Assessing the Integrity of Pharmaceutical packaging using the Sepha BlisterScan and Conventional Blue Dye Leak Testing Methods

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Abstract

The aim of this study is to compare a proprietary vacuum based system which uses laser measurements to detect faulty packs, with conventional blue dye testing. The quantitative BlisterScan technique offers a non-destructive alternative to traditional blue dye testing. The study compares the reliability of both techniques to detect defective pockets in pharmaceutical blister packs. Defect free packs, or those containing a 12 or 20µm sized laser drilled hole were tested via BlisterScan and by conventional blue dye technique. Ninety pockets of each of the three sample types were tested using both techniques. Neither BlisterScan nor blue dye testing incorrectly indentified any of the defect free pockets as faulty. While BlisterScan failed to detect only one of the ninety pockets containing a 12µm hole, nine such pockets were missed in blue dye testing. In testing the pockets containing a 20µm sized hole, the detection rates by BlisterScan and via blue dye were 100 and 98.9% respectively.

Background

Testing the integrity of pharmaceutical blister packages is of vital importance in providing assurance of product shelf life. Over recent year's blister packs, have become the predominant method of packaging pharmaceuticals. Blister packs offer a number of key advantages including improved product integrity, tamper evidence, a reduced likelihood of accidental misuse and the ability to produce calendar packs[1,2]. Blister packaging consists of a thermoformed polymer or aluminium cold formed tray with a number of pockets into which the product is placed. These pockets are then sealed with a paper or aluminium foil laminate sheet. Many sensitive and high value pharmaceutical products are susceptible to degradation during storage, and are subsequently packaged in an inert atmosphere. The presence of defects such as pin holes in the sealing foil or trays, or defects in the seal may affect the stability and thus the efficacy of the pharmaceutical contents. The potential for microbiological contamination is also a concern.

A number of methods exist for R&D and routine leak testing of pharmaceutical blister packs, the most common of which is blue dye testing. This consists of placing selected packs into blue stained water, subjecting the packs to a vacuum of typically 400-600mBar for several minutes and then removing the vacuum. This allows any defective pockets to take up the dye. The packs are then manually deblistered, and inspected for dye ingress[3]. In addition to problems related to human subjectivity and cumbersome documentation requirements, the time consuming technique is destructive, creating large amounts of waste. Rather than visually inspecting for dye ingression, BlisterScan is a dry non-destructive technique which measures changes in the pack profile which result from applying a vacuum. The lidding material of defective pockets will respond in a different manner to a sealed pocket when a vacuum is applied. These changes in pack profile are measured using a non contact laser technique. The approach is generally preferable to systems which rely on contacting the lid material with a probe in order to measure pressure or displacement.

Alternative test methods include helium leak testing, which uses changes in pressure to force helium into defective packs, which is subsequently drawn out by vacuum and detected[4]. Whilst the technique is able to detect small changes in pack integrity, it is unable to differentiate between individual pockets, and is typically too time consuming and expensive for routine quality control. The vacuum decay method operates by measuring changes in pressure inside a vessel, as a result of air egress from a faulty pack (ASTM F2338-09). It has been reported that the method can detect 5µm sized holes in rigid glass syringes[5]. However, when applied to blister packs the method is not location specific (i.e it does not highlight which pocket is defective), and is unable to detect holes larger than ~50µm. The small amount of air present in a typical pocket will tend to evacuate through a large hole before any measurement can take place[6].

Materials and Methods

30 cavity PVC thermoformed packs sealed with a 25µm foil laminate were used. The 20 x 9 mm pockets were designed to contain size 1 capsules. 90 pockets were tested for each of the three sample types investigated (defect free, or containing a 12µm or 20µm hole). The model defects were laser drilled in the approximate centre of the foil laminate covering each pocket. The dimensions of the holes were confirmed to a tolerance of +/-2µm by scanning electron microscopy.

BlisterScan testing consists of initially scanning the surface of each pocket in order to provide a datum value for subsequent deflection measurements. A vacuum level of 500mbar is then applied and held for 10 seconds and the pack re-measured. Deflection refers to the difference in average height when the vacuum is applied compared to the datum value. The vacuum level is then reduced to 400mBar and held for a further 30 seconds before the pack is scanned again. The variation in average height at the full and reduced vacuum is referred to as collapse.

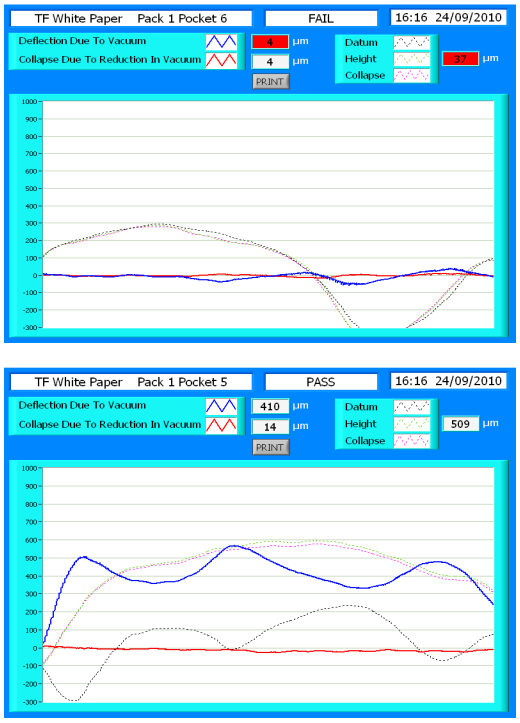

Figure 1. Blisterscan results of a pack containing a 30µm hole (top) and a defect free pack (bottom).

Figure 1 illustrates the typical difference in deflection behaviour measured by BlisterScan between a defect free pocket (bottom) and one containing a 30µm sized laser drilled defect (top). In Figure 1 the black dotted line is the profile of the foil surface before the vacuum is applied. It can be seen that a variation in profile exists between packs. The profiles after the full and reduced vacuum is applied are shown by the green and purple lines respectively. The solid blue line denotes the deflection, which is the difference between the profiles before and after the vacuum is applied, while the red line illustrates collapse (difference between profiles at full and reduced vacuum). It can be seen from Figure 1 that the pack with a 30µm hole does not deflect significantly from the initial profile when the vacuum is applied. The defect free pocket (bottom) however displays a large deflection and adopts a domed profile as a result of the applied vacuum. In this case a deflection of 410µm was recorded for the defect free packed compared to only 4µm for the pack containing the 30µm hole. A large hole i.e. one greater than ~20µm allows the pressure inside the pocket to equalise to the applied vacuum inhibiting foil movement.

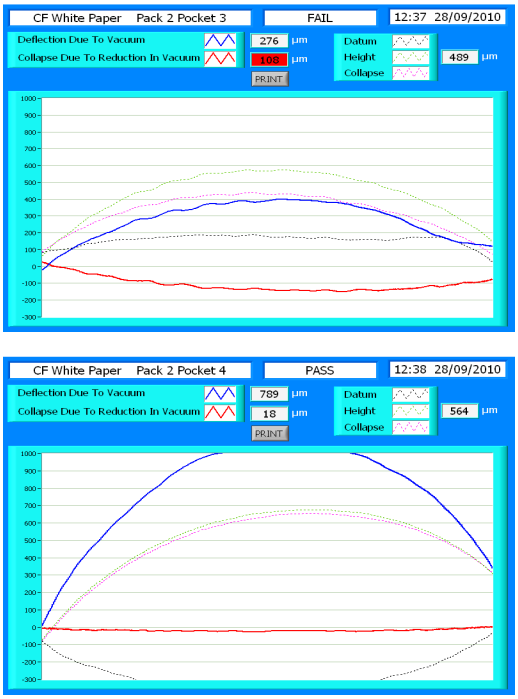

Figure 2. Blisterscan results of a pack containing a 15µm hole (top) and a defect free pack (bottom).

Small holes manifest as a greater than normal collapse when the vacuum level is reduced, as shown in Figure 2. This occurs as the air slowly escapes through a small defect allowing the pressure inside the pocket to equalise with the applied vacuum.

Extensive trials observed that repeat testing packs on BlisterScan had no observable effect on the deflection behaviour of the pack, or on the dimensions of any defects. Multiple BlisterScan testing of the same defective pocket produced repeatable results. The non-destructive nature of the BlisterScan technique was also confirmed by electron microscopy analysis of defects before and after testing.

Once the packs had been tested on the BlisterScan they were run through blue dye testing.

No international standard exists regarding the parameters used during blue dye testing such as vacuum level or soak time. A preliminary study which investigated vacuum levels from 200-500mBar and soak times of 0-2 minutes found that a vacuum of at least 400mBar with a 1 minute soak resulted in the highest detection rate of 12µm defects. Drawing a higher vacuum level or increasing the soak time did not improve the test's ability to detect defects.

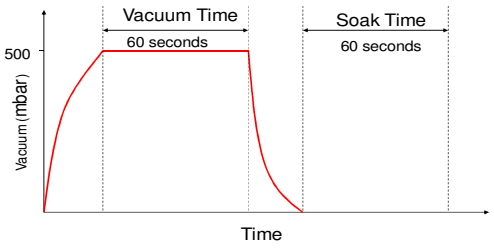

Figure 3. Blue dye testing vacuum cycle

Therefore the vacuum cycle shown in Figure 3 was used during the blue dye testing. To guarantee an effective test the packs were submerged in methylene blue stained water and a vacuum of 500mBar was applied. This vacuum level was maintained for a soak time of 1 minute. The vacuum was then released with the packs remaining in the dye for a further period of 1 minute to allow the dye to penetrate any defective pockets. The pockets were then opened and the contents visually inspected for signs of dye ingress.

Verification

Scanning electron microscopy (SEM) was conducted on all pockets containing laser drilled holes which were not detected as failures by either BlisterScan or blue dye testing. The SEM analysis of these pockets found that approximately 10% of the 12µm holes were incorrectly laser drilled. In these cases the laser drilled hole did not fully penetrate the foil laminate as shown in figure 4a. These issues with the reliability of the laser drilling process were only observed in the 12µm holes. It is inherently difficult to laser drill holes smaller than approximately 15µm in such sealing foils due to issues associated with laser alignment and the tendency of the molten material to reseal the defect. An example of a hole partly obscured by debris is shown in figure 4b. The results shown in table 1, does not contain data from any such incorrectly drilled pockets.

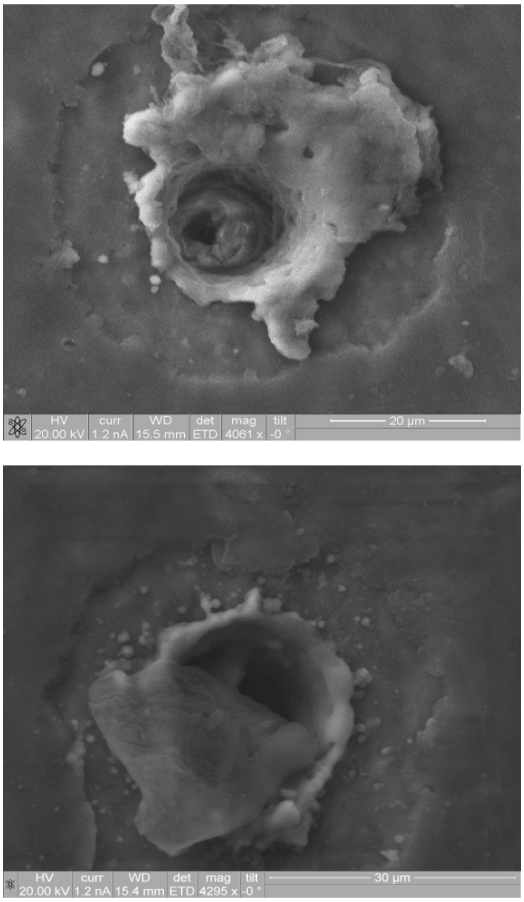

Figure 4a (top) and 4b (bottom)

Results/Discussion.

The BlisterScan and blue dye pass rates shown in table 1 below were calculated based on tests conducted on 90 pockets for each of the sample types namely pockets containing 12 or 20µm holes or those which were defect free. It is noteworthy that neither BlisterScan nor blue dye testing recorded any false positives in the defect free packs.

	Defect free	12µm hole	20µm hole
Blisterscan	100%	1.1%	0%
Blue Dye	100%	10%	1.1%

Table 1, Blisterscan and blue dye pass rates for pockets containing no defects, 12 or 20µm holes

BlisterScan correctly indentified 100% of the pockets containing 20µm sized holes as being defective. Only one of the ninety or ~1.1%, of the pockets containing 12µm sized holes was incorrectly indentified as a pass by the BlisterScan technique. Conversely blue dye testing failed to detect 10% of the 12µm holes and also missed one of the 20µm sized holes or 1.1%.

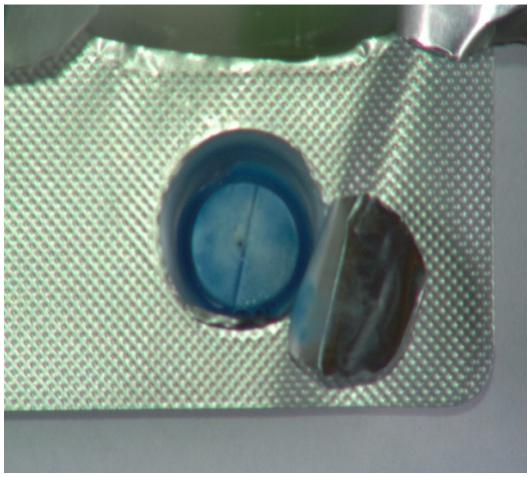

Figure 5. Typical results of blue dye testing a pocket containing a 50µm laser drilled defect

It can be seen in figure 5, that a large defect such as a 50µm hole produces an obvious fail on blue dye testing with a significant amount of liquid observed in the pocket. However, detecting smaller defects, such as the 12µm sized holes studied in this trial, is much more difficult due to the small amount of liquid ingress. It is unlikely that the 90% detection rate for 12µm holes by blue dye testing reported in this study would be achievable during routine quality control. The ease with which any dye ingression can be observed also depends to a degree on the tablet or capsule type and colour.

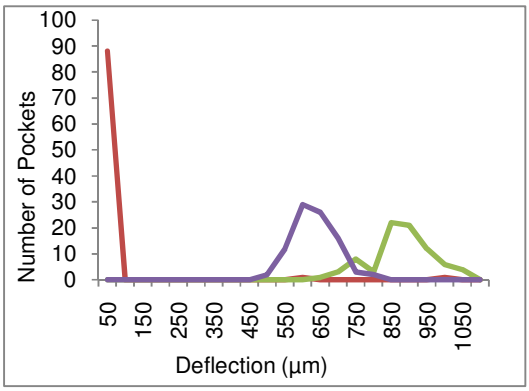

Figure 6, BlisterScan data illustrating variation in deflection between defect free packs (blue line) and those containing 12µm holes (green line) and 20µm holes (red line)

It can be seen from figure 6 that the packs containing 20µm sized holes deflected by <50µm when the 500mBar vacuum was applied compared to some 500-1100µm in the case of defect free packs or those containing 12µm holes. This lack of deflection in response to an applied vacuum is typical of gross holes. Any pocket which deflected less than a threshold value of 100µm was recorded as a failed pocket. It can be seen from Figure 3 that variations in deflection behaviour can not be used to reliably differentiate between defect free pockets and those containing 12µm sized defects.

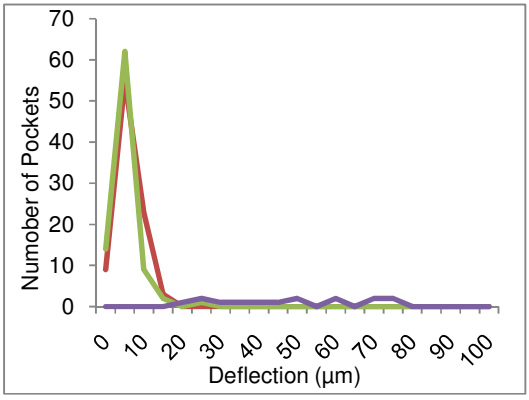

Figure 7, BlisterScan data illustrating variation in collapse between defect free packs (green line) and those containing 12µm holes (red line) and 20µm holes (blue line)

While pockets which are defect free and those containing small holes show similar values for deflection, the collapse behaviour differs. As

previously discussed the collapse value is the difference between the foil height at full vacuum and reduced vacuum. Those pockets which contain a small defect tend to leak air under vacuum resulting in a greater collapse than those packs which are defect free. Collapse values in the range 0-13µm were recorded for the defect free packs compared to 20-802µm for the pockets containing 12µm holes. The distribution of recorded deflection values over the range 0-100µm for the 3 sample types is shown in figure 7. A threshold value of 20µm was used to differentiate between defect free packs or those containing a small hole. In order for a particular pocket to pass the BlisterScan test it must pass both the deflection and collapse criteria. Using these criteria one of pockets containing a 12µm defect was not correctly indentified as defective by BlisterScan. This is equivalent to a detection rate of 98.9%. Blue dye testing missed 9 such pockets giving a detection rate of 90% for 12µm defects. Selecting appropriate levels for these deflection and collapse pass/fail thresholds is critical and must be determined for each pack type. The levels of these thresholds can be set to detect defects of a particular size.

Conclusions

This study which compared the BlisterScan technique with blue dye testing found that neither method incorrectly indentified any defect free pockets as faulty. It was found that BlisterScan detected the presence of 12 and 20µm sized defects in pharmaceutical blister packaging with a higher degree of reliability than conventional blue dye testing and that the amount of blue dye ingress in the pockets containing a 12µm hole made their identification difficult. The non-subjective nature of Blisterscan testing removes operator judgement, which is particularly important in the correct identification of small defects. Further to this the 21 CFR part 11 complaint non-destructive method produces numerical data which can be used to provide assurance of pharmaceutical packaging integrity.

References

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