

OPTIMISED FORMULATION OF METOCLOPRAMIDE ORALLY DISINTEGRATING TABLET

SAMRAN^{1*}, KARSONO², MATHEUS TIMBUL SIMANJUNTAK² AND
JANSEN SILALAH³

¹Indah Academy of Pharmacy, Medan, Indonesia

²Department of Technology of Pharmacy,

³Department of Chemistry of Pharmacy,

Faculty of Pharmacy, University of North Sumatera, Indonesia

*Orally disintegrating tablet (ODT) was developed to solve the difficulty of swallowing conventional tablet for paediatric 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 seconds. The solid tapai extract (STE) has sweet taste, is 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 characterise STE as excipient and to use STE as excipient in the formulation of ODT by lyophilisation method. The ingredients were glutinous rice (*Oryza sativa* L. var. Glutinous) used to form 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. Metoclopramide HCl was used as a drug model. The design of formula used the simplex lattice design (SLD) model with a three components mixture: STE, dextrose and avicel as excipients. The parameters of lyophilised 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 function as disintegrant and formed porosity in the lyophilised method. Based on equation and contour plot of superimposed method, a formula consisting of STE (24.18 mg), dextrose (19.71 mg) and avicel (96.11 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, convenience and low cost of therapy (Shukla *et al.* 2009). Tablets and hard gelatine capsules constitute a major portion of drug delivery systems that are currently available. However, for some patient groups such as paediatric and geriatric patients who have underdeveloped muscular and nervous control, dysphagia, hand tremor, mentally retarded, feeling nauseated, or on reduced of liquid-intake/diets have difficulties swallowing these dosage forms. Furthermore, patients travelling to places with little or no access to water, limit utility of orally administered conventional tablets or capsules.

Therefore, to fulfil the needs of such patients, a novel oral dosage form has been developed and is known as orally disintegrating tablet (ODT). ODT has several advantages such as, it does not need swallowing because it disintegrates rapidly on the tongue; it is usually quickly dissolved (in a few seconds) with little water. Thus, ODT provides rapid early onset of action and significantly increases the bioavailability of the conventional dosage form (Shyamala and Narmada 2002). ODT is a solid dosage form

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

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 characteristics such as disintegrated or dissolved in the oral cavity in a few seconds without leaving residues, mask the odour and unpleasant taste, and resistant to changes in humidity or temperature (Bansal 2003).

STE is a product originating from liquid *tapai* extract which was heated until viscous and cooled down to form the STE. STE has a sweet and slightly sour taste and dissolves when it is placed on the tongue (Meigia 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 is also less expensive than other excipients. STE, dextrose and avicel were optimised to obtain suitable excipients in the preparation of ODT using metoclopramide as a drug model.

An antiemetic, metoclopramide is indicated for gastrointestinal motility disorders (particularly gastric stasis), gastro oesophageal reflux, prevention or treatment of nausea and vomiting due to chemotherapy drugs, radiation therapy or treatment after surgery. Metoclopramide 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, metoclopramide (Ipca Laboratories Limited, Mumbai, batch no. 8007MRIIX), yeast (NKL[®], Surakarta, Indonesia), dextrose (Qinhuangdao Lihua Starch Co. Ltd., Qinhuangdao, China, batch no. 20121208), avicel (Flocel[®] 102, Nandasari, India, batch no. E0904).

Formula Optimisation Design

This study covered the formulation of *tapai* and STE which were used as additives in the manufacture of ODTs with SLD optimisation design of a three-component formula. Each formula (FL) contained STE (A), dextrose (B) and avicel (C) in certain proportion (0–1 part). Lyophilised ODT (LODT)-metoclopramide highest response of 1 part was 140 mg and smallest response of 0 part was 0 mg. The formula derived from the SLD method was presented in Table 1. The mass was moulded into tablets using lyophilisation method.

The Making of Glutinous Rice *Tapai*

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

Table 1: Formula of LODT-metoclopramide from the mixture of three components (STE, dextrose and avicel) as excipients.

Formula	Ingredients (mg)					Total (mg)
	A	B	C	MCP	Aspartam	
FL-1	140	0	0	10	5	155
FL-2	0	140	0	10	5	155
FL-3	0	0	140	10	5	155
FL-4	70	70	0	10	5	155
FL-5	0	70	70	10	5	155
FL-6	70	0	70	10	5	155
FL-7	23.33	23.33	93.33	10	5	155
FL-8	23.33	93.33	23.33	10	5	155
FL-9	93.33	23.33	23.33	10	5	155
FL-10	46.67	46.67	46.67	10	5	155

Note: MCP – metoclopramide, A – STE, B – dextrose, C – avicel

Organoleptic Test of Glutinous Rice *Tapai*

Organoleptic test of *tapai* taste was conducted by hedonic test (Tanuwijaya 2011). This test was carried out by conducting a sensory test for 10 panellists and determined by a numerical scale.

The Making of STE

Tapai mass was pressed using a suppressor. The aqueous extract of *tapai* obtained from the process was filtered using a 60 mesh sieve and the waste was disposed. *Tapai* water was heated at 50°C–60°C by using a stainless steel container to give a yellowish-brown viscous mass. Viscous mass was filtered when still hot, then added to the inoculum (comprising of yeast) and mixed at the speed of 1500 rpm for 15 minutes. The whole mass was then poured into stainless steel moulds, allowed to stand for one night to form a solid STE mass.

STE Characteristic Determination

Analysis of pH

The pH of STE was analysed by suspending 1 g of STE in 50 mL of CO₂-free distilled water. The suspension was stirred until homogenous and then the pH was measured using a pH meter (Hanna[®], Mauritius) (Health Department of Republic of Indonesia 1979).

The Water Level

The water level was measured by putting 200 mL of toluene and 2 mL of distilled water into the distillation apparatus then distilled for 2 hours (at 100°C). Five grams of STE was weighed and added to the distillation apparatus containing toluene. The mixture was distilled for a further 20 minutes. At the end of the distillation, the volume of water and toluene were noted. The water level was calculated in percentage (Health Department of Republic of Indonesia 1979).

The Ash Level

The ash level was measured by weighing a porcelain dish, and then 3 g of STE was placed into the dish. The ashing process was carried out at 675°C in the furnace for approximately 5 hours. The porcelain dish was cooled in an exicator and weighed. The treatment was repeated until a constant weight of ash was obtained (Health Department of Republic of Indonesia 1979).

Angle of Repose

The angle of repose was measured using a tensiometer apparatus (Kruss[®], Hamburg, Germany). The tensiometer was rinsed with distilled water, and then 10 mL sample was placed into the tensiometer. The sample solution was introduced into a capillary tube, and slowly lowered until the sample solution level was steady in the capillary tube. The height of the sample solution that remained in the capillary was recorded (Yazid 2005).

Flowing Time

The flowing time was measured by placing the STE granules into a funnel which has been assembled when the surface was levelled. 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 placing STE granules into a measuring cup on compressibility index apparatus (Copley[®], Nottingham, United Kingdom) to mark the lines which are expressed as initial volume (V1); the apparatus was then run approximately 30 times to obtain a final volume (V2). Compressibility index was calculated in percentage (Lachman, Lieberman and Kanig 1994).

The Formulation of Metoclopramide ODT by Lyophilisation Method Using STE, Dextrose and Avicel as Excipients

STE was put into a container, followed by dextrose, avicel and metoclopramide. The excipients were stirred until metoclopramide was evenly dispersed. The mixture was poured into blister moulds, weighing 150 mg tablet for each mould. Once the moulds had been filled, they were put in freezer to harden and then freeze-dried to form the lyophilised tablets. The resulting tablets were evaluated for the wetting time, disintegration time and dissolution rate parameters. The process of metoclopramide ODT formulation by lyophilisation method can be seen in Figure 1.

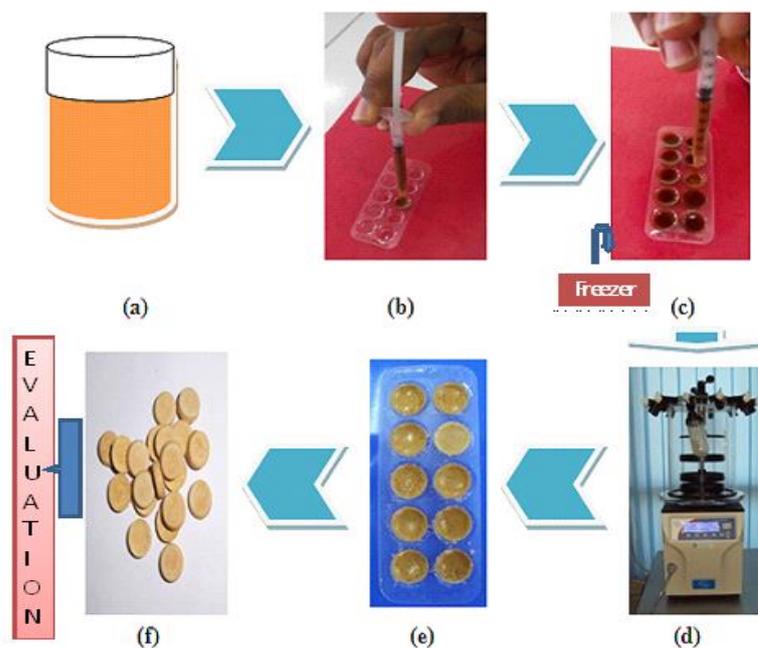


Fig. 1: The making of LODT-metoclopramide by lyophilisation method: (a) suspension of STE/dextrose/avicel that contains metoclopramide, (b) filling the blister with the suspension using 1 mL syringe, (c) filled blister frozen in freezer, (d) the blister containing the frozen drug solution freeze dried with a freeze dryer, (e) the blister containing LODT-metoclopramide and (f) LODT-metoclopramide that had been removed from the blister.

Evaluation of Metoclopramide ODT

Hardness Test

One tablet was placed vertically between the anvil and the punch of Strong Cobb Hardness Tester (Erweka[®], Heusenstomm, Germany). The tablet was clamped by turning the regulator screw until the signal "stop" lighted, and then the button was pressed until the tablet broke. After the tablet broke, the scale number was recorded. The tablet hardness was 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 (Copley[®], Nottingham, United Kingdom) and the tool was run for 4 minutes (100 rpm). After the time limit, tablets were cleaned and then weighed again (b gram). Friability value = $(a-b)/a \times 100\%$ (Lachman, Lieberman and Kanig 1994).

Water Absorption Ratio Test

Circular filter paper was placed into 9 cm diameter petri dish containing 9 mL carmiosin solution 0.1% (w/v). One tablet was placed gently in the middle of petri dish, and the complete wetting time of the tablet was recorded. Tablet was weighed before and after water absorption. Water absorption ratio was calculated by the formula of $R = 100 \times (w_a - w_b) / w_b$, where w_b is the weight of the tablet before water absorption and w_a is the weight of the tablet after water absorption (Bhowmik *et al.* 2009).

Disintegrating Time Test Using Disintegration Tester

One tablet was placed to each tube of the basket of the disintegration tester, and then the disintegration apparatus (Copley®, Nottingham, United Kingdom) was run. Water was used as a medium with temperature of $37 \pm 2^\circ\text{C}$. All tablets should be crushed perfectly in less than 20–30 seconds (Manivannan 2009).

Disintegrating Time Test in Oral Cavity

Ten volunteers participated in this disintegrating time test for ODT. Before starting the test, each volunteer was required to rinse out their oral cavity. The ODT tablet was placed on volunteers' tongue and allowed to disintegrate completely. Then, the tablet was spat out. The time for the tablet to disintegrate completely in the oral cavity perfectly was recorded (Manivannan 2009).

Dissolution Test

In vitro dissolution test was conducted using a type 2 dissolution apparatus (paddle) (Copley®, Nottingham, United Kingdom), using 900 mL of medium with pH of 1.2 and 7.4, and temperature of $37 \pm 0.5^\circ\text{C}$ with a rotation speed of 50 rpm. Ten mL of sample solution was taken and measured at a wavelength of 272.5 nm with intervals of 1, 3, 5, 10, 15, 20, 25 and 30 minutes (Health Department of Republic of Indonesia 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 a contact angle of 2.01° , an angle of response of 29.6° , a flowing time of 3.76 ± 0.07 seconds and a compressibility index of 10.67%. These results indicated that the STE met the requirements as an excipient in the manufacture of ODT.

LODT Formulation

Freeze dry is a process to produce a porous amorphous structure that can help the drug to dissolve rapidly (Bhowmik *et al.* 2009). Table 3 showed that the formula FL-2 and FL-3 failed to form LODT-metoclopramide. LODT-metoclopramide was evaluated for friability, wetting time, disintegrating time, disintegrating time in the oral cavity and the dissolution rate.

Table 2: Characteristics of STE.

Test	Characteristic of STE
Macroscopic	Granules/bars
Form	Granules/bars
Colour	Tawny
Odour	Typical STE aroma
Taste	Sweet, a little sour
Fehling test	Brick red precipitate
pH	6.31±0.01
Infrared analysis	-CH ₂ , -C-H, -C-O, -OH
Contact angle	2.01°
Water level	9.44±0.35%
Ash level	0.41%
Reducing sugar levels	70.4%
Solubility	Freely soluble (<1.0 mL water)
Angle of repose	29.6°
Flowing time	3.76±0.07 seconds
Compressibility index	10.67%

Table 3: LODT-metoclopramide evaluation results from a variety of formulas.

Formula	Wetting time (second)	Disintegrating time		% cumulative of released metoclopramide at 60 seconds
		Disintegrator (second)	Oral cavity (second)	
FL-1	1.88±0.25	2.84±0.88	28.67±5.72	51.06±2.00
*FL-2	–	–	–	–
*FL-3	–	–	–	–
FL-4	2.48±0.26	4.92±0.54	48.00±2.61	74.46±2.38
FL-5	1.62±0.32	3.07±0.65	44.17±2.23	45.05±2.17
FL-6	3.49±0.18	3.13±0.65	45.67±1.75	60.26±2.62
FL-7	4.36±0.52	3.08±0.89	43.17±1.17	42.75±3.23
FL-8	1.80±0.41	3.58±0.90	44.33±2.25	51.61±1.60
FL-9	2.23±0.08	2.87±0.69	57.67±1.21	62.43±2.81
FL-10	2.74±0.47	4.48±1.06	59.33±3.01	44.37±1.87

Notes: * FL-2 and FL-3 (LODT-metoclopramide not formed); A – STE, B – dextrose, C – avicel
 FL-1 = (A:B:C:1:0:0) FL-6 = (A:B:C 0:0.5:0.5)
 FL-2 = (A:B:C:0:1:0) FL-7 = (A:B:C:0.17:0.17:0.67)
 FL-3 = (A:B:C:0:0:1) FL-8 = (A:B:C:0.17:0.67:0.17)
 FL-4 = (A:B:C:0.5:0.5:0) FL-9 = (A:B:C:0.67:0.17:0.17)
 FL-5 = (A:B:C:0.5:0:0.5) FL-10 = (A:B:C:0.33:0.33:0.33)

Hardness and Friability Test

The hardness and friability test of LODT-metoclopramide 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-metoclopramide presented in Table 3 showed all the formulas met the requirement criteria of less than 60 seconds (Kundu and Sahoo 2008).

Disintegrating Time Test Using Disintegrator

The disintegrating time of LODT-metoclopramide met the requirements criteria of 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 formulas of LODT-metoclopramide 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-metoclopramide formulas were presented in Figure 2. The results showed that all formulations of LODT-metoclopramide met the requirements (Health Department of Republic of Indonesia 1995).

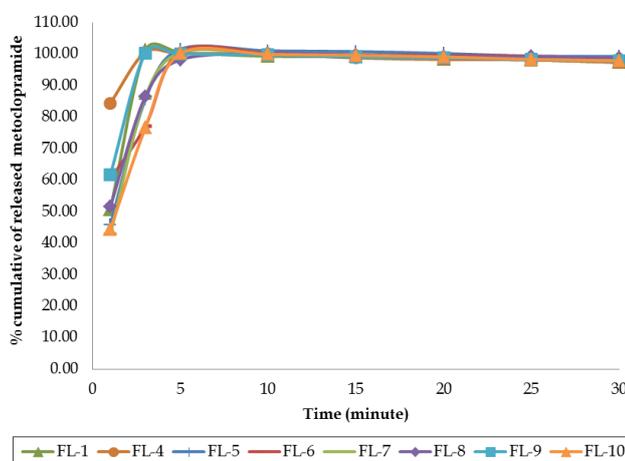


Fig. 2: The released profile of LODT-metoclopramide from FL-1, FL-4, FL-5, FL-6, FL-7, FL-8, FL-9 and FL-10.

DISCUSSION

LODT Formulation

Table 3 showed that the formula FL-2 and FL-3 failed to form LODT-metoclopramide because the additives used were avicel (FL-2) alone which was a disintegrant material that had low power of cohesion, therefore it did not form LODT. Dextrose (FL-3) has a good cohesive power, but the formed LODT-metoclopramide was difficult to remove from the

mould which broke the LODT-metoclopramide, whereas STE (FL-1) alone has a good cohesive power forming LODT-metoclopramide that was easily removed from the mould. Thus, this study shows that STE can be used as filler for LODT formulation.

Hardness and Friability Test

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

Previous researchers had used mannitol and gelatine as additives to make LODT and used sodium phenobarbital as a drug model. The results showed the LODT was hard and fragile with a 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 wetting time showed rapid tablet disintegration (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 had a good disintegrator characteristic (Siregar and Wikarsa 2010).

Wetting time data in Table 3 can be made into the following equation:

$$Y = 1.88A + 6.16AB + 10.20AC + 6.48BC - 11.46ABC$$

where, Y = wetting time (second), A = number of STE used, B = number of dextrose used and 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 for water penetration, and is porous 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 FL-1 (STE:dextrose:avicel,140:0:0). This is probably due to a small contact angle of STE, thus FL-1 was easily wetted. FL-1 also rapidly disintegrated and dissolved since the STE had many pores which made it easy to be penetrated by water.

Disintegrating time data in Table 3 can be made into the following equation:

$$Y = 2.84A + 14.00AB + 6.84AC + 12.28BC - 3.96ABC$$

where, Y = wetting time (second), A = number of STE used, B = number of dextrose used and 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-metoclopramide met the requirements of ODT because the disintegrating time was less than 60 seconds. This suggested that LODT-metoclopramide was destroyed on contact with saliva in the oral cavity (Popescu, Zhou and Joshi 2010). FL-1 formula had a faster disintegrating time in the oral cavity compared to the other formulas of LODT-metoclopramide. It can be concluded that FL-1 had a high porosity (Budgujar and Mundada 2011) which facilitated penetration of water into LODT-metoclopramide tablets and led to quick disintegration.

Disintegrating time in oral cavity data in Table 3 can be made into the following equation:

$$Y = 26.67A + 134.66AB + 125.34AC + 176.68BC + 33.84ABC$$

where, Y = wetting time (second), A = number of STE used, B = number of dextrose used and C = number of avicel used.

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

Drug Dissolution Test

On the 5th minute, all LODT-metoclopramide formulations were dissolved 100%. This was because LODT-metoclopramide had a high porosity (Budgujar and Mundada 2011), therefore it was easily penetrated by water and the disintegrating time was less than 10 seconds. As a result, metoclopramide dissolved quicker. Moreover, freeze-drying technique also produced a porous structure that made metoclopramide dissolve rapidly.

Based on cumulative dissolution data in Table 3, it can be made into the following equation:

$$Y = 51.06A + 196.52AB + 138.92AC + 180.20BC - 808.47ABC$$

where, Y = wetting time (second), A = number of STE used, B = number of dextrose used and C = number of avicel used.

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

Overall, STE has the ability to be used as excipient in formulations of ODT, and based on the wetting time test, disintegrating time test and drug dissolution test, STE was the dominant factor that accelerated the time of the tests.

Determination of Optimum Formula

Based on the superimposed contour plot in Figure 3, it showed that the optimum areas with LODT-metoclopramide wetting time and disintegrating time in oral cavity parameters 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 (24.18 mg), dextrose (19.71 mg) and avicel (96.11 mg) to obtain the optimum formula for a tablet which can be seen in Table 4. The optimised formula in Table 4 was formulated and tested for the ODT parameters: the wetting time and the disintegrating time. The results showed that the optimised formula gave an average wetting time of 4.47 seconds and an average disintegrating time of 39.97 seconds.

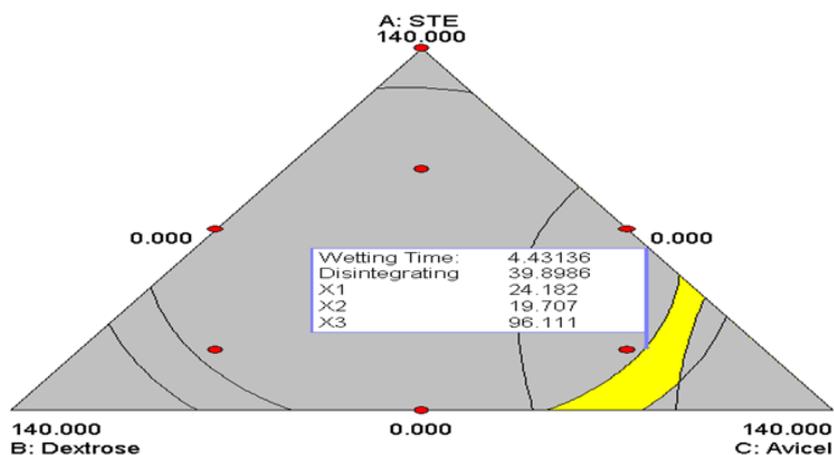


Fig. 3: Superimposed contour plot of wetting time and disintegrating time in oral cavity.

Table 4: LODT-metoclopramide optimised formula of three components: STE, dextrose and avicel with lyophilised method.

Composition	Amount (mg)
STE	24.18
Dextrose	19.71
Avicel	96.11
Metoclopramide HCl	10.00
Aspartam	5.00
Total weight	155

CONCLUSION

This study revealed that STE has good characteristics as an ODT excipient and can be used as additive of LODT with function as fillers, disintegrant and pore forming. Individually STE was able to form LODT while dextrose and avicel could not form LODT. STE and dextrose mixture components could form LODT, and a combination of STE, dextrose, and avicel mixture showed improved characteristics of LODT. The optimised formula of LODT-metoclopramide based on superimposed contour plot is 24.18 mg of

STE, 19.71 mg of dextrose, 96.11 mg of avicel, 10 mg of metoclopramide and 5 mg of aspartam with total weight of tablet being 155 mg. Based on the results, it can be concluded that STE can be used as excipient to manufacture ODT in a more cost-effective way.

ACKNOWLEDGEMENT

Special thanks and gratitude goes to Mr. Fekodin and Mrs. Rumina for providing training in formulation of tape and brem at Seruling's brem home industry, Madiun, East Java and also to Mustika Furi, Abdi and Ruslan Abdul Gani for their assistance in this research.

REFERENCES

- BANSAL, A. K. (2003) Improved excipients by solid-state manipulation, *The Industrial Pharmacist*, 31: 9–12.
- BHOWMIK, D., CHIRANJIB, B., KRISHNAKANTH, PANKAJ & MARGRET, C. R. (2009) Fast dissolving tablet: An overview, *Journal of Chemical and Pharmaceutical Research*, 1: 1–5.
- BUDGUJAR, B. P. & MUNDADA, A. S. (2011) The technologies used for developing orally disintegrating tablets: A review, *Acta Pharmaceutica*, 61: 117–139.
- HEALTH DEPARTMENT OF REPUBLIC OF INDONESIA. (1979) *Farmakope Indonesia*, 3th edition (Jakarta: Health Department of Republic of Indonesia).
- . (1995) *Farmakope Indonesia*, 4th edition, pp. 649 (Jakarta: Health Department of Republic of Indonesia).
- HIRANI, J. J., DHAVAL, A. R. & KANTILAL, R. V. (2009) Orally disintegrating tablets: A review, *Tropical Journal of Pharmaceutical Research*, 8: 161–172.
- KUNDU, S. & SAHOO, P. K. (2008) Recent trends in the developments of orally disintegrating tablet technology, *Pharma Times*, 40: 11–21.
- LACHMAN, L., LIEBERMAN, H. A. & KANIG, J. L. (1994) *Theory and practice of industry pharmacy*, 3th edition (Jakarta: UI Press).
- MANIVANNAN, R. (2009) Orally disintegrating tablets: Future compaction, *International Journal of Research and Development*, 1: 1–10.
- MEIGIA, H. (2004) *The making of solid STE assorted flavors and financial analysis* (Study of water tape proportion of black and white glutinous rice) (Malang, Indonesia: Brawijawa University).
- PARROT, E. L. (1970) *Pharmaceutical technology*, pp. 82 (Minneapolis, USA: Burgess Publishing Company).
- POPESCU, C., ZHOU, L. & JOSHI, A. (2010) *Selection of non-synthetic disintegrants for pharmaceutical and nutraceutical orally disintegrating tablets: Tablets and capsules*. <http://www.roquette-pharma.com/media/deliacms/media/62/6292-079959.pdf> (27 July 2012).

- RAO, N. G. R., PATEL, T. & GANDHI, S. (2009) Development and evaluation of carbamazepine fast dissolving tablets prepared with a complex by direct compression technique, *Asian Journal of Pharmaceutical Sciences*, 3: 97–103.
- SHUKLA, D., CHAKRABORTY, S., SINGH, S. & MISHRA, B. (2009) Mouth dissolving tablets I: An overview of formulation technology, *Scientia Pharmaceutica*, 77: 309–326.
- SHYAMALA, B. & NARMADA, G. Y. (2002) Rapid dissolving tablets: A novel dosage form, *The Indian Pharmacist*, 13: 9–12.
- SIREGAR, C. J. P. & WIKARSA, S. (2010) *Pharmaceutical technology of tablet formulation*, pp. 161, 575–577 (Jakarta: Elex Gramedia Computindo).
- SZNITOWSKA, M., PLACEK, M. & KLUNDER, M. (2005) The physical characteristics of lyophilized tablet containing a model drug in different chemical form and concentrations, *Acta Polonicae Pharmaceutica-Drug Research*, 62: 25–29.
- TANUWIJAYA, J. (2011). *Characterization of piroxicam nanoparticles in orally disintegrating tablet (ODT)*. M.Sc. diss., North Sumatera University.
- VELMURUGAN, S. & VINUSHITA, S. (2010) Oral disintegrating tablets: An overview, *International Journal of Chemical and Pharmaceutical Science*, 1: 1–12.
- YAZID, E. (2005). *Physics and chemistry for paramedic*, pp. 121–123 (Yogyakarta: Andi Yogyakarta).