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Determination of Optimum Operating Parameters for Gas Permeation

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DETERMINATION OF OPTIMUM OPERATING
PARAMETERS FOR GAS PERMEATION

BY

ANTHONY PALMIERI III

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF

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MASTER OF SCIENCE THESIS

OF

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1973

TITLE ABSTRACT

Optimum Parameters - Gas Permeation

ABSTRACT

Deaeration via gas permeation was investigated as a means of protection for oxygen sensitive pharmaceuticals and the optimum operating pressure for deaeration determined. The theory of permeation and selected parameters governing permeation were discussed.

Gas permeation has been suggested as a viable alternative to currently accepted methods for reduction of dissolved oxygen levels. If this system is to be accepted as a method of protecting sensitive drug moieties, acceptable flow rates with analogous reduction of dissolved oxygen levels must be attained. The applicability of protection must be broad to include systems of interest in pharmaceuticals. The intent of this study was to determine dissolved oxygen levels at various pressures and subsequent flow rates of effluent which would produce efficient dissolved oxygen removal at flow rates acceptable for pharmaceutical processes. The acceptability of the protection afforded a model drug system (pyrogallol) was also determined.

Dissolved oxygen levels were reduced from approximately 9 ppm to less than 1 ppm with a single pass through the permeator and to trace levels (< 0.05 ppm) with a second pass. The effluent

flow rate was shown to be proportional to the pressure with which the solvent was forced through the permeator.

Water with lower dissolved oxygen levels proved to lessen the rate of degradation of pyrogallol. With both single and double pass systems, the protection afforded was significant.

The investigation also suggests that pyrogallol will degradate by non-oxidative means if oxidative degradation processes are not viable.

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DEDICATION

To Cindy

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I. INTRODUCTION AND LITERATURE SEARCH

Drug stability is an important factor in the liquid dose form since the shelf-life or stated usefulness of a particular substance depends upon the components of the provided environment. In particular, the sensitivity of several useful drugs to oxidative effects has been amply documented (epinephrine, ascorbic acid). This area of kinetics has been studied (14) and most of the work has centered around a depletion of molecular oxygen or purging molecular oxygen from the unit dose form.

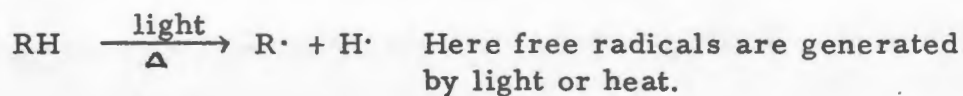
The universal presence of dissolved gases in liquid vehicles for drug solution has, in some cases, led to adverse effects with oxygen sensitive systems. Since most drug moieties are semi-polar in nature, they possess chemical groupings such as carbonyls that are susceptible to oxidative effects. In many 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.

In some cases (2), both oxidative and non-oxidative mechanisms are operative for the same molecular species.

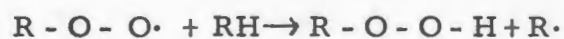
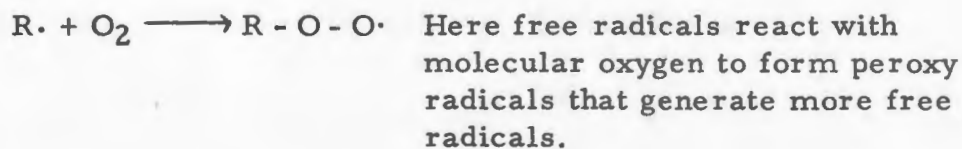
Auto-oxidation simply infers the generation of the free radical form of a molecular species which, in turn, is propagated by a reaction with oxygen and continues the oxidative process.

Lachman (1) simplified the autoxidation of pharmaceuticals mediated by the free radical chain process to three steps.

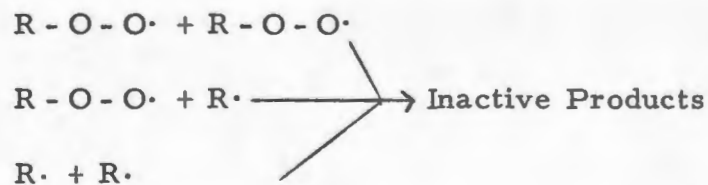
(1) Initiation



(2) Propagation



(3) Termination



Here free radicals and peroxy radicals react to form various inactive compounds.

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

Alterations in the susceptible system can further complicate the problem of stability. Trace impurities, pH changes, and preservatives can alter decomposition rates. Temperature may affect the system in two fashions. With respect to stability, increased temperature results in increased molecular collisions and the availability of molecular oxygen to increase the rate of the propagation step in oxidative decomposition. With increased temperature, however, the solubility of molecular oxygen in the solvent is decreased causing less allowable oxygen to react in the propagation step. The affect of increased molecular collisions is accepted as being greater than that of the decreased oxygen availability so that the overall result would be an increased rate of degradation.

The effect of dissolved oxygen concentration on the autoxidation reactions is not readily apparent (2). Shou (3) has indicated that

oxygen levels are not usually considered since it is difficult to alter the oxygen concentration with present equipment. Shou stated that, "it is impossible to reduce oxygen levels below a critical value necessary for oxidative degradation." Shou did not, however, validate this statement by illustration.

Presently three methods are available which inhibit oxidative decomposition with variable efficiencies: gas flushing, sequester addition, and antioxidant addition. Gas flushing consists of passing a gas through the solvent resulting in oxygen removal through partial pressures with respect to Henry's Law and the Bunsen co-efficient.

$$\frac{V_{\text{gas}}}{V_{\text{soln}}} = p \alpha$$

where V_{gas} and V_{soln} is the volume of gas and solution at a partial gas pressure of p ; α is the Bunsen co-efficient.

Since at 25°C, the Bunsen co-efficient of molecular nitrogen is less than that of oxygen, nitrogen may be employed as a replacement gas. Although carbon dioxide may also be used, it may have an unknown role in the degradation processes of certain drug moieties. Therefore, nitrogen should be employed and considered the gas of choice.

Since trace metals may also catalyze certain degradation processes, their removal aids in retarding the rate of oxidative decomposition. Lachman (4) investigated several chelating agents and compared their effectiveness. Martin (5) 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 (6), (13).

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 (7) have reported the successful removal of carbonates and dissolved oxygen using a polypropylene hollow fiber apparatus. Removal of certain volatile components from waste water was also reported.

Li, et al.(8) reported on gas diffusion concerning membrane separation in a review article. The most common methods of determining solubility of gas in the fibers and permeation were discussed.

The "classical" formula being:

$$P = DS$$

where P = permeability of the membrane
D = coefficient of diffusivity
S = solubility of permeant in the membrane

Permeation by mass transport was categorized by Lebovits to occur in three steps(9):

- (1) The permeant "dissolves" in the membrane on the side of higher concentration.

- (2) The permeant diffuses through holes in the network towards the side of lower concentration.
- (3) The permeant is desorbed on the side of lower concentration.

Permeation of the gas or penetrant through the fiber would be governed by parameters such as the size of the penetrant molecule, the ease of condensation, and the cohesive forces between the polymer and the vapor.

In general the permeability of plastic membranes to gases has been shown to obey Fick's Law:

$$Q = \frac{P (A \cdot \Delta p)}{t}$$

where Q = mass of penetrant

D = permeability

A = area of the membrane

t = thickness of the membrane

Δp = pressure difference across membrane

While Genetelli and Cole demonstrated the possible employment of poly(ethylene terephthalate) to remove gas from waste water, Lausier, et al. (10) theorized and demonstrated the polymers usefulness in protection of oxygen sensitive pharmaceuticals. Gas

permeation was shown to be surpassed in effectiveness only by antioxidant addition. Gas permeation was proven to effect stability of phenylephrine and hydroquinone systems. Dissolved oxygen levels attained were 0.77 ppm with one pass and 0.14 ppm with two consecutive passes. Since the pressure with which the solvent was passed through the fiber bundle was approximately 100 psig, the resonance time for the water-fiber contact was considerable and the flow rate of effluent water was dropwise. If this system is to be acceptable as a viable alternative for oxidative degradation protection, greater flow rates with similar reduction of dissolved oxygen levels must be obtained. Also the applicability of the protection must be broadened to include other systems of interest in the pharmaceutical field. The intent of the present study is to determine dissolved oxygen levels at various pressures and subsequent flow rates of effluent solvent. The acceptability of afforded protection using a model drug system will also be presented.

II. EXPERIMENTAL

I. Preparation of Deoxygenated Water

A DuPont Permasep^{(R)(a)} gas permeator was connected to a high pressure stainless steel holding tank^(b) by means of flexible stainless steel tubing. A three-way ball valve^(c) provided the necessary connections for water addition and allowed for pressurization by high purity nitrogen.

Distilled water was passed through a Barnstead deionizer-demineralizer^(d) into the holding tank. The system was then brought to the desired pressure causing water to pass through the permeator to a collection vessel^(e) where it remained in a nitrogen environment.

(a) Permasep, DuPont de Nemours & Co., Wilmington, Del. See Appendix I for specifications.

(b) Hoke Sampling Cylinder, cat. no. 8HD2 1/2 G, Hoke Industries.

(c) Selectomite, Hoke Industries.

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

(e) Pyrex, 2 gal. capacity.

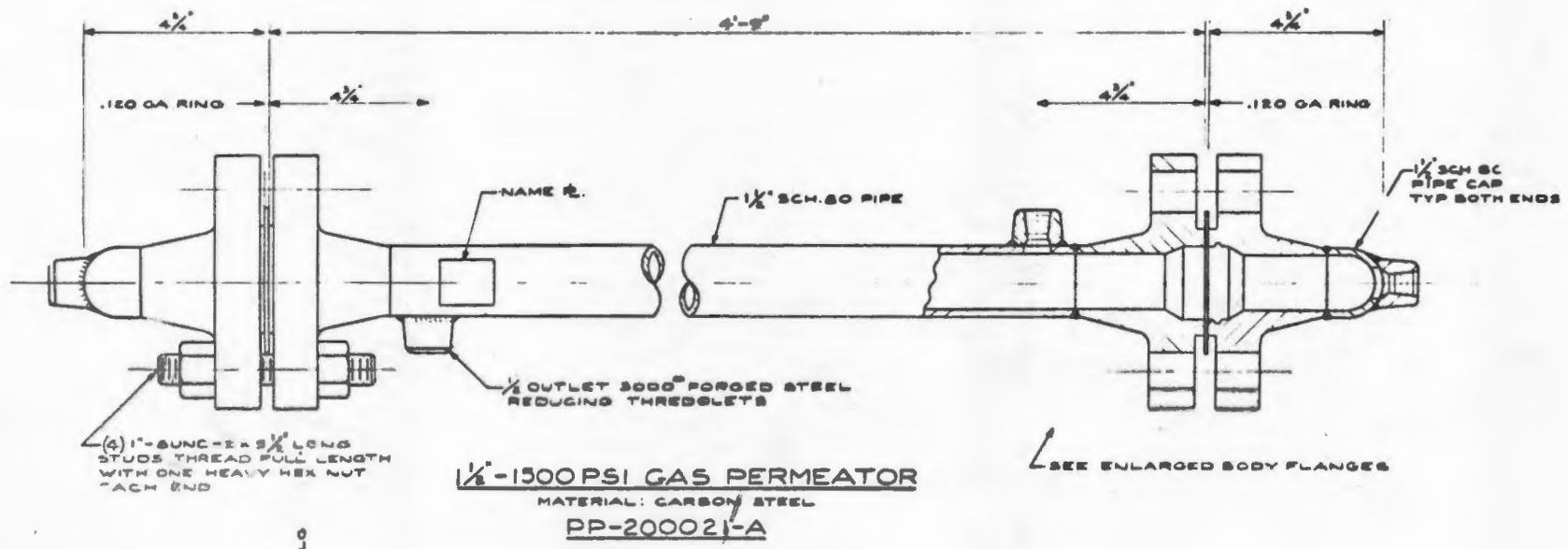


Figure 1. Schematic Diagram of Gas Permeator.

A nitrogen flush was passed around the fiber bundle to remove permeated gases. A second pass for deaeration was accomplished by placing the water from the first deoxygenation pass into the holding tank by employment of a positive nitrogen siphon and repeating the deoxygenation procedure.

Determination of Flow Rate

The holding tank was charged with distilled deionized water and brought to the desired pressure by nitrogen addition.

After a five minute stabilization period, readings were recorded in milliliters per minute. Results were obtained at pressures ranging from 100 to 1000 pounds in 100 pound intervals.

All pressures were uncorrected and read directly from the gas regulator. (a)

Preparation and Analysis of the Model Drug System

Pyrogallol (1, 2, 3 trihydroxybenzene)^(b) was employed as an oxygen sensitive system and utilized to determine the feasibility

(a) Matheson Gas Co.

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

and effectiveness of the deaeration. The rate of degradation of pyrogallol was used to determine the feasibility of mechanical deoxygenation as a method of protection from oxidative decomposition. Chemicals utilized in this study were of at least IUPAC reagent quality. Melting points were determined as a check for purity. Pyrogallol (mp 132-133°C) and vanillin (mp 81-83°C)^(c) melting points were recorded on a Thomas-Hoover melting point apparatus.^(d)

Deoxygenated water prepared at various pressure ratings was employed as solvents for the model drug system at an initial concentration of six milligrams/liter. Six hundred milligrams of pyrogallol was weighed on a Mettler balance^(c), dissolved in a liter of solvent and a ten milliliter aliquot of this then brought to one liter. Distilled, deionized water was used to prepare the control sample. Each thirty milliliter vial was filled to capacity, capped

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

(b) Unimelt Capillary Melting Point Apparatus, Arthur H. Thomas, Phila., Pa.

(c) Mettler H-8, Will Scientific Co., Inc.

with a teflon coated screw cap and sealed with six coats of a high melting wax to prevent oxygen intrusion. After labeling, the vials were stored in a dark, constant-temperature apparatus^(a) at 30°C for the duration of the study. Unopened vials were removed periodically and assayed for pyrogallol content.

Pyrogallol was assayed according to the procedure of Grant and Patel (11). At preselected intervals, a three milliliter sample of pyrogallol solution was withdrawn, and six milliliter of a one percent vanillin in seventy percent sulfuric acid were added. The absorbance was determined spectrophotometrically after eighteen minutes against an appropriate blank at a wavelength of 520 mu. A control sample was also assayed concurrently.

Swain and Goldstein (12) have shown that the concentration curve was linear from 0 to 5.3×10^{-5} M and passed through the origin. Readings with absorbance from 0.0 to 0.670 exhibited linearity and were accurate \pm five percent. Construction of a Lambert-Beer's plot demonstrated analogous results.

(a) Hotpack Corp., Phila., Pa.

A dissolved oxygen analyzer^(a) with a sensitivity of ± 0.01 ppm dissolved oxygen, operated at -0.6 volts was used to measure dissolved oxygen levels. One milliliter of suppressor reagent was added to two-hundred fifty milliliters of water collected in low actinic glassware. Since the sensitivity of the analyzer was ± 0.01 ppm, any dissolved oxygen level of less than 0.05 ppm was considered to be a trace amount in order to remain within the limits of the instrumentation.

Computer programs were utilized to perform mathematical manipulations for changing absorbance to molar concentration, to determine validity of data through employment of correlation co-efficients and analysis of variance.

(a) Delta Scientific Co. Model 106, Lindenhurst, N. J.

III. RESULTS AND DISCUSSION

Evaluation of gas permeation entails efficiency of gas removal as well as protection afforded a model drug system. If gas permeation is to be considered for industrial use, an effluent flow rate must be achieved which allows a practical, readily adaptable application to current unit processes. Table I indicates, as expected, a direct relationship, between the pressure with which the effluent is forced through the permeator and the flow rate. If the efficiency of oxygen removal follows a similar pattern, the pressure that allows the greatest flow rate would be considered an optimum operating parameter.

At pressures greater than 1000 psig difficulties may be encountered which would decrease operating efficiency. For example, most present equipment is not rated for high pressure operations. Also since the permeator shell employed has a pressure rating of 1500 psig, it would be impossible to use higher pressures with this apparatus. The amount of fiber that dissolves in the effluent is directly related to the temperature and pressure thereby affecting the efficiency of the permeator.

Deaeration efficiency of the permeator was determined at the various pressures for single and double passes of the water by measuring dissolved oxygen levels of the effluent as reported in Table II and Table III. Study shows that passes through the permeator at all pressures reduce the dissolved oxygen levels significantly. One pass through the permeator reduces the dissolved oxygen levels from 9.05 ppm to less than 0.78 ppm as a function of pressure as demonstrated in Table III and Figure 3. A single pass at 100 psig reduces the level of molecular oxygen considerably more than a single pass at 1000 psig. This phenomenon is possible since the "residence" time of the effluent in the fibers is approximately ten times as great at the lower pressure.

A double pass through the permeator reduced oxygen levels to trace amounts (< 0.05 ppm) in all instances except 400 psig where the oxygen level was 0.07 ppm. Since all other double pass systems produced trace levels and repeated readings at this pressure produced similar results, this deviation can probably be regarded as an anomaly. This would indicate the advisability of a second pass through the permeator for optimum removal of oxygen.

If the apparatus were to be employed in a unit process system, the necessity of manually recharging the system for a second pass would have to be avoided or simulated in another manner since this would disrupt the steady flow of a unit process and result in increased cost.

To alleviate this problem two methods may be employed. First, the permeator length might be increased to allow the solvent a greater "residence" time with resultant increased removal of the gases.

Secondly, two permeators could be connected in series with the effluent of the first permeator passing directly into the second, thereby producing an efficient second pass.

Certain drug moieties having a critical oxygen concentration greater than 0.1 ppm could utilize a single pass set-up to afford adequate protection from oxidative degradation. However, as Shou (3) reported, this critical oxygen level is unknown since previous research has been hindered by inability to produce the extremely low dissolved oxygen levels required.

TABLE I

Flow Rate of Effluent as a Function of Pressure

Pressure psig	Flow Rate mls/min	Std. Dev. mls/min
100	8.4	0.5
200	22.1	0.6
300	33.5	0.3
400	40.5	0.9
500	50.9	0.5
600	60.9	0.9
700	74.9	0.8
800	81.6	0.8
900	91.1	1.5
1000	99.9	0.5

effluent = distilled, deionized water

all pressures reported as uncorrected

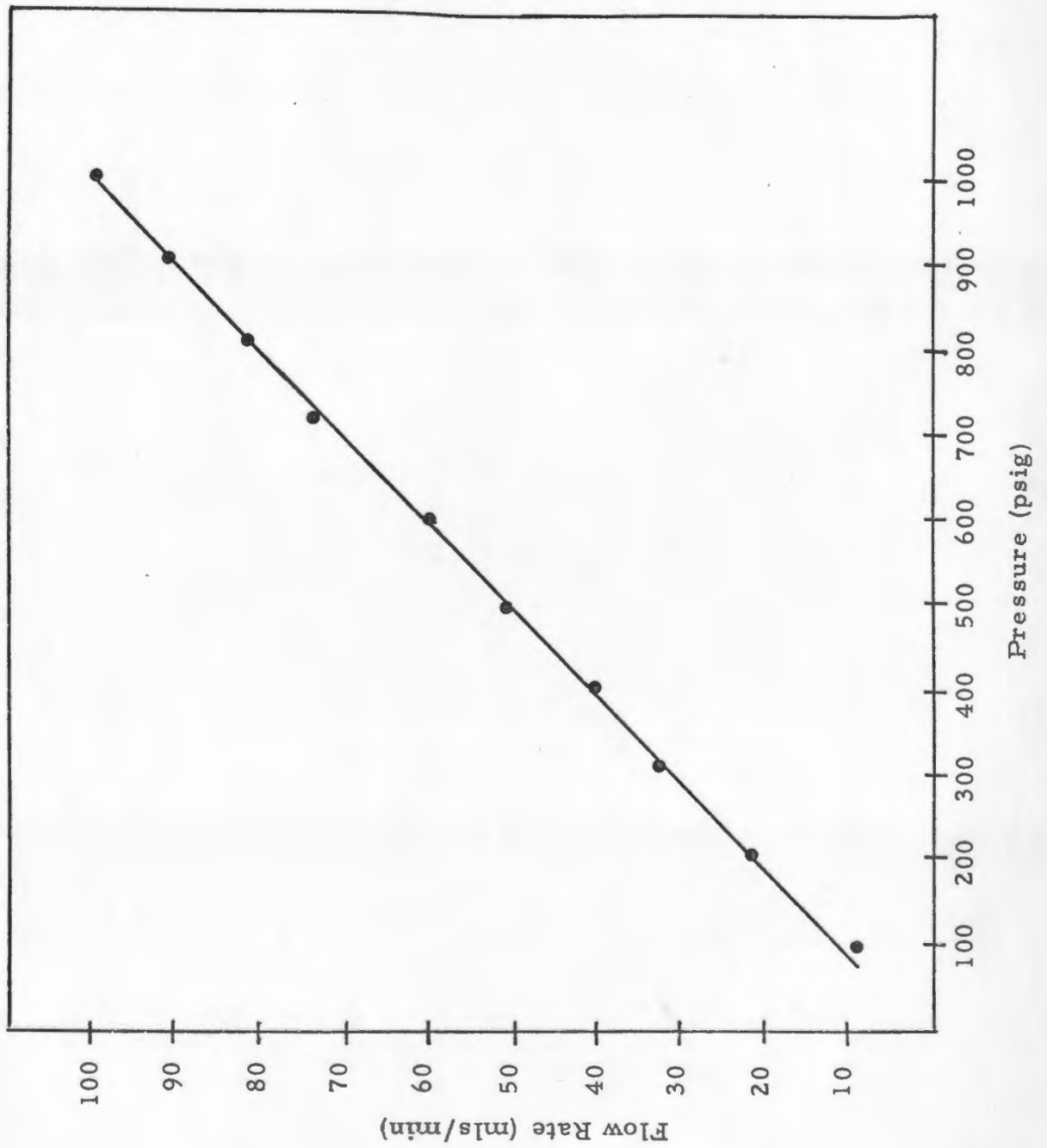


Figure 2. Flow Rate of Effluent as a Function of Pressure.

TABLE II

Deoxygenation via Gas Permeation as a Function
of Pressure for Double Pass Systems

Method	Dissolved Oxygen Level (ppm)
Distilled water	9.05
100 x 2 passes	trace
200 x 2 passes	trace
400 x 2 passes	0.07
600 x 2 passes	trace
800 x 2 passes	trace
1000 x 2 passes	trace

trace = less than 0.05 ppm

TABLE III

Efficiency of Single Pass vs. Double Pass

Pressure (psig)	Dissolved Oxygen Levels 1 pass	Dissolved Oxygen Levels 2 passes
100	.05	trace
600	.48	trace
1000	.78	trace

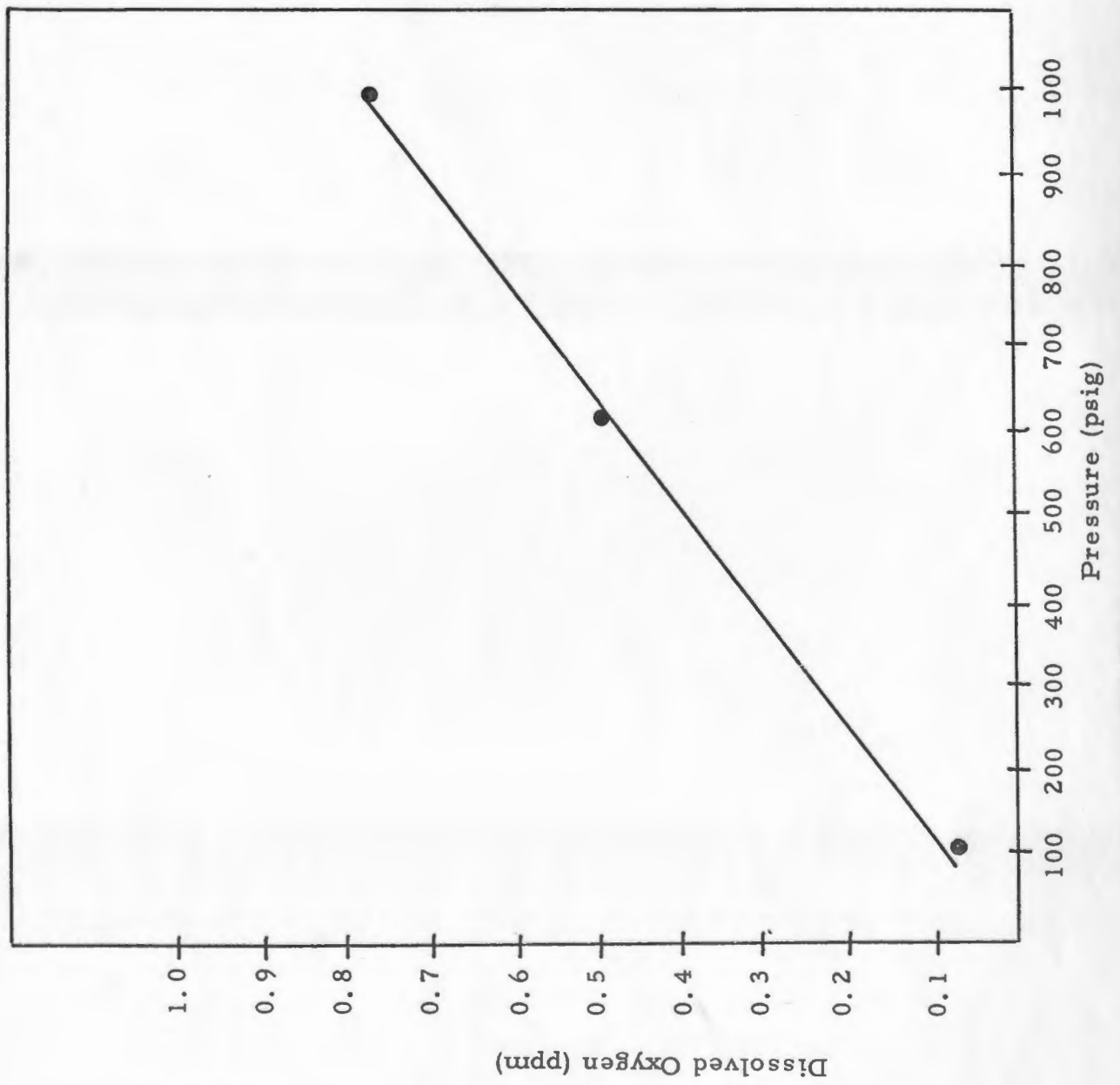


Figure 3. Pressure Versus Dissolved Oxygen Levels.

The effect of reduced dissolved oxygen levels on the degradation rate of a susceptible system was studied using pyrogallol as a model drug. This drug moiety is especially susceptible to oxidative decomposition due to the three adjacent hydroxyl groups and the unsaturated nature of the compound. Table IV illustrates the rate of degradation of an unprotected system prepared with deionized, distilled water. The rate of degradation is rapid (5.57×10^{-2} days⁻¹). Figure 2 shows that the degradation is apparently first order, which is expected for most oxidative processes. Half of the drug is decomposed in 10.3 hours and the T90 is 1.9 hours.

Removal of most of the dissolved oxygen in the solvent should retard reaction kinetics since the molecular oxygen concentration has an effect on the propagation step. However, since it has been shown that susceptible systems may degrade by a secondary pathway (2) if oxygen is not readily available, the removal of molecular oxygen might not afford complete protection.

Tables V through XIII depict the degradation of pyrogallol in water prepared at various pressures and either a single or double pass with resultant various dissolved oxygen levels.

Since a colorimetric assay was utilized, data is reported as ranges to allow the usual variations in this analytical procedure. Difficulties and variations of results were further compounds since the assay has been shown to be time dependent. (12)

Systems protected via gas permeation have apparent first order degradation. Although the molecular oxygen concentration of single pass systems were less than 1 ppm, degradation occurred. The extent of the degradation however was significantly less than that of the unprotected system. Thus, single pass systems (less than 1.0 ppm) do afford protection to a system of pyrogallol since the oxygen available for degradation is considerably less than in unprotected systems.

Study of systems protected by a double pass, producing trace dissolved oxygen levels, lead to interesting observations. First, at trace oxygen levels, degradation occurs; probably because the drug moiety degrades by a non-oxidative process. Many drugs having primarily oxidative pathways for degradation will degrade by other means as well. The degradation rates however are considerably less and appear to "stabilize" after a slight initial degradation.

TABLE IV

Pyrogallol Degradation at 30°C with Respect to Time

in Distilled Water, pH 7.0; D. O. Level = 9.05

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.6	100	5.4 - 5.8
2.5	5.2	92.3	5.1 - 5.3
5.5	5.2	92.3	5.15 - 5.25
18.0	2.4	42.8	2.3 - 2.5
24.0	1.5	26.7	1.2 - 1.8

TABLE V

Pyrogallol Degradation at 30°C with **Respect** to Time
in Permeated Water Prepared at 100 **psig.** Single Pass

Dissolved Oxygen Level = **trace**

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.73	100	5.4 - 6.0
24	4.9	85.5	4.7 - 5.1
48	3.9	68.1	3.7 - 4.1
96	3.6	62.8	3.4 - 3.8
192	3.1	54.1	2.8 - 3.4
296	2.5	43.6	2.3 - 2.7

TABLE VI

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 100 psig, Double Pass

Dissolved Oxygen Level = trace

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.6	100	4.8 - 6.4
24	4.6	82.1	4.0 - 5.2
48	4.5	80.3	4.3 - 4.2
144	3.2	57.1	3.1 - 3.3
192	2.9	51.8	2.6 - 3.2

TABLE VII

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 200 psig, Double Pass

Dissolved Oxygen Level = trace

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	6.2	100	5.9 - 6.5
24	4.2	67.7	4.0 - 4.4
48	4.4	71.1	4.1 - 4.7
96	4.1	66.1	3.9 - 4.3
192	3.8	61.3	3.7 - 3.9
288	3.7	59.7	3.6 - 3.8
384	3.6	58.1	3.1 - 4.1

TABLE VIII

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 400 psig, Double Pass

Dissolved Oxygen Level = 0.07 ppm

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.4	100	4.9 - 5.9
24	4.3	79.6	4.1 - 4.5
48	4.2	77.8	3.7 - 4.7
96	3.9	72.2	3.6 - 4.2
192	3.5	64.8	3.1 - 3.9
288	3.4	63.0	3.1 - 3.7
384	3.5	64.8	3.4 - 3.6

TABLE IX

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 600 psig, Single Pass

Dissolved Oxygen Level = 0.48 ppm

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	6.3	100	6.0 - 6.6
24	4.8	76.2	4.3 - 5.2
48	4.3	68.3	4.0 - 4.6
96	4.2	66.7	3.6 - 4.8
192	5.4	85.7	5.2 - 5.6
288	3.7	58.7	3.4 - 4.0
384	2.8	44.4	2.7 - 2.9

TABLE X

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 600 psig, Double Pass

Dissolved Oxygen Level = trace

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.6	100	5.3 - 5.9
24	4.4	78.6	3.8 - 5.0
48	4.2	75.0	3.8 - 4.6
96	4.4	78.6	4.3 - 4.5
192	4.0	71.4	3.9 - 4.1
288	4.5	80.3	3.6 - 4.6
384	3.6	64.3	3.1 - 4.1

TABLE XI

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 800 psig, Double Pass

Dissolved Oxygen Level = trace

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	6.0	100	5.8 - 6.2
24	5.4	90	5.1 - 5.7
48	4.9	81.7	4.6 - 5.2
96	5.0	83.3	4.6 - 5.4
192	4.3	71.7	3.7 - 4.9
288	4.8	80	4.6 - 5.0
384	4.2	70	4.0 - 4.4

TABLE XII

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 1000 psig, Single Pass

Dissolved Oxygen Level = 0.78 ppm

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.9	100	5.3 - 6.5
24	5.3	89.8	4.6 - 6.0
48	5.3	89.8	4.9 - 5.7
96	4.0	76.7	3.7 - 4.3
192	3.1	52.5	2.6 - 3.6
288	3.2	54.2	2.7 - 3.7
384	3.3	55.9	2.9 - 3.7

TABLE XIII

Pyrogallol Degradation at 30°C with Respect to Time
in Permeated Water Prepared at 1000 psig, Double Pass

Dissolved Oxygen Level = trace

Time (hours)	Pyrogallol mg/liter	Percent Remaining	Range mg/liter
0	5.7	100	5.2 - 6.2
24	5.0	87.7	4.5 - 5.5
48	5.0	87.7	4.5 - 5.5
96	4.5	78.9	4.2 - 4.8
192	3.7	64.9	3.1-- 4.3
288	3.1	54.4	2.7 - 3.5
384	3.1	54.4	2.9 - 3.3

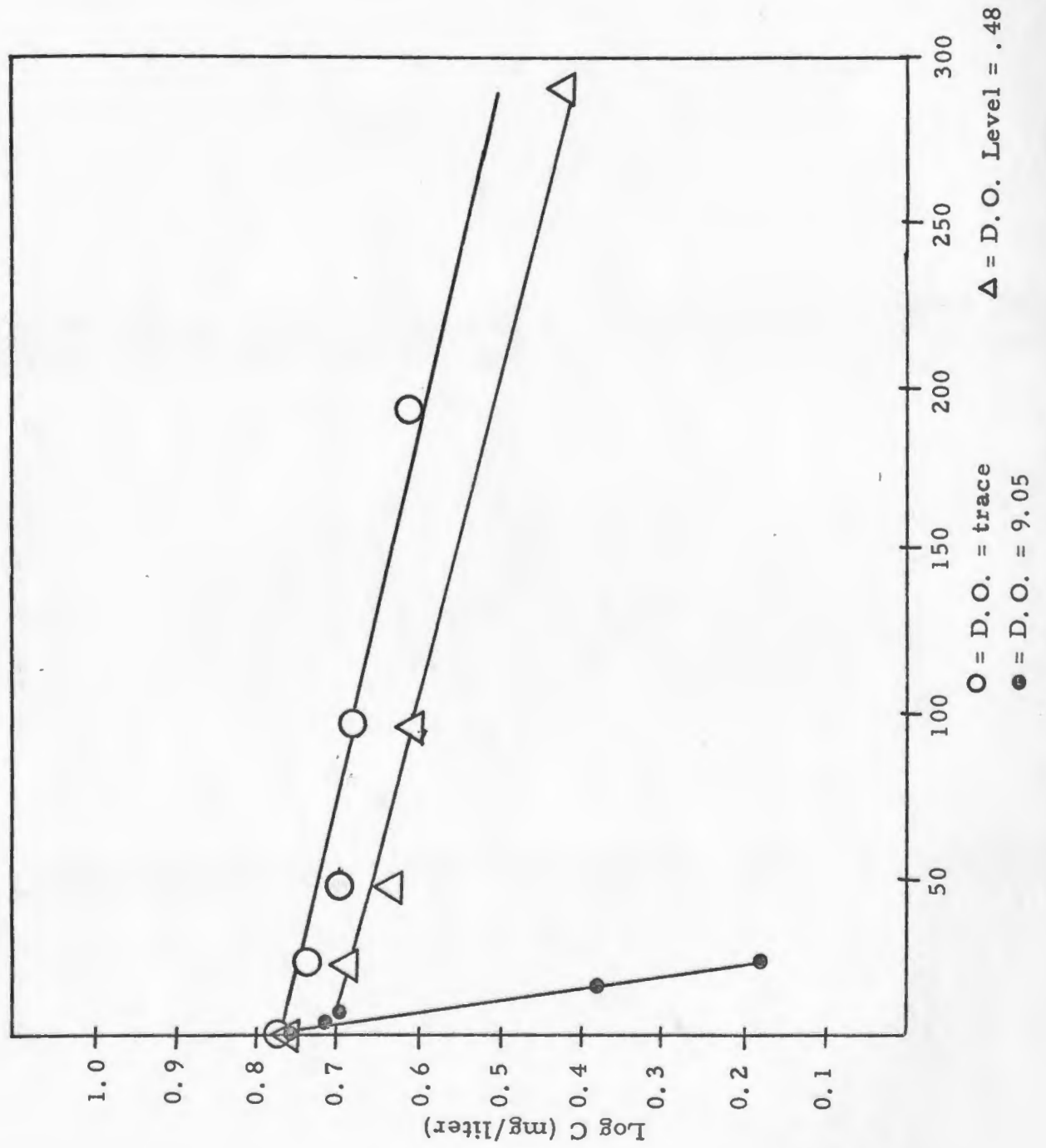


Figure 4. Comparative Degradation of Pyrogallol at 30°C in Various Dissolved Oxygen Levels.

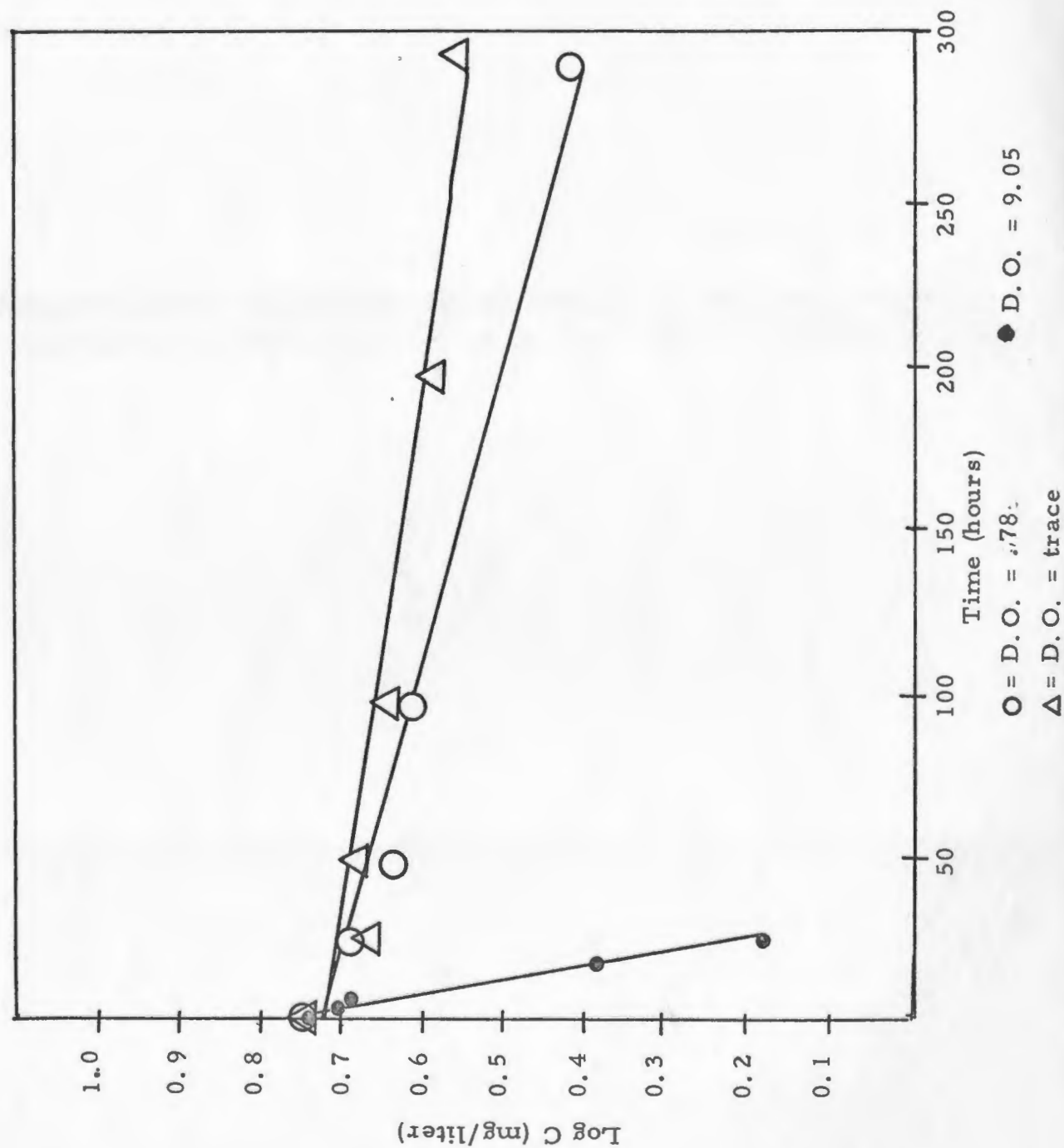


Figure 5. Comparative Degradation of Pyrogallol at 30°C in Various Dissolved Oxygen Levels.

TABLE XIV

Comparative Degradation of Protected and Unprotected
Systems of Pyrogallol at 30°C

Protection	Dissolved Oxygen Levels (ppm)	$K(\text{mg/L} \times 10^{-4} \times \text{days}^{-1})$	T_{90}	Protection Index*
unprotected	9.05	557.5	1.9	1.0
single pass	0.05-0.78	14.6	72.8	.026
double pass	trace	10.2	114.4	.018

* ratio of k rates relative to unprotected system

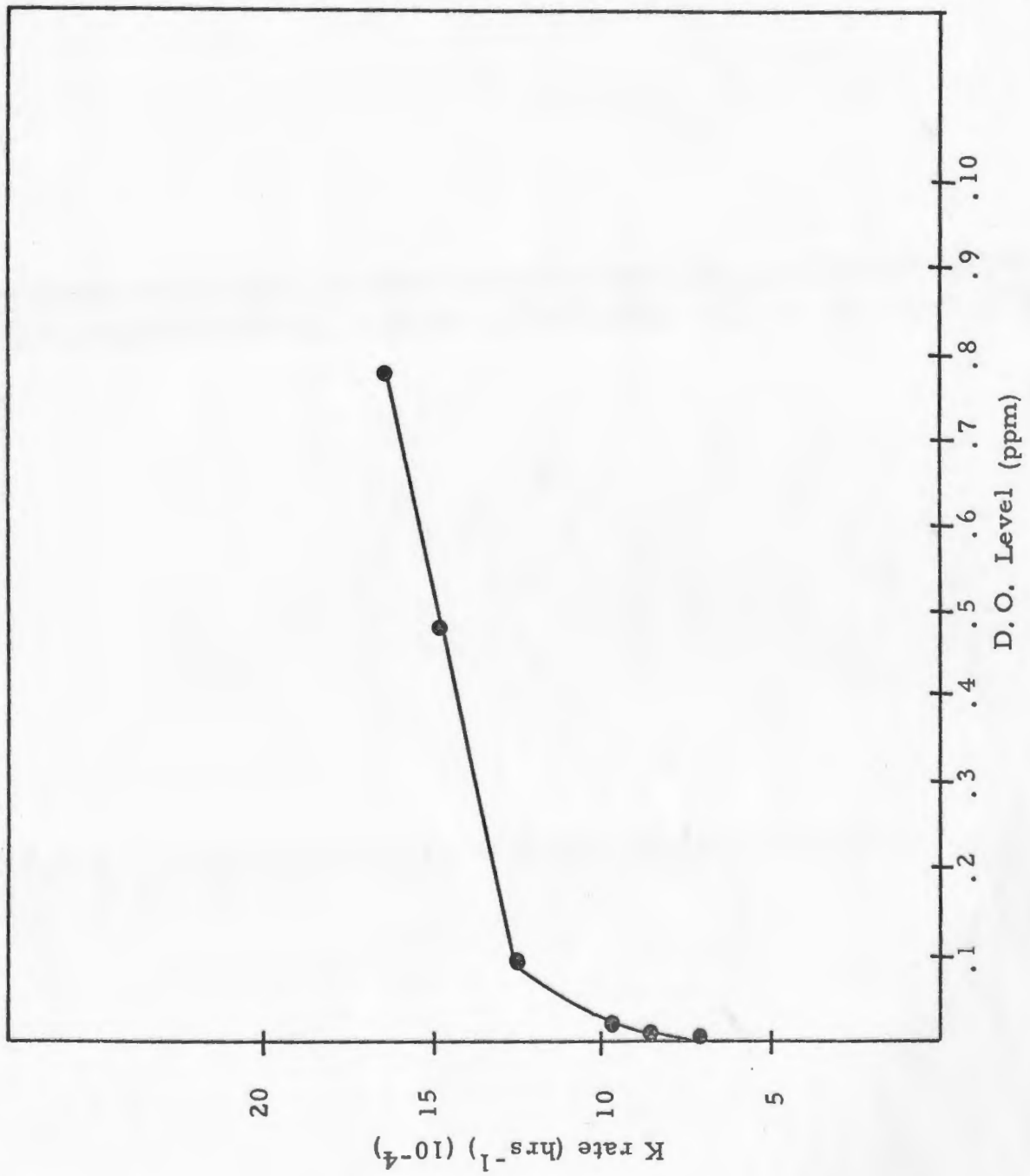


Figure 6. Effect of Oxygen Concentration on Rate of Degradation of Pyrogallol at 30°C .

Figure 4 substantiates the hypothesis of non-oxidative degradation of pyrogallol since even extremely low levels of dissolved oxygen (.01 ppm) do not cause complete inhibition of degradation.

Table XIV depicts the comparative degradation of unprotected and protected systems. In both single and double pass systems, there is a significant reduction in degradation due to the depletion of molecular oxygen.

An indication of the protection afforded via gas permeation is the relative protection ratio. If the unprotected system is assigned an index value of unity, a single pass system has an index of 0.026 and a double pass system an index of 0.018. This is to say that a single pass system (d. o. 0.05-0.78) would degrade 38 times slower than an unprotected system (d. o. = 9.05) while a double pass system (d. o. = trace) would degrade 55 times as slowly as the control. The protection afforded permeated systems is readily apparent from Table XIV and it has been shown that a double pass system decreases degradation significantly enough to warrant the employment of a second permeation pass.

IV. CONCLUSIONS

1. Effluent flow rate is directly proportional to the pressure with which the effluent is forced through the permeator.
2. A single pass of effluent through the permeator will reduce the dissolved oxygen levels in proportion to the resident in the apparatus, or the effluent flow rate. The efficiency of molecular oxygen removal is greatest at slowest flow rates and lowest pressures.
3. Double pass systems are reduced to trace levels of dissolved oxygen regardless of the flow rate at which they are prepared.
4. For efficient oxygen removal at acceptable flow rates for industrial processes, the optimum operating parameters for the Permasep^(R) would be 1000 psig with two permeators connected in series.
5. Dissolved oxygen levels of less than 1 ppm reduce pyrogallol degradation considerably although the degradation is not inhibited completely.
6. Trace dissolved oxygen levels reduce pyrogallol degradation significantly, probably completely, except for degradation by non-oxidative pathways.

V. REFERENCES

1. Lachman, L., "-Antioxidants and Chelating Agents as Stabilizers in Liquid Dosage Forms I" - Drug & Cosm. Ind. 102:36 (1968).
2. Lausier, J. M., et al. An Application of Gas Permeation, Dissertation Abs. Int. 32:10, 5895B.
3. Shou, S. A., "Decomposition of Pharmaceutical Preparations Due to Chemical Changes," Am. J. Hosp. Pharm. 17, 153.
4. Lachman, L., "Antioxidants and Chelating Agents as Stabilizers in Liquid Dosage Forms - II." Drug & Cosm. Ind. 102:146 (1968).
5. Martin, A. N., Physical Pharmacy, 2nd Edition 1970, pg. 330.
6. Brown, M. and Leeson, L., "Protection of Oxygen Sensitive Pharmaceuticals with Nitrogen," J. Pharm. Sci. 58, 242 (1969).
7. Cole, C. A. and Genetelli, E. J. "Decarbonations and Decarbon of Water by Use of Selective Hollow Fibers," Environ. Sci. & Tech., 4 (#6) 451 (1970).
8. Li, N., Long, R. and Henly, A., "Membrane Separation Processes," Ind. & Eng. Chem., 57, 18 (1965).
9. Lebovits, D. "Permeability of Polymers to Gases, Vapors, and Liquids," Mod. Plast., 43, 139 (1966).

10. Lausier, J., Gerraughty, R., Paruta, A. N., "Efficient Deoxygenation of Water by Gas Permeation," J. Pharm. Sci., 60:1906 (1971).
11. Grant, J. and Patel, J., "Determination of Each Constituent in Mixtures of Catechol and Protocatechiuc Acid, Quinol and Gentisic Acid, Phenol and p-Hydroxybenzoic Acid and Pyrogallol and Gallic Acid," Anal. Biochem. 28:139 (1969).
12. Swain, T. and Goldstein, J. "The Quantitative Analyses of Phenolic Compounds," Methods of Polyphenol Chemistry, Pergamon Press (1963).
13. Cullen, L. F. and Papariello, G., "Sampling and Analysis of Oxygen in the Void Volume of Ampuls and Vials," J. Pharm. Sci. 59:94 (1970).
14. Martin, A. N., Swarbrick, J., Cammarata, A., Physical Pharmacy, Lea & Febiger, 2nd Edition, pg. 390-392.

APPENDIX I

Specifications for Permasep Gas Permeator

Permeator Number	015-70-0264
Serial Number	DP-168
Shell Inner Diameter	1.50 inches
Shell Pressure Rating	1500 psig
Fibers	Dacron
Number of Tubes	741,600
Tube Outside Diameter	32.8 microns
Tube Percent Hollow	16.5 microns
Number of Leaking Tubes	38
Percentage of Leaking Tubes	0.005%
Shell Material	Carbon Steel
Capacity	0.6 Gallons