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Metochlopramide Orally Disintegrating Tablet Formulation using Co-Processed Excipient of Solid *Tapai* Extract and Corn Starch

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Abstract: Orally disintegrating tablets were developed to solve the difficulty of swallowing the conventional tablet in pediatrics and geriatrics patients. In administration of orally disintegrating tablets, tablets are placed on the tongue in oral cavity and it disintegrated less than 60 second. Since Solid T*apai E*xtract (STE) is slightly soluble when it puts on the tounge and has sweet taste, it has potential as a natural excipient in orally disintegrating tablets formulation. The objective of the study was to make co-processed from solid t*apai* extract and corn starch as excipient in the formulation of metochlopramide orally disintegrating tablets. Co-oprocessed Solid t*apai* extract and corn starch was designed using simplex lattice design with two component. The best co-processed was F-4 and used as excipient for orally disintegrating tablet that's made by sublimation method with direct compressed. There were six formulations that contained camphor with different concentration: FS-1(0%), FS-2(2%), FS-3(4%), FS-4(6%), FS-5(8%) and FS-6(10%). As the result show that the more percentage of camphor was used, the wetting time, disintegrating time and dissolution rate became faster. The best formula metochlopramide ODT with sublimation method was FS-4 that contained camphor 6%.
Keyword: metochlopramide HCL, co-processed, direct compressed, sublimation methods.

Introduction

Orally Disintegrating Tablet (ODT) 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]. ODT 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]. It means ODT dosage form could be one choice to overcome the drug administration problem experienced by the elderly or pediatrics in swallowing the conventional solid dosage form/tablets.

Co-processed was based on the recent concept of two or more excipients combining at sub particle level to provide a synergy of functionality improvement as well as masking undesirable properties of individual. Co-processed excipients lead to the formation of granule with the excellent characteristic compare with single component excipients.

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 demonstrated that STE has the possibility to be used as a natural additive for ODT dosage form.

STE was freely soluble in water because it had contact angle of 2.01^0, angle of response of 29.6^0, flowing time of 3.76 ± 0.074 seconds and compressibility index of 10.67%. These characteristics indicated that STE met the requirements to be used as an excipient in the formulation of ODT[5]. In the previous study, STE was combine with corn starch which resulted co-proceesed granul for direct compressed and it is utilized in formulation of metochlopramide HCl ODT by sublimation method and camphor as sublimation materials.

Metochlopramide is used 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. Since metochlopramide can be administered to patients who have travel sickness and may have no water supply at the time to take the medicine, it was chosen as a model drug in this study.

Experimental

Materials

White Glutinous Rice, metochlopramide (PT. First Medifarma), yeast (*Saccharomyces cereviceae)*, HCl (E Merck), Mg-stearat (PT. Bratako), Talcum BP (PT. Bratako), LH-11 (NV. Lauzim), Corn starch (PT. Bratako).

Instrument

Compression apparatus (Modification), pH meter (Hanna), oven (Gallenkamp), Sieve mesh no. 60, UV spectrophotometer (Shimadzu UV-1800), disintegration tester (Erweka), disolution tester (Erweka DT), friabilator (Roche), single punch tablet machine (Pharmec).

The Preparation of Glutinous Rice *Tapai*

White glutinous rice (*Oryza sativa* L. Var. Glutinous) was cooked, then cooled to a temperature of 27-30^0C. *Tapai* of Glutinous rice was made by using a concentration of 1.5% yeast containing *Saccharomyces cereviceae* then fermented for 6 days[5].

The Preparation of Solid *Tapai* Extract (STE)

Tapai mass was pressed by using a suppresor. The water of tapai obtained from the process was filtered using a 60 mesh sieve and the waste was disposed. Tapai water was heated at 50-600C by using a stainless steel container to obtain a yellowish-brown viscous mass. Viscous mass was filtered when still hot, then added with the inoculum and mixed with speed 1500 rpm for 15 minutes afterwards poured into stainless steel molds, then allowed to stand for one night to form a solid mass called STE[5].

Co-processed Formula Optimization Design

This study covered the formulation of co-processed with Simplex Lattice Design (LSD) optimization design of two-component formula, each formula contained STE (A), Corn starch (B) in certain proportion (0-1 part). Direct Compression excipients co-processed formula has the highest response of 1 part = 103 mg and smallest response 0 parts = 0 mg. Formula derived from the SLD method is presented in Table 1.

Table 1. Direct Compression Formula of co-processed from the mixed of two components: STE (A), Corn Starch (B).

No.	STE(A) (g)	*Corn Starch* (B)(g)	Formula
1.	103	0	F-1 (100%:0)
2.	51,5	51,5	F-2 (50%:50%)
3.	34,33	68,67	F-3 (33,33%:66,67%)
4.	25,75	77,25	F-4 (25%:75%)
5.	20,6	82,4	F-5 (20%:80%)
6.	82,4	20,6	F-6 (80%%:20)
7.	77,25	25,75	F-7 (75%:25%)
8.	68,67	33,33	F-8 (66,67%:33,33%)
9.	0	103	F-9 (0%:100%)

Co-processed formulation

Corn starch and STE were added into a stamper then crushed until the mass become flabby and loamy. The mass then undergo the wet granulation process using 10 mesh sieve and dried in an oven with a temperature of 50^0 C for 8 hours. The mass was continued for the dried granulation process again using 12 mesh sieve. This granul was called co-procesed granul for direct compressed.

Metochlopramide ODT Formula with Sublimation methods using optimized Co-processed formulation

Metochlopramide ODT Formula with Sublimation method (MODTSM) using optimized Co-processed formulation could be seen on Table 2.

Table 2. MODTSM using optimized Co-processed formulation

No.	Bahan	Formula					
		FS-1 (mg)	FS-2 (mg)	FS-3 (mg)	FS-4 (mg)	FS-5 (mg)	FS-6 (mg)
		0%	2%	4%	6%	8%	10%
1.	Camphor	0	3	6	9	12	15
2.	Co-processed excipient F-4	108	105	102	99	96	93
3.	LH-11	22,5	22,5	22,5	22,5	22,5	22,5
4.	Aspartam	5	5	5	5	5	5
5.	Metochlomamide HCl	10	10	10	10	10	10
6.	Talcum BP	3	3	3	3	3	3
7.	Mg Stearate	1,5	1,5	1,5	1,5	1,5	1,5
8.	Total	150	150	150	150	150	150

Metochlopramide ODT Formulation

Co-processed granul, camphor, LH-11, metochlopramide HCl, talcum and Mg stearate were added into a stamper then crushed until homogeneous. The lubricated granules were tested for preformulation test then press into a tablet using direct compression method and then dried in an oven with a temperature of 60 ^oC till the mass constant.

Evaluation Method

Hardness Test

One tablet was placed vertically between the anvil and the punch of Strong Cobb Hardness Tester, tablet clamped by turning the regulator screw until the light signal "stop" lighted, then pressed the button until the tablet broke. After the tablet broke, the scale was read as shown by the needle. The tablets hardness was the figures as shown by the needle on the scale. Hardness test was performed on 6 tablets[6].

Friability Test

Twenty tablet were cleaned of dust, then weighted (a gram), put into the friability tool. The tool was run for 4 minutes (100 rpm). After the time limit, tablet were weighed again (b gram). Friability value = (a-b) / a x 100%[7].

Wetting Time Test

The wetting time is the time that needed to made all of the tablet surface become wet perfectly in ≤ 60 seconds[1].

Disintegrating Time Test

One tablet was added to each tube of the basket of disintegration tester. The apparatus was then run. Water for the medium had temperature of 37 ± 2°C. All tablets should be crushed perfectly less than 20-30 seconds[8].

Modified Disintegrating Time Test

One tablet was added into 9 mm Ø petri dish with 9 ml of tap water. The time that needed by the tablet to disintegrate perfectly was recorded[1].

Disintegrating Time Test in Oral Cavity

The disintegrating time test used 10 volunteers. Before starting the test, each volunteer was required to rinse out their mouth first. The ODT tablet was placed on the tongue and allowed to disintegrate perfectly. The time that needed for the tablet to disintegrate in the oral perfectly was recorded[8].

Dissolution Test

In vitro dissolution test was done using a type 2 dissolution apparatus (paddle), with medium pH 1.2 and 7.4 as much as 900 mL, temperature of 37 ± 0.5°C with a rotation speed of 50 rpm. At intervals of 1, 3, 5, 10, 15, 20, 25 and 30 minutes, 10 mL of sample solution was taken and measured at a wave length of 272.5 nm using UV spectrophotometer[9].

Results

Co-processed Formulation

The various formula of co-processed from the mixed of two component: STE and Corn Starch (B) was shown in Table 1. The biggest response was 1 part = 103 mg and the smallest response was 0 part = 0 mg. The physical characteristic of co-process mass from various formula was shown in Table 3.

Table 3. Physical characteristics of granules of two component: STE and Corn Starch

Formula	Angle of respon (^{o})	Flowing time (second)	Compressibility Indeks (%)	Compactibility (Kg)
F-1	32,44 ± 0,76	3,76 ± 0,08	10,67 ± 1,21	5,50 ± 0,63
F-2	33,41 ± 1,40	5,20 ± 0,11	14,00 ± 1,79	4,00 ± 0,57
F-3	33,96 ± 0,61	3,79 ± 0,22	14,67 ± 2,07	3,71 ± 0,51
F-4	33,04 ± 0,53	5,08 ± 0,04	12,67 ± 1,63	3,17 ± 0,52
F-5	34,07 ± 1,49	8,68 ± 1,36	15,50 ± 2,17	3,50 ± 0,26
F-6	33,77 ± 1,18	5,40 ± 0,31	15,50 ± 1,76	5,25 ± 0,42
F-7	31,96 ± 0,84	5,50 ± 0,51	17,17 ± 1,21	4,58 ± 0,97
F-8	32,70 ± 0,53	5,75 ± 0,52	19,17 ± 0,98	4,08 ± 0,49
F-9	-	-	-	-
requirements	$20^o<\infty<40^o$	< 10 detik	< 20 %	4-8 Kg

Angle Respone

The Angle respon mark of granul co-processed mass was presented in Table 3. The requirement of angle respon was well except F-9 because it was lower than 40^o and greater than 20^o.

Flowing Time

The flowing time data of granul co-processed mass was presented in Table 3. The requirement of good flowing time was under 10 seconds[7]. All of formulas met the requirement excepting F-9 because all of the flowing time was under 10 seconds.

Compressibility Indexs

The compressibility index values of granul co-processed mass was shown in Table 3. All of formulas were met the requirement of compressibility index as much as <20% besides F-9. The preformulation test above showed that the optimization formula from co-processed granul was F-4 with combination STE and corn starch 25% and 75%. This formula was used to make metochlopramide ODT formulation with sublimation method that could be refer on Table 2.

Metochlopramide ODT formulation with sublimation method

Sublimation is a method of ODT formulation that used sublimation substances. Sublimation substances evaporated to form the porous in the ODT. The formulation of ODT-metochlopramide was made by sublimation method using camphor as a sublimation substance.

Camphor has been used by previous researchers as camphor is a good sublimation substance and widely used[10]. The excipient that used in this method was a co-processed of F-4, as the co-processed F-4 met the physical mass characteristics for used in direct compress formulation. Camphor used concentration varied. Mass of granules was through the pre-formulation test formulated into ODT by direct compress. The result of pre-formulation test showed in Table 3.

Table 3. Pre-formulation test of ODT formula granules

Formula	Pre-formulation Test		
	Flowing Time (second)	indexs Tabs	Angle respon
FS-1 (0%)	3,57 ± 0,37	14,67 ± 1,15	21,45 ± 1,68
FS-2 (2%)	3,46 ± 0,35	14,67 ± 2,31	20,87 ± 0,59
FS-3 (4%)	3,25 ± 0,07	19,33 ± 1,15	31,63 ± 6,82
FS-4 (6%)	3,48 ± 0,14	18,00 ± 2,00	21,44 ± 1,81
FS-5 (8%)	Not eligible	25,33 ± 3,06	Not eligible
FS-6 (10%)	Not eligible	28,00 ± 2,00	Not eligible

FS-5 and FS-6 did not meet the flowing time and angle respon requirement for the ODT formula because the physical characteristic of camphor was rather humid in high concentration (8% and 10%). The ODT-Metochlopramide was evaluated for the ODT requirement including: hardness, friability, wetting time, disintegrating time and dissolution.

Hardness Test

The result of hardness tests of MODTSM was shown in the Table 5. The hardness test was done in 2 (two) phase, before (a) and after (b) the evaporating process. Table 5 showed that the hardness of MODTSM was 2.13-2.71kg. This value was smaller than the conventional hardness[7].

Table 5. MODTSM evaluation result from six formula: hardness, friability and wetting time

Formula	Hardness (a) (Kg)	Hardness (b) (Kg)	Friability (%)	Wetting Time (Second)
FS-1(0%)	2,71 ± 0,29	2,71 ± 0,29	0,670	120,50 ± 7,66
FS-2(2%)	2,17 ± 0,30	0,83 ± 0,20	0,990	99,67 ± 7,12
FS-3(4%)	2,25 ± 0,39	0,67 ± 0,13	1,568	56,00 ± 2,61
FS-4(6%)	2,21 ± 0,10	0,58 ± 0,13	1,260	55,17 ± 2,79
FS-5(8%)	2,13 ± 0,21	0,46 ± 0,22	1,31	53,33 ± 2,73
FS-6(10%)	2,25 ± 0,35	0,50 ± 0,19	2,91	46,17 ± 0,98

Friability Test

The friability test represented the impact of physical hit on the tablet when it was undergo the packing or distribution process. The test results showed that the friability of MODTSM did not met the requirement. The friability requirement $\leq 0.8\%$.

Wetting Time Test

The wetting time is the time that needed to made all of the tablet surface become wet perfectly. The test result was presented in Table 5. Only F-3 and F-4 were met the requirement as much as ≤ 60 seconds.

Disintegrating time test using Disintegrator

The disintegrating time is the time that needed to destroy the tablet become granules or particle. The disintegrating process reached perfectly if the tablet residue that left on the test apparatus did not show the clear core. The test result was presented in Table 6.

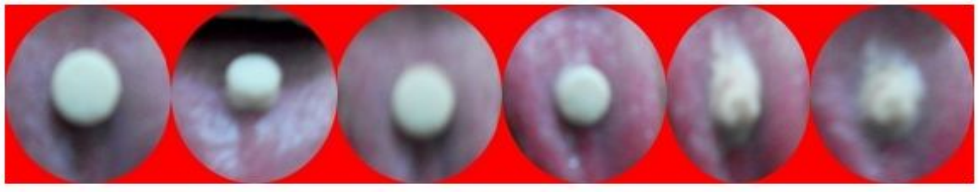
Table 6. MODTSM evaluation result from a variety of formula: disintegrating time and modification disintegrating time evaluation

Formula	Disintegrating Time (seconds)	Modified Disintegrating Time (seconds)
FS-1(0%)	117,67 ± 2,34	121,33 ±2,50
FS-2(2%)	105,83 ± 10,68	98,67 ± 5,13
FS-3(4%)	74,50 ± 11,38	63,00 ± 7,27
FS-4(6%)	53,50 ± 7,97	46,33 ± 7,09
FS-5(8%)	42,83 ± 5,88	41,00 ± 4,73
FS-6(10%)	44,50 ± 6,06	39,17 ± 2,23

The result showed that the disintegrating time only FS-4 met the requirement criteria (less then 60 seconds).

Disintegrating Time in Oral Cavity Test

Disintegrating time in oral cavity test was done only for FS-4 formula. The process was showed in Figure 1.



(a) (b) (c) (d) (e) (f)

Figure 1. Disintegrating time in oral cavity process on FS-4 formula (6%) (a: in 5 seconds), (b: in 10 seconds), (c: in 20 seconds), (d: in 30 seconds), (e: in 40 seconds) and (f: in 59 seconds)

Figure 1 revealed that FS-4 has 59 seconds of disintegrating time in oral cavity, it's still fulfill the requirements of ODT (less than 60 seconds)[11].

DCODT-Metochlopramide Dissolution Test

The result of in vitro DCODT-Metochlopramide dissolution test using dissolution test apparatus was shown in Table 7 and Figure 2.

Table 7. The result of DCODT-Metochlopramide Dissolution Test

Time (Minutes)	FS1-(0)%)	FS-2(2%)	FS-3(4%)	FS-4(6%)	FS-5(8%)	FS-6(10%)
1	23,65	15,57	18,51	20,21	21,45	20,55
3	50,47	53,84	56,83	60,66	69,57	72,89
5	80,11	78,48	82,58	89,19	96,87	97,89
10	90,86	94,63	98,48	99,56	99,83	99,62
15	94,19	100,10	99,40	99,45	99,17	99,01
20	100,42	99,41	98,95	98,97	99,07	98,73
25	99,01	98,37	98,85	98,82	98,97	98,84
30	98,92	99,11	99,13	98,42	98,99	99,04

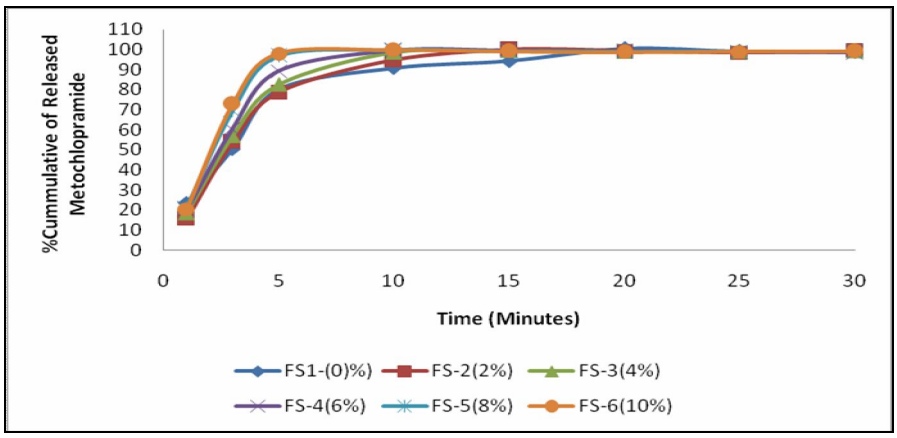


Figure 2. Dissolution rate of DCODT-Metochlopramide

Discussion

Hardness Test

The hardness of ODT-metochlopramide was measured before and after the heating process shown in Table 5. The hardness of ODT decreased due to the heating process (60^0C) in the oven. The heating process was done at 60°C temperature in the oven until a constant mass reached. The constant mass showed that camphor was sublime perfectly to formed pores[10]. Pores formed generated the decline in the hardness of ODT-metochlopramide and increasing the friability of ODT. The higher amount of camphor then the hardness of ODT-metoclopramide declined.

Wetting Time Test

The process of dissolution of a tablet depends on ODT wetting time followed by the disintegration of the tablet. That is why the wetting time is one of the important parameter in the evaluation of ODT[12].

The wetting time of ODT-metochlopramide can be seen in Table 4. The data showed that the wetting time of ODT-metoclopramide faster with higher content of camphor. This showed that the higher amount of camphor, the pore amount increased so the ODT more easily penetrated by water and wetting times became faster. Table 4 showed that the perfect wetting time of ODT- metochlopramide FS-4 occurred at 55.17 ± 2.79 seconds which met the requirements set, ≤ 60 seconds[11].

Previous research has used starch of potatoes and Primojel as filler and disintegrant and camphor as sublimation substance (5% and 7%), the results showed that the concentration of 7% camphor has faster wetting time (16.1 ± 0.15 seconds) than the concentration of 5% (22.5 ± 0.19 sec)[10]. This means the amount of camphor used affected ODT's wetting time.

Modified Disintegrating Time Test

ODT-Metochlopramide modified disintegrating time can be seen in Table 5, which showed that the higher amount of camphor, the ODT modified disintegrating time became faster. This is due to ODT-metochlopramide easily penetrated by water and expands so the ODT quickly disintegrated.

Dissolution Test

The dissolution test of ODT-Metochlopramide result can be seen in Table 6. It showed that the higher amount of camphor, the % cumulative of released Metochlopramide increased. This is due to the higher content of camphor caused the increasing of pores formation so the ODT more quickly disintegrated and dissolved and increasing the concentration of released Metochlopramide as the consequences.

Conclusion

This study showed that the optimized formula of coprocessed granules was from two mixed component: STE 25% (25.75g) and Corn Starch 75% (77.25g). The best formula of metochloparmide ODT with sublimation method was FS-4 that contained camphor 6%.

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