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Disintegration Test for Hard Gelatin Capsules

Keyphrases □ Disintegration—hard gelatin capsules, modification of USP and NF tests for tablet disintegration □ Dosage forms—hard gelatin capsules, disintegration test, modification of USP and NF tests for tablet disintegration

To the Editor:

A proposed disintegration test procedure for capsules was published in the USP XX Comment Proof (Vol. 3, No. 56) dated August 14, 1978. This procedure was based on a series of collaborative studies conducted by the Disintegration Test Review Committee of the Pharmaceutical Manufacturers Association (PMA) Quality Control Section. Highlights of these studies are presented in this communication.

The USP and NF describe disintegration tests for five tablet categories. The PMA project was aimed at developing a similar test for hard gelatin capsule products using the apparatus and methodology for tablet disintegration with as few changes as necessary. Three test samples (No. 2 hard gelatin capsules containing 0.5, 1.0, and 1.5% magnesium stearate in lactose) were used in the studies to evaluate procedure variables. Comments on each variable follow.

A cross section of disintegration baskets used in industry was examined. The baskets generally fell into two categories: those with notched shafts and those having shafts equipped with hooks. The former type provides a rigid mounting to the motorized device, and the motion is primarily vertical; the latter basket type provides a nonrigid attachment where the motion is both vertical and rotational. Studies showed that the mounting mode had no influence on the test results. Disintegration times were identical, within normal variation, regardless of the type of mounting used.

The disintegration time of the three test samples could not be differentiated when the plastic disks described in the USP and NF were placed into the basket-rack assembly. The disintegration time for each sample was ~3 min. By eliminating the disks and placing a 10-mesh wire screen on top of the baskets to retain the capsules within the tubes, the disintegration times for the 0.5, 1.0, and 1.5% samples were 12, 25, and 39 min, respectively.

The compendia are not specific about the disintegration test vessel. Committee members reported that both the size of the vessel and the volume of the test vehicle affected the hydrodynamics of the system, thereby influencing the disintegration rate. A 1000-ml, low-form beaker containing ~900 ml of medium was the most convenient and compatible with the dimensions of the basket-rack assembly.

Purified water was a satisfactory test vehicle for the three samples. Reproducibility in disintegration time was improved by the addition of 0.1% benzalkonium chloride. The use of simulated gastric fluid was investigated, but it was reported that hydrogen chloride vapors emanating from the fluid slowly corrode the equipment. Because of variation in the composition of compendial capsule products, collaborators recommended that both the test medium and the disintegration time limit be specified in the individual monographs.

The Committee observed that the longer the path through which the basket travels in its vertical motion, the more rapid is the disintegration time. The USP and NF specify a stroke length of 5–6 cm. In a study involving one test specimen (1.0% magnesium stearate in lactose with an average disintegration time of 25 min), the disintegration time decreased by almost 6 min when the stroke was adjusted from the lower limit, 5 cm, to the upper limit, 6 cm. Therefore, a stroke length of 5.3–5.7 cm was recommended.

The final procedure was submitted to the USP after it was found to be workable in the laboratories of 13 PMA-member companies.

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Effect of Smoking on Binding of Lidocaine to Human Serum Proteins

Keyphrases □ Lidocaine—effect of smoking on binding to human serum proteins □ Protein binding—lidocaine, effect of smoking, human serum □ Smoking—effect on binding of lidocaine to human serum proteins

To the Editor:

Cigarette smoking can have striking effects on the disposition of theophylline (1, 2), propranolol (3), and other drugs (4, 5). These changes generally have been ascribed to increased intrinsic hepatic clearance secondary to enzyme induction. However, other mechanisms may be operative. This communication describes the apparent effect

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of tobacco smoking on the binding of lidocaine to human serum proteins. Furthermore, we report a significant increase in the lidocaine free fraction as the concentration was increased through the range usually observed in the treatment of ventricular arrhythmias. This observation is consistent with the data reported by Tucker *et al.* (6) and is inconsistent with other reports (7, 8).

Serum samples were obtained from 16 volunteers, eight smokers and eight nonsmokers. Seven of the eight smokers stated that they smoked between 0.88 and 1.25 packs/day, while the other subject smoked either one cigar or one pipeful of tobacco/day (the data from this individual are specifically identified in Fig. 1). The nonsmoking and smoking groups were well matched with respect to sex (six males and two females in each group), age (45 ± 20 *versus* 42 ± 12 years, mean ± *SD*), concurrent medication (none except diuretic therapy for hypertension), serum albumin concentration (4.9 ± 0.5 *versus* 4.7 ± 0.3 g/100 ml), and total serum protein concentration (7.5 ± 0.3 *versus* 7.2 ± 0.4 g/100 ml). All subjects had normal renal and liver function as assessed by an automatic analyzer[1], and all were apparently free of malignant or inflammatory disease.

Venous blood collected into glass syringes after an overnight fast was allowed to clot at room temperature for ~2 hr and then was centrifuged for ~20 min at 1000×*g*. The serum was removed and stored at −20°. The protein binding of lidocaine was determined by equilibrium dialysis using a dialysis membrane[2] in Plexiglas cells. Lidocaine was added to the buffer solution (0.134 *M* phosphate buffer at pH 7.4) to achieve concentrations of 2.0 and 14.0 μg/ml. A trace amount of radiolabeled drug (30 mCi of [*carbonyl*-^{14}C]lidocaine[3] hydrochloride/mmole obtained commercially with >98% radiochemical purity) also was added to the buffer. Serum aliquots were dialyzed in duplicate against an equal volume of buffer for 5 hr at 37°. Final (postdialysis) lidocaine concentrations in all samples were quantitated by liquid scintillation counting.

Substantial intersubject variability of lidocaine free fraction values was observed; at a final concentration of 1.4 μg/ml, the free fraction ranged from 0.208 to 0.342 (mean of 0.280). Little of the variability can be explained by the reproducibility of the method since the relative standard deviation of the determination of the free fraction was 5.6% (n = 22). However, part of this variability appeared to be related to the smoking status of the subjects. The data in Fig. 1 show that at a final lidocaine concentration of 1.4 μg/ml (left panel), smokers had a significantly lower free fraction than nonsmokers (0.258 ± 0.039 *versus* 0.307 ± 0.030; $p < 0.02$). Although there was a trend toward a lower free fraction at a final concentration of 9.0 μg/ml (right panel), the difference between serum binding in smokers and nonsmokers was not statistically significant ($p > 0.15$).

There are several possible explanations for the increased protein binding of lidocaine in the serum of smokers. An exogenous substance contained in tobacco smoke could cause a cooperative interaction between lidocaine and at least one of the binding proteins. However, a more plausible explanation is that the concentration of at least one

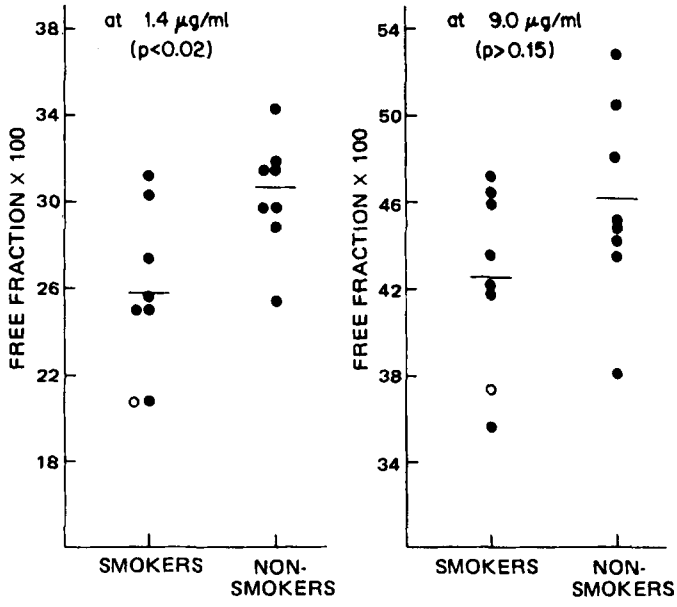

Figure 1—*Effect of smoking on the lidocaine free fraction in volunteers. Serum binding results at final lidocaine concentrations of 1.4 (left) and 9.0 (right) μg/ml are shown. The horizontal bar equals the mean free fraction value. The open symbol represents the data from the one smoker who did not smoke cigarettes.*

protein to which lidocaine binds is elevated in the serum of smokers. Some evidence suggests that the serum concentration of α_1-acid glycoprotein is elevated in smokers (9), and it is known that lidocaine binds to this acute phase reactant protein (10). Thus, the increased binding of lidocaine to the serum proteins of smokers at 1.4 μg/ml could be the result of elevated concentrations of α_1-acid glycoprotein. The failure to achieve statistical significance at a final lidocaine concentration of 9.0 μg/ml probably is related to the facts that, at this concentration, binding to albumin has greater importance (11, 12) than does binding to the glycoprotein (the 50% increase in the free fraction at 9.0 μg/ml suggests saturation of at least one class of binding sites) and, as stated earlier, albumin concentrations were nearly identical in our two populations.

Since increased binding of drugs to serum proteins is known to influence drug disposition and since increased binding of drugs to serum proteins of smokers has not been reported previously, our data may represent a significant new observation for an understanding of the effects of environmental factors on drug disposition. Furthermore, our data support the findings of Tucker *et al.* (6), who reported a lidocaine free fraction of ~0.30 at a serum drug concentration of 2 μg/ml. Finally, we confirmed the striking concentration dependence of lidocaine binding reported by Tucker *et al.* (6).

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Effect of Changes in Plasma Protein Binding on Half-Life of Drugs

Keyphrases □ Pharmacokinetics—effect of changes in plasma protein binding on biological half-life of drugs □ Protein binding—effect of changes in plasma protein binding on biological half-life of drugs □ Half-life—effect of changes in plasma protein binding on biological half-life of drugs

To the Editor:

The binding of drugs to plasma proteins and extravascular tissues affects their distribution, elimination, and overall pharmacological activity. If the extent of such binding is altered by the presence of other drugs or the accumulation of certain endogenous compounds in various disease states, subsequent changes in the pharmacokinetic characteristics of the drug may be anticipated. Gibaldi *et al.* (1) suggested that the biological half-life of a drug bound to plasma proteins and tissues in a drug concentration-independent manner is a function largely of tissue binding but is independent of changes in binding to plasma proteins. However, they pointed out that this phenomenon generally is true only for drugs with apparent distribution volumes substantially larger than the plasma space. These drugs include those that distribute throughout the total body water and, more commonly, those that demonstrate extensive tissue binding as well.

The present discussion focuses on situations where the drug is bound to plasma proteins and the unbound drug is excluded from intracellular fluids. While these conditions may apply to only a few drugs, they can be important. A good example is the antibacterial agent sulfisoxazole. This compound is ~86% bound to plasma proteins after therapeutic doses (2) and is distributed only in extracellular fluids (3, 4). Since the drug does not enter the cells, it exhibits a slightly diminished toxicity while producing higher blood levels at lower doses as compared with sulfanilamide and sulfadiazine, both of which distribute throughout body water. Another example is streptomycin, which is distributed in the extracellular fluids and also is bound to plasma proteins, although to a lesser extent than sulfisoxazole (5).

Based on the physiological approach to drug distribution originally developed by Gillette (6), Øie and Tozer (7) recently proposed the following expression for the apparent volume of distribution, V:

$$V = V_P(1 + R_{E/I}) + f_P V_P(V_E/V_P - R_{E/I}) + \frac{V_T f_P}{f_T} \quad \text{(Eq. 1)}$$

where V_P is the plasma volume; V_E is the extracellular space minus the plasma volume; V_T is the physical volume into which the drug distributes minus the extracellular space; $R_{E/I}$ is the ratio of the amount of protein to which the drug binds in extracellular fluids outside the plasma to that in the plasma; and f_P and f_T are the drug fractions unbound in the spaces V_P and V_T, respectively. Furthermore, by assuming the extracellular fluid volume outside the plasma to be 12 liters and the plasma volume to be 3 liters and by assuming that the total extracellular drug-binding protein is distributed so that $R_{E/I}$ is ~1.4, Eq. 1 can be approximated as:

$$V = 7 + 8f_P + V_T\left(\frac{f_P}{f_T}\right) \quad \text{(Eq. 2)}$$

It then was pointed out (7) that if the distribution of a drug is restricted to the extracellular fluid, its apparent volume of distribution becomes:

$$V = 7 + 8f_P \quad \text{(Eq. 3)}$$

It has been shown (8) that the total clearance, Cl, of a drug whose elimination is linear and not perfusion rate limited in the organ of elimination is directly proportional to its free fraction in plasma, *i.e.*:

$$Cl = f_P Cl^* \quad \text{(Eq. 4)}$$

where Cl^* represents the intrinsic clearance. Moreover, since:

$$Cl = V\beta \quad \text{(Eq. 5)}$$

it follows that:

$$\beta = \frac{f_P Cl^*}{V} \quad \text{(Eq. 6)}$$

where, for a drug obeying two-compartment model kinetics, V is V_{area} and β equals ln 2 divided by the terminal half-life, $t_{1/2}$. Substituting Eq. 3 into Eq. 6 gives:

$$\beta = \frac{f_P Cl^*}{7 + 8f_P} \quad \text{(Eq. 7a)}$$

or:

$$t_{1/2} = \frac{\ln 2(7 + 8f_P)}{f_P Cl^*} \quad \text{(Eq. 7b)}$$

Equation 7*b* describes the effect of plasma protein binding on drug biological half-lives. When the fraction of drug unbound in plasma is changed to f'_P and the new β and $t_{1/2}$ are designated as β' and $t'_{1/2}$, respectively, then:

$$\frac{\beta'}{\beta} = \frac{t_{1/2}}{t'_{1/2}} = \frac{f'_P(7 + 8f_P)}{f_P(7 + 8f'_P)} \quad \text{(Eq. 8)}$$

or:

$$\frac{\beta'}{\beta} = \frac{7f'_P + 8f_P f'_P}{7f_P + 8f_P f'_P} \quad \text{(Eq. 9)}$$

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