

The corresponding means for the control group were 42.2 ± 0.5 Gm. and 160.5 ± 4.1 Gm., respectively.

Gross examination at autopsy showed no abnormalities. Histopathological examination of the perirenal fat also showed no abnormalities.

The results indicate that either saturation of the double bond or masking of the hydroxyl group of the hydroxy-double bond system of ricinoleic acid nullifies the cathartic action. On the other hand, neither isomerization of the double bond from the *cis* to the *trans* configuration, nor conversion of the neutral triglyceride to the methyl ester or to the free acid, appears to affect the cathartic action to an appreciable extent. The fact that the highly purified (distilled and crystallized) methyl ricinoleate is very effective militates against the possibility that the cathartic action of castor oil may be due to a trace contaminant.

The quite different results obtained when castor oil was given to fasted rats by stomach tube or as a part of the diet is striking. In the latter case no catharsis was observed, although the daily food intake toward the end of the feeding experiment provided well over 1 Gm. of castor oil per rat. This is in agreement with the observations of others, e.g., Stewart and Sinclair (2) found that no catharsis

occurred even when castor oil was included in the diets of rats at levels as high as 48.4%. There is no ready explanation for this difference. The reported use of castor oil as an article of the diet in China (8), presumably without untoward effects, may be related to this phenomenon. It is noteworthy that when used as a cathartic, castor oil is usually taken on an empty stomach (9).

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— Technical Articles —

Water Vapor Sorption and Diffusion through Hard Gelatin Capsules

By W. A. STRICKLAND, Jr., and MARTHA MOSS

Gelatin contains appreciable amounts of water under normal environmental conditions. This water may be transferred to a hygroscopic powder contained in a gelatin capsule. This report describes a study of this water transfer and of the diffusion of water vapor through gelatin capsules.

THE TWO-PIECE hard gelatin capsule is a convenient single dose medicine container that prevents ill taste on swallowing and promptly dissolves on reaching the stomach. The development of high speed filling equipment and the availability of well made, low cost capsules has prompted renewed interest in capsules as a dosage form. Capsules are made from refined animal gelatin and may contain very small amounts of other substances such as dyes or preservatives; however, the physical properties of hard gelatin capsules are essentially the

properties of the gelatin from which they were made. Gelatin normally contains 9 to 12% water, but the water content can vary from about 4 to about 16%, depending on the environment. It is conceivable that the water content of normal capsules may exercise a deleterious effect on the capsule content provided it can be transferred. In addition, atmospheric water vapor may diffuse through capsules if the content is hygroscopic. Gelatin cannot be completely dehydrated by normal desiccating procedures and, if low water content is achieved, the capsules become brittle and fracture easily; conversely, greater than normal water content causes

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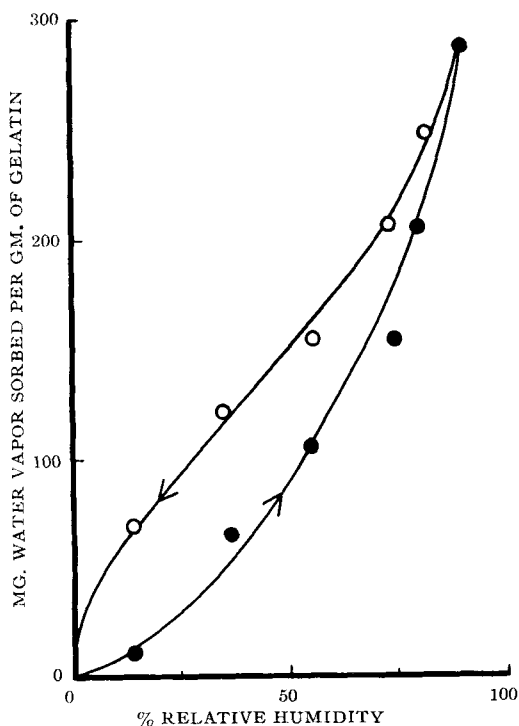


Fig. 1.—Typical sorption-desorption isotherm of crushed gelatin capsules in relative humidity chamber showing pronounced hysteresis of the desorption portion (open points) of the curve.

sticking and ultimate softening of capsules (1, 2).

This communication describes a study of water vapor transfer from capsules to hygroscopic powders and vice versa, and an apparatus used to study rate of water diffusion through gelatin capsules with typical results to show its application. A single lot of size 00 capsules (Parke, Davis and Co., Lot No. G5210-20) was used throughout this study.

EXPERIMENTAL

Sorption and Desorption of Water Vapor by Gelatin.—Isotherms showing the sorption and desorption of water vapor by gelatin were determined in relative humidity chambers by changing the relative humidity by increments at weekly intervals, as previously described (3), at 24°. Figure 1 shows a typical isotherm using crushed gelatin capsules (8 mesh) prepared by drying to constant weight over concentrated sulfuric acid. While the shape of the curve is subject to some variance with different gelatins, invariably there is pronounced hysteresis of the desorption portion of the curve. Perhaps the hysteresis is due to failure to achieve equilibrium, but it is reproducible and, therefore, significant in this work because desorption characteristics govern the availability of water for absorption by hygroscopic materials enclosed in capsules.

Water Vapor Transfer from Gelatin to Hygroscopic Medicinal Powders.—Transfer of water vapor from gelatin to hygroscopic powders, and vice

versa, was studied by placing approximately 5 Gm. of accurately weighed samples of crushed gelatin capsules (8 mesh) and of hygroscopic powders (60 to 100 mesh) in aluminum foil dishes, about 5 cm. diameter, and bringing them to constant weight in relative humidity chambers maintained at the desired relative humidity by saturated salt solutions (4). Pairs of samples, one of gelatin and one of a hygroscopic powder, were placed in well closed containers of 1 L. capacity for 1 week at $21 \pm 2^\circ$, after which time the gain or loss of sample weight was found by weighing. Table I gives typical data found in one such study.

Rate of Water Diffusion through the Capsule Wall.—The apparatus shown in Fig. 2 was devised to study rate of water diffusion through the capsule wall. Nitrogen gas, bubbled through a column of water to saturate it with water vapor, was passed through an equilibrating tube, then into the sample chamber at a constant rate of approximately 50 ml. per minute. The quartz helix springs, previously described (3), employed to determine the gain or loss of weight of sample capsules gravimetrically, had a maximum capacity of 2 Gm. at an extension of

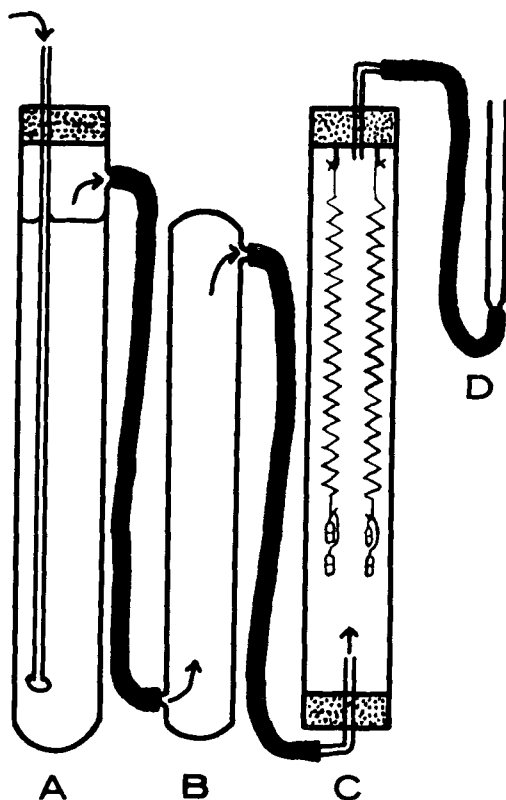


Fig. 2.—Diagram of apparatus used to determine lag time of water vapor diffusion through capsule walls. A, Water reservoir through which nitrogen was bubbled to saturate the gas; B, empty tube to assure temperature equilibrium and precise vapor saturation; C, sample chamber with sample capsules suspended from quartz springs; D, flow meter. The entire apparatus was immersed in a water bath maintained at $24 \pm 0.2^\circ$.

TABLE I.—VAPOR PHASE TRANSFER OF WATER BETWEEN CRUSHED GELATIN CAPSULES AND PENTOBARBITAL SODIUM POWDER, U.S.P.

Material	Weight of Samples at Equilibrium (% Relative Humidity)	Wt. after 1 Week in Closed Containers (21°)	Net Gain or Loss, Gm. ^a
Pentobarbital sodium	4.9789 (0)	5.0380	+0.0925
Gelatin (8 mesh)	4.5047 (72)	4.4210	-0.0837
Pentobarbital sodium	5.1541 (72)	5.0426	-0.1115
Gelatin (8 mesh)	4.2911 (0)	4.4789	+0.1878

^a The difference in gain and loss is accounted for by the atmospheric water vapor present and the end point relative humidity in the liter container.

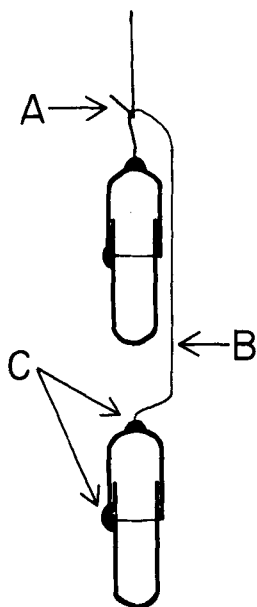


Fig. 3.—Pairs of capsules suspended from the lower hook of quartz spring, A; a small wire, B, was attached to capsules by spots of melted gelatin, C.

approximately 1 cm. for each 51 mg. added weight. A cathetometer reading to 0.01 cm. was used to determine spring extension.

Sample capsules were suspended in pairs (Fig. 3) from the lower hook of the quartz spring. Capsules employed in this study weighed about 0.120 Gm. each and had a capacity of about 0.50 Gm. corn starch. After the larger section of the capsule was filled with a dried hygroscopic powder, the two parts of the capsule were gently pushed together and a spot of melted gelatin placed on the juncture to prevent the two sections from coming apart during experimental procedures. Glass beads were placed in the blank capsules to give a total weight near that of powder-filled capsules. Pairs of capsules were attached to a small wire, as shown in Fig. 3, then the assembled capsules were placed in a desiccator for 1 week or more and dried to constant weight prior to use. Figure 4 gives the results obtained when empty

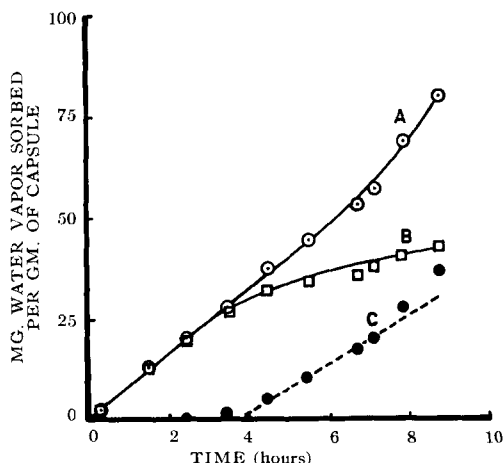


Fig. 4.—The result of a typical determination of water vapor diffusion through gelatin capsules. The weight gain, per Gm., of unfilled capsules, B, subtracted from the weight gain of starch filled capsules, A, yields the lag time of diffusion, C.

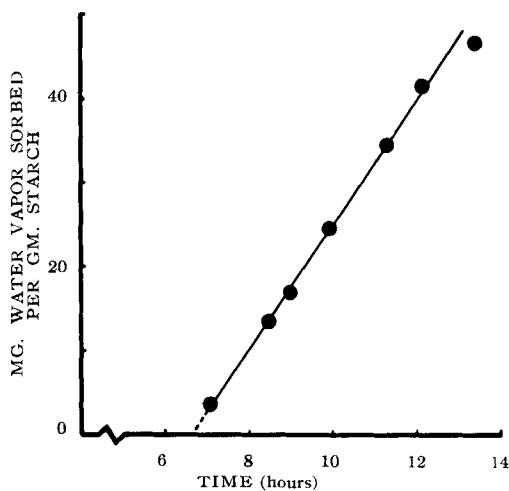


Fig. 5.—The lag in diffusion of water vapor through gelatin capsules filled with dried corn starch and coated with stearic acid.

capsules and corn starch-filled capsules were placed in the apparatus and weight gain *vs.* time was determined. The time lag for water penetration through the capsule wall was about 4 ± 1 hours. Hygroscopic powders other than starch were used to fill capsules and yielded essentially the same results. Figure 5 depicts the results of determining the diffusion rate of water through capsules coated with stearic acid prepared by immersing capsules in a 2% carbon tetrachloride solution of stearic acid. The capsules appeared to be incompletely coated on visual inspection, which may account for the less than expected increase in lag time.

On occasion, primary softening or melting of capsule content at the juncture of the capsules was noted; however, in most determinations it appeared as if the juncture formed a good seal and the water

vapor diffused rather uniformly through the entire surface of the capsule.

CONCLUSIONS

The water content of gelatin capsules may be subject to desorption in the presence of hygroscopic materials. Relative hygroscopicity of the gelatin capsules and the filling materials determines the direction of vapor phase transfer of water in the closed capsule system. Gelatin capsules offer little protection to a hygroscopic

content from atmospheric water vapor. Certain coatings may enhance this protective function, and the extent of protection may be evaluated in terms of prolonged diffusion lag time.

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Notes

Determination of Calcium Carbonate Moisture Content by a Radioisotope Technique

By MEI CHEN SCHNEITER†, WAYNE V. KESSLER, and JOHN E. CHRISTIAN

The transmission of beta particles through calcium carbonate samples with different moisture contents was studied. It was found that the transmission was linearly related to the moisture content.

IN MANY pharmaceutical manufacturing processes the moisture content of various materials is important. Conventional methods for moisture analysis are time consuming and delay further processing and subsequent production steps. Thus, a definite need exists for a rapid, simple method for moisture analysis. The objective of this investigation was to study the feasibility of determining the moisture content of pharmaceutical products using the beta-particle transmission technique. Although this technique has been used for determining the moisture content of certain materials such as wood (1) and paper (2), no reference to its use for moisture analysis of pharmaceutical products has been reported.

Calcium carbonate was selected for this study because it is a component of many pharmaceutical

products. The transmission of the beta particles from a SrY-90 source through calcium carbonate samples with known moisture contents was measured. It was found that the transmission was linearly related to the moisture content.

EXPERIMENTAL

Radiation Counting Equipment and Radioactive Source.—A conventional decade scaler, a Geiger-Müller tube with a 1.4 mg./cm.² end window, and a lead shield with a Lucite tube mount were used for the counter. The radioactive source was a ³/₁₆-in. diameter deposit of SrY-90 in the center of a 1¹/₄-in. aluminum planchet having five concentric circular grooves on the bottom. The activity of the deposit was 218,000 c.p.m. at a distance of 2.4 cm. from the detector window. The deposit was covered with a thin coat of label glaze. The planchet was attached to an aluminum planchet holder which, in turn, was placed in the Lucite tube mount of the lead shield.

Preparation and Measurement of Samples.—Stock samples of wetted calcium carbonate were prepared from calcium carbonate powder (A.R. grade) and distilled water. For each stock sample, 100 Gm. of calcium carbonate was mixed with the

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