DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(9), 1465-1472 (1990)

THE DETERMINATION OF WATER IN FREEZE DRIED PHARMACEUTICAL PRODUCTS BY PERFORMING THE KARL FISCHER TITRATION IN THE GLASS CONTAINER ITSELF

J.P.H. Wekx and J.P. de Kleijn
Organon International BV
Quality Assurance
P.O. Box 20, 5340 BH OSS, The Netherlands

Abstract. A micro device is described by which it is possible to perform the Karl Fischer titration in the ampoule or vial containing a freeze dried pharmaceutical product. Using this device, it is not necessary to transfer the product from the original container into another vessel which means less manipulations to be performed and a lower risk to changes in moisture content during the analytical procedure.

INTRODUCTION

The residue of water present in a freeze dried pharmaceutical product may be of critical importance in view of the stability of the product.
This forces the pharmaceutical manufacturer a) to minimize the amount of residual water by a well-tuned freeze drying process, b) to avoid re-entry of water before the ampoule or vial is closed, and c) to determine the amount of water in the finished product.
The determination of water is achieved, in most cases, by a titration according to Karl Fischer[1,2].
Also gas chromatography offers a way to estimate the water content of a lyophilized product[3].
Both approaches have certain disadvantages: a KF-titration requires the transfer of the sample material from the container into a reaction vessel which introduces uncertainty about the initial water content and a GC-analysis needs more sophisticated equipment and may be time consuming.
So there is a need for a rapid determination of water in the original container itself. This technical note describes the construction of a micro-device which allows a KF-titration to be performed in individual ampoules or vials.

EXPERIMENTAL

Figures 1 and 2 outline the principle of the instrument. Two Pt-electrodes, stirring threads and a dispensing tube for the Karl Fischer reagent, respectivily, are combined into one device with a diameter of 4 mm.

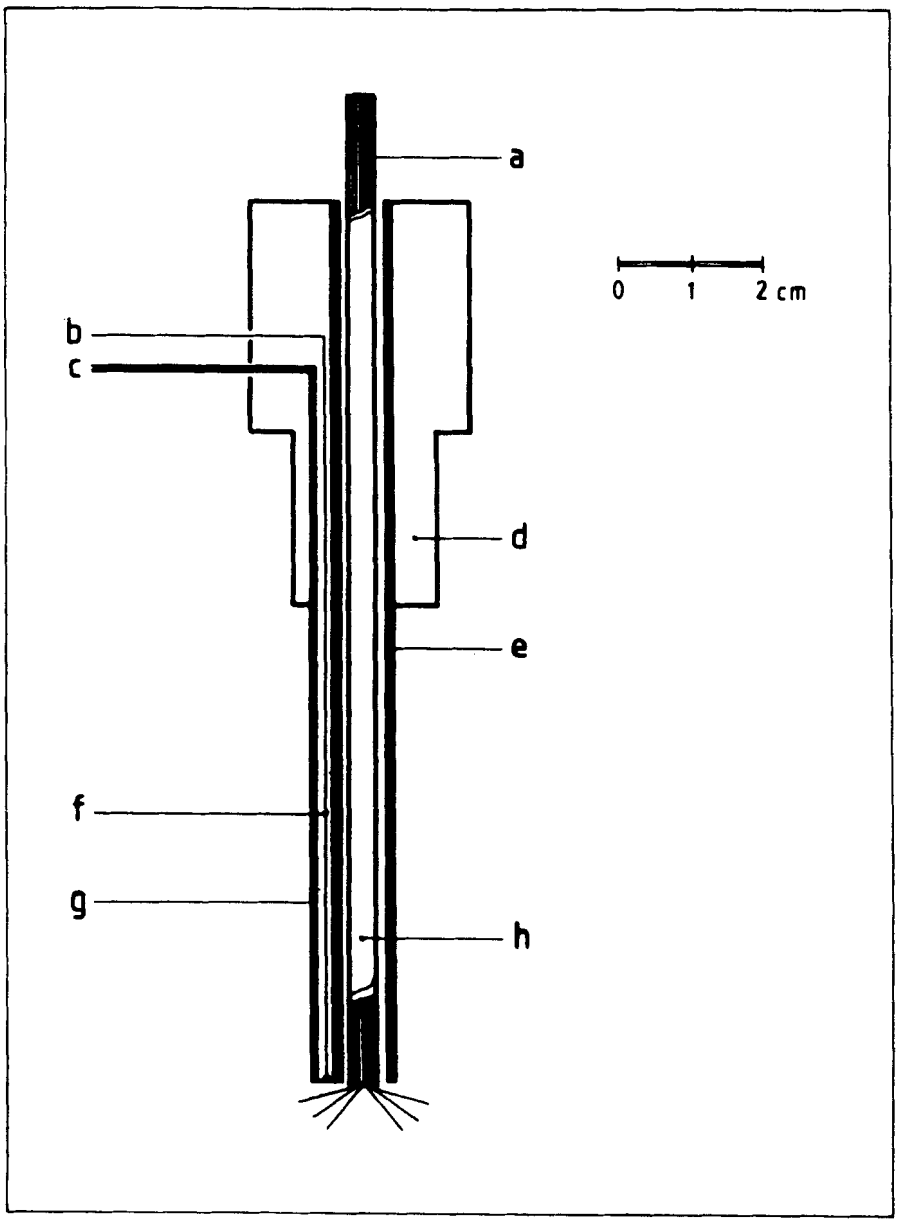

Figure 1

Cross section of the combined device

a) connection bundle of threads - stirring motor

b) connection electrodes - electrometer

c) connection dispensing tube - burette

d) teflon block

e) metal tube

f) Pt-electrodes

g) dispensing tube

h) bundled stirring threads

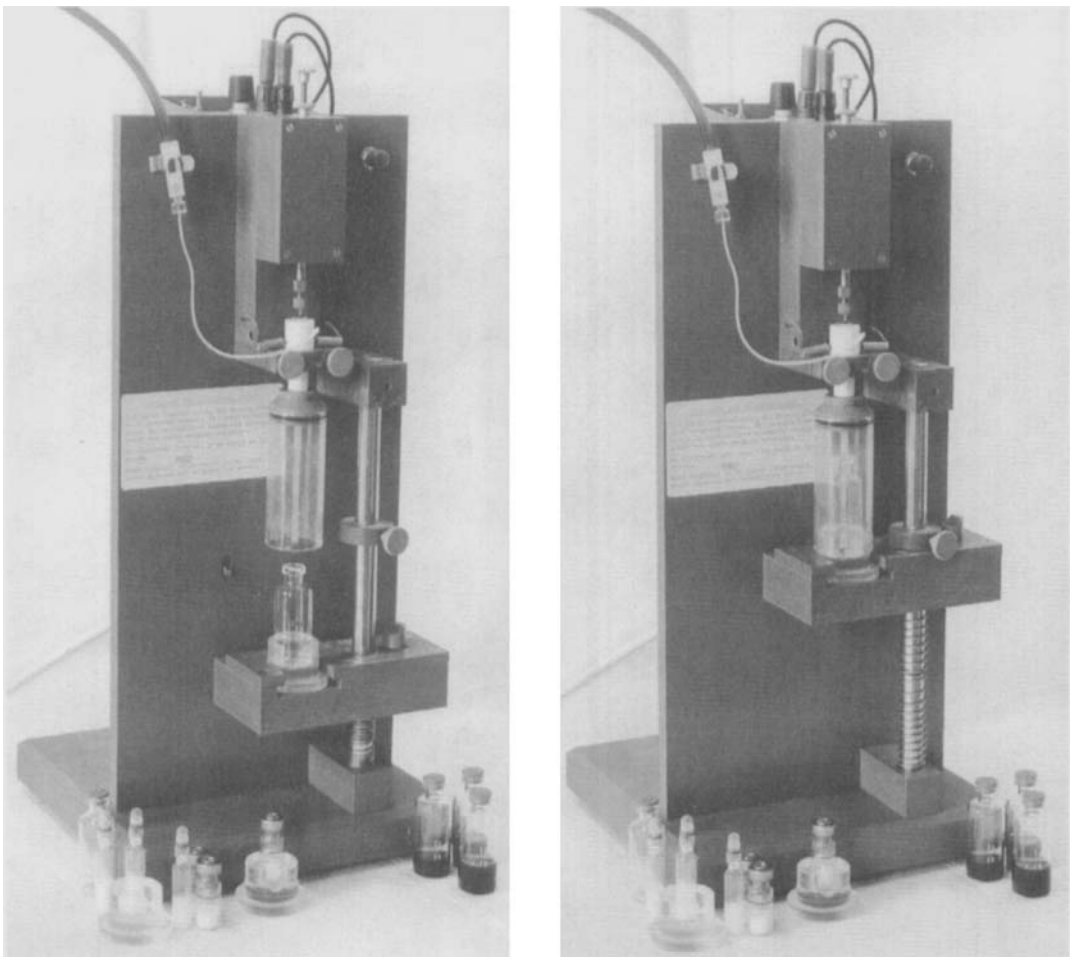

Figure 2

Picture of the titration set-up

a) ampoule in lowered position

b) ampoule in raised position shielded by a transparent tube; the micro device is in the ampoule

The threads are connected with a stirring motor (low voltage DC motor with adjustable speed) and the Pt-electrodes are connected with a suitable KF-titrator (e.g a Mettler Memotitrator DL40RC or equivalent). Hydranal® (Riedel-de Haën) is used as titrant, diluted to a water equivalent of 0,5 - 1 mg water/ml.

The stirring threads are made from polyamid fishing line, O 0,25 mm. Four to six pieces of thread are held together with teflon tube and poured through a teflon coated metal tube, with an internal diameter of 1,3 mm.

The bundle of threads reaches out from one side of the metal tube for about 3 mm and from the other side for about 12 mm.

The short ends serve as stirring blades and the longer ends are connected to the stirring motor.

This device is the essential part of the instrument.

Alongside the tube, the two Pt-electrodes and one teflon capillary tube are fixed by the application of shrinking tube.

The upper end of the metal tube is mounted in a teflon block which enables the fixing of the stirring threads with the stirring motor and also the connection of the electrodes and tubes with the external instruments involved. The teflon tube is connected with the burette of the KF-titrator. The ampoule or vial to be analysed and the device described here are shielded against atmospheric moisture with a transparent tube.

Figures 1 and 2 show more about the set up.

TABLE 1

Accuracy of Results Obtained by Various Methods to Determine the Amount of Water in Freeze Dried Pharmaceuticals

product	KF-titration in the ampoule itself	gaschrom.	coulometric KF reaction	statistical test
A	66 µg (n = 15)	69 µg (n = 15)		no sign. difference
B	410 µg (n = 10)		390 µg (n = 18)	no sign. difference

A = protein containing product
B = steroidal product

PROCEDURE

The ampoule or vial to be analysed is opened and immediately placed on a plateau which is raised to a position at which the stirrer threads reach 2-3 mm from the bottom of the container. Then the titration program on the KF-titrator as well as the stirring motor are started.
After finishing the titration, the ampoule or vial is removed and the next titration may be started.

RESULTS AND DISCUSSION

Results of measurements performed on a series of ampoules or vials from one production batch show a variation which is the combined effect of both the

production and the analysis. So, in order to establish the precision of the method, 2 ml vials were filled exactly 2 µl of water and subsequently analyzed.
This procedure yielded a RSD of 2%.

Table 1 gives some figures obtained by the device described here and, as an alternative, by gaschromatography and a coulometric Karl Fischer method, respectively.

Amounts of water as low as 50 µg per individual container can be determined reproducibly and reliably.
This detection limit is related with the quantity of titrant necessary to make contact between the two Pt-electrodes.
(For low concentrations of water, two extra teflon capillary tubes are fixed alongside the tube. One for adding some water-free solvent and one for blowing dry nitrogen onto the sample solution. With this design the detection limit of the titration may be reduced to 10 µg).

On the average, it takes 30 minutes for a technician to analyse 10 samples including the opening manipulations.
It is concluded that the device which allows the Karl Fischer titration to be performed in the container of a freeze dried pharmaceutical itself, has been proved to be a valuable aid in the QC laboratory.

ACKNOWLEDGEMENT

Messrs. C.G. van Herpen and J.A.E. van Heukelom are gratefully acknowledged for the initial idea and the development of the device. The skilful help of our Electronic and Fine Mechanical Shop was indispensable.

REFERENCES

1. K.A. Connors, Drug Dev. Ind. Pharm. 14, 1891 (1988).
2. E. Scholz, "Karl Fischer Titration", Springer-Verlag, Berlin Heidelberg, 1984.
3. Gas-Solid Chromatographic Determination of Moisture in Lyophilized Pharmaceutical Products. G.W. Lyman and R.N. Johnson, J. Assoc. Off. Anal. Chem. 62, 71 (1979).