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UTILIZATION OF DEAERATION VIA GAS PERMEATION AND OXIDATIVE STABILIZATION OF PYROGALLOL

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ABSTRACT

The rates of oxidative decomposition for pyrogallol were determined at 30° in vehicles which had been prepared by passing deionized distilled water through a gas permeator. The vehicles prepared by gas permeation possessed varying dissolved oxygen concentrations which depended upon charging pressure and the residence time of effluent. A single pass through the permeator produced vehicles possessing dissolved oxygen concentrations of .05 ppm to 0.78 ppm with respect to a normal oxygen content of 8-9 ppm. A double pass through the permeator gave only trace amounts of dissolved oxygen, i.e., 0.01-0.02 ppm and this was found to be independent of charging pressure.

Although there was a substantial increase in the protection of the oxidative decomposition of pyrogallol with trace amounts of dissolved oxygen, the reaction still proceeded at diminished rates. This probably implies that a vehicle must be almost completely devoid of oxygen in order to prevent oxidative decomposition.

INTRODUCTION

Drug stabilization is an important factor in liquid close forms since the shelf life or stated usefulness of a particular substance depends upon the components of these types of dose forms. One of the major pathways of decomposition, other than hydrolysis is an oxidative pathway. In particular, the sensitivity of several useful drugs to oxidative effects has been documented (1-5). This area of kinetics has been studied and several techniques of protection of drugs from oxidative decomposition have been utilized. Drugs undergoing oxidative decomposition may be protected or stabilized by oxygen purging of vehicles, buffering to a minimum rate pH, using metal scavengers, adding antioxidants and adding inhibitors. The intent of this work was based upon the deaeration of distilled deionized water by the simple method of utilizing a gas permeation technique to determine the effect of lower oxygen levels upon oxidative decomposition of pyrogallol.

The universal presence of dissolved gases in liquid vehicles for drug solutions has, in some cases, led to adverse effects with oxygen sensitive systems. Since most drug moieties are semipolar in nature, they possess chemical groupings such as carbonyls that are susceptible to oxidative effects. In many cases aromaticity, implying unsaturation, is usually some component of drug substances; therefore, a potential for autoxidation also exists. Because the pi bond system can be easily perturbed by distortion polarization in liquid systems, electron loss (oxidation) can readily occur.

Auto-oxidation simply infers the generation of the free radical form of a molecular species which, in turn is propogated by a reaction with oxygen and continues the oxidative process.

Lachman (6) simplified the autoxidation of pharmaceuticals mediated by the free radical chain process to three steps, which are initiation of the reaction, propagation of the reaction via free radicals produced and termination of the reaction to inactive products.

It can be postulated that if the molecular oxygen necessary for the propagation step were substantially eliminated, oxidative processes could be significantly reduced. Therefore, the propagation step assumes major importance in free radical mediated reactions for pharmaceutical systems.

Shou (7) has indicated that it may not be possible to reduce oxygen levels below a critical value such that no decomposition takes place.

The gas flushing technique consists of oxygen removal in the solvent through partial pressures with respect to Henry's Law and the Bunsen coefficient. Since, at ambient temperatures, the Bunsen coefficient of molecular nitrogen is less than that of oxygen, it may be used as a replacement gas. The process utilized in this study also uses nitrogen purging but has the added advantage of decarbonation as well. In solutions, carbon dioxide forms carbonic acid and this usually alters the pH of unpurged distilled water about 2 units below neutrality.

Since trace metals may also catalyze certain degradation processes, their removal aids in retarding the rate of oxidative decomposition. Lachman (8) investigated several chelating agents and compared their effectiveness. Martin (9) has reported that EDTA is useful in retardation of oxidative decomposition in certain drug moieties. Since the metals act only as catalysts, sequestering agents will only slow the degradation process and not cause complete inhibition.

Antioxidants, or negative catalysts, decrease the rate of oxidative degradation reactions. Although antioxidants reduce oxygen levels to trace amounts by preferentially reacting with the molecular oxygen, it can have an adverse effect on the stability of the system since the added moiety may interfere with the drug. Sulfites have proven notorious for this interaction. Although the above processes have been employed as aids in reduction of oxidative decomposition, none have afforded complete protection. To date, the most effective protection has been achieved through employment of a combination of nitrogen flushing and antioxidant addition. Air displacement with layered nitrogen has also been reported to aid protection of oxygen sensitive pharmaceuticals (10, 11).

In recent years, interest has developed, and study devoted to, employment of gas permeation as a method to reduce dissolved oxygen levels. Although gas permeation to protect pharmaceuticals is relatively new, it has been successfully employed in other areas. Genetelli and Cole (12) have rpoerted the successful removal of carbonates and dissolved oxygen using a polypropylene hollow fiber apparatus. Removal of certain volatile components from waste water was also repeated.

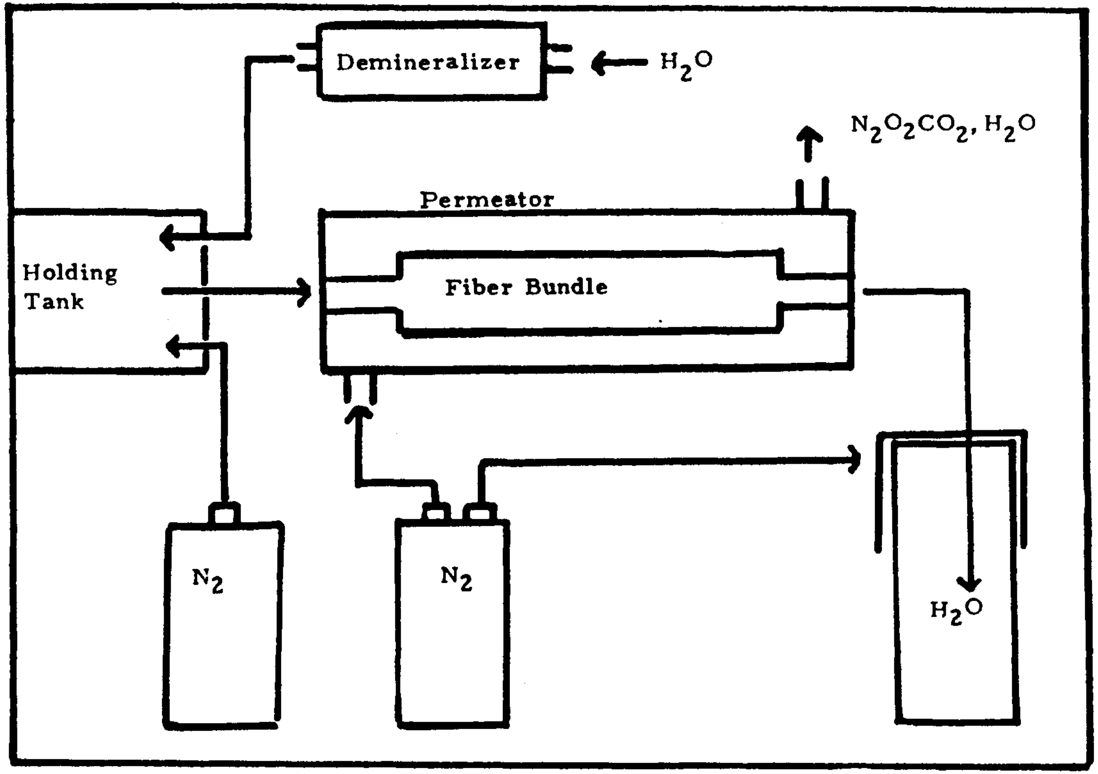
Li, et al (13) reported on gas diffusion concerning membrane separation in a review article.

EXPERIMENTAL

I. PREPARATION OF DEOXYGENATED WATER

A DuPont$^{(R)(1)}$ gas permeator was connected to a high pressure stainless steel holding tank$^{(2)}$ with high pressure stainless steel tubing. A three-way ball value$^{(3)}$ attached to the holding tank provided the necessary connections for water addition, pressurization for operation by high purity nitrogen$^{(4)}$ and return to atmospheric pressure following the permeation procedure.

Distilled water was deionized with a mixed bed cartridge on a Barnstead deionizer-demineralizer$^{(5)}$ and fed into the holding tank. The holding tank was pressurized to selected levels, causing the water to flow through the permeator where deoxygenation and decarbonation occurred. The effluent was collected in a type I glass vessel which had been previously flushed with nitrogen. A nitrogen atmosphere was maintained at the mouth of the collection vessel$^{(6)}$ by means of an aluminum hood, (see schematic) to prevent air ingress into the prepared water.



Schematic for Gas Permeation Process

Permeation of oxygen, carbon dioxide, and nitrogen was effected by the use of dacron fibers in the permeator and a nitrogen flush around the fiber bundle to remove permeated material. A second pass of the water through the permeator was accomplished by using a positive nitrogen siphon to transfer the deoxygenated water from the collection vessel to the holding tank, and repeating the permeation operation.

Dissolved oxygen levels (ppm) were determined on an average of 15-25 samples at each operating pressure using the Delta Model 106 Dissolved oxygen analyzer$^{(7)}$. This instrument is a polarograph having a dropping Mercury microelectrode with a rated sensitivity of ± 0.01 ppm D.O.

II. DETERMINATION OF FLOW RATE

The holding tank was charged with distilled deionized water and pressurized with high purity nitrogen at successive pressures ranging from 100 to 1000 pounds in 100 pound intervals to determine the effect of pressure on effluent flow rates and deoxygenation efficiency. All pressures were uncorrected and were read directly from the gas regulator$^{(8)}$.

III. DETERMINATION OF PROTECTION EFFICIENCY ON MODEL SYSTEM

Pyrogallol (1, 2, 3 trichdroxybenzene)[9] was employed as an oxygen sensitive model to determine the effectiveness of the permeator in removing dissolved oxygen from the water. Chemicals utilized in this study were of at least reagent quality(10). Melting points were determined with a Thomas-Hoover melting point apparatus(11). Pyrogallol was recrystallized from cold ethanol, stored in a dessicator, and placed in a dark cupboard to prevent decomposition by light. A melting point range of 132-133°C was determined which was well within literature values (131-133°C).

Water prepared with the deionizer and the permeator at various pressures was used as the solvent for pyrogallol solutions at an initial concentration of 6 mg/liter. The control system was prepared at the same concentration using distilled deionized water as the solvent. Thirty milliliter vials were filled to capacity, capped with a teflon coated screw cap, and sealed with six coats of a wax mixture having a melting point of 65°C(12) to prevent air ingress. After labeling, the vials were stored in a dark constant temperature apparatus(13) at 30°C for the duration of the study. Since decarbonation also occurred with passing the vehicle through the permeator, the pH of the resulting vehicle was very nearly neutral and was used as such in these studies. Vials were removed periodically and assayed for pyrogallol content according to the procedures of Grant and Patel (14). A three milliliter sample of pyrogallol solution was withdrawn and added to six milliliters of 1% vanillin in 70% sulfuric acid. The absorbance was determined spectrophotometrically after 18 minutes against the appropriate blank at a wavelength of 520 mu . Three minute intervals were allowed to elapse between sample readings to allow for precise timing of the colorimetric reaction. In addition, duplicate readings were taken one minute after the appropriate time interval to insure that the reaction had been read at its peak color development. Swain and Goldstein (15) have shown that the concentration absorbance curve was linear from 0 to 5.3×10^{-5} M, and passed through the origin. Absorbance readings from 0.0-0.67 produced analagous Beer-Lambert plots.

RESULTS AND DISCUSSION

The evaluation of gas permeation as a method for the preparation of deaerated vehicles entails both a study of the efficiency of gas removal in a vehicle, and the protection afforded a model system using this vehicle. For gas permeation to possess potential application for industrial use, an effluent flow rate must be achieved which is compatible with current unit processes. The purpose of this study was to ascertain the effect of pressure on flow rate and dissolved oxygen levels in the effluent of a vehicle propared by gas permeation and to note the efficiency of oxygen removal by a double pass through the permeator. The efficiency of the deaeration process was also determined by following the decomposition of a chemical moiety susceptible to oxidation in vehicles prepared with the permeator.

Table 1 and Figure 1 summarize the effect of operating pressure on the flow rate of distilled deionized water through the permeator. In Figure 1 it is seen that there is a direct linear relationship of flow rate with flushing pressure. Residual dissolved oxygen levels in effluent water as a function of operating pressure are tabulated in Table 1 and described in Figure 2 for single and double pass procedures. A direct relationship can be observed between dissolved oxygen levels and operating pressures for vehicles prepared by a single pass through the permeator. As operating pressures increased, dissolved oxygen levels in the effluent increased. This is expected when residence time in the permeator is considered. Calculated residence times based on the flow rates achieved at various pressures are given in Table 1 and illustrated in Figure 3. At lower pressures, the water was sub-

TABLE 1. A summary of the efficiency of the permeator in terms of flow rate, residence time, and dissolved oxygen levels of the effluent as a function of pressure

Pressure (psig)	Flow Rate (mls/min)	Residence Time (Minutes)	Dissolved O_2 (ppm-1 pass)	*Dissolved O_2 (ppm-2 passes)
100	8	26.0	0.05	0.01
200	22	10.0	0.07	0.02
300	34	6.5	-	-
400	41	5.5	0.30	0.02
500	51	4.3	-	-
600	61	3.6	0.48	0.02
700	75	2.9	-	-
800	82	2.6	0.62	0.02
900	91	2.4	-	-
1000	100	2.2	0.78	0.02

* Considered to be trace amounts

jected to the gas permeation process for a longer period of time, and hence had more efficient removal of dissolved oxygen.

Vehicles prepared by a double pass through the permeator contained only trace amounts of oxygen irrespective of operating process. These results would suggest that a series arrangement

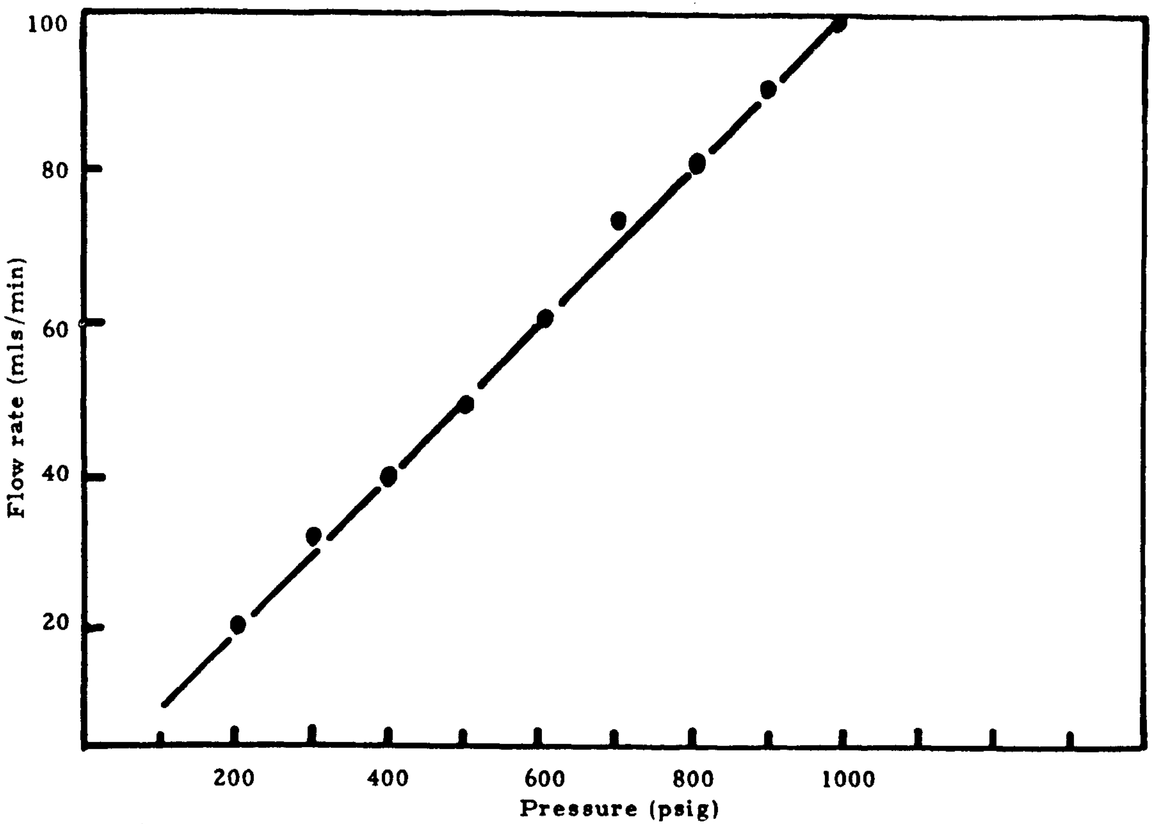


Figure 1. Flow Rate of Effluent as a Function of Operating Pressure

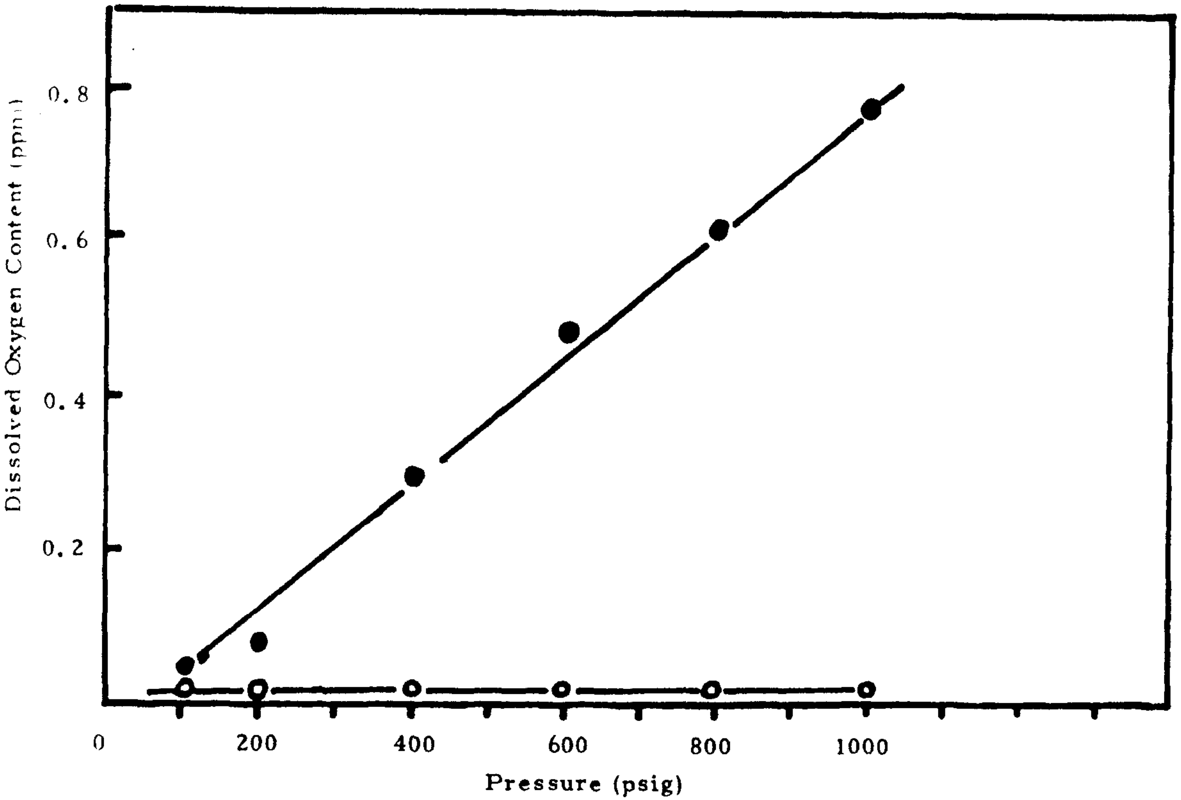


Fig. 2. Residual Dissolved Oxygen Level as a function of operating pressure
● - single pass o - double pass

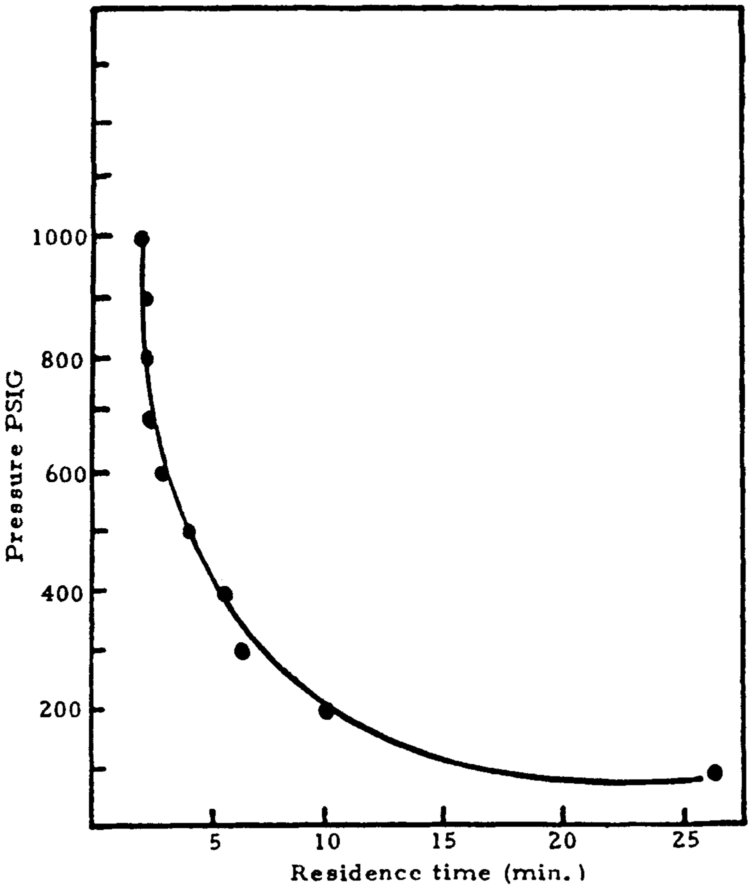


Figure 3.

of permeators would perhaps be the most efficient assembly for continuous processing of the vehicle.

Typical values for the decomposition of an oxygen sensitive system in water prepared by gas permeation at specified operating pressures are listed in Table II and represented in Figure 4. The

TABLE II. A Summary of typical values for the decomposition of pyrogallol at 30°C for control, single pass, and double pass vehicles

Time (hr)	Control	% Remaining[a] Single Pass 100 psig	% Remaining[a] Double Pass 100 psig
0	100	100	100
2	93.4	99.8	99.9
5	83.5	99.5	99.7
8	74.6	99.2	99.5
16	51.8	98.4	99.1
20	34.0	98.0	98.8
24	26.7	97.6	98.6
35	-	96.5	97.9
48	-	95.2	97.1
72	-	92.8	95.8
96	-	90.4	94.2
192	-	80.8	88.5
288	-	71.2	82.7
384	-	62.8	76.8

a = values are averages of 8 determinations at each time interval

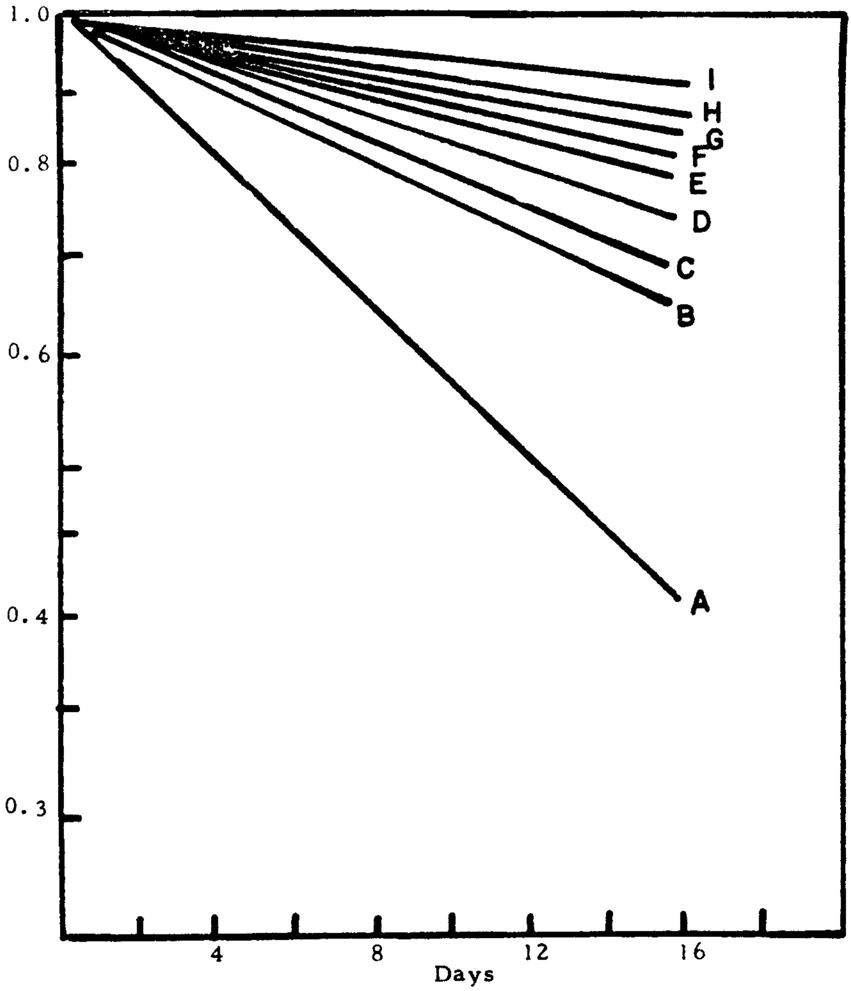


Figure 4. A plot of decomposition of pyrogallol at 30°C
A - control; B - 1000 psig*; C - 800 psig*;
D - 600 psig*; E - 400 psig*; F - 200 psig*;
G - 100 psig*; H - 400, 600, 800, 1000 psig**;
I - 100, 200 psig**
* = 1 pass permeation, ** = 2 pass permeation

control after 24 hours decomposed to a concentration of approximately 23% of the original level. All vehicles prepared by gas permeation afforded some protection from oxidative decomposition. The approximate linearity observed implies first order decomposition. The decomposition of the model compound increased in vehicles prepared at higher operating pressures since they contained higher levels of dissolved oxygen. At lower pressures such as 100 and 200 psig, the extent of the decomposition is approximately the same since dissolved oxygen levels are similar in magnitude. In contrast, all systems prepared by a double pass procedure fall within a narrow band of decomposition. These systems contain trace amounts of dissolved oxygen and are considered to be invariant and independent of operating presure. It should be noted, however, that even these trace amounts of oxygen, i.e. 0.02 ppm is still sufficient to cause decomposition. This would probably indicate that only the rate of decomposition can be reduced by reduced oxygen levels and not the cessation of the oxidative reaction.

In Table III, the results obtained for the various vehicles are given and the respective dissolved oxygen concentrations. The rate of decomposition in hours is also given for the vehicles and a protection index is shown which was obtained by a ratio of rates by defining the control as unity.

TABLE III: Summary of Dissolved Oxygen Levels, decomposition rates of pyrogallol at 30° and relative protection index for the vehicles prepared at various operating pressures

System	D. O. (ppm)	Rate x 10^3 hr^{-1}	Protection Index
Control	9.04	43.2	1
1000[a]	0.78	1.87	23
800[a]	0.62	1.71	25
600[a]	0.48	1.49	29
400[a]	0.30	1.42	30
200[a]	0.07	1.22	35
100[a]	0.05	1.24	34
100[b]	0.01	0.078	550
200[b]	0.02	0.078	550
400[b]	0.02	0.091	470
600[b]	0.02	0.102	410
800[b]	0.02	0.102	410
1000[b]	0.02	0.102	410

a = single pass

b = double pass (considered to be trace amounts of dissolved oxygen. Values given are averages of 15 determinations as each pressure)

It can be seen that the rates decreased with a decrease in oxygen concentration but disproportionate to oxygen content. For example, the rate at 0.78 ppm D.O. is 1.87×10^{-3} hr^{-1} whereas the rate at 0.05 ppm D.O. is 1.24×10^{-3} hr^{-1} about the same order of magnitude, although there has been a 16 fold reduction in oxygen concentration. Trace amounts of oxygen, ie about 0.01-0.02 ppm gave about a 10-15 fold decrease in the rate of decomposition with respect to vehicles containing 0.05 to 0.78 ppm D.O.

Although there was a rather significant increase in the stability with trace amounts of D.O. levels, the reaction still proceeded. It would seem that the critical amounts of dissolved oxygen required to initiate the reaction is even lower than the concentrations considered here.

It might be possible that a vehicle which has been prepared by a double pass through the permeator and an antioxidant on concentration lower than usual may be capable of completely protecting an oxygen sensitive moiety for substantial periods of time.

FOOTNOTES

(1) Permasep, DuPont deNemours & Co., Wilmington Del. See appensix for specifications.

(2) Hoke Sampling Cylinder, Cat. No. 8HD2 1/2 G. Hoke Industries.

(3) Selectomite valve. Hoke Industries.

(4) Cranston Welding Co., N_2 Content $\underline{7}$ 99.90 O_2Content 0.09.

(5) Barnstead Demineralizer Model BD-1, Barnstead Still and Sterilizer Co.

(6) Pyrex, Type I..2 gal capacity.

(7) Delta Scientifics.

(8) Matheson Gas Co.

(9) Allied Chemical Co., N. Y.

(10) Amend Drug & Chemical Co., Inc. N. Y.

(11) Unimelt Capillary Melting Point Apparatus, Arthur H. Thomas, Philadelphia, Pa.

(12) Mixture of Carnanba, paraffin, and bees waxes.

(13) Hotpack Corporation, Philadelphia, Pa.

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