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A multivariate method to predict the water vapour diffusion rate through polypropylene packaging

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Abstract

Semipermeable containers typically allow water to diffuse upon storage. The water diffusion rate of the widely distributed X-ray contrast agent Visipaque™ in polypropylene bottles and MR contrast agent Omniscan™ in polypropylene syringes has been evaluated. The goal was to develop a mathematical method for estimating the rate constant for water diffusion through the polypropylene wall as a function of several variables. The method presents an opportunity to measure the effect of the variables influencing product stability and thereby predicting the shelf-life at an early stage of the stability study. The effect of temperature, humidity, surface area, wall thickness, concentration of active ingredient and fill volume on the logarithmic rate constant for diffusion was estimated by partial least squares regression. The predictive ability of the cross-validated models was good ($r = 0.99$) for the two contrast agents. The models were used to predict shelf-life for relevant combinations of temperature and humidity, for the four defined climatic zones. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Water vapour diffusion; Plastic packaging; Multiple regression; PLS

1. Introduction

Polypropylene (PP) may typically substitute glass as primary packaging for various products. Plastic packaging is often preferred for clinical use, transport and waste handling and in some cases plastic packaging is more compatible with the product formulation than glass with various stoppers. PP is known to have low water permeability when compared to other plastics such as polystyrene, polycarbonate, low-density polyethylene, etc. However, the diffusion of water through the PP plastic wall will gradually concentrate the constituents in liquids during long-term storage and is often the shelf-life limiting parameter for chemically stable aqueous solutions in PP bottles. The diffusion rate may depend on several parameters such as wall thickness, bottle and syringe surface area, storage temperature, storage humidity, concentration of ingredients and fill volume. The objective of this paper is to present a multivariate method to estimate the rate constant

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Table 1
The variables and levels tested and interpreted for Visipaque™

Temperature (°C)	Humidity (%)	Bottle area (cm^2)	Wall thickness (mm)	Fill volume (ml)	Concentration (mg/ml)
25, 30, 40	20, 40, 60, 75	72, 124, 170	1.0–1.6	10, 20, 40, 50, 75, 100	150, 270, 320

for water diffusion through the polypropylene wall as a function of these parameters. Typically, temperature and humidity of relevant climatic zones can be inserted into the model to predict the water diffusion rate, and thereby the acceptable storage time for a given product in a particular climatic zone. A related statistic procedure (OST) has been described by Dyrstad et al. (1999) where the rate constants were estimated by a multivariate model developed by partial least squares regression. The storage conditions for the stability studies presented were chosen to meet ICH requirements and to give good experimental resolution to evaluate the effect of variables. Comparable factorial design for formal stability testing has been suggested in recent literature (Helboe, 1992; Fairweather et al., 1995; Yoshika et al., 1996). The method of data interpretation described in this paper has successfully been used in stability testing of several products at Nycomed Imaging AS.

2. Materials and methods

Stability data from 11 batches of the diagnostic X-ray contrast agent Visipaque™ (Aars and Eivindvik, 1995) at various concentrations and three batches of the magnetic resonance contrast agent Omniscan™ (Weinman et al., 1984) 287 mg/ml, have been evaluated. The variables tested in the stability study are given in Tables 1 and 2. Visipaque™ was filled in polypropylene bottles of material Rexene 23 M2 (Rexene, TX). Omniscan™ was filled in 20-ml polypropylene syringes of material X21 (Beckton Dickinson, Franklin Lakes, NJ). The active ingredients in the above mentioned products were produced at Lindesnes Plant, Nycomed Imaging AS, Norway, while the finished products, Visipaque™ and Omniscan™ were manufactured at Oslo Plant, Nycomed Imaging AS, Norway.

For both products 10 units were individually numbered from 1 to 10 and placed at every storage condition. The bottles/syringes were weighed initially, every third month for the first year, twice the second year and then annually. Water vapour diffusion was measured as the mean weight difference from initial weight (g) (DIN) and the change was expressed as g/month. The diffusion rate constants, k_w, were estimated by univariate regression for the storage conditions represented by several batches. The linearity for the regression lines was verified by the correlation coefficient. The measured k_w was logarithmically transformed (ln (k_w)), to be used for mathematical modelling. The univariate and multivariate models were developed using Unscrambler 6.11 (Camo ASA, Trondheim, Norway).

3. Results and discussion

The effect of variables on water vapour diffusion rate constants was found by partial least squares regression (PLSR) (Frank and Friedman, 1993) for Visipaque™ and Omniscan™, respectively. PLSR has improved prediction ability for data consisting of collinear Xs, compared to classical multiple least square regression (Martens and Næs, 1989; Frank and Friedman, 1993; Dyrstad and Sontum, 1997). The X variables were standardized with their standard deviation to give

Table 2
The variables and levels tested and interpreted for Omniscan™

Temperature (°C)	Humidity (%)	Fill volume (ml)
25, 30, 40	20, 40, 60, 75	10, 20

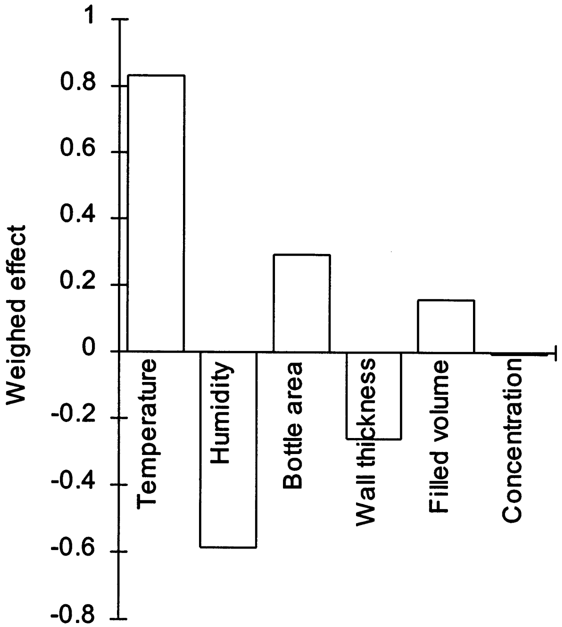

Fig. 1. The weighed regression coefficients for ranking of the influencing factors on water vapor diffusion in Visipaque™ bottles.

each variable equal weight. The following multivariate relationship between diffusion rate and the variables was established:

$$Y=\beta_0+\beta_1X_1+\ldots+{}_nX_n$$

where $Y=\ln(k_w)$, the logarithmic diffusion rate constant; X_n is the value of the nth variable; β_0 is a constant and β_n is the regression coefficient (effect of the nth variable).

3.1. *Visipaque™ filled in polypropylene bottles*

The correlation coefficients (r) for each of the 40 univariate calculations were >0.98 indicating a strong linear relationship between loss of weight (g) and time (months) during storage. The final multivariate PLSR model was constructed by using full cross-validation (see ranking of regression coefficients in Fig. 1). The leave-one-sample-out procedure suggested three principal components for the optimal model. The model precision is described by comparing the cross-validated predicted $\ln(k_w)$ and the corresponding measured $\ln(k_w)$, shown in Fig. 2. The covariance between bottle area and filled volume ($r=0.95$) indicated ordinary least squares as a nonoptimal regression method for these stability data.

Initially, a model was created with weight loss data obtained from early studies of four batches stored at different conditions. Upgrading the model with diffusion rates by additional batches reduced the correlation coefficient caused by one batch not fitting into the model. This generated a search for possible changes related to the manufacturing process and product characteristics. It was found that an increase in polypropylene wall thickness for this batch resulted in reduced water diffusion. By adding the wall thickness for all batches as one of the influencing variables, the good predictive ability was significantly improved. The model without wall thickness as a variable needed four principal components to explain the data and gave a correlation coefficient (r) of 0.975 and slope between predicted and measured values of 0.95. By including wall thickness, the corresponding values were 0.989 and 0.99 indicating good precision and small systematic error in the final model (Fig. 2). The mathematical modelling procedure followed during this trouble-searching

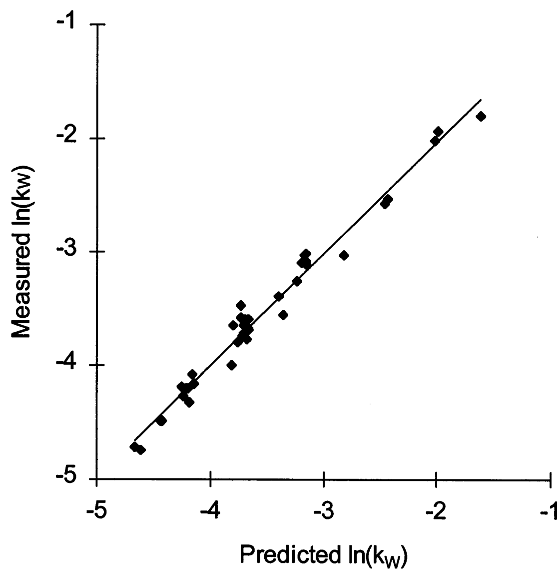

Fig. 2. The cross-validated prediction of $\ln(k_w)$ for Visipaque™. Slope is 0.99, intercept is -0.037 and r is 0.989.

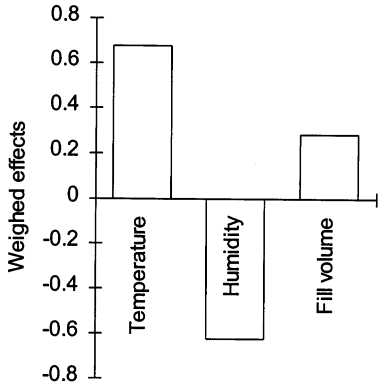

Fig. 3. The weighed regression coefficients for ranking of the influencing factors on water vapor diffusion in Omniscan™ syringes.

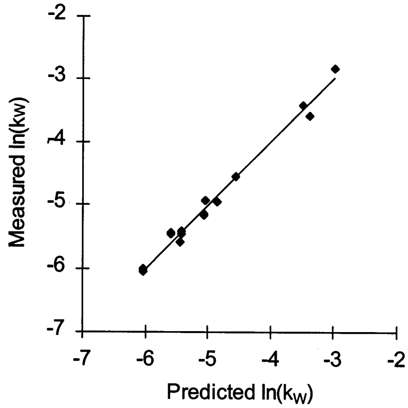

Fig. 4. The cross-validated prediction of ln (k_w) for Omniscan™. Slope is 1.006, intercept is 0.026 and r is 0.993.

was according to the OSSY as proposed by Dyrstad et al. (1999).

3.2. Omniscan™ filled in polypropylene syringes

Studies of water vapour diffusion during storage of Omniscan™ in polypropylene syringes have shown a nonlinear relationship between time and weight loss, resulting in a complex but interpretable stability. The weight loss from initial had to be transformed to achieve an optimized linear relationship. The following transformation was chosen:

$$Y = (1 - \text{mean weight difference from initial})^{-1}$$

By linear regression of Y on months, k_w was estimated. The correlation coefficients (r) for each of the 15 univariate calculations were > 0.98 indicating a strong linear relationship. The estimation of the multivariate influence on k_w was constructed by full cross-validation suggesting two principal components for the final PLSR model. The effect of different variables on water diffusion is presented in Fig. 3 and the predicted ln (k_w) versus measured ln (k_w) is presented in Fig. 4.

4. Conclusion

Visipaque™ and Omniscan™ are registered world-wide and the prediction of the shelf-life in various climatic zones is of great relevance. Of the four defined climatic zones: 21°C/45% RH (climatic zone I), 25°C/60% RH (climatic zone II), 30°C/40% RH (climatic zone III) and 30°C/70% RH (climatic zone IV), only 25°C/60% RH is supported by real time stability data. Due to the multivariate model, describing the water diffusion rate through semipermeable polypropylene wall as a function of several variables, the shelf-life might be predicted for any relevant climates. The early detection of stability influencing factors is one of the benefits of the applied stability strategy.

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