Effect of pregelatinized starch on dissolution of paracetamol extended release bilayer tablets

Tawatchai Thiptinnakorn*, Patcharida Wangnonglad and Rujagorn Wasombat

Department of Pharmaceutical Manufacturing, Faculty of Pharmacy,

Huachiew Chalermprakiet University, Samutprakarn 10540

Received: 5 June 2019/ Revised: 23 June 2020/ Accepted: 25 June 2020

Abstract

This research was conducted to study on the effect of pregelatinized starch on dissolution of paracetamol extended release bilayer tablets consisting of the immediate and extended release layers. Both layers were prepared by wet granulation method. Extended release layer was prepared by using hydroxyethyl cellulose as matrix former at 3.75 percent of extended release layer weight. Pregelatinized starch was used as disintegrant with concentrations of 0, 1.5, 2 and 2.5 percent by weight. *In vitro* release studies were performed using USP 40 type II apparatus and compared with USP 40 specification. The results indicated that the release rate was increased according to the higher concentration of pregelatinized starch. The tablets with pregelatinized starch 2.5 percent performed the similar dissolution profile compared to the innovator. Both innovator and the formulated tablet with pregelatinized starch 2.5 percent were conformed the accepted criteria at the level L_1 of USP 40. The dissolution test result was compared to the innovator to determine the difference factor (), and similarity factor (). The difference factor was 3 and the similarity factor was 78. The release kinetics indicated that release form the matrix tablets was followed by Fickian diffusion. The mechanism of drug release through the matrix was found to be diffusion swollen and erosion controls. In this study, hydroxyethyl cellulose 3.75 percent as a matrix former and pregelatinized starch 2.5 percent as disintegrant would be benefit for the extended release layer. Thus, the extended release bilayer tablets could be a potential dosage form for delivering paracetamol.

Keywords: Bilayer tablets, Matrix, Extended release, Paracetamol, Hydroxyethyl cellulose, Pregelatinized starch

Corresponding author: tawatchai_t@hotmail.com

Introduction

Acetaminophen is one of the most popular over-the-counter drugs and is used as a common household analgesic by children and adults. It has an analgesic and antipyretic effects similar to those of aspirin, but only weak inflammatory effects [1]. It is available in different dosage forms: tablets, capsules, syrups, drops, elixirs, suspensions and suppositories [2]. Most of the immediate release tablets provide therapeutically effective plasma drug concentration for a short period of time. Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Extended release (ER) tablet formulations are preferred in some cases because they maintain uniform drug levels reduce dose and side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance [3]. Bilayer extended release tablet generally has a fast releasing layer and control releasing layer to extend the drug release [4]. The tablet and caplet dosage forms typically contain 325 mg paracetamol as "regular strength. Normally, regular strength tablets or caplets are taken as one or two every four hours. It would be desirable to extend the dosing interval while maintaining the initial plasma concentrations achievable with conventional tablets or caplets. This would provide immediate and extended therapeutic analgesic or antipyretic effect and reduce the number of doses necessary, thereby making therapy more convenient. A way to do this has now been found, whereby two tablets or caplets each containing 325 mg paracetamol can be formulated to provide both immediate release and extended release such that the dosing interval can be extended to at least eight hours [5].

Banu et al. [6] developed bilayer paracetamol tablets for extended release by using hydroxypropylmethyl cellulose (HPMC 15 cps, HPMC 100 cps and Methocel® K4M CR) as release rate retardant. Formulation containing 10% HPMC 100 cps and 1.5% sodium starch glycolate and formulation containing 1.5% Methocel K4M CR and 0.5% sodium starch glycolate were found to follow compendial USP 30 specification for drug release profile. Chabkangwan and Kittitherakun [7] found the dissolution of paracetamol bilayer tablets using Methocel® K4M CR as matrix former at 1.25% of extended release layer weight with 1.5% sodium starch glycolate was similar to that of the innovator. Both were conformed to the acceptance criteria level L_1 of USP 40. The values of difference factor (f_1) and similarity factor (f_2) were 4 and 68, respectively. Radebaugh et al. [5] found that paracetamol-sustained release tablet or tablet layer is formed by making a wet granulation, using povidone in water or alcohol-water as the granulating fluid which is mixed with paracetamol, hydroxyethyl cellulose, a wicking agent e.g. microcrystalline cellulose, then drying and milling the granulation and blending with dry powdered erosion promoter, e.g. pregelatinized starch, wicking agent, lubricant e.g. magnesium stearate and glidant e.g. silicon dioxide, and compressing the resultant granulation, which upon administration results in a slow release of the paracetamol.

The objective of this present study was to prepare and kinetically evaluate the suitability concentration of pregelatinizes starch at 0, 1.5, 2

and 2.5% of weight of extended release layer and HEC at 3.75% of weight of extended release layer. Formulations were also evaluated with various parameters such as physical properties of granaules and tablets, drug contents and dissolution profiles. The similarity factor and the difference factor were also investigated.

Materials and Methods

Materials

Paracetamol was manufactured by Zhejiieng Kankle Pharma, Hydroxyethyl cellulose (Natrosol®/250L) and povidone K30 (Plasdone® K30) were a kind gift from Maxway Chemical Co., Ltd. Tapioca starch was obtained from National Starch and Chemical (Thailand) Co., Ltd. Other excipients, microcrystalline cellulose PH 101, magnesium state, sodium starch glycolate (Primojel®) and pregelatinized starch (Starch® 1500) were procured commercially and were used as received. Hydrochloric acid and other reagents were analytical-reagent grade and purchased from Merck Millipore, Thailand. Batch number of the innovator was 20969B, Mfg date: 02.2018, Exp date: 01.2021.

Mehtods

Preparation of paracetamol bilayer matrix tablets

The bilayer matrix tablets of acetaminophen were prepared by the wet granulation technique. Acetaminophen, HEC and other excipients for both fast release and extended release layer were passed through sieve #80 before their use in the formulation.

Formulation of the immediate release layer

Half of the dose of drug in the formulation was used for immediate release layer. The fast release granules were prepared as per composition in table 1. Paracetamol was mixed uniformly with microcrystalline cellulose PH 101 and tapioca starch. Aqueous solution of povidone K30 was added to the powder to make it damp mass that was passed through # 10 to form granules and the granules were dried at 55°C in a hot air oven. The dried granules were passed through # 12 and added starch glycolate by further blending for 3 minutes. Magnesium stearate was used as lubricant in final blending.

Table 1 Composition of acetaminophen bilayer tablets (mg/tablet)

Ingredients / Formulas	IR (mg/tab)	ER-1 (mg/tab)	ER-2 (mg/tab)	ER-3 (mg/tab)	ER-4 (mg/tab)
Paracetamol	325.0	325.0	325.0	325.0	325.0
Microcrystalline cellulose PH 101	31.8	28.0	28.0	28.0	28.0
Tapioca starch	20.0	-	-	-	-
Povidone K30	6.0	8.0	8.0	8.0	8.0
Hydroxyethyl Cellulose	-	15.0	15.0	15.0	15.0
Pregelatinized starch	-	-	6.0	8.0	10.0
Microcrystalline cellulose PH 101	-	20.0	14.0	12.0	10.0
Sodium starch glycolate	13.2	-	-	-	-
Magnesium stearate	4.0	4.0	4.0	4.0	4.0

Formulation of the extended release layer

The extended granules were prepared by mixing paracetamol uniformly with diluents and matrix materials (HEC) following the formulas given in table 1. The powders were granulated by adding aqueous solution of povidone K30 until a damp mass was formed. The cohesive mass thus obtained was passed through #10 and the granules were dried at 55°C in a hot air oven. The dried granules were sieved by passing through #12. The granules were blended with pregelatinized starch and finally lubricated with magnesium stearate.

Compression of bilayer tablets

Extended release layer was compressed first at the hardness of 2-4 kp and followed by immediate release layer. The quantity of granules for the extended release layer was compressed lightly using 13 mm-diameter die of a hydraulic press. Over this compressed layer, required quantity of the immediate release layer was placed and compressed with a compression force to obtain hardness in the range of 19-23 Kp

Physical evaluation of granules and tablets

Flowability

The granules were evaluated for bulk density, tapped density using a tapped volumeter (Erweka SVM 12, Germany). Compressibility index and Hausner ratio were calculated as per the official procedure. These compressibility index and Hausner ratio were calculated using bulk density and tapped density as follows:

Compressibility index = [(tapped density – bulk density) / tapped density] x 100

Hausner ratio = tapped density / bulk density

The acceptable scale of flowability should be equivalent to "fair" or better flow scale.

Angle of repose (α) was determined on a fixed base method using powder flow meter (Electrolab EFT-01, India). An average of three determinations was calculated from the following equation. The angle of repose equals to 40^{o} and lesser is acceptable.

$$\tan \alpha = \text{height of the powder cone} / 0.5 \text{ base diameter}$$

Hardness test

The hardness of the compressed tablet was determined by using a hardness tester (Erweka TBH10, Germany) and hardness recorded was average of ten determinations.

Friability test

Tablets were randomly selected and weighed with total weight close to 6.5 g. Friability was performed using Roche type friabilator (Brother Join, Thailand) rotated at 25 rpm for 4 minutes. The tablets then were dedusted and reweighed. The loss in weight was recorded as percentage friability that should be less than 1.0%.

$$\% \text{ Friability} = [1 - (\text{weight of tablets after friability} / \text{ weight of tablets before friability})] \times 100$$

Drug content

Weigh and powder 20 tablets. Add a quantity of the powder containing 0.15 g of paracetamol to 50 mL of 0.1M sodium hydroxide, dilute with 100 mL of water, shake for 15 minutes and add sufficient water to produce 200 mL. Mix, filter and dilute 10 mL of the filtrate to 100 mL with water. Add 10 mL of the resulting solution to 10 mL of 0.1M sodium hydroxide, dilute to 100 mL with water and prepare the standard paracetamol solution as the same manner. Measure the absorbance of the standard paracetamol preparation and the sample preparation at the maximum at 257 nm. Potency was calculated by comparison of the absorbance of the standard preparation and the sample preparation [8].

***In vitro* drug release study**

The dissolution test [9] was undertaken using tablet dissolution tester (EDT-08LX, Electrolab, India) in 12 replicates for each formulation. Dissolution media was simulated gastric fluid without enzyme USP 40. The medium was maintained at 37 ± 0.5°C. In all the experiments, 5 ml of dissolution sample was withdrawn at various time intervals at 15, 30 minutes, 1, 2, 3 and 4 hours and replaced with equal volume immediately. Samples were filtered and assayed by measuring absorbance at 280 nm. The concentration of each sample was determined from the standard paracetamol calibration curve.

Drug release kinetics

To study the release kinetics [10], data obtained form in vitro drug release study were tested with the zero order model, first order model, Higuchi model, Korsmeyer–Peppas model and Hixson-Crowell model.

1. Zero order model assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

$$Q_t = K_0 t$$

where, Q_t is the amount of drug un-dissolved at t time, K_0 is the zero order rate constant expressed in unit concentration/time, t is the time in hour.

2. First order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows:

$$\log Q_t = \log Q_0 - (K_1 t /2.303)$$

where, Q_t is the amount of drug un-dissolved at t time, Q_0 is drug concentration at $t = 0$, K_1 is corresponding release rate constant.

3. The Higuchi model describes the cumulative percentage of drug release vs square root of time. The equation may be as follows:

$$Q_t = K_H \sqrt{t}$$

where, Q_t is the amount of drug dissolved at time t, K_H is the constant reflecting the design variables of the system.

4. Korsmeyer-Peppas model derives a simple, semi-empirical model relating exponentially the drug release to the elapsed time. The equation may be as follows:

$$M_t = Q_t/Q_\infty = Kt^n$$

where, $Q/Q0$ is the fraction of drug released at time t, K is constant comprising the structural geometric characteristics, n is the diffusion exponent that depends on the release mechanism.

If $n \leq 0.5$, the release mechanism follows a Fickian diffusion, and if $0.5<n<1$, the release follows a non-Fickian diffusion or anomalous transport [11]. The drug release follows zero order drug release and case II transport if n=1. But when n>1, then the release mechanism is super case II transport. This model is used in the polymeric dosage form when the release mechanism is unknown or more than one release phenomena is present in the preparation.

5. Hixson-Crowell model evaluates the drug release with changes in the surface area and the diameter of the particles/tablets. The data were also plotted

$$(Q_0)^{1/3} - (Q_t)^{1/3} = K_{HC} \times t$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet, and K_{HC} is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix vs time.

Data Analysis

The dissolution profiles were analyzed with difference factor (f_1), and similarity factor (f_2).

$$f_1 = [(\sum | Rt-Tt|)/\sum Rt] \times 100$$

$$f_2 = 50 \times \log [\{1+(Rt-Tt)\times 1/n\}^{-0.5}]$$

Where, n is the number of time points, Rt is the dissolution value of reference product at time t and Tt is the dissolution value for the test product at time t.

Result and Discussion

Characterization of granules

Moisture contents of prepared granules were in the range 1.01±0.03 to 1.43±0.06. Granules prepared for compression of bilayer matrix tablets were evaluated for their flow properties like angle of repose, loose bulk density, tapped density, flow rate, Hausner ratio and compressibility index. The results of granular properties of formulation IR and ER-1 to ER-4 were shown in table 2. Angle of repose was in the range of 33-34°. The bulk density of the granules was in the range of 0.45±0.01 g/mL to 0.48±0.01 g/mL; the tapped density was in the range of 0.52±0.00 g/mL to 0.55±0.01g/ml which indicates that the granules were not bulky. The compressibility index was found to be in the range of 12.00±0.17% to 13.86±1.72%. Hausner ratio was in the range 1.14±0.00 to 1.16±0.88. Flow rate was in the range 5.91±0.16 g/second to 6.13±0.07 g/second. Compressibility index value less than 15% resulted in good to excellent flow properties [9]. So the granules showed good flow properties. The results of angle of repose 31-35° indicated good flow properties of granules [9] which was supported the results found from compressibility index. All these results indicated that the granules possessed satisfactory flow properties.

Table 2 Physical properties of the prepared granules of different formulations

Parameters	IR± SD	ER-1± SD	ER-2± SD	ER-3± SD	ER-4± SD
% Moisture content ± SD	1.43±0.06	1.09±0.20	1.01±0.03	1.01±0.03	1.09±0.06
Angle of repose (°) ± SD	32.9±0.12	32.8±0.05	33.8±0.09	33.9±0.13	33.4±0.15
Flow rate (g/sec) ± SD	5.99±0.02	6.03 ±0.13	6.13±0.07	6.13±0.07	5.91±0.16
Bulk density (g/ml) ± SD	0.48±0.01	0.48±0.01	0.45±0.01	0.45±0.00	0.45±0.01
Tapped density (g/ml) ± SD	0.55±0.01	0.55±0.00	0.52±0.01	0.52±0.01	0.52±0.00
Hausner ratio ± SD	1.14±0.00	1.15±0.86	1.15±0.88	1.16±0.88	1.15±0.89
%Compressibility index ± SD	12.00±0.17	12.69±1.68	12.87±1.08	13.86±1.72	13.58±1.05

Physicochemical evaluation of tablets

The results of physical parameters (hardness, thickness, friability) and drug content of the prepared matrix tablets are shown in table 3. The thickness of the tablets were found between 5.84±0.03 mm to 5.86 ±0.03 mm, hardness of the tablets ranged from 22.04±1.39 kp to 23.35±0.09 kp and friability ranged from 0.40% to 0.55%. The weight variations of prepared tablets, AV <15.0% complied with USP 41 specifications. The drug content of every formulation was found in the range 99.8-103.4% of labeled amount which met USP 41 requirement. So it can be said that physical properties and drug content of the compressed matrix tablets were satisfactory.

Table 3 Physical properties of the prepared tablets of different formulations

Parameters	Innovator	Rx-1	Rx-2	Rx-3	Rx-4
Thickness (mm)± SD (n=10)	*	5.86±0.03	5.84±0.03	5.84±0.03	5.76 ±0.02
Hardness (Kp)± SD (n=10)	*	23.35±0.90	22.39 ±1.76	22.04±1.39	22.17±1.33
% Friability	*	0.52	0.40	0.48	0.55
Average weight (n=20)	784.6	100.8	102.8	103.4	102.3
% LA	99.8	100.8	102.8	103.4	102.3
Weight variation: AV (%)	1.4	3.3	2.7	1.5	2.9

* The innovator is film coated tablets so that these parameters are not needed.

***In vitro* drug release study**

Dissolution profiles of all developed bilayer tablets were compared to that of the commercial product. The release profiles of different formulations (Rx-1 to Rx-4) of paracetamol bilayer matrix tablets were shown in figure 1 and table 4. The dissolution profiles from figure 1 illustrated the effect of quantity of pregelatinized starch on the release of paracetamol from bilayer matrix tablets. The overall release rate of paracetamol from formulations containing different amounts of pregelatinized starch. The release rate was increased according to the higher concentration of pregelatinized starch. USP 41 drug release specification for paracetamol extended release tablet (for L_1, 45%-65% in 15 minutes, 60%-85% in 1 hour, NLT 85% in 3 hours) was used as specification [9].

All tablets from the innovator released paracetamol 45-65% in 15 minutes, 60-85% in 1 hour and more than 85% in 3 hours. The formulation met all USP 41 specification. Tablets of formulation Rx-1 released paracetamol slowly regarding to no disintegrant. All six tablets dissolved 45-65% in 15 minutes, three tablets dissolved lower than 60% in 1 hour and all six tablets dissolved lower than 80%. The formulation did not comply USP 41 specification in 1 hour and 3 hours. Tablets of formulation Rx-2 released paracetamol at a faster rate than Rx-1, but it did not comply USP drug release specification completely. From this formulation all six tablets dissolved 45-65% in 15 minutes, all six tablets met the specification at 1 hour time point, but five tablets released lower than 85% in 3 hours.

Tablets of formulation Rx-3 released paracetamol at a faster rate than Rx-2. From this formulation all six tablets dissolved 45-65% in 15 minute, all six tablets dissolved 60-85% in 1 hour, but four tablets released lower than 85% in 3 hours. Tablets of formulation Rx-4 released paracetamol at a faster rate than Rx-3. From this formulation all six tablets dissolved 45-65% in 15 minutes, all six tablets dissolved 60-85% in 1 hour, all six tablets dissolved 60-85% in 1 hour, but 4 tablets released faster than 85%, two tablets released equally to 85% in 3 hours. This formulation met all USP release criteria.

Table 4 Dissolution profiles of the innovator and different formulations (n=12)

Time (hour)	% Dissolved (mean±SD)				
	Innovator	Rx-1	Rx-2	Rx-3	Rx-4
0.25	55.14±1.83	51.42±3.73	53.18±2.37	56.36±2.93	59.29 ±2.58
0.5	61.65±1.72	54.61±4.33	58.63.±3.93	61.20±3.75	62.28±3.90
1.00	71.03±1.34	61.10±3.84	65.80±4.24	68.48±2.41	72.21±4.05
2.00	85.11±1.89	65.74±3.67	74.00±4.07	77.04±3.04	80.46±3.11
3.00	89.31±1.89	67.45±3.96	81.31±4.08	84.04±1.86	86.69±2.20
4.00	91.62±1.91	70.74±3.43	85.21±3.96	88.87±4.25	90.87±3.72

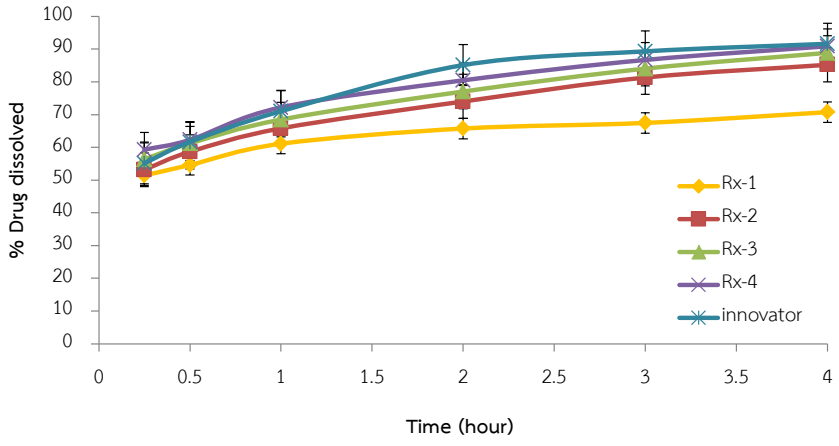

Figure 1. %Drug dissolved from the innovator and different formulations (Rx-1 to Rx-4)

Analysis of dissolution data

To compare the dissolution profiles of different formulation, a model independent approach of difference factor f_1 and similarity factor f_2) were employed. Difference factor f_1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between two curves. The results of difference factor and similarity factor were presented in table 4. Two dissolution profiles are considered similar and bioequivalent, when f_1 is between 0 and 15 and f_2 is between 50 and 100. Formulation Rx-2 - Rx-4 having f_2 more than 50. The f_2 values of Rx-2, Rx-3 and Rx-4 were 46, 64 and 73, respectively, while the f_2 values of Rx-2, Rx-3 and Rx-4 were 8, 4 and 3 respectively. Rx-1 having f_2 value less than 50 and having f_1 value more than 15 was not similar to the innovator.

Table 5 The different factor (f_1) and the similarity factor (f_2) of Rx-1 – Rx-4 (n=12)

Formulas	Different factor (f_1)	Similarity factor (f_2)
Rx-1	18	46
Rx-2	8	64
Rx-3	4	73
Rx-4	3	78

Drug release kinetics

The drug release data were fitted to different model equations representing zero order (cumulative amount of drug released vs. time), first order (log percentage of drug unreleased vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), Korsmeyer's equation (log cumulative percentage of drug released vs. log of time) and Hixson-Crowell cube root law (the cube root of the percentage of drug remaining in the matrix vs. time) to know the release mechanisms. The results were shown in table 5.

The data from table 6 showed that most of the formulations and the innovator were found to follow Kormeyer-Peppas equation (r^2 from 0.9860 to 0.9956). The exponent (n) values ranging from 0.116 to 0.194 indicated Fickian diffusion type drug release as when $n \leq 0.5$, the mechanism follows a Fickian diffusion, and if $0.5<n<1$, the release follows a non-Fickian diffusion or anomalous transport.

Table 6 Kinetic values obtained from different plots of innovator and formulations (Rx-1 to Rx-4) (n=12)

Formula	Zero order		First order		Higuchi's		Korsmeyer- Peppass			Hisxon-Crowell	
	r^2	K	r^2	K	r^2	K	r^2	K	n	r^2	K
Innovator	0.8877	9.691	0.8566	0.057	0.9637	25.464	0.9860	0.713	0.194	0.877	-3.230
Rx-1	0.8925	4.817	0.8679	0.034	0.9645	12.627	0.9902	0.600	0.116	0.8925	-1.606
Rx-2	0.9525	8.327	0.9236	0.052	0.9955	21.467	0.9956	0.673	0.172	0.9525	-2.776
Rx-3	0.9619	8.478	0.9361	0.051	0.9983	21.779	0.9929	0.706	0.166	0.9619	-2.826
Rx-4	0.9415	8.430	0.9149	0.049	0.9889	21.786	0.9902	0.730	0.161	0.9415	-2.810

Conclusion

All the four formulations of paracetamol bilayer tablets and the innovator showed good results in case of physicochemical parameters. They showed good weight variation, thickness, hardness and content of parcetamol. The more rapid dissolution was occurred, the higher concentration of pregelatinized starch was added. Pregelatinized starch acted as erosion promoter while hydroxyehtylcellulose used as matrix former. Tablets from innovator and hydroxyethyl cellulose 3.75 percent with pregelatinized starch 2.5 percent

showed drug release complied to USP 41 dissolution criteria and the value of similarity factor was 73. However, *in vivo* test is required for this formulation and to compare the bioequivalence.

References

1. Bruton LL, Hilal-Dandon R, Knollmann BC. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill; 2018.
2. Brayfield A. Martindale: the complete drugrReference. 39th ed. UK: Pharmaceutical Press; 2017.
3. Shargel L, Yu A. Applied biopharmaceutics and pharmacokinetics. 7th ed. New York: McGraw-Hill; 2016.
4. Gopinath C, Bindu VH, Nischala M. An overview on bilayered tablet technology. J Glob Trend Pharm Sci 2013;4(2):1077-85.
5. Radebaugh GW, Murtha JL, Glinecke R. Oral sustained release acetaminophen formulation and process. United State: Johnson and Johnson Consumer Inc, 1987.
6. Banu H, Sahariar MR, Sayeed MSB, Dewan I, Islam A. Formulation development of bi-layer acetaminophen tablets for extended drug release. J Chem Pharm Res 2011;3(6):348-60.
7. Chabkangwan P, Kittitherakun S, Effect of sodium starch glycolate on dissolution of paracetamol extended release bilayer tablets. Special problem, Huachiew Chalermprakiet University. Samutprakan; 2017.
8. British Pharmacopeia 2018, London: British Pharmacopeia Commission; 2017.
9. The United States Pharmacopeia, 41st rev, The National Formulary. 36th ed. Baltimore: United Book Press, Inc.; 2017.
10. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm 2010;67(3):217-23.
11. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985;60(4):110-1.