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The Effect Of Uncontrolled Addition Of Gelatin In Paracetamol Tablet Formulation

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ABSTRACT
Acetaminophen is an over-the-counter drug commonly used to reduce pain and fever. It is available in tablet form. In this research, acetaminophen tablet is manufactured using wet granulation method. Evaluation of granule resulting flow time 0.16 gram/s, angle of repose 51.78°, compression index 30%. During tablet compression process, tablet was damaged during the initial printing, thus resulting in capping. The result of tablet evaluation test are weight uniformity 24 8mg, friability 3.22%, disintegration time 1 minute, dissolution in 60 minutes is 2.2817. The formulation of paracetamol tablets made by the researchers did not meet the specifications for marketability, where the discrepancy in tablet specifications occurred in the physical and chemical properties of the tablets.

Keywords: *Acetaminophen, tablet, wet granulation, evaluation*

BACKGROUND

Paracetamol, synonyms of Acetaminophen, is an analgesic-antipyretic drug that is widely produced and used because of its safety profile. Paracetamol ($C_8H_9NO_2$) tablets contain not less than 90.0% and not more than 110.0% of the amount indicated on the label (Depkes RI, 2014). Acetaminophen is a pain-relieving (analgesic) and fever-treating (antipyretic) medication that can be obtained over-the-counter. Pharmaceutically it is a different kind of medication than other over-the-counter medications, such as ibuprofen and naproxen, which are also used to treat pain and fever. Acetaminophen is widely used for pediatric and adult fever and pain and comes in pill, liquid, injectable, and rectal suppository forms (Iloamaeke and Iwuozor, 2018).

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Paracetamol lacks of anti inflammatory action in rheumatic disorders. However, it is less toxic than aspirin and does not produce anemia and liver damage. Paracetamol is used in the treatment of reduction of fever, relief of muscle joint and pain, relief of cold and flu symptoms, relief of common headache (Iwuozor, 2019). Paracetamol is a material with poor compatibility and poor flow properties. To improve the flow properties and compactibility, the wet granulation method is used in the manufacture of tablets. Wet granulation is processing a mixture of active substance and excipient particles into larger particles by adding the right amount of binder liquid so that a moist mass can be granulated. Wet granulation is used for active substances that are resistant to moisture and heat. The principle of this method is to wet the mass or mixture of active substances and excipients with a certain binder solution until a certain level of wetness is obtained (Sharimina Venu Gopalan, 2018).

Tablets are drug preparations in solid form which are usually made with the addition of pharmaceutical ingredients appropriate. Tablets are compressed preparations, made by compression, in the form of a flat or circular tube, both surfaces are flat or convex, containing one or more types of drug with or without additives. To make good quality tablets, certain excipients are needed that can support the physical form and performance when evaluating tablets (Sudarsono et al., 2021).

METHODS

Wet Granulation

Paracetamol and Sodium Bicarbonate were sieved through a number 40 sieve. The powder was prepared with ethanol to form a moist mass then sieved through a number 40 sieve. Other excipient such as Citric acid, Na bicarbonate, spray dried lactose, starch, gelatin were mixed and mashed then sieved through a number 40 sieve. The granules were made with a binding agent in the form of ethanol and then dried at a temperature of 60°C for 30 minutes. The two granules were mixed and then dried at 60°C for 15 minutes.

Evaluation of Granules

Flowability of granules tested by putting granules into a funnel as high as 2/3 the height of the funnel and then flow through the end of the funnel and the flow time is calculated. The angle of repose test was carried out using a funnel with a diameter of 12 cm at the top, 1 cm at the bottom and 10 cm in height. The granules are inserted into the funnel, then flowed through the end of the funnel and the angle of repose is determined. Tapped density is carried out by placing 10 grams of granules into a graduated cylinder, then observing the initial volume of the graduatee cylinder and then tapping it manually 100 times until the granule volume is constant (Sa'adah et al., 2016).

Tablet Compressing

The paracetamol granules from the wet granulation, talc, and Mg stearate were weighed and then mixed together. The tablet is compressed using machine and then evaluated. To test weight uniformity, 20 tablets are weighed individually. Then note the results and seen storage that occurs where for drugs with weight 300 mg on tablet A and for tablet B 10% which is appropriate with the Ministry of Health of the Republic of Indonesia which cannot be more of the two tablets that save from the average weight. Friability tests are conducted on 20 samples of tablet. The tablets are cleaned from dust, then weighed and put into a friability tester at a speed of 25 rpm for 100 rotations. Disintegration time test is carried out using 3 tablets that are put into the disintegration tester.

RESULTS AND DISCUSSION

The manufacture of tablets begins with the wet granulation method. Paracetamol is an analgesic-antipyretic drug commonly used by the public. Paracetamol (C_8H_9NO2) tablets contain not less than 90% and not more than 110% of the amount indicated on the label (DepKes RI, 2014). Stability of paracetamol to water and heat is good, therefore it is used by wet granulation method. In addition, the wet granulation method may improve the flowability of API.

Table 1. Formulation Used for Manufacturing of Paracetamol Tablet

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Formulation	Concentration
Paracetamol	500 mg
Amylum manihot	7,5%
Mg Stearate	1%
Lactose	q.s
Gelatine	5%
Talc	1%

Wet granulation is a formulation technology which involving stirring powder or powder mixture in the presence of a liquid as a binder which is mixed with dry powder (Fatmawati et al., 2021). In the process of making granules, there are obstacles in increasing the amount of binder. Where should the provision of a binder be sufficient but still added. So that the powder that was originally already a granule that fits into a wet granule and shaped like a dough. The distribution of the binder in the granules affects its ability to produce strong, non-brittle granules. Factors that hinder the distribution of the binder solution during wet granulation will reduce the efficiency of the binder. So the effectiveness of a binder must be evaluated experimentally (Siregar, 2010). In order to prevent the same incident from happening, the binding agent should be given gradually to form a fine granule.

Wet granules are then placed in the oven and sifted. According to the United State Pharmacopeia (USP) method to test the size of a powder is a certain sample mass is placed on a suitable sieve and shaken mechanically. The powder is shaken for a certain time, and the material that passes through one sieve will be retained by the next finer sieve and collected, then weighed.

The characteristics of the physical properties of the granules not only affect the tabletting process, but also affect the quality of the tablets themselves. In this study, the physical properties of the granules tested were flow time, angle of repose, and tapped density. The flow time shows whether or not the granules flow easily in the tablet press. Good or bad granule flow time is influenced by several factors i.e. granule size, granule shape, and relative humidity. Granules with poor flow will cause the flow of granules from the hopper to the die is not perfect, as a result the weight of the tablet is not constant so that it will affect the uniformity of the active substance (Khaidir, 2015). The evaluation of granule available in Table 2.

Table 2. Result Evaluation of Granules.

Parameters	**Result**
Flow rate	0.16 g/s
Angle of repose	51.78^{o}
Tapped density	30%

A granule mixture is said to have good flow properties if the flow rate is not less than 10 g/s (Reiza, 2010) or 100 g not less than 10 seconds (Lachman et al., 1994). The granules used in this test are 10 g so that a good granule will fulfill if the flow time is less than 1 second or the flow rate is not less than 10 g/second. Flow properties can be measured by direct methods (flow time test) and indirect methods (angle repose test and tapped density). The result of measuring the flow properties of our granules is 0.16 gram/second. This indicates that the granules we made have very poor flow properties. This can be caused by several factors. The flow rate is influenced by the shape, size, surface conditions, granule moisture and the addition of a lubricant (Hayatus Sa'adah, 2016).

The angle of repose is the fixed angle that occurs between the pile of conical particles and the horizontal plane. If the angle of repose is less than 30˚, it usually indicates that the material can flow freely, if the angle

is greater than or equal to 40˚, the flow is usually poor. The result of measuring the angle of repose of the granules that we made is 51.78˚. This indicates that our granules have a poor angle of repose. Factors that affect the size of the angle of repose are caused by the shape, size and humidity of the granules (Hayatus Sa'adah, 2016).

Compressibility index is a decrease in the volume of a number of granules or powders due to tapping and vibration. Granules with a settling index of less than 20% showed good flow properties. The determination index is carried out by placing 10 grams of granules into a graduated cylinder, then recording the initial volume of the graduated cylinder and then tapping it manually 100 times until the granule volume is constant (Sa'adah et al., 2016). The results obtained in granule were 30%, which does not meet the acceptance criteria. This discrepancy occurs because of the wetting process of the granules which can increase the compressibility so that the granules become moist and solidify. Good compressibility will produce a good and compact tablet. The shape and texture of the granules formed will affect the compressibility (Kurniati et al., 2017). The results of the paracetamol granules evaluation did not fulfill the requirements of the Indonesian pharmacopeia.

Tablet press machine is a high pressure printing machine that converts crystalline powder into tablet granules. The way this machine works is by inserting the granules into the hopper and will flow into the molding plate and fill the mold cavity, then pressed with pressure pistons so that the crystalline powder/granules become solid and come out in the form of tablets (Saputra and Wahyudin, 2020).

During the first compression process, there was a failure in the process namely Capping. Capping is the separation of part or all of the upper or lower crown of the tablet from the main body of the tablet due to air trapped in the impression mass (Zaman and Sopyan, 2020). The solution to this problem is to increase the humidity of the granules by adding wetting agents, increasing the punch pressure during the compression process. The evaluation of tablets available in Table 3.

Tablets are said to be suitable for use if they pass the evaluation stage or pass the final test. Tests carried out after tablet manufacture include weight uniformity test, friability tester, and disintegration time test (Banne et al., 2017). In the weight uniformity test using 20 tablets, then calculate the average weight of each tablet. If weighing is carried out one by one, there may not be more than two tablets whose weight deviates from the average weight1 greater than the price set in column A and not one tablet whose weight deviates from the average by more than the price set in column B (Rahmat, 2019).

Table 3. Evaluation Results of Paracetamol Tablets

Evaluation	Result
Weight uniformity	248 mg
Friability test	3,22%
Disintegration test	1 minutes

The weight uniformity test is carried out to see the uniformity of the dose of the drug that enters the body so that the dose of each tablet is expected to be the same and in accordance with the therapeutic safety of the preparation. The results of the test by weighing 20 tablets of 248 mg. Then looking for deviation A and deviation B, the results are 229.4 mg - 266.6 mg for range A, while range B is 210.8 mg - 285, 2 mg. From the test results for the uniformity of weights carried out using a sample of tablets that have been made, it is found that the sample does not meet the test requirements is more than 2 tablets of 20 test tablets that deviate from column A and there are 3 tablets that deviate from column B.

In the weight uniformity test, it was found that it didn't meet the specified requirements. The uniformity of weight is related to the flow properties of the powder, if the flow properties are good, it will facilitate the compression process where the granules will run continuously from the hopper to the compression chamber and produce tablets with the same weight. (Rohmani and Rosyanti, 2019). Meanwhile, at the time of making granules in the flow time test, it was found that the flow time was bad, so this could affect the uniformity of tablet weights that were not suitable.

Friability test is a test of the resistance of the tablet surface to the friction experienced during packaging,

shipping and storage (Banne et al., 2017). The principle of this test is to determine the lose weight of a number of tablets when rotated in a friability tester for a certain time (Gopalan and Gozali, 2018). The testing process was carried out on 20 tablets that had been dusted free, then weighed and put into a friability tester at a speed of 25 rpm for 100 rotations. From the results of the tablet friability test, it was found that all the test samples did not meet the tablet requirements, because the requirements were not more than 0.8%. (Ulfa et al., 2018).

The tablet disintegration time test is very important in the biopharmaceutical phase of the drug. In order to the active substance to be fully absorbed from the gastrointestinal tract, the tablet must disintegrate into body fluids to be dissolved. Disintegration time can be affected by the disintegrant and the amount of binder used in the tablet formulation, because the disintegrant is a substance that will cause the tablet to break and disintegrate in water or gastric fluids.

Tablets that have a disintegration time in accordance with the requirements that have been set can provide a rapid therapeutic effect. The time allowed to crush tablets is not more than 15 minutes (Depkes RI, 2020). Based on the results of the tests that have been carried out, it can be concluded that the paracetamol tablets made in this test have met the requirements of the disintegration time test.

The dissolution test was carried out to determine the effect of the formulation and fabrication processes on the dissolution profile in estimating the bioavailability and bioequivalence between the test and comparison products. (Kurniawan et al., 2022). In this test, the linear regression equation was obtained: $y = 0.0411x - 0.1111$ with $R^2 = 0.9891$. Result of dissolution test available in Table 4. In making the standard curve, only concentrations of 4, 6, 8, and 10 ppm were used because at concentrations of 2 and 12 ppm, the absorbance was not in a good absorbance range.

Table 4. Result of dissolution test

Time (minute)	% Dissolution
0	0.2558
3	0.5966
5	1.1774
10	1.4498
15	1.8501
30	2.3591
45	2.6464
60	2.8217

From the calculation of the dissolution drug levels, the results obtained were 2.3591% of the dissolved drug levels in the 30th minute. These results indicate that the paracetamol tablets made did not meet the requirements stated in the Indonesian Pharmacopeia Edition VI and the United States Pharmacopeia where the dissolution requirement for paracetamol tablets was not less than 80% of the paracetamol tablet content which was dissolving during 30 minutes of testing. Factors that affect the dissolution results include physical chemical factors, formulation factors, additives and tablet hardness (Hasanah, 2008; Swarbrick, 1970; Lachman et al., 1976; Evrina, 1991).

CONCLUSION

The formulation of paracetamol tablets made by the researchers did not meet the specifications for marketability, where the discrepancy in tablet specifications occurred in the physical and chemical properties of the tablets. The physical properties of the tablets tested included the flow properties of the granules, the tapped density of the granules, the angle of repose of the granules, the uniformity of the tablet weights, the friability of the tablets, and the disintegration time of the tablets. The test of chemical properties tested on

tablets is an in vitro dissolution test. The discrepancy of tablet specifications against the requirements is caused by inappropriate formulations and also the production process is not up to standard.

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CONFLICT OF INTEREST

There is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors read and approved the final manuscript.

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AUTHOR DETAILS

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