are shown in Table II. As the concentration of calcium increases, the dye deteriorates more rapidly. It is apparent that no correlation exists between degree of fading and the initial or final pH. Therefore, it can be concluded that the higher solubility of calcium sulfate dihydrate (0.2 Gm./100 ml. at 25°) is the cause for the more rapid fading. The solubility of dicalcium phosphate is about 0.05 Gm./100 ml. at 25°, an amount apparently insufficient to cause a significant increase in the fading rate.

Effect of Colorant Nature.—No significant differences in the fading rates existed between the dye and the lake on either dicalcium phosphate or lactose. However, in the case of calcium sulfate a marked reduction in the rate was afforded by use of the lake over the dye as seen in Table I and Figs. 1 and 3. The reason for increased stability with the lake can be attributed to the adsorption of the dye to its substrate. In this form the dye is not free to react freely with available calcium ion.

SUMMARY AND CONCLUSIONS

The usefulness of semilogarithmic plots of the Kubelka-Munk function and the product of time x intensity has been shown applicable to tablet systems other than those originally employed. The rate constants for tablets of calcium sulfate dihydrate lake, dibasic calcium phosphate-dye or lake, and lactose-dye or lake are not statistically different. However, tablets of calcium sulfate dihydrate and dye show a fading rate significantly higher than other tablet formulas studied. The method of size reduction did not significantly alter the fading rate in those tablets that were mottled or speckled when prepared by micropulverization.

It is believed that better control of pressure and the selection of more closely matched tablets will reduce experimental error due to tablet-to-tablet variation. This factor along with the use of color differences calculated from tristimulus values will no doubt lead to new interpretations of color fading.

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In Vitro Evaluation of Sustained-Release Tablets by Dual Channel Scintillation Counting

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A rapid procedure was developed for the study of the *in vitro* release characteristics of two radiolabeled drugs in a tertiary drug system. The use of dual channel scintillation spectroscopy allowed for simultaneous determinations of per cent release of each labeled drug from the single sustained-action core tablet.

RADIOISOTOPES have been used extensively in the testing of various pharmaceutical dosage forms (1). The literature contains several reports of evaluative methodology regarding *in vivo* and *in vitro* uses of radioisotopes with the sustained-release dosage form (2–5). This report will be restricted to the determination of the release characteristics of Cl-36 labeled phenylephrine hydrochloride and C-14 labeled aspirin in the presence of chlorpheniramine hydrochloride *in vitro* from the single sustained-release core tablet. The method employed was that of dual channel scintillation spectroscopy which permitted the simultaneous determination of the percentage released of the individual radiolabeled drugs.

EXPERIMENTAL

Preparation of Labeled Compounds.—Chlorine-36 labeled phenylephrine hydrochloride was prepared by dissolving 3 Gm. of compound in distilled water and crystallizing out the free base from the solution rendered alkaline with ammonia. The base was filtered, washed, and dried. Fifty microcuries of chlorine-36 labeled hydrochloric acid was then added to a mixture of 1.23 Gm. of the base and 4 ml. of distilled water. One drop of methyl red T.S. was added; the solution was neutralized with dilute hydrochloric acid. This solution was later added to the mass during the preparation of the tablet cores. Carbon-14 labeled aspirin was synthesized using 50 μc. of carbon-14 labeled acetic anhydride and salicylic acid A.R. using routine procedures (6). The labeled aspirin was then blended with about 25 Gm. aspirin C.P. by dissolving both in an ether–petroleum ether mixture. The blend was then crystallized and dried. The specific activities for the respective compounds were 15 μc./Gm. for phenylephrine hydrochloride and 45 μc./Gm. for aspirin prior to dilution.

Preparation of Tablets.—A batch of 100 core tablets, each made to weigh 405 mg., was prepared by using a single punch tablet press fitted with a $^{11}/_{32}$-in. die and standard concave punches. Each tablet contained 180 mg. of labeled aspirin, 1.3 mg. of labeled phenylephrine hydrochloride, and 8.3 mg. of chlorpheniramine hydrochloride after preparation by the methods of Nash and Jeffries (7, 8). The cores were not compression coated. An immediate release portion—additional quantities of drugs in lactose—would lend nothing to the evaluation of the sustained-action formula and, therefore, was not used.

Received December 20, 1962, from the Research Center, Pitman-Moore Co., Division of the Dow Chemical Co., Indianapolis, Ind.
Accepted for publication July 23, 1963.
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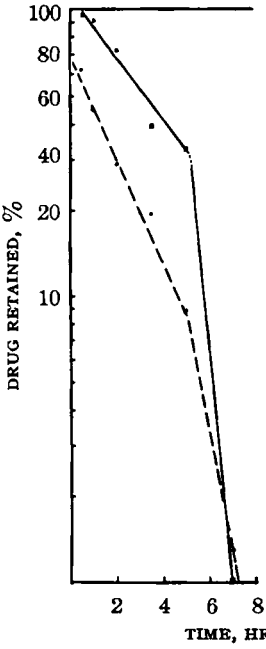

Fig. 1.—Release *in vitro* of aspirin and phenylephrine hydrochloride in simulated gastric juice T.S. Key: ——, aspirin; - - -, phenylephrine hydrochloride.

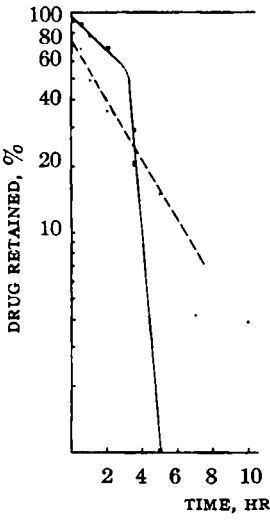

Fig. 2.—Release *in vitro* of aspirin and phenylephrine hydrochloride in simulated intestinal fluid T.S. Key: ——, aspirin; - - -, phenylephrine hydrochloride.

Dissolution and Sampling Procedure.—The rotating bottle apparatus of Souder and Ellenbogen (9) was placed in a water bath with a temperature of 37.5 ± 1°. Into three separate bottles was added 60 ml. of simulated gastric fluid T.S. Each of three more bottles received 60 ml. of simulated intestinal fluid T.S. One core tablet was placed in each bottle and the instrument rotated with a speed of 44 r.p.m. Samples ranging from 0.1 ml. to 0.2 ml. were withdrawn from each bottle at periodic intervals. Each sample was added to a counting bottle[1] which contained 10 ml. of the liquid scintillation solvent (0.4% 2,5-diphenyloxazole, 0.01% 2,2-*p*-phenylene bis-5-phenyloxazole, 5% naphthalene, 20% ethanol, *q.s.* to 100% with toluene). The counting bottles were then refrigerated at −5° for 24 hours for dark adaptation and temperature stability. A blank consisting of 10 ml. of liquid scintillation solvent and 0.2 ml. of distilled water served as the sample for background determinations.

Counting of Samples.—All vials were placed in the detector[2] at −5° for a 10-minute count. The scaler[3] and pulse height analyzer[3] were adjusted to permit simultaneous measurement of the carbon-14 and chlorine-36 by means of dual channel counting. At the selected settings the counting efficiencies were determined using standards of known activity (10). Each sample was counted for 10 minutes. The three count determinations for each sampling time were averaged for each channel. Because each isotope used possesses an energy spectrum and is not monoenergetic, it was necessary to correct the preliminary results to eliminate the contribution of activity of each isotope in each channel.

[1] Wheaton glass counting vials, T. C. Wheaton, Milville, N. J.
[2] Ekco universal counter No. N664, American Tradair Corp., Long Island City, N. Y.
[3] Ekco scaler No. N610 A, American Tradair Corp., Long Island City, N. Y.

RESULTS AND DISCUSSION

The sensitivity of the isotope tracer method allows for selection of extremely small samples. The data presented consist of averages of runs for only three tablets. It could well have been only one tablet because the range of gross counts at each time interval did not exceed ±5% of the mean gross count.

In graphically recording drug release it was most convenient to plot the log of the per cent of drug retained *versus* time. In this study the highest corrected activity was arbitrarily chosen as 100% release. Plots of the release patterns of aspirin and phenylephrine hydrochloride in two media may be seen in Figs. 1 and 2, which illustrate that the release in both media assumes typical pseudo-first order behavior (11, 12). Thus, it appears that this procedure may have merit in studying the rate and reliability of release of single tablets at the stage of formulation.

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