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Metoclopramide-OROS Dispersible Tablets Optimized Formula Bioavailability Study

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Abstract

BACKGROUND: Bioavailability and bioequivalence studies required by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test product and a reference product.

AIM: This study aimed to evaluate the bioavailability performance between the optimum formula of OROS dispersible tablet-metoclopramide dosage forms (FCL-6) and the Primperan® as the reference product.

METHODS: The FCL-6 formula was design by simplex lattice design model with a three components mixture of excipients: Solid *tapai* extract, corn starch, and Avicel. The optimum formula of OROS dispersible tablet (ODT)-metoclopramide consists of solid *tapai* extract (27.038 mg), corn starch (27.407 mg), and Avicel (53.555 mg), metoclopramide hydrochloric acid (HCl) (10.00 mg), LH-11 (22.50 mg), aspartame (5.00 mg), talcum BP (3.00 mg), and Mg stearate (1.50 mg). The *in vivo* test was done by cross-over design method using six rabbits. The level of metoclopramide concentration from *in vivo* test was measured by high-performance liquid chromatography instrument.

RESULTS: The study revealed that the t_{max}, C_{max}, and area under curve (AUC) of ODT-metoclopramide FCL-6 were 60 min, 1.95 ± 0.13 μg/mL, and 1118.20 ± 150 μg/mL. min consecutively. The C_{max} and the concentration of the drug absorbed in the blood (AUC) of ODT-metoclopramide were larger than Primperan® tablets. Statistical data of the optimized ODT-metoclopramide compared with Primperan® showed that the C_{max} and AUC significance values were <0.05 ($p < 0.05$).

CONCLUSION: The optimized formula of ODT-metoclopramide revealed a better characteristic of C_{max} and AUC concentration compared with Primperan®. The optimized ODT-metoclopramide with *tapai* extract was found to be promising to improved bioavailability of metoclopramide.

Introduction

OROS dispersible tablets (ODTs) are a solid dosage form containing active ingredients of drugs and destroyed quickly within a few seconds when placed on the surface of the tongue [1], [2], [3]. ODTs have several advantages such as disintegrate rapidly on the tongue, usually only takes a few seconds without the need for water to swallow, providing rapid early onset of action, and significantly increase the bioavailability of the conventional dosage form [4], [5], [6]. The drug administration problem occurred by the geriatric or pediatrics in consume the solid dosage form/tablets could be resolve by ODT preparation [7], [8].

Metoclopramide administered to the patients who have travel sickness and may have no water supply at the time to take the medicine and it was chosen as a model drug in this study. The ODT-metoclopramide formulas were design by simplex lattice design model with a three components mixture of excipients (solid *tapai* extract, corn starch, and Avicel). The optimum formula of ODT-metoclopramide (FCL-6) consists of solid *tapai* extract (27.038 mg), corn starch (27.407 mg), and Avicel (53.555 mg), metoclopramide HCl (10.00 mg), LH-11 (22.50 mg), aspartame (5.00 mg), talcum BP (3.00 mg), and Mg stearate (1.50 mg) [9].

Bioavailability and bioequivalence studies required by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test product and a reference product. Several *in vivo* and *in vitro* methods used to measure product quality. Bioequivalence documentation was also needed to establish links between early and late clinical trial formulations, formulations used in clinical trials and stability studies, clinical trial formulations and to be marketed drug products, and other comparisons, as appropriate. In each comparison, the new formulation or new method of manufactured shall be the test product and the prior formulation (or respective method of manufacture) shall be the reference product [10], [11]. This study aims to study the bioavailability performance between the optimum formula of ODT-metoclopramide dosage forms (FCL-6) and the Primperan® as the reference product.

Materials and Methods

Materials that used in this study were metoclopramide (PT. First Medifarma), acetic acid (glacial), acetonitrile, methanol, aqua pro-injection, metoclopramide HCl BP (PT. Kairos Tritunggal), trichloroacetic acid (TCA) 20%, and heparin. High-performance liquid chromatography (HPLC) (Agilent 1120 Compact LC), Colom ODS C-18, solvent container (Oberol), vial (Agilent), animal box, vacuum pump (Gast DO), sonicator (Branson), paper membrane filter *cellulose nitrate* 0.45 μm (Whatman), paper membrane filter nylon 0.45 μm (Whatman), PTFE 02 μm (Whatman), Primperan® (PT. SOHO), Avicel PH 102, Solid *tapai* extract, Corn starch, LH-11, and Mg stearate were used.

The *in vivo* test was done by cross-over design method [12] using six rabbits. The rabbits used in this study were male, aged 6 months old and weighed 1.5–2.0 kg. The rabbits were acclimatized for 2 weeks to adapt with the environment. Administration of metoclopramide in rabbit by this method is shown in Table 1. The conventional Primperan® tablets were used as a positive control in evaluating the FCL-6 bioavailability performance.

The rabbit fasted for approximately 12 h and administered with the optimized ODT-metoclopramide (FCL-6) and Primperan® on an oral basis which is shown in Table 1. The rabbit's blood was taken through a marginal vein at certain intervals of time: 10, 20, 30, 45, 60, 90, 120, 180, 300, and 420 min using a 1.0 mL syringe. The needle was rinsed first with heparin. The rabbit blood then inserted into the centrifuge tube that has two drops of heparin. Then, 1.0 mL of TCA 20% was added to the tube and homogenized by vortex instrument. The tube centrifuged at 3000 rpm for 10 min then the supernatant filtered using a 0.2 μm PTFE filter membrane and measured using a HPLC instrument by injecting 10 μL of supernatant.

Bioavailability test of metoclopramide in plasma of rabbit blood was measured by next procedure: The rabbits were given the oral medications in accordance with the bioequivalence test design that is shown in Table 2. At intervals, 10, 20, 30, 45, 90, 120, 180, 300, and 420 min, the rabbits blood were taken with the help of a 1.0 mL syringe that has been rinsed with heparin, transferred to a centrifuge tube containing two drops of heparin and added TCA 20% 1 mL, centrifuged at 3000 rpm for 10 min then take the supernatant. The supernatant filtered with PTFE 0.2 μm filter membrane then determined the concentration of metoclopramide using HPLC instrument. Data analysis has been carried out using Microsoft Excel to calculate the value of t_{max}, C_{max}, and area under curve (AUC). The AUC concentration was determined by trapezoidal formula. The statistical comparison of C_{max} and AUC values between the two formulas was analyzed using the independent sample t-test method.

Table 1: Administration of FCL-6 and Primperan® in rabbits

Treatment I			Treatment II	
Rabbit	Drug		Rabbit	Drug
1	A	Rest for 1 week	1	B
2	A		2	B
3	A		3	B
4	B		4	A
5	B		5	A
6	B		6	A

A = FCL-6, B = Tablet Primperan®10 mg.

Results

The study result revealed an average maximum peak time (tmax) was 60 min. This means that the maximum concentration was reached at minute 60. The relationship between plasma drug concentration (C) and cumulative percentage of time-off drugs (t) of optimized ODT-metoclopramide (FCL-6) and Primperan® revealed in Figure 1.

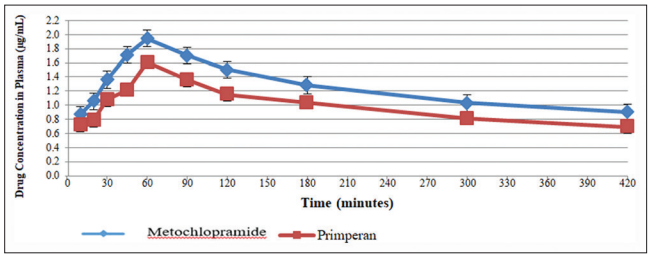

Figure 1: The relationship of mean drug concentrations versus times in rabbits plasma

Based on the data in Figure 1, it can be determined tmax, C_{max}, and AUC. The results revealed in Table 2. It showed that the maximum concentration (C_{max} C_{max}) of FCL-6 (1.94456 ± 0.1340 μg/mL) was larger than Primperan tablets (1.61240 ± 0.1843 μg/mL). This means that FCL-6 was absorbed faster than Primperan®.

Table 2: The values of t_{max}, C_{max}, and AUC

Formula	Means ± SD		
	t_{max} (min)	C_{max} (μg/mL)	AUC (μg/mL. min)
FCL-6	60	1.95 ± 0.1340	1118.20 ± 149.99
Primperan®	60	1.61 ± 0.1843	759.26 ± 108.46

AUC: Area under curve.

The AUC calculated by the trapezoidal formula (against the amount of the drug absorbed in the blood). AUC of FCL-6 (1118.20 ± 149.99 μg/mL min) was larger compared with Primperan® tablets (854.45 ± 251.7 μg/mL min). This is because STP has a highly soluble nature in water and Avicel and CS have disintegrating agent properties so that FCL-6 was more rapidly dissolved and absorbed. As the result, the amount of the drug absorbed in the blood (AUC) was larger than Primperan® tablets [13].

The bioequivalence data between optimized ODT-metoclopramide and Primperan® revealed in Table 3.

Table 3 shows that the Relative Bio-Availability (RBA) was larger than 1.25 and larger than 0.8, t_{max} and C_{max} were in range. Based on these results, the two preparations were claimed to be not bioequivalence. This condition was occur because the optimized ODT-metoclopramide contains water-soluble STP, Avicel and CS have disintegrator properties so that this optimized ODT-metoclopramide dissolves and absorbed faster than Primperan® tablets. As the result, the C_{max} and the concentration of the drug absorbed in the blood (AUC) of ODT-metoclopramide (FCL-6) were larger than Primperan® tablets.

Table 3: Optimized ODT-metoclopramide and Primperan® bioequivalence data

Parameters	Comparing value A/B	Range parameters
AUC	1.47	0.8 <AUC (A/B)< 1.25
t_{max}	1	0.8 < t_{max} (A/B)< 1.25
C_{max}	1.21	0.8 < C_{max} (A/B) < 1.25

A= FCL-6, B= Primperan®. AUC: Area under curve, ODT: OROS dispersible tablet

Results of the FCL-6 and Primperan® parameters of bioavailability statistically analysis are shown in Table 4.

Table 4: Result of statistical data analysis of the FCL-6 and Primperan® test

Treatments	No. of treatment	Means±SD	p
C_{max} FCL-6	6	1.94456 ± 0.1340	0.005
C_{max} Primperan		1.61240 ± 0.1843	
AUC FCL-6	6	1118.20 ± 149.99	0.001
AUC Primperan		854.45 ± 251.7	

AUC: Area under curve

Statistical data of the optimized and Primperan ® ODT-metoclopramide testing with t-test in Table 4 showed that the C_{max} and AUC significance values were <0.05 ($p < 0.05$) and this means that at a 95% confidence level, there was a significant difference between C_{max} and AUC value of the two drugs compared.

Discussion

The study was determined pharmacokinetic parameters of the optimized ODT-metoclopramide formula, FCL-6, from the observed plasma concentration time profiles. The marketed preparation through oral administration, Primperan®, was selected for reference product since these preparations are already clinically proven. From bioavailability studies, it can be concluded that FCL-6 was capable to deliver the drug in systemic circulation since the RBA by ODT formulation with *tapai* extract was found to be 147%. The comparison of C_{max} and AUC value also showed the significantly differences between FCL-6 and Primperan® where FCL-6 showed the superiority to Primperan®. These facts are in similar with the findings revealed by Shyamala and Narmada [4], Pawar and Junagade [5], and Shah and Mehta [6] that ODT formulation was capable to significantly increase the bioavailability of the conventional dosage form.

The AUC value of FCL-6 (1118.20 ± 149.99 μg/mL. min) showed the higher value when compared with the AUC value (2716±4.62 ng.h/mL) from Galgatte and Chaudhari [14] that study the bioavailability of mucoadhesive thermo reversible *in situ* gel-metoclopramide that administered nasally to New Zealand rabbits. Meanwhile, another study by Ward *et al.* [15] stated that the intranasal route did not allow rapid absorption of the metoclopramide and was not associated with greater bioavailability than the oral route. Therefore, the order of bioavailability is i.v. > ODT > nasal [14], [15], [16].

The RBA study also referred as a pilot pharmacokinetics study was used by the drug development sponsor to assess potential *in vivo* performance differences between dosage forms. The data obtained from the RBA study allow the sponsor to move forward in clinical development with a new dosage form [17], [18], [19], [20]. The RBA of FCL-6 (147%) also showed the higher value compare with the RBA value of metoclopramide nasal spray dosage form (62.3%) that mentioned by Li *et al.* study [21]. It revealed that the optimized ODT-metoclopramide with *tapai* extract (FCL-6) has the ability to increased bioavailability of metoclopramide.

Conclusion

It can be concluded that the optimized formula of ODT-metoclopramide (FCL-6) has a better characteristic of C_{max} and AUC concentration compared with Primperan®. The optimized ODT-metoclopramide with *tapai* extract dosage forms (FCL-6) was found to be promising to improved bioavailability of metoclopramide.

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