RESEARCH ON THE PREPARATION OF PARACETAMOL 650 MG PROLONGED-RELEASE TABLETS

Huynh Thi My Duyen*, Nguyen Huu Nhan, Le Thi Minh Ngoc
Can Tho University of Medicine and Pharmacy
**Corresponding author: htmduyen@ctump.edu.vn*
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ABSTRACT

Background: *Paracetamol is one of the most commonly used active ingredients, even without a doctor's prescription for most people. It has effects on relieving pain and treating fever, especially with an analgesic effect for the elderly who have to suffer from degenerative joint disease. However, the half-life of paracetamol is relatively short, from 1 to 3 hours, so patients need to use it many times a day. The use of large amounts of paracetamol for a long time constantly can cause irreversible liver damage, so the prolonged release dosage form is chosen for the following reasons. Not only does it maintain the therapeutic drug concentration, and help reduce the number of use times but it also limits unwanted side effects.* ***Objectives****: the dissolution and the release kinetics of the active ingredient of the reference tablet Tylenol 8 Hour 650 mg were surveyed in order to formulate the paracetamol 650mg prolonged release tablet and there was an in vitro equivalent evaluation between the prepared paracetamol 650mg prolonged release tablet and the reference tablet Tylenol 8 Hour 650 mg.* ***Materials and methods****: an active ingredient (paracetamol); excipients are used in double-layer formulations that include an immediate release layer and a*

sustained release one; an experimental study that used a wet granulation method was conducted on a rotary tablet press. ***Results****: the formulation of paracetamol 650 mg prolonged release tablets with f2, compared with the reference tablets Tylenol 8 Hour 650 mg in all three media with pH of 1.2, 4.5, and 6.8, was greater than 50.* ***Conclusions****: the result of the study is one of the most essential bases in order to upgrade to a pilot scale, gradually develop to an industrial scale, test in vivo equivalence, and then bring products with well-made quality and safety to consumers as well as patients.*

Keywords*: paracetamol, prolonged release, HPMC K15M.*

I. INTRODUCTION

Paracetamol, also known as acetaminophen, is considered the most classic, widely used, and preferred drug for pain relief and fever reduction for most patients because of its effectiveness and safety. However, if patients use it incorrectly or use high doses for a long time constantly, it can easily lead to poisoning because paracetamol is absorbed and metabolized in the liver before being eliminated from the body. Using high doses of paracetamol from 6 to 10 g/day in adults will cause liver cell necrosis because the liver will not produce enough glutathione to metabolize paracetamol, and toxic substances in the process of paracetamol metabolism will accumulate and poison [1]. To increase the therapeutic effect, limit some side effects, and reduce the number of use times, while still maintaining the analgesic and antipyretic effects, the dosage form of extended-release tablets has been successfully researched and applied on paracetamol in many countries. Currently, prolonged-release tablets containing paracetamol are available on the pharmaceutical market in various countries.

Through the actual survey on Vietnamese market, the prolonged-release tablets containing paracetamol are mostly imported at a high cost. Therefore, this study aimed to make a special effective dosage form with a reasonable price, contributing to meeting the demand for health care for residents. The topic is done with the following goals:

1. Survey on the dissolution and release kinetics of the reference tablet, Tylenol 8 Hour 650 mg.

2. Formulation of paracetamol 650 mg extended-release tablets.

II. MATERIALS AND METHODS

2.1. Materials

Paracetamol was obtained from the US; reference paracetamol (99.54%) was purchased from the Institute of Drug Quality Control Ho Chi Minh City; PVP K30, HPMC K15M, HPMC K100M, and xanthan gum were imported from the US; Avicel 101, Di-Tab, and DST were from Taiwan; magnesium stearate was bought from Malaysia. All chemicals were pure and from analytical grade.

Tylenol 8 Hour 650 mg, manufactured by Janssen Korea Ltd, Korea, with a 16-month expiry date, was purchased at a pharmacy in Can Tho with an invoice proving the origin.

2.2. Methods

2.2.1. Survey on Tylenol 8 Hour 650 mg

It showed that the tablet had a double-layer structure, including paracetamol 325 mg immediate-release layer and 325 mg paracetamol extended-release one. The dissolution of Tylenol tablets was tested in three media with pH of 1.2, 4.5, and 6.8, which is considered as a base for the formulation of paracetamol 650 mg prolonged-release tablets.

Conditions for dissolution test: paddle method at 50 rpm; medium volume (900 mL at pH of 1.2, 4.5, and 6.8); temperature (37 ± 0.5°C); sampling time (15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours); sample volume (20 mL).

Sample processing: the solution was filtered through plain filter paper. After discarding a few first milliliters, the remaining filtrate was mixed well. One mL of the filtrate was withdrawn into a 100 mL volumetric flask, then we supplemented it with the test pH solution. A blank sample was a survey pH solution. The absorbance of the test sample and the reference sample was measured.

The results were calculated by the following equation:

$$C_t = \frac{A_t}{A_c} \times C_c \times 100 \qquad (1)$$

where C_t, C_c was the concentration of the test sample and the reference sample (ppm), respectively, and A_t, A_c was the absorbance of the test sample and the reference sample, respectively.

The percentage of dissolved paracetamol was calculated by the following equation:

$$\%\ PTHC = \frac{\{Cn \times [V - (n-1) \times Vs] + (C1 + C2 + \ldots + Cn{-}1) \times Vs \times 100\}}{m} \qquad (2)$$

where Cn was the concentration of paracetamol in the dissolution medium at time n (ppm), V was the volume of the dissolution medium (900 mL), Vs was the sample volume (20 mL), and m was the content of paracetamol on the label (650 mg). Detector: UV-Vis at a wavelength of 257 nm (the procedure was properly validated according to the guidelines of the Drug Registration Guidance-Drug Administration of Vietnam).

After that, we analyzed the active ingredient release kinetics of the reference tablets.

2.2.2. Formulation of paracetamol 650 mg prolonged-release tablets

The predictive formula is shown in *Table 1* based on references [2], [3], [4], [5].

Table 1. The predictive ingredients for 1 tablet

No.	Ingredients	Immediate-release layer (mg)	Sustained-release layer (mg)
1	Paracetamol	325	325
2	Matrix generator	0	20–50
3	PVP K30	8	11
4	DST (Sodium starch glycolate)	13	0
5	Magnesium stearate	4	4
6	Avicel 101/ Di-Tab	15–30	ad. 400
Total weight		**365–380**	**400**

Stage 1: Survey on the type and the amount of excipient

Survey on the percentage of fillers affecting the immediate-release layer: Avicel and Di-Tab with two content levels of 15 mg and 30 mg are presented in *Table 2*.

Table 2. Survey on fillers

Ingredients/ Formulas	CT1	CT2	CT3	CT4	CT5
Paracetamol	325				
DST	13				
Magnesium stearate	4				

Ingredients/ Formulas	CT1	CT2	CT3	CT4	CT5
PVP K30	8	8	8	8	8
Avicel 101	15	30	0	0	15
Di-Tab	0	0	15	30	15
Total amount	**365**	**380**	**365**	**380**	**380**

Survey on excipients affecting the sustained-release layer: investigating the effects of three polymers including xanthan gum, HPMC K100M, and HPMC K15M. Each one was surveyed at three content levels of 20 mg, 35 mg, and 50 mg, shown in *Table 3*.

Table 3. Survey on the type and the amount of polymer

Formulas/ Ingredients (mg)	CT6	CT7	CT8	CT9	CT10	CT11	CT12	CT13	CT14
Paracetamol	325								
Xanthan gum	20	35	50						
HPMC K100M				20	35	50			
HPMC K15M							20	35	50
PVP K30	11								
Magnesium stearate	4								
Fillers	ad. 400								

At the end of Stage 1, the formulations of the test tablets with active ingredient release patterns that are the same as the reference tablet and reach the standard would be selected. If there were qualified tablets, the study would skip stage 2 and perform an *in vitro* equivalent evaluation with the reference tablet. If stage 1 did not meet the requirements, the study would step to Stage 2.

Stage 2: Optimization of the formulation

From the results of Stage 1, suitable polymers were selected for investigation. Simultaneously, the kinetic patterns on the active ingredient release were also studied to determine the most appropriate kinetic model to describe the release process. With this kinetic model, the correlation between the slope of the kinetic equation and the polymer content were investigated to find the optimal formula.

Prolonged-release tablets were prepared based on the optimal formula. An *in vitro* equivalence between test tablets with reference tablets was assayed over three media with pH of 1.2, 4.5, and 6.8. Data on the active ingredient release over time of two products were evaluated as *in vitro* equivalence through the below f_2 equation.

$$f_2 = 50 \text{ x } \log \{[1 + 1/n \text{ x} \Sigma(R_t - T_t)^2]^{-0.5} \text{ x } 100\} \qquad (3)$$

where n was the number of time points, R_t was the mean dissolution value for the reference product at time t, and T_t was the mean dissolution value for the test product at time t. f_2 value greater than 50 would ensure an *in vitro* equivalence of the two profiles.

Method for preparing double-layer tablets [6]

As for the sustained-release layer: each ingredient was sieved through a 0.3-mm sieve. PVP K30 was dissolved in alcohol. Paracetamol was mixed with fillers and polymers. Then, the mixture was moistened and wet-granulated with PVP K30 solution through a 2-mm sieve. The granules were dried at 60^{o}C to a moisture of ≤ 3%, passed through a 1-mm sieve, and mixed with magnesium stearate. Finally, the powder was compressed on a rotary tablet press with a force of 70 ± 20 N.

As for the immediate-release layer: each ingredient was sieved through a 0.3-mm sieve. PVP K30 was dissolved in alcohol. Paracetamol was mixed with fillers and DST. Then, the mixture was moistened and wet-granulated with PVP K30 solution through a 2-mm sieve. The granules were dried at 60ºC to a moisture of ≤ 3%, passed through a 1-mm sieve, and mixed with magnesium stearate. The hardness of the finished tablets was 180 ± 20 N with a mass difference of not more than 5%.

III. RESULTS

3.1. Survey on Tylenol 8 Hour 650 mg

Table 4. Results of the dissolution test of Tylenol tablets in three media

Time	The percentage of paracetamol release (%)		
	pH 1.2 (n=6)	pH 4.5 (n=6)	pH 6.8 (n=6)
15 minutes	55.31	54.71	59.96
30 minutes	63.60	67.54	65.48
1 hour	75.37	82.00	82.26
2 hours	87.43	88.41	91.87
3 hours	95.15	97.61	103.09

Active ingredient release kinetics of Tylenol 8 Hour 650 mg: the dissolution data of the reference tablet was input in the zero-order kinetic equation and the Higuchi equation. The results are shown in *Figures 1 and 2.*

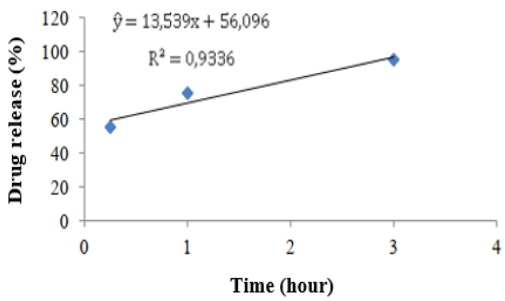

Figure 1. Active ingredient release kinetics from the reference tablet of according to Zero-order kinetics

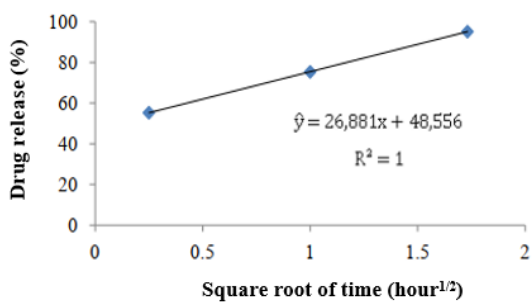

Figure 2. Active ingredient release kinetics from the reference tablet of according to the Higuchi model

There were two following reasons to choose the Higuchi model to describe the active ingredient process of the reference tablets. First, the correlation coefficient R^2 of Higuchi was larger than that of zero-order kinematics. Second, the value of the correlation coefficient R^2 obtained from Higuchi was 1 (> 0.97).

3.2. Formulation of paracetamol 650 mg extended-release tablets

Effects of the percentage of fillers on the immediate-release layer

The results of drug release are shown in *Table 5.*

Table 5. The percentages of drug release of formulas

Time	Drug release percentage (%)				
	CT1	CT2	CT3	CT4	CT5
15 minutes	68.26	76.41	74.76	**91.66**	85.36

According to USP 43, the active ingredient content must be released between 45 and 65% within 15, which means that the immediate-release layer must release the active ingredient nearly completely. CT4 was qualified for this standard, so it was selected. This study used Di-Tab to research the sustained-release layer.

Effects of polymers on the sustained-release layer

The percentages of drug release are presented in *Figure 3.*

The results show that when the amount of polymer decreased, the level of the active ingredient release increased. The study separately surveyed each layer, while the regulation on the dissolution test according to USP 43 is for the whole tablet. Therefore, in the process of studying the extended-release layer, this study used the dissolution of the immediate-release layer in the selected formula (CT4) to evaluate together with the sustained-release layer to find the optimal formula.

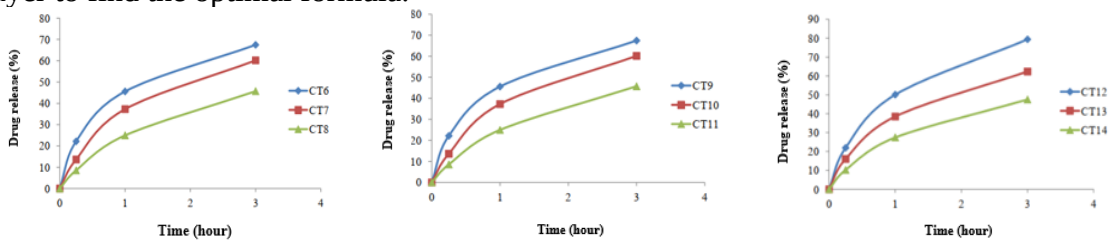

Figure 3. The percentages of drug release of formulas

Combining the fast-release layer from CT4 with the extended-release layer from CT12 could estimate that the active ingredient would be released about 56.80% within 15 minutes, 70.87% in 1 hour, and 85.51% after 3 hours. Thus, the double-layer tablet compressed from CT4 and CT12 met the USP 43 standard in active substance release, but the endpoint was not as expected compared to the control of the reference tablet. Therefore, the study continued investigating the content of HPMC K15M to optimize the formulation.

Optimization of the formulation

***Kinetics of active ingredient release in formulas*:** the dissolution data was applied to the Higuchi kinetic model when combining each formula of the sustained-release layer (CT12, CT13, and CT14) with the formula of the immediate-release layer (CT4). The results are presented in *Table 6.*

Table 6. The correlation coefficient R^2 of the formulas

Formulas	R^2	
	The zero-order kinetic equation	The Higuchi equation
CT12	0.9411	0.9937
CT13	0.9437	0.9914
CT14	0.9561	0.9955

The results indicate that the zero-order kinetic model could not describe the process of active ingredient release of formulas, but the Higuchi model could do it ($R^2 > 0.97$) [7].

***The relationship between the slope coefficient of the Higuchi equation and the polymer content*:** the results show that there was a linear association between the polymer content and the slope coefficient K in the Higuchi equation, shown in *Figure 4.*

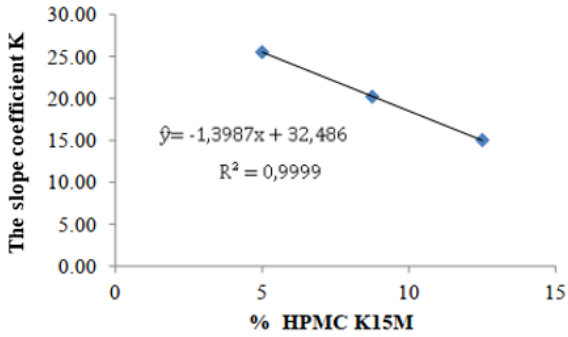

Figure 4. The relationship between HPMC K15M content and the slope coefficient K

There was a correlation between the content of HPMC K15M and the slope coefficient K through regression equation with correlation coefficient R^2 = 0.9999. From the regression equation with the slope K of the reference tablet (26.881), it followed that the percentage of HPMC K15M was 4.01% (equivalent to 16 mg) to obtain the level of active ingredient release close to that of the reference tablet. Therefore, the study combined CT4 and CT 15 (the content of HPMC K15M was 16 mg) for further steps. The dissolution results are shown in *Figure 5.*

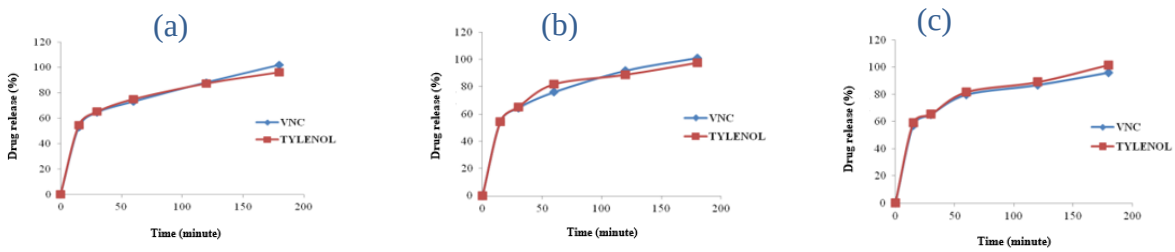

Figure 5. Graph for comparison on active ingredient release of the two profiles in media with pH of 1.2 (a), pH of 4.5 (b), and pH of 6.8 (c)

In all three media (pH 1.2, pH 4.5, and pH 6.8), the active ingredient release of the two profiles was equivalent to each other with the coefficient f_2 of 74.53, 70.61, and 72.76, respectively.

IV. DISCUSSION

The reference tablet met all the criteria in terms of appearance, assay, and dissolution. Its active ingredient release rate was high from 55.31% to 59.96% within 15 minutes, between 75.37% and 82.26% after 1 hour, and from 95.15% to 103.09% after 3 hours, which met USP 43 standard, so the release rate of the test tablet needed to be so high that there would be an *in vitro* equivalence between the test tablet and the reference tablet. Higuchi kinetics almost completely describes the release of active substances in long-acting mechanisms, including diffusion or erosion, or a combination of these processes. Paracetamol is a water-soluble drug, so the main release mechanism is diffusion. Therefore, the Higuchi kinetic model was the most appropriate, which is consistent with the experimental results.

According to USP 43, paracetamol content released from the tablets must be from 45% to 65% within 15 minutes, so the immediate-release layer making up 50% of the active

ingredient content of the formula must release most of the active substance during this period. Therefore, the study used a super disintegrant (DST) to increase the active ingredient release. At the same time, the research investigated the influence of fillers (Avicel PH101 and Di-Tab) on the active substance release. These fillers are commonly used and water-insoluble. Di-Tab hardly absorbs moisture, while Avicel absorbs much moisture and can swell in water [8]. This difference can be the reason why the active ingredient release of CT1, CT2 (Avicel) and CT3, CT4 (Di-Tab) was different from each other. It is found that Di-Tab gave a better release of active ingredients than Avicel and met the requirements, so CT4 was chosen for the immediate release layer.

HPMC and xanthan gum were used to investigate the long-acting effects of the active ingredient. The results show that the control in active ingredient release of polymers decreases in the following order: HPMC K100M, xanthan gum, and HPMC K15M. Comparison between these polymers was carried out by a study by Jaleh V. et al (2006) who researched the applications of natural gums in the preparation of tramadol hydrochloride extended-release tablets [9]. The results indicate that xanthan gum, compared with HPMC K100M, did not cause a massive release in early times, but xanthan gum had poorer release control than HPMC K100M in later times. The author argued that the difference was because xanthan gum swelled faster, which leads to better control in early times, however, the gel layer was loose, so the active ingredient was released much more in later times. Our research findings also indicate that HPMC K100M had better control than HPMC K15M, compatible with the results of a study by Ravi et al. (2008) [10] who showed that the swelling capacity and erosion resistance of HPMC were completely dependent on its viscosity. When the viscosity was higher, the swelling capacity and erosion resistance of the gel layer would be better. Simultaneously, the number of water molecules captured would be also bigger, so the gel layer would be firmer and more homogeneous. These factors made the diffusion of active ingredients through the gel layer more difficult.

With the slope in the Higuchi equation, the optimal content of HPMC K15M found was 16 mg. The study compressed bi-layer tablets composed of an extended-release layer (CT15) firstly compressed with a force of 70 ± 20N to make the shape and ensure the cohesion of the granules and a fast-release layer (CT4) compressed later and adjusted to reach the finished tablet hardness of 180 ± 20N. Compressing the immediate-release layer before the sustained-release layer will greatly affect the active substance release of the immediate-release layer because of the two compressions. Therefore, the study compressed the prolonged-release layer first to make sure that the immediate-release layer would disintegrate and dissolve almost completely after 15 minutes, the active-ingredient release would be controlled more efficiently, and the matrix would be more solid.

The results show that there was an equivalence in the percentage of paracetamol release at each time between the test tablet and the reference tablet in three different media with $f_2 > 50$. According to USP 43, the dissolution of paracetamol extended-release tablets is only measured at 15 minutes, 1 hour, and 3 hours, however, the study added two more points at 30 minutes and 2 hours to make an *in vitro* evaluation more accurate and closer to reality. Moreover, the control in active ingredient release of HMPC K15M was independent of pH, which means the drug was absorbed the same throughout the digestive tract.

V. CONCLUSION

Paracetamol 650 mg prolonged-release paracetamol tablets had been formulated with ingredients including paracetamol (650 mg), HPMC K15M (16 mg), PVP K30 (19 mg), DST (13 mg), magnesium stearate (8 mg), and Di-tab (74 mg). The test tablets had the active ingredient release process equivalent to the reference tablets in three different pH media (f_2 was 74.53, 70.61, and 72.76 in three media with pH of 1.2, 4.5, and 6.8, respectively). Therefore, this study is considered a base to upgrade the batch size, test the *in vivo* equivalence, and bring the product to market.

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