Predictions of Vacuum Loss of Evacuated Vials from Initial Air Leak Rates

MICHAEL R. PRISCO,[1] JORGE A. OCHOA,[1] ATIF M. YARDIMCI[2]

[1]Exponent Engineering and Scientific Consulting, Biomedical Engineering Practice, Menlo Park, CA

[2]Baxter Healthcare Corporation, Technology Resources, Round Lake, IL

Received 19 March 2013; revised 30 May 2013; accepted 12 June 2013

Published online 9 July 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23652

ABSTRACT: Container closure integrity is a critical factor for maintaining product sterility and stability. Therefore, closure systems (found in vials, syringes, and cartridges) are designed to provide a seal between rubber stoppers and glass containers. To ensure that the contained product has maintained its sterility and stability at the time of deployment, the seal must remain intact within acceptable limits. To this end, a mathematical model has been developed to describe vacuum loss in evacuated drug vials. The model computes equivalent leak diameter corresponding to initial air leak rate as well as vacuum loss as a function of time and vial size. The theory accounts for three flow regimes that may be encountered. Initial leak rates from 10^{-8} to 10^{3} sccm (standard cubic centimeters per minute) were investigated for vials ranging from 1 to 100 mL. Corresponding leak diameters of 0.25–173 μm were predicted. The time for a vial to lose half of its vacuum, the T_{50} value, ranged from many years at the lowest leak rates and largest vials, to fractions of a second at the highest leak rates and smallest vials. These results may be used to determine what level of initial vacuum leak is acceptable for a given product. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2730–2737, 2013
Keywords: mathematical model; glass; algorithm; drug delivery systems; simulations; physical characterization

INTRODUCTION

In order for sterility and stability of drugs contained in evacuated vials to be maintained, it is important that the original level of vacuum be maintained throughout the production process and the storage life of the vial. No vial can maintain a vacuum indefinitely.

To experimentally monitor the vacuum level within the vial, one would need to insert a pressure probe into the vial, which gives rise to the potential of causing leakage around the probe, thus confounding the results. However, recently, noninvasive methods have been developed to measure headspace composition in drug vials under vacuum using laser absorption methods.[1,2] Although these methods enable rapid screening of leaks, they do not inform the practitioner of the potential leak sizes that may prove useful in subsequent investigation of leaks.

However, any type of experimental technique (invasive or noninvasive) would be inadequate to study the low leak rates considered in this study because the time associated with the vacuum loss could be many years. Also, the difficulties associated with experimentally producing a series of controlled leaks with the necessary accuracy could be quite difficult. Thus, a purely mathematical approach has been taken that obviates both of these difficulties. The model is based upon well-established mathematical models for the three flow regimes of interest, namely laminar, molecular slip, and Knudsen flow. Using these three models, a new model has been developed with the unique ability to automatically determine the correct flow regime from the computed mean free path of the air, select the proper model of the three, and switch to a new flow regime, if necessary, during loss of vacuum calculations.

The purpose of this work, then, is to gain some insight into the behavior and dimensions of small

Correspondence to: Michael R. Prisco (Telephone: +630-658-7510; Fax: +630-658-7559; E-mail: mprisco@exponent.com)

Journal of Pharmaceutical Sciences, Vol. 102, 2730–2737 (2013)
© 2013 Wiley Periodicals, Inc. and the American Pharmacists Association

leaks in vacuum vials by computing the leak diameter corresponding to leak path lengths of 0.5 and 3.625 mm, for common vial sizes from 1 to 100 mL, and initial leak rates range of 10^{-8}–10^{3} standard cubic centimeters per minute (sccm) of air. In addition, the time course of loss of vial vacuum was computed. The two leak path lengths correspond to the approximate range of possible leak path lengths in a glass vial with a rubber stopper for the previously mentioned glass vial sizes. The shorter of the two lengths corresponds approximately to the glass–rubber interface across the top surface of the vial neck, and the longer length corresponds approximately to the glass/rubber interface inside the vial neck. Using this information, manufacturers can assess what initial leak rates are tolerable to maintain the desired level of vacuum over the required shelf life of the product.

METHODS—MATHEMATICAL FORMULATION

The following mathematical formulation presumes that the leak behaves as an equivalent straight, cylindrical hole with a flow resistance equal to the flow resistance of an actual leak. This is a good approximation for leaks whose maximum and minimum cross-sectional dimensions are similar. However, the behavior leaks that are extremely flat in cross-sectional shape may in reality be more biased toward the non-continuum flow regimes (slip and Knudsen flow) than this analysis predicts.

An important factor in the flow of air into an evacuated vial is that at low absolute pressure and small leak size, air may not behave as a continuum fluid–rather, it may behave more like a collection of distinct molecules. At low leak rates with small leak dimensions, three flow regimes are possible: laminar flow (air behaves as a continuum), Knudsen flow (air behaves as discrete molecules), and molecular slip flow (an intermediate flow regime in which the air flow behavior is partly continuum and partly molecular). The particular flow regime at any given condition is determined by the ratio of the mean free path of the air molecule, λ, to the path diameter, D. From Ref. 3, we have employed the "rule of thumb" shown in Table 1.

The mean free path, λ, as air flows into the vial may be calculated from Ref. 4 using the average of the inlet and outlet pressures of the leak according to:

$$\lambda = \left(\frac{2\mu}{P + P_\infty}\right)\sqrt{\frac{\pi R T}{2}} \tag{1}$$

where P is the vial pressure, P_∞ is the barometric pressure, T is the absolute temperature, μ is the air viscosity, and R is the gas constant for air, 287.09 m^2/s^2 K (53.36 ft-lb_f/lb_m °R). The air viscosity, μ, in dyne s/cm^2, is obtained by a polynomial curve fit as a function of temperature, T, in °F to data[5] as $\mu = 2.7104 \times 10^{-7}\ T + 1.6270 \times 10^{-4}$.

Table 1. Description of Flow Regimes (Ref. 3)

Flow Regime	
Laminar, incompressible flow	$\lambda/D < 0.1$
Molecular slip flow	$0.1 \le \lambda/D < 1$
Knudsen flow	$\lambda/D > 1$

Leak Size Corresponding to a Known Initial Leak Rate

If a "log leak rate," LLR, of air is known and expressed as $\log_{10}$ of the initial leak rate in sccm, then the volumetric leak rate, Q, expressed in sccm ($T = 20$°C, $P = 1$ atm).

$$Q = 10^{\mathrm{LLR}} \tag{2a}$$

and the mass flow rate, m, is given by

$$m = \rho_S\,(T_S, P_S)\,Q \tag{2b}$$

where ρ_S is the air density at standard temperature and pressure, T_S and P_S.

Laminar, Incompressible Flow

From Ref. 6, the pressure–velocity relationship for laminar, incompressible air flowing into a vial from the ambient through the abovementioned leak of length, L, is:

$$V = \frac{(P_\infty - P)D^2}{32\mu L} \tag{3}$$

The viscosity, μ, is a function of the temperature, T, as well as the average pressure, $P_{avg} = (P + P_\infty)/2$. The volumetric flow rate, Q, then, is given by

$$Q = \frac{\pi D^4 (P_\infty - P)}{128\mu L} \tag{4}$$

Equation 4 may be solved for D to give:

$$D = \left[\frac{128\mu Q L}{\pi (P_\infty - P)}\right]^{1/4} \tag{5}$$

Download English Version:

https://daneshyari.com/en/article/10162703

Download Persian Version:

https://daneshyari.com/article/10162703

Daneshyari.com