OPTIMIZED FORMULATION OF METOCLOPRAMIDE ORALLY DISINTEGRATING TABLET

SAMRAN¹, KARSONO², M. T. SIMANJUNTAK², JANSEN SILALAHI³

¹Academy Pharmacy of Indah
²Technology of Pharmacy Department, Pharmacy Faculty, University of North Sumatera
³Chemistry of Pharmacy Department, Pharmacy Faculty, University of North Sumatera

*Corresponding author: Samran, email: samranamatrejo@gmail.com

Orally Disintegrating Tablet (ODT) was developed to solve the difficulty to swallow conventional tablet for pediatric and geriatric patients. In administration of ODT, tablets are placed on the tongue in oral cavity and it will disintegrate rapidly in less than 60 second. The Solid Tapai Extract (STE) has sweet taste, rather sour and slightly soluble when it is put on the tongue. This is the reason why it has potential as a natural excipient in ODT. The objective of the study was to characterize STE as excipient and to use STE as excipient in the formulation of ODT by lyophilization method. The ingredients were glutinous rice (Oryza sativa L. Var. Glutinous) which was made to tapai and the liquid extract of tapai which was used to make STE. STE was used as excipient by combining STE with dextrose and avicel. Metochlopramide HCl was used as a drug model. The design of formula used Simplex Lattice Design (SLD) model with a three components mixture: STE, Dextrose and Avicel as excipients. The parameter of lyophilized ODT (LODT) were hardness and friability, wetting time, disintegrating time and dissolution rate. The results showed STE can be used as filler and binder for LODT. STE could also functioned as disintegrant and formed porosity in lyophilized method. Based on equation and contour plot of superimposed method, formula consisting of STE (24.182 mg), Dektrose (19.707 mg) and Avicel (96.111 mg) was the optimum formula of LODT.

Keywords: Solid Tapai Extract, Orally Disintegrating Tablet, Simplex Lattice Design

INTRODUCTION

The oral route remains the most preferred route for administration of drugs because of its safety, convinience, and low cost of therapy (Shukla et al. 2009). Tablets and hard gelatin
capsules constitute a major portion of drug delivery systems that are currently available. However, for some patient groups such as pediatric and geriatric patients who have underdeveloped muscular and nervous control, dysphagia, hand tremor, mentally retarded, nauseated, or on reduced of liquid-intake/diets have difficulties swallowing these dosage forms. Further more, travelling patients with little or no access to water, limit utility of orally administered conventional tablets or capsules.

Therefore, to fulfill the needs of such patients, the scientist have developed a novel oral dosage form known as Orally Disintegrating Tablet (ODT), which has several advantages such as: no need to swallow because its disintegrate rapidly on the tongue, usually only takes a few seconds without the need of water to swallow, providing rapid early onset of action, and significantly increase the bioavailability of the conventional dosage form (Shyamala and Narmada 2002). ODT is a solid dosage form containing medicinal ingredients that are destroyed quickly usually within a few seconds when placed on the surface of the tongue (Hirani, Dhaval and Kantilal 2009).

A good ODT formulation need the excipients that have characteristic such as dispersed or dissolved in the oral cavity in a few seconds without leaving residual, mask the odor and unpleasant taste, resistant to changes in humidity or temperature (Bansal 2003).

STE is a product that originated from liquid tapai extract that was heated to viscous the liquid then cooled to form solid tapai extract. STE has a sweet and slightly sour taste and dissolves when it is placed on the tongue (Meigia, Nurhidayat and Hindun 2004). STE has the possibility to be used as a natural additive dosage form of ODT since STE dissolves when it is placed on the tongue and STE also has less expensive price than other excipients. STE, dextrose and avicel were optimized as excipients to obtain a suitable excipients in the preparation of ODT that using metochlopramide as a drug model.

An antiemetic metochlopramide which is indicated for gastrointestinal motility disorders (particularly gastric stasis), gastroesophageal reflux, prevention or treatment of nausea and vomiting due to chemotherapy drugs, radiation therapy or treatment after surgery was chosen as a drug model in this study, as metochlopramide can be administered to the patients who have travel sickness and may have no water supply at the time to take the medicine.
METHODS

Materials

White Glutinous Rice, STE, Metochlopramide (Ipca Laboratories Limited, Batch No.8007MRIIX), Yeast (NKL®), Dextrose (Qinhuangdao Lihua Starch Co LTD, Batch No.20121208), Avicel (Flocel® 102, Batch No.E0904).

Formula Optimization Design

This study covered the formulation of tapai and STE which were used as additive in the manufacture of ODTs with SLD optimization design of three-component formula. Each formula (F) contained STE (A), Dextrose (B) dan Avicel (C) in certain proportion (0-1 part). Lyophilized ODT (LODT)-metochlopramide has the highest response of 1 part = 140 mg and smallest response 0 parts = 0 mg. Formula derived from the SLD method was presented in Table 1. The mass was molded into tablets with lyophilization method.

The Making of Glutinous Rice Tapai

White glutinous rice (Oryza sativa L. Var. Glutinous) was cooked, then cooled to temperature of 27-30°C. Tapai of glutinous rice was made by using a concentration of 1.5% yeast containing Saccharomyces cereviceae then fermented for 6 days.

Organoleptic Test of Glutinous Rice Tapai

Organoleptic test of Tapai taste was conducted by hedonic test. Organoleptic test was carried out by using a sensory test for 10 panelists and determined by a numerical scale.

The Making of Solid Tapai Extract (STE)

Tapai mass was pressed using a suppresor. The water of tapai that obtained from the process was filtered using a 60 mesh sieve and the waste was disposed. Tapai water was heated at 50-
60°C by using a stainless steel container to obtain a yellowish-brown of viscous mass. Viscous mass was filtered when still hot, then added to the inoculum and mixed with speed of 1500 rpm for 15 minutes then poured into stainless steel molds, allowed to stand for 1 night to form a solid mass called STE.

**STE Characteristic Determination**

**Analysis of pH**

pH of STE was analysed by suspending 1 gram of STE in 50 mL of distilled water free of CO₂. The suspension was stirred until homogen and then measured using pH meter (Ditjen POM, 1979).

**The Water Level**

The water level was measured by put 200 mL of toluene and 2 mL of distilled water into the distillation apparatus then distilled for 2 hours. STE was weighed for 5 g and inserted into the distillation apparatus that already contains toluene and then distilled for 20 minutes. The volume of water and toluene were read on the receiver tube. Water level was calculated in percentage (Ditjen POM, 1979).

**The Ash Level**

The ash level was measured by weighing a porcelain dish, and put 3 grams of STE into it, then ashing process was carried out at temperature of 675°C in the furnace for approximately 5 hours. The porcelain dish was cooled in an excicator and weighed. The treatment was repeated until obtained a constant weight of ash (Ditjen POM, 1979).

**Angle of Response**

The angle of reponse was measured using Tensiometer apparatus. Tensiometer rinsed with distilled water, then 10 mL sample was put into tensiometer. Sample solution was poured into a
capillary tube, then slowly lowered until balanced. The high of the sample solution that left in the capillary was recorded (Yazid, 2005).

**Flowing Time**

The flowing time was measured by put the STE granules into a funnel which has been assembled then leveled surface. The cover located on the bottom of the funnel was opened and the stopwatch was turned on simultaneously. Stopwatch was stopped just in time when all the granules discharged through the funnel and the flowing time was noted. The requirement of granular flow time is less than 10 seconds (Lachman, Lieberman and Kanig 1994).

**Compressibility Index**

Compressibility index was measured by put STE granules into a measuring cup on compressibility index apparatus to mark the lines and expressed as initial volume (V1), then the tool was run causing the beat as much as approximately 30 times to obtain a final volume (V2). Compressibility index was calculated in percentage (Lachman, Lieberman and Kanig 1994).

**The Formulation of Metochlopramide ODT by Lyophilization Method Using STE (A), Dextrose (B) and Avicel (C) as Excipients**

STE was put into a container, then dextrose, Avicel and Metochlopramide were added into the container and stirred until metochlopramide dispersed perfectly. The mixture was poured into molds blister, weighing 150 mg tablet for each mold. Once the mold had been filled, it was put in freezer to harden and then the freeze dryer procedure was used to form the lyophilized tablet. The resulting tablets were evaluated for the wetting time, disintegration time and dissolution rate parameters. The process of metochlopramide ODT formulation by lyophilization method can be seen in Figure 1.
Evaluation of Metochlopramide Orally Disintegrating Tablet

Hardness Test

One tablet was placed vertically between the anvil and the punch of Strong Cobb Hardness Tester. The tablet was clamped by turning the regulator screw until the signal "stop" lighted, then the button was pressed until the tablet broke. After the tablet broke, the scale number was recorded. The tablet hardness were the figure of the needle on the scale. Hardness test was performed for 6 tablets (Parrot, 1970).

Friability Test

Twenty tablets were weighed and cleaned from dust. The weight was recorded (a gram). The tablets were put into the friability tool, and the tool was run for 4 minutes (100 rpm). After the time limit, tablets were cleaned from dust, then weighed again (b gram). Friability value = (a-b) / a x 100% (Lachman, Lieberman and Kanig 1994).

Water Absorption Ratio Test

Circular filter paper was placed into 9 cm diameter petridish containing 9 mL carmiosin solution 0.1% w/v in distilled water. One tablet was placed gently in the middle of petridish, then a perfect wetting time of the tablet was recorded. Tablet was weighed before and after wetted. Water absorption ratio was calculated by the formula of R = 100 x (wa-wb) / wb, where wb is the weight of the tablet before it absorbed water and wa is the weight of the tablet after absorbed water (Bhowmik et al. 2009).

Disintegrating Time Test Using Disintegration Tester

One tablet was placed to each tube of the basket of disintegration tester, then the disintegration apparatus was run. Water was used as a medium with temperature of 37 ± 2°C. All tablets should be crushed perfectly in less than 20-30 seconds (Manivannan 2009).
Disintegrating Time Test in Oral Cavity

This test used 10 volunteers. Before starting the test, each volunteer was required to rinse out their oral. The ODT tablet was placed on the tongue and allowed to disintegrate perfectly. After that, the tablet could be spitted. The time for the tablet to disintegrate in the oral perfectly was recorded (Manivannan 2009).

Dissolution Test

In vitro dissolution test was conducted using a type 2 dissolution apparatus (paddle), using pH 1.2 and 7.4 medium as much as 900 mL, temperature of 37 ± 0.5°C with a rotation speed of 50 rpm. Ten milliliters of sample solution was taken and measured at a wave length of 272.5 nm with intervals of 1, 3, 5, 10, 15, 20, 25 and 30 minutes (Ditjen POM 1995).

RESULTS

Characteristics Analysis of STE

The results of the analysis on the characteristics of STE were presented in Table 2. STE was freely soluble in water because it had contact angle of 2.01°, angle of response 29.6°, flowing time 3.76 ± 0.074 seconds, and compressibility index 10.67%. This indicated that the STE met the requirements to be used as an excipient in the manufacture of ODT.

LODT Formulation

Freeze dry is the process in which water is sublimed after freezing. This technique produces a porous amorphous structure that can dissolve quickly (Bhowmik et al. 2009). Table 3 showed that the formula FL-2 and FL-3 was failed to formed LODT-metochlopramide. LODT-metochlopramide was evaluated for friability, wetting time, disintegrating time, disintegrating time in the oral cavity and the dissolution rate.
Hardness and Friability Test

The hardness and friability test of LODT-metochlopramide of FL-1, FL-4, FL-5, FL-6, FL-7, FL-8, FL-9 and FL-10 did not meet the requirements value.

Wetting Time Test

Wetting time test result of LODT-metochlopramide presented in Table 3 showed all the formulas were met the requirement criteria: less than 60 seconds (Kundu and Sahoo 2008).

Disintegrating Time Test Using Disintegrator

The disintegrating time of LODT-metochlopramide met the requirements criteria: less than 30 seconds (Hirani, Dhaval and Kantilal 2009). The data were presented in Table 3.

Disintegrating Time Test in Oral Cavity

The result of disintegrating time test in oral cavity was presented in Table 3 which revealed that all formula of LODT-metochlopramide met the requirements of ODT because the disintegrating time was less than 60 seconds.

Drug Dissolution Test

The results of in vitro dissolution rate test using dissolution tester of all LODT-metochlopramide formula were presented in Figure 2. The results showed that all the formulations LODT-metochlopramide met the requirements (Ditjen POM, 1995).
DISCUSSION

LODT Formulation

Table 3 showed that the formula FL-2 and FL-3 was failed to formed LODT-metochlopramide because the additives used were Avicel (FL-2) alone which was a disintegran material that had low power of cohesion so it did not form LODT. Dextrose (FL-3) has a cohesive power, but the formed LODT-metochlopramide was difficult to remove from the mold which broke the LODT-metochlopramide, whereas STE (FL-1) alone has a good cohesive power that produced LODT-metochlopramide which easily removed from the mold. This meant that STE can be used as a filler of LODT formulation.

Hardness and Friability Test

None of the formula met the hardness and friability test requirements. This is because LODT-metochlopramide was formed only by the power of cohesion without giving pressure, so the formed LODT became fragile. The fragility of LODT-metochlopramide is a weakness of the lyophilization method, the conventional packaging is not appropriate and require special packaging thus require expensive costs (Velmurugan and Vinushitha 2010).

Previous researchers had used mannitol and gelatin as additives to make LODT and using sodium phenobarbital as a drug model. The results showed the LODT was hard and fragile with the porous surface (Sznitowska, Placek and Klunder 2005).

Wetting Time Test

Wetting time is the most important parameter in the evaluation of ODT, because wetting process is the initial phase of ODT disintegrating process (Rao, Patel and Gandhi 2009). A short time of wetting time showed a rapid tablet disintegration time (Hirani, Dhaval and Kantilal 2009). The most rapid wetting time was represented by the formula FL-5 with 1.62 seconds. It was because the FL-5 containing dextrose and avicel that had characteristic as a good disintegrator ingredient (Siregar and Wikarsa 2010).
Wetting time data in Table 3 can be made equation:

\[ Y = 1.88A + 6.16AB + 10.2AC + 6.48BC - 11.46ABC \]

Where,

- \( Y \) = Wetting Time (sec)
- \( A \) = number of STE used
- \( B \) = number of dextrose used
- \( C \) = number of Avicel used.

Based on the regression coefficients, the STE (1.88) was the dominant factor in accelerating the wetting time compared with dextrose and avicel. STE had a small contact angle, making it very easy to be penetrated by water and pores resulting in rapid wetting time. STE mixed with dextrose and or avicel accelerated the wetting time.

**Disintegrating Time Test Using Disintegrator**

The most rapid disintegration time was formula FL-1 (STE : Dextrose : Avicel : 140 : 0 : 0). This is probably due to the STE had a smaller contact angle so it was easily to be wetted and had many pores so it was easily to be penetrated by water and STE freely soluble in water thus disintegrated and dissolved the tablet.

Disintegrating time data in Table 3 can be made equation:

\[ Y = 2.84A + 14AB + 6.84AC + 12.28BC - 3.96ABC \]

Where,

- \( Y \) = Wetting Time (sec)
- \( A \) = number of STE used
- \( B \) = number of dextrose used
- \( C \) = number of Avicel used.
Based on the STE regression coefficient (2.84), STE was the dominant factor in accelerating the disintegration time compared with dextrose and Avicel.

**Disintegrating Time Test in Oral Cavity**

All formula of LODT-metochlopramide met the requirements of ODT because the disintegrating time was less than 60 seconds. This suggested that LODT-metochlopramide was destroyed when contact with saliva in the oral (Popescu, Zhou and Joshi 2010). FL-1 was a formula that had a faster disintegrating time in the oral compared than other formula of LODT-Metochlopramide. This meant FL-1 had a high porous (Budgajar and Mundada 2011) which facilitated LODT-metochlopramide tablets to be penetrated by water and quickly disintegrated.

Disintegrating time in oral cavity data in Table 3 can be made equation

\[
Y = 26.67A + 134.66AB + 125.34AC + 176.68BC + 33.84ABC,
\]

Where,

- \(Y\) = Wetting Time (sec)
- \(A\) = number of STE used
- \(B\) = number of dextrose used
- \(C\) = number of Avicel used

Based on the regression coefficient STE (26.67), the STE is the dominant factor accelerating disintegrating time in the mouth compared with dextrose and Avicel as STE had a smaller contact angle, freely soluble in water and formed pores after freeze-dried. So it is easily penetrated by saliva solution and LODT was immediately disintegrated. The mixed of STE and dextrose (134.667) and the mixed of STE and avicel accelerated the disintegrating time in the mouth too. The higher concentration of dextrose and avicel showed a rapid disintegrating time of LODT in oral cavity.
**Drug Dissolution Test**

In the 5th minute, all formula of LODT-metochlopramide were dissolved to 100%. This was because LODT-metochlopramide had a high porous (Budgujar and Mundada 2011), so it was easily penetrated by water and the disintegrating time was less than 10 seconds and as a result, metochlopramide was dissolved sooner. Moreover, freeze-drying technique also produced a porous structure that made metochlopramide was dissolved rapidly.

Based on cumulative dissolution data in Table 3, it was obtained equation:

\[ Y = 51.06A + 196.52AB + 138.92AC + 180.20BC - 808.47ABC \]

Where,

- \( Y \) = Wetting Time (sec)
- \( A \) = number of STE used
- \( B \) = number of dextrose used
- \( C \) = number of Avicel used.

Based on the regression coefficients, STE (51.06) was the most dominant influence in increasing the % cumulative of released metochlopramide compared with dextrose and Avicel as STE had a smaller contact angle, freely soluble in water and formed pores after freeze-dried so it was easily penetrated by medium and LODT was disintegrated immediately. The higher concentration of STE showed the faster dissolution time of LODT-metochlopramide. The mixed of STE and dextrose and the mixed of STE and Avicel also increased % cumulative of released metochlopramide.

Overall, STE has the ability to be use as excipients in formulation of ODT and, based on the the wetting time test, disintegrating time test and also drug dissolution test, STE was the dominant factor that accelerated the time of the test resulted.
**Determination of Optimum Formula**

Based on the superimposed contour plot in Figure 3, it was obtained optimum areas (areas colored yellow) with parameters LODT-metochlopramide wetting time (prediction rate under 3 seconds and over 5 seconds) and disintegrating time in oral cavity (prediction rate under 30 seconds and over 40 seconds) that met the requirements. The point on the flag area was one of the formulas in the optimum area. The point contained a proportion of STE (24.182 mg), Dextrose (19.707 mg), dan Avicel (96.111 mg) to obtain the optimum formula for a tablet which can be seen in Table 4. The optimized formula in Table 4 was formulated and tested for the ODT parameters: the wetting time and the disintegrating time. The results showed that the optimization formula had the average of wetting time of 4.47 seconds and the average of disintegrating time of 39.97 seconds.

**CONCLUSION**

This study revealed that STE has good characteristics to be use as ODT excipients and can be used as additive of LODT with function as fillers, disintegrant and pores forming. A single STE was able to formed LODT while dextrose and avicel respectively can not formed LODT; STE and dextrose mixture components could form LODT; and STE, dextrose, and avicel component mixture were able to improve the characteristics of LODT. The optimized formula of LODT-metochlopramide from three mixed component: STE, dextrose, and Avicel that produced with lyophilized method based on superimposed contour plot is STE 24.182 mg, Dextrose 19.707 mg, Avicel 96.111 mg, Metochlopramide HCl 10 mg, Aspartam 5 mg with total weight of tablet is 155 mg. The pharmaceutical industry has an opportunity to manufacture ODT in a more cost-effective way by using STE as excipients since STE was produced easily and has abundant of natural raw materials that cheap and can be obtained easily.

**ACKNOWLEDGEMENT**

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Special thanks and gratitude, goes to Mr. Fekodin and Mrs. Rumina for trained me in formulation of tape and brem at Seruling’s brem home industry, Madiun, East Java. Last, I am grateful to Mustika Furi, Abdi and Ruslan Abdul Gani for their assistance in this research.

**REFERENCE**


**Table 1:** Formula of LODT-metochlopramide from the mixed of three component: STE (A), dextrose (B) and avicel (C) as excipients.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Ingredients (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STE</td>
<td>Dextrose</td>
</tr>
<tr>
<td>FL-1</td>
<td>140</td>
<td>0</td>
</tr>
<tr>
<td>FL-2</td>
<td>0</td>
<td>140</td>
</tr>
<tr>
<td>FL-3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>FL-4</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>FL-5</td>
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<td>70</td>
</tr>
<tr>
<td>FL-6</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>F-L7</td>
<td>23.33</td>
<td>23.33</td>
</tr>
<tr>
<td>FL-8</td>
<td>23.33</td>
<td>93.33</td>
</tr>
<tr>
<td>FL-9</td>
<td>93.33</td>
<td>23.33</td>
</tr>
<tr>
<td>FL-10</td>
<td>46.667</td>
<td>46.667</td>
</tr>
</tbody>
</table>

*Note:* MCP: Metochlopramide

STE: Solid Tapai Extract
Table 2: Characteristic of STE.

<table>
<thead>
<tr>
<th>Test</th>
<th>Characteristic of STE</th>
</tr>
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<tbody>
<tr>
<td>Macroscopic</td>
<td>Granuls/Bars</td>
</tr>
<tr>
<td>Form</td>
<td>Granuls/bars</td>
</tr>
<tr>
<td>Colour</td>
<td>Tawny</td>
</tr>
<tr>
<td>Odor</td>
<td>Typical aromas STE</td>
</tr>
<tr>
<td>Taste</td>
<td>Sweet little sour</td>
</tr>
<tr>
<td>Fehling test</td>
<td>Brick red precipitate</td>
</tr>
<tr>
<td>pH</td>
<td>6.31 ± 0.01</td>
</tr>
<tr>
<td>Infra red analysis</td>
<td>-CH₃, -C-H, -C-O, -OH</td>
</tr>
<tr>
<td>Contact angle</td>
<td>2.01°</td>
</tr>
<tr>
<td>Water level</td>
<td>9.44 ± 0.35 %</td>
</tr>
<tr>
<td>Ash Level</td>
<td>0.41%</td>
</tr>
<tr>
<td>Reducing Sugar Levels</td>
<td>70.4%</td>
</tr>
<tr>
<td>Solubility</td>
<td>Freely soluble ( &lt;1.0 mL water)</td>
</tr>
<tr>
<td>Angle of response</td>
<td>29.6°</td>
</tr>
<tr>
<td>Flowing time</td>
<td>3.76 ± 0.074 second</td>
</tr>
<tr>
<td>Compressibility index</td>
<td>10.67%</td>
</tr>
</tbody>
</table>
Table 3: LODT-metochlopramide evaluation result from a variety of formulas.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Wetting time (second)</th>
<th>Disintegrating time (second)</th>
<th>% cummulatif of released Metochlopramide at 60 second (1 minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FL-1</td>
<td>1.88±0.25</td>
<td>2.84±0.88</td>
<td>51.06±2.00</td>
</tr>
<tr>
<td>*FL-2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>*FL-3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FL-4</td>
<td>2.48±0.26</td>
<td>4.92±0.54</td>
<td>74.46±2.38</td>
</tr>
<tr>
<td>FL-5</td>
<td>1.62±0.32</td>
<td>3.07±0.65</td>
<td>45.05±2.17</td>
</tr>
<tr>
<td>FL-6</td>
<td>3.49±0.18</td>
<td>3.13±0.65</td>
<td>60.26±2.62</td>
</tr>
<tr>
<td>FL-7</td>
<td>4.36±0.52</td>
<td>3.08±0.89</td>
<td>42.75±3.23</td>
</tr>
<tr>
<td>FL-8</td>
<td>1.80±0.41</td>
<td>3.58±0.90</td>
<td>51.61±1.60</td>
</tr>
<tr>
<td>FL-9</td>
<td>2.23±0.08</td>
<td>2.87±0.69</td>
<td>62.43±2.81</td>
</tr>
<tr>
<td>FL-10</td>
<td>2.74±0.47</td>
<td>4.48±1.06</td>
<td>44.37±1.87</td>
</tr>
</tbody>
</table>

Note: * FL-2 dan FL-3 (LODT-metoclopramide not formed)

FL-1 = (STE:Dextrose:Avicel:1:0:0) FL-6 = (STE:Dextrose:Avicel:0:0.5:0.5)
FL-2 = (STE:Dextrose:Avicel:0:1:0) FL-7 = (STE:Dextrose:Avicel:0.166:0.166:0.667)
FL-3 = (STE:Dextrose:Avicel:0:0:1) FL-8 = (STE:Dextrose:Avicel:0.166:0.667:0.166)
FL-4 = (STE:Dextrose:Avicel:0.5:0:5) FL-9 = (STE:Dextrose:Avicel:0.667:0.166:0.166)
FL-5 = (STE:Dextrose:Avicel:0.5:0:0.5) FL-10 = (STE:Dextrose:Avicel:0.333:0.333:0.333)

Table 4: LODT-metochlopramide optimized formula of three mixed component: STE, Dextrose, and Avicel with lyophilized method.

<table>
<thead>
<tr>
<th>Composition</th>
<th>Amount (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STE</td>
<td>24.182</td>
</tr>
<tr>
<td>Dextrose</td>
<td>19.707</td>
</tr>
<tr>
<td>Avicel</td>
<td>96.111</td>
</tr>
<tr>
<td>Metochlopramide HCl</td>
<td>10</td>
</tr>
<tr>
<td>Aspartam</td>
<td>5</td>
</tr>
<tr>
<td>Total Weigh</td>
<td>155</td>
</tr>
</tbody>
</table>
Fig. 1: The making of LODT-metochlopramide by lyophilization method (a) suspension of STE/dextrose/Avicel that contain metochlopramide), (b) The blister filling with the suspension using 1 mL syringe, (c) Filled blister frozen in freezer, (d) The blister containing the frozen drug solution freeze dried with a freeze dryer, (e) The blister containing LODT-metochlopramide, (f) LODT-metochlopramide that had been removed from the blister.
Fig. 2: The released profile of LODT-metochlopramide from FL-1, FL-4, FL-5, FL-6, FL-7, FL-8, FL-9 and FL-10.

Fig. 3: Superimposed Contour Plot of wetting time and disintegrating time in oral cavity.