Table I—Average Partition Coefficients ± *SD* of the Three Propellants in Solutions of Plain Buffer and 5% (w/v) Bovine and Human γ-Globulins

Propellant	Plain Buffer	Bovine γ-Globulin	Human γ-Globulin
Trichloromonofluoromethane	0.298 ± 0.0084	0.273 ± 0.0053 ($p < 0.01$)	0.308 ± 0.0085 ($p < 0.1$)
Dichlorodifluoromethane	0.0916 ± 0.0008	0.0887 ± 0.0017 ($p < 0.05$)	0.0882 ± 0.0013 ($p < 0.02$)
Dichlorotetrafluoroethane	0.0296 ± 0.0009	0.0294 ± 0.0013 ($p < 0.8$)	0.0275 ± 0.0010 ($p < 0.05$)

Since it is important to identify various components of plasma that may interact with these propellants and since γ-globulin has the second highest concentration among various plasma proteins, a preliminary study was conducted on the possible interaction between the three most widely used propellants and human and bovine globulins using the partition coefficient method (3, 4).

The crystallized and lyophilized bovine and human γ-globulins were obtained commercially[1] and were used without further purification. Protein solutions (5% w/v) were freshly prepared in pH 7.4 phosphate buffer (3). The equilibrium study was conducted in a water bath maintained at 21.5–22°. The equilibrium concentrations of the propellants in the aqueous phase were about 0.05, 0.08, and 0.015 mg/ml for trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane, respectively.

All propellants were studied individually, and at least four runs were performed on each propellant. The propellant concentrations in both the aqueous phase and the head space in sealed serum bottles were analyzed by a GC method using an electron-capture detector (6). The enhancing effect of *n*-hexane used in the extraction on peak heights in the GC analysis for each propellant was corrected in the calculations (7).

The results of this preliminary study are summarized in Table I. Contrary to the albumin study, all of the partition coefficients in globulin–air systems are only slightly different from those in the plain buffer–air system, indicating an insignificant degree of interaction in spite of statistically significant differences in some systems. The slight decrease of the partition coefficients of some propellants in the globulin solutions is most likely due to the salting-out effect of globulin.

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Novel, Low Cost Approach to Digitizing Tablet Hardness Values

Keyphrases □ Tablet hardness tester—modified to give digitized values □ Digitized tablet hardness values—equipment described

To the Editor:

When formulating tablets with deliberately low hardness values, *i.e.*, <2 kg, it is difficult to determine these values repeatedly and accurately to 0.1 kg on the meter scale of a hardness tester[1]. Shown in Fig. 1 is an inexpensive addition to the hardness tester which will give a digitized reading of these hardness values and print them on an optional printer if desired.

The transducer used for sensing the force applied to break the tablet is a Hall generator[2]. The output signal from a Hall generator is a voltage that is proportional to the current flowing through it and the magnetic flux density (1).

As shown in Fig. 1, a Hall generator is attached to the movable counterweight shaft and a small magnet is attached to the case of the instrument approximately 5 mm from the Hall device. As force is applied to the tablet, the shaft moves, causing the Hall device to move away from the magnet. This change in magnetic flux density is sensed by the Hall generator; its

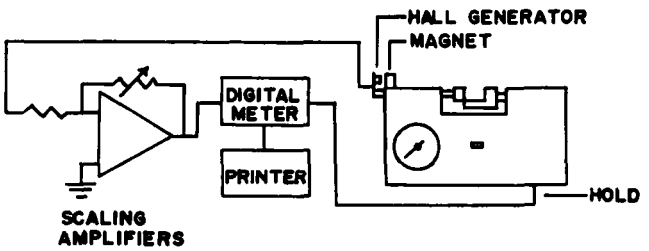

Figure 1—*Schematic diagram of instrument for digitizing tablet hardness.*

[1] Heberlein tester, Cherry-Burell, Park Ridge, Ill.
[2] Hall effect magnetic field sensor, model 63SS2-1, Micro Switch, Freeport, IL 61032

output voltage, which is proportional to force, is amplified, scaled, and displayed on a digital voltmeter calibrated directly in kilograms. The display on the digital panel meter is held at the maximum force value by utilizing the tablet breakage point sensing circuitry in the hardness tester.

Calibration and linearity of the digital readings can be checked by displacing the anvil on the hardness tester in small increments while noting the reading on the meter incorporated in the hardness tester. Magnet placement, Hall device power supply voltage, and scaling amplifiers are adjusted for the proper reading.

A method for calibrating the hardness tester was mentioned previously (2).

Advantages of the digital approach include: *(a)* accuracy, *(b)* low cost of the transducer and system, *(c)* ease of construction, *(d)* no change in operating procedures, *(e)* automatic printout if desired, and *(f)* hardness tester not affected by operation of the transducer.

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Drug–Nitrite Interactions: Formation of *N*-Nitroso, C-Nitroso, and Nitro Compounds from Sodium Nitrite and Various Drugs under Physiological Conditions

Keyphrases □ Nitrite–drug interactions—formation of *N*-nitroso, C-nitroso, and nitro compounds from sodium nitrite and 20 drugs under physiological conditions □ Nitroso compounds—formation from sodium nitrite and 20 orally administered drugs under physiological conditions □ Interactions—20 orally administered drugs with sodium nitrite, formation of *N*-nitroso, C-nitroso, and nitro compounds under physiological conditions

To the Editor:

Many alkyl, aryl, and cyclic *N*-nitroso compounds are known to be carcinogenic (1, 2). Recently, several drugs containing secondary and tertiary amino groups were found to react with sodium nitrite *in vitro* and *in vivo* to yield *N*-nitroso compounds (3–8). Coadministration of aminopyrine and sodium nitrite by the oral route produced liver tumors in rats identical to those produced by *N*-nitrosodimethylamine, a product of drug–nitrite interaction in the stomach (9, 10). Similarly, concurrent administration of piperazine and sodium nitrite to mice induced lung adenomas attributable to *N*-nitrosopiperazine formed *in vivo* (11).

Since many orally administered drugs contain secondary and tertiary amino groups which could form potentially toxic *N*-nitroso compounds in the stomach, where suitable acidic conditions and significant concentrations of nitrite through dietary intake may prevail, the drug–nitrite interaction has been implicated in the etiology of human cancer (2, 12–15).

In the present communication, the isolation and mass spectrometric identification of *N*-nitroso, C-nitroso, and nitro compounds that arise from the reaction of sodium nitrite with 20 drugs (Table I) are described. These drugs were selected because they are commonly administered by the oral route and represent a wide variety of chemical structures. These studies were initiated to gain a better understanding of drug–nitrite interactions and to delineate the structural features of the drugs most likely to yield potentially toxic nitroso compounds.

The nitrosative cleavage of tertiary amines was studied previously (16–18). We observed that, depending upon the structure of drugs, five types of nitroso compounds may be formed as a result of drug–nitrite interactions (Table I). For the reactions at pH 1–2, 100 mg of drug was incubated with 200 mg of sodium nitrite in 10 ml of 10% hydrochloric acid at 37° for 4 hr; the reactions at pH 3–4 were carried out in 10 ml of 10% acetic acid. The reaction mixtures were adjusted to pH 11 with solid sodium hydroxide and extracted twice with 8 ml of methylene chloride and twice with 8 ml of ethyl acetate.

The volatile *N*-nitroso compounds in the methylene chloride extracts were identified by GC–mass spectrometry and quantitated by GC (19). The nonvolatile nitroso and nitro compounds in the ethyl acetate extract were purified by TLC on silica gel, using a solvent system of ethyl acetate–methanol (1:1), and characterized by mass spectrometry. The yields were calculated on the basis of the isolation of homogeneous products (8, 20). The methylene chloride extracts contained the products listed in Groups 1 and 2, while the ethyl acetate extracts contained the products in Groups 3–5.

The mass spectra of all *N*-nitroso compounds in Groups 1 and 2 (Table I) were consistent with those reported in the literature (19, 21). The *N*-nitroso derivatives in Groups 3 and 4 exhibited fragmentation patterns typical of *N*-nitroso compounds (the characteristic loss of NO from the parent ion) as well as those consistent with the drug structure (8, 20). The mass spectra of synthetic 4-nitrosoantipyrine and 4-nitroantipyrine (22) were identical to the spectra of the respective products from the reaction of antipyrine (XX) with nitrite.

The following comments may be made regarding the formation of nitroso and nitro compounds from drug–nitrite interactions.

Group 1 Products (*N*-Nitrosodialkylamines)—