probability (P_f) that a specimen from a large batch will exhibit a tensile strength of σ_t is given by the expression:

$$P_f = 1 - \exp\left\{-\left(\frac{1}{m}!\right)^m\left(\frac{\sigma_t}{\bar{\sigma}_t}\right)^m\right\}$$

where m, the Weibull modulus, is a reciprocal measure of the strength variability of the material; (1/m)!, the "gamma" function, is a standard tabulated function and $\bar{\sigma}_t$ is the mean tensile strength of the batch. The applicability of this approach to pharmaceutical materials has been studied.

A batch of 30 flat-faced cylindrical tablets prepared from a -90, $+63$ μm size fraction of α- lactose monohydrate, using identical compaction conditions, has been tested in diametral compression. Having determined tensile strengths from the individual fracture loads, a "best" value of m was computed from the above equation using a "least squares" fitting procedure, with "mean ranking" values of P_f. The best m value was 13·0; the root mean square deviation of fit was 0·0307; the mean tensile strength ($\bar{\sigma}_t$) was 3·52 MN m^{-2}.

The root mean square deviation value indicates that the Weibull distribution satisfactorily models the strength variability of this material. The strength properties are therefore completely characterized in terms of the *two* quantities $\bar{\sigma}_t$, the mean tensile strength, and m, the Weibull modulus, rather than the former alone.

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A preliminary evaluation of a mercury intrusion method for assessing film continuity on coated tablets

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Film continuity and the presence of pinholes in a film coated tablet are important parameters to be considered when assessing the advantages of a new film former in a coating formulation or the efficiency of the coating procedure adopted. For insoluble films these parameters can be assessed either by measuring the amount of drug released in the case of sustained release polymer films, or by monitoring the resistance of the tablet to solutions of varying pH in the case of entero-soluble films. In both cases the presence of pinholes in the film coating will result in more than the theoretical amount of drug being released. This technique is not applicable to tablets coated with water soluble films since the film coating does not remain intact. Because of this drawback the possibility of using a mercury intrusion method for assessing film continuity has been investigated.

Since mercury will not penetrate holes or pores in a film unless an external pressure is applied, it follows that the proportion of film coated tablets penetrated by mercury under a constant intrusion pressure will be a comparative measure of the continuity of the film and hence the efficiency of the coating procedure. Experiments have shown that provided an intrusion pressure in excess of 5 MN m^{-2} is used the method is very reproducible. In our case the intrusion pressure was standardized at 100 MN m^{-2} using a mercury penetration porosimeter [Model 65H, Carlo–Erba Scientific Instruments Division]; twenty tablets were used in each determination and the number of tablets penetrated determined either by individual weighings or visual inspection.

Results illustrating the effect of tablet size and the presence of imprints on film continuity are shown in Table 1. The higher proportion of imprinted tablets failing the test indicates that film continuity is worst at the edges of the impressions. The effect of tablet size and

weight is more complex and may be due, in part, to the increased attrition of the larger heavier tablets when striking the baffles and the sides of the coating pan.

The method has also been used to:—

(*a*) assess the efficiency of new film coating formulations;

(*b*) compare the coating efficiency of the side-vented perforated drum coating pan [Accelacota] with the Wurster air suspension technique;

(*c*) assess the probable efficiency of entero-soluble films.

Table 1.

Tablet characteristics				Proportion of tablets failing test
Diameter (mm)	Weight (mg)	Concavity	Impressions	%
6·5	125	Normal	—	5
9·5	340	Normal	—	20
9·5	340	Normal	+	40
11·0	460	Normal	—	40

Apparent biological half-life values determined by administration of drug by methods other than rapid intravenous injection

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Biological $t_{\frac{1}{2}}$ is commonly estimated from the negative slope (β) of a first-order plot for concentration of drug in blood using $t_{\frac{1}{2}} = 0{\cdot}693/\beta$. The rate constant for loss from blood, k_2 (Notari, 1971), is related to the apparent rate constant for loss from the body, β_{app}, by $k_2P = \beta_{app}(P + T)$.

Reliable estimates are obtained if a drug administered by rapid intravenous injection (i.v. bolus) achieves a relatively constant value for the fraction of the total drug in the body that is contained in the central compartment, $fc = P/(P + T)$. Using computer simulation, we have demonstrated cases wherein i.v. bolus administration yields adequate $t_{\frac{1}{2}}$ estimates but other modes of administration result in "apparent $t_{\frac{1}{2}}$" values. The estimate by i.v. bolus was considered satisfactory if $\beta_{app} \rightarrow \beta$. Values were estimated for: (1) i.v. bolus (2) constant-rate i.v. infusion and (3) extravascular bolus with first-order absorption. A two-compartment model drug which achieves a constant fc by i.v. bolus may fail to achieve a constant fc value by the oral or i.m. route. "Apparent $t_{\frac{1}{2}}$" values in such cases differ significantly from the correct values.

Gibaldi & Weintraub (1971) have shown that the $t_{\frac{1}{2}}$ may be estimated from the plasma steady-state concentration, $\bar{C}$, if the values for F and V_β are known. Perrier & Gibaldi (1973) showed that the average amount in the body during steady-state is equal to $(\bar{C})\cdot(V_{ss}$, and the use of V_β may provide incorrect estimates. Since fc increases during i.v. infusion) the value for β_{app} increases until steady state is achieved and

$$\beta_{ss} = k_{21}k_2/(k_{12} + k_{21})$$

The β_{ss} value can differ from β by several orders of magnitude. Our work on oxytetracycline in horses illustrates some of these effects (Notari, Powers & Paul, unpublished observations).

Table 1. *Half-life estimates for* $\beta = 0{\cdot}109$, $t_{\frac{1}{2}} = 6{\cdot}36$ h.[a]

Mode	fc	$k_2$fc	β_{app}	$(t_{\frac{1}{2}})_{app}$
i.v. bolus	0·0529	0·109	0·109[b]	6·36[b]
i.m. bolus	variable		0·0532[b]	13·0[b]
steady state	0·0954	0·197	0·197[a]	3·5[a]

a. Calculated from k_{12}, k_{21} and k_2 describing mean data for 6 horses.
b. Experimentally observed.

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