Journal of Tropical Pharmacy and Chemistry

Journal homepage: https://jtpc.farmasi.unmul.ac.id

Quality Test of Extemporaneously Prepared Tramadol and Paracetamol Capsules Combination Derived from a Private Hospital in Semarang

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Abstract

Tramadol and paracetamol are analgesic drugs that are often combined and made in the form of extemporaneously prepared capsules dosage form to treat moderate to severe pain management. This study aims to determine the quality of prescribed medication of extemporaneously prepared tramadol and paracetamol capsules combination taken from a private hospital in Semarang covering weight uniformity, moisture content, disintegration, and content uniformity. This type of research is a descriptive observational cross-sectional design. Samples were taken using simple random sampling at a pharmaceutical installation in a private hospital in Semarang. The observation result from four types of testing was compared against the standard values of each test's parameter listed in the Indonesian Pharmacopoeia V. The results are, samples meet the weight uniformity test with an acceptance value of 7.34%; meet the moisture content test with an average moisture content of 2.647% for the first day and 3.04% for the seventh day; meet the disintegration test with a breakdown time of fewer than 15 minutes; and did not meet the uniformity test with acceptance value of 34.06% for paracetamol and 34.30% for tramadol. It can be concluded that the prescribed medication of extemporaneously prepared capsule samples derived from a private hospital in Semarang can fulfill the standard values listed in the Indonesian Pharmacopoeia V except for the content uniformity test.

Keywords: uniformity of weight and content; moisture content; paracetamol; tramadol; disintegration

Submitted: 18 October 2020 **Accepted**: 26 June 2021 **DOI**: https://doi.org/10.25026/jtpc.v5i4.587

1 Introduction

Extemporaneous preparation is preparation for the order or prescription from a doctor or dentist, from individually selected starting materials it is dispensed immediately after preparation and not kept in stock.

Extemporaneous dispensing is still being used up until today because there are circumstances in which there is no licensed medicine that fully meets the clinical needs of patients. In these circumstances, it is sometimes necessary for the pharmacist to extemporaneously prepare a limited quantity of a custom-made medicine for a specific patient [1].

Whilst extemporaneous preparation do not go through the same stages with licensed medicine from the pharmaceutical industry, extemporaneously prepared medicines must be confirmed to have proper quality thus can provide a good outcome for patient therapy. Standard quality that must be fulfilled from extemporaneous preparation must achieve suitable physical, chemical, and microbiological stability [1]. One of much physical qualities from extemporaneous solid oral dosage form formulation is content uniformity as it can provide an overview that the active ingredients within the prepared formulation are homogeneous [2].

Several studies regarding physical quality from solid extemporaneous formulation has been published only 4 out of 10 pharmacies in Yogyakarta can fulfill the weight and content uniformity quality requirement for prescribed paracetamol pulverize [3], hydrochlorothiazide pulverize in Yogyakarta were not able to fulfil the weight and content uniformity quality parameter but were able to fulfil the moisture content quality parameter [4], diltiazem pulverize in X hospital were not able to fulfil the weight and content uniformity quality parameter but were able to fulfil the moisture content quality parameter [5].

Some example on why the quality from extemporaneous solid oral dosage form formulation fails to be accomplished are error that occurs in the extemporaneous preparation process, such as some medicine powders are left behind in the mortar that is being used to crush and mix the medicine and limitations in visual observation, precision, skill, and time whilst preparing the extemporaneous formulation [6] [7]. The emerging consequence of an error while preparing the extemporaneous preparation for instance labeling, mistake while picking up the starting materials, and input on dispensing equipment may take away the patient's life [8] [9] [10] [11].

Pharmaceutical installation at a private hospital in Semarang dispense lots of tramadol and paracetamol capsules combination extemporaneous formulation although licensed medicine on the market is commercially available. This compounding practice still accessible for the destitute patient and this dispensed capsules are prescribed to substitute for brand name drugs such as Acetram®, Analtram®, Dotramol®, and Sincronik® since this medicine can cost more expensive. Tramadol and paracetamol synergistically work as a barrier in the central nervous system and peripheral nervous system. Tramadol 25 mg and paracetamol 250 mg capsules combination is being used in hospitals for the treatment of moderate to severe pain management [12].

Medicines are required to possess a certain quality before given to the patient. The quality of extemporaneously prepared capsules dosage form must meet with the standard values listed in the Indonesian Pharmacopoeia V, such as weight uniformity, content uniformity, moisture content, disintegration, and dissolution. Dissolution testing is technically can not be done since the precise quantity of the active ingredients from the extemporaneously prepared capsule samples is unavailable [13].

A pharmacist must ensure that patients receive medicines of the appropriate quality to safeguard the patient quality of life and safety by monitoring extemporaneous preparation activities in the hospital [14]. Nevertheless, this study discovers that dispensing activities are left unsupervised by the pharmacist, so the quality of the dispensed medicine is questionable [15]. Therefore, it is necessary to study the quality of extemporaneously prepared capsules dosage form comprises weight uniformity, content uniformity, moisture content, and disintegration.

2 Materials and Methods

This type of research is a descriptive observational cross-sectional design. Samples were taken using simple random sampling at a pharmaceutical installation in a private hospital in Semarang, Central Java.

2.1 Materials

Working standards of tramadol (Ferron Industries, Indonesia) and paracetamol (Dexa Medika Industries, Indonesia) it is certified to contain 99.2% tramadol and 99.3% paracetamol on a dry weight basis. Methanol gradient grade for liquid chromatography (E. Merck®, Indonesia), aquabidest was obtained from Water Purification System Easy Pure II RF, extemporaneously prepared capsules dosage form of tramadol 12.5 mg and paracetamol 125 mg taken from a private hospital in Semarang.

2.2 Samples

The total number of samples was derived from the literature study of each test parameter. It was concluded that 30 samples were required with 10 samples for weight uniformity test, 9 samples for the moisture content test, 3 samples for disintegration test, 6 samples for content uniformity test, and 2 extra samples. All samples are handpick using a simple random sampling technique, pharmaceutical installation in the hospital is required to hand over 3 batches (@10 capsules) of samples (Figure 1) from the prescribed medication (Figure 2).

Figure 1. Extemporaneously prepared tramadol and paracetamol capsules combination taken from a private hospital in Semarang.

R/ Pamol 500 mg 1/2 tab
Tramadol 50 mg 1/2 tab
mf pulv da in caps dtd no XXI
S 3 dd 1

Figure 2. Prescribed medication of extemporaneously prepared tramadol and paracetamol capsules combination taken from a private hospital in Semarang.

2.3 Weight uniformity test

Weight uniformity test is performed using analytical balance Ohaus® (PAJ1003, USA) with 0.1 mg precision limit (max 120 g, min 0.001 g). The test is carried out on 10 samples of each batch to calculate the acceptance value which then will be compared with the maximum allowed acceptance value (L1%). Weight uniformity is determined by calculating the weight of each sample, perceive the theoretical quantity of active ingredients, reference value, acceptance constant referring to the literature [13].

2.4 Moisture content test

Moisture content test is performed using a moisture analyzer (KERN MLS®, Germany). As much as 3 capsules are each taken from 3 batches of dispensed samples, then 9 samples are divided into 2 to be tested on day 1 and day 7. The powder from the capsule is placed into the analyzer then sealed and left until the value of moisture content appeared [13].

2.5 Disintegration test

Disintegration test is performed using disintegration tester (Shanghai Develop Machinery BJ-2®, China). The amount of samples required is 3 capsules, each is placed inside the tube tester and pressured by the disc. The machine is left running for 15 minutes with 37^{o}C water as a medium as we observe the samples begin to change [13].

2.6 Content uniformity test

2.6.1 Instrumentation and chromatographic conditions

The HPLC system (Shimadzu® LC-2010HT, Japan) which consisted of an ACE C_{18} column (250×4.6 mm i.d., 5 µm particle size), pump with manual sampler injector programmed at 10 µl capacity per injection, UV/Vis detector, data were processed with a computer (Hewlett Packard®, Indonesia), the mobile phase consisted of 40:60 (v/v); methanol: aquabidest, the flow rate was set to 0.6 mL/min and UV detection was carried out at 271 nm in room temperature [16].

2.6.2 Standard solutions and calibration graphs

Stock standard solution containing tramadol (1000 µg/mL) and paracetamol (1000 µg/mL) was prepared by dissolving 10.0 mg of tramadol and 10.0 mg of paracetamol in 10.0 mL volumetric flask with the mobile phase consisted of 40:60 (v/v); methanol: aquabidest. This was further diluted to obtain working standard solutions in a concentration range of 1-19 µg/mL (i.e. 1; 4; 7; 10; 16; and 19µg/mL) for tramadol and 20-80 µg/mL (i.e 20; 30; 40; 50; 70; and 80 µg/mL) for paracetamol. A constant volume of 10 µL standard solution with the chosen concentration ratio was injected and chromatographed under the above-mentioned conditions. The peak areas were plotted against the corresponding concentrations to obtain the calibration graphs [16].

2.6.3 Sample preparation

As much as 6 samples capsules were divided into two part of equal amount, part one was analyzed on day 1 and part two were analyzed on day 7. Each sample part is taken and transferred into 25 mL volumetric flask with methanol and aquabidest (40:60) mobile phase. From the volumetric flask, 10,0 µL solution is diluted in 1,0 mL microtube with the mobile phase. This solution was homogeneously shaken and filtered through a 0.45 µm millipore filter then transferred to HPLC vials and sonicated for 10 min. A constant 10 µL volume of sample solution was injected under the above-mentioned conditions [16].

2.6.4 Results analysis

Data from weight uniformity test, moisture content test, disintegration test, and content uniformity test are compared with standard values listed in the Indonesian Pharmacopoeia V. Standard values for capsule weight uniformity and content uniformity are the amounts of acceptance value is no more than 15,0 of L1% value. The standard value for capsule moisture content is less than 5 % for magnesium stearate and cellulose-containing powder. The standard disintegration time for capsule is the length of time for the dosage form to disintegrate or equal to 15 minutes.

3 Results and Discussion

3.1 Weight Uniformity test

Weight uniformity test aims to discover the uniformity degree of active ingredient within medicinal preparation using the weight of each sample capsule. Weight uniformity test can be implemented if the samples fulfill the required condition that is containing 25 mg or more of active ingredient comprising 25% or more by weight of the dosage unit. The obtained result has a range of 0.3874 to 0.4832 gram whilst the acceptance value is 7.34%, these results show that the extemporaneously prepared capsule samples meet with the quality conditions of weight uniformity test since the sample acceptance value is smaller than the maximum allowed acceptance value (L1%) that is 15.0% [13].

3.2 Moisture Content test

Moisture content test is performed by comparing the powder weight before and after being dried. The purpose of this test is to examine the amount of water inside the capsule's powder. The moisture content result attained from day 1 have a range of 2.315–3.524% with a mean value of 2.647% and day 7 have a range of 2.632–3.571% with a mean value of 3.04%. These results show that the extemporaneously prepared capsule's powder meets with the quality conditions of a good moisture content since the results is under 5%, with storage conditions carried out in accordance with the storage instructions given by the hospital pharmacist to the patient which is to store inside a medicine box at room temperature, protected from direct sunlight, and silica gel is also given inside the medicine secondary package [13] [17]. Although the obtained result fell under the maximum standard limit quality in general, there was an increase of moisture content after the storage period. This increase is influenced by the active ingredient, namely, tramadol. Tramadol is a chemical compound that is formulated in a salt form to increase its solubility in water, which results in tramadol's susceptible character to absorb humidity through the capsule shell causing the extemporaneously prepared capsule's powder moisture content to rise after

storage [18]. Another influence comes from excipient ingredient within extemporaneous dosage form formulation since some excipient possesses certain characteristics that can absorb humidity more easily than the active ingredient hence increasing the moisture content of the extemporaneous dosage form formulation. Therefore, during the extemporaneous preparation process excipient ingredient must be selected while considering the physical and chemical properties of the active ingredient for example the stability of the active ingredient such as hygroscopicity, oxidation, hydrolysis [19].

3.3 Disintegration test

Disintegration test objective is to observe the duration for capsules to thoroughly disintegrate, it can be seen visibly that only a soft mass without a core left inside the disintegration tester. Table 1 shows that the extemporaneously prepared capsule sample falls within the standard quality requirement for extemporaneous solid oral dosage form formulation which is under 15 minutes to completely disintegrate [13].

Table 1 Disintegration test observation result

Time	Observation Result
3 minutes	Samples disintegrates
9 minutes	Capsule shell remains
12 minutes	Unclear, not obvious
15 minutes	Completely disintegrate

3.4 Content uniformity test

Content uniformity test is carried out for extemporaneous solid oral dosage form formulation which contains more than one active ingredient to provide a clearer view of its degree of uniformity by determining the amount of each sample's active ingredient. This study use reversed-phase HPLC method to analyze the content of active ingredient from the extemporaneous samples capsule formulation, the results are then used to calculate the sample's acceptance value which is determined by individual weight contents of the capsule, active ingredient content of each capsule, mean of weight contents of the capsule, capsule weight content deviation, and a constant [13]. Reversed-phase HPLC is widely used for drug analysis method because of its sensitivity, short analysis time, and reliability [20]. Table 2 show that the acceptance value of tramadol is 34,30% and 34,06% for paracetamol, these results shows that the extemporaneously prepared capsule samples do not fulfill the quality conditions of content uniformity test since the sample acceptance value is above the maximum allowed acceptance value (L1%) that is 15,0%. In other words, the active ingredients within extemporaneously prepared capsule samples are not evenly spread or distributed as a consequence of incorrect and improper samples dispensing process carried out by the hospital's pharmaceutical installation, especially during the mixing stage in the extemporaneous preparation process.

4 Conclusions

It can be concluded that weight uniformity test, moisture content test, and disintegration test from the extemporaneously prepared capsule samples derived from a private hospital in Semarang can fulfill the standard values listed in the Indonesian Pharmacopoeia V except for content uniformity test.

Tabel 2 Content uniformity test observation result

Capsules	Tramadol Content (% w/w)	Paracetamol Content (% w/w)
C1	72.68	106.93
C2	95.92	86.48
C3	78.07	62.62
C4	98.24	81.34
C5	102.39	86.67
C6	103.46	87.73

5 Acknowledgments

The authors are grateful to the Faculty of Pharmacy, Sanata Dharma University for the provided facilities, and Institute for Research and Community Services, Sanata Dharma University for financially funded this research by The Young Lecturer Research Grant on July - November 2018 (032/Penel./LPPM-USD/VII/2018).

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