Understanding the drug release mechanism from a montmorillonite matrix and its binary mixture with a hydrophilic polymer using a compartmental modelling approach

S Choiri1,2, A Ainurofiq1
1 Department of Pharmacy, Sebelas Maret University, Ir. Sutami 36A Surakarta, Indonesia, 57126
2 Faculty of Pharmacy, Gadjah Mada University, Sekip Utara, Yogjakarta, Indonesia, 55281

Email: syaiful.apt@student.uns.ac.id

Abstract. Drug release from a montmorillonite (MMT) matrix is a complex mechanism controlled by swelling mechanism of MMT and an interaction of drug and MMT. The aim of this research was to explain a suitable model of the drug release mechanism from MMT and its binary mixture with a hydrophilic polymer in the controlled release formulation based on a compartmental modelling approach. Theophylline was used as a drug model and incorporated into MMT and a binary mixture with hydroxyl propyl methyl cellulose (HPMC) as a hydrophilic polymer, by a kneading method. The dissolution test was performed and the modelling of drug release was assisted by a WinSAAM software. A 2 model was purposed based on the swelling capability and basal spacing of MMT compartments. The model evaluation was carried out to goodness of fit and statistical parameters and models were validated by a cross-validation technique. The drug release from MMT matrix regulated by a burst release mechanism of unloaded drug, swelling ability, basal spacing of MMT compartment, and equilibrium between basal spacing and swelling compartments. Furthermore, the addition of HPMC in MMT system altered the presence of swelling compartment and equilibrium between swelling and basal spacing compartment systems. In addition, a hydrophilic polymer reduced the burst release mechanism of unloaded drug.

1. Introduction
Drug release from a controlled release formulation was a complex mechanism and several mechanisms involved e.g. diffusion, erosion, swelling, and interaction between drug and matrix [1,2]. Drug release mechanism and kinetics could be recognized by a model of drug release [3–5]. A simplification of drug release kinetics and mechanisms had been reported by several models i.e. zero-order kinetics, first-order kinetics, Higuchi, Korsmeyer Peppas, Peppas Sahlin, Weibull, and Hixcon Crowel. However, this model explained based on a simplification of drug release mechanism [4,6,7].

Clay was widely used to modify the drug release from sustained or controlled release formulations [8,9]. Montmorillonite (MMT) was a major component in a bentonite clay which had been approved as an excipient [10,11]. MMT that consist of octahedral silica and alumina in a specific ratio had a basal spacing which can be used to incorporate the drug in the MMT-drug nanocomposite system. Meanwhile,
MMT had a swelling ability which can be applied to control the drug release [9]. Application of MMT in the drug delivery had been reported by several researchers [8,10–12]. In addition, the use of polymers in a controlled release formulation was a fundamental aspect. A hydrophilic polymer was conventionally used to retard the drug release [13,14]. The mechanism to control the drug release in the hydrophilic polymer was distinct from MMT. Although, in the MMT system, there were no reported data i.e. the mechanism and kinetic of drug release depending on a compartmental analysis.

Compartmental analysis was used to analyze the mass transport based on a compartmental system [15,16], this compartment can be designed hypothetically. The mechanism of mass transport from each compartment was distinct in kinetics and mechanism e.g. drug transport in the swelling or leached matrix region [7]. The drug transport kinetics in each compartment can be elucidated by the compartmental analysis [17]. Furthermore, the purpose of this study was to explain the suitable model of drug release mechanism from the MMT matrix and binary mixture between MMT and hydrophilic matrix depending on the compartment modelling approach.

2. Experimental

2.1. Material
Montmorillonite (MMT) was prepared from purification of bentonite clay which obtained from Wonosegoro (Boyolali, Indonesia), Theofilin (THP) (Shandong Pharm, China) was purchased from Brataco (Surakarta, Indonesia), Methocel K4M (MK4M) was obtained from Colorcon (Herlyesville, PA).

2.2. Purification of montmorillonite
Bentonite clay was washed using demineralized water and colloidal phase was collected. Furthermore, it was centrifuged and washed two times followed by centrifugation. The sediment was dried in oven for 24 hours and passed through a 200 mesh sieve.

2.3. Incorporation of theophylline in montmorillonite and binary matrices
An equal weight ratio of THP and MMT was kneading using ethanol and water (7:3) and dried in oven for 24 hours. A different matrix using HPMC was used at level of MMT:MK4M (1:1). In addition, an equal weight ration of THP and a binary mixture MMT:MK4M (1:1) was kneaded using ethanol and water (7:3), then followed by drying in oven for 24 hours. All sample was passed through a 18 mesh sieve.

2.4. Preparation of tablet
An equivalent to 200 mg of THP in THP/MMT or THP/MMT-MK4M was weighed. Furthermore, THP/MMT or THP/MMT-MK4M, 1% of magnesium stearate as lubricant, and lactose to obtain 500 mg of tablet weight were mixed and compressed into tablet at hardness of 80-90 N.

2.5. Dissolution of tablet
Tablet contained THP/MMT or THP/MMT-MK4M was tested the drug release using an Electrolab DT-08 (Mumbay, India) dissolution tester. A 900 mL of phosphate buffer pH 7.2 was used as a medium at a temperature of 37±0.5°C. Aliquots at 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min were withdrawn and filtered using a 0.45 µm membrane filter. Samples were analyzed by a Shimadzu UV2100 (Kyoto, Japan) spectrophotometer at a wavelength 272 nm.

2.6. Analysis of drug release modelling
The drug release was modelled using a WinSAAM (University of Pennsylvania; Kenneth Square, PA). Cumulative of drug release data were plotted using two models depending on distinct of the compartmental approach. Model 1 consisted of 3 compartments i.e. tablet core, swelling front, and dissolution medium. Model 2 consisted of 4 compartment i.e. tablet core, swelling front, equilibrium compartment between MMT basal spacing and swelling front, and dissolution medium. The model was
defined using a WinSAAM notation: IC(1) i.e. initial dose at core compartment (100%); L(A,B) i.e. constant of rate at first order transport from compartment a to the compartment b (e.g. L(2,1), L(3,2), L(3,1), L(4,1), and L(4,2)); DT and DN(C) i.e. delay time and delay number of C compartment, respectively. Specific models are depicted in Fig. 1.

These parameters were calculated using a WinSAAM and the model was evaluated using goodness of fit (GoF), Akaike’s information criterion (AIC) and root mean square error (RMSE). The model was validated using a leave one out cross-validation technique using fitting parameters i.e. coefficient of determination (R²), adjusted coefficient of determination (Adj. R²), predicted coefficient of correlation (Pred R²), and RMSE cross-validation (RMSECV).

3. Results and Discussion

The designed model is presented in Fig 1, it principally obtained from the theoretical drug release mechanism from a hydrophilic matrix system [7]. Transport mechanism of drug naturally followed the diffusional release system thus it depends on the driving force of this system i.e. a concentration gradient [2]. In addition, MMT has ability to swelling, this mechanism can be used to control the drug release as a physical barrier [9]. Furthermore, the model 1 was designed based on these mechanisms. Meanwhile, the model 2 was designed depending on the presence of basal spacing of MMT which can be used as a nano-porous system and drug loaded into nano-porous then had interaction via a hydrogen bonding or other interactions with a Si-O-Si group function. This interaction caused releasing of the drug as a controlled manner. Each model had a compartmental system e.g. 1: tablet’s core, 2: swelling front, 3: dissolution medium, and 4 as a basal spacing compartment. The mass transport from each compartment followed the direction which was depicted in each model scheme.

Figure 1. Schematic compartment model of drug transport from montmorillonite and binary mixture with a hydrophilic polymer matrix. The compartment model without an equilibrium system (a) and compartment model with an equilibrium system between swelling and montmorillonite basal spacing (b)

The drug release from MMT matrix was modelled using model 1 and model 2 that is presented in Fig. 2. The 50% of drug released during 6 hours (Fig. 2i). The drug release from MMT matrix hypothetically controlled by swelling and interaction between drug and Si-O-Si functional group in the basal spacing [9]. These mechanisms governed and modulated the drug release. In order to understand the swelling and basal spacing interaction, the drug release was modelled by a system. The model 1 implied that the drug release controlled based on a swelling mechanism, although the model 2 controlled by swelling and interaction between drug and basal spacing of MMT. The result showed that, a L(3,1) was about three times than L(2,1) and L(3,2). Depending on the rate constant of each compartment, the drug release form MMT depending on model 1 is dominantly controlled by a burst release mechanism. The burst release mechanism was proved with no delay time in the swelling compartment due to unloaded drug. Theoretically, the swelling of material needed more time to produce a good enough viscosity to control the drug release [18]. The burst release mechanism can be seen in the initial time in
the Fig. 2i. Meanwhile, the drug release based on the model 2 not only was controlled by the burst release mechanism but also the interaction in the basal spacing. There was an equilibrium mass transport between swelling and basal spacing compartments and the mass transport delayed in these compartments. It proved by enabling the rate constant transport between basal spacing (compartment 2) and swelling compartment (compartment 4).

Figure 2. Drug release profile (i), calibration model (ii), and cross-validation model (iii) of montmorillonite matrix system. Model 1(a) and Model 2 (b)

Figure 3. Drug release profile (i), calibration model (ii), and cross-validation model (iii) of binary mixture between montmorillonite and HPMC matrices system. Model 1(a) and Model 2 (b)

In order to reduce the burst release effect, a hydrophilic polymer, MK4M was added in this formulation as a binary mixture of MMT-MK4M. The observed and modelled drug release is presented in Fig. 3(i). The drug release showed the reduction of initial drug release compared to the single MMT
system, although the amount of drug release reduced after 3 hours. This system altered the kinetics and mechanism transport from each compartment. Based on two purposed models, it proved that addition of hydrophilic polymers had an absence of the burst release effect and the equilibrium between basal spacing and swelling compartments was disappear. These phenomena showed by a zero constant rate of L(2,1) and L(4,2). Therefore, this system had no mass transport from compartment tablet’s core to swelling or no equilibrium phase from basal spacing to swelling compartment. Hence, it can be concluded that addition of hydrophilic polymer reduced the number of the compartment system i.e. three or four compartments to two compartments.

The best fitting model could be used to describe the kinetics and mechanism of drug release [3]. Therefore, the selection of an appropriate model was preformed statistically. Furthermore, fitting parameters were used to estimate how adequate the model to predict the drug release which are presented in Table 1. Compared to the both models in MMT matrix, model 2 was selected to describe the drug release from MMT matrix because AIC and RMSE was lower than that of model 1. These parameters depict the distinct between predicted and observed data [6,17]. Although, GoF parameters, the R² and Adj R² was lower than that of model 1 but these parameters were not significant difference and the residual was mainly considered compared to the coefficient of determination. Residual of each model can be observed in calibration of model which is presented in Fig 2 (ii) or 3 (ii). Cross-validation technique using an one leave out technique was successfully used to validate the model based on a calibration model [19,20]. The calibration model of cross-validation of each model is presented in Fig 2(iii) or 3(iii). In addition, the selection of model 2 to describe the drug release considered the cross-validation results, the RMSECV was lower than that of model 1. Hence, this model was adequate to describe the model due to high coefficient of determination (more than 0.9) and low residual error (RMSE and Adj R²-Pred. R² less than 0.2)[21].

| Parameter     | Montmorillonite System | Montmorillonite and HPMC binary system |
|---------------|------------------------|----------------------------------------|
|               | Model 1 | Model 2 | Model 1 | Model 2 |
| R²            | 0.9577 | 0.9560 | 0.9784 | 0.9785 |
| Adjusted R²   | 0.9517 | 0.9497 | 0.9753 | 0.9754 |
| RMSE          | 3.58   | 3.44   | 2.05   | 2.05   |
| AIC           | 43.69  | 42.96  | 33.61  | 33.62  |
| Cross-validation |        |        |        |        |
| Pred. R²      | 0.9245 | 0.9199 | 0.9688 | 0.9689 |
| (Adj. R²-Pred. R²) | 0.0332 | 0.0361 | 0.0065 | 0.0065 |
| RMSECV        | 3.87   | 3.72   | 2.13   | 2.13   |

4. Conclusion
The drug release kinetics and mechanism from MMT and binary mixture MMT-hydrophilic polymer has been studied. Model 2 was the suitable model to describe the drug release form the montmorillonite and its binary mixture with the hydrophilic polymer. The modeling depicted the MMT system had ability to controlled the drug release by swelling ability and interaction with basal spacing i.e. drug intercalated. In addition, a hydrophilic polymer in this system altered the kinetic and mechanism of drug release, although it has been successfully proved to reduce the initial drug release.

Acknowledgement
This research was supported by “Lembaga Pengelola Dana Pendidikan” (Indonesian Endowment Fund for Education). Syaiful Choiri would like to thank Colorcon (West Point, PA) for providing the Methocel K4M.
References

[1] Siepmann J and Peppas N A 2012 Adv. Drug Deliv. Rev. 64, Supplement 163–74
[2] Siepmann J and Siepmann F 2012 J. Controlled Release 161 351–62
[3] Ainurofiq A and Choiri S 2015 Lat. Am. J. Pharm. 34 1328–37
[4] Costa P and Sousa Lobo J M 2001 Eur. J. Pharm. Sci. 13 123–33
[5] Peppas N A and Narasimhan B 2014 J. Controlled Release 190 75–81
[6] Ainurofiq A and Choiri S 2015 Trop. J. Pharm. Res. 14 1129
[7] Siepmann J, Kranz H, Bodmeier R and Peppas N A 1999 Pharm. Res. 16 1748–56
[8] Iannuccelli V, Maretti E, Montorsi M, Rustichelli C, Sacchetti F and Leo E 2015 Int. J. Pharm. 493 295–304
[9] Jayrajsinh S, Shankar G, Agrawal Y K and Bakre L 2017 J. Drug Deliv. Sci. Technol. 39 200–9
[10] Oliveira A S, Alcântara A C S and Pergher S B C 2017 Mater. Sci. Eng. C 75 1250–8
[11] Thakur G, Singh A and Singh I 2015 Sci. Pharm. 84 603–17
[12] Bera H, Ippagunta S R, Kumar S and Vangala P 2017 Mater. Sci. Eng. C 76 715–26
[13] Tiwari S B and Rajabi-Siahboomi A R 2009 Drug Deliv Tech 9 20–7
[14] Zhou D, Law D, Reynolds J, Davis L, Smith C, Torres J L, Dave V, Gopinathan N, Hernandez D T, Springman M K and Zhou C C 2014 J. Pharm. Sci. 103 1664–72
[15] Nugroho A K, Della-Pasqua O, Danhof M and Bouwstra J A 2005 Pharm. Res. 22 335–46
[16] Nugroho A K, Pasqua O D, Danhof M and Bouwstra J A 2004 Pharm. Res. 21 1974–84
[17] Nugroho A K 2014 Indonesian J. Pharm. 25 31
[18] Borgquist P, Körner A, Piculell L, Larsson A and Axelsson A 2006 J. Controlled Release 113 216–25
[19] Kurniawati E, Rohman A and Triyana K 2014 Meat Sci. 96 94–8
[20] Rohman A, Sismindari, Erwanto Y and Che Man Y B 2011 Meat Sci. 88 91–5
[21] Ainurofiq A, Choiri S, Azhari M A, Siagian C R, Suryadi B B, Prihapsara F and Rohmani S 2016 Adv. Pharm. Bull. 6 399–406