5th ICRIEMS Proceedings
Published by Faculty Of Mathematics And Natural Sciences
Yogyakarta State University, ISBN 978-602-74529-3-0

Preparation and Quality Control of I-131 Capsules for Therapy

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ABSTRACT. The most common abnormalities of the thyroid glands in Indonesia are hyperthyroidism and thyroid cancer. Radioactive iodine therapy has been commonly used in some hospitals as one effective way for treatment of hyperthyroidism and thyroid cancer. The aim of this study was to completed the production and quality control data of I-131 capsule therapy that have not been well documented. To produce a good and qualified I-131 capsule, a preliminary study of the materials and in process products of I-131 capsules was done by determining the maximum volume filling and dissolution time of I-131 capsule. Parameters to be validated for I-131 capsule product in this study were variability of activities, pH, radiochemical purity and stability. From the preliminary study, radioactive concentration of I-131 should be more than 1000 mCi / ml, especially for 100 mCi of I-131 capsule, radioactive concentration should be 2000 mCi/ml. Dissolution test results showed that all of I-131 radioactivity has come out from capsule into the water less than 15 minutes and capsule filling volume less than 100 uL per capsule. Variability activities of each capsule showed the activities were less than 10% of the desired activity for capsule size 30 mCi, 50 mCi and 100 mCi. The pH range of I-131 capsule was obtained between 7.5 – 8.0. Radiochemical purity of I-131 capsule in the form of I^- was more than 95 %, and iodine-131 capsule was still stable for more than 1 month at room temperature. It is concluded that the quality control test for I-131 capsule included the variability of radioactivity, pH and radiochemical purity still meet the established requirement.

Keywords : thyroid, I-131 capsule, radioactive concentration, radiochemical purity, stability

INTRODUCTION

The most common abnormalities that often occur in the thyroid gland are hyperthyroid, hypothyroid and thyroid cancer, but most cases that require serious treatment is a hyperthyroidism. Director of Prevention and Control of Non-Transmitted Diseases Ministry of Health (Kemenkes) Republic of Indonesia, dr. Lily Sriwahyuni Sulistyowati, MM stated that based on IMS Health research results, in 2015 Indonesia ranks as the country with the highest thyroid disorder in Southeast Asia [1-2]. Thyroid disease is often underestimated by the people so it is not immediately handled. In fact, thyroid disorders can affect all individuals at different ages. Impaired thyroid disorders that are not handled quickly and precisely can affect the quality of life and have a serious psychological impact [3]. Common treatments performed on hyperthyroid patients are using anti thyroid drugs, beta blockers, surgery and radioactive iodine therapy. As one effective way of treatment for hyperthyroidism and thyroid cancer, radioactive iodine therapy has been commonly used in hospitals in Indonesia provided with Nuclear Medicine facilities. In recent years, it has become common to administer radioactive I-131 as part of the therapeutic strategies in patients with thyroid carcinoma following the surgical procedure of total or partial thyroidectomy.. Radioisotopes I-131 will be accumulated in the thyroid gland as well as iodine in general so it can be used for diagnosis and treatment [4-10].

Currently , most of the hospital in Indonesia has been used I-131 for abnormality in the thyroid glands in the form of oral solution [11-14]. The use of I-131 oral solution in the treatment of abnormalities in the thyroid gland has some disadvantages such as less accurate doses due to the presence of some remaining I-131 on the vial and also significant risk of the droplets of the spillage I-131 solution from the patients at the time of drinking the solution. Oral administration with capsule form is the best choice because besides the proper dose and also will not cause spillage during therapy. Each I-131 was individually packed in a double capsule, in which the inner capsule was prepared by filling an empty gelatin capsule with anhydrous dibasic sodium phosphate [15-18].

In accordance with the use for therapeutic purposes, the capsule preparation or oral dosage of I-131 must certainly meet the rules as a drug in which case there must be a license from BPOM and Bapeten before its use. Production data and quality control for I-131 capsules are currently not available, whereas the data is required to be certified by BPOM and Bapeten as regulatory bodies. In this research, each capsules of 30 mCi, 50 mCi and 100 mCi I-131 were prepared by injecting I-131 solution into the inner capsules [19-20]. Parameters to be validated for I-131 capsule product in this study were variability of activities, pH, radiochemical purity and stability.

EXPERIMENTAL

Materials

Materials used in this study included TeO_2, NaOH, HCl, Na_2HPO_4 , NaI and MEK obtained from Sigma Aldrich. Salin and water for injection obtained from IPHA. Bulk solution of I-131 produced by PTRR.

Instruments

Instruments used in this study were Gamma Spectrometer (Canberra), Dose Calibrator (Biodex Medical System, Atomlab 300), Gamma Counter(Caprac) , analytical balance, hot plate stirrer and dessicator. Glass equipment for dry destilation system was made by local supplier.

Production of I-131 bulk solution

The process of separation of I-131 radionuclide from TeO_2 in PTRR was carried out by dry distillation method. Tellurium Oxide activated target was heated at 750 ^{0}C for 5 hours and the iodine vapor will be trapped inside the charcoal column. Iodine-131 radionuclide was released from the column using sodium hydroxide (NaOH) solution. Activity of I-131 bulk solution was measured by using Gamma Ionization Chamber (GIC).

Preliminary study of materials and in process control of I-131 capsules production

Determination of the maximum filling volume : into the capsule that has been filled with Na_2HPO_4 was injected I-131 solution using HPLC syringe with variation volume of 25 µL, 50 µL, 75 µL and 100 µL , then the physical form of the capsule was observed. Distribution of I-131 radionuclide in I-131 capsules was determined using autoradiography method.

Dissolution time of I-131 from inner capsule : the radioactive capsule is introduced into the water test solution, then the solution was shaken with 20 rpm, each minute sampling is 100 µL and the radioactivity was measured. Observations were made until the measured radioactivity of the samples was no longer increased.

Variability activities of I-131 capsule

Preparation of I-131 capsule was carried our by filling Na2HPO4 into the capsule, then the capsule is closed and the I-131 solution was injected into the capsule using an HPLC syringe. Variability activity of I-131 capsules was determined using Gamma Ionization Chamber (GIC).

Determination of pH and radiochemical purity test

Measurements of I-131 capsule was performed by dissolving the capsules in aquadest and pH values was measured using pH paper. Radiochemical purity test was done by paper chromatography method using whatman I paper as stationary phase and methanol 75 % as mobile phase. Radioactive distribution on the whatman I paper was measured using gamma counter instrument.

Stability test

Stability test of I-131 capsules has been done. Observations were made on ^{1st}day, ^{5th}day and ^{30th}day after preparation. The results of the observations are more emphasized on the change of the physical form of the capsule.

RESULTS AND DISCUSSION

Production of I-131 bulk solution

The distillation method is commonly used because iodine physically has a boiling point lower than tellurium so it is easily to separated from the tellurium target. Separation of I-131 from TeO2 was carried out at 750 ^{o}C. Iodine-131 which has been separated from the TeO2 phase was absorbed to charcoal column and I-131 eluted from charcoal column with 0.05 N NaOH solution. By using 5 grams of TeO2 target, activity of I-131 obtained was of 500-800 mCi. The results of quality control of I-131 bulk showed the solution pH > 11, radioactive concentration > 100 mCi / ml, radionuclide purity 100% as I-131 and radiochemical purity > 95 % as I^-.

Preliminary study of materials and in process of I-131 capsules production

Determination of the maximum filling volume

The determination of maximum filling volume of capsule was used with number 3 capsule size using volume of 25 uL, 50 uL, 75 uL and 100 uL and this capsule was put inside number 2 capsule. The results of observations in the form of the distribution of radioactivity of I-131 can be seen in Figure 1. From Figure 1, the results of the imaging by autoradiographic methods showed that the spot of I-131activity at volumes 25 µL and 50 µL was not too large and I-131 activity was presented in the center of the capsule whereas at volume of 75 µL and 100 µL the imaging results showed the spread of activity was fulfilled on the whole volume of capsule. However, the used of a second capsule to cover the first capsule will protect from the damage of the I-131 capsule.

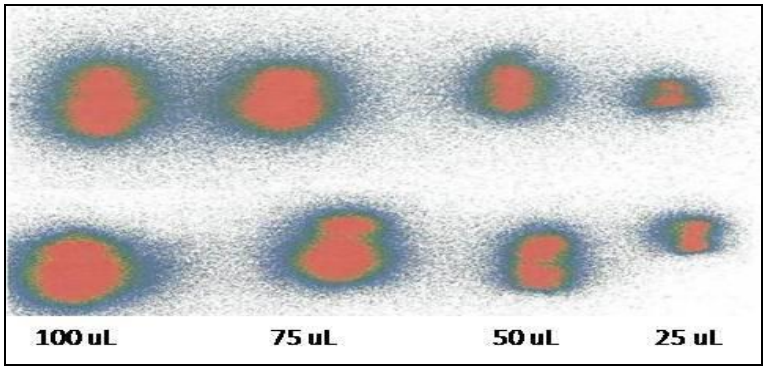

Fig 1. Distribution of I-131 activity inside capsule measured by Autoradiography method

Table 1 shows the relationship between the radioactive concentration of I-131 solution and the volume of the capsule filling. Based on distribution activity experiments of I-131 (Figure 1), the most ideal I-131 volume injected into capsule should be less than 50 uL. The ideal radioactive concentration of I-131 solution was 2000 mCi/ml, where as for100 mCi it required only 50 uL I-131 solution to be injected into the capsule.

Table 1. Relation between radioactive concentration I-131 and volume of capsule filling

No.	Radioactive concentration (mCi/ml)	Capsule size (mCi)	Volume (uL)
1	1000	30 50 100	30 50 100
2	1500	30 50 100	20 33 67
2	2000	30 50 100	15 25 50

Dissolution time of I-131

Capsule dissolution testing was performed to see how many times for all of I-131radioisotope to release from the capsule. Dissolution profiles of I-131 capsules are illustrated in Figure 2 showed that after 5 minutes, radioactivity counts of I-131 contained in the solution already stable, it means that all of I-131 activity has got out from the capsule. The time required to remove all of I-131 activity from the capsule is 5 minutes. The data should not be extrapolated into clinical situations without further studies. Studies are needed to establish the dissolution profiles of capsules in simulated gastric fluid and the relationship between dissolution profiles and ***in vivo*** thyroidal uptake of ^{131}I.

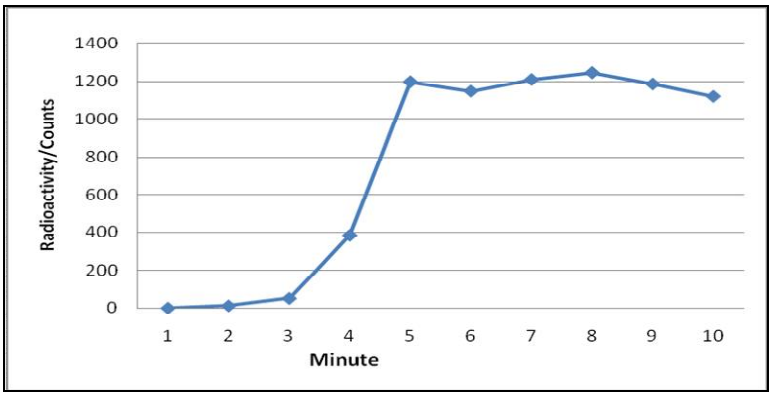

Fig 2. Dissolution test of I-131 capsule

Variability activities of I-131 capsule

Before the I-131 solution is injected into the capsule, the radioactivity concentration is first determined so that the volume of capsule filling can be calculated. From Table 1, the ideal radioactive concentration of I-131 solution is 2000 mCi/ml, so, for 100 mCi I-131 capsule only 50 uL bulk solution of I-131 radioisotope to be injected to the capsule. In this experiments, we used 2 capsule size i.e. No.3 and No.2. The capsule filling procedure with the I-131 solution was carried out as follows, in the first step capsule was filled with Na_2HPO_4, closed and then the I-131 solution was injected into the capsule using an HPLC syringe and in the second step the I-131 first capsule was inserted into the second capsules.

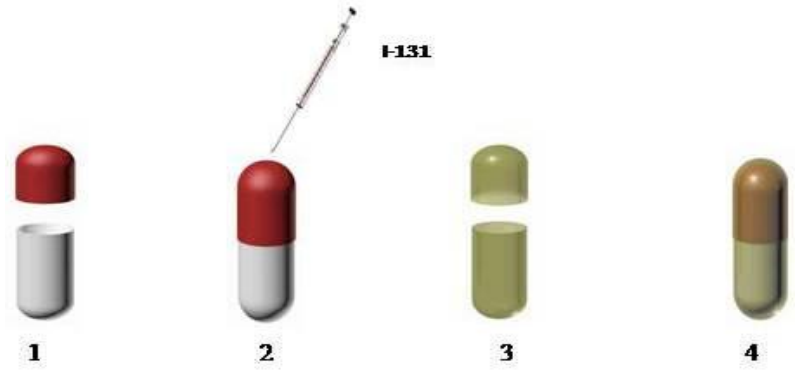

Fig 3. Preparation of I-131 capsules

Variability test of I-131 capsules was performed using 4 capsules I-131 for each 30 mCi, 50 mCi and 100 mCi respectively. The results of variability test can be seen in Figure 4, variability activities for all capsule size (30 mCi, 50 mCi and 100 mCi) still meets pharmacopoeia requirement that is less than10%.

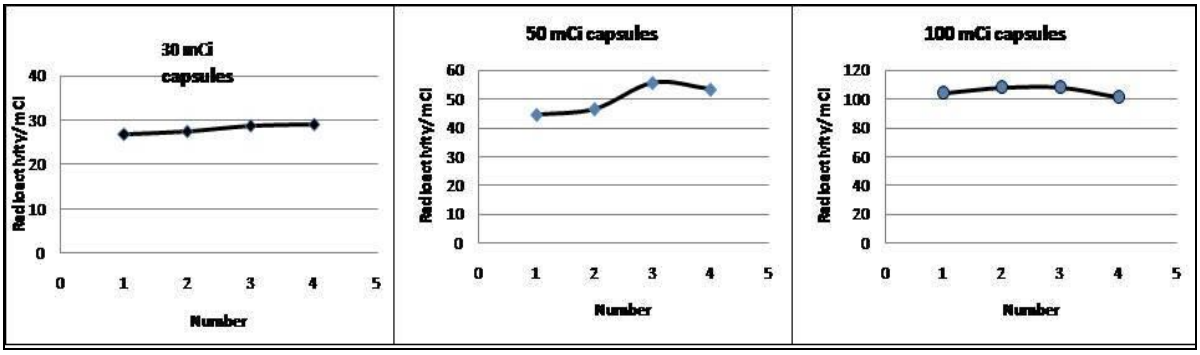

Fig 4. Variability test results using 30 mCi, 50 mCi and 100 mCi I-131 capsules

pH and Radiochemical Purity

Measurement of pH of the I-131 capsule solution was done by using short-range pH paper. The information was shown in Table 2 indicated that the range of pH value (pH 7.5 – 8.0) meets to the specified requirements. Radiochemical purity test in Table 2 indicated that radiochemical purity all the capsules were more than 95 % in the form of iodide ion (I^-).

Table 2. pH value and radiochemical purity of I-131 capsules

No.	Capsul size (mCi)	pH	Radiochemical purity (%)	Spesification
1	30	8.0 8.0 7.5 7.5	97.6 97.6 96.2 96.2	pH = 7.0 – 9.0 Radiochemical purity > 95 %
2	50	7.5 7.5 7.5 7.5	96.0 96.0 95.2 95.2	
3	100	8.0 8.0 8.0 8.0	98.8 98.8 99.5 99.5	

Stability

Stability of I-131 capsules as indicated in Figure 5 showed that up to 30 days after preparation, the outside of the capsule is still in good condition and there is no damage on the outer of the capsule. It means I-131 capsule was stable up to 30 days .

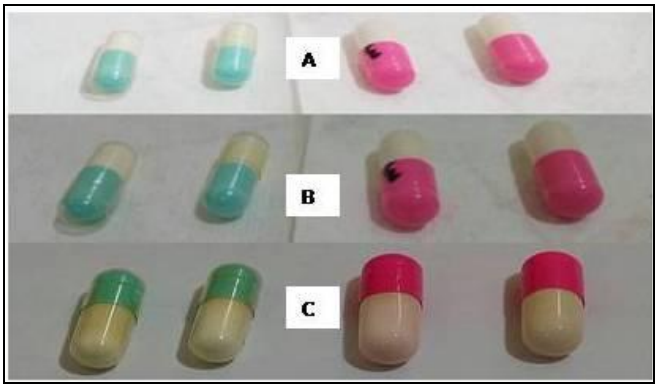

Figure 5. Stability test of I-131 capsules 1day (A), 5 days (B) and 30 days (C) after preparation

CONCLUSION

The ideal amount of I-131 solution to be injected into the capsule should be no more than 50 microliters for capsule No. 3. Dissolution test method using water as a medium indicated that I-131 radioisotope in double capsule released from the capsule within ~ 5 minutes. All of the quality control test for I-131 capsule included the variability of radioactivity, pH and radiochemical purity still meet the established requirements.

ACKNOWLEDGMENT

Authors express thanks to Director of Center for Radioisotope and Radiopharmaceuticals Technology for permission to publish this work, and PT Kimia Farma is also thanked for the cooperation in this work.

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