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In Vitro- In Vivo Correlation Study of Metochlopramide-Orally Disintegrating Tablets

Samran[1]*, Hari Ronaldo Tanjung[2]

[1]Pharmacy Department of Mathematics and Natural Sciences Faculty, Universitas Muslim Nusantara Al-Washliyah, Jl. S.M. Raja No.10, Medan, Indonesia
[2]Faculty of Pharmacy, Universitas Sumatera Utara, Jl. Dr. Mansur, Padang Bulan, Medan, Indonesia

Abstract : Solid *tapai* extract had been applied as excipient in formulating orally disintegrating tablets (ODTs). Solid t*apai* extract was used as excipient by combining solid t*apai* extract with corn starch and avicel. The formula was designed using simplex lattice design method with three component mixture. The optimized formula was determined by in vitro and in vivo study. The objective of this pilot study was to discover *in vitro* and *in vivo* correlation of optimized metochlopramide-ODTs. The design of in vivo test designed by using six rabbits. The drug released in the plasma was measured by HPLC instrument using glacial acetic acid 1% in aquabidestilata and metanol-acetonitrile (1:3.7) with ratio 60:40. The result showed that in vitro test on pH 1.2 and 7.4 had correlation to in vivo test with coefficient correlation of 0.996 and 0.975.
Keywords: metochlopramide, in vivo, in vitro.

Introduction

Drug release from ODTs and subsequent absorption through the mucosa or gastro intestine tract (GIT) involves several stages, starting from penetration of saliva fluid into the ODTs, wetting, swelling, disintegration and finally drug solubilization in saliva fluids or dispersion and then drug absorbtion into peripheral blood vessels or GIT.[1,11]

Orally Disintegrating Tablets (ODTs) is a solid dosage form containing active ingredients of drugs and destroyed quickly within a few seconds when placed on the surface of the tongue.[1,8,13] ODTs has 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[2,10,12]. ODT dosage form could be one choice to overcome the drug administration problem experienced by the elderly or pediatrics in administering the conventional solid dosage form/tablets[9,14].

A few characteristics such as: can be dispersed or dissolved in the oral cavity in a fewseconds without leaving residual, mask the odor and unpleasant taste, resistant to changes in humidity or temperature are needed by the excipients in a good ODT formulation[3,15,17].

Solid *Tapai* Extract (STE) was made from liquid tapai extract that heated until thick then cooled to form solid tapai extract. STE has a sweet and slightly sour taste and dissolves when placed on the tongue[4]. STE's characteristics demonstrate that STE has the possibility to be used as a natural additive for ODT dosage

form. Metochlopramide administered to 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 design of formula used simplex lacttice design model with a three components mixture of excipients: solid t*apai* extract, corn starch and avicel had been formulated. The optimum formula metochlopramide of orally disintegrating tablets (FCL-6) was consist of solid t*apai* extract (27.038 mg), corn starch (27.407 mg) and avicel (53.555 mg). Beside that contained fixed ingradient such as: methochlopramide HCl (10.00 mg), LH-11 (22.50 mg), aspartam (5.00 mg), talcum BP (3.00 mg) and Mg stearate (1.50 mg)[5].

The optimum formula metochlopramide of orally disintegrating tablets was studied for in vitro and in vivo performance dosage forms. A good in vitro-in vivo correlation (IVIVC) can allow the use of in vitro dissolution studies for production control and allows prediction of in vivo performance based on laboratory data.

Materials And Method

Materials

Metochlopramide (PT. First Medifarma), asam acetate glasial, asetonitril, metanol, aquabidestillata, metochlopramide HCl BP (PT. Kairos Tritunggal), trichoroasetat acid (TCA) 20% and heparin. spectrophotometer (Shimadzu UV-1800), disintegration tester (Erweka), disolution tester, HPLC (Agilent 1120 Compact LC), Colom ODS C-18, solvent container (oberol), vial (agilent), animal box, vakum pump (Gast DO), sonicator (branson), paper membrane filter *cellulosa nitrate* 0,45 μm (whatman), paper membrane filter nylon 0.45 μm (whatman), PTFE 02 μm (whatman).

Method

In Vitro Test

Dissolution test

Dissolution test was performed using a dissolution apparatus type 2 (paddle), with 900 mL medium pH 1.2 and pH 7.4 and temperature of 37 ± 0.5 ° C with a rotation speed of 50 rpm. At certain time intervals of 1, 3, 5, 10, 15, 20, 25 and 30 minutes, the sample solution was taken 10 mL and measured at a wavelength of 273 nm.[19]

Animal experiments

Animal test used in this study were male rabbits weighing 1.5-2 kg, which has been conditioned to the environment and feeded for 1 week with kale and carrots during the study. Blood sampling time is 10 minutes after drug administration.

Plasma preparation

Rabbits were fasted at least 8 hours prior to the experiment. Weighed and cleaned fur ears clean. The blood was taken from 2 male rabbits approximately 5 ml each, divided into 4 tubes which had contained 2 drops of heparin, added 2 ml TCA 20%, then centrifuged at 3000 rpm for 10 minutes. Each supernatant was taken and used as a blanko and a calibration curve.

In Vivo Test

The test was conducted using six rabbits. The administration of metoclopramide in rabbits with this method can be seen in Table 1.

Tabe1 1. Provision of metochlopramide-ODTs in rabbits.

Treatment	
Rabbits	**Dosageform**
1	A
2	A
3	A
4	A
5	A
6	A

Note: A = optimized formula FCL-6,

Rabbits were fasted for 12 hours and administered orally with FCL-6 which can be seen in Table 1. The Rabbit's blood was taken through the marginal vein at specified time intervals are: 10, 20, 30, 45, 60, 90, 120, 180, 300 and 420 minutes using 1.0 mL syringe. Syringes rinsed beforehand with heparin. Blood inserted into the centrifuge tube which already contains 2 drops of heparin. Then TCA 20% as much as 1.0 mL tubes were added and shaked using vortex apparatus until homogeneous. The tube was centrifuged at 3000 rpm for 10 minutes and the supernatants were collected. Each supernatant was filtered using a 0.2 μm PTFE membrane filter and the metochlopramide concentrations measured using HPLC instrument by injecting as much as 10 uL supernatant.[19]

Correlation of In Vitro and in Vivo

Correlation of in vitro and in vivo was determined by using a level A correlation that explains the relationship between the rate of drug release (% cumulative drug apart) in vitro and speed of drug release in vivo (plasma drug concentration).[6,16]

Analysis of Blood Plasma Levels of metoclopramide in Rabbits

Rabbits that have been granted in accordance with the oral drug bioequivalence trial design that can be seen in Table 1. At intervals; 10, 20, 30, 45, 90, 120, 180, 300 and 420 minutes rabbit blood drawn with the help of 1.0 mL syringe that has been rinsed with heparin, was transferred to a centrifuge tube which already contains heparin, and add 2 drops of 20% TCA 1 mL, centrifuged at 3000 rpm for 10 min, the supernatant was taken, filtered with a 0.2 μm PTFE membrane filter and assayed using HPLC.

Result and Discussion

The optimized formula was FCL-6 that contained solid tape extract 27 mg, corn starch 27 mg and avicel 54 mg. FCL-6 was studied in vitro and in vivo dosage form performance. The result can be seen in Table 2 and Figure 1. Drug release from ODTs and subsequent absorption through the mucosa involves several stages, starting from penetration of saliva fluid into the ODTs , wetting, swelling, disintegration and finally drug solubilization in saliva fluids and then drug absorbtion into peripheral blood vessels. Furthermore, This IVIVC test was conducted in pH 1.2 (represent the mouth cavity condition) and pH 7.4 (represent the gastrointestinal condition).

In vitro* dan *In Vivo Assays Correlation

Chilukuri, et al., (2007) stated the correlation between *in vitro* assay with *in vivo* assay can be explained by using the correlation IVIVC level A which is a relation between the cumulative percent of the drug released of in vitro assay and the percent amount of absorbed drug in blood plasma of in vivo assay.[6,18] The release of metochlopramide from the metochlopramide-ODT of FCL-6 for the *in vitro test* and the average level of the absorbed metochlopramide in the blood plasma can be seen in Table 2.

Table 2. The cumulative percent of released metochlopramide-optimized ODT of *in vitro assay* (pH 1,2) and the average concentration (%) of metochlopramide in blood plasma.

Time (Minutes)	*In Vivo Test (%)*	Time (Minutes)	*In VitroTest* (pH 1,2) *(%)*
10	44,79 ± 7,29	1	53,76 ± 1,58
20	54,24 ± 4,19	3	65,23 ± 1,71
30	70,19 ± 7,38	5	77,73 ± 2,47
45	88,35 ± 3,67	10	93,93 ± 2,14
60	100,00 ± 0,00	15	100,42 ± 0,67

Based on correlation index (R^2 = 0.996), it can be stated that there is a correlation between formula tested *in vitro* to *in vivo* tests because of correlation index was greater than 0.8, meaning that for the next test, the *in vitro* assay data is sufficient for the formulation so as not need to be tested for in vivo assay[7,17].

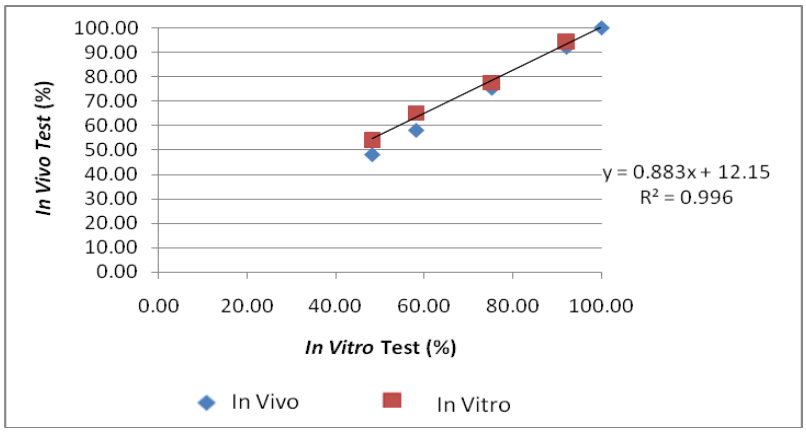

Figure 1. *In Vitro* pH 1,2 and *In Vivo* Correlation

ODT-metoclopramide (FCL-6) dissolution test was also conducted in the medium of pH 7.4 and the results can be seen in Table 3 and the Figure 2. Based on correlation index (R^2 = 0.975), it also can be stated that there is a correlation between formula tested *in vitro* to *in vivo* tests because of correlation index was greater than 0.8, and it is revealed that the *in vitro* assay data is sufficient for the formulation so as no need to be tested for in vivo assay[7].

Table 3. The cumulative percent of released metochlopramide-optimized ODT of *in vitro assay* (pH 7.4) and the average concentration (%) of metochlopramide in blood plasma.

Time (Minutes)	*In Vivo Test (%)*	Time (Minutes)	*In VitroTest* (pH 7,4) *(%)*
10	44.79 ± 7.29	1	36.37 ± 1.02
20	54.24 ± 4.19	3	60.23 ± 10.25
30	70.19 ± 7.38	5	101.89 ± 4.29
45	88.35 ± 3.67	10	99.41 ± 4.29
60	100.00 ± 0.00	15	97.81 ± 2.47

The *in vitro* assay at pH 1.2 and pH 7.4 revealed a correlation with in vivo assay with coefficient correlation of R^2 = 0.996 and 0.975.

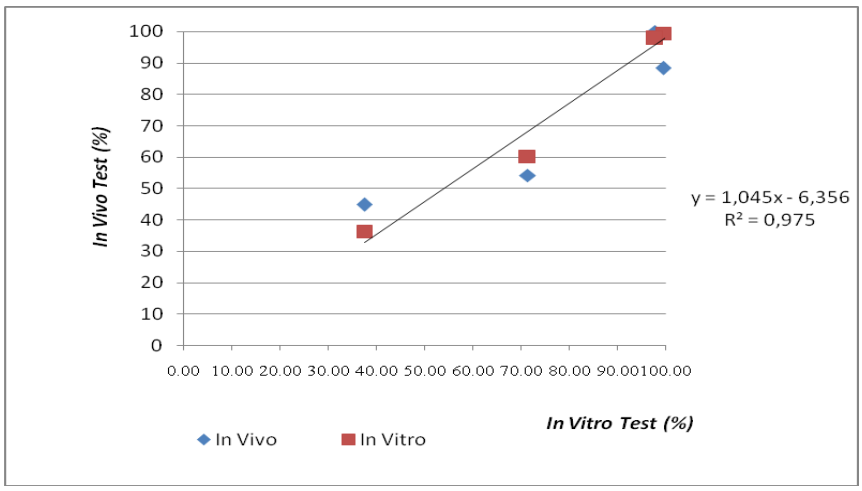

Figure 2. *In Vitro* pH 7,4 and *In Vivo* correlation

By studying the release properties of metochlopramide-ODTs in vitro and evaluating their properties in vivo, the biopharmaceutics and pharmacokinetics properties of the newly designed metochlopramide-ODTs could be better characterized and understood as a basis for the future application in the patients.

Conclusion

This IVIVC pilot study was revealed a good coefficient correlation (R^2 = 0.996 and 0.975) between in vitro and in vivo assays of optimized formula of metochlopramide-ODTs (FCL-6).

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