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Formulation of *Orally Dissolving Film* (ODF) Metoclopramide Using HydroxyPropylMethylCellulose and Polyvinyl Alcohol with Solvent Casting Method

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Abstract : Orally Dissolving Film (ODF) is a new drug delivery systems as an alternative medication for geriatric and pediatric patients who have difficulty in consuming conventional dosage form such as tablets and capsules. HPMC is known to have good film forming properties and good acceptability but are often combined with other film-forming because it is a bit fragile and have slightly rough surfaces. PVA produced films with smooth surfaces, not brittle but using them alone produce sticky film. The combination of HPMC and PVA can produced ODF with better characteristics.ODF formulation was prepared by solvent casting method using HPMC and PVA polymer (HPMC:PVA) with a ratio of each F1 (3:0), F2 (2:1), F3 (1.5:1.5), F4 (1:2) and F5 (0:3). Evaluation tests of the films were organoleptic evaluation, weight uniformity, film thickness, surface pH, swelling index, content uniformity, disintegration time and dissolution. The results of the test were statistically analyzed to determine the effect of polymer concentration with disintegration time and dissolution of ODF. The results showed that the use of a single HPMC produce films with rough surfaces, the use of a single PVA produce sticky film and the combination of HPMC and PVA produced films are smooth and not sticky. From all five formulas, F4 (HPMC:PVA = 1: 2) showed the best characteristics of film, where the film is smooth and not sticky, swelling index of 20 seconds was 221%, disintegration time was 37 seconds, as well as the cumulative percent of dissolved drug of 45 seconds was 92,20%.
Keywords : *Orally Dissolving Film (ODF), metoclopramide, HPMC, PVA, solvent casting.*

Introduction

The oral administration is the most preferred for drug delivery until today because it has advantages over the the other route of administration, but the oral route still needs further development because it has several drawbacks, especially for patients within specific groups such as geriatric, pediatric, and dysphasia which due to certain medical conditions so that they had difficulty in swallowing or chewing solid dosage forms[1].

A study revealed that more than 26% of patients have difficulty swallowing tablets. Therefore, medical practitioners and pharmacies are required to considers this problem in developing a drug formulation that is appropriate for the patient. Formulation of the drug that can dissolve or disintegrate in the mouth in a short time without drinking water, can solve this problem. Drugs like that would provide greater benefits compared to conventional tablets, more convenient to use, and potentially increase patient compliance in taking the drug[2,3].

ODF is a new drug delivery systems as an alternative to medication for geriatric and pediatric patients who have difficulty in consuming conventional dosage such as tablets and capsules. This system consists of solid oral dosage which disintegrate and dissolve quickly in the mouth with the help of saliva[4]. Mouth

dissolving film has several advantages such as availability of larger surface area that leads to rapid disintegration and dissolution in the oral cavity, site specific and rapid onset ofaction, stability for longer duration of time, avoidance of first pass effect, no risk of chocking afteradministration, etc[5]. A typical composition contains the following: Drug 1-25%, Water soluble polymer 40-50%, Plasticizers 0-20%, Fillers, colours, flavours etc. 0-40%[6].

Experimental

Instruments

Spectrophotometer uv-vis (Shimadzu), drying cabinets, dissolution tester (Erweka), disintegration tester (Erweka), analytical balance (Sartorius), pH meter (Eutech), Thermometer (Boeko), micrometer screw, mortar and stamper, aluminum foil, scissors and tools glass.

Meterials

Metoclopramide Hydrochloride (IPCA Laboratories Ltd), HPMC (Shanghai Honest Chem), PEG 400 (BRATACO), PVA (Prima Global Chemical), sorbitol (BRATACO), sucralose (Unitech Sweet), ascorbic acid (Merck), sodium hydroxide (Merck), potassium dihydrogen phosphate (Merck), distilled water (BRATACO).

The calculation of drug content in the film

Film mold size = 9 cm x 10 cm = 90 cm^2

A dose of 5 mg in 2 cm x 3 cm = 6 cm^2

contains 5 mg of the drug, resulting in a 90 cm2 contains 75 mg drugs

The number of films in a mold $\frac{90cm^2}{6\ cm^2} = 15$ films

The procedure of making metoclopramide HCl ODF

All materials were weighed. Some polymers are dissolved in distilled water. Then left in for 10 minutes to swell. Drug is dissolved in distilled water, then added sorbitol, sucralose and ascorbic acid. The solution was stirred until all the material is completely dissolved. Drug substance solution is added to the base polymer. PEG 400 was added to the polymer solution while stirring. 2 drops of orange essence added to the solution and then stirred until homogeneous. The solution was left in at room temperature to remove air bubbles. After the air bubbles disappear, the solution was poured into a mold 9 cm x 10 cm until blended. Film dried at 40°C in the drying cabinet for 24 hours. After drying, the film removed from the mold carefully and cut the size of 2 cm x 3 cm.The components of the formulation were shown in Table 1.

Table1.ODF Metoclopramide HCl Formula

Component	Formula				
	F1	F2	F3	F4	F5
Metoclopramide HCl (mg)	75	75	75	75	75
HPMC (mg)	405	270	202.5	135	-
PVA(mg)	-	135	202.5	270	405
PEG 400 (mg)	45	45	45	45	45
Sucralose (mg)	18	18	18	18	18
Sorbitol (mg)	36	36	36	36	36
Ascorbic acid (mg)	45	45	45	45	45
Orange essence (mg)	q.s	q.s	q.s	q.s	q.s
Distilled water (ml)	20	20	20	20	20

Note:
F1 = Formula 1 uses a polymer combination (HPMC:PVA = 3:0)
F2 = Formula 2 uses a polymer combination (HPMC:PVA = 2:1)
F3 = Formula 3 uses a polymer combination (HPMC:PVA = 1,5:1,5)
F4 = Formula 4 uses a polymer combination (HPMC:PVA = 1:2)
F5 = Formula 5 uses a polymer combination (HPMC:PVA = 0:3)
q.s = 2 drops

Evaluation ODF MetoklopramideHCl

Organoleptic characteristics

Organoleptic characteristics ODF metoclopramide hydrochloride observed homogeneity, color, smell and texture seen visually.

Uniformity of weight and thickness of the film

For the evaluation of the weight of the film, six sheets of film from every result of the formula is taken and weighed one by one then standard deviation were determined. The film thickness was measured at the center and four corners, calculated the average and standard deviation.

pH surface

For the evaluation of the pH of the surface, a film was dissolved in 10 ml of distilled water in the container and the surface pH was measured by using a pH meter.

Content uniformity of metoclopramide hydrochloride in Film

One sheet of film dissolved with phosphate buffer pH 6.8 in a flask of 25 ml, 0.5 ml of the solution is then diluted with phosphate buffer pH 6.8 to 10 ml. Levels of metoclopramide hydrochloride content is determined by spectrophotometry at a wavelength of 270 nm.

Disintegration time

Films were put in each tube of the basket, then the tool is run by using the medium of pH 6.8 phosphate buffer solution temperature of 37 ± 0.5°C. Disintegration time was observed in each film. Film said to be destroyed when no longer film is left in the basket.

Swelling index

Films allowed to swell in 15 ml medium of phosphate buffer pH 6.8 in a petri dish. Film taken from the petri dish and dewatered with filter paper, then films is weighed. Swelling index was calculated by the following equation:

$$\text{Swelling index (\%)} = \frac{\text{wt} - \text{wo}}{wo} \times 100\ \%$$

wt :Film weight on time t
wo :Film weight on time 0

Dissolution

The dissolution test performed with type-two dissolution apparatus, rotational speed 50 rpm, dissolution medium pH 6.8 phosphate buffer 900 ml of 37 ± 0.5°C. A film was put in dissolution apparatus. 2 ml solution was taken at the second 15, 30, 45, 60, and 90. The same medium was replaced with 2 ml so that the volume remained. Absorption solution is calculatedat the maximum wavelength.

Result and Discussion

Organoleptic evaluation

The resulting film has a good homogeneity. The use of orange essence in the formula produces an orange film, orange-scented and have the same sweetness. F1 has a rough surface, this is caused by the use of a single polymer HPMC. F2 has a slightly rough surface due to the amount of HPMC is more than the PVA (2: 1). Meanwhile, F3, F4 and F5 have a smooth surface as influenced by the nature of the PVA. The results is shown in Figure 1.

Uniformity of weight and thickness of the film evaluation

The evaluation of the weight and thickness of film is important to determine the weight and thickness uniformity of dosage because it relates directly to the accuracy of dose dosage. The result of the weight and film thickness uniformityshown in Table 2.

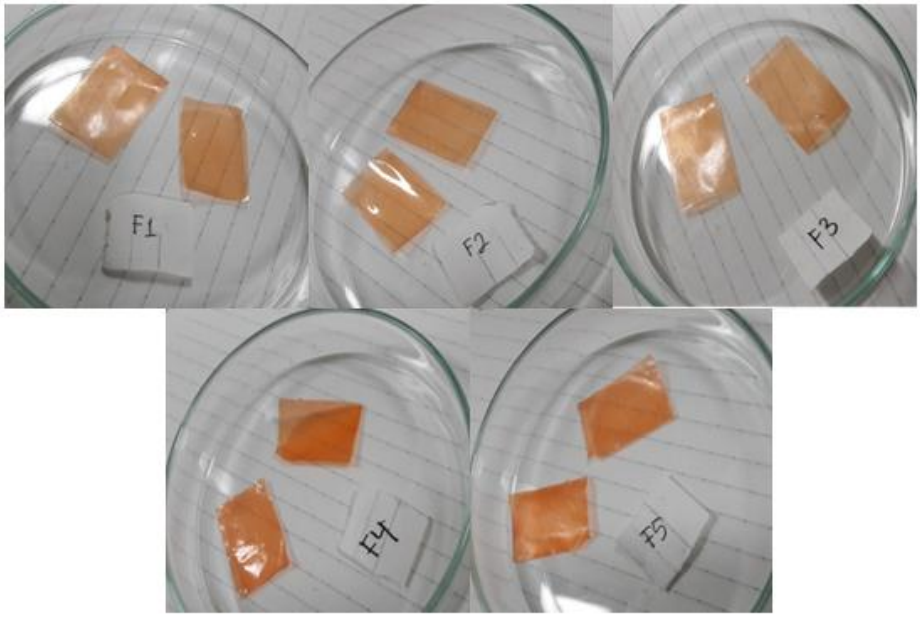

Figure 1.Orally Dissolving Film (ODF) Metoclopramide

Table2.The result of the weight and film thickness uniformity

Formula	Weight (mg)	Thickness (mm)
F1	50.75 ± 0.975	0.054 ± 0.0004
F2	50.83 ± 1.329	0.060 ± 0.0004
F3	51.66 ± 1.966	0.070 ± 0.0017
F4	51.16 ± 1.471	0.065 ± 0.0004
F5	51.16 ± 1.602	0.065 ± 0.0004

pH Surface Evaluation

Test the pH of the surface of oral film needs to be done to investigate the risk of side effects. Because of the acidic or alkaline pH may cause irritation to the oral mucosa, so it is important to maintain the pH remains close to neutral pH.From Table 3 it can be seen that the film has a near neutral pH which is in the range of 7.26 to 7.53. So the dosage has a very small probability to irritate the oral mucosa.

Content Uniformity Evaluation

Content uniformity test performed to ensure that all films contain a number of drugs as desired. Content uniformity is determined by estimating the active ingredient contained in each film. Limit of content uniformity is 85%-115% with a standard deviation must be less than or equal to 6%[7]. From Table 3 it can be seen that the levels of drug in the film ranges between 99.23%-100.13%. It showed levels of drug in oral film fulfil the thelimit of content uniformity.

Disintegration Time Evaluation

Disintegration time is expected to provide an overview of ODF time of disintegration. From Table 3 it can be seen that the fast disintegration time of ODF is F5 (HPMC and PVA polymer ratio 0:3) with a time of 32.33 seconds ± 1.527 and the slowest is F1 (HPMC and PVA polymer ratio 3:0) with a time of 70.66 seconds

± 1.527. This is caused by the water's ability to hydrate PVA better than HPMC, causing oral film to disintegrate quickly[8].

Swelling Index Evaluation

The results of swelling index is shown in Table 4. From these results it is known that ODF that swelled and experiencing erosion faster sequentially is F5, F4, F3, F2 and F1. Swelling index of ODF is important to predict drug release. Drug release will occur faster when the polymer is faster hydrated and experienced swelling. Films containing PVA hasexcellent swelling index, it is due to PVA's ability to hydrate the water faster so it will be ultimately expands then disintegrate and dissolve.

Table3. The results of the test surface pH, disintegration time, and drug content in the film evaluation

Formula	Surface pH	Drug Content (%)	Disintegration time
F1	7.26 ± 0.057	99.49 ± 0.275	70.66 ± 1.527
F2	7.33 ± 0.057	99.23 ± 0.470	51.33 ± 1.527
F3	7.43 ± 0.057	99.92 ± 0.427	47.33 ± 1.154
F4	7.46 ± 0.057	99.24 ± 0.577	37.00 ± 1.732
F5	7.53 ± 0.057	100.13 ± 0.212	32.33 ± 1.527

Table 4.The result of swelling index evaluation

Formula	Time (seconds)	Swelling Index (%)
F1	10	44.50 ± 4.175
	20	164.66 ± 3.801
	30	217.16 ± 1.484
	40	232.66 ± 2.802
F2	10	42.83 ± 7.605
	20	166.56 ± 3.625
	30	213.86 ± 2.589
	40	-
F3	10	56.56 ± 1.569
	20	179.23 ± 6.557
	30	226.50 ± 7.373
	40	-
F4	10	58.33 ± 5.604
	20	221.90 ± 2.971
	30	-
	40	-
F5	10	72.94 ± 4.421
	20	236.56 ± 4.463
	30	-
	40	-

Dissolution test result

Parameters to declare the dissolution rate is the percent cumulative, ie, percentage of metoclopramide that comes out of the dosage form ODF at time intervals of 15, 30, 45, 60, and 90 seconds.The cumulative percent lower in seconds of 15 since the release of the drug from the form of dosage and then increased to seconds of 90 to a dissolution process. The fastest dissolution rate profile shown by F5, then F4, F3, F2 and F1.Metoclopramide dissolution rate profile is shown in Figure 2.

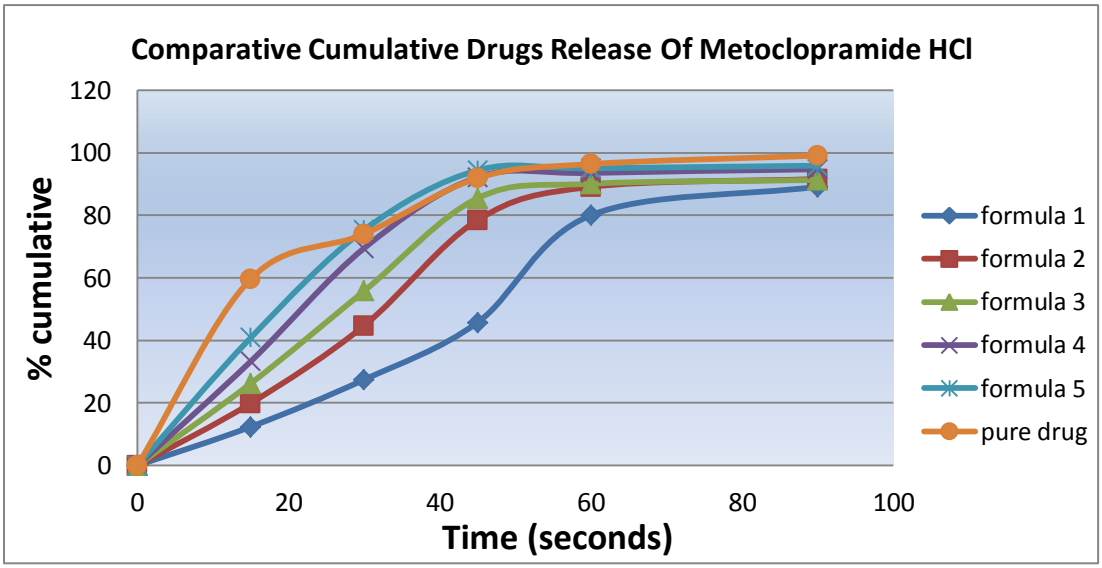

Figure 2.Comparative cumulative drug release of metoclopramidHCl

Conclusion

1. Based on the results of this research known that metoclopramide can be formulated in dosage forms ODF (orally dissolving film) using a combination of HPMC and PVA polymer.
2. Based on the results of this research known that there are significant influence from combination of HPMC and PVA towards disintegration time and in vitro release testing of all films formula. Films that combined with a greater amount of PVA (F4) gives disintegration time and release drugs time were 37 seconds and the cumulative percent of drug dissolved in 60thsecond which is 95.02%.

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