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DETECTING INTEGRITY BREACHES IN A RANGE OF PHARMACEUTICAL BLISTER PACKAGE TYPES USING SEPHA VISIONSCAN.

WHITE PAPER OVERVIEW

DETECTING INTEGRITY BREACHES IN A RANGE OF PHARMACEUTICAL BLISTER PACKAGE TYPES USING SEPHA VISIONSCAN.

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Background

Demonstrating the integrity of pharmaceutical blister packs is critically important, as any defects can affect the shelf life and efficacy of the contents. Compared to bulk packaging, blister packs offer improved product integrity, tamper evidence and reduce the likelihood of misuse[1, 2]. Packs can be composed of either a thermoformed polymer or cold formed aluminium tray, with a number of individual pockets to hold the product. After the tablets or capsules are placed in the pockets, the packs are heat sealed with a paper or foil laminate sheet. These various stages can be completed separately or integrated into a single form, fill and seal process. There is a risk of microbial containment or degradation of the contents if any defects are present in the packaging. Such defects can take the form of rips or pinholes in the tray, or lid materials, faulty seals and channel leaks between pockets.

Methylene blue dye testing is commonly used for the routine testing of blister packs. Packs are immersed in water which has been dyed blue and subjected to a vacuum of typically 400-600mBar for several minutes. The vacuum will draw air from faulty packs leading to the ingress of dye when the vacuum is released. Inspection for the presence of dyed water inside the blister packs is undertaken manually[3]. While the technique is widely accepted industrially, the detection of small defects is reliant on human subjectivity and operator vigilance. Blue dye testing is also destructive with the requirement to destroy all tested packs.

Sepha have developed a number of technologies capable of the non-destructive evaluation of package integrity, enabling all tested defect free packs to be returned to production if required. VisionScan is a development of their proprietary BlisterScan system. BlisterScan measures pack deflection using a laser in response to an applied vacuum. The lidding material of a good pack will deform when a vacuum is applied due to differences in pressure between the pocket interior and the applied vacuum. Any defect will allow this pressure differential to equalise and change the way in which the pack deflects when the vacuum is applied. The dry system is non-destructive and the use of suitable thresholds allows the detection of faulty packs without operator subjectivity. The VisionScan system operates on a similar principle but uses vision technology as opposed to laser measurements. Images of the pack surface before and after the application of two vacuum levels are compared. The approach removes the need for dedicated tooling for each pack type and allows multiple packs to be tested in a single test cycle.

Vacuum decay and tracer gas methods can also be used in leak detection. While tracer gas methods using gases such as helium can find sub-micron sized holes, the technique is typically too expensive and time consuming for routine testing[4]. 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].

Table 1

Pack	Pack Material	Lid Material	Pocket Size & Number	Pack Contents
1	PVC	20µm Hard Tempered Aluminium	16mm x 6mm 10	Size 4 Capsule
2	PVC	20µm Hard Tempered Aluminium	20mm (D) 6	Round Tablet (20mm(D) x 10mm(H))
3	Aluminium	20µm Hard Tempered Aluminium	27mm x 18mm 7	Tablet (14mm(L) x 7mm(W) x 5mm(D))
4	Aclar	Paper Backed Aluminium	22mm x 22mm 5	Empty

Materials and Methods

In order to investigate the ability of the VisionScan system to detect faulty pockets, 15µm and 50µm holes were laser drilled into 170 blister packs, across a range of designs. Four pack types were evaluated, two thermoformed polymer packs sealed with foil, a foil capsule pack sealed with paper and a cold formed aluminium pack, as detailed in Table 1 above.

These pack configurations represent some of the most commonly employed materials and designs and cover a variety of tablet and capsule sizes. Laser drilled holes of either 15µm or 50µm, were drilled into the foil or paper laminate of 25 of each pack type creating 170 test packs. Only one pocket in each pack was laser drilled leaving the other pockets undamaged as controls. The dimensions of the laser drilled holes were confirmed via scanning electron microscopy (SEM), with five of each hole size measured for the different pack designs. The dimensions of the holes were confirmed to a tolerance of +/- 3 µm and +/- 5µm for the 15µm and 50µm sized holes respectively. The laser drilled holes were measured on the interior surface of the laminate. Figure 1 illustrates a typical 15µm hole laser drilled into a foil laminate.

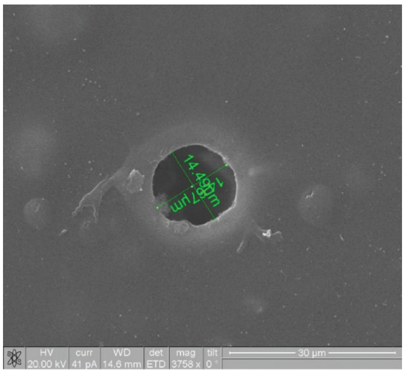

Figure 1
SEM micrograph of a nominally 15 µm diameter hole drilled into an aluminium laminate viewed from the interior.

"VISIONSCAN REPRESENTS A SIGNIFICANT IMPROVEMENT OVER TRADITIONAL BLUE DYE TESTING."

The VisionScan system operates by taking an initial monotone image of the pack surface and then applying a pre-set vacuum, typically between 150-500mBar and then taking another image. The two images are subtracted from each other electronically and any pixels displaying a change in brightness above a predetermined level are coded white. The ratio of black to white pixels in the pocket region is a measure of deformation of the pack in response to the vacuum and is referred to as the Gross ratio (G). A small value signifies a high proportion of white pixels and that the pocket surface has deflected. The presence of large or gross defects can be detected by a larger than normal G ratio. The presence of a large defect will allow the pressure inside a pocket to equilibrate with the applied vacuum. This results in little deflection of the pocket giving rise to few white coded pixels and a high G ratio.

Figure 2, a screenshot from VisionScan, shows the image created from the difference between the initial image and that taken after the application of the initial vacuum. An example of a gross hole is visible in each of the packs with the absence of white pixels indicating that the pocket did not inflate in a normal manner. Such a pocket would be highlighted in red and coded as a fail.

After collection of the second image the vacuum is held in the test chamber and then reduced, typically by around 80mBar. A third image of the pack surface is then collected. This period of holding and then reducing the vacuum enables the detection of small defects. Air will continue to leak from any defects over this period causing the air inside the pocket to equalise and then the reduced vacuum causes the pocket surface to deflate in comparison to good pockets. The image after this period of reduced vacuum is compared to the initial vacuum image, and pixels with a change in brightness above a threshold level are coded white as before. The ratio of black/white pixels in this composite image is referred to as the Decay ratio (D). A smaller than expected value of D denotes a large amount of deflation during the reduced vacuum phase which is characteristic of the presence a small hole.

The threshold values of D and G used for the identification of defective packs are dependent on the pack type and are determined as part of the machine setup. A specific recipe/method for each pack is created. The size and shape of the pockets, the forming process, the lidding material and its finish (such as patterning or printing) can all have an influence on VisionScan testing. Self-adhesive tabs containing holes of known sizes can also be used to create model defects and to determine the required threshold levels, but care needs to be taken when applying these to ensure that they do not affect the validity of the testing. Packs with a G value above the threshold (denoting a lack of pack deflection in response to the initial vacuum) or a D value below a critical value showing a higher than expected level of deflection at the reduced vacuum level are flagged as failures and highlighted red and pink respectively on screen at the end of a test cycle.

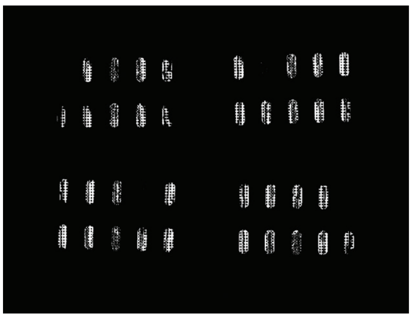

Figure 2
VisionScan screen shot.

Table 2

Pack Type/ Hole Size	Correctly identified Good Pockets/ Good Pockets	Faulty Pockets identified by Gross Failure (G)	Faulty Pockets identified by Decay Failure (D)	Number of defective pockets identified %	Total Pockets
1/15µm	180/180	13	3	100%	196/200**
1/50µm	180/180	18	0	100%	198/200**
2/15µm	100/100	0	19	100%	119/120**
2/50µm	94/95*	0	18	100%	112/115**
3/15µm	120/120	0	19	100%	139/140**
3/50µm	120/120	20	0	100%	140/140
4/15µm	99/100*	0	21	100%	120/125**
4/50µm	100/100	16	3	100%	119/125**

* SEM inspection of 2 nominally defective-free pack pockets found pre-existing defects
**On SEM inspection those laser drilled pockets not identified as faulty were found to have either missing holes or incompletely drilled holes.

Results and Discussion

In the case of the cold formed aluminium packs and the two types of foil laminate sealed polymer packs, twenty packs of each hole size were tested three times. Only one hole was laser drilled in each pack in a random location leaving the remainder of the pockets defect free as a control. For the thermoformed polymer pack sealed with paper, 25 packs for each of the two hole sizes were tested twice.[7]

If one removes all such incorrectly drilled pockets from the data, then the VisionScan correctly identified 100% of both the 15µm and 50µm sized defects in all four types of blister pack tested.

Table 2 above illustrates that all of the laser drilled defects were correctly identified as defective using the VisionScan system. The table also shows whether the packs failed via deflection (G) or collapse (D). It can be seen that while the system did not incorrectly code any defect free packs as defective, the system failed to detect a number of pockets which should have contained a defect. After analysing these packs by SEM it was observed in all cases that the laser hole was not correctly drilled. Data from these pockets identified as having defective holes was not included in the subsequent analysis. SEM images of two such incorrectly drilled holes are shown in Figs. 3 & 4 below. In some cases such as in Fig. 3 the laser did not fully penetrate the laminate, while in other cases only partial penetration was observed with the laser only creating a hole of some ~ 5µm. In one case no hole was observed.

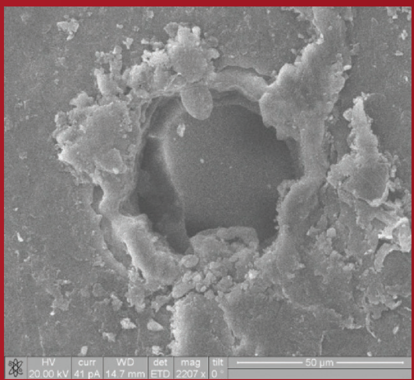

Figure 3

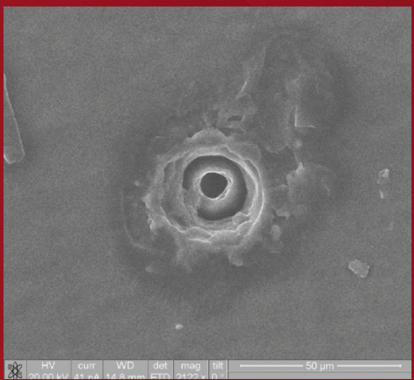

Figure 4

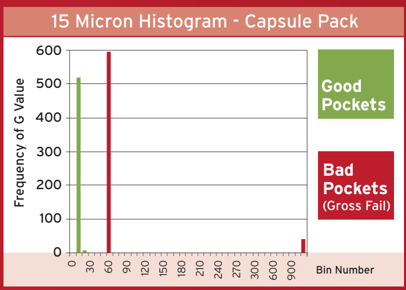

Figure 5a

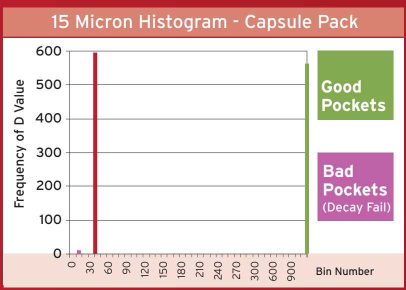

Figure 5b
Distribution of G values (Fig. 5a) and D values (Fig. 5b) for good pockets and those containing 15μm holes for Pack 1.

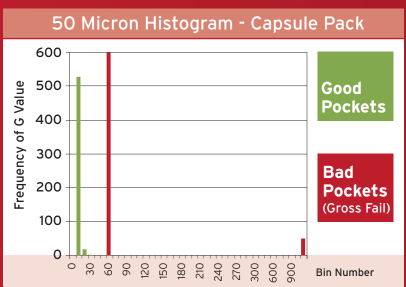

Figure 6
Distribution of G values for pockets containing either no defect or a 50μm hole (foil sealed capsule polymer pack).

From Fig. 5, one can see the distribution of G and D values for defect free packs and those containing a 15μm sized hole. The packs found to have incorrectly drilled defects have been removed from the data and the results of repeat testing are included. Those pockets with a laser drilled hole are coded as red in the histogram, while good pockets are shown in green. It can be seen from the figure that a marked difference is observed between the good packs and those with a defect. This allows a suitable threshold limit (shown as a red line) to be set enabling the reliable detection of faulty packs. Most of the pockets containing a defect were detected due to a difference in G value (deflection after the initial vacuum), while the remainder of the 15μm defects displayed failure via collapse during the period of reduced vacuum. Failures detected from the initial vacuum are referred to as gross holes, while the presence of smaller defects can be seen during the reduced vacuum phase. The ability to alter the vacuum and threshold levels allows the sensitivity of the system to be altered so that defects of a particular size are detected. The way in which the 15μm defect was detected in pack 1 varied from the other pack types, with the pockets failing due to lack of initial deflection as opposed to collapse as seen with the other pack types. This could be down to the size of the pocket, resulting in a lower volume of air in the pocket and more rigid pocket lidding.

Fig. 6 illustrates the distribution of G values from good packs and those with a 50μm hole. A marked difference is observed between the behaviour of the good pockets and those containing a laser drilled defect. In the case of the 50μm defects all the failures were detected due to differences in G value. All other packs tested during this study showed failure due to differences in G when looking for 50μm defects, aside from Pack type 2 which contained large round tablets. It was found that these pockets failed due to differences in D which could be down to the larger pocket volume.

Conclusions

The VisionScan system enables the accurate non-destructive detection of faulty pockets in a range of pack designs and material types. In repeat testing of 170 packs each containing a pocket with a laser drilled hole, the VisionScan system correctly identified 100% of the defective pockets (once pockets with incorrectly drilled holes were removed from the data). None of the good packs were incorrectly identified as defective. The magnitude of the difference in behaviour between good and defective packs enables the accurate and robust testing of pack integrity. The ability to adjust test parameters, such as vacuum and threshold levels enables the sensitivity of the system to be controlled.

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