Quality by Design Approach to Improve Process Related Impurities and Stability of Iobenguane(^{131}I) injection

Yumi Jung[*], Eun-ha Cho, Young-wook Park, Ki-hwan Park, Yoo-hwang Lee, Tae-hoon Lee, Jae-won Lee, Hyukmin Kim

Radioisotope Research Division, Korea Atomic Energy Research Institute, Daejeon, Korea
[*]*Corresponding author: jym0731@kaeri.re.kr*

***Keywords : radiopharmaceutical, QbD, Quality by Design, radiochemical purity**

1. Introduction

Until recently, quality control of drugs was based on the concept of quality by test, which ensures the quality of drugs by testing in-process or final products. Tne U.S. FDA proposed the application of QbD(Quality by Design) to the pharmaceutical industry in 2002, and QbD is a method of ensuring quality through systematic management by setting quality goals in advance from the development stage of a drug product.[1][2]

Iobenguane (^{131}I) injection is made by radiolabeling 3-iodobenzylguanidine(mIBG) to replace the stable isotope ^{127}I with the radioactive isotope ^{131}I. Unreacted radiochemicals such as [^{131}I]iodide can interfere with the stability of the drug and cause side effects in patients, so the purification process to remove them is controlled as an important process in drug manufacturing.

In the Korean Pharmacopoeia, radiochemical impurities in Iobenguane (^{131}I) injection are allowed to be no more than 5% of the total radioactivity.

The purpose of this study is to analyze the impact of process improvements on the process related impurities derived from the Critical Quality Attribute (CQA) by performing a risk assessment during the stepwise application of Quality by Design (QbD) for Iobenguane (**^{131}I**) injection.

2. Material and Method

The risk assessment of Iobenguane(^{131}I) injection evaluated the RRF(risk ranking and filtering) for Impact Score, Uncertainty Score, and Risk Score(Criticality) for Efficacy, PK(Pharmacokinetics), and Safety evaluation items. Risk Score was calculated by multiplying the Impact Score and Uncertainty Score. The maximum value of each items RPN(Risk Priority Number) was 20 points.

Table 1. Risk Assessment with RRF of Iobenguane(^{131}I) injection

Category of Attribute		Impact Score	Uncertainty Score	Risk Score	RPN
impurities	Efficacy	20	1	20	20
	PK	20	1	20	
	Safety	20	1	20	

In the manufacturing process of Iobenguane(^{131}I) injection, Sephadex was used to remove 131-Iodide present in the Iobenguane(^{131}I) solution.

The previous method required operators to manually mix the drug solution with Sephadex, collecting only the supernatant and passing it through a sterile filtration filter. The new process utilizes a kit with a filter inside a Empty PP Rev Tube, which allows the drug solution to flow evenly into the Sephadex solution. (Hereafter, we will refer to this method as the KIT method). The solution is then continuously passed through a sterile filtration filter and collected in sterile vials.

Fig. 1. KIT method device

Iobenguane(^{131}I) injection samples purified by each method were stored below -20℃, the storage temperature of the finished product. The samples were then subjected to the same thawing process as the finished product for each test date, and the radiochemical impurities was measured using a radioisotope TLC scanner up to day 7.

3. Results

Iobenguane (^{131}I) injection manufactured by KAERI is licensed with an expiration date of 3 days from the date of manufacture and a radiochemical impurities value of 5% or less.

In the purification method utilizing the existing method, the radiochemical impurities was confirmed to be more than 5% of the total radioactivity after 3 days from the date of manufacture, which did not meet the radiochemical purity of 95% or more.

We conducted process-validation (KIT method) according to the validation principles prescribed by the Pharmaceutical Affairs Act, and the new purification method utilizing the 'KIT method' showed stable radiochemical impurity values for 7 days in 5 batches. (Table. 2.).

Table 2. Radiochemical impurities(%) over time from date of manufacture

KIT method	Day 0	Day 1	Day 3	Day 7
Batch 1	2.13	2.56	3.39	4.84
Batch 2	1.97	4.26	4.36	4.91
Batch 3	3.23	3.76	4.02	4.58
Batch 4	2.30	3.00	3.26	4.16
Batch 5	1.65	2.05	2.66	3.06

4. Conclusions

In this study, we analyzed the stability period of radiochemical purity of Iobenguane (^{131}I) injection due to differences in purification process. In the operator-operated purification method, free iodide generated during the uneven purification process is thought to impair the stability of the drug.

In the purification process utilizing the "KIT method", the drug solution was uniformly contacted with Sephadex, and the free iodide was efficiently removed.

The results of this study are expected to be used to extend the expiration date of Iobenguane (^{131}I) injection manufactured by KAERI. In addition, "KIT method" will be applied to the automatic synthesis and dispensing system of Iobenguane (^{131}I) injection to improve the purity of radiopharmaceuticals and reduce radiation exposure to workers.

REFERENCES

[1] International Conference of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Pharmaceutical Development Q8

[2] Quality Audit Guide to Prepare for the Introduction of Quality by Design (Qb D)_KFDA_2018.11.