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Model development for O_2 and N_2 permeation rates through CZ-resin vials

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Abstract

The headspace of vials containing oxygen-sensitive formulations is filled with a nitrogen blanket. This paper presents the development of a mathematical model to predict the oxygen and nitrogen permeation rates through the walls of plastic CZ-resin vials. The model estimates the time required for a nitrogen-filled vial to reach ambient nitrogen and oxygen levels. The permeation of oxygen and nitrogen through the vial is governed by Fick's law and may be described by an exponential equation. Using the values for oxygen and nitrogen permeation through CZ-resin vial, the half-lives for the decrease in nitrogen level and increase in oxygen level was found to be 150 days and 15 days, respectively. This result can be attributed to the greater permeability of CZ-resin vial to oxygen (79.06 cm^3-mm/m^2-24 h-atm) when compared with nitrogen (12 cm^3-mm/m^2-24 h-atm). The ingress of oxygen into CZ-resin vials was determined experimentally and it was found to verify the model. These results indicate that CZ-resin vials may be inappropriate for packaging oxygen-sensitive formulations even in the presence of a nitrogen-filled headspace.
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1. Introduction

Currently, most of the liquid parenteral formulations are packaged in glass vials, which are impermeable to gases. It is well established that some proteins in parenteral formulations have a tendency to bind significantly to pharmaceutical container surfaces. Previous reports have indicated that no correlation exists between the amount of protein adsorbed and molecular mass or isoelectric point, although glass surfaces appeared to bind more protein under the experimental conditions examined (Burke et al., 1992). Formulation overages are often required to compensate for the loss as a result of protein adsorption to the glass surface. This overage of protein is not only expensive, but may not be acceptable in the future from the regulatory perspective. In situations where protein adsorption is significant, the inclusion of high concentrations of an inert

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protein (e.g. serum albumin) to saturate the container surface or the presence of compounds to reduce surface interactions such as surfactants (Duncan et al., 1995), carbohydrates, or amino acids can be employed to reduce the problem (Suelter and DeLuca 1983; Wang and Hanson 1988).

Therefore, an alternate packaging material that demonstrates no protein binding would be desirable. One type of vial is made from CZ resin (Daikyo, Seiko, Ltd., The West Company, Lionville, PA, USA), which is a high molecular weight plastic material. Since these vials are made up of plastic, they are permeable to gases. Therefore, in order to use these vials for packaging oxygen-sensitive formulations, these vials must be evaluated with respect to their permeability to oxygen and nitrogen. This paper presents the development of a mathematical model to predict the rates of oxygen and nitrogen permeation through the CZ-resin vials surface.

2. Theory

In order to develop a model to determine the time it takes for the CZ-vial headspace to reach ambient concentrations of nitrogen and oxygen, the following assumptions were made.

- The vial contains a 1 cm^3 liquid fill and its total fill capacity is 2.6 cm^3 (headspace 1.6 cm^3).
- Nitrogen permeation occurs only at the solid–vapor interface, through the walls corresponding to the headspace of the vial. There is no nitrogen loss through the stopper.
- Oxygen permeation from the outside into the vial may occur at all air/vial interfaces (i.e. through the total surface area of the vial). There is no oxygen permeation through the stopper.
- There is an insignificant amount of either oxygen or nitrogen dissolved in the liquid.
- The vial headspace initially contains 100% nitrogen at 1 atm and the internal vial pressure can increase.
- Ambient air outside the vial has a composition of 79% nitrogen and 21% oxygen (mole basis).
- At infinite time the concentration of nitrogen and oxygen inside the vial will reach ambient levels.
- The values for oxygen and nitrogen permeability through CZ resin at 25°C are 79.06 cm^3-mm/m^2-day-atm (average of four CZ vials tested by Mocon, Minneapolis, MN for oxygen permeation at 23°C/ambient%RH) and 12 cm^3-mm/m^2-day-atm (reported by Daikyo Seiko Ltd, Technical report 1995), respectively.

A comparison of the oxygen and nitrogen permeability values show that oxygen permeates the plastic at a rate 6.6 times greater than that for nitrogen. Therefore, in assessing the potential use of a nitrogen blanket for vials containing oxygen-sensitive formulations, both the loss of nitrogen from inside the vial and the corresponding ingress of oxygen must be considered.

The following is the development of equations to describe the change in nitrogen concentration inside the CZ-resin vial. The same approach was then applied to derive an equation for the ingress of oxygen from the environment into the vial.

Consider a CZ-resin vial containing 1 cm^3 liquid fill and containing 1.6 cm^3 nitrogen in the headspace with a partial pressure, p_d, corresponding to its concentration, C_d.

The surface area (8.49 cm^2) corresponding to 1.6 cm^3 headspace of CZ-resin vial was obtained by calculating (S_1–S_2), where: S_1 = total surface area of the vial corresponding to total volume of 2.6 cm^3 (12.92 cm^2) and S_2 = surface area corresponding to 1 cm^3 fill volume (4.43 cm^2). S_1 and S_2 were calculated as described below.

1. Total surface area of the vial corresponding to 2.6 cm^3 ($S_1 = 12.92$ cm^2): The total surface area of the CZ-resin vial was determined using the vial body radius ($r_1 = 0.625$ cm) with the corresponding height ($h_1 = 2.67$ cm) and the vial neck radius ($r_2 = 0.35$ cm) with the corresponding height ($h_2 = 0.55$ cm). Following formula was used to calculate the surface area corresponding to 2.6 cm^3: $\pi r_1^2 + 2\pi r_1 h_1 + 2\pi r_2 h_2$
2. Surface area corresponding to 1 cm^3 fill volume ($S_2 = 4.43$ cm^2). The height corresponding to 1 cm^3 fill volume (h_3) was calculated as $[1/(\pi r_1^2)] = 0.815$ cm. Following formula was

used to calculate the surface area corresponding to 1 cm^3 fill volume. $\pi r_1^2 + 2\pi r_1 h_3$

The rate of loss of nitrogen through the CZ resin vial can be calculated using Fick's Law (Treybal, 1981):

$$-\frac{dV}{dt} = \frac{S_N G_N (p_d - p_r)}{L} \quad (1)$$

where: $-dV/dt$, rate of nitrogen loss from the vial (cm^3/s) at standard temperature (273 K) and pressure (1 atm) (STP); S_N, surface area (8.49 cm^2) corresponding to the head space (1.6 cm^3) of the vial, through which nitrogen permeation occurs; G_N, permeability of the CZ resin to nitrogen (cm^3(STP)-cm)/(cm^2-s-atm) at 25°C; p_d, partial pressure (atm) of nitrogen on the donor side, which is the headspace of the CZ resin vial; p_r, partial pressure (atm) of nitrogen on the receptor side, which is the air outside the CZ resin vial; L, thickness of the vial (0.15 cm).

The driving force for nitrogen loss from the vial is the difference in nitrogen partial pressure between the donor and receptor sides. As nitrogen permeates through the vial, p_d decreases and the driving force is lessened until p_d equals p_r. The time required for p_d to equal p_r may be determined by integrating Eq. (1).

Using the relationship $P = CRT$ (Martin et al., 1993), and expressing the rate of nitrogen loss in units of gmole, the following equation is obtained.

$$-\frac{dC_d}{dt} = K_N(C_d - C_r) \quad (2)$$

where: C_d, concentration of nitrogen in the headspace of the vial (gmole/l); C_r, concentration of nitrogen outside the vial at room temperature (0.0323 gmole/l) using $C_r = p_r/\mathrm{RT}$, where p_r = 0.79 atm, $T = 298$ K, $R = 0.082$(l-atm)/(gmole K).

The rate constant, K_N, represents the term $S_N G_N p_s T_e/(V_h L T_s)$.where: T_e, experimental temperature (298 K); p_s, standard pressure = 1 atm; T_s, standard temperature = 273 K; V_h, volume of headspace.

Integration of Eq. (2) gives an expression for the concentration of nitrogen in the vial as a function of time as shown in Eq. (3).

$$C_d = C_r + (C_{do} - C_r)e^{-K_N t} \quad (3)$$

where: C_{do}, initial nitrogen concentration in the vial at time equal to zero at room temperature (0.04092 gmole/l), where $C_{do} = p_{do}/RT$ ($p_{do} = 1$ atm, $T = 298$ K, $R = 0.082$ (l-atm)/(gmole-K)); K_N, 0.00463 /day, where $K_N = S_N G_N p_s T_e/(V_h L T_s)$; $S_N =$ 8.49 cm^2, $G_N = 12$ (cm^3-mm)/(m^2-day-atm), $p_s = 1$ atm, $T_e = 298$K, $V_h = 1.6$ cm^3, $L = 1.5$ mm, $T_s = 273$ K.

The nitrogen concentration versus time at 25°C for a vial filled with 1 cm^3 liquid, as represented by Eq. (3), is shown as the solid line in Fig. 1. The plot shows that nitrogen reaches the ambient concentration (79 mole% or 0.0323 gmole/l) in about 900 days. However, it takes much less time for the nitrogen concentration to reach the midpoint between the initial 100 mole% (0.04092 gmole/l) and the ambient 79 mole% (0.0323 gmole/l). Given that K_N is equal to 0.00463 $days^{-1}$, the half-life for the drop in nitrogen concentration may be determined from $t_{1/2} = 0.693/K_N$, which is 150 days.

The rate of oxygen ingress into the CZ resin vial may be calculated in a similar fashion to that outlined above for nitrogen loss from the vial. However, the oxygen concentration in the donor compartment (the interior of the vial) starts at zero and increases to an ambient level of 21 mole%. The rate of change of oxygen concentration in the headspace of the CZ resin vial can be represented by an equation similar to Eq. (2):

$$\frac{dC'_d}{dt} = K'_o(C'_r - C'_d) \quad (4)$$

where: C'_d, is the concentration of oxygen in the headspace of the CZ resin vial; C'_r, concentration of oxygen in the air outside the vial (0.0086 gmole/l) where $C'_r = p'_r/\mathrm{RT}$ ($p'_r = 0.21$ atm, $T =$ 298 K, $R = 0.082$ (l-atm)/(gmole-K)); K'_o, 0.0464 day^{-1} where $K'_o = S_o G_o p_s T_e/(V_h L T_s)$ $S_o = 12.92$ cm^2, $G_o = 79.06$ (cm^3-mm)/(m^2-day-atm), $p_s = 1$ atm, $T_e = 298$K, $V_h = 1.6$ cm^3, $L = 1.5$ mm, $T_s =$ 273 K; S_o, total surface area (12.92 cm^2) available for oxygen permeation; G_o, permeability of oxygen through the CZ resin vial at 25°C = 79.06 (cm^3-mm)/(m^2-day-atm).

Integrating Eq. (4) gives an equation which represents the concentration of oxygen inside the vial as a function of time.

$$C'_d = C'_r(1 - e^{-K'_o t}) \quad (5)$$

The oxygen concentration inside the vial at 25°C, as represented by Eq. (5), shown by the dotted line in Fig. 1, increases exponentially with time. The plot shows that the oxygen concentration inside the vial will reach the ambient (21 mole% or 0.0086 gmole/l) level in about 120 days. Note again, however, that using a K'_o of 0.0464 day^{-1}, the half-life for the increase in oxygen is only 15 days.

3. Materials and methods

CZ resin vials in the 2 cm^3 size with a capacity of 2.6 cm^3 were provided by Daikyo, Seiko, Ltd., The West Company, Lionville, PA, USA.

Fifteen sets of CZ-resin vials each consisting of four vials, were set up to verify the model for oxygen and nitrogen permeation through the vial. The results were used to determine the oxygen permeation rate into a CZ-resin vial filled completely with nitrogen and containing no liquid fill volume. The following procedure was performed:

1. CZ vials were capped with 13 mm Daikyo 713 stoppers using 5 min Epoxy glue.
2. Four vials per set were flushed with nitrogen for 60 min with a flow rate ranging from 50 to 60 cm^3/min. This flow rate was found to be sufficient to ensure the replacement of all air with nitrogen.
3. The vials were placed in a preset oven at 25 ± 2°C.
4. Each set of vials was tested for oxygen concentration at various time points using a calibrated Orbisphere Headspace Analyzer 2715 (Orbisphere Laboratories, Boonton, NJ, 07005, USA).The theory of Orbisphere headspace analyzer is based on measuring the oxygen concentration in terms of partial pressure of oxygen. This can be converted to mole% by dividing the partial pressure with total pressure and multiplying it by 100. Therefore, the concentration terms (C'_d and C'_r) in Eq. (5) have been used in terms of mole% for verification of the model.
5. At each time point, vials that were not flushed with nitrogen (containing air) were used to measure the oxygen concentration as the control.

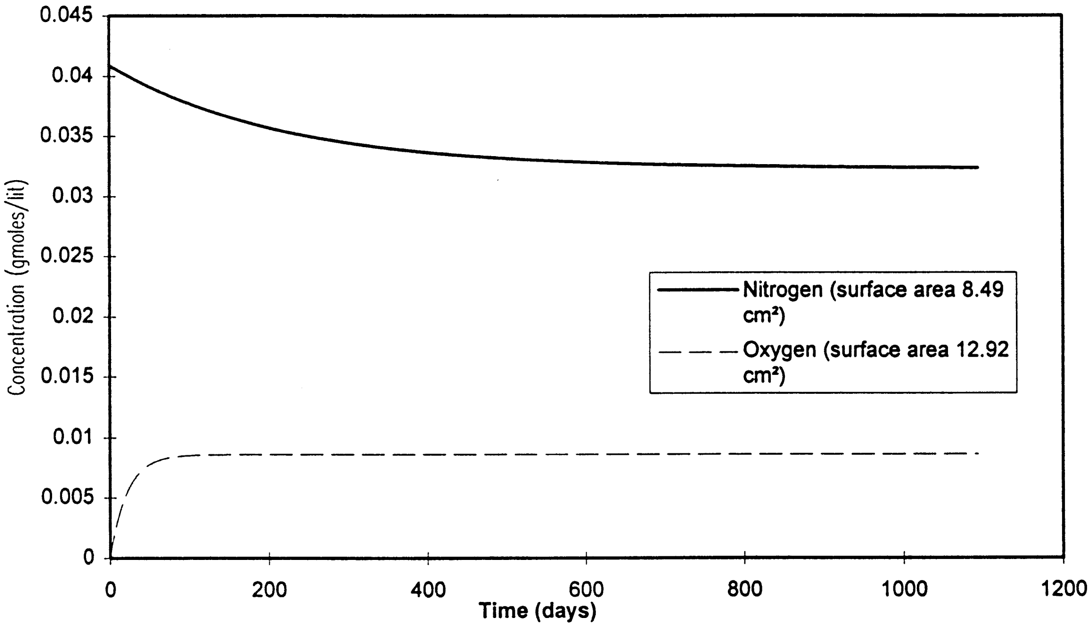

Fig. 1. Theoretical curves of nitrogen and oxygen concentrations in the headspace (1.6 cm^3) of a CZ-resin vial versus time at 25°C.

Table 1
A comparison between the theoretical and experimental results for the oxygen concentration (mole%) in the headspace of CZ-resin vials

Time (days)	Experimental oxygen determinations (mole%)			
	O_2 in control vials (containing air)	O_2 in vials flushed with N_2	Calculated curve fitting O_2 results ($C'_r = 18.3$ mole%) ($K'_o = 0.0406$ day^{-1})	O_2 (mole%) theoretical ($C'_r =$ 21.0 mole%) ($K'_o =$ 0.0286 day^{-1})
0	18.5	0.4	0.0	0.0
1	19.3	2.2	0.7	0.6
3	20.0	2.7	2.1	1.7
6	19.9	4.8	4.0	3.3
8	20.2	6.6	5.1	4.3
10	19.5	7.1	6.1	5.2
13	19.5	8.1	7.5	6.5
15	19.2	9.4	8.4	7.3
18	19.6	9.4	9.5	8.4
29	18.4	10.3	12.7	11.8
68	19.0	14.2	17.2	18.0
109	19.1	18.0	18.1	20.1
123	18.3	18.9	18.2	20.4
152	19.9	19.3	18.3	20.7
182	19.1	19.6	18.3	20.9
Average =	19.3			
S.D. =	0.6			

4. Results and discussion

4.1. Verification of the model

The following values were used for the model verification and validation: C'_r, ambient oxygen concentration = 21 mole%; K'_o, 0.0286 day^{-1}, where $K'_o = S_o G_o p_s T_e / V_h L T_s$ where S_o, surface area of the vial available for oxygen permeation = 12.92 cm^2; G_o, 79.06 cm^3-mm/m^2- day-atm; p_s, standard pressure = 1 atm; T_e, experimental temperature = 298 K; V_h, volume of the headspace.Since the vial is empty, total volume of the vial is 2.6 cm^3; L, thickness = 1.5 mm; T_s, standard temperature = 273 K.

Table 1 shows the experimental and theoretical data for oxygen permeation through empty CZ-resin vials. The results show that both experimental (vials flushed with nitrogen) and theoretical permeation values increase with time. The oxygen permeation values obtained experimentally for the vials flushed with nitrogen increased from 0.4 to 19.6 mole%. These results were similar to those obtained theoretically, which increased from 0 to 20.9 mole%, as time increased from 0 to 182 days. The control vials containing air (vials not flushed with nitrogen) show an average value of 19.3 ± 0.6 mole% oxygen, which is similar to the theoretical value of 21 mole% oxygen in air. If 19.3 mole% was used instead of 21 mole% for the theoretical calculations then the theoretical data would match more closely to the experimental data in the latter part of the curve as shown in the last two columns of Table 1.

The oxygen-concentration data for vials flushed with nitrogen was used to obtain the two parameters (C'_r and K'_o, 18.3 and 0.0406, respectively) in the exponential rise equation for oxygen permeation (Eq. (5)). A curve fitting of the experimental data was generated by substituting these two parameters (C'_r and K'_o) into Eq. (5) to obtain the curve fitting results of oxygen permeation through empty CZ resin vials. The value for C'_r (18.3) was similar to that average value (19.3 ± 0.6) obtained from the control vials. The value of K'_o obtained was 0.0406 day^{-1} as compared to the calculated value of 0.0286 day^{-1}. The coefficient R^2 value obtained from the curve fitting was 0.96, showing a good fit for the experimental data.

Fig. 2. shows a comparison between the curve fitting results of the experimental data and theoretical oxygen permeation. Also shown is the variation in oxygen concentration of the control samples.

In addition, it was initially assumed that nitrogen and oxygen diffusion only occurred through the walls of the CZ-resin vial. However, in the real situation, a semi-permeable rubber stopper may also enable the diffusion of these molecules. Also, bulk diffusion may occur at the vial-stopper interface.

5. Conclusion

It takes much less time for oxygen to increase to ambient levels in the CZ-resin vial than it takes for the nitrogen to decrease to ambient levels. This is because of the greater permeability of the CZ resin to oxygen versus nitrogen. Looking at nitrogen levels only, one may conclude that a nitrogen blanket in CZ vials containing oxygen-sensitive formulations may be useful. The half-life for nitrogen decrease is 150 days which may be acceptable for formulations with 1–2 year shelf lives. However, given a half-life of 15 days for oxygen to reach one half of the ambient concentration, a nitrogen blanket will not protect oxygen-sensitive formulations. Indeed, CZ vials should not be used to package oxygen-sensitive parenteral formulations unless sufficient stability data is generated.

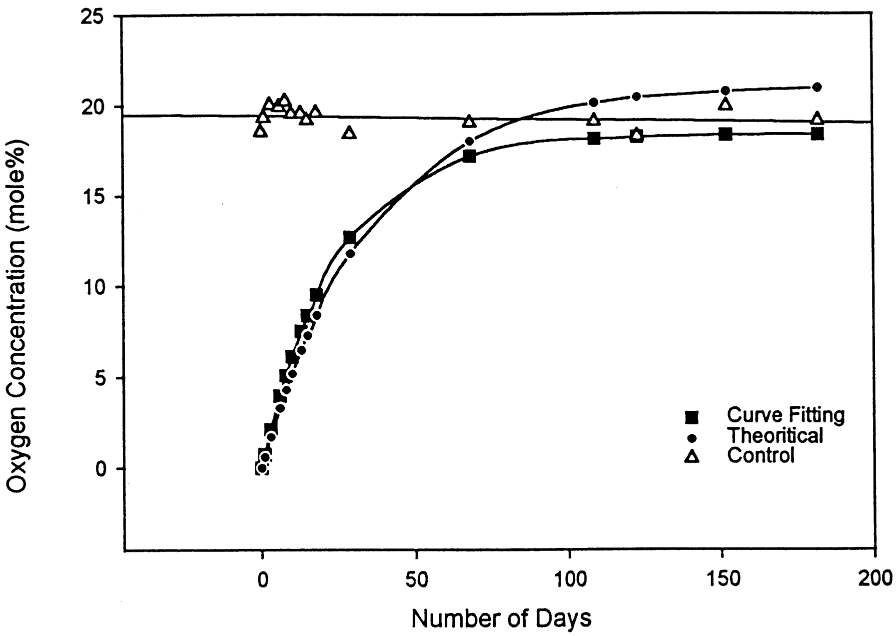

Fig. 2. Comparison of theoretical, curve fit of experimental data and control data showing oxygen concentration at different time intervals.

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