 d^{-1}) and lower large intestine (1 d^{-1}), respectively as presented in Figure 3 (ICRP 1997).

Meanwhile, the transfer of cadmium from small intestine to blood plasma take account f_1 factor as the fraction of cadmium that is absorbed to the blood plasma

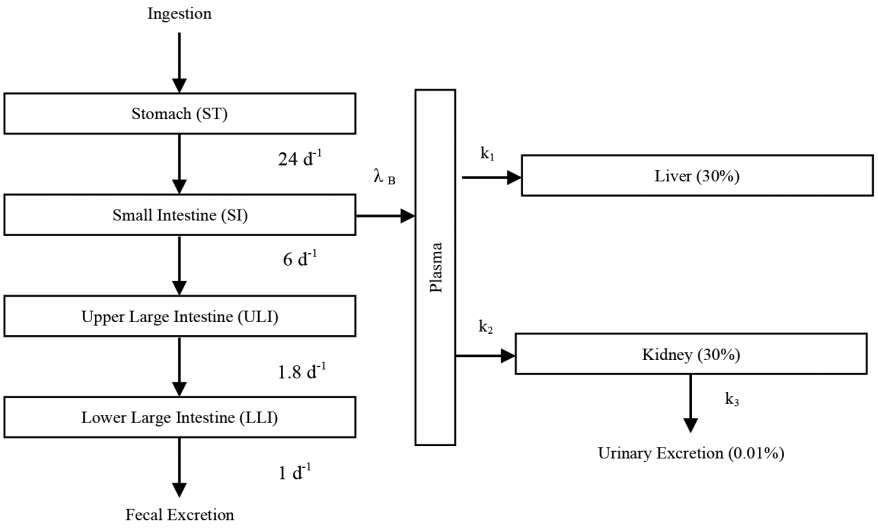

FIGURE 3. Biokinetic model to describe cadmium intake into the gastroinestinal tract recommended by ICRP Pub 30 (IAEA 2004; ICRP 1997; Li et al. 2005)

directly without passing through other regions of the humans digestive tract system. The f_1 (gut transit factor) for cadmium was 0.05 (Eckerman et al. 1988). The transference coefficient for cadmum from small intestine to blood plasma can be calculated using (2) given based on the ICRP guidelines.

Small Intestine to Blood Plasma Transference Coefficient, λ_B

$$\lambda_B = \frac{f_1 \lambda_{SI}}{1 - f_1} \quad (2)$$

where f_1 is the gut transfer factor; and λ_{SI} is the transference coefficient of small intestine (day).

Once absorbed, cadmium is distributed to several organs including 30% to liver ($t_{b1/2}$ of 19 years) and kidneys ($t_{b1/2}$ of 38 years) and 0.01% excreted through urine ($t_{b1/2}$ of 7 days). The fractional transfer rates for k_1, k_2 and k_3 denoted for liver, kidney and urinary excretion, respectively can be derived using Equation 3 (Li et al. 2005).

Fractional Transfer Rates, k_x

$$k_x = a \frac{\ln(2)}{t_{b1/2}} \quad (3)$$

where a is the amount of materials transferred to the compartment; and $t_{b1/2}$ is the biological half-time (day).

The model structures were constructed according to the experimental study where the samples *s1, s2, s3* represent cadmium concentration in the gastric fluids whereas samples *s4, s5, s6* represent cadmium concentration in the gastrointestinal fluids. The transfer coefficient parameter, *k(i,j)* is denoted by arrow connecting each compartments to enact as the fraction of substances transferred from compartment *j* to compartment *i* per unit time (SAAM II 2011). To simulate the experimental study, an exogenous input (*ex1*) was introduced to stand for the amount of instantenous input that occured at the specified time. The equation for sampled value *s1 = q1/vol* that refer to the total amount of tracer divided with the volume of the compartment was formed. To allow the use of prior knowledge related to the fractional transfer rates of cadmium for ingestion model, Bayesian estimation option was selected (Redeker & Blust 2004). The compartmental model was adjusted based on the differential equations until predictions and experimental measurements agree and provide a statistical criterion of goodness of fit and model adequacy.

RESULTS AND DISCUSSION

In this model, cadmium is introduced as an oral bolus input to the mouth compartment that acts as the first compartment following ingestion. The *ex1* for cadmium was 0.75 mg kg^{-1} that was obtained via WDXRF analysis as the total concentration of cadmium contained in the WLP residue samples. Simultaneously, the sample data obtained from the ICPMS analysis for digested cadmium was introduced to the corresponding compartments of *q1* (stomach) and *q2* (small intestine), respectively. As shown in Figure 4, eight gastro-compartments (*q1 – q8*) were modeled to describe the cadmium absorption, distribution and elimination in the human alimentary tract. The absorption mainly occurs in *q2* (small intestine) compartment to *q5* (blood plasma) compartment, distribution in *q5* (blood plasma) compartment to q6 (liver) compartment and *q7* (kidney) compartment and elimination involves *q7* (kidney) compartment to urinary excretion.

The transfer of cadmium between each compartments were characterized by the first-order kinetics expressed as $\frac{dq}{dt} = -kq$ (NCRP 2006). The differential equations in Table 1 were created to describe the change in the amount of cadmium in the compartment over time for

TABLE 1. The model differential equations and flux transfer rates equations employed to describe each specified compartments for cadmium kinetic behavior in the gastrointestinal tract over unit of time

Compartment model differential equations	Flux transfer rate equations
$\frac{dq7}{dt} = +k(7,5)\ {}^{*}q5 - k(0,7)\ {}^{*}q7$	$flux\ (1,8) = k(1,8)\ {}^{*}q8$
$\frac{dq6}{dt} = +k(6,5)\ {}^{*}q5$	$flux\ (2,1) = k(2,1)\ {}^{*}q1$
$\frac{dq5}{dt} = +k(5,2)\ {}^{*}q2 - \mathrm{k}(6,5)\ {}^{*}q5 - k(7,5)\ {}^{*}q5$	$flux\ (3,2) = k(3,2)\ {}^{*}q2$
$\frac{dq4}{dt} = +k(4,3)\ {}^{*}q3 - k(0,4)\ {}^{*}q4$	$flux\ (4,3) = k(4,3)\ {}^{*}q3$
$\frac{dq3}{dt} = +k(3,2)\ {}^{*}q2 - k(4,3)\ {}^{*}q3$	$flux\ (5,2) = k(5,2)\ {}^{*}q2$
$\frac{dq2}{dt} = +k(2,1)\ {}^{*}q1 - k(3,2)\ {}^{*}q2 - k(5,2)\ {}^{*}q2$	$flux\ (6,5) = k(6,5)\ {}^{*}q5$
$\frac{dq1}{dt} = +k(1,8)\ {}^{*}q8 - k(2,1)\ {}^{*}q1$	$flux\ (7,5) = \mathrm{k}(7,5)\ {}^{*}\mathrm{q}5$
$\frac{dq8}{dt} = -k(1,8)\ {}^{*}q8 + ex1$	$flux\ (0,4) = k(0,4)\ {}^{*}q4$
	$flux\ (0,7) = k(0,7)\ {}^{*}q7$

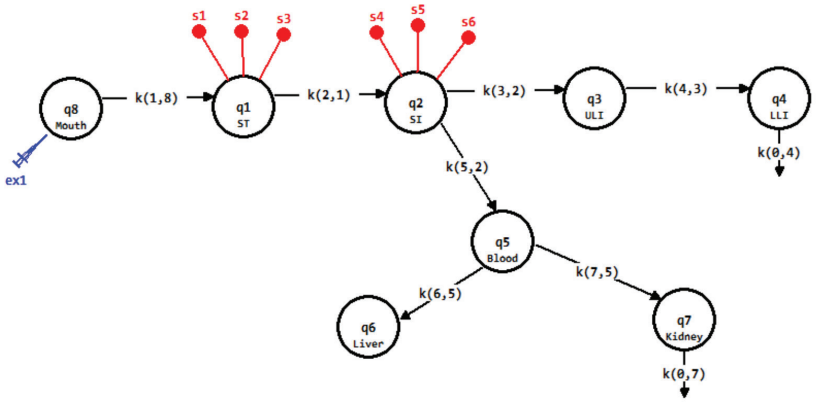

FIGURE 4. Mathematical representation of eight gastro-compartment model (*q1 - q8*) constructed using SAAM II to illustrate pathways of cadmium intake into the gastrointestinal system where *ex1* (exogenous input), *ST* (stomach), *SI* (small intestine), *ULI* (upper large intestine) *and LLI* (lower large intestine. The samples employed were *s1*, *s2*, *s3* (cadmium concentration in gastric phase) and *s4*, *s5*, *s6* (cadmium concentration in gastrointestinal phase)

each compartments. Simultaneously, the flux transfer rate equations were created from the model to represent the fractions of cadmium contained in particular compartment that leaves the compartment in a unit of time.

In compartmental modeling, oral administration of substances involve absorption, distribution and elimination processes as illustrated in Figure 5 (Gunaratna 2001). The absorption phase is mainly the initial process where the substances ingested are absorbed into the body through absorption site such as small intestine in the human gastrointestinal system. The substances distribute rapidly from the administration site into the systemic blood circulation. Meanwhile, the elimination process is irreversible where the removals of substances from the body occur (Gunaratna 2001).

Following a successful fit of the model to the experimental data, a graphical concentration of cadmium for both gastric and gastrointestinal fluids was plotted as shown in Figure 6. The observed concentration values were denoted by the bullet while on the contrary the predicted outputs were represented by the dotted line against the time interval. The first curves shown were the absorption phase of

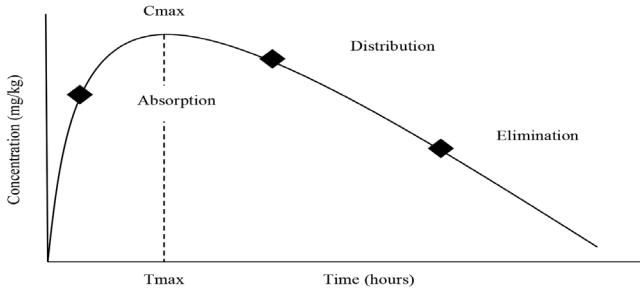

FIGURE 5. Schematic representation of concentration-time curve for oral ingestion (Gunaratna 2001)

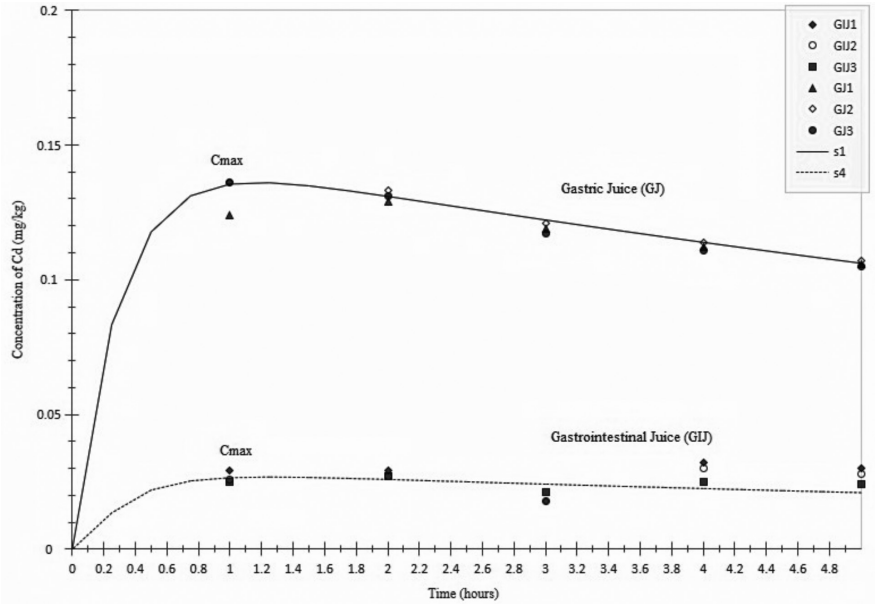

FIGURE 6. Concentration of cadmium (mg/kg) against time (hours) curves was plotted using SAAM II for comparison between observed gastric (GJ) and gastrointestinal juice (GIJ) concentration (bullet) in comparison to predicted concentration (line)

the cadmium-concentration time profile. The curves plotted presented cadmium concentration in gastric fluid was much higher than the gastrointestinal fluid where the gastric acidity of the stomach affects the kinetic dissolution of cadmium (Calvey & Williams 2007). During the absorption phase, the rate of cadmium absorption was greater than the elimination rate. Some of the factors that affects the rate and extent of cadmium absorption are stomach-emptying rate, surface area of the GI tract and blood flow (Shargel et al. 2012).

The second phase involves the distribution phase which begins after the peak of the curves, maximum concentration (Cmax) curves at time interval of first hours (tmax). In this latter phase, ingested cadmium was equally distributed within the organs that were transported from the blood circulatory system. The Cmax for cadmium in the gastric fluid was 0.135 and 0.025 mg kg^{-1} for gastrointestinal fluid. Both maximum concentrations were much higher than the minimal risk level (MRL) for chronic duration of cadmium oral exposure (≥1 year) which was 4.17×10^{-6} mg kg^{-1} per h (0.0001 mg Cd/kg/day) (ATSDR 2012). Subsequently, the major portion of the cadmium distributed will accumulate in the liver and kidney for a relatively long time up to 30 years.

The descending slope of the curves was dominated by the elimination phase that begins at third hours of the time interval. The absorption rate reaches zero (0) as the cadmium concentration reached the elimination phase (Vo 2017). The rate of excretion depends on the body burden and as renal dysfunction develops, the concentration of cadmium in the hepatic and renal will fall due to increased leakage of bound cadmium for urinary excretion (von Apeldoorn & Speijers 2016).

Based on Table 2, the experimental design measured three concentration values of cadmium digested via *in vitro* DIN for 5 h of interval time. Meanwhile, the outputs of simulated model in SAAM II generated predicted concentration values corresponding to each observed concentration against the time interval. Based on *t*-test statistical analysis shown in Table 2, the cadmium concentration in gastric fluids resulted in p-value of 0.134 whereas the cadmium concentration in gastrointestinal fluids has the outcome of p-value of 0.133. This showed

TABLE 2. The concentration of cadmium in both gastric and gastrointestinal fluids per unit of time (hours) for observed (experimental study) and predicted (SAAM II model) measurements

Time, *t* (hours)	Gastric fluids concentration (mg kg^{-1})		Gastrointestinal fluids concentration (mg kg^{-1})	
	Observed	Predicted (s1)	Observed	Predicted (s4)
1	0.136	0.136	0.029	0.026
	0.136	0.136	0.026	0.027
	0.124	0.136	0.029	0.027
2	0.131	0.131	0.027	0.026
	0.133	0.131	0.027	0.026
	0.129	0.131	0.029	0.026
3	0.111	0.114	0.021	0.024
	0.121	0.122	0.018	0.024
	0.119	0.122	0.018	0.024
4	0.105	0.106	0.025	0.025
	0.114	0.114	0.030	0.022
	0.106	0.106	0.032	0.023
5	0.105	0.106	0.024	0.021
	0.107	0.106	0.028	0.021
	0.106	0.106	0.030	0.021
t-test	0.134		0.133	

cadmium concentration for both gastric and gastrointestinal phases were not significantly different between the observed and predicted values. The model constructed to simulate the intake of cadmium in the human digestive tract was in good agreement for both experimental and modelling output concentration.

CONCLUSION

The experimental data incorporated to the development of gastro-compartment model help in aid to simulate the intake of cadmium into the human digestive tract. The compartments specified with differential equations were solved numerically using SAAM II software where fitted model to the data was obtained. The concentration of cadmium against time curves obtained was characterized by initial slope for absorption phase (first hour), the distribution phase (second to third hours) following the maximum concentration peak and the elimination phase (third to fifth hours) in both gastric and gastrointestinal fluids. The statistical *t*-test performed showed that the values were not significantly different between the observed experimental data and predicted model measurements. Therefore, the simulated gastro-compartment model is in good agreement with the model output obtained that describe the kinetic process of absorption, distribution and elimination phases of cadmium incorporated into the human gastrointestinal system.

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