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STABILITY OF PARENTERALS*

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I. INTRODUCTION

Although the broad topic of sterile product stability could encompass a number of rather specialized cases as well as the traditional small volume parenteral (SVP) injectables, the scope of this paper will be limited to SVP's in ampuls or multidose vials. Generally, these tend to be the more complex case and most problems encountered with other sterile products, including large volume parenterals (LVP's), will be encompassed in a discussion of SVP stability considerations. Another subject not specifically addressed is the burgeoning area of secondary packaging at the point of use (i.e., reconstituted and frozen I.V. additives, syringes, etc.); as evidenced by voluminous reports in professional journals, this is a topic of great interest to the hospital pharmacy practitioner. However, this subject tends to be too individualized for adequate treatment in a limited presentation

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such as this. Nonetheless, those engaged in such practices should be aware that the same stability liabilities discussed here are also applicable to these short term re-packaged dosage forms and as such specialized packaging and storage should be done only with adequate supporting stability information, usually available from the manufacturer.

In general, parenteral dosage forms are relatively simple from a formulation point of view, most often simple aqueous solutions of the drug with buffers and salts added to maintain pH and the proper osmotic pressure. Stability projections for such solutions under ideal conditions (i.e., stored in non-interactive containers, protected from light and under an inert atmosphere) are usually straightforward once the reaction pathway(s) and kinetics are known. The reader may already be familiar with such treatments which are also reviewed in other presentations on this program. Therefore, the usual solution decomposition pathways, such as solvolysis, will not be covered here; rather this discussion will focus on instability mechanisms somewhat unique or exaggerated with parenteral products.

Unique packaging, processing and performance requirements for sterile products have important stability ramifications. Economics and user convenience often dictate packaging in containers intended for multiple dosage administration. Thus, rubber closures are used when multi-dose vials are preferred over single-dose glass ampuls, exposing the drug formulation to a complex heterogeneous polymeric mixture which may radically alter its stability. In addition, small volume parenteral packaging offers near optimum conditions for photochemical and oxidative decomposition reactions: a large surface area to formulation volume ratio and an ample headspace. Requirements for particulate and sterility stability for parenteral products introduces another area of stability concerns for the formulator unique to this dosage form. Terminal sterilization by autoclaving may occasionally have important stability ramifications as well. Finally, lyophilized products are a somewhat unique subset of SVP's which have their

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own stability liabilities. It is these differences in parenteral dosage forms and their stability implications that will be discussed in this paper.

II. INTERACTION WITH PACKAGING COMPONENTS

A. Sorption of Formulation Ingredients

The use of rubber components in contact with solution dosage forms in multi-dose vials simultaneously introduces a potential sink for volatile, lower molecular weight formulation components and a reservoir of potentially reactive extractables. The loss of aromatic preservatives to the rubber closures of multi-dose vials and syringes is well known. Lachman *et al*[1] demonstrated that both p-chlorophenylethanol and chlorobutanol were rapidly lost from solution when in contact with neoprene stoppers (Fig. 1). A fairly typical rapid initial loss quickly levels off to an apparent equilibrium, indicative of a simple partitioning mechanism. Interestingly, in this case loss of antimicrobial activity did not correlate well with chemical preservative loss presumably due to the antimicrobial activity of extractables leached from the rubber. Similar losses have been shown for benzyl alcohol, methylparabens, and thimerosal to various stopper compositons[2-4]. Considerable variation between the apparent equilibrium distribution of various preservatives and rubber compounds was also shown (Table 1) suggesting one screening approach to select an optimum rubber formulation for a given preservative system[2]. Teflon coated stoppers have been shown to essentially eliminate this problem[5], although at a substantial cost premium; epoxy coatings were, however, found to be ineffective in decreasing preservative sorption[6].

Volatile active ingredients in parenteral formula's can show similar losses. This has recently been widely demonstrated for nitroglycerin (NTG) solutions in contact with either rubber or plastic packaging components[7-10]. A rapid initial loss followed by a more prolonged distribution phase is typically seen in all of

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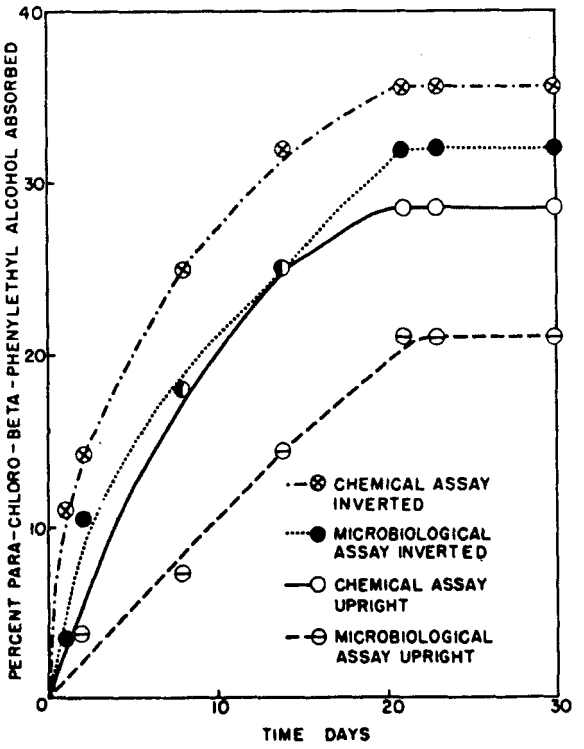

FIGURE 1

The percent of p-chloro-β-phenylethyl alcohol absorbed by neoprene stoppers from vial solutions stored upright and inverted at 60° as determined chemically and microbiologically. From Lachman et al, J. Pharm. Sci., 52, 241 (1963); reproduced with permission of the copyright owner.

these studies. Malick et al[9] proposed a two part model based on rapid reversible adsorption (A to B) followed by a slower absorption phase (B to C) into the packaging matrix from a NTG solution in plastic bags (Eq. 1 and 2); a good fit was shown to this bi-

$$A \underset{k_2}{\overset{k_1}{\rightleftarrows}} B \xrightarrow{k_3} C \qquad \text{Eq. 1}$$

$$A = \beta e^{-k_3 t} + (A_o - \beta)\, e^{-k_1 t} \qquad \text{Eq. 2}$$

exponential model (Fig. 2). A similar model is probably appli-

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TABLE 1

Apparent distribution coefficient (K_T) of various preservatives between different rubbers and a pH 4.0 buffer solution after 4 weeks at the indicated temperatures; the distribution coefficients reported were determined by dividing the concentration of the preservative remaining in the buffer (C_B) into the concentration calculated to be in the rubber (C_R). Data from Lachman et al, J. Pharm. Sci., 52, 244 (1963).

		$K_T = C_R/C_B$		
PRESERVATIVE	**RUBBER CLOSURE**	**25°**	**40°**	**60°**
PHENYLETHYL ALCOHOL	NATURAL	1.72	1.39	—
	NEOPRENE	4.23	4.13	—
p-CHLORO-β-PHENYL-ETHYL ALCOHOL	NATURAL	6.05	5.70	—
	NEOPRENE	16.40	21.80	—
CHLOROBUTANOL	NATURAL	9.05	6.83	—
	NEOPRENE	14.50	14.50	—
BENZYL ALCOHOL	NATURAL	0.63	0.63	—
	NEOPRENE	1.66	1.93	—
	BUTYL	—	—	~0
METHYLPARABEN	NATURAL	1.36	1.43	—
	NEOPRENE	7.27	8.40	—
	BUTYL	—	—	~0

cable to preservative and drug loss to rubber closures although, depending on the drugs and packaging components involved, adsorption may be alternatively insignificant or very rapid compared with the absorption phase and thus the model often collapses to a first order loss process. However, equilibrium with the packaging "phase" may not be practically reached over the shelf life of the product. For example, shown in Fig. 3 is some data from our labs on the loss of benzyl alcohol over time to a butyl rubber closure which appears to continue well beyond the two year shelf life of the product. While loss of drugs to primary packaging components is apparently relatively uncommon, diazepam, vitamin A, sodium warfarin, sodium methohexital, carmustine, and bleomycin have also been shown to be absorbed to a significant degree by various

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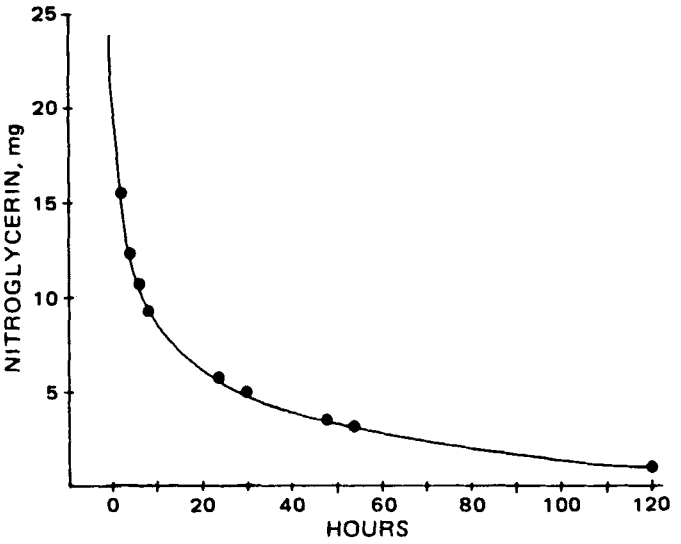

FIGURE 2

The amount of nitroglycerin remaining in a 100-ml aqueous solution contained in a plastic bag as a function of time after addition of the drug. The circles are experimental points and the solid line is the predicted curve according to Eq. 2. From Malick et al, J. Pharm. Sci., 70, 798 (1981); reproduced with permission of the copyright owner.

plastic IV bags and administration sets[11-14] underscoring this as a potential stability loss pathway in inappropriately selected packaging systems.

From the formulator's point of view, identifying potential formulation or packaging incompatibilities early on in the development program is critical to minimize the expenditure of research resources and to shorten the timetable for introduction of important therapeutic agents. Thus much effort has been expended in developing predictive stability techniques. Shown in Fig. 4 is a first order plot of some data on the loss of benzyl alcohol from an aqueous formulation in contact with a butyl rubber closure at several temperatures; in this case, the adsorption phase, indicated by the non-100% intercept, is very fast compared

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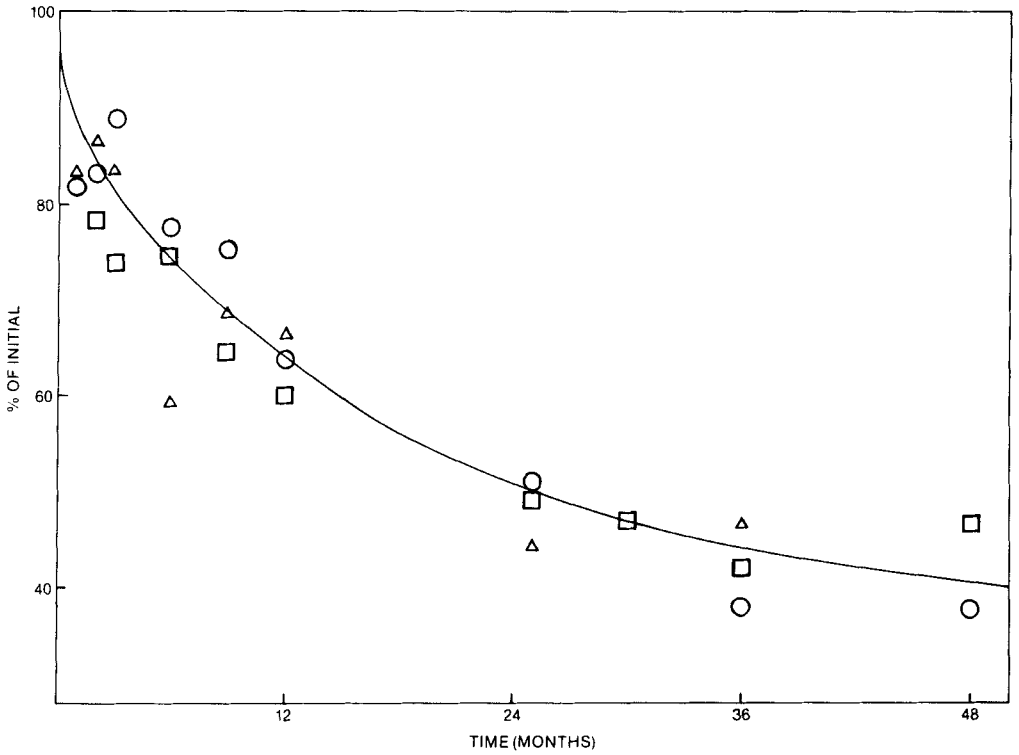

FIGURE 3

Los of benzyl alcohol from a 1.21% aqueous formulation to butyl rubber closures over time at 30°C; experimental data from three different lots (symbols) is shown along with an approximate curve of the average levels.

to the prolonged, apparent non-equilibrium absorption phase. Basically, this follows the same model proposed by Malick et al[9]. Rate constants derived from this simplistic analysis can then be plotted in an Arrhenius fashion to project the preservative content at 3 years (Fig. 5). While the fit of the data and the method are crude, the prediction was found to be in reasonable agreement with the actual loss found at 30°. Although only modest losses of active ingredients are generally tolerable (usually no more than ~10%), sufficient excesses of preservatives can usually

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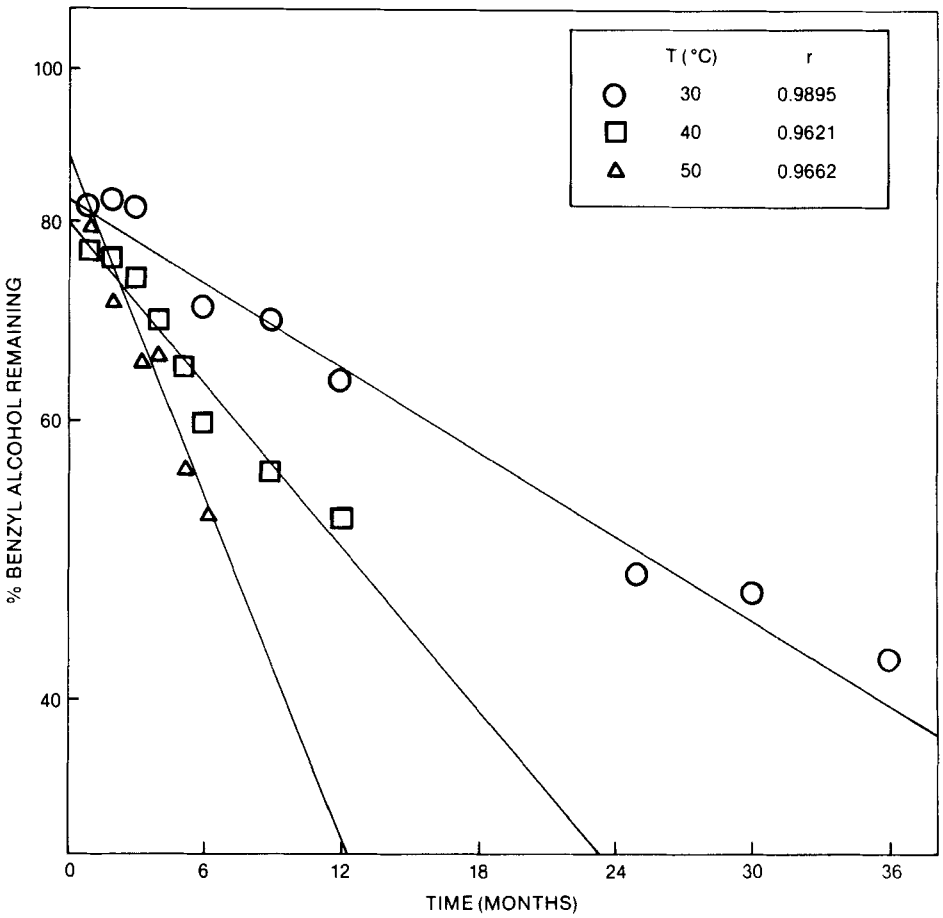

FIGURE 4

First order plots of benzyl alcohol loss to butyl rubber closures at 30°, 40° and 50° from a 1.21% aqueous formulation; each data point is the average of three lots and the lines represent the best fit linear regression curve with the indicated correlation coefficients (r).

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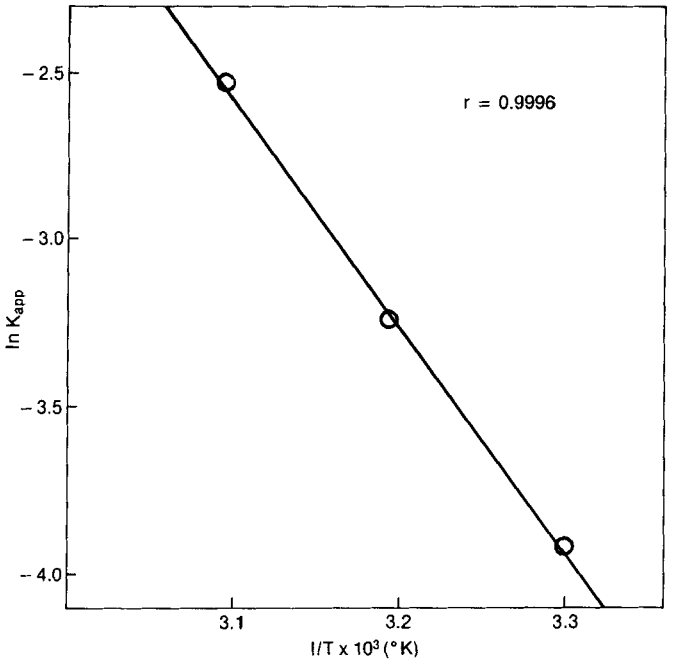

FIGURE 5

Arrhenius plot of benzyl alcohol loss rate data from Fig. 4.

be safely included in the formula to assure a reasonable shelf life in spite of such facile loss pathways. In this case, studies of presevative efficacy as a function of benzyl alcohol content indicated levels as low as 40% of initial were satisfactory. Thus from a preservative point of view this formulation would be acceptable for at least 3 years.

Such studies should generally be carried out with vials in the worst case inverted position to allow for maximum intimate contact of the solution with the stopper. However, in the unusual case where suitable non-absorbing packaging components cannot be identified, special labeling requiring upright storage may allow use of components which would otherwise not be acceptable if diffusion of the labile component through the headspace is limiting.

Illum and Bundgaard recently demonstrated that the hexane-water partition coefficient of various drugs is a reasonably

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accurate predictor of their sorption (at equilibrium) by PVC IV bags[15]. Such methods may provide the formulator or pharmacist with an early indictation of sorption potential, although the rate and thus stability risk would still have to be determined experimentally. A more quantitative model to determine the rate of absorption of volatile solution components in contact with rubber closures was proposed by Anderson and Motzi[16]; an adapted diffusion cell was used to determine the steady state flux of methylparabens through thin films of silicone and a candidate natural rubber compound. From this data the cummulative preservative loss as a function of time was estimated for the actual closures and found to be in moderate agreement with experimentally measured absorption by closures immersed in a 0.2% methylparabens solution.

B. Extraction of Contaminants from Packaging Materials

Another potential stability liability of parenteral packaging components, particularly rubber closures, is the gradual extraction of contaminants from the package components into the formulation. These can adversely affect the chemical or physical stability of the formulation, its appearance, or acceptability from a safety point of view. The widely reported extraction of phthalate plasticizers from plastic I.V. bags[17,18] is an issue of continuing concern to industry and government agencies alike. Aqueous solutions in contact with many rubber formulations used to manufacture closures have likewise been shown to leach significant quantities of catalysts and accelerators. These are most commonly metal salts, stearates and mercaptobenzothiazoles. The former would be of obvious concern when dealing with formulation ingredients subject to oxidative decompositions, reactions which are often catalysed by heavy metals. An example of this was recently reported [19] for a lidocaine with epinephrine formulation in which decomposition of the epinephrine was shown to be catalysed by aluminum at levels which were readily extractable from chlorobutyl closures[20]. Inclusion of EDTA in the formula may minimize the risk of adverse effects of such metal catalysis.

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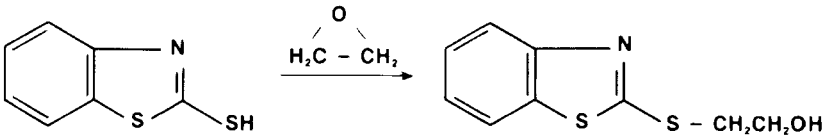
Mercaptobenzothiazole can likewise participate in oxidation-reduction reactions to reduce formulation potency or produce undesirable degradation products. For example, an apparent ethylene oxide addition product with mercaptobenzothiazole (Scheme 1) of unknown toxicity was recently isolated from a disposable syringe[21]; the source of this compound was attributed to accelerant from the rubber plunger face which reacted with the ethylene oxide used to sterilize the empty syringe. In addition to their chemical reactivity the limited solubility of these thiazole accelerants may contribute to haze or particulate problems over time, particularly if another formulation component (e.g., a preservative), which acts to help solubilize the thiazole, is gradually sorbed by the rubber closure thus eventually leaving the formulation supersaturated with respect to the thiazole. As will be discussed later, extraction of trace components from glass may also occasionally contribute to instability.

Avis and Boyett[22,23] have shown that leaching of rubber components from closures often follows a square root of time dependency, suggesting this is a diffusion rate limited migration process of extractables thru the rubber (Fig. 6). However, Milano et al found that data for aluminum extraction from chlorobutyl closures fit a "desorption" model equally well[20]; migration of water into the closure to dissolve the extractable aluminum salts was postulated as the rate limiting step rather than migration of the lipophobic inorganic salt itself through the rubber matrix. Various rubber preparation techniques (e.g., EDTA or solvent treatment) have met with only limited success in removing contaminants[23,24]; thus, the formulator's only protection from related long term stability problems is judicious selection of the



SCHEME 1

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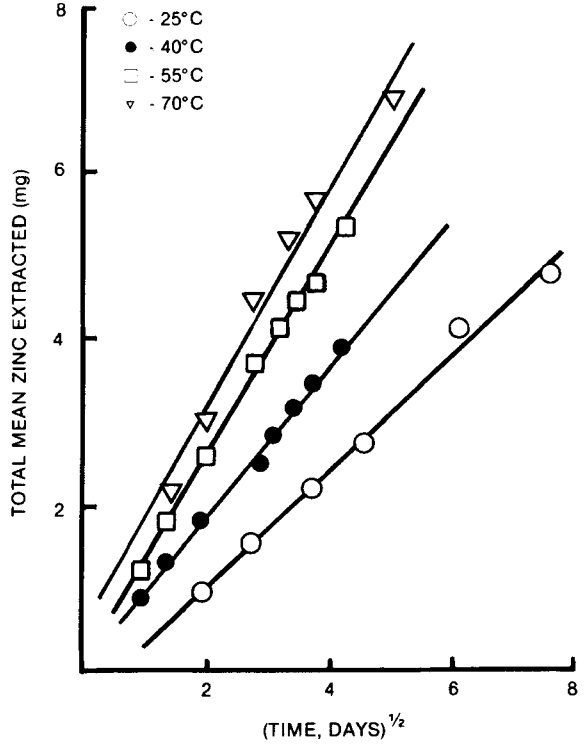

FIGURE 6

The effect of temperature on the rate of zinc extraction from butyl rubber closures in pH 1.9 buffer solution.

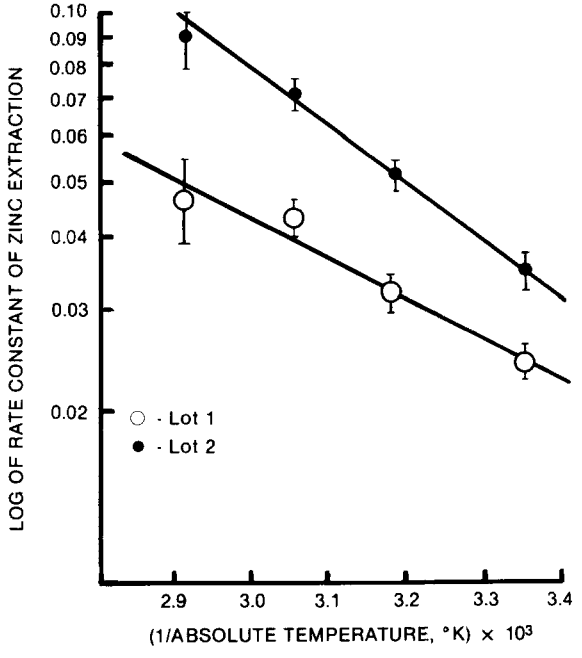

FIGURE 7

Arrhenius plot of the rate constants of zinc extraction from butyl closures; data from two lots of the same closure are shown, the open circles being the same lot studied in Fig. 6.

Both figures from Boyett and Avis, Bull. Parenter. Drug Assoc., 30, 169 (1976); reproduced with permission of the Parenteral Drug Association.

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rubber formulation (usually in consultation with the rubber vendor) combined with accelerated extraction and compatibility tests with the formulation of interest. Boyett and Avis[23] showed that Arrhenius-type predictions from high temperature accelerated extraction studies may sometimes be useful (Fig. 7), but cannot be applied to all rubber formulas not all of which followed such simplistic models. Alternatively, epoxy coated and teflon coated stoppers have been shown to decrease extractables dramatically so long as they have not been punctured frequently[5,6]; however, the cost premium for these articles makes them unattractive except as a last resort. With the use of non-aqueous solvents and/or aqueous cosolvent mixtures, the qualitative and quantitative composition of extractables can be expected to change significantly.

III. STERILITY

Maintenance of sterility itself over the shelf-life of the product is of obvious critical importance requiring assurance of continued closure seal integrity. Methodology to accomplish this is currently being debated by regulatory and industry groups. FDA representatives have recently argued for periodic compendial sterility testing as part of the formal stability program[25]. Others feel that physical testing of closure integrity over time by a variety of methods (including leak, dye immersion, pressure hold, vacuum and microbial broth immersion tests) is more meaningful since, for an even modestly effective closure system, a sterility testing failure requires the intersection of two relatively low probability events: a fissure or opening in the closure seal and entry of a micro-organism through the defective seal. Thus physical testing will be a more rigorous and accurate predictor of overall closure performance as well as less demanding on testing resources. The Parenteral Drug Association has announced a bulletin describing methodology to assure container-closure integrity will be published shortly.

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IV. PHOTOCHEMICAL/OXIDATIVE DECOMPOSITIONS

Another packaging related stability liability, somewhat exaggerated with parenteral products (particularly SVP's) are photochemical and oxidative decomposition reactions. These two reaction categories are treated without distinction in this discussion. Both are usually free radical mediated and thus one pathway is not easily distinguishable from the other. However, it should be kept in mind that photochemical reactions can occur in the absence of oxygen (or other independent electron donnor or acceptor) and, obviously, oxidative reactions can occur in the absence of the catalytic effect of light.

The relatively large surface area to formulation volume ratio found with SVP's (as for example ampuls) assures maximum light impingement on the relatively dilute drug solution and a short path length. Furthermore, headspace gas to formulation volume ratios tend to be much higher with SVP's, offering an ample reservoir of molecular oxygen in non-purged packages. Such decompositions should always be given careful attention in the development of parenteral products since they may produce complicated structures, far removed from the parent compound. The production of even trace amounts of unusual chemical entities (i.e., those which would not normally be produced by hydrolytic or metabolic degradation routes and thus screened in safety studies whether or not they are specifically recognized, identified and/or quantitated) is cause for serious concern. Screening programs should therefore thoroughly investigate potential oxidative decomposition pathways even if substantial losses (e.g.,>5%) are not projected over the intended shelf life under normal storage conditions.

I do not intend to attempt to review the mechanisms of these types of free radical decomposition pathways in the limited space available; this really could be the subject of a separate discussion by itself. Rather I would like to focus on the various approaches to defining at an early stage the stability risks via

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these routes and the strategies available to extend the product shelf life by preventing or inhibiting these reactions.

Once the formulator has been alerted to the potential of a given molecule for oxidative or photochemical stability problems via, for example, a 2 by 2 factorial stress test (Fig. 8) in the preformulation work-up, the next task is to quickly estimate whether the identified decomposition route is significant with respect to the desired shelf-life. Stress testing in a predictable manner such that decomposition rates and shelf lives can be estimated in a short period of time is the next rational step. However, for a true chain reaction with an efficient propagation step (relative to termination pathways), stress testing is not very meaningful for stability projections. As illustrated in Fig. 9, depending on the nature and intensity of the applied stress, the normal order, rate determining step and possibly primary decompositon pathway may change. Thus, unless the often elaborate kinetic mechanisms involved have been fully elucidated (an effort usually far beyond the early preformulation investigation), stress testing of efficiently propagated free radical or oxidative chain reactions are really only useful for relative qualitative comparisons of alternative formulations and the efficacy of stabilizing agents (e.g., antioxidants, chelating agents), and then only with a great deal of caution. It may be tempting to try to utilize thermal stress alone to facilitate such predictions, rationalizing that lowering the energy of activation

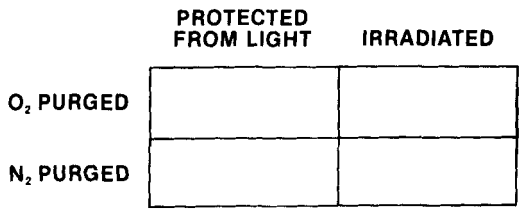

FIGURE 8

2 x 2 factorial matrix for determination of oxidative and/or photochemical decomposition sensitivity of parenteral solutions.

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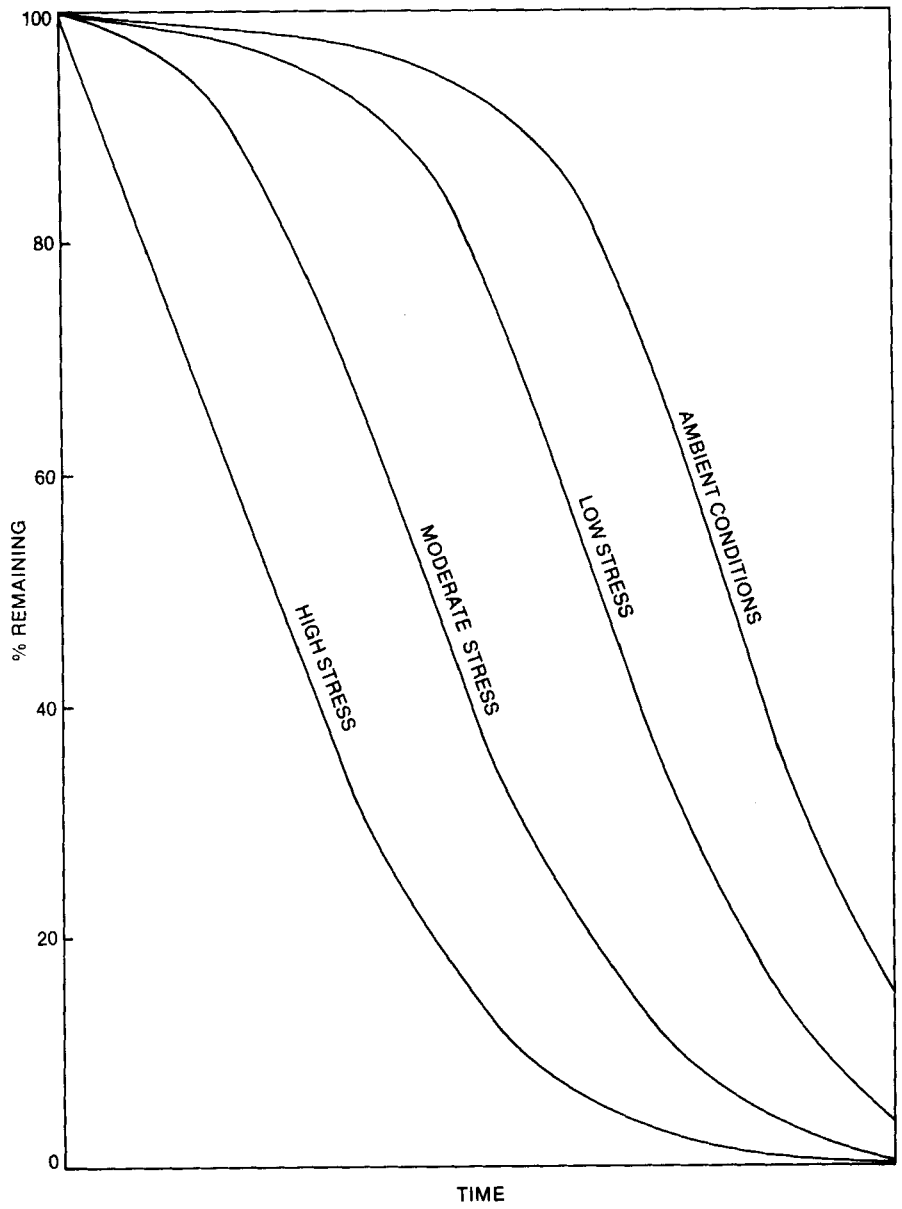

FIGURE 9

Hypothetical decomposition profiles for a solution subject to free radical chain reaction under various stress conditions.

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will not effect the qualitative course of the reaction, only its rate. However, limited investigations of this premise have not supported this simplistic assumption. For example, the unreliability of using thermal stress as a predictor of room temperature stability performance with respect to oxidation reactions was recently illustrated for epinephryl borate solutions containing different antioxidants[26].

For quantitative prediction of oxidative reactions which are not readily propagated (i.e., effectively every radical produced is "terminally" consumed when it reacts with the drug), at least two stress parameters appear relevant and practical: oxygen tension and irradiation.

A. Oxygen Stress Testing

As illustrated in Table 2, by manipulation of the oxygen partial pressure in the headspace gas and solution temperature a broad range of oxygen concentrations (well above ambient levels) is achievable in aqueous formulations. If then the decomposition reaction being studied involves reaction of a fixed number of molecules of oxygen with a molecule of drug, 2nd order (or pseudo-first order) kinetic treatment of stability data at a known high oxygen concentration should yield a rate constant which can be used to accurately predict ambient shelf lives.* Unfortunately, the limited number of published reports on oxidative decomposition in which solution oxygen content is varied either do not address the quantitative potential of this approach or deal with reactions which are apparently too complex for such treatments. For example Sokoloski and Higuchi's study of epinephrine decomposition in solution[27] indicated a complex mechanism in which the order with respect to both epinephrine and oxygen changed as a function of the concentration of the reactants. The less than unity order with higher concentrations of both reactants and the catalysis

*Obviously, reactions carried out at lower temperatures to take advantage of increased oxygen solubiltiy will have to be corrected for thermal effects on reaction rates.

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TABLE 2

Oxygen solubility in water under various temperatures and pressures. Data from Seidell's "Solubilities of Inorganic and Metal Organic Compounds", 3rd and 4th editions.

	cc O_2 (S.T.P.) PER 100 g in Equil. with			
T (°C)	AIR at 1 ATM.*	O_2 at 1 ATM.*	O_2 at 6.67 ATM.	O_2 at 20 ATM.
0	0.99	4.87	—	—
5	0.87	4.25	—	—
10	0.76	3.76	—	—
15	0.72	3.36	—	—
20	0.62	3.04	—	—
25	0.57	2.75	—	—
30	0.53	2.51	—	—
35	0.49	—	—	—
38	—	—	16.0	33.0
40	—	2.16	—	—
50	—	1.86	—	—
60	—	1.59	—	—
70	—	1.30	—	—
80	—	0.97	—	—
90	—	0.55	—	—
93	—	—	10.0	23.0
100	—	0.00	—	—

*Partial pressure of gas plus vapor pressure of water

observed with copper in this study were both suggestive of a free radical chain reaction mechanism even though no lag phase typical of such reactions was seen. A recent report on decomposition of morphine in formulations up to 43 years old showed a dramatic, though non-quantitative, correlation of headspace gas (and thus total available dissolved oxygen) with extent of degradation for several parenteral dosage forms [28]. Thus, although definitive evidence is lacking, such an approach appears worthy of further investigation for quantitative stabilty predictions for simpler mechanistic systems.

B. Photo-Irradiation Stress Testing

Irradiation stress testing, while apparently much more widely used, is usually interpreted soley from a qualitative standpoint,

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although empirical estimates of "equivalent normal lighting" are frequently used. The Cooper-Lachman light cabinet, originally described in the early 60's[29], remains the industry standard. Although this cabinet has the potential of giving variable light intensities, either by adjustment of the sample distance from the light source or by direct variation of the light intensity by the use of a rheostat, it would appear that photolytic stability studies are most commonly carried out at one or two intensities as a means of qualitatively assessing the relative effect of various environmental and formulation factors (e.g., air vs. nitrogen purging, antioxidants, etc.) on product shelf life. The latter may be estimated on the basis of color change, but the risks of this approach without confirmatory stability indicating chemical assays are considerable[30]. Regrettably, as has been pointed out by others[30,31], attempts to quantitatively estimate photolytic decomposition under use conditions based on stress testing are almost non-existent in the pharmaceutical literature.

In our labs we are interested in developing such a method in order to predict photostability at an early stage so that we may develop suitable protective packaging or formulation alternatives, if necessary, before clinical testing. Specifically, we would like to be able to predict the photostability of a formulation under ambient lighting based on its behavior under high intensity light.

For a drug molecule in solution which undergoes a photolytic decomposition reaction in which free radical chain propogation is essentially non-existent (i.e., the excited state electronic energy is dissipated via intra-molecular rearrangement or bond cleavage without the creation of another reactive species), the reaction can be viewed as a simple second order process (Eq. 3) involving a photon of light, $h\nu$, of the appropriate wavelength colliding with the photolabile species, A. Under constant irradiation conditions, the "concentration" of photons striking the solution can be considered to be constant and thus instantaneous pseudo-first order kinetics are predicted in the "1st

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layer" the light impinges on (Eq. 4). The right side of Equation 4 can be more usefully represented by the product of the amount

$$A + h\gamma \rightarrow B \qquad \text{Eq. 3}$$

$$-dA/dt = kh\gamma A = k'A \qquad \text{Eq. 4}$$

$$-dA/dt = \phi I_a \qquad \text{Eq. 4a}$$

$$I_a = I_o - I \qquad \text{Eq. 5}$$

$$\text{Log } I_o/I = \epsilon bA \qquad \text{Eq. 6}$$

$$I = I_o\, 10^{-\epsilon bA} \qquad \text{Eq. 6a}$$

$$-dA/dt = \phi I_o (1 - 10^{-\epsilon bA}) \qquad \text{Eq. 7}$$

$$\text{Log } \frac{10^{-\epsilon bA}}{1 - 10^{-\epsilon bA}} = \phi\, I_o t \qquad \text{Eq. 8}$$

$$A = A_o - \phi\, I_o t \qquad \text{Eq. 8a}$$

$$\text{Log } A = \text{Log } A_o - \phi\, I_o t \qquad \text{Eq. 8b}$$

of light absorbed, I_a (proportional to the concentration for any given layer), and the quantum efficiency, Φ, a proportionality constant which, analgous to a rate constant, accounts for the number of molecules of A converted to B per photon of light of the appropriate wavelength absorbed (Eq. 4a). The amount of light absorbed by a solution is given by the difference between the amount of light incident on the solution, I_o, and the that transmitted, I (Eq. 5). However, the amount of light transmitted by successive layers as the light traverses the bulk solution falls off exponentially according to Beers Law, Equation 6, wherein ϵ is

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the molar absorptivity and b is the pathlength. Rearranging and substituting Equations 5 and 6a into Equation 4a gives an expression for the rate of loss as a function of light intensity (Eq. 7). Integration of this expression leads to a relatively complex appearing relationship (Eq. 8); however, for cases of practical interest to the formulator (i.e., irradiation of the commercial dosage form, the package and concentration most likely to be subject to long term exposure to light) the denominator of the logarithmic term in Equation 8 approaches unity* and thus 8a is a reasonable approximation for at least the initial rate of loss (from t_0 to time t covering the first 10-20% of degradation) which is most significant to the formulator. Such apparent zero order behavior has been reported for many compounds of pharmaceutical interest[32-36]. Alternatively, for very dilute solutions, as may be experienced with I.V. additives, it can be shown[37] that the left side of Equation 8 approaches as a limit a simple logarithmic function (Eq. 8b) predicting a first order relationship.** Similarly, dilute solutions of a number of compounds of pharmaceutical interest have been shown to photodecompose according to this log-linear pattern[36, 38-44].

Thus, according to Equations 8a and 8b a plot of the apparent zero order or first order rate constants at different light intensities should then be a linear function of the incident light intensity with a slope of Φ. However, in investigating the decomposition rates of a photochemically sensitive research compound as

*For even a relatively dilute parenteral formulation (e.g., 1 mg/ml of a compound with a molecular weight of 300), a molar absorptivity as low as 600 (well below that usually found for most organic drug molecules in the 250-350 nm range of wavelengths responsible for practical photolytic cleavages) will allow only 1% of the incident light in this range to pass thru one centimeter of solution; this approximation will then cause less than a 1% error in equation 8 for pathlengths greater than 1 cm.

**This transition from apparent zero-order to apparent first-order behavior occurs over an approximate two order of magnitude concentration range.

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a function of light intensity, we found this relationship did not appear to hold. Alternatively, when the log of the apparent first order rate constants were plotted against the reciprocol of light intensity, we found excellent linearity (Fig. 10). While it may be tempting to hypothesize that, analgous to Arrhenius treatment of thermal rate data, the reciprocol of any measure of energy input would show such a relationship to the rate, we are unaware of any theoretical support for this empirical observation. Quantum theory requires that light energy be absorbed in discrete packets as opposed to the continuum of thermal energy upon which the theoretical soundness of the Arrhenius relationship is based; thus, light energy is more properly treated as a reactant, whose "concentration" (or photon density) is increased with light

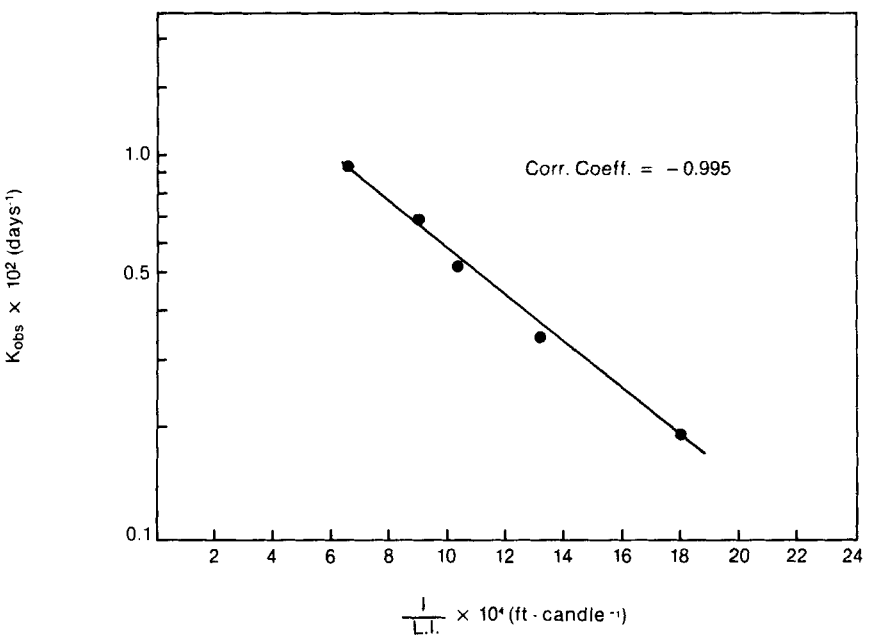

FIGURE 10

Plot of the log of the apparent first order decomposition rate versus the reciprocol of light intensity for an experimental drug formulation under various fluorescent light intensities, all at 30°.

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intensity. Dr. Larry Hsu in our laboratories is extending this preliminary investigation to other photosensitive drugs and we hope to be able to confirm that this accelerated light stability indicating method is useful, accurately projecting decomposition rates under normal room lighting.

C. Protective Measures

Once oxidative or photocatalysed decomposition reactions have been identified as a problem, several strategies are available to the formulator to enhance stability. For oxygen sensitive compounds, the most straightforward approach might appear to be simply purging the solution and headspace with an inert gas such as nitrogen. Depending on the packaging and other processing considerations this approach may not however be practical nor cost effective. Furthermore, for reactions in which oxygen participates only catalytically or for very dilute drug solutions, even trace amounts of residual oxygen which cannot practically be removed may render the product unstable. Other "brute force" approaches such as light protective packaging (e.g., amber glass or individual cartoning) may also be effective but are not preferred due to inspection difficulties and cost considerations. Thus, formulation approaches, such as antioxidants, are usually the first choice to enhance the shelf life of such products.

A variety of antioxidants and chelating agents are available for use in aqueous or non-aqueous parenteral products (Table 3). Of these, by far the most commonly used in aqueous parenteral formulations are bisulfite and EDTA. Selection of the optimum agent (or combination of agents) is often, regrettably, largely empirical since oxidation potentials alone are not wholly indicative of the antioxidant's performance in the actual formulation[26]. Akers has suggested a 3 stage screening approach for identifying the best antioxidant system wherein the stability of an aqueous solution of the antioxidant itself is first determined, alone and then in combination with other agents. The most promising agents, as determined by both initial re-dox potential

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TABLE 3

Antioxidants	Usual Concentration (%)
Acetylcysteine	0.5
Ascorbic Acid	0.02 - 1.0
Hindered Phenols (e.g., BHT)	0.005 - 0.02
Propylgallate	0.005 - 0.02
Sodium Bisulfite	0.1 - 0.15
Sodium Metabisulfite	0.1 - 0.15
Thioglycerol	0.1 - 1.0
Thiourea	0.5 - 1.0
Tocopherols	0.05 - 0.075
Chelating Agents	
Citric Acid	—
EDTA	0.01 - 0.075

determinations and relative stability, were finally formulated with drug and subjected to high temperature stability evaluation. Results did not wholly confirm screening studies, illustrating the need to carry out such studies in the presence of all formulation components since they may affect the ability of the antioxidant to effectively quench the free radical mediated process regardless of relative oxidation potentials. Interestingly, the most effective system found in that study involved ascorbic acid as the primary antioxidant which itself was stabilized by inclusion of thiourea.

Although one of the most effective and widely used antioxidants, sodium bisulfite is also a potent nucleophile and may itself contribute to a decrease in drug potency if active ingredients possess centers for nucleophilic attack. As illustrated in Scheme 2, epinephrine and dopamine are both susceptible to similar oxidative degradation, resulting in intramolecular cyclization of the ring and discoloration[45]. Sodium bisulfite effectively blocks this reaction for both compounds, presumably by blocking propogation of the oxygen and semiquinone radicals. However, Higuchi and Schroeter[46] demonstrated that bisulfite also attacks

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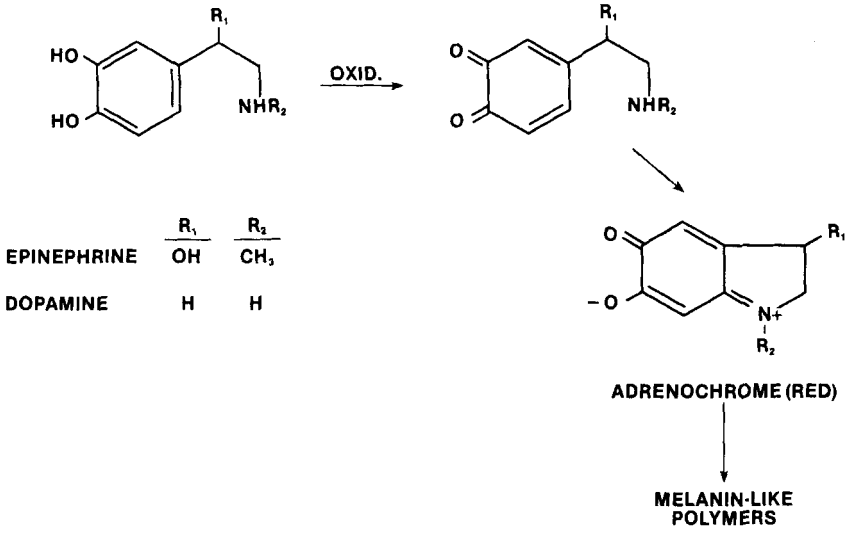

SCHEME 2

the benzylic carbon of epinephrine, apparently via both an SN1 and SN2 mechanism depending on pH, resulting in a loss of optical activity and corresponding potency (Scheme 3). Similarly, oxidation of morphine to pseudomorphine has been shown to be blocked by sodium bisulfite, although substantial amounts of a sulfite adduct can also be formed[47,48]. Such reactions may not always preclude use of bisulfite. For example, in a recent report by Hussain and Iga[49] on bisulfite addition to physostigmine, the reaction was shown to be readily reversible to yield the active drug even though the attack involves an optically active center (Scheme 4). More recently, Massey and Long[50] reported an unusual reaction of dobutamine in the presence of bisulfite at autoclave temperatures; the reaction rate was dependent on bisulfite concentration and appeared to involve bisulfite itself acting as an oxidizing agent although no specific mechanism was proposed. Many other drugs have also shown reactivity towards bisulfite, and thus its effect on all pathways of drug instability should be carefully evaluated before use.

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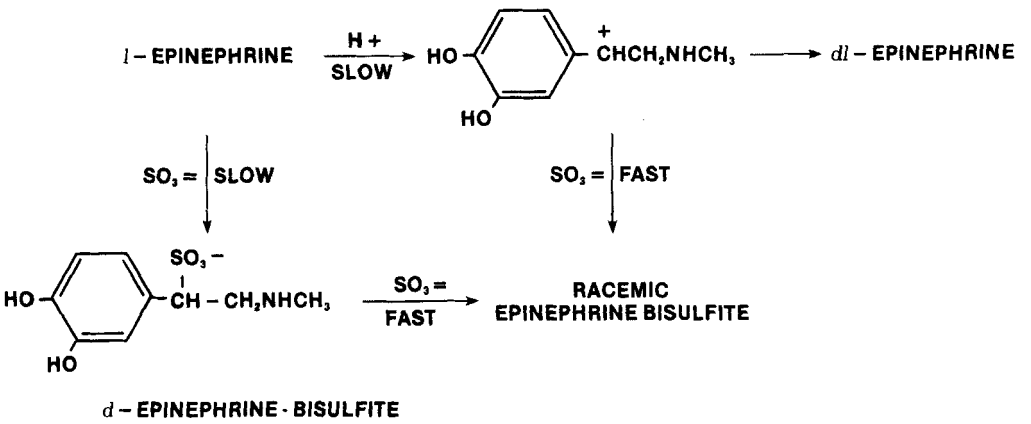
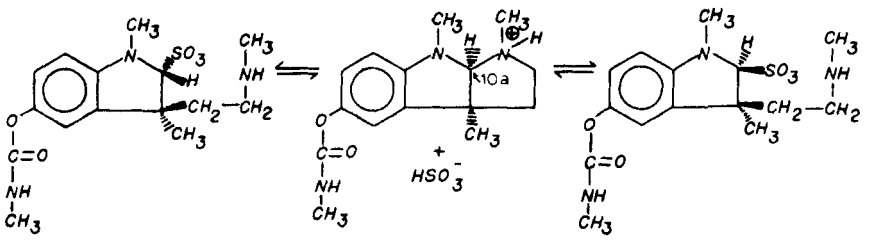


SCHEME 3



SCHEME 4

From Hussain and Iga, J. Parenter. Drug Assoc., 33, 32 (1979); reproduced with the permission of the Parenteral Drug Association.

Although not nearly as significant a problem, EDTA has also been shown to catalyse decomposition of a number of drugs, including neomycin, epinephrine, isoproterenol, and physostigmine [51 and references therein]. Although the mechanism(s) of this accelerated degradation in the presence of EDTA has not been clearly elucidated, it would seem most likely that it involves general acid or general base catalysis.

For photosensitive parenteral drugs, a common strategy is to employ amber glass to eliminate the higher energy, lower wavelength radiation responsible for light-initiated degradation of organic compounds (Fig. 11). Although usually very effective,

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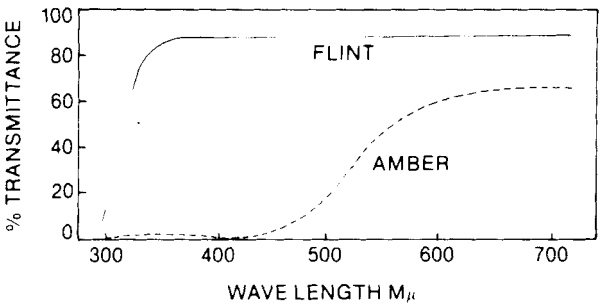

FIGURE 11

Light transmission curves for typical flint and amber glass.

this approach also has some liabilities in addition to the inspectional difficulties and corresponding increased costs. Lipper and Nevola[52] recently reported an unexpected increase in the rate of thimersol decomposition in amber glass containers compared with flint (Table 4). EDTA appeared to decrease but not eliminate this phenomenon. The authors concluded that leaching of iron and/or manganese, both of which are present in substantial quantities in amber glass compared with flint[53], caused this decreased stability. Similar decreased stability in amber containers compared with flint has been observed with both amitriptyline[54] and ascorbic acid[55], presumably attributable to the same phenomenon.

V. PARTICULATES

Another area of stability concerns unique to parenteral products is particulates. U.S.P. requires parenteral formulations (in the liquid state) to be free of visable particles when viewed in normal room lighting; in addition compendial limits for subvisual particulates presently exist for LVP's (not more than 50 > 10u and 5 $\geq$ 25u/ml) and are being developed for SVP's for possible inclusion in the next U.S.P. Although published data are not presently available for this sensitive problem, it is known that

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TABLE 4

Percent of initial thimersol after 34 weeks storage in ampuls at the given conditions. Data from Lipper and Novela, paper presented to 31st National APHA Academy of Pharmaceutical Sciences Meeting, Orlando, Florida, November 15-19, 1981.

		Exposed to Light		Foil Covered	
T (°C)	Glass	Without EDTA	With EDTA	Without EDTA	With EDTA
5	FLINT	102	94	101	99
	AMBER	102	98	101	102
37	FLINT	88	97	88	100
	AMBER	58	80	58	80
50	FLINT	27	85	31	91
	AMBER	0	46	0	50

particulate levels do increase with time in some cases and may prove to be limiting to the shelf life of some products. Sources of particulates include container components (e.g., shedding of Type II glass containers, pieces of rubber closure), insoluble formulation decomposition products or closure extractables. Furthermore, reconstituted lyophilized products have substantially greater particulate levels than solutions; this may be due to the phenomenon of "micro-meltbacks" which produce a small fraction of essentially insoluble or very slowly dissolving solid product. Alternatively, soluble trace contaminants in the raw material may redissolve only very slowly once forced out of solution by lyophilization. This particulate stability issue can be expected to become more visible as government, industry and compendia groups continue to work towards standards which will insure the continued production of safe products at technically achievable particulate levels.

VI. DISPERSED PHASE SYSTEMS

Although the vast majority of commercial sterile products are provided as true solutions or powders for reconstitution, a

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limited number of dispersed phase (i.e., suspensions, emulsions or colloids) parenteral formulations are available. Parenteral formulations in these dosage forms are fundamentally no different than non-sterile dispersed phase systems (covered elsewhere in this program), having the same physical and chemical stability liabilities. However, one aspect, related again to rubber closures, may be somewhat exaggerated with emulsions or suspensions packaged in multidose containers and thus deserves special mention. Dispersed phase systems often depend on a delicate balance of formulation constituents (e.g., surfactants, emulsifiers, cosolvents, etc.) to maintain their metastable physical state. Thus loss of even small amounts of these usually low concentration components to the rubber closure over time may adversely effect the physical stability of the system, resulting in floculation, caking, coalesence, separation, etc. This potential, chemically dependent physical instability pathway should be kept in mind in designing such formulations and selecting packaging components.

VII. AUTOCLAVING

Liquid products which are terminally sterilized by autoclaving are confronted with a short but intense thermal stress which can have important stability ramifications, especially for formulation components having decomposition pathways with high energies of activation. Generally, products are exposed to peak autoclave temperatures (usually no more than a few degrees greater than 121°C) for only 30-60 minutes; however, depending on batch size, packing, container mass, etc., heat up and cool down times can extend this high temperature exposure up to 24 hours. Yang *et al* recently reported on a non-isothermal model which could be used to predict the amount of drug decomposed in an autoclave cycle[56]. The oxidation of dobutamine by bisulfite previously mentioned occurred only under autoclave conditions, yielding unacceptable parent drug loss[50]; in this case, aseptic filling instead of autoclaving eliminated the problem..

Yang and co-workers also pointed out a little considered if not unusual formulation stability effect of autoclaving[57]. A sig-

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nificant difference in the hydrolytic decomposition of diatrizoic acid, a radio-opaquing agent, during autoclaving was observed depending on the counterion used in neutralizing the acid to the same pH, either sodium or meglumine. It was found that this was due to differences in the ionization constants of meglumine versus water as a function of temperature. Effectively, meglumine is a relatively weaker base at higher temperatures and thus formulations titrated with this base become measurably more acidic during autoclaving compared with the sodium hydroxide neutralized formula. Since the decomposition reaction is base dependent, the meglumine containing formula was therefore significantly more stable during the autoclave cycle, yielding a more acceptable product with a longer shelf life.

A recent study on the stability of an organophosphate antidote "cocktail" in glass and plastic containers was suggestive of an additional stability liability for terminally sterilized parenterals in contact with potentially absorptive packaging components[58]. A significant drop in pH at higher temperature (80°) in plastic containers compared with glass was correlated with a marked increase in the rate of loss of one of the formulation components, trimedoxime bromide; whether the pH shift in the unbuffered formulation (probably due to selective adsorption of a formulation component or desorption of a packaging component) was the cause of the increased drug loss or a result of it was not shown nor whether actual decomposition catalysis was involved. Nonetheless, the formulation was clearly not suitable for autoclaving in plastic containers despite apparently acceptable kinetic data in glass containers.

VIII. LYOPHILIZED PRODUCTS

Lyophilized dosage forms have their own unique set of stability problems which can be categorized into several groups:

A. Affect of Residual Solvent/Moisture

Since economics preclude freeze-drying of a drug unless poor solution stability demands it, lyophilized products are

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essentially by definition unstable in their intended reconstitution solvent, usually water. Thus, the stability profile of these dosage forms will be dependent on residual moisture in the lyophilized product. At low moisture levels (as would be found in the dried cake), solvolytic degradation can be expected to approach zero order conditions since the reaction will depend solely on the essentially constant amount of moisture available to dissolve the drug; since there is always an excess of drug in the solid phase, this adsorbed moisture layer will remain saturated with drug throughout and zero order kinetics will result (until, of course, significant amounts of the available moisture are consumed in the hydrolysis reaction). This is illustrated in Eq. 9 and 10, where A_s is the saturation aqueous solubility of the

$$-dA/dt = kA = kA_s \qquad \text{Eq. 9}$$

$$A = A_o - kA_st \qquad \text{Eq. 10}$$

decomposing species A whose initial mass is A_o. Huber et al[59] showed good qualitative correlation of the potency of sincalide, a labile peptide, and headspace humidity, an indicator of cake moisture content (Table 5). This dependency was demonstrated more quantitatively in our labs recently for a labile lyophilized ester product; zero order decompositon rates at 30° were plotted against residual moisture levels (Fig. 12), showing excellent linearity. Using this type of data, the maximum residual moisture content tolerable in order to maintain the desired shelf life without unnecessarily overdrying the product can be estimated; such data is also necessary to determine allowable environmental humidity levels for powder fill products.

For such moisture sensitive formulations, the choice of packaging components may be critical to provide a sufficient moisture barrier to maintain product stability. For the conventional glass vialed products, the rubber closure moisture permeability must be determined and will usually be an important

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TABLE 5

Sincalide stability as a function of residual moisture. Data from Huber et al, J. Pharm. Sci., 67, 1239 (1978).

Humidity Condition Exposed to Before Sealing	Months at 22°C	Measured Headspace Relative Humidity (%)	Sincalide Potency (Bioassay, %)
None	Initial	Est. <30	106
	25	19-29	103
Moderate	3	46-47	114
	14	34-35	94
High	3	81-88	66
	14	54-72	36

selection parameter in deciding on the preferred package for optimum shelf life. Typically, natural rubber closure are far more permeable to water than butyl closures, the latter providing a wide range of moisture vapor transmission rates depending on the specific rubber formula composition. The recent introduction of an antibiotic powder for reconsitution packaged in a plastic bag illustrates the even greater potential for rapid moisture absorption by these materials; in this case, the manufacturer specifies a 30 day shelf life after the essentially moisture impermeable foil overwrap is removed.

B. Excipient Effects

As with simple solutions, excipients or buffers used in a lyophilized product can markedly effect the stability of labile components in the dried cake. For example, Sugimoto et al[60] recently reported that the stability of lyophilized sodium prasterone sulfate, a steroid used in obstetrics, could be considerably enhanced by inclusion of polyvinylpyrrolidone or glycine (Fig. 13). Since it was independently shown that sodium bisulfite catalysed the ester hydrolysis (probably simply by lowering the pH

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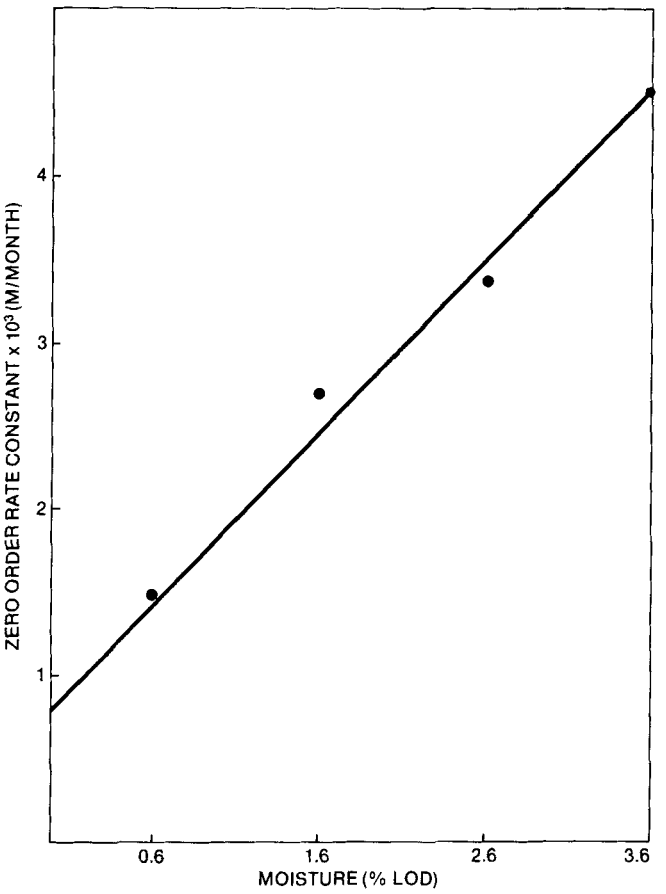

FIGURE 12

Plot of the zero order decomposition rates of a hydrolytically sensitive ester as a function of the residual moisture in the lyophilized product; the points shown are experimental and the line is the best fit linear regression curve.

of the adsorbed moisture layer, although general acid catalysis cannot be ruled out), it was postulated that these basic excipients slowed the decomposition by neutralizing the bisulfite liberated in the hydrolysis of the ester.

C. Bulk Solutions

Manufacture of lyophilized products generally requires production of a bulk solution prior to aseptic filling and

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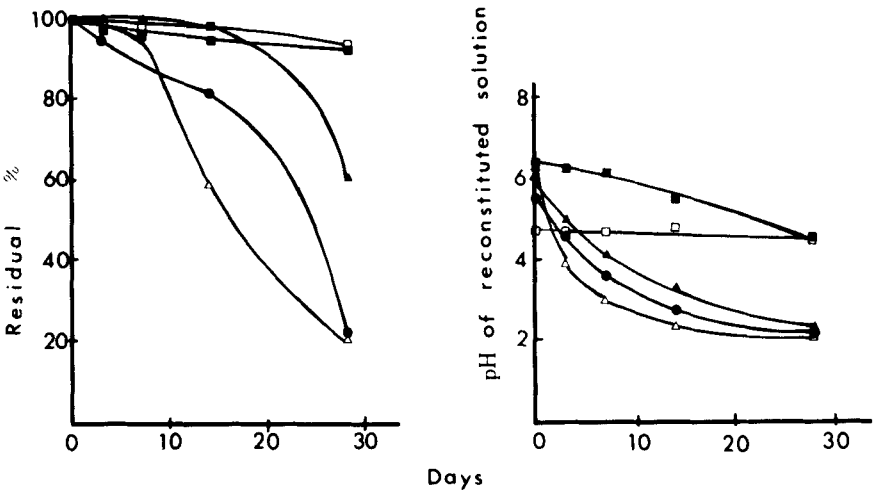

FIGURE 13

Stability and pH changes over time of lyophilized sodium prasterone sulfate at 50° containing the following additives: □, PVP; ■, glycine; ▲, dextran 40; △, mannitol; ●, control. From Sugimoto et al, J. Parenter. Sci. & Tech., 35, 88 (1981); reproduced with permission of the Parenteral Drug Association.

lyophilization. Besides the minimum time necessary for such processing operations, it is a frequent practice to assay this solution before filling in vials in order to allow any necessary per vial potency adjustment to be made in fill volume. Thus the drug may be held in the relatively unstable solution state from a few hours up to several days before filling into vials and freezing; for particularly labile drugs, even this relatively short period may result in substantial decomposition, shortening the ultimate shelf life of the product. One approach to minimize this type of in process instability is to include a volatile organic cosolvent in the bulk solution to depress the solvolysis rate[61]. For example, Nelson et al[62] demonstrated a marked depression in the hydrolysis rate of a piperazylphenylbenzofuran antiviral candidate by inclusion of isoprpyl alcohol (IPA) in the buffered drug solution (Fig. 14); in fact, a linear relationship

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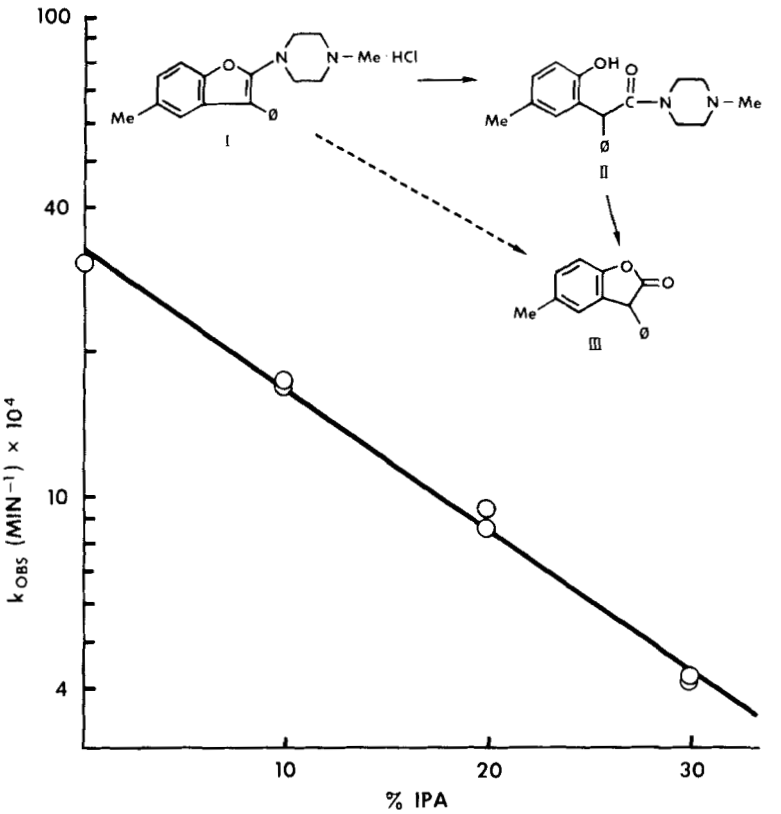

FIGURE 14

Plot of the log of the apparent first order rate constants for the hydrolysis of S-22844 (I) to its decomposition products (II and III) versus the isopropyl alcohol (IPA) content of pH 6.5 McIlvaine buffer solution at 50°; the circles are experimental data points and the line is the best fit linear regression of the data (correlation coefficient 0.993). From Nelson, Kolars and Mendenhall, paper presented to 31st National APhA Academy of Pharmaceutical Sciences Meeting, Orlando, Florida, November 15-19, 1981.

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was shown between the log of the rate constant and the IPA level. However, as Seager pointed out[61], removal of even a relatively volatile cosolvent during lyophilization may require an extended cycle as well as special condenser traps; furthermore, depending on the toxicity of the organic cosolvent being used, achieving residual levels which are acceptable from a safety point of view may be quite difficult.

D. Effects of Lyophilization Cycle Conditions

An interesting aspect of lyophilized products is the potential for processing conditions, such as freezing and heating rates in the freeze drying cycle, to effect final product stability. The well known accelerated decomposition of some penicillins in "frozen" solutions* [63,64] illustrates the potential for prolonged or poorly controlled freezing cycles to yield variable and possibly unacceptable decomposition. A more subtle and perhaps insidious effect of lyophilization cycle conditions on product stability is the potential to isolate the solid drug in a variety of physical states, i.e., amorphous or in different crystalline polymorphs. Bogardus, for example, recently reported[65] that, depending on freezing and reheating rates, at least 4 different polymorphs of sodium nafcillin could be isolated within the temperature range normally used in a lyophilization cycle. Each of these can be expected to exhibit different chemical reactivity in the solid state and may have differing affinities for residual solvents with obvious stability implications. Pikal and coworkers[66,67] have shown differences of at least an order of magnitude between the rates of decomposition of anhydrous amorphous cephalosporins and their corresponding unsolvated crystalline forms. Furthermore, in these studies the relative rates of decomposition of mixtures of crystalline and amorphous drug

*In retrospect, these examples probably were not truly frozen, but involve pockets of highly concentrated "pre-eutectic" solution of drug in the ice mass in which autocatalysis or pH changes resulted in rapid decomposition in spite of the less favorable thermal conditions.

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TABLE 6

Comparison of the degree of crystallinity, as measured by several methods, and the solid state stability of cephalothin sodium at 50° under dry and high humidity conditions; the degree of crystallinity is expressed as the percent of crystalline (vs. amorphous) drug. Data from Pikal et al, J. Pharm. Sci. 67, 767 (1978).

X-Ray			50° Stability*	
External Method	Internal Method	Calorimetry	Dry	31% R.H.
100	100	100	100	100
72	67	93	101	100
69	55	92	102	97
62	51	88	101	100
57	48	74	86	—
47	40	54	77	85
37	34	47	54	44

* % = 100 (1 − k sample/k amorphous)

were correlated with the degree of crystallinity (Table 6); this may be at least in part due to the observed increased affinity of the amorphous material for residual solvent. Similarly, for cefoxitin sodium, a cephamycin antibiotic, a marked difference in solid state decomposition rates has been shown between the amorphous and crystalline forms[68]; identification and development of a stable crystalline salt was in fact a critical step in the development of a commercially viable parenteral dosage form of this compound[69]. Similar difficulties with isolating a stable form of sodium ethacrynate for a lyophilized dosage form have been reported[70]. Thus, without adequate characterization of the various physical states in which the active drug can exist, their relative stability profiles, and appropriate cycle design and control to insure consistent isolation of the desired solid phase, manufacturers run the risk of inadvertently producing a dosage form having a significant lot-to-lot shelf life variability.

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E. Natural Product Isolates

Lot-to-lot variability in decomposition rates may arise from another, less controllable source with lyophilized products. Many such products are of natural origin, i.e., isolates from plant or animal sources. As such, even in the most rigorous isolation process, some batch to batch variability in trace contaminants which may significantly effect the stability profile of the active agent can be expected. Shown in Table 7 is comparable data on multiple enzymatic activities of two different lots of a plant isolate; as is dramatically illustrated, the stability profile is considerably different for two of the four activities even over the short time intervals and conservative storage conditions involved. This is a problem to be very conscious of in establishing an expiration date for natural products.

F. Haze

As distinct from particulates, appearance of a non-descript haze or turbidity in lyophilized or powder-filled dosage forms is a relatively common occurrence. In terms of potency loss, haze is

TABLE 7

Comparison of the relative stability of two lots of a lyophilized natural product isolate.

		Enzymatic Activities			
		"A"	"B"	"C"	"D"
Reference Lot	Initial	3.4	49	3.9	1.6
	4 Months, 5°	3.5	47	3.0	1.5
	Reconstituted, Frozen 48 hrs.	3.7	49	2.9	—
Sample Lot	Initial	3.4	51	2.8	3.3
	4 Months, 5°	2.9	48	2.7	2.7
	Reconstituted, Frozen 48 hrs.	2.5	49	0.5	—

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not a significant problem; however, from an aesthetic point of view it is usually unacceptable (nor will the product meet the usually applied compendial standard for clarity of a constituted injectable solution). Thus haze is a problem of serious concern to the formulator.

Identification of the specific cause of such problems (usually assumed to be due to product interaction with packaging components) can be a challenging (and frustrating) problem since the quantitative amounts of material involved are very minute, not easily isolatable or quantifiable without heroic measures. Pikal and Lang showed that adsorption of volatile closure components (i.e., wax and sulfur) by the product was the cause of haze problems with a number of lyophilized cephalosporin formulations[71]; furthermore, they proposed a method of screening closures for their tendency to "bleed" such volatiles and for these in turn to interact with the formulation of interest. Nonetheless, the occurrence of haze does not always lend itself to such rational predictive methods. For example, Portnoff et al recently reported[69] that haze problems began to occur in an antibiotic formulation coincident with changeover from in-the-vial lyophilization to powder filling, the only demonstrable physical or chemical difference between the products being the physical state of the drug (amorphous versus crystalline; packaging materials remained the same). As the use of non-glass packaging for powder-filled dosage forms increases, the occurrence of such packaging interaction problems can be expected to increase.

While often not considered a true stability parameter (i.e., this problem is frequently evident with fresh samples), we have observed instances in our labs where such haze formation definitely increases with time. Furthermore, Pikal and Lang demonstrated the expected time dependency of the sublimation of closure volatiles under vacuum[71]; under ambient pressure conditions or more mild vacuum (as some parenteral dosage forms are currently marketed), this sublimation process can be expected

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to be considerably extended and may thus result in the gradual increase of haze to an unacceptable level over time.

G. Statistical Treatment of Shelf Life Estimates

Highly unstable lyophilized products present an interesting statistical problem in accurately estimating product shelf life. For dosage forms manufactured, packaged and ultimately used in the same physical state (e.g., a solution), stability projections involve a relatively straightforward estimate of the time at which product potency or degradation products respectively reach some pre-established minimum or maximum allowable level. Usually this is done utilizing kinetic projections (with supporting actual storage data) for product stored under worst case labeled storage conditions; data from process, raw material and analytical variability and the conservative 95% confidence boundary is most often used in establishing product expiration dating. However, for lyophilized products, the decomposition profile in at least three distinct phases must be determined and then combined to estimate an actual product shelf life. These are, of course, the pre-lyophilized bulk solution (including manufacturing, intermediate storage and filling), the lyophilized cake and the reconstituted solution. To use the conservative 95% confidence limit for each of these phases is probably unnecessarily restrictive. To illustrate this point (Fig. 15), a 95% CI gives a 5% probability of failing the target specification limit; if all three processes are similarly treated, then the probability of the final product failing specification is actually $(0.05)^3$ or 0.0125% instead of the usual 5%. Rather, in this simple case where the

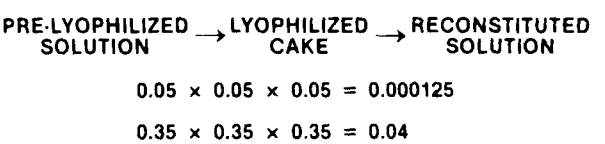

FIGURE 15

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magnitude of decomposition is determined to be the same in all three phases, one should use a confidence limit of 65% at each stage to achieve a 95% assurance the final product will meet the relevant specifications at expiration. This argument assumes each decomposition phase is independent; this will not be the case when a common stability dependent variable, such as pH, is critical. Also, if the magnitude of the variance for each decomposition phase is not approximately equal, it is probably appropriate to weight the individual confidence limits accordingly.

Adjei and coworkers have very recently presented a statiscally based algorithm for determining the shelf-life of such products at a given confidence level encompassing all the various stability stages[72].

IX. CONCLUSION

I have attempted in this paper to highlight the major stability related problems unique to sterile product formulations, both solutions and lyophilizates. The chief differentiating factors with these dosage forms compared with other pharmaceutical dosage forms are their special packaging and use requirements which exaggerate several loss pathways and dictate concern over some stability parameters not relevant to non-sterile products.

If the tone of this discussion seems unduly tilted towards formulation design and predictive methodology, it is an acknowledged prejudice; the reason is my strong belief that application of sound theoretical concepts and predictive techniques in the formulation development stage by the pharmacist should insure subsequent long term formal stability studies will be largely a confirmatory exercise. This is certainly not to say that our knowledge level is such that development of stable parenteral formulations is a routine task with predictable, guaranteed success; unexpected problems can and do occur and there are clearly many areas in need of work to develop and improve predictive methodology. However, it is hoped that application of

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some of the methods and principles reviewed in this paper will assist the formulation pharmacist in efficiently developing an acceptable product in which he can have a high degree of confidence in its long term stability.

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