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ASPECTS OF PACKAGING FROM NDA <-- IND

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ABSTRACT

The strategic decisions regarding package stability in an NDA should be thought out even before the IND stage (hence the inversion of the order of the words NDA and IND in the title). The philosophy of clinical blister packaging is discussed as are the tests necessary to ensure perfection of seal. The principles of molecular and pinhole moisture permeation are discussed. Suggested fractional factorial schemes for package testing are presented.

INTRODUCTION

The process of successful launching and continual marketing of a drug product consists of several phases, viz. preformulation, formulation, clinical, pre-NDA scale-up, first production, and routine

production. The aspects of development and testing are many and differ depending on the specific phase. The article to follow deals with some aspects of packaging, both theoretical and practical, in the development stage of the product.

The final goal of product development is the NDA. (The final goal, of course, is a successfully marketed product, but for the purpose of this discussion, the end goal is the NDA). At the inception of the drug substance, there is only broad pharmacological indications obtained from animal studies, and part of the over-all development strategy is to convert the neat drug into a dosage form, to present this in a human clinical setting, and, as a first step, to establish a correct dose (or series of doses).

CLINICAL PACKAGING.

Clinical formulation and packaging require a great deal of flexibility. At the onset of the development of a drug (in the initial phases of the clinical trial program), for instance, the final dosage level(s) are not known. Some of the resulting formulation complications can be overcome (and have been circumvented) by use of blister cards for clinical testing. This is a tactical advantage, as shall be outlined below, and also gives the Development and Clinical Packaging Laboratories an opportunity to assess the first package/drug dosage form (e.g. tablet)-interaction from a stability point of view.

In blister packages it is possible to achieve multiple strengths by combining different strengths in the blister dose. The process, in broad strokes, is usually as follows: blisters are filled in configurations depending on the filling equipment (for instance in a 6 x 8 configuration on a Alloyd blister machine). These blisters are then cut into strips of e.g. 2x8 or 3x8. The 2x8 or 3x8 blister-card is then a one week card (with one day's excess), if both dosage units (tablets) in a row are required per treatment.

The blister is color-coded or marked, so it may be identified in its native state. In the following operation it is placed in a card (a - "mask") with holes e.g. 8 rows down and either 2 or 3 panels (columns). Sometimes more than one dosage unit is packed in a blister pocket (e.g. the card could have one strip of 50 mg, one strip of 25 mg), so that many combinations are possible.

CLINICAL PACKAGE TESTING.

Procedurally, the use of cards requires primary and secondary packaging, carried out in separate, designated areas. E.g. the dosage form is placed in the (e.g. 6x8) blister in one room, cut up in (e.g. 3x8) configurations in a separate room, and placed in cards on a yet different line (where 100% configuration inspection is carried out). The point of concern from the point of view of this article is the sealing operation.

The guidelines require that a company assures the stability of the product during the clinical trial. Many methods for doing this exist. Some companies place one batch on stability, and assumes it to be representative of other batches of the same strength. If, in blister packaging, it is tentatively assumed that the process parameters are under control (a point which will be elaborated on), then the stability of a product strength (e.g. 25 mg) in the blister may be assumed to be independent of configuration. E.g. whether the 25 mg is one panel of a 25 mg card, or one panel of a 75 mg card, it may be logistically assumed that its stability is the same. (If this were not assumed, there would be an enormous amount of testing necessary. E.g. a trial could consist of one week of 25 mg dosing, one week of 50 mg dosing etc. as indicated by the week number on the card. If each of those configurations were to be placed on stability, there would be an excessive amount of testing required). If, therefore, the policy of assuring clinical stability is as stated above, then it is only necessary to carry out stability on cards of each manufactured strength. In any event, assays should be obtained for the *longest* period of a study.

Of the tests that are carried out, the one applying directly to packaging is the *Joel Davis test* (37-40°C, 75-100%RH) as required in the Guidelines (I987). The moisture pick-up experienced is due to (a) the degree of impermeability of the plastic, (b) the tightness of the seal and (c) the hygroscopicity of the dosage form enclosed in the blister. If a control test is carried out at 37°C in a dry atmosphere,

then the weight difference between the two tests reflects the rate of moisture permeation into the particular blister containing the particular drug dosage form . The Joel Davis test is important, because it is the one test where most products exhibit stability flaws, be they chemical or physical (e.g. disintegration /dissolution (Chowhan, l979, Amidon and Middleton, l988)).

The test is obviously one where moisture penetrates the package and interacts with the dosage form, and moisture/ temperature interactions can be more severe than any other type of stress (Carstensen, l988, l989), e.g. more severe combined than when only temperature stress or only moisture stress is applied. Hence, the more moisture penetrates, the poorer the stability. Moisture penetration occurs by three modes:

(a) molecular penetration (penetration through plastic)

(b) pin hole leaks

(c) seal leaks.

Saboe (l988) has shown that molecular penetration occurs at leak rates of less than 10^{-9} atm cc/sec. He has also shown that a good seal (in an aluminum blister) should give leak rates of less than 10^{-7} atm cc/sec. Hence, this is the best that can be expected. Gross leaks in a blister would be above such an intrusion rate. But, of course, if there are pin hole leaks, or inadequate sealing, then these will

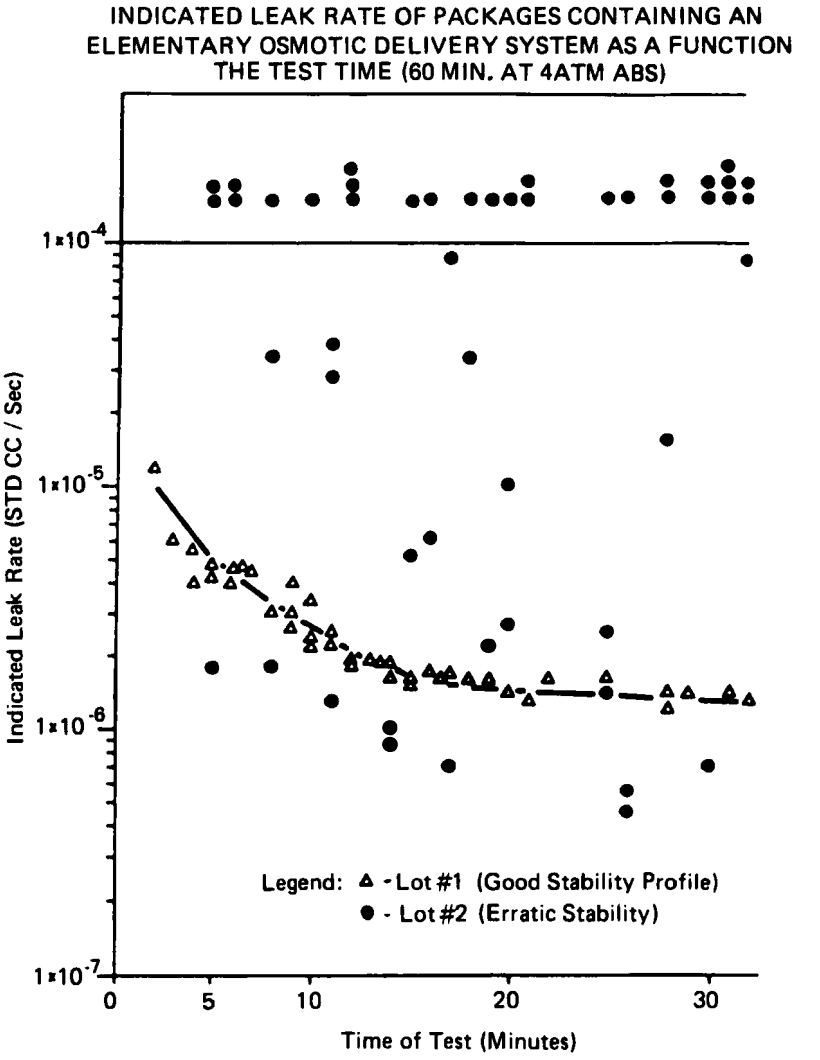

Fig. 1. Helium bomb results for a good stability lot and a lot with large variation in stability. After Saboe (l988)

provide avenues of moisture penetration which could adversely affect stability.

Furthermore, for stability studies to be meaningful, there must be relatively good uniformity in the product. Usually this is conceived as content uniformity, but uniformity of seal is as important. Fig. 1 is constructed from data published by Saboe (l988) and shows the difference between a good lot and an unsatisfactory lot of a product. The results are obtained by a helium bomb instrument which is capable of measuring leak rates down to at least 10^{-8} std cc per sec (1 std cc per three years).

In a helium leak tester, the parameters will follow the equation

$$S = P \cdot L \cdot \{1 - e^{-aT}\} \cdot e^{-at} \qquad (1)$$

where

S = leak rate (std cc/sec)

P = bombing pressure (atm)

T = bombing time (sec)

t = time leaked (sec)

L = actual leak rate (std cc/sec/atm) = rate if 100% helium in package

a = L/V, where V = package volume.

It is noted that the conversion to international units is obtained by dividing the number of atm cc/sec by 0.01 to obtain the value in Pa-liter/sec.

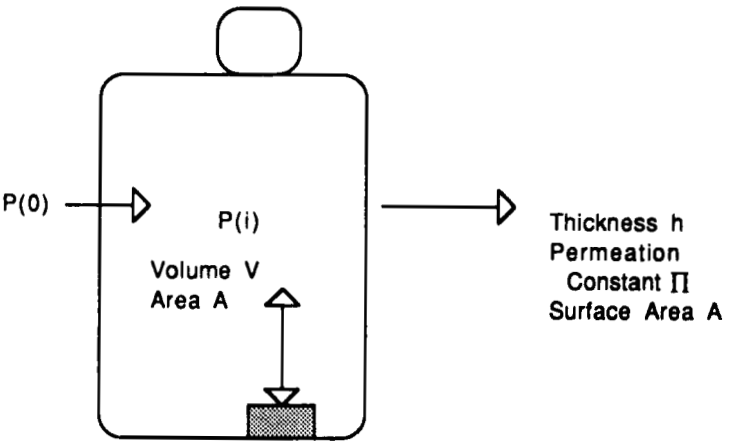

Fig. 2. Moisture penetration into a bottle.

STABILITY.

Moisture uptake rate, be they through molecular diffusion, pin hole leaks or seal leaks, will follow an equation where

$$dM/dt = Q \cdot [P_0 - P] \qquad (2)$$

where M is mass diffused in time t, P_0 is outside water vapor pressure, P is water vapor pressure within the container, and Q is a constant. As shown in Fig. 2, moisture penetrates the bottle, and equilibrates with the solid in the container. Solids have an equilibrium moisture content which is a function of moisture content of the solid (Carstensen, 1989), the simplest case being a linear isotherm, given by the equation:

$$x = KP \quad (3)$$

where x is fraction of moisture in the dosage form, K is a constant, and P, as mentioned, is the water vapor pressure in the container.

It has been shown (Carstensen, l988), that solid state decomposition for moisture sensitive drugs follows a Leeson-Mattocks model (Leeson-Mattocks, l958), except there is a critical moisture content, below which the drug is stable (or considerably more stable). This moisture content is called the bound moisture content (x^*), and could correspond, e.g., to water of crystallization or water bound tightly in the rubbery state of a polymer. The rate of decomposition (-dM/dt, where M is mass of intact drug substance) in the solid is given by

$$dM/dt = -k_1 S \cdot [x - x^*] \quad (4)$$

for $x > x^*$. k_1 is here first order decomposition rate constant in solution and S is solubility of drug in water in grams/gram.

Suppose a dosage form contains *a* grams of moisture to start with, and is packaged, N units @ m grams in a package where the moisture penetration rate is *q* grams per day. The allowable moisture uptake is now $N \cdot m \cdot [x^* - a]$, so it will take

$$t^* = N \cdot m \cdot [x^* - a]/q \quad (5)$$

days for the critical moisture content to be reached. *q*, of course, is a function of leakage rate. A desiccant bag will arithmetically prolong this, and it is usually assumed that the desiccant will take up 20% of moisture, then be exhausted, and after that the moisture uptake by the drug will commence as shown above. E.g. if the desiccant bag weighed 1 gram, then it could consume 0.2 grams of water, and this would prolong the time to reach x* by 0.2/q. If q were 1 mg/day = 0.001 g/day, then the extension would amount to 200 days. This, however, should be established, experimentally. It is easily done by placing the desiccant bag and the dosage form, and (separately from bag and dosage form) a weighed amount of water (corresponding to e.g. 30% of the desiccant bag weight) in closed containers, and checking the bags and the dosage forms for weight at periodic intervals (sacrificing one container per test).

Beyond t*, the decompostion of the solid will be given by:

$$dM/dt = -k_1 S \cdot [q(t-t^*)/(N \cdot m)] = -(2q)(t-t^*) \quad (6)$$

where

$$q = k_1 S \cdot [q/(N \cdot m)]/2 \quad (7)$$

Eq. 6, for t>t*, integrates to

$$M = M_0 - q(t-t^*)^2 \quad (8)$$

A typical trace of this is shown in Fig. 3.

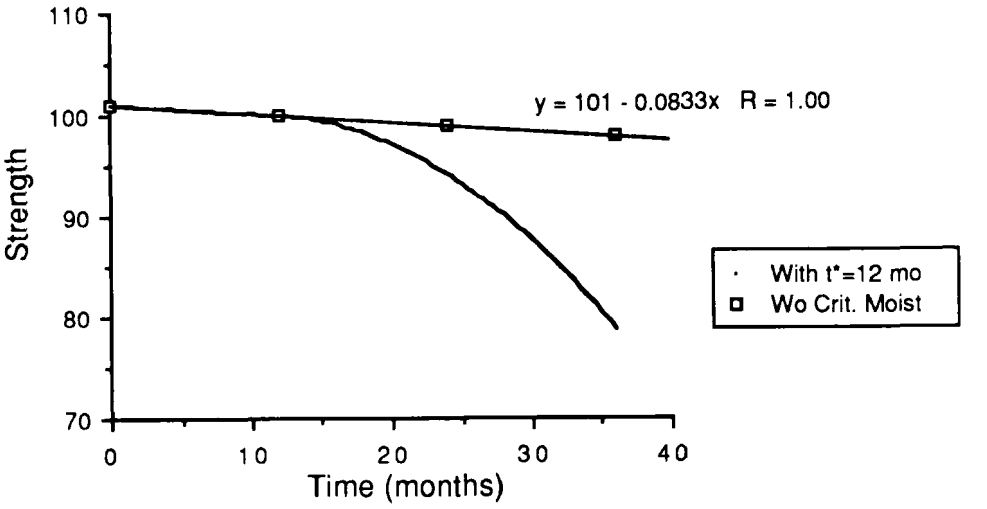

Fig. 3. Decomposition of a solid beyond the critical moisture content.

PREREQUISITES FOR STABILITY.

It stands to reason, that the Joel Davis test should be carried out on properly sealed and processed container units, and that the clinical trial itself likewise should be properly fashioned. It is common to test for seal in a process assurance sense, by a dye/leak test. Here a blister configuration (after having been cut to size) is placed in a dye solution in a desiccator; it is conventional to weight the blister down so that it stays submerged during the test. The desiccator is closed and vacuum (usually 10-15 cm Hg pressure) is applied for 5-10 minutes. Upon removal there should be no leakers. The test relies on visual detection of dye, and is usually carried out

on blank blisters at start-up (to ensure proper functioning of sealing components), and on actual packages periodically during the run.

If it is assumed , simply as an example, that the blister is 2 mm thick, and that the pressure head is P = 15 Torr = 1/50 atm (=$2 \cdot 10^4$ dynes/cm^2), then Poiseuille's law dictates a penetration rate given by:

$$V/t = \pi \cdot P \cdot r^4/(8 \cdot h \cdot \mu) \qquad (9)$$

where r is the radius of the pore, h is the thickness (0.2 cm), μ is the viscosity of the water from the desiccator (0.01 Poise), P is pressure head. If the detectable volume is 0.001 cm^3 (and it is probably more than that), then the critical flow rate would be this amount in 5 minutes, i.e.

$$V/t = 0.001/(5 \cdot 60) = \pi \cdot 2 \cdot 10^4 \cdot (r_{crit})^4/(8 \cdot 0.2 \cdot 0.01) \qquad (9)$$

from which it may be calculated that holes with radius less than a critical size, r* cannot be detected. r* is given by:

$$r^* = 5.5 \cdot 10^{-4} \text{ cm} = 5.5 \ \mu\text{m} \qquad (10)$$

It is hence seen that the test simply supports, but does not prove, that holes are not present. It is obviously a good test for gross seal leaks. There are, finally, the USP tests which test for moisture permeation using blisters packed with calcium chloride.

MOLECULAR PERMEATION.

If the situation in Fig. 2 is observed, then moisture penetration rates can be calculated theoretically by Peppas-kinetic principles. It is assumed that the diffusion of the water vapor into the bottle is proportional to the pressure differential, i.e. the relative humidity outside the bottle minus that inside the bottle (Peppas, l972).

It is assumed that the vapor pressure inside the bottle rapidly equilibrates with the solid, so that the equilibrium moisture pressure prevails throughout. Under these circumstances pressure curves can be generated based on permeation constants, π (or pin hole coefficients, Q), thickness of bottle, area of bottle, amount of tablets in the bottle, and the rate of moisture absorption. In the simplest case of a linear isotherm, the resulting equations can be solved in closed form (Carstensen, l989), and the various curves of importance generated.

Fig. 4 shows the generation of pressure in an empty bottle, and Fig. 5 the data plotted first order and Fig. 6 shows the effect of hygroscopicity of the solid in the bottle on the moisture uptake rate. Fig. 7 shows the effect of increasing the bottle size (or alternatively by reducing the amount of tablets in the bottle. Fig. 8 shows the effect of changing Q, be it the permeation coefficient or the size of a pin hole or defective seal. Increase in bottle thickness decreases the permeation rate (not shown in a figure here).

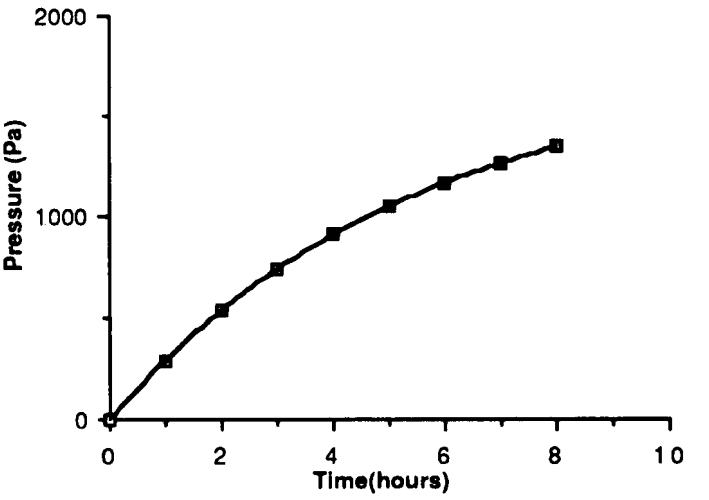

Fig. 4 Pressure development in an empty bottle.

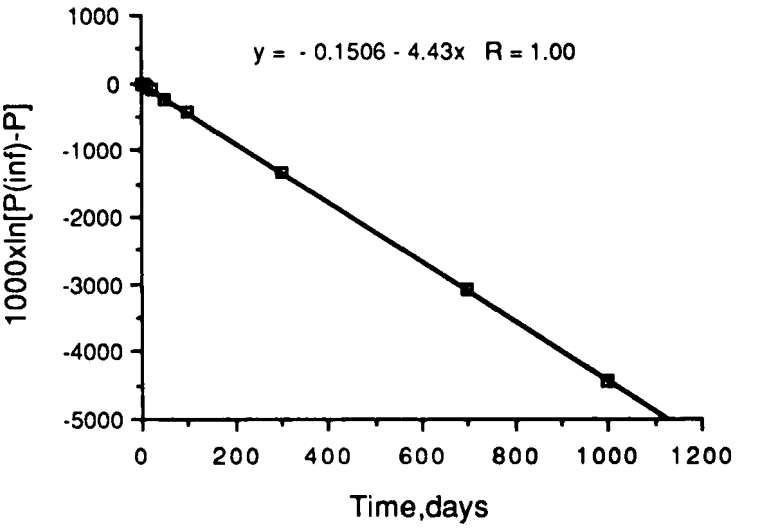

Fig. 5. Data in Fig. 4 presented logarithmically

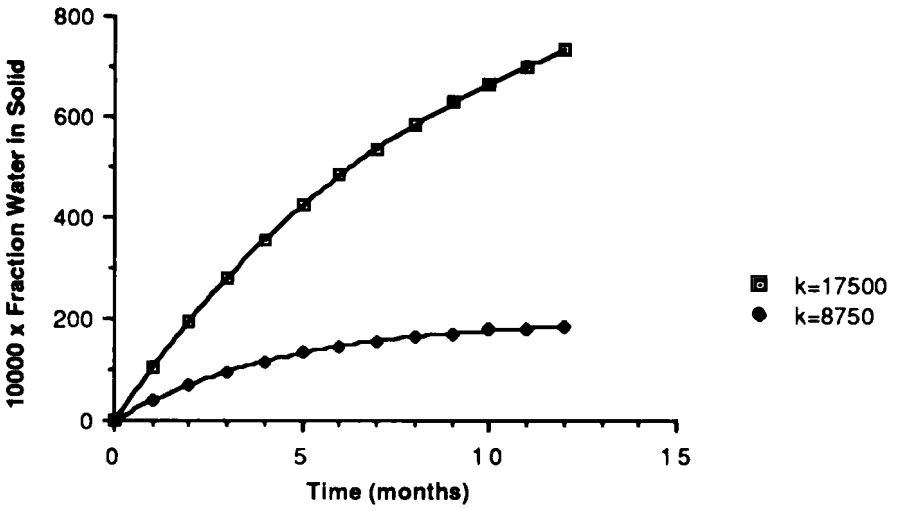

Fig. 6 Effect of hygroscopicity on water uptake rates in a bottle.

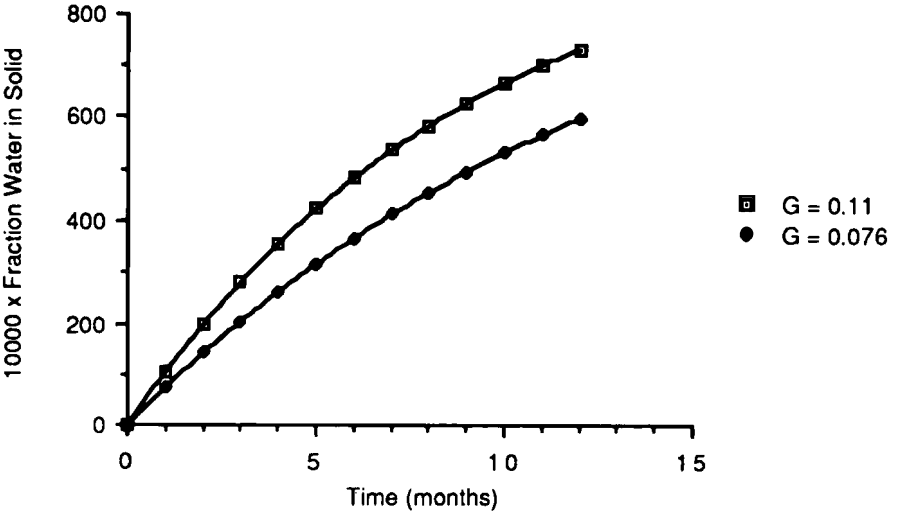

Fig. 7 Effect of bottle size (or amount of tablets in a bottle). G = 0.11 is twice the bottle size of G = 0.076

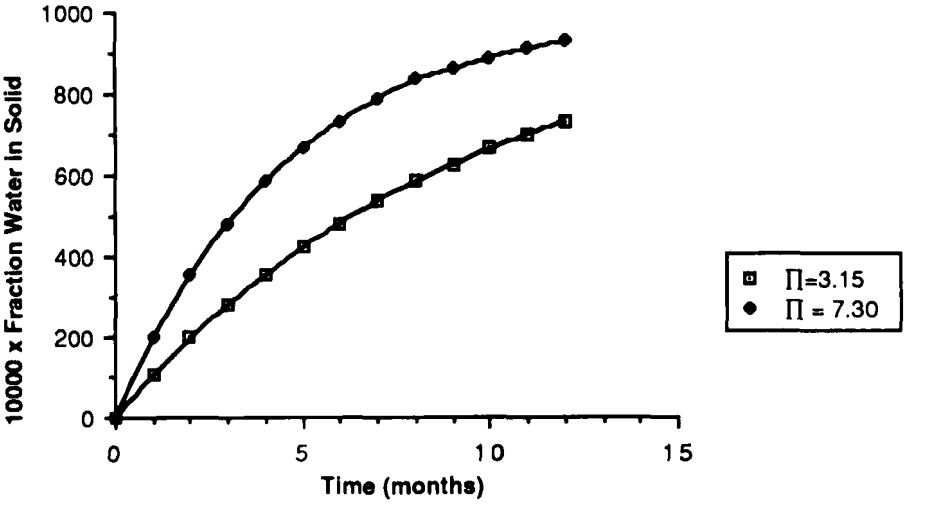

Fig. 8. Effect of Q (either permeation coefficient or pin hole size)

In all of the above, it is obvious that leaks can occur in bottles through the closure (the cap or the covering). Hence, torque testing is a must in the developmental phase (as well as in later manufacturing phases).

PACKAGING ASPECTS OF LIQUIDS.

An aspect of packaging of liquids (not applicable to solids) is that solutes may partition into plastic walls or closures. Coversely solutes in the plastics (e.g. plasticizers or monomers) may leach out into the drug solution. There are two aspects to this:

(a) the extent to which this can happen (partition coefficient)

(b) the rate with which it may happen.

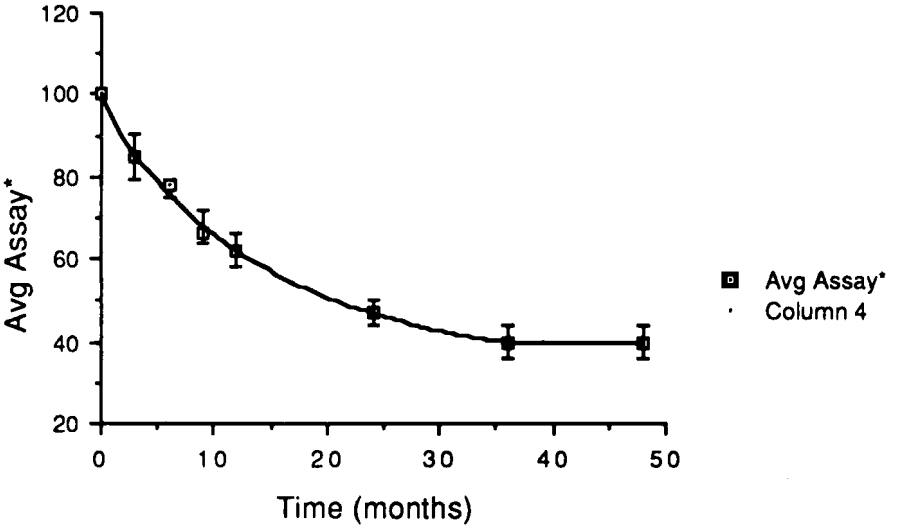

Fig. 9. Partitioning of solute into plastic container. Graph constructed from data by Mendenhall (l988).

Excellent reports on all the aspects of this have been published by Mendenhall (l984). Fig. 9 shows the partioning process, and Fig. 10 the kinetic treatment of it:

$$\ln\{C-C_\infty\} = -kt + \ln\{C_0-C_\infty\} \qquad (11)$$

The equilibrium constant is obtained by iteration, and the partition coefficient is then:

$$K = [C_0-C_\infty]/[C_\infty] \qquad (12)$$

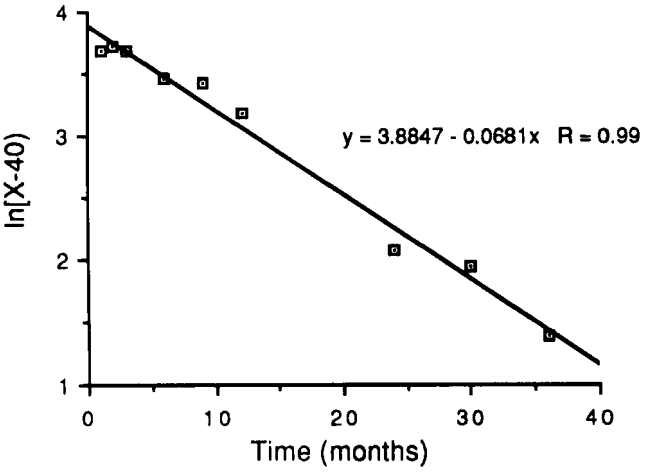

Fig. 10. Data treated according to Eq. 12. Graph constructed from data by Mendenhall (l988).

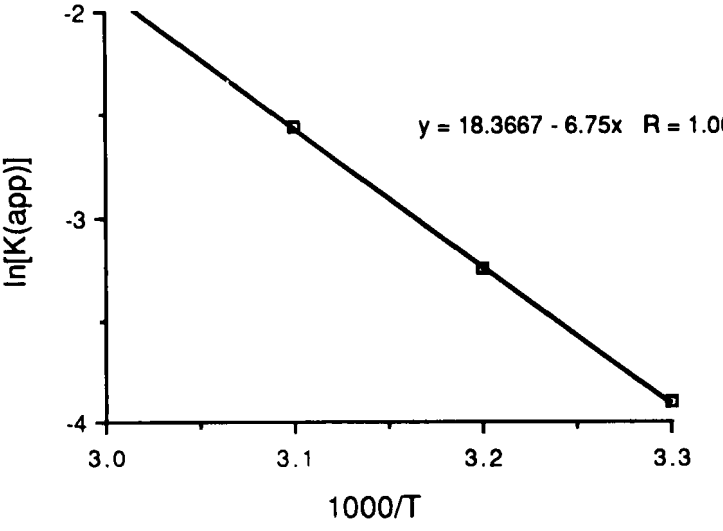

Fig. 11. Arrhenius plot of rate constants of the type shown in Fig. 10.

The first order rate constants for the approach to equilibrium (Eq. 11) may be treated by Arrhenius treatment as shown in Fig. 11:

$$\ln[k] = -(E_a/RT) + \ln Z \qquad (13)$$

It is hence important both to determine K and k at various temperature fairly early in the program, and to establish whether small changes in the polymer changes the partition and the rates.

REGULATORY REQUIREMENTS.

The Stability Guidelines (1987) require that the largest and smallest of each container/closure system be tested in the stability program. Originally there was the concept that all bottle/closure systems should be tested, but even the reduction to two of a combinations is quite labor-intensive. It also suffers from the fact that the two extreme sizes may not include the most common bottle size, and that is really the one of importance. The other container of importance would be the one giving the highest moisture penetration per dosage form unit.

Schultz (1987) has suggested using a matrix approach, but later (Schultz, 1988) underlined that if such an approach were to be used, then it would have to be pre-approved by the FDA on a case-to-case basis. This, however, may be useful, and an example of a method for

Table I. Incomplete Factorial Testing Scheme. (Not randomized)

Container	Closure	Months at RT: 1RH	2RH	3RH	RT3	RT6	RT9	12	18	24	36	48
A	i			•		•		•				•
A	j		*			•		•			*	
A	k	•		•			•			•		
B	i	*			*			•			•	
B	j		•			*		•				•
B	k			•			•			*		*
C	i				*	*		•			*	
C	j		•			•		•			*	
C	k	•		•			•			*		
Totals			4	3		4	3	3		3	3	3	3	3	4

labor saving would be to use a fractional factorial. If, for instance, there were three container types (A,B,C) and three closure types (i,j,k) and the conditions of testing were: RH: 1,2,3 months and 25°C: 3,6,9,12, l8, 24, 36 months, then a full factorial would call for 3 x 3 x 10 = 90 stations and assays. (By station is meant, here, that a container is placed in a particular storage location). The approach

calling for only the largest and smallest container would call for 2 x 3 x 10 = 60 stations and assays.

For a full factorial the program would be as shown in the scheme in Table I but with each condition checked. An example of a fractio nal factorial is shown.

This would constitute a total of 36 stations and assays, about 3 per conditions, and a total of four for each container/closure. The above is only one example (and is rather striated), and could be randomized by various criteria. In any event, if such a program is used, then it would be outside the Stability Guidelines (1987) presently in use, and would require pre-approval by the FDA.

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