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The Application of Amylum Manihot as Disintegrant in The Formulation of Paracetamol Tablets by Wet Granulation Method

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ABSTRACT

The oral route of drug administration is preferred by most of the patients. One of the most preferred oral preparations are tablets. Tablets are solid dosage forms containing active ingredients with or without fillers. One of excipient used in formulation of tablet is a binder. The manufacture of tablets depends on the nature of the active pharmaceutical ingredient used. Paracetamol is an active substance that has poor flow properties and compressibility, so it requires a binder and a wet granulation method for making tablets in order to increase fluidity and good compressibility. Amylum manihot is one of the starches used as excipient in the pharmaceutical industry. This starch is very suitable to be used as a binder in the manufacturing of tablets by the wet granulation method. In this article, we manufacture paracetamol tablet with wet granulation method using amylum manihot as a binder. Evaluation result shows that amylum manihot is potential to be used for manufacturing paracetamol tablet using wet granulation method. Amylum manihot may increase porosity to facilitate water permeation into tablet, thus accelerate disintegration of tablet. However, the use of amylum manihot must be adjusted to optimum concentration because at certain concentration, it will lower dissolution of paracetamol.

Keywords: *Paracetamol, wet granulation method, amylum manihot, tablet*

BACKGROUND

Paracetamol is part of the class of drugs known as "aniline analgesics"; which the only drug still exist up to date. It is not considered an NSAID because it does not exhibit significant anti-inflammatory activity (it is a weak COX inhibitor). This is despite the evidence that Paracetamol and NSAIDs have some similar pharmacological activity. Paracetamol or acetaminophen is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, Paracetamol can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients. The onset of analgesia is approximately 11 minutes after oral administration of Paracetamol, and its half-life is 1-4 hours. Although acetaminophen is used to treat inflammatory pain, it is not generally classified as an NSAID because it exhibits only weak anti-inflammatory activity. (Behera, 2012).

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To date, the mechanism of action of Paracetamol is not completely understood. The main mechanism proposed is the inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2 (Hinz B et al., 2008). While it has analgesic and antipyretic properties, its peripheral anti-inflammatory activity is usually limited by several factors, one of which is the high level of peroxides present in inflammatory lesions. However, in some circumstances, even peripheral anti-inflammatory activity comparable to other NSAIDs can be observed. An article (Andersson DA et al., 2011) in Nature Communications from researchers in London, UK and Lund, Sweden in November 2011 has found a hint to the analgesic mechanism of acetaminophen (Paracetamol), being that the metabolites of acetaminophen e.g. NAPQI act on TRPA1-receptors in the spinal cord to suppress the signal transduction from the superficial layers of the dorsal horn, to alleviate pain. Paracetamol table is one of OTC drug that widely used. However, one of its physicochemical properties, flowability, is poor. Therefore, we manufacture paracetamol tablet with wet granulation method using amylum manihot as a binder.

METHODS

Materials

Materials used in this research are: Paracetamol 500 mg, Amylum manihot 50 mg, Polivinilpirolidon (PVP) 35 mg, Talcum 10 mg, Mg stearate 5 mg. The reason for the addition of talc as a glidant is because talc serves to make it easier for the granules to flow through the funnel to the tablet printing space.

Apparatus

Analytical balance, mortar and pestle, spatula, petri dish, porcelain dish, disintegration tester, set of glassware, horn spoon, ruler, oven, tablet press, friability tester, dissolution tester, beaker glass, stirring rod, parchment paper, graduated cylinder 250 ml, 500 ml, volumetric flask, watch glass, 5 ml measuring pipette, ball pipette, vial, spatula, Ultraviolet-visibile spectrophotometry, filter paper.

Preparation of Tablets

All the materials to be used are weighed according to the calculation. Mucilage of binder is made by mixing PVP and ethanol. Paracetamol and amylum are ground in the mortar. Mucilage is added to mortar gradually until a granule mass is formed. The granule is sifted with a mesh sieve Number 20. Granule is dried using oven for 24 hours. Dried granule is then re-sifted with a mesh sieve of 20. Formulation of tablet is shown in Table 1.

Table 1. Formulation of Paracetamol Tablet

Ingredients	Weight
Paracetamol	500 mg
Amylum manihot	50 mg
Polivinilpirolidon (PVP)	35 mg
Talcum	10 mg
Mg stearate	5 mg

Evaluation of Granules

Flow time

As much as 20 grams of granules were put into the funnel flow tester. The funnel cover is opened and the time of flow of the granules falling from the funnel on the surface of the flat plane of the tool is calculated. A good granule has a flow rate of ≥ 10 grams second (Sulaiman,2007).

Angle of Repose

The angle of repose test is carried out in conjunction with the flow rate test. The diameter using the formula and the height of the resulting mound is measured and calculated certainly. A good granule should have a resting angle of between 20° - 45°, however excellent flow will show a resting angle <20° (Sinko, 2011).

Compressibility Index

Granules are put into measuring cylinder to obtain the initial volume. Measuring cylinder is vibrated 100 times, to get final volume. The shrinkage of the granules on the measuring cylinder is calculated. A good granules have depreciation of less than 20% have good flowing qualities (Fassihi and Kanfer, 1986).

Tablet Pressing Procedure

Granules that have been sifted are mixed with the outer phase of the tablet (Talcum and Mg stearate). After homogeneous, the tablets can be directly press with a tablet press machine. The strength of compression tablet machine is increased to the maximum. Continue pressing the tablet with automatic machine after manual pressing of the first 3 tablets.

Evaluation of Tablets

Weight uniformity test

As much as 20 tablets are weighed individually. The average of weight is calculated. There should not be a single tablet whose weight deviates greater than the average weight set in column "A" nor column "B". (Depkes, 1979).

Friability

As much as 20 tablets are cleaned from dust. They are weighed (W0 grams) individually. Then, tablets are put into friability test. The tester is set for 4 minutes with speed of 20 rpm. The tablets are removed, cleaned from dust, and weighed (W1 grams). The friability is calculated by formula $\frac{W0-W1}{W0} x100\%$. Fragility above 1.0% indicates a brittle tablet and is considered poor (Parrot, 1971).

Disintegration time test

As much as 3 tablets are put into a basket-shaped tube, then regularly lowered the tool in a water medium at a temperature of 37° C. Tablets are considered to be fully disintegrate if there are no tablets left on the gauze. The disintegration time of fast dissolving tablets is less than 1 minute (Bhown et al., 2009).

RESULTS AND DISCUSSION

Paracetamol is an active substance in a drug that is widely used as an analgesic and antipyretic. Paracetamol has poor flow properties and compactivity with its crystalline shape, so it is necessary to make granules by the wet granulation method so that it can increase fluidity and good compressibility (Voight, 1984). The reason for the addition of talc as a glidant is because talc serves to make it easier for the granules to flow through the funnel to the tablet printing space.

Table 1. Evaluation of Granule Results

Evaluation	Outcome	Standard
Flow time	0.23 gram/s	<10 gram/s
Angle of repose	51.3°	20°-45°
Compressibility index	24%	<20%

Granule evaluation test is carried out to find out whether the granule is already in accordance with the requirements of the literature. Based on table 2, three evaluation results were obtained in the form of a flow time of 0.23 gram/s, these results were not in accordance with the provisions and requirements of a good granule, where a good granule had a flow rate of ≥ 10 grams/second (Sulaiman 2007). The result of angle repose test does not meet the requirements of a good granule, for a good granule it should have a resting angle of between 20° and 45° (Sinko, 2011). The results of the third evaluation, compression test, results in the form of granules that have depreciated by 24%, this is not in accordance with the requirements of good granules where good granules have depreciation of less than 20% have good flowing qualities (Fassihi and Kanfer,

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1986).

Based on granule evaluation results, all granule evaluation test results are not in accordance with the existing terms and conditions. This can be caused by a procedure error when making a granule, besides that the room temperature when making the granule also has an influence on the results of the granule evaluation test. The humidity factor also affects the results of the granule evaluation test, where moisture content is a statement of water content based on dry weight, which shows the water content contained in a granule. Granules that have a moist content of <5% will be stable and good at the time of storage (Rowe, et al, 2009). With the moisture content, the bond between particles will be strong so it will also affect the storage of granules for tablet printing to be carried out.

For the evaluation of the tablet itself there is a weight uniformity test, friability test, and disintegration time test. The acceptance criteria of weight uniformity test is none of the tablets deviated more than the average weight of A and none of the tablets deviated more than the average weight of B (Depkes, 1979). From the test results obtained, the average weight of the tablet is 210 mg. Deviation A has a range between 194.25-225.75. Deviation B has a range between 178.5-241.5. This result is in accordance with the requirement that none of the tablet weights deviate from column A or column B.

Table 2. Deviation of the average weight

Average weight	**Deviation**	
	A	**B**
25 mg/less	15%	30%
26 mg-150 mg	10%	20%
151 mg-300 mg	7,5%	15%
>300 mg	5%	10%

The second evaluation is that there is a fragility test. Fragility above 1.0% indicates a brittle tablet and is considered poor (Parrot, 1971). From the laboratory practice, the results obtained are 2.2% friability percentage. The tablets showed a poor friability. The third evaluation is the disintegration time test. The acceptance criteria for tablet disintegration time is not more than 15 minutes. Meanwhile, the disintegration time of fast dissolving tablets is less than 1 minute (Bhown et al, 2009). The results obtained were that the three tablets were immediately destroyed in less than 1 minute, hence the tablet met the acceptance criteria.

Dissolution studies provide an idea of the amount of drug absorption that occurs after oral administration. Drugs with poor dissolution profile will not be dispersed in body systems or target organs tissues to obtain a therapeutic effect (Nayak, n.d.). The pH of the buffer used was 5.8. This was chosen because the sample preparation is a conventional tablet that sinks in the stomach as it passes through the digestive tract. So the pH used is lower stomach pH. The temperature of the medium can be chosen at 37°C because the human body temperature is around this temperature to simulate drug dissolution as closely as possible to body conditions. The amount of buffer medium used was 900 ml and each sample was taken back with the same volume of buffer after collection. During sampling, filtering was also carried out and the filter paper was moistened with the buffer first. This is to avoid any undissolved particles being picked up as well. Wetting of filter paper is done to avoid the presence of reduced particles due to sticking to dry filter paper. Meanwhile, what is being studied in this practicum is the dissolution of the active substance. Because if the undissolved particles are taken, they will also produce different absorbances.

In addition to the less valid calibration curve, it is possible that the dissolution rate will be small due to the oven being carried out during the granule oven. A study stated that the drying temperature of the granules affected the physical properties of paracetamol tablets, where the best temperature was 50°-60°C with a drying time of 3 hours for granules (Sudarsono et al., 2021). Meanwhile, the oven was carried out on the sample preparations for 24 hours because too much solvent was added during the preparation of the preparations.

There is also a study that states the relationship between the percentage of the active substance

contained in it and the physico-chemical properties of the brittle tablet so that there is a lack of active substance during distribution (Octavia, n.d.). While it is known in the previous practice the tablet sample preparation is very easy to destroy. Even when printing sample tablets, the highest printing pressure must be used.

CONCLUSION

From the results of research carried out making paracetamol tablets can use the wet granulation method to improve the flow properties and compactibility of the paracetamol, as a filling and crushing agent tablets can be used amylum manihot because amylum manihot has the property of increasing porosity so as to make it easier for water to enter the tablet which speeds up the time of destruction of the tablet, but the use of amylum manihot must be adjusted because it also makes the results of the dissolution test bad due to the excessive amount of use of amylum manihot. From all the results of the granule and tablet evaluation test, it can be concluded that paracetamol tablets are not yet suitable for consumption. For this reason, it is necessary to re-formulation of paracetamol.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

AUTHORS' CONTRIBUTION

All authors read and approved the final manuscript.

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None

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