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Research paper

Helium leak testing of packages for oral drug products

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ABSTRACT

This article presents an overview on what helium leak testing is and how it can be implemented as a test method to determine the tightness of packages for oral drug products in a quality control or development laboratory. Whereas earlier publications on helium leak testing mainly focused on testing vials and the correlation between helium leak rates and microbial ingress, this paper provides various examples how helium leak testing contributes to assure the integrity of containers for oral formulations. The results clearly show whether optimal tightness is achieved or an improvement in materials or the closing/sealing conditions should be envisaged. Helium leak testing using a flexible test chamber and a mass spectrometer as detector is of advantage in particular for flexible packages containing moisture and oxygen sensitive products, where a dye ingress test is not applicable and other detectors or methods might not be sensitive enough or give qualitative results only.

1. Introduction

Sufficient tightness is a critical quality attribute of a container closure system, since this is important for the protection of both the product and the environment. To verify that materials, construction and closing conditions of a specific container system are properly selected, a huge selection of tests is available.

Four factors contribute to a tightness test: (1) the penetrating medium that typically is a gas or liquid that can enter or leave a container, (2) the partial pressure difference or gradient of the penetrating medium between inside and outside of the container, (3) the time required to allow flow or permeation and (4) the detection system for the penetrating medium (direct method) or for a physical property (e.g. pressure, conductivity) of the container system, its content or the test chamber (indirect method). The detection system can range from the human eye to sophisticated technical equipment. In exceptional cases, specific types of amplification are applied, e.g. the incubation of the test items in microbiological container closure integrity tests. Tightness can be qualitatively described by "tight" or "leaky". However, tightness is not an absolute term and simple pass–fail results might not be sufficient. It is becoming more and more important to quantify tightness and to set specifications according to the sensitivity of the product and the intended storage time.

In various methods a gas flow is measured, either from inside out or from outside into the container. Depending on the gas used (helium, oxygen, carbon dioxide, hydrogen, air and many others), various analytical techniques are applied such as mass spectrometry, coulometry, spectroscopy, ultrasonic techniques, volumetry as well as visual detection of bubbles, etc. An example for liquid flow methods is the classical dye ingress method at reduced pressure mostly using methylene blue solution with visual detection as described in the European Pharmacopoeia (edition 6.6, Section 3.2.9). The period of vacuum needs to be followed by a relaxation period at atmospheric pressure. To exacerbate the test conditions, a higher vacuum can be applied or the vacuum is followed by an overpressure. Microbial challenge tests with liquid immersion are often applied on container systems for sterile products to check for possible ingress of a bacteria suspension. The headspace of a container can be analyzed with spectroscopic means (e.g. IR, frequency modulation spectroscopy) or with conductivity or capacitance tests. Pressure measurements are performed to detect vacuum or pressure decay. For weight gain and weight loss methods, the containers are filled with liquids or a hygroscopic material, subjected to humid or dry conditions, respectively, and the weight change is determined. In the so-called lid deflection tests, the movement of a flexible package component (e.g. blister lid foil) under pressure and/or vacuum is monitored via optical, electromagnetic, force or other methods. A good overview on these and further methods is given the PDA report "Pharmaceutical Package Integrity" [1].

Among the various test gases, helium has been proven as ideal. Helium is inert, easy to handle and readily available. Due to its low concentration of 5 ppm in the atmosphere and the extreme selectivity and sensitivity of mass spectroscopy, quantitative results over several orders of magnitude are possible within short measuring times. Helium leak testing with mass spectrometric detection

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Table 1
Relevance of leakage rates and leakage rate limits.

Leakage rate (mbar L/s)	Relevance
Approx. 10^{-2}	Tight against water drops (short time, atmospheric pressure) [5]
Approx. 10^{-5}	Tight against water at 1 bar pressure difference [6] and tight against bacteria (microbial challenge tests) [7,8]
Approx. 10^{-6}	Tight against viruses
10^{-7}	Detection limit of Contura Z in routine tests (5 s measuring time)
10^{-8}	Detection limit of Contura Z (60 s measuring time)
10^{-10}	Detection limit of recent helium leak testers with rigid test chamber, e.g. from Leak Detection Association (LDA)
10^{-13}	Detection limit of research equipment [9]

seems to be the most sensitive and convenient leak detection method.

Helium leak testing has been established since a long time in the field of vacuum technique. It was developed in the 1940s to detect and locate leaks in vacuum systems [2]. Often helium is sprayed onto critical areas of a vacuum system. In case of leaks, it becomes drawn into a mass spectrometer connected to the vacuum system. Thus, a leaky area can be pinpointed. An overview on vacuum leak detection and the role of helium leak testing in this field can be found in the book Modern Vacuum Practice [3]. After its application in various technical fields, helium leak testing was established in the food industry, for example on cans [4], and finally the pharmaceutical industry took advantage of the experience gained in the other fields.

This article focuses on tests applying the inside–out technique: the packages to be analyzed are filled in-line or off-line with helium, sealed and put into a test chamber that is evacuated. Any leaking helium is detected and quantified by mass spectrometry. In the outside–in techniques, the packages are placed in-line with the mass spectrometer. Either the package is put into a chamber containing helium (hood method) or the helium is sprayed around the outside of the package (tracer method).

To a flow rate result both leakage through a hole (or multiple holes) and transmission through the container wall contribute. The two effects follow different principles of gas transport. Unless thin plastic films are analyzed, the transmission can be neglected, and it is justified to use the term "leakage rate" for the amount of helium received per time at the detector. The helium leakage rates are mostly stated in mbar L/s. The unit mbar L describes the amount of a gas independent of the pressure. 1 mbar L/s corresponds to a flow of 1 mL per second at 1 bar, what is equivalent to 0.1 Pa m^3 s^{-1}. To facilitate the interpretation of helium leakage rates, Table 1 gives some indication. Leakage rates mentioned in company brochures related to the tightness against a certain test gas or liquid should be regarded with care, since their penetration depends on time, pressure, temperature and on what is regarded as a significant amount penetrated. For particles, a clearer border can be stated as particles cannot enter holes of a size smaller than they are and the critical hole size clearly corresponds to a flow rate. Before giving examples of its application, it is exemplified how helium leak testing can be implemented in a pharmaceutical quality control or development laboratory.

2. Implementation of helium leak testing in a pharmaceutical laboratory

2.1. Selection and installation of equipment

After choosing helium as tracer gas, the leak tester was selected based on the following criteria: detection limit $\leqslant 10^{-7}$ mbar L/s, suitable for flexible and rigid containers of various sizes. In order to ensure such a low detection limit, a low headspace is of advantage, and the size of the test chamber might need to be selected according to the size of the samples. To be able to test samples of various sizes in one equipment, an apparatus with a test chamber of flexible size, the Contura Z, developed by Inficon in Cologne-Germany was selected. A brochure of the equipment can be found under [5]. The test chamber has an upper and lower lid of flexible plastic material of approximately 65 cm diameter that nestles to the sample. Thus, the head space is reduced and the sensitivity increased. This allows using the same test chamber for samples with a volume from few milliliters up to a couple of liters (depending on the height of the sample). In addition, a flexible test chamber is very useful for flexible heat-sealed samples such as sachets and stick packs. In a rigid test chamber, the evacuation leads to a high mechanical stress to the seams with potential bursting. If a sample is placed between two elastic plastic films (with negligible helium permeation of course), the inner pressure is compensated by the pressure of the plastic films against the sample and the stress to the seams is minimized. To prevent covering a leak in a test sample with a chamber lid, a fleece is attached to the chamber lids.

Prior to the installation, a functional risk assessment was performed according to the use of the equipment in a GMP environment, the intended use of the results and the criticality of possible consequences. The installation was performed by the supplier in close co-operation with the analytical staff.

2.2. Calibration

The calibration of the equipment is done as a 3-point calibration with a blank (empty test chamber), an internal calibration leak of approximately 7×10^{-7} mbar L/s and an external calibration leak of approximately 10^{-4} mbar L/s. The calibration leaks are metal cans with a capillary leak. The correct calibration can be checked daily by a system suitability test (SST) using three additional calibrated leaks in the most interesting range, for example at 10^{-3}, 10^{-4} and 10^{-5} mbar L/s, with blank determinations in between. Optionally, further leaks at e.g. 10^{-2} mbar L/s and 10^{-6} mbar L/s can be used. The calibration leaks should be re-calibrated and refilled in suitable intervals depending on the nominal leakage rate and the frequency of use. Any change of the measuring time requires re-calibration.

2.3. Sample preparation

Whenever possible, the containers to be tested should be filled directly on the production line. This is the optimal way to use helium leak testing as in-process control. In a development laboratory and in production laboratories, where in-line filling is not possible, the samples need to be filled manually with helium. To avoid contamination of the leak tester with helium, the filling of the test items is preferably done in a separate room or in a hood.

Flexible containers like bags, sachets and stick packs are normally filled using a small needle connected to the helium supply. The needle is inserted into the test item. Care should be taken not to pierce the back layer of the item. Any air in the sample is pressed out and the sample is filled with helium. Exerting too much stress on the seals should be avoided. The filling hole is resealed with an aluminum tape or a crystal clear standard tape. The tape used should be checked for sufficient tightness, i.e. a low transmission and a high gluing effect. Sealing with a tape is not suitable for samples that have an outer layer of paper, since the helium will disperse in the pulp. Here, it is necessary to fill the samples close to an edge and re-seal the samples using a heat-seal equipment. Any powder contained in the sample should be shaken to the side opposite to the selected edge to prevent

insufficient re-sealing leading to false positive results. To balance the risk that leaks at the edge used for filling with helium are not detected, the selected edge should be systematically varied and the sample number increased. Rigid containers are filled in inverted orientation and then re-closed. Sufficient time needs to be allowed for the complete or at least a reproducible exchange of air with helium. For blister cavities, the lid foil is pierced at two positions and filled via one hole.

Since the helium leakage rates are proportional to the helium concentration in the sample, it needs to be ensured that the helium concentration is known and reproducible. Where a helium concentration close to 100% is not assured by the sample preparation, the concentration should be determined (see Section 3.4.5) and the obtained leakage rates corrected accordingly.

Filling the samples with helium can also be done via simple diffusion, when the test items are subjected to a helium atmosphere. This technique requires a defined sufficient charging time/pressure and subsequent dwell time prior to testing. The correlation between the leakage rate at 100% helium concentration and that achieved by charging the samples should be established. This charging or 'bombing' of samples is applied, if other filling techniques are not possible or too cumbersome. For example, it can be used to analyze the tightness of a complaint bottle without touching the closure or influencing the content by a gravimetrical tightness test at increased temperature. Otherwise, it would be necessary to drill one or two holes into the bottle (only if this can be done safely with the given content!), empty and clean the bottle, fill with helium and re-seal the holes with glue, hot melt or tape.

2.4. Testing

2.4.1. Sample testing

The testing with the Contura Z is automated: just put the sample into the test chamber and close the lid. The evacuation of the test chamber and subsequent determination of the helium flow rate starts when a pressure below 2 mbar is achieved. In case a sample has a big leak, a valve system directs a portion of the gas flow to the mass spectrometer to prevent an overload. Upon completion of the test cycle, the leakage rate is displayed, the lid opens and the test chamber is ready for the next sample. In addition, a green lamp flashes if the leakage rate is below a pre-set limit. For results above the limit, the red lamp flashes and an acoustic signal is heard. As the positioning of the samples might have a slight influence on the results, a standardized placement of the samples is recommended. For most tests, a measuring time of 5 s (after 8–10 s evacuation of the test chamber) is sufficient. In order to extend the detection limit from 10^{-7} mbar L/s to 10^{-8} mbar L/s, the measuring time needs to be prolonged to 60 s.

2.4.2. Blank testing

Blank tests should be performed before testing, after a certain number of tests and in case high leakage rates are observed. If the helium concentration in the test chamber increases, it is necessary to vent the test chamber and support the exchange of the air. The sealing area of the test chamber needs to be free from defects and dust to avoid entry of air.

2.4.3. Control of leakage rates and localization of leaks

Unexpected high leakage rates should be controlled in order to exclude improper re-sealing. In addition, it is of interest to pinpoint the position of any leak. The Contura Z is equipped with a pen-sized detector probe ("sniffer") that allows the localization of holes. The sealing seams of a vertically held bag or sachet should be checked from bottom to top to avoid misinterpretation due to helium streaming upwards. The sniffer system has a short response and clean-up time (approximately 1 s) and gives a visible and audible signal of the detected increase and decrease in the helium concentration when approaching a leak and removing from it. The leaks of flexible containers can also be localized applying the simple bubble test every cyclist knows: the samples are put under water and slightly pressed. The position where bubbles arise can easily be pinpointed.

2.4.4. Positive controls

Not only unexpected high leakage rates should be questioned, but also low leakage rates observed on small samples such as blister cavities. The smaller the sample and the larger the leak, the greater is the risk that all of the helium is already removed out of the test sample during the evacuation of the test chamber. Flexible samples and not too rigid blister cavities will become flat in case of big leaks. To detect false negative results on rigid containers, the sample can be re-tested after a seal is broken or a small artificial hole is made into the sample. The re-test will show whether the sample still contained any helium after the first test. To avoid the risk that artificial holes are too big, samples with a thin plastic fiber (cf. Section 4.2) placed at sealing area can be tested in parallel.

2.4.5. Determination of the helium concentration in a sample

The helium concentration can either directly be determined using a special helium concentration probe or indirectly with less accuracy on a sample proven to be tight (e.g. $\leqslant 2.0\,10^{-6}$ mbar L/s): a hole is made into the sample and covered with a self-sticking fluoropolymer film of defined helium transmission (e.g. 2.0×10^{-4} mbar L/s). The sample is then tested again. Any helium flow rate below the nominal transmission rate is due to the presence of air in the sample. If the equipment is set to the concentration mode, the helium concentration is directly displayed. As mentioned earlier, samples with an outer paper layer are not suitable for such test. The helium concentration can also be roughly determined via the buoyancy, i.e. the weight difference of a container filled with air and the same container filled with helium. If the gross weight of the samples allows, a microbalance is of advantage, otherwise an analytical balance is sufficient for most cases. For a helium concentration of 100%, a buoyancy of approximately 1.0 mg per ml container volume is expected. The approximate helium concentration in the container can be easily calculated from this.

2.5. Samples with low helium concentration

Helium concentrations of 100% or almost 100% are of advantage for sensitivity reasons. For practical or cost reasons, the tests can be performed on samples with much lower helium concentration. As the results can cover seven orders of magnitude, a helium concentration in the range between 70% and 100% might be acceptable. A filling with 7–10% or with 0.7–1% can also be considered, as long as an increase in the detection limit from 10^{-7} mbar L/s to 10^{-6} mbar L/s or 10^{-5} mbar L/s (calculated for 100% helium concentration) is acceptable. As a rule of thumb, the detection limit should be not more than a tenth of the leakage rate limit defined.

3. Materials and methods

3.1. Materials

The tests were performed on sachets, stick packs, aluminum bags and glass bottles used for various Novartis Pharma drug products in development.

For calibration and system suitability tests, the capillary leaks of the types TL3, TL4, TL5 and TL6 were used, supplier: Inficon GmbH, D-Cologne.

Aluminum tape for re-sealing of test samples: article number 50575PV1, thickness of aluminum layer 0.08 mm, supplier: Tesa.

Self-adhesive fluoropolymer films for helium concentration measurement and comparison between helium and oxygen transmission rate, thickness 25 μm, article number 12268, supplier: Inficon.

Nylon fibers used to create artificial leaks: Tynex® type 0900, NC 410 clear, diameter 64 μm, supplier: DuPont.

3.2. Methods

The methods for helium leak testing are described in detail in Sections 2.3 and 2.4. The tests were performed at usual laboratory conditions, i.e. approximately 23 °C.

The oxygen leakage rates were determined with a manometer according to DIN 53380-2 at 23 °C with the adaptation that the capillary leaks were attached to two test chambers of different size.

The oxygen transmission rate was determined according ISO 15105-2, Annex A at 23 °C/50% RH using a coulometric sensor. The results were re-calculated to a pressure difference of 1 bar for comparison with the helium transmission results.

4. Results and discussion

Various studies on different materials for oral formulations, such as sachets, stick packs, bags blisters and bottle-closures systems have been performed. The experience obtained on sample preparation and testing is shared in Section 2. Most leakage rates obtained were below 10^{-6} mbar L/s. The focus of the following sections is put on the influence of sealing/closing parameters and on studies where a risk for leakage was expected and/or leaky test items found, including a study on bags with artificial leaks.

4.1. Repeatability

The repeatability of the leakage rates was determined on rigid samples such as capillary test leaks, as well as on flexible samples like empty aluminum bags, filled sachets and filled stick packs. The results for the relative standard deviation obtained on 10 repetitions are summarized in Table 2. The repeatability of the results on containers without product can be regarded as very good, in particular in consideration of the fact that the results cover seven orders of magnitude. In contrast to this, repeated testing of flexible samples filled with powder can result in much higher variation. A leak causing a high leakage rate in the first test could be jammed thus leading to a reduced leakage rate in the next test. On the other hand, a certain mechanical stress cannot be fully avoided – even in a flexible test chamber. In case the sealing was not optimal, this stress can create a leak or widen an existing leak. Therefore, the leak test on flexible samples containing product should be considered as destructive. Without detailed studies, the first value obtained should be regarded as the correct value.

4.2. Possible influence of the helium volume filled into flexible samples

To check whether the helium volume in flexible samples (at approximately 100% concentration) has an influence on the leakage rate, ten aluminum bags of a maximum volume of approximately 150 ml were prepared as follows: two nylon fibers of 0.064 mm diameter were placed at the sealing seam and the bags were heat-sealed. The bags were filled with 20 ml and 130 ml helium by means of a syringe, sealed with aluminum tape and tested for the leakage rate after each filling. The test was repeated to have 20 determinations per fill volume. The results are summarized in Table 3. A statistical evaluation was performed to compare the variances applying an F-test ($p = 0.95$) and to compare the mean values applying a paired t-test (two-sided, $p = 0.95$). No significant differences were observed neither between the variances nor between the mean values. As long as the possible influence of the fill volume is not checked, it is recommended to standardize the fill volume and to avoid an overpressure at filling that could weaken the seam and create or increase leakage.

4.3. Improvement in sealing conditions

Older fill and seal machines may have a lot of disadvantages against new ones, such as lower speed, higher power consumption, control of fewer parameters and lower stability of the parameters due to wear over the many operating cycles. Based on the helium leak rates obtained on sachets produced on an older filling line, it was decided to purchase a new fill and seal machine. Fig. 1 shows the results obtained on sachets from the old machine as well as from the new machine during qualification and during routine production. This example shows how the selection of a new fill and seal machine pays off. In the routine production, the tightness was further improved when compared to the qualification tests. Helium leak testing proved to be ideal to quantify the improvement in tightness. In addition to this, seal strength tests can further support the selection of the optimal sealing conditions.

Table 3
Helium leakage rate in mbar L/s of aluminum bags with artificial leaks filled with different volumes of helium.

	20 ml (first test)	20 ml (second test)	130 ml (first test)	130 ml (second test)
Mean	6.0×10^{-5}	5.9×10^{-5}	6.2×10^{-5}	6.1×10^{-5}
Min	2.5×10^{-5}	3.2×10^{-5}	2.3×10^{-5}	2.9×10^{-5}
Max	1.0×10^{-4}	9.7×10^{-5}	9.4×10^{-5}	9.3×10^{-5}

Table 2
Repeatability and intermediate precision of helium flow rates at 5 s measuring time, relative standard deviation, mean values in mbar L/s.

	Capillary leak A	Capillary leak B	Capillary leak C	Empty aluminum bag with artificial leak	Filled sachets and stick packs	Fluoro-polymer transmission film
Mean value	1.3×10^{-3}	1.5×10^{-4}	1.4×10^{-5}	9.6×10^{-4}	Various mean values between 10^{-4} and 10^{-1}	1.57×10^{-4}
Repeatability ($n = 10$) typical value (%)	5	6	4	12.3[a]	8	2.9[a]
Range (%)	2–16	5–9	0–8	–	3–35	–
Intermediate precision	10.3% ($n = 20$)[b]	12.2% ($n = 20$)[b]	8.4% ($n = 20$)[b]	Not tested	–[c]	Not tested

[a] Single test.
[b] Results from 20 different days with seven re-calibrations in between.
[c] On eight powder-filled sachets with leak rates between 4.5×10^{-4} and 3.5×10^{-2} mbar L/min, the second result (after refilling with helium) varied between 56% and 122% of the first result. On tests performed on different days the variation was between 5% and 250%.

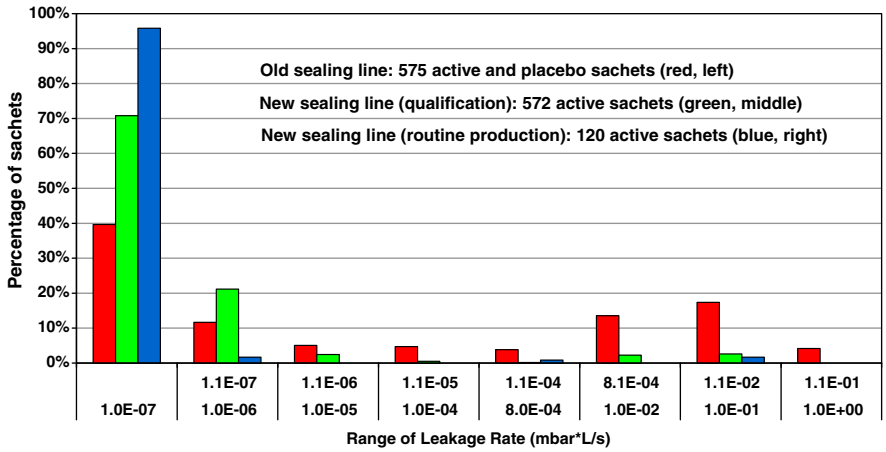

Fig. 1. Distribution of helium leakage rates on sachets produced on an old sealing line and on a new sealing line during qualification and routine production.

4.4. Influence of production speed and sealing temperature

To find optimal sealing conditions and production speed, sachets were filled and sealed at three different filling speeds and three sealing temperatures each. The helium leakage rate was determined on 20 sachets per combination. Sachets with a rate below 1.0×10^{-4} mbar L/s were classified as tight. Fig. 2 shows the results. As is can be seen, the risk of leaky sachets increases with higher production speed and lower sealing temperature.

4.5. Changes during production

The following example shows that the stability of the machine parameters is of special relevance. The sealing of stick packs is more critical than the sealing of sachets, because the stick packs have a longitudinal seal resulting in the overlap of multiple layers. Fig. 3 visualizes the results obtained on stick packs filled and sealed on two lines during one and a half week. Five stick packs per time point and line were checked. It is clear that any unintentional change in process parameters or incorrect setting can dramatically impair the tightness. Besides the temperature of the sealing plates and the sealing pressure, the exact alignment of the plates and the temperature within the plates is of special importance. Continuous monitoring of the relevant process parameters and of the tightness will either prevent a decline of tightness or at least rapidly detect it and minimize the reject rate.

4.6. Comparison between dye ingress test and helium leak testing

Dye ingress tests at reduced pressure are standard tests on rigid packages, e.g. bottles and blisters. The suitability of dye ingress tests on flexible packages is questionable. If a leak is present, air is sucked out of the sample. At return to atmospheric pressure, the dye solution might not penetrate the sample, but the sample just slightly collapses and looses the force to suck the test liquid in. To prove this, a total of 36 sachets with helium leakage rates between 6.9×10^{-7} mbar L/s and 2.8×10^{-1} mbar L/s were exposed to a dye ingress test. The distribution of helium leakage rates in mbar L/s was as follows: 1 sample $< 1.0 \times 10^{-4}$, 2 samples between 1.0×10^{-4} and 9.9×10^{-4}, 13 samples between 1.0×10^{-3} and 9.9×10^{-3}, 16 samples between 1.0×10^{-2} and 9.9×10^{-2} and 4 samples $\geqslant 1.0 \times 10^{-1}$. The samples were randomly selected and exposed to the following test conditions: 100 mbar for 1 h, 300 mbar for 1 h, 530 mbar for 1 h (8 samples per condition), 100 mbar for 5 min, 300 mbar for 5 min and 530 mbar for 5 min (4 samples per condition). After releasing the vacuum, the samples were kept in the methylene blue solution for 2–3 min to allow penetration of the dye solution in case of a leak. The outside of the samples was cleaned, the samples opened and it was checked,

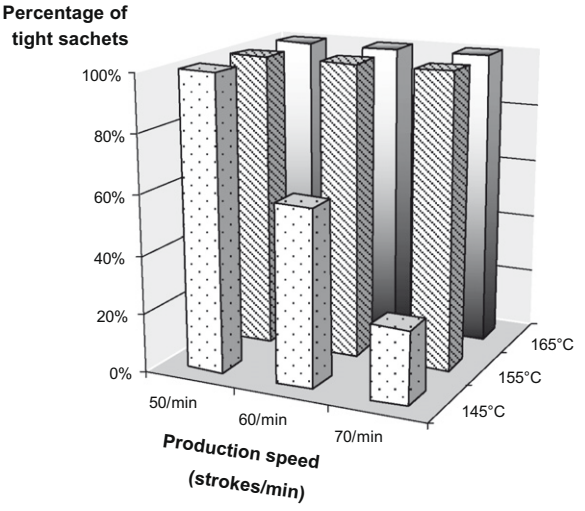

Fig. 2. Influence of sealing temperature and production speed on the tightness of sachets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

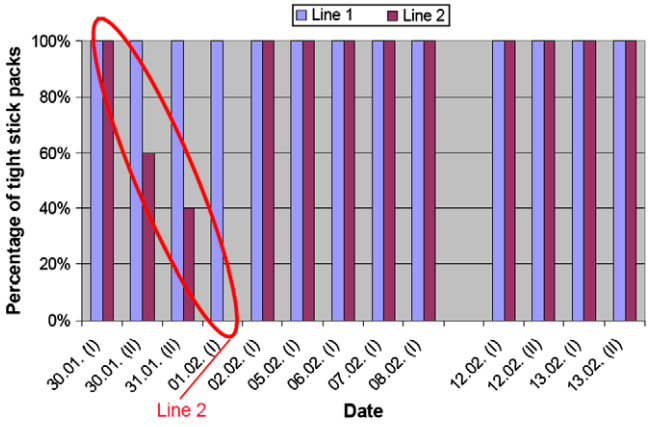

Fig. 3. Helium leakage rate of sachets produced on two lines over 1.5 weeks. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

whether dye had entered the sachets. No dye was found within any of the sachets, not even in the sealing area although 32 of the 36 samples had to be considered as leaky based on the results of the helium tests.

During stability tests performed on sachets containing a moisture sensitive drug product at 30 °C/75% RH, it was found after 12 months that the content of sachets with helium leakage rates above 1.0×10^{-4} mbar L/s agglomerated and discolored. This proves again that the dye ingress test is not suitable to verify sufficient tightness of flexible containers used for moisture sensitive and oxygen sensitive drug products. Helium leak testing provides sufficient sensitivity to cope with packages containing even more sensitive products than in above example, with longer storage times or more critical storage conditions. For less critical conditions alternative tests, such as vacuum decay, lid deflection or bubble tests with vacuum can be envisaged.

4.7. Correlation of bubble test results with helium leakage rates

Stick packs and sachets with helium leakage rates above 1.0×10^{-4} mbar L/s were routinely checked to locate the leak using the sniffer probe and/or applying a bubble test by manually pressing the sample under water and checking for air bubbles. The evaluation of the bubble test results obtained from 188 samples with leakage rates $\geqslant 1.0 \times 10^{-4}$ mbar L/s and 12 samples with leakage rates between 10^{-6} mbar L/s and 10^{-4} mbar L/s is summarized in Table 4. All samples with a leakage rate $\geqslant 1.0 \times 10^{-4}$ mbar L/s showed bubbles. At leakage rates $\leqslant 5.5 \times 10^{-5}$ mbar L/s, no bubbles were observed. The range between 5.6×10^{-5} mbar L/s and 9.9×10^{-5} mbar L/s is a transition range of some samples with bubbles observed and others without bubbles. This is a good correlation despite the fact that the tests was performed manually, i.e. the force applied was not standardized and there was some variation in the observation time. Of course, it was an advantage that the samples contained sufficient gas volume in the head space. This might not be the case for all flexible containers.

Based on the above-mentioned helium leakage rate limit of 1.0×10^{-4} mbar L/s, the manual bubble test was proven to be sensitive enough to detect leakages, which would lead to agglomeration and degradation of this specific drug product. For standardization, an automated bubble test under vacuum is recommended. Such test is certainly more sensitive than a dye ingress test.

There were two additional manual bubble tests performed: (1) to compare samples filled with helium with those filled with air, (2) to check whether the surface tension of the test liquid (water) had an influence on the results. No difference was observed between air-filled and helium-filled samples. The addition of dish washer liquid as surfactant facilitated the detaching of the air bubbles from the sample and thus improved the detectability of the air bubbles.

Table 4
Correlation of helium leakage rates with manual bubble test.

Range of leakage rates (mbar L/s)	Samples tested	Samples with bubbles
$\geqslant 1.0 \times 10^{-1}$	25	25
1.0×10^{-2}–9.9×10^{-2}	61	61
1.0×10^{-3}–9.9×10^{-3}	66	66
1.0×10^{-4}–9.9×10^{-4}	36	36
5.6×10^{-5}–9.9×10^{-5}	6	3
1.0×10^{-5}–5.5×10^{-5}	4	0
1.0×10^{-6}–9.9×10^{-6}	2	0

4.8. Comparison between helium and oxygen flow rates

A drug product might be sensitive to oxygen, but the leakage or permeation rates are determined with helium. Therefore, it is useful to establish the correlation between helium and oxygen flow rates. According to the law of Poiseuille (Eq. (1)) for laminar flow, the leakage rates are expected to be inverse proportional to the viscosity.

$$q = \pi * r^4 * (p_1^2 - p_2^2)/(16\eta * l) \quad (1)$$

where q is the flow rate, r the radius of the capillary, p_1 the higher pressure, p_2 the lower pressure, η the viscosity of the gas and l the length of the capillary.

Table 5 shows the leakage rates of capillary leaks for helium and oxygen as well as the transmission rate of a fluoropolymer film for both gases. The viscosity of some gases is given in Table 6. The oxygen rates measured on capillary leaks are approximately 78% of the helium rates. According to the law of Poiseuille, the oxygen rates should be 96% of the helium rates. As test leaks are certified with an accuracy ±15% and leakage rate results vary up to ±30%, the difference between observed and theory is explainable and oxygen and helium flow rates can be regarded as comparable in the ranges examined.

4.9. Influence of small cracks at a bottle mouth

At the visual inspection of the mouth of an amber glass bottle with PP 28 neck finish (pilfer proof, 28 mm diameter) fine cracks were observed. Most cracks were seen with the help of slight magnification and/or special illumination only. The question arose whether these cracks would present a risk for the stability of a suspension sensitive to oxygen. Twenty bottles with cracks and another 20 bottles without cracks were closed on a fast speed production line at 2.5 N m. An equivalent set of bottles was closed manually at 1.5 N m. Both sets of bottles were subjected to helium leak testing. The results summarized in Table 7 clearly indicate that the cracks will not impact the quality of the suspension.

4.10. Tightness of closure liners

Closures assembled with expanded PE liners of two suppliers were screwed at various closing torques onto the corresponding

Table 5
Helium and oxygen flow rates (mbar L/s) for leakage from capillary leaks and transmission of a fluoropolymer film.

	Helium flow rate	Oxygen flow rate	Ratio of oxygen to helium flow rate (%)
Capillary leak 1	1.4×10^{-4}	1.04×10^{-4}	74
Capillary leak 2	1.3×10^{-5}	1.00×10^{-5}	77
Capillary leak 3	1.2×10^{-6}	0.99×10^{-6}	83
Fluoropolymer film	1.57×10^{-4} [a]	1.35×10^{-4} [b]	86

[a] Mean of 10 samples.
[b] Mean of 6 samples.

Table 6
Dynamic viscosity of selected gases at 23 °C [10].

Gas	Viscosity (mPa s)
Carbon dioxide	0.0148
Helium	0.0196
Hydrogen	0.0089
Nitrogen	0.0178
Oxygen	0.0204

Table 7
Helium leakage rates (mbar L/s) of glass bottles with and without slight cracks at the mouth, average results on 20 bottles.

Closing	Bottles with slight cracks	Bottles without cracks
High speed production machine at 2.5 N m	3.7×10^{-6}	3.6×10^{-6}
Manual closing at 1.5 N m	6.2×10^{-6}	8.2×10^{-6}

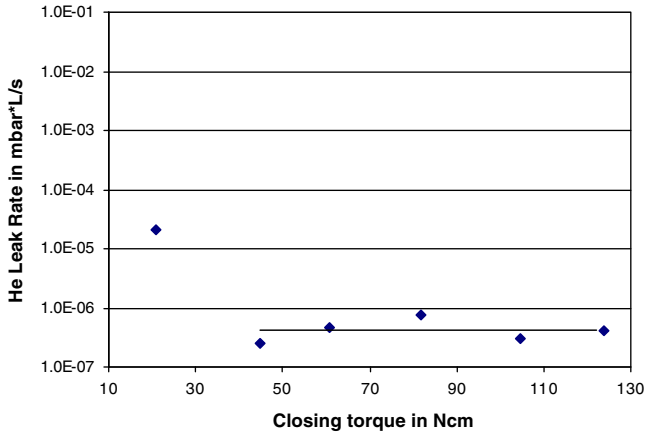

Fig. 4. Helium leakage rate of glass bottles closed with a screw closure containing an expanded PE liner of supplier A. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

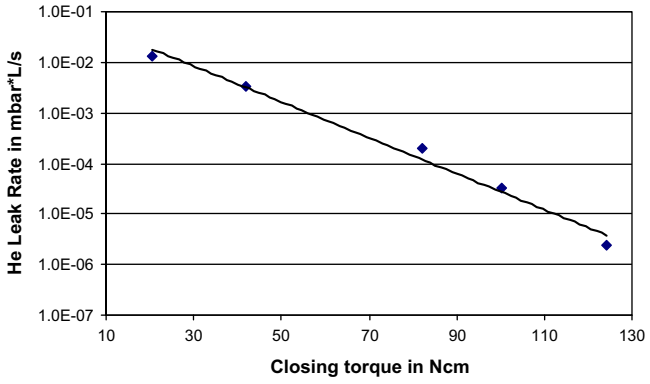

Fig. 5. Helium leakage rate of glass bottles closed with a screw closure containing an expanded PE liner of supplier B. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

bottles with a 18 mm neck finish. Two samples per closing torque were tested. The average results are presented in the Figs. 4 and 5. The liner of supplier A gave generally low helium flow rates that were independent of the closing torque over a broad range. In contrast to this, the gas transmission of the liner of supplier B linearly depended on the closing torque. This liner could assure a sufficient tightness of bottles containing sensitive products only when it is fully compressed and is therefore less suitable than the other liner.

5. Conclusions

In this paper, it was explained how helium leak testing could be implemented as an integrity method for various types of flexible and rigid containers. Various examples showed the advantages of helium leak testing in the selection of a container system and the optimization of the closing parameters thus ensuring the drug product quality and stability. The studies performed also demonstrate the versatility of a helium leak tester with a flexible test chamber for flexible and rigid containers for oral drug products.

6. Outlook

As the sensitivity of helium leak detectors increased during last years, rigid samples of various sizes can now be tested in one chamber. Also, new technologies become available, for example quartz membranes allowing a separation of helium from all other gases. With the help of more sensitive pressure sensors helium leakages rates down to 10^{-6} mbar L/s can be determined using a test chamber at normal pressure. Helium leak testing of packages for oral formulations will then in most cases not require mass spectrometry anymore and can be tested without any mechanical stress. In addition, helium leak detectors can be more easily integrated in a filling line.

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