

# Determination of Moisture Content of Lactose by Neutron Thermalization

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A procedure has been developed for the determination of moisture in an organic material by the thermalization of neutrons. The method developed utilized commercially available equipment designed for depth moisture determinations of soils. The moisture content of three series (replications) of water in lactose U.S.P. was determined at various concentration levels by the neutron method and by two official methods (gravimetric and Karl Fischer titration). The number of thermal neutrons produced at the various moisture concentrations prepared were plotted against the corresponding moisture content indicated by each of the two official moisture determination methods. Regression curves were prepared using least squares calculations. With *t* tests it was shown that the means of the slopes of the three series were estimates of the true slope of the regression curves, and 0.95 confidence limits were also set on the slopes. The applicability of this new method of determining the moisture content of pharmaceutical systems is discussed.

IN THE PREPARATION and evaluation of pharmaceutical products numerous methods of analysis are used to control the quality of the finished product. The control procedures for pharmaceutical products include in-process controls as well as the final release of the products for patient consumption. A determination which is critical in pharmaceutical processing of solids is the determination of moisture content. This determination usually requires the removal of a representative sample from a large mass of material with one of the official methods of the U.S.P. being used to determine the moisture content (1). A method has been developed for the sampling of large volumes of soil *in situ* (2-4), using a probe containing a radioactive source. The method determines both bound and unbound water. The purpose of this study was to evaluate this method with commercially available equipment for possible pharmaceutical applications in systems containing organic compounds. Since the proposed method is based on the thermalization of fast neutrons by the hydrogen atoms of water, it was necessary to investigate the ability of the nuclear system to measure the change in hydrogen atom content due to added water in the presence of large amounts of hydrogen atoms present in organic medicinals.

The moisture measurements by this nuclear method depend on the moderation of fast neutrons by the hydrogen atoms of water producing slow or thermal neutrons which are detectable by a boron trifluoride detector (2). The number of slow neutrons resulting from the moderation is directly proportional to the number of hydrogen atoms in the sample. Since the density of

the material being studied would determine the amount of hydrogen atoms observed by the neutron source per unit volume, it is necessary to observe the relative density. The amount of absorption and backscattering of gamma rays by the outer electrons of the atoms in a given sample is a measure of the material's density (2). The amount of backscattering is inversely proportional to the density. In this study the gamma source was used only to observe any large changes in sample density.

## EXPERIMENTAL

Since lactose is commonly used as a diluent and filler in many solid pharmaceutical preparations, it was chosen to represent organic substances commonly encountered in the manufacture of medicinals. Because of the sphere of influence of the neutron source used in this study, which was 12 in. in water, it was necessary to work with a 40 Kg. sample. Figure 1 illustrates the system used for the moisture determination procedure. The samples were evaluated in a standard container 35 cm. in diameter and 66 cm. deep. Supports were placed inside the drum to hold an access tube required to permit the insertion of the depth moisture and density probes. The supports also served to insure reproducible geometry of the system. The size of the container was within the limits suggested by previous work with sand, earth, and cement (5). The nuclear equipment used in this study was obtained from the Nuclear-Chicago Corp., Des Plaines, Ill. It consisted of their model P 19 depth moisture probe, model P 20 depth density probe, and model 2800 portable scaler.

The moisture probe is 15 in. in length and 1½ in.

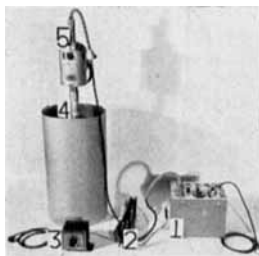


Fig. 1.—Moisture gauging equipment and sample container. Key: 1, scaler; 2, graduated cable; 3, attached external timer; 4, sample container and access tube; and 5, neutron probe inside paraffin shield.

Received June 3, 1963, from the School of Pharmacy, Purdue University, Lafayette, Ind.

Accepted for publication August 12, 1963.

Presented to the Scientific Section, A.P.H.A., Miami Beach meeting, May 1963.

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TABLE I.—CALIBRATION DATA FOR THE MOISTURE DETERMINATION OF LACTOSE, SERIES 3

Sample	Moisture Content Method 1 <sup>a</sup>	Moisture Content Method 2 <sup>b</sup>	Neutron Count, c.p.m.	Gamma Count, c.p.m.
1	5.0734	0.10	10,381.25	22,048.20
2	5.4479	0.48	10,616.25	22,310.15
3	6.0835	1.10	10,635.50	22,356.15
4	6.4655	1.70	10,761.25	22,256.55
5	6.7794	2.30	10,569.50	22,373.80
6	8.0475	3.10	11,026.75	22,660.90
7	8.5398	4.00	11,610.60	22,563.55
8	9.3001	4.90	11,987.05	22,443.35
9	10.4767	5.35	11,837.70	22,379.00
10	11.0067	5.70	12,503.80	22,423.70
11	11.4877	6.70	12,923.95	22,401.60
12	11.9584	6.90	12,928.65	22,418.60
13	12.1929	7.60	12,722.45	22,539.30
14	12.5308	8.70	13,318.05	22,297.95
15	12.7883	8.80	13,239.75	22,374.00

<sup>a</sup> Karl Fischer titration, in per cent. <sup>b</sup> Moisture balance method, in per cent. <sup>c</sup> Average of five 4-minute counts.

in diameter. The probe consists of the neutron source (radium-beryllium), detector, and preamplifier. The neutron output of the source was  $6.78 \times 10^4$  neutrons per second. A boron trifluoride slow neutron detector is used in the probe. The probe is connected to the scaler with a cable which is graduated every 2 in. When not in use, the probe is stored in a paraffin shield. The density probe consisted of a gamma source (2.83 mc. of cesium-137), detector (three G. M. tubes), and a preamplifier. It was also connected to the scaler with a graduated cable. The portable scaler supplied has a built-in timing device; this timer was not accurate enough for this study. A Liebil-Flarshlein, model 42 motor driven time switch was connected to the leads to the built-in timer. The scaler was operated in the A-C position.

**Moisture Determination Procedure.**—Certain preliminary observations were necessary before the final procedure was established. To insure that the system was operating properly, the moisture probe was inserted into a 20 gal. tank (16 in. in diameter and 18 in. deep) containing water. This water sample was used to study the effect of the height of the probe in the sample and to check the system before measuring lactose samples. In water the probe was operated at a height 4 in. from the bottom of the water container and 6 in. from the bottom of the sample container for the lactose. These heights gave the maximum readings for the respective samples. To check the reproducibility of the neutron count rate, the sample container was filled with lactose and counts were taken at the 6-in. level on 3 successive days. On each occasion the neutron probe was inserted to the appropriate level, counts taken, and the probe removed. Similar measurements were made in water. For the density measurements the position of the probe in the sample was at a height 4 in. from the bottom. All measurements were within the normal counting error of the respective systems.

**Standard Curve Preparation.**—The lactose used in this study was powdered by passage through a No. 60 mesh screen using the Fitzpatrick comminutor, model M,<sup>1</sup> with the hammers forward. The material was placed in the sample container and

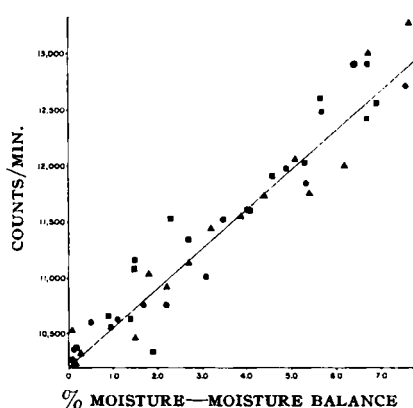


Fig. 2.—Standard curve for the moisture determination of lactose: neutron counts vs. moisture balance. Key: ■, Series 1; ▲, Series 2; and ●, Series 3.

nuclear measurements were taken. After removal of the lactose from the sample container, it was divided into two batches of 20 Kg. each. Distilled water was added to each batch and mixed using a Stokes 21 AA mixer<sup>2</sup> for 20 minutes. The batches were combined and passed through a suitable screen (No. 12 to No. 4 depending upon the amount of moisture added) using the Stokes oscillating granulator, model 43 A.<sup>2</sup> This was done to insure further complete distribution of the added water within the lactose. The moistened samples were stored in a single plastic bag for 24 hours before measurements were made with the probes. At low moisture contents this storage period was very important—to be certain that the added water was in equilibrium throughout the lactose sample. The following stepwise procedure was used for preparation and observation of the samples:

The lactose was added to the standard container by carefully scooping to avoid the entrapment of large voids within the container.

A 2-oz. composite sample was removed during the filling of the sample container for moisture determination by the Karl Fischer method and the moisture balance method.

The container was then shaken by hand to remove void spaces in the large sample volume.

The density probe was checked in its shield against the standard source (five 4-minute counts taken) after a 30 minute warm-up time and was then inserted into the sample *via* the access tube.

Five 4-minute counts were taken with the probe 4 in. from the bottom of the container.

The moisture probe was connected to the scaler, and the system warmed up for 30 minutes.

Five 4-minute counts were taken in the water tank with the probe inside an access tube and 4 in. from the bottom.

The probe was then placed in the sample container filled with the lactose, and five 4-minute counts were taken. After the density readings were taken, the density was adjusted by further shaking of the sample container to bring the density value close to a previous sample.

## RESULTS AND ANALYSIS

To state that it is possible to determine the moisture content of an organic substance such as lactose,

<sup>1</sup> W. J. Fitzpatrick Co., Chicago, Ill.

F. J. Stokes Corp., Philadelphia, Pa.

TABLE II.—EVALUATION OF MOISTURE CALIBRATION DATA FOR LACTOSE

Series	$\sigma_x^a$	$b^b$	$t$ test <sup>c</sup>	Slope <sup>d</sup>	Limits <sup>e</sup> on Slopes
Karl Fischer Method					
1	2.0988	309.265	0.02618	397.361	$\pm 85.2297$
2	2.1506	203.741	0.52519	409.175	$\pm 52.8375$
3	2.5086	232.545	-0.57986	382.449	$\pm 51.6993$
Moisture Balance Method					
1	2.2669	348.818	-0.0145	360.693	$\pm 95.2322$
2	2.3875	276.665	0.1278	365.156	$\pm 64.6296$
3	2.8388	235.585	-0.0911	359.047	$\pm 46.2847$

<sup>a</sup> Standard deviation of  $X$  (moisture content). <sup>b</sup> Standard error of estimate for the universe. <sup>c</sup> Critical region for  $t$  test:  $\pm 2.160$  for  $\alpha = 0.05$  and  $n - 2$  degrees of freedom. <sup>d</sup> Slope in c.p.m. per 1.0% water content. <sup>e</sup> 0.95 confidence limits for slopes:  $b \pm t_{0.975} s/\sigma_x \sqrt{N}$ .

utilizing the principle of neutron thermalization, it must first be shown that a useful calibration curve can be prepared. Lactose contains sufficient hydrogen atoms ( $C_{12}H_{22}O_{11} \cdot H_2O$ ) to produce a significant slow neutron count by itself when dry. In this study lactose was moistened with water and the change in slow neutron count was observed at the various moisture levels. Three series (replications) of the measurements were made. An example of the data collected in this study is given in Table I. The samples used to determine the moisture content by the Karl Fischer titration and the moisture balance were taken from the same composite samples of each series. Figure 2 is a plot of the slow neutron count for each sample *versus* the per cent moisture content obtained using the moisture balance. The equations for each series as determined by least squares calculations are

$$\begin{aligned} \text{Series 1} & Y = 10,192.595 + 360.693 X \\ \text{Series 2} & Y = 10,169.221 + 365.156 X \\ \text{Series 3} & Y = 10,190.250 + 359.047 X \end{aligned}$$

Because of the closeness of these values, it is impossible to show more than one regression curve for the data found in Fig. 2. This would indicate that the total reproducibility of this calibration method is satisfactory. A hypothesis was proposed to test the calculated slopes against the mean of these slopes. To test the hypothesis that each slope was either equal or unequal to the mean slope the following equations were used (6):

Standard deviation of  $X$

$$\sigma_x = \frac{\sqrt{n \sum X^2 - (\sum X)^2}}{n} \quad (\text{Eq. 1})$$

Standard error estimate for the universe

$$s_{yx} = \sqrt{\frac{Y^2 - a \sum Y - b \sum XY}{n - 2}} \quad (\text{Eq. 2})$$

Hypothesis test for the slope

$$t_{n-2} = \frac{b - b_{\text{mean}}}{\frac{s_{yx}}{\sigma_x \sqrt{n}}} \quad (\text{Eq. 3})$$

Table II is a summary of the results of the calculations. The  $t$  test used in this study was based on a 0.95 confidence level and  $n - 2$  degrees of freedom. From these data it may be stated that the hypothesis cannot be rejected and that the slopes are equal, since all calculated  $t$  test values fall within the critical region. Therefore, when the moisture content was determined by the moisture balance method,

each change of 1% moisture content was represented by an average change in slow neutron count of 361 c.p.m. as indicated by the calculated average slope.

Figure 3 represents another expression of the data from the three series of measurements, with the neutron counts being the same as the above, but the moisture content having been determined by Karl Fischer titration. The equations for the regression curves were also determined by the least squares method and are

$$\begin{aligned} \text{Series 1} & Y = 7,908.187 - 397.361 X \\ \text{Series 2} & Y = 8,169.249 - 409.175 X \\ \text{Series 3} & Y = 8,281.084 - 382.449 X \end{aligned}$$

Table II illustrates the results from the same  $t$  test used for the moisture balance method. Again, for the three series of measurements the hypothesis that the slopes were equal to the mean slope could be accepted. Therefore, it may be stated that when the moisture content was determined by the Karl Fischer titrations, each change of 1% moisture content was represented by an average change in slow neutron count of 396 c.p.m. as indicated by the calculated average slope.

It is possible to set confidence limits on the calculated slopes using the following equation (6)

$$b'_{yx} = b_{yx} \pm (t, 2 \text{ tails} =) \frac{s_{yx}}{\sigma_x \sqrt{n}} \quad (\text{Eq. 4})$$

Table II shows the calculated 0.95 confidence limits with  $n - 2$  of freedom. All the slopes fall within

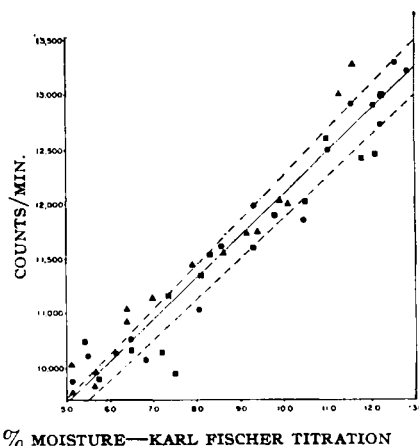


Fig. 3.—Standard curve for the moisture determination of lactose: neutron counts *vs.* Karl Fischer titration. Key: ■, Series 1 - - - - -; ▲, Series 2 - - - - -; ●, Series 3 ———.

the limits, regardless of which slope is used to set these limits. This would indicate that any of the slopes of the regression curves are good estimates of the true slope,  $b'$ .

Table I includes the scattered gamma readings taken with the depth density probe. These measurements were made to observe and control, if necessary, the density within a given series of measurements. An attempt was made to correct for apparent differences in density within a series and from one series to the other; but when the corrections were applied, no improvements in the calibration curves resulted.

## DISCUSSION

The neutron thermalization method of determining moisture in organic materials has two limitations that should be mentioned. First, the system used in this study requires a rather large sample. This is because the sphere of influence of the neutron probe is large, being 12 in. in water. Lactose, with its large number of hydrogen atoms per molecule, has a sphere of influence for the neutron source close to the value for pure water. If the sample size is inadequate, the neutron source will sample material outside the sample container. The sample size required for lactose was about 40 Kg.

The second principal limitation of this method is the complexity of achieving a satisfactory standard curve for the substance under study. A degree of scattering of the points of the calibration curves may be expected, requiring that a larger number of points be determined for the standard curves required for each compound or mixture. Some of the sources of error that may contribute to the scattering of the points are (a) a nonuniform incorporation of the added water, (b) variations in sample packing, (c) the normal slow neutron detection error which is about 1%, (d) the error in the determination of moisture content by the moisture balance or the Karl Fischer titration, and (e) any slight variation in geometry of the probe within the sample.

These errors may or may not be additive. However, with a sufficient number of samples at various moisture concentrations, a suitable calibration curve can be obtained which is reproducible.

The advantages of the neutron thermalization method for moisture determination are: (a) nondestructive testing of the test sample, (b) adaptability to continuous and automated programs, (c) elimination of the removal of small composite samples from large volumes of material with a concomitant reduction in sampling problems and sample error, and (d) the measurement of a system for an acceptable or unacceptable moisture level.

In certain pharmaceutical systems the neutron probe could be used simply to indicate an acceptable or unacceptable moisture concentration and would not require a complete calibration curve for various materials. The elimination of the need of removal of a composite sample from a quantity of material would be time saving as well as more accurate.

The increase in accuracy of the moisture determination would be because the neutron probe analyzes a much larger sample because of its large sphere of influence. Most conventional methods analyze a small sample.

Two special areas of application are proposed. First, incoming bulk chemicals could be analyzed quickly and easily for moisture content by simply inserting an access tube, lowering the neutron probe, and measuring the slow neutron count rate. This would require only a simple calibration over a rather narrow range. Second, the use of the neutron probe for in-process control could enjoy wide application. For example, it would be possible to mount the probe inside the shaft of a large dough mixer or on one of the walls of the mixer. The neutron source could be then exposed at desired intervals to determine the extent of moistening taking place. This system could be calibrated for water or for other hydrogen containing moistening agents.

## CONCLUSIONS

1. It was possible to prepare a calibration curve for the determination of moisture content of lactose by neutron thermalization using commercially available equipment.

2. The calibration curves for the moisture determination of lactose were prepared by plotting the slow neutron count *versus* the moisture determined by the moisture balance and by Karl Fischer titration. The best reproducibility was obtained using the neutron count *versus* the moisture balance for evaluation. However, acceptable reproducibility was obtained when the calibration curves were based on the Karl Fischer titrations.

3. A hypothesis test that the individual slopes (replications) were equal to the mean slope resulted in an acceptance of the hypothesis for the calibration curves based on the moisture balance method or the Karl Fischer titration.

4. In either case it was possible to set 0.95 confidence limits on the slopes.

5. For the series in which the moisture content was determined by the moisture balance a change of 1% moisture content was on the average indicated by a change in neutron count of 361 c.p.m.

6. For the series in which the moisture content was determined by the Karl Fischer method a change of 1% moisture content was on the average indicated by a change in neutron count of 396 c.p.m.

## REFERENCES

- (1) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, pp. 925, 939-941.
- (2) Kuranz, J. L., *Am. Soc. Testing Mater., Spec. Tech. Publ.*, (No. 268), 40-44(1960).
- (3) Underwood, N., Van Bavel, C., and Swanson, R. W., *Soil Sci.*, **77**, 339(1954).
- (4) Stone, J. F., Kirkham, D., and Read, A. A., *Soil Sci. Soc. Am. Proc.*, **19**, 419(1955).
- (5) Sloupenski, J., and Voresck, M., *Inzynierski Stawby*, **6**, 246(1958).
- (6) Duncan, A. J., "Quality Control and Industrial Statistics," Richard D. Irwin, Inc., Homewood, Ill., 1959, pp. 646-659.