Modelling of controlled drug release in gastrointestinal tract simulation

I Permanadewi, A C Kumoro, D H Wardhani* and N Aryanti
Department of Chemical Engineering, Diponegoro University, Tembalang, Semarang

*Corresponding author: dhwardhani@che.undip.ac.id

Abstract. The drug release system is a process in which a bioactive substance discharged from a drug product and enters the process of absorption, distribution and metabolism to deliver its pharmacological action. The drug release is maintained at a specific rate to maximize the benefits as well as to suppress the side impacts. The release rate behaviour is affected by physiological conditions such as ion charge, pH level and enzymatic environment. Since the intestinal tract itself varies broadly in a pH environment, hence it is important to study the profile of drug release in different pH conditions. Mathematical model turns out very useful in predicting the drug release as well as reducing experimental works. The objective of this work was to study the mathematical model in describing the drug release profile in gastrointestinal tract liquid simulation. The release profiles of furosemide and sodium-iron chlorophyllin encapsulation were studied in the pH ranges 1.3-1.5 and 6.8-7.4 to simulate the different part of gastrointestinal tract acidity. The Korsemeyer-Peppas, Weibull and Gompertz were applied in describing the profile. Korsmeyer-Peppas model shows more superior (R²>0.912) than Weibull and Gompertz in describing the release kinetic of furosemide and sodium-iron chlorophyllin encapsulations in both pHs of GTS. The n values of Korsmeyer-Peppas are mostly less than 0.5 suggesting the release mechanism was governed by diffusion.

Keywords: controlled drug release, in vitro, a kinetic model

1. Introduction
Consuming drug for a long period could give a negative effect to the body. It requires a specific approach in drug consumption to eliminate this negative impact due to overdose but still maintaining to consume the effective dose [1]. Controlled delivery systems help in achieving the desired level of drug range in the blood at fewer administrations. The dose of the drug can be released between the minimum effective concentration and minimum toxic concentration in the body to reduce side effects to normal tissue [2].

Drug release depends on some intrinsic properties of the matrix such as drug solubility, molecular weight, and matrix swelling. Among the physical mechanism of release, diffusion, water-triggered transport (swelling) and degradation/erosion are the most important ones [1]. Diffusion is the spontaneous transport of active compound from regions of higher concentration to regions of lower concentration. If this compound present in very low solubility or if its dissolution rate is very low, hence only minor amounts of the drug become available for diffusion [3]. Erosion denotes the process in which the surface of the matrix is exposed to the surrounding extracellular fluids, erode the matrix and open the pores resulted in active compound escapes.
Some drugs release immediately soon after the consumption. Others are modified release hence delayed or extended after a while of the delayed and extended period of consumption, respectively. While a type of pulsatile release allows a drug-free at specific time intervals. In drug release studies, kinetic is an important factor because it provides information on the presence of drug concentration in plasma which is the available facile parameter to determine. Applying the kinetic model is a key in clarifying release mechanism which is helpful in designing the drug release control [4].

The release profile is an important part of assessing the success of a dosage formulation, especially when the controlled release rate of the drug is the main focus. The experimental approaches are not only time consuming, but they also come at a cost. The use of mathematical modelling turned out to be very useful in the drug release process study. It helps in designing the delivery system during a certain period, predict the drug release rate and the time when the next dosage needs to be administered. Moreover, modelling avoid excessive experimental works. The physical mechanism of drug release is determined by comparing the release data with mathematical models. This study can predict the effects of design parameters namely shape, size and composition on the level of drug release as a whole and accurately predict drug release profile to improve overall therapeutic effectiveness and safety of this drug [5]. It is an important tool to design pharmaceutical formulations, evaluate drug release processes both in vitro and in vivo study and, in general, come up with the optimal design approach. It resorts to model fitting on experimental release data and provides the measurement of some important physical parameters (e.g., drug diffusion coefficient).

The amount and type of active agent, type of matrix and adjuvants as well as the size and shape of the system designed to achieve a certain drug release profile can be predicted theoretically [6]. There are many mathematical models which proposed to predict release kinetic models such as the zero order, first order, Higuchi, Korsmeyer–Peppas, Weibull, and Gompertz [6]. None of these mathematical models could cover all possible release mechanism [7, 1].

Previously, Berry and Likar [8] studied dissolution and drug release profile similarity using a model-dependent approach using the statistical approach of an active compound from an asymmetric membrane (AM) film-coated osmotic table. This work aimed to study the mathematical model of controlled release encapsulation in gastrointestinal tract system (GTS). Two pH conditions were selected to represent the acidity of GTS liquid. Model-fitting of Korsmeyer-Peppas, Weibull and Gompertiz were used to study the in-vitro release mechanism of the active compounds from its encapsulation. The choice of the appropriate mathematical model strongly depends on the type of drug, type of excipients and composition of the device [1].

2. Material and method

In this work, the release of active compound i.e. furosemide and sodium-iron chlorophyllin from its excipient was modelled. Release data of furosemide and sodium-iron chlorophyllin was taken from Ai et al. [9] and Wang and Chu et al. [10], respectively. The main materials for the release of furosemide were furosemide (MW= 330.7, Spectrum Chemicals and Laboratory Products), poly cationic (dimethylldl ammonium chloride) (PDDA, MW= 200,000, Aldrich), poly (ethyleneimine) (PEI, MW= 50,000, Aldrich) and anionic sodium poly (styrenesulfonate) (PSS, 70,000 MW, Aldrich). Meanwhile, the main materials for the release of sodium-iron chlorophyllin were sodium-iron chlorophyllin (CP, Haining Fengming Chlorophyll Co. Ltd.) and ethylcellulose (Shanghai Chemical Agent Station Packaging Factory).

Furosemide was encapsulated using a combination of multilayers of polions with gelatin. While the sodium-iron chlorophyllin powder was encapsulated using ethylcellulose (EC) which prepared by a solvent-non solvent method. Both the active compounds were released invitro of gastrointestinal tract simulation. These data were chosen because of their similarity in releasing condition in which they used...
non-enzymatic dissolution conditions, namely in the pH range of 1.3-1.5 to represent the gastric simulation fluid (0.1 mol/L HCl) and 6.8-7.4 of phosphate buffer to represent the intestinal liquid.

All release studies were carried out at room temperature. Three mathematical models *i.e.* the Korsmeyer-Peppas, Weibull and Gompertz models were applied to represent the release of the active compound. Once an appropriate model has been selected, the evaluation of dissolution profile can be carried out and hence the drug release profile can be correlated with drug release kinetic models [11].

Korsmeyer-Peppas was a simple model known as “Power law” describing drug release from a polymeric system. Korsmeyer-Peppas model (1) describe some release mechanisms simultaneously such as the diffusion of water into the matrix, swelling of the matrix and dissolution of the matrix [12].

\[
\frac{C_t}{C_\infty} = kt^n
\]  

C_t/C_\infty = fraction of drug release at time  
k = rate constant  
n = release exponent

The Weibull model is used for the release process with the equation (2):

\[
C = 1 - \exp\left[\frac{-(t-T_0)^b}{a}\right]
\]

C= amount of dissolved drug as a function of time (t)  
C0= total amount of drug being released  
T= lag time measured as a result of dissolution process parameters  
a= scale parameter that describe the time dependence  
b= shape of dissolution curve

Gompertz model is commonly used in the in-vitro dissolution profile, expressed by the equation:

\[
C(t) = C_{\text{max}} \exp[-ae^{b \log t}]
\]

C(t) = percent dissolved at time t divided by 100;  
C_{\text{max}} = maximum dissolution  
a = undissolved proportion at time t = 1 and described as location or scale parameter  
b = dissolution rate per unit of time described as shape parameter.

This model shows a steep increase in the beginning and converges slowly to the asymptotic maximal dissolution [13].

### 3. Result and Discussion

*In vitro* dissolution and drug release tests use as a guideline in developing solid drug such as to monitor the quality, consistency, and stability of those products. This study helps in predicting in vivo drug absorption [8]. Generally, the release of active compound from its matrix can be controlled by various methods, such as dissolution, diffusion, partitioning, osmosis, swelling, and erosion. The diffusion of the active agent is a strong function of the matrix structure [6].
The release of furosemide and sodium-iron chlorophyllin from their encapsulated form was selected in this work to determine the discharge profile of the active compounds \textit{in vitro} of gastric juice and intestinal liquid. This release control was modelled using three equations, namely Korsmeyer-Peppas, Weibull and Gompertz. Fitting models of furosemide release from a multilayer of polyions in the gastric liquid are shown in Figure 1-3, while the sodium-iron chlorophyllin release is presented in Figure 4. Meanwhile, the releases in the intestinal trach are presented at Figure 5-7 and Figure 8 for furosemide and sodium-iron chlorophyllin, respectively.

Figure 1. Profile controlled furosemide release at pH 1.4 from a combination of multilayer polyions with 6 layers of gelatin

Figure 2. Profile controlled furosemide release at pH 1.4 from a combination of multilayer polyions with 4 layers of gelatin

All the models showed a similar trend with the release of experimental data of those pHs of the solution. The best-fitted model with the release data was evaluated by coefficient of determination ($R^2$). All the model constants are presented in Table 1 together with the $R^2$ values. Among the fitted models,
Korsmeyer-Peppas model showed superior to describe the release of furosemide and sodium-iron chlorophyllin in both pHs. The $R^2$ value of this model is higher than 0.912 with all the release exponent of the Korsmeyer-Peppas ($n$) for both pH conditions are $<0.5$. The $n$ value indicates the mechanisms to describe how the active compound released from their matrix. In this case, the solvent diffusion is much greater than the process of polymeric chain relaxation. The kinetics of this phenomenon are characterized by diffusivity [6, 14].

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{furosemide_release.png}
\caption{Profile controlled furosemide release at pH 1.4 from a combination of multilayer polyions with 2 layers of gelatin}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|c|c|}
\hline
Data & \multicolumn{2}{|c|}{Korsmeyer-peppas} & \multicolumn{2}{|c|}{Weibull} & \multicolumn{2}{|c|}{Gompertz} \\
\hline
 & K & n & R$^2$ & b & A & R$^2$ & a & b & R$^2$ \\
\hline
\textbf{Gastric simulation fluid (pH 1.3 and 1.4)} & & & & & & & & & \\
\hline
furosemide-gelatine-6 layers & 0.570 & 0.504 & 0.963 & 0.753 & 1.057 & \textbf{0.968} & 0.4071 & -1.895 & 0.892 \\
furosemide-gelatine-4 layers & 0.707 & 0.257 & \textbf{0.963} & 0.473 & 0.759 & 0.958 & 0.2798 & -1.533 & 0.910 \\
furosemide-gelatine-2 layers & 0.746 & 0.198 & \textbf{0.984} & 0.389 & 0.694 & 0.981 & 0.2508 & -1.347 & 0.936 \\
chlorophyllin-ethylcelulose & 0.377 & 0.351 & \textbf{0.992} & 0.573 & 2.095 & 0.974 & 0.9669 & -1.627 & 0.905 \\
\hline
\textbf{Intestinal simulation liquid (pH 6.8 and 7.4)} & & & & & & & & & \\
\hline
furosemide-gelatine-6 layers & 0.870 & 0.305 & \textbf{0.915} & 0.434 & 1.705 & 0.865 & 0.222 & -1.104 & 0.768 \\
furosemide-gelatine-4 layers & 0.990 & 0.132 & \textbf{0.918} & 0.312 & 3.014 & 0.838 & 0.0588 & -1.299 & 0.754 \\
furosemide-gelatine-2 layers & 1.004 & 0.057 & \textbf{0.944} & 0.204 & 0.274 & 0.831 & 0.037 & -1.353 & 0.570 \\
chlorophyllin-ethylcelulose & 0.334 & 0.423 & 0.912 & 0.647 & 2.376 & \textbf{0.955} & 1.0059 & -1.675 & 0.938 \\
\hline
\end{tabular}
\caption{The constants and coefficient of determinations ($R^2$) for each model}
\end{table}

Table 1 shows most of the $n$ values of the Korsmeyer-Peppas model are under the threshold for the Korsmeyer-Peppas ($n=0.43$). Although the $n$ value is lower than 0.5, however, these values still indicates
a diffusion-controlled drug release mechanism [15]. If $n$ is less than 0.43 in the case of spherical encapsulation shape, then a Fickian diffusion release mechanism is implied [12].

Figure 6 and 7 show an initial burst are observed from a fewer layer of the coated sample in the first 3 min of dissolution followed by a slow release which tends to the asymptote of saturation concentration (total dissolution) of the drug [9]. An “initial burst” of drug release often occurs wherein a significant percentage of the drug is released during the early stage of the release process. This result suggests that the more layers of encapsulation provide a denser matrix to give more protection for dissolution the active compound [16]. These figures also support the goodness of Korsmeyer-Peppas model in describing this initial burst.

![Figure 4](image4.png)
**Figure 4.** Profile controlled sodium-iron chlorophyllin release at pH 1.3

![Figure 5](image5.png)
**Figure 5.** Profile controlled furosemide release at pH 7.4 from a combination of multilayer polyions with 6 layers of gelatin
Figure 6. Profile controlled furosemide release at pH 7.4 from a combination of multilayer polyions with 4 layers of gelatin

Figure 7. Profile controlled furosemide release at pH 7.4 from a combination of multilayer polyions with 2 layers of gelatin

4. Conclusion
Mathematical models help to design a controlled drug release system where many types of modelling are commonly used. Korsmeyer-Peppas model shows more superior ($R^2 > 0.912$) than Weibull and Gompertz in describing the release kinetic of furosemide and sodium-iron chlorophyllin encapsulations in both pHs of GTS. The $n$ values of Korsmeyer-Peppas are mostly less than 0.5 suggesting the release mechanism was governed by diffusion.
Figure 8. Profile controlled sodium-iron chlorophyllin release at pH 6.8

Acknowledgement
The authors acknowledge the Ministry of Research, Technology and Higher Education the Republic of Indonesia for financial support through Tim Pascasarjana Research Grant under contract No. 101-186/UN7.P4.3/PP/2018.

References
[1] Khan, M and Shefeeq. T. J. 2009. J. Sci. Res. 1 (3) 539-550
[2] Ninama U., Pal J., Chaudhary, S., Bhimani, B., and Dalsaniya, D. 2015. Int. J. Pharm. Res. Bio Sci. 4 (2) 98-114
[3] Siepmann J, Siepmann F. 2013. Int. J. Pharm. 453 12-24
[4] Jafari M, Kaffashi B. 2016. Nanomed Res J. 1 (2) 90-96
[5] Shaikh HK, Kshirsagar R V, Patil SG. 2015. World J. Pharm. Pharmaceut. Online. 4, 04 324-338
[6] Bruschi ML. 2015. Woodhead Publishing. (Cambridge:Elsevier) p 64
[7] Collins R, Jinuntuya N, Petirom P and Wasuwanich S. 1998. Ann. N.Y. Acad. Sci. 858 116-126
[8] Berry MR, Likar MD. 2007. J. Pharm. Biomed. Anal. 45 194-200
[9] Ai H, Jones SA, Villiers MM De, Lvov YM. 2003. J. Controlled Release. 86 59-68
[10] Wang L and Chu J. 2011. Proc. Environ. Sci. 8 270-275
[11] Gouda R, Baishya H, Qing Z. 2017. J. Develop Drugs. 6 171
[12] Supramaniam J, Adnan R, Kaus NHM, Bushra R. 2017. Int. J. Biol. Macromol. 118 A 640-648
[13] Dash S, Murthy PN, Nath L and Chowdhury P. 2010. Acta Pol. Pharm. Drug. Res. 67 (3) 217-223
[14] Basak SC, Kumar KS, Ramalingam M. 2008. Brazil. J. Pharm. Sci. 44 (3)
[15] Singhvi G, Singh M. 2011. Int. J. Pharm. Stud. Res. II 77-84
[16] Versypt ANF, Pack DW, Braatz RD. 2013. J. Controlled Release 165 29-37