DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(6), 713-727 (1993)

TEST METHOD FOR EXTRACTABLE MATTER IN ELASTOMERIC SEALS FOR INHALATION AEROSOL PRODUCTS

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A test method is described for the quantitative determination of total extractable material from elastomeric aerosol seals, and for the reproducible production of a sample of the extractable material. The method was applied by six different laboratories to rubber samples similar to those found in aerosol valves, using solvent systems which may be found in typical inhalation aerosol products. The reproducibility within laboratories was found to be excellent, and in general the agreement between laboratories was good, but close adherence to the protocol was required.

INTRODUCTION

Virtually all inhalation aerosol products employ elastomeric seals (gaskets, diaphragms, plugs, cups, O-rings, etc.) to form a pressure-tight seal for the container. In a similar fashion, all aerosol valves employ elastomeric seals to provide a pressure-tight seal to the container during storage and to moving valve parts during use. The nomenclature and structure of various elastomers used for aerosol valves have been described by Johnsen[1]. The actual elastomeric seals, however, are generally complex mixtures of dozens of ingredients[2]. A perfect elastomeric seal has not yet been developed; every elastomeric seal must be regarded as a potential source of extractable matter.

While procedures for generating extracts from closures for parenteral preparations[3] and disposable syringes[4] have been published, the solvents and procedures are not representative of inhalation aerosol systems. Although the effect of aerosol propellants[5,6] and aerosol solvents[7] on elastomeric seals has been reported, these studies were directed primarily at the properties of the seal and not the extractables. Another study[8] identified many of the compounds obtained from aerosol gaskets after exhaustive Soxhlet extraction, but did not attempt to quantify the total amount of extractable material with solvent systems typical of those used in aerosol formulations.

It was the objective of this study, therefore, to devise a test method that would enable the quantitative determination of the total extractable materials from elastomeric aerosol seals, in addition to generating a sample of the extract for qualitative analysis via new or established procedures[9-16], while employing solvents typical of aerosol systems. The method was intended to provide a paradigm for determining the extractables from actual formulations by simply substituting the formulation or its solvent system for the solvents in the method presented herein (with, of course, appropriate modification to contain the pressure generated by an actual aerosol formulation). The study was carried out as an activity of the Aerosol Committee of the Pharmaceutical Technology section of the American Association of Pharmaceutical Scientists. Participants were involved in their respective companies in formulation development for inhalation products.

EXPERIMENTAL

The method evolved from preliminary extraction experiments conducted by the test participants. These preliminary experiments showed that fine details of the procedure needed to be stipulated, and that close adherence to the protocol was required to obtain comparable results in different laboratories. The experimental protocol is attached as an appendix.

RESULTS

Experiments were carried out according to the protocol in Appendix I by laboratories in six locations, using a single lot of sheet rubber gaskets and a single lot of glass vials and lids.

Initial review of the results suggested that the amount of extractable material and the amount of weight loss was dependent on the amount of solvent lost during the one month storage period. This was especially true for Propellant 11 where four individual samples lost over half the weight of solvent. However, no correlation was observed between solvent loss (container weight change) and the amount of extractables and/or amount of weight loss of the rubber when samples with solvent loss of less than 7.5 grams were analyzed. The four observations with greater than 7.5 grams of solvent loss were rejected from further analysis. The number of trials with acceptable solvent loss out of the five attempts for each extracting solvent, and the mean and standard deviation of the weight loss and of the mass of collected extractables are recorded in Table 1 for each of the six laboratories which participated in the study. Figures 1 and 2 show key aspects of the weight loss and extractable results.

Bartlett's test for homogeneity (17) was performed on the intralaboratory variance estimates for determinations for weight loss of the rubber and for the amount of extractables using each of the solvents. For Propellant 11, statistically significant heterogeneity of variances was observed for both the weight loss and extractable determinations. This is due primarily to the

TABLE 1.
Rubber Extractables and Weight Loss with Propellant 11 as Solvent.

Lab	Number of Samples	Weight Loss[1] Mean	Weight Loss[1] Std Dev[2]	Extract Weight[1] Mean	Extract Weight[1] Std Dev[2]
1	5	9.71	0.45	9.26	0.61
2	4	9.45	0.30	9.72	0.10
3	4	8.89	0.04	9.00	0.06
4	5	10.26	0.42	9.52	0.48
5	3	8.97	0.19	8.36	0.45
6	5	8.46	1.91	9.55	1.60

[1] expressed as per cent of initial weight
[2] statistically significant, $p<0.001$, heterogeneity of intralaboratory variance estimates

TABLE 2.
Rubber extractables and weight loss with ethanol, 95% as solvent.

Lab	Number of Samples	Weight Loss[1] Mean[3]	Weight Loss[1] Std Dev[2]	Extract Weight[1] Mean[3]	Extract Weight[1] Std Dev[2]
1	5	10.01	0.20	10.37	0.45
2	5	10.11	0.31	10.33	0.40
3	5	9.98	0.26	9.85	0.20
4	5	5.56	0.18	4.94	0.20
5	5	10.31	0.28	9.48	2.58
6	5	10.69	0.15	12.18	1.36

[1] expressed as per cent of initial weight
[2] statistically significant, $p<0.001$, heterogeneity of intralaboratory variance estimates
[3] statistically significant difference between laboratories

extremely low variability observed in the Lab 3 results as compared to the variability for Lab 6. For the ethanol solvent, statistically significant heterogeneity was observed only for the determination of extractables. In this case, Lab 5 and Lab 6 had substantially higher intralaboratory variability.

Analysis of variance methods were used to test for the significance of interlaboratory differences in results for each solvent used in the experiments. The results for Propellant 11 showed excellent agreement among all six

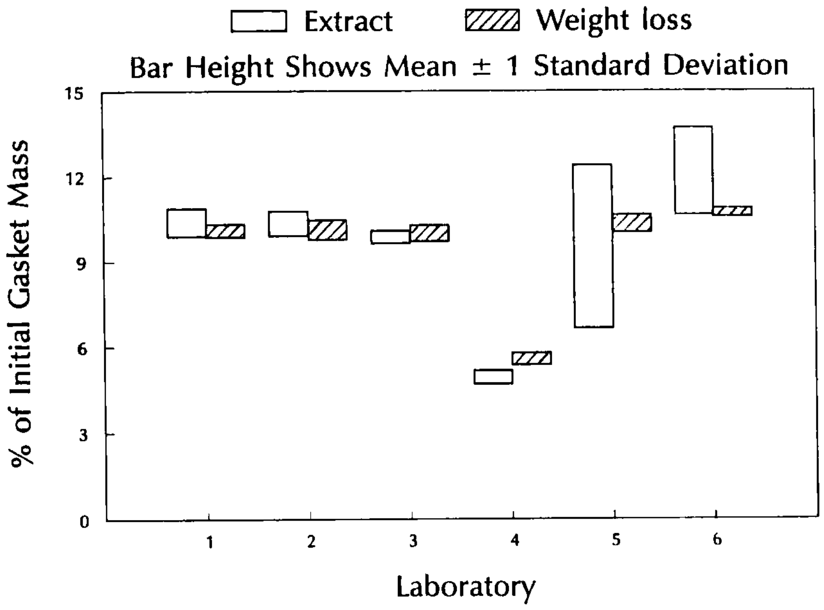

FIGURE 1

Gasket Extractables obtained with Ethanol, 95% as Solvent

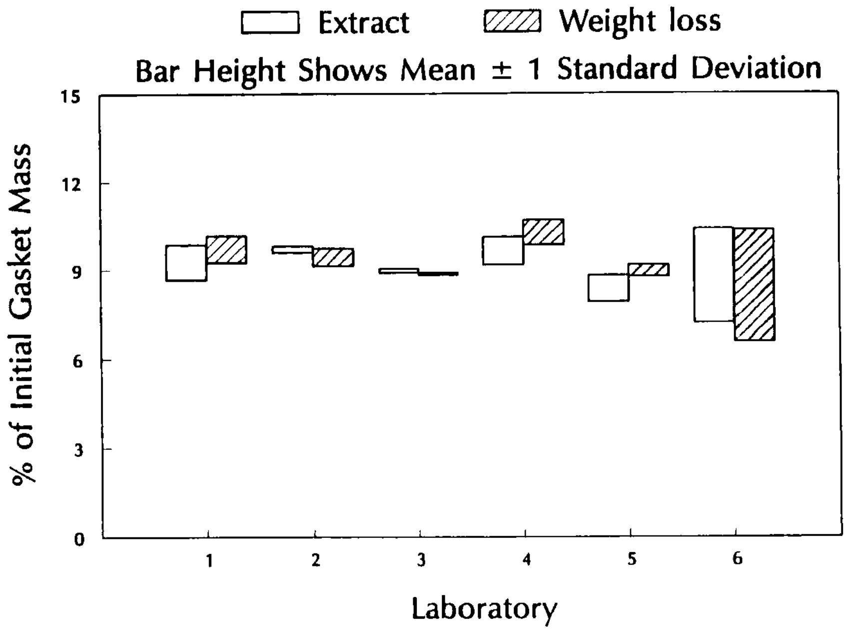

FIGURE 2

Gasket Extractables obtained with Propellant 11 as Solvent laboratories for weight loss and amount of extractables. With ethanol as solvent, Lab 4 had significantly lower mean weight loss and mean extractables when compared to the other five laboratories. This difference resulted in a statistically significant interlaboratory variance component for the method using ethanol as the solvent.

Least squares regression was performed to determine how well the weight loss (expressed as %) correlated with the extractables. Separate regression analyses were performed for the results using Propellant 11 and ethanol. Since the samples used were of approximately the same size and interlaboratory agreement was good, the range of observed values tended to be quite small; therefore the correlation, according to the precise statistical definition, between weight loss and extractables could not be demonstrated despite the obvious quantitative agreement.

DISCUSSION

Ethanol and Propellant 11 were chosen as the solvents used in this study because they are each commonly used in current inhalation aerosol formulations, they are regarded as good solvents (at least compared to other formulation components) and they have relatively low volatility (18). They should be expected to differ in their extraction characteristics on elastomeric seals.

A preliminary round of experiments was carried out, using molded nitrile rubber O-rings in addition to the calendared sheet rubber reported here. Propellant 11 and ethanol, 50% were used as solvents. These preliminary experiments showed a plateau in total extractables after solvent exposures of about 7 days. The results showed great sensitivity to the drying conditions for both the extract and the rubber part. This held true both for sheet rubber parts and molded rubber parts. Individual laboratories succeeded in obtaining generally excellent agreement among duplicate determinations on both types of rubber, but results were widely inconsistent between laboratories. The major difficulties in obtaining consistent interlaboratory data were attributed to the escape of the first extracting solvent (Propellant 11) during extraction and to the incomplete evaporation of the ethanol, 50% during drying.

In the experiments reported here, the lid was hand-tightened after adding solvent, then tightened again after approximately one hour, and then again after one or two days during the extraction period. Even with these precautions, four of the individual samples showed a loss of over half of the initial amount of Propellant 11 during the extraction process, which resulted in incomplete extraction from the gasket. The loss of smaller amounts of solvent did not result in significantly lower weight loss. The extraction temperature of 40 °C is slightly above the normal boiling point of Propellant 11 (23.8 °C), and a very good seal is required to contain the liquid. It is inevitable that individual containers will leak occasionally, and the results of a measurement are properly disregarded if excess leakage is observed.

In the preliminary studies, evaporation of the extractable-containing liquid Propellant 11 at 50 °C resulted in the loss of some liquid due to vigorous boiling, while evaporation of 50% ethanol at room temperature under air or nitrogen required an excessively long time. Therefore, the 50% ethanol was replaced by 95% ethanol in the final protocol so that the same drying conditions could be used for both solvent systems. The solvents were allowed to evaporate at room temperature or slightly above, and then dried in a vacuum oven overnight at 50 °C.

The preliminary studies showed that the weight of the lid varied significantly depending on its exposure to drying conditions and to ambient air during the weighing operation. Therefore, the final protocol specified that weighing of the unsealed container would be made without the lid.

Preliminary drying experiments on rubber recovered from a variety of aerosol valve samples showed less than 0.2% weight loss when the rubber was heated at 50 °C for one month, so the drying conditions of 50 °C for the few days required to achieve constant weight did not contribute to weight loss on the extracted rubber samples.

The method presented prepares extractable material using solvents normally present in solution and suspension aerosol systems. The results obtained by this method show that for a given elastomer the level of potentially extractable material could be quite high (10% by weight). However, this level of extractable material probably does not enter actual formulations because the aggressive solvents chosen in this study are present only in small proportions in actual aerosol formulations. Furthermore, in actual valve-sealed pharmaceutical aerosols only one side of the seal is in contact with the formulation at all times, whereas in these experiments the extraction occurred simultaneously from all surfaces of the elastomer seals.

On the other hand, since a vacuum drying step at 50 °C was employed, volatile components of the extractables might be suspected to have been removed, which would result in an underestimate of the level of extractables. The close agreement between extractables and weight loss indicates that no significant amount of volatile components were present in the extract from the test rubber.

When comparing extract collected from rubber materials used in the variety of aerosol valve models which are commercially available, it is important to consider the total weight of each rubber component which is used in the valve in addition to the portion of the component which can be extracted. The gaskets used to seal the valve to the can, for example, are usually much larger than the small gaskets which form internal seals within the valve.

These extracts, when used with other analytical techniques such as high pressure liquid chromatography or gas chromatography/mass spectrometry, create a "fingerprint" which can be used to compare different formulations and lot variations. Once the identity of extractables has been established for the elastomer of choice with a particular formulation, tests can be carried out to measure the amount appearing in actual product. When the identity of the extractable matter is not of interest, the total mass of extractable material can be determined simply from weight loss of the rubber parts.

The isolation and identification of potential contaminants (extractables) can be a very labor intensive and time consuming process. This simple gravimetric method is intended as a first step to produce small quantities of material for subsequent quantitative analysis. Even with this simple method, unexplained variability among laboratories may be expected to occur, and presumably among different individuals performing the test within the same laboratory.

This test will be of particular relevance during the development of elastomers that are compatible with the newly emerging "alternative propellants," which may have different solvent properties. The tests are suitable for screening new elastomer candidates and comparisons can be made between existing and potential replacements, based on the level of extractables.

CONCLUSIONS

A test method has been devised which enables the quantitative determination of total extractables from elastomeric aerosol seals and also provides an extract sample for qualitative analysis. The method was successfully applied by six different laboratories on typical seal material. It is hoped that this method will also serve as a model for use with actual aerosol formulations.

ACKNOWLEDGEMENTS

The authors would like to thank American Gasket and Rubber Company for supplying the calendared sheet rubber parts, and Newman Sanitary Gasket Company for supplying the molded rubber O-rings. Bryan Lasser, Warner Lambert Company, made significant contributions to this study, as did Tamara Creek, Upjohn, and Anita Quinn, Rhone-Poulenc Rorer. This study was carried out under the auspice of the Aerosol Committee of the Pharmaceutical Technology section of the American Association of Pharmaceutical Scientists.

APPENDIX 1 TEST PROTOCOL

Definitions

An Elastomeric Seal is a packaging component (gasket, diaphragm, seal or O-ring) that is, or may be, in direct contact with the drug. The Sample is the seal specimen under test or the extract prepared from such a specimen. A Blank consists of the same quantities of the same solvents used for the test, treated in the same manner as the solvent containing the specimen under test, or else an elastomeric seal that is handled in the same containers as the samples except that it is not contacted with solvent.

Method Synopsis

The seal under test is cut from sheet rubber. A rubber part is placed in contact with a volume of extracting fluid approximately equal to that which it would see in use. After a period of time at slightly elevated temperature, the weight loss in the part is obtained by difference, and is compared with the gain in weight of non-volatile component in the extracting fluid. Test fluids are selected for relative non-volatility and to represent a range of solvent properties. Blanks are run for both rubber parts and extraction fluids.

The solid seal remaining after the extraction period is an extracted part, suitable for further testing if desired for physical properties. The liquid phase contains rubber extracts, which may be examined for chemical composition by appropriate methods, if desired.

A single extraction time of four weeks is used.

Apparatus

Oven - Capable of maintaining an operating temperature of 38 ± 2 °C

Vacuum oven - operating at 50 ± 2 °C.

Vials - 2 oz. narrow mouth Boston round bottom bottles of flint glass with Teflon-lined closures, Fisher catalog number 03-320-7A, or equivalent.

Material

Extraction liquids: Propellant 11 (Trichlorofluoromethane)
Ethanol, 95 % w/w in water

Samples: Rubber sheet, nitrile, food grade, 0.042 inch thick, cut into 0.385 inch circles, with 0.12 inch center hole, 12 parts

Protocol

From a common supply, each test site will receive a set of samples as described above. Vials will be provided also. Make all weighings to 0.1 mg except as noted, and promptly after removing from environmental storage conditions. Handle all parts with stainless steel tongs where possible, or with latex gloves, to reduce weighing errors.

Procedure

1) Select a Sheet Rubber part, blow with compressed air to remove any superficial solid contamination, and weigh. Record as Sample 1.

2) Weigh a clean glass vial, without lid. Record as "Empty Vial." Insert the weighed rubber part and 20 ± 1 g of Propellant 11, then seal with the supplied screw cap. Tighten the cap as firmly as possible using hand pressure, and re-tighten after about an hour.

3) Repeat for Sheet Rubber parts 2 through 5.

4) Prepare a Solvent Blank as follows: Weigh a clean glass vial without lid, and record weight as Sample 6. Add 20 ± 1 g of Propellant 11 to the vial, then seal as in Step 1) with the supplied screw cap.

5) Repeat for a second Solvent Blank, and identify as Sample 7.

6) Repeat for another set of five (5) Sheet Rubber parts and two (2) Solvent Blanks, substituting 15 ± 0.5 g 95% ethanol for Propellant 11, and numbering samples consecutively as Sample 8 through Sample 14.

7) Prepare a Sample Blank as in step 1), placing the Sheet Rubber part into a clean glass vial without solvent. Identify as Sample 15.

8) Prepare a second Sample Blank, identified as Sample 16.

9) After tightening screw caps well, weigh all filled, capped vials to 0.1 gram and record weights.

10) Store vials in constant temperature conditions (38 ± 2 °C) for 28 ± 2 days. Re-check the lids for tightness before placing samples in storage. Re-check again for tightness after samples have been in storage for one or two days.

11) At the end of the storage period, remove vials from temperature storage, and allow to cool to room temperature.

12) Weigh filled vials with lids to 0.1 g precision, and record as "Filled vial."

13) Using small forceps, remove the rubber part from each vial, taking care not to remove more liquid from the vial than is necessary.

14) Evaporate the remaining liquid in the vial to near dryness at room temperature or slightly elevated temperatures, then dry in vacuum oven at 50 °C until the weight changes by less than 0.5 mg on consecutive days. Record only the final constant weight of the vial (without lid).

15) Dry each rubber part in a vacuum oven at 50 °C, until the weight changes by less than 0.5 mg on consecutive days. Record only the final constant weight of the rubber part.

16) Calculate results for Sheet Rubber in Propellant 11 as follows:

Solvent Blank = Dried Vial - Empty Vial
for samples 6 and 7

Average Solvent Blank = (Blank 6 + Blank 7)/2

Extract = (Dried Vial-Empty Vial-Average Solvent Blank)*
100/Rubber as rc'd
for samples 1 through 5

Rubber Blank = Rubber as rc'd - Dried Rubber
for samples 15 and 16

Average Rubber Blank = (Blank 15 + Blank 16)/2

Weight Loss = (Rubber as rc'd - dried Rubber - Average
Rubber Blank)*100/Rubber as rc'd
for samples 1 through 5

17) Repeat step 16) for Sheet Rubber in Ethanol/water.

REFERENCES

1. M. A. Johnsen, "The Aerosol Handbook," 2nd ed. Wayne Dorland Co, Mendham, NJ, 1982, p. 162

2. "Rubber Compounds." In "Kirk-Othmer Encyclopedia of Chemical Technology," 3rd ed, Vol 20, Wiley, New York, 1982

3. The United States Pharmacopeia, 22nd. rev., Easton, PA, Mack Publishing Co, 1990, p 1533

4. M. A. Inchiosa, "Water-Soluble Extractives of Disposable Syringes. Nature and Significance," J. Pharm. Sci. 54:1379-1381, 1965

5. "Freon" Technical Bulletin B-12A, "Effect of "Freon" Fluorocarbons on Elastomers," E. I. Du Pont De Nemours & Company, Wilmington, Deleware, 1960

6. J. R. Coley and J. W. Howard, "Effects of Pressurized Aerosol Systems on Elastomeric Seals," Mfg. Chemist Aerosol News 40(Aug):56-60, 1969

7. M. A. Johnsen, "The Aerosol Handbook" 2nd ed. Wayne Dorland Co. Mendham, NJ, 1982, p. 160

8. H. Kim-Kang, S.G. Gilbert, A. W. Malick, J. B. Johnson, "Methods for Predicting Migration to Packaged Pharmaceuticals," J. Pharm. Sci. 79:120-123, 1990

9. ASTM D297, "Standard Methods for Chemical Analysis, Rubber Products," ASTM Annual Standards 1979, Part #37.

10. ASTM D2702, "Standard Recommended Practice for Rubber Chemicals - Determination of Infrared Absorption Characteristics," ASTM Annual Standards 1979, Part #37

11. ASTM D3156, "Standard Recommended Practice for Rubber - Chromatographic Analysis of Antidegradants (Stabilizers, Antioxidants, and Antiozonants)" ASTM Annual Standards 1979, Part #37

12. ASTM D3677, "Standard Test Methods for Rubber - Identification by Infrared Spectrophotometry," ASTM Annual Standards 1979, Part #37

13. D. E. Korte, "Collaborative Study on Determination of Extractables for Rubber Materials," J. Assoc. Offic. Anal. Chemists 53(Jan):43, 1970

14. K. E. Kress and F. G. S. Mees, "Identification of Curing Agents in Rubber Products by Ultraviolet Absorptiometeric Analysis of Selective Solvent Extracts," Anal. Chem., 528-534, 1955

15. Parenteral Drug Association, "Extractables for Elastomeric Closures: Analytical Procedures for Functional Group Characterization/Identification," Technical Methods Bulletin No. 1, Philadelphia, PA, 1980

16. J. L. Hopkins, K. A. Cohen, F. W. Hatch, T. P. Pitner, J. M. Stevenson, and F. K. Hess, "Pharmaceuticals: tracking down an unidentified trace constituent," Analytical Chemistry 59(11), 784A-786A, 788A, 790A, 1987

17. G. W. Snedecor and W. G. Cochran, "Statistical Methods," 6th ed, Iowa State University Press, Ames, Iowa, 1967, p. 296-298

18. P. R. Byron, "Aerosol Formulation, Generation, and Delivery in Metered Systems," in "Respiratory Drug Deliver," P. R. Byron, ed. CRC Press, Boca Raton, 1990