DESIGN OPTIMIZATION AND RAPID PROTOTYPING SOLUTIONS FOR BLISTER PACK DESIGN, DEVELOPMENT, AND TESTING

a four-part series of white papers

INTRODUCTION

This series of white papers examines the latest tools for the design and development of blister packaging for the pharmaceutical industry. The first paper gave an overview of the entirety of the rapid prototyping process—from delivery of product specs, through stability assessment, to design and prototype evaluation, and eventually to production support. All of these steps can be accomplished with a state-of-the-art blister design facility such as Klöckner Pentaplast's (kp) Blister Technology Center.

The second paper in the series addressed new capabilities for accelerated stability assessment, which delivers detailed performance parameters for the packaging. Stability assessment defines what moisture and oxygen and light exposure the drug can tolerate before losing its efficacy.

With those performance parameters in hand, the blister pack design process can begin. In the past, this initial design phase required a good deal of informed guesswork. Blister performance was estimated, and performance evaluation leaned heavily on the building of physical prototypes and long periods of shelf testing.

Now, however, using cutting-edge computer design and evaluation tools, blister designers can perform sophisticated performance evaluation digitally, before any physical prototype is built. These new techniques in "virtual prototyping" greatly streamline the design and testing process.

This third paper in the series looks in detail at the digital tools that make virtual prototyping possible.

PAPER III:
DIGITAL TOOLS FOR THE DESIGN AND VIRTUAL PROTOTYPING OF BLISTER PACKAGING

BASIC CONSIDERATIONS FOR BLISTER PACK DESIGN

Successful designs for Blister Packs must match the requirements of the product (its size and shape and vulnerability to environmental exposure) to the performance of materials and design (the ability to shield against moisture and oxygen transmission for long periods of time). The key material in all blister packs is *thermoformed film*—a flexible, layered, plastic film that is shaped into individual blisters that will carry and protect doses of the product. These films have two key properties that must be managed in the development of a blister design:

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- **Barrier Properties** – Different films have different rates of transmission of moisture vapor (MVTR) and oxygen (OTR) and light – the three major environmental conditions affecting pharmaceutical longevity.
- **Formability** – The thermoforming process takes rolls of flat film, and subjects them to temperature and pressure to shape them into blister cavities. Different films have different tolerances and performance under these stresses.

In the process of forming, the film is subjected to forces which *stretch it,* and *thin it*. As a result, the formability of the film and the specific form that it is shaped into have a feedback effect on barrier performance—the process of shaping alters the MVTR and OTR resistance of the blister. A successful blister pack design will minimize the stretching and thinning that occur when the blister cavity is very deep (known as a "deep draw" or a high "draw ratio"). It will also seek to avoid the creation of sharp corners, which are typically the point of greatest thinning, where the cavity becomes most fragile and where the barrier becomes most permeable.*

And these aren't the only considerations affecting performance. The number of cavities and the layout of the blister card can affect cavity shape and the performance of the film. And climate conditions in different market countries complicate the barrier requirements of the packaging. All of these considerations can conflict and feed back on each other—and need to be balanced against cost of the packaging materials selected. Not every application will allow for the selection of the highest cost and highest performing film.

These are among the many complex considerations that the new tools of virtual prototyping seek to model, evaluate, and predict. A cutting-edge suite of software tools can weigh and adjust many of these factors digitally—avoiding wrong turns and underperforming designs. This means that only the most promising models are moved through to prototyping and testing, saving time and money.

INITIAL BLISTER DESIGN

The first stage of the design process takes place using traditional Computer-Aided Design (CAD) software. Working from shape and size information supplied by the manufacturer, engineers build 3-D models of a cavity that will hold the pharmaceutical. In the first paper in this series, we outlined the requirements of a sample product—a chewable lozenge, trapezoidal in shape and large enough to require a deep blister cavity, thus testing the performance limits of the film being used. The trapezoidal shape also requires relatively sharp corners on the blister cavity, further challenging the performance of the film. The figure below shows a preliminary CAD design for the blister, with the lozenge in blue and the blister cavity in grey.

This rendering (Figure 1 on next page) displays a number of the key design parameters that can be modeled and manipulated through the CAD process. The linear measurements are straightforward and easily arrived at. But the design software also accepts as inputs and can measure and work with angles and radii of curves, some of which are critical to blister performance. The two R numbers in the rendering, for example, indicate the radii of two important curved corners. Such corners are the places

** kp has published two other white papers, which give more detail about the relationship between film performance, cavity shape, and blister performance. They are: "Practical Considerations for Thermoformed Films in Blister Package Design" and "Tips for Selecting Pharmaceutical Blister Packaging Film." Both are available on the News > Technical Articles page of our website at www.kpfilms.com.*

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where the greatest degree of thinning of the film takes place. A smaller radius indicates a sharper curve, which introduces greater stress on the performance of the film. But increasing the radius of a corner is not always possible, as it could adversely affect the shape and size of the cavity.

The 7.50° measurement between the two arrows is a similarly critical measurement. It represents the "draft angle," which is the measurement of the amount that the side of the blister cavity departs from perpendicular. A larger draft angle results in less thinning of the film, but this will also increase the size of the blister cavity. A larger cavity means increased unit cost and could possibly result in damage to the product by allowing it to shift more during handling.

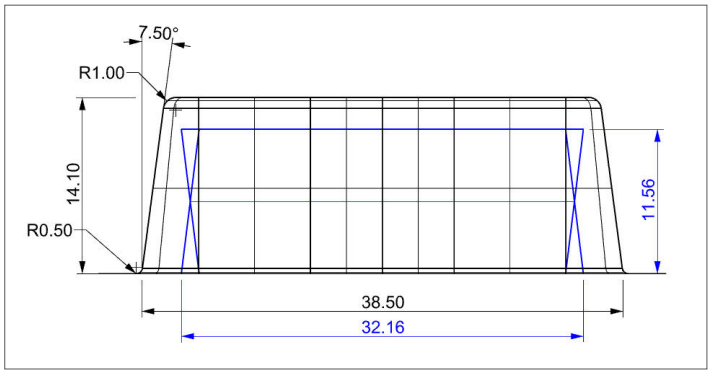

Figure 1: Preliminary CAD design for a blister cavity holding a trapezoidal lozenge.

CAD software allows each of the individual elements of cavity shape to be adjusted, and trade-offs to be measured between cavity shape, size, and barrier performance. The ideal shape for preserving the film's moisture and oxygen resistance would be a circular blister with a large radius, a larger draft angle, and no sharp corners. But as our example product makes plain, often pharmaceutical products depart far from that ideal, requiring complex considerations of blister geometry and performance to be weighed against each other.

The success of weighing those conflicting considerations depends on how fine-grained you can make the information about film thinning and barrier performance. The next step in the process uses cutting edge proprietary software to predict that information with an unprecedented level of detail.

PERFORMANCE EVALUATION WITH FEA SOFTWARE

In the second white paper in this series, we discussed the value of accelerated stability assessment in projecting a pharmaceutical's vulnerability to environmental degradation. Stability assessment produces a set of parameters for moisture and oxygen sensitivity (as well as light sensitivity) at a range of temperatures and humidities. In the case of our sample product, the demands are high—less than half a milligram of moisture per day and less than 2 cubic mm of oxygen.

Specification for Lozenge	
Highly Moisture Sensitive	*(Estimated at < 0.5 mg day at 40C & 75% Relative Humidity storage)*
Highly Oxygen Sensitive	*(Estimated at < 2mm3 / day at 23C & 50% Relative Humidity storage)*
Highly Light Sensitive	*(Sensitive to light in the 290nm – 450nm range)*

Figure 2: Stability assessment of sample product

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We know which films can give that level of barrier performance, but until recently it has been difficult to estimate the effect of specific cavity geometries on a film's MVTR and OTR. Now, however, it is possible to model the barrier performance of even the most complex blister design to a very high degree of accuracy before manufacturing the physical prototypes.

In 2005, kp developed its proprietary BlisterPro® software, which uses a mathematical procedure called Finite Element Analysis (FEA) to map the displacement and thinning of the film for any cavity design. When the CAD design for the provision blister shape is input into to BlisterPro®, FEA calculates the thickness of very small sections of the formed cavity at a large number of locations. That data can then easily be output to a modeling program which produces an enhanced 3D contour map of the cavity. This contour map shows the cavity as a mesh and registers the thickness of the film at each node in the mesh. In the figure below, the key at right shows the color values assigned to different thicknesses.

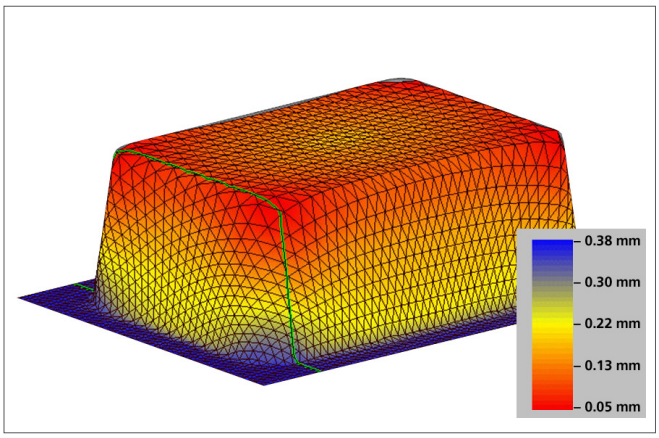

Figure 3: Contour map of provisional cavity design for a sample product.

This contour plot shows that, in fact, the design of the preliminary blister cavity for our sample trapezoidal lozenge pharmaceutical, with its deep draw and relatively sharp corners, produces a very thin barrier along the edges of the cavity bottom. BlisterPro™ can analyze this information in several ways. The green line crossing the edge of the contour map in Figure 3, above, marks a cross section selected by the engineers for more detailed analysis. Figure 4, below shows a sample of the raw thickness data for points along that line. Figure 5 on the following page shows the same information output as a thickness distribution plot. Engineers can select any important cross-section of the blister cavity and output thickness information in tables or charts.

BL0611-02 R04				
MIN (IDEAL) [mm]		0.059		
WORST CASE [mm]		0.028		
ARC [mm]	**FILM THICKNESS [mm]**	**x**	**y**	**z**
0	0.340	16	-16.94	0
1	0.338	16	-15.94	6.77E-07
2	0.335	16	-14.94	6.86E-07
3	0.329	16	-13.94	4.70E-03
4	0.308	16	-13.1835	5.66E-01
5	0.283	16	-12.9805	1.53E+00
6	0.259	16	-12.8285	2.51819
7	0.236	16	-12.6796	3.50647
...	...	...	...	...

Figure 4: Thickness analysis for the first 8 (of 55) points along a cross-section of the blister cavity

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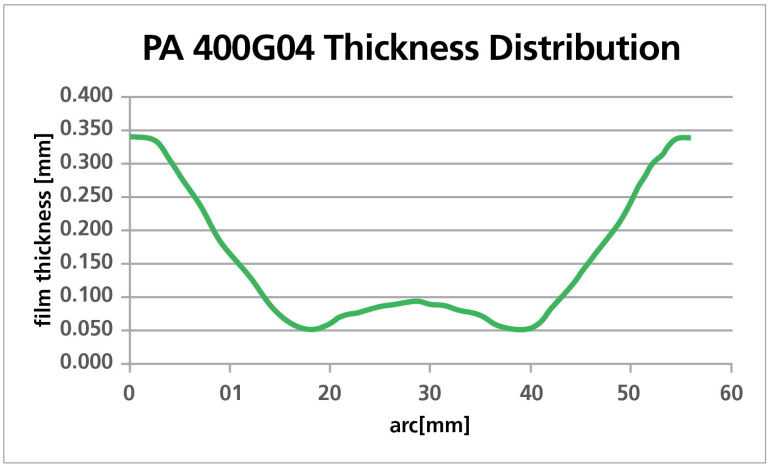

Figure 5: The same data output as a thickness plot.

The key capability of BlisterPro® that makes virtual prototyping possible is that it allows the engineers to input the barrier performance of specific films. The software then applies those figures to the film thickness distribution and calculates the barrier performance of the cavity design. This can be done for multiple films, or for multiple cavity designs, thus allowing side by side comparison of cavity designs and materials. Figure 6 shows a sample comparison for our provisional cavity design for two candidate films.

		FILM 1	FILM 2
1	FlatSheet_MVTR_38C_90RH [g/sq.m/day]	0.109	0.058
2	FlatSheet_MVTR_38C_90RH [g/sq.m/day]	0.109	0.058
3	FlatSheet_MVTR_40C_100RH [g/sq.m/day]	0.126	0.067
4	FlatSheet_MVTR_40C_75RH [g/sq.m/day]	0.094	0.050
5	FlatSheet_MVTR_30C_75RH [g/sq.m/day]	0.052	0.028
6	FlatSheet_MVTR_30C_65RH [g/sq.m/day]	0.045	0.024
7	FlatSheet_MVTR_30C_60RH [g/sq.m/day]	0.041	0.022
8	FlatSheet_MVTR_25C_75RH [g/sq.m/day]	0.018	0.010
9	FlatSheet_MVTR_25C_65RH [g/sq.m/day]	0.016	0.009
10	FlatSheet_MVTR_25C_60RH [g/sq.m/day]	0.015	0.008
11	FlatSheet_OTR_23C_100RH [cc/sq.m/day]	0.31	0.31
12	Flat Film Thickness [my]	289	340
13	Blister Draw Ratio	2.21	2.21
14	Average Film Thinning [%]	45.3	45.3
15	Initial Area [mm2]	1076	1076
16	Surface Area [mm2]	2374	2374
17	Average Thickness [my]	131	154
18	Blister_MVTR_38C_90-0RH [mg/day]	0.514	0.273
19	Blister_MVTR_40C_100-0RH [mg/day]	0.660	0.351
20	Blister_MVTR_40C_75-0RH [mg/day]	0.369	0.196
21	Blister_MVTR_30C_75-0RH [mg/day]	0.204	0.110
22	Blister_MVTR_30C_65-0RH [mg/day]	0.153	0.082
23	Blister_MVTR_30C_60-0RH [mg/day]	0.129	0.069
24	Blister_MVTR_25C_75-0RH [mg/day]	0.071	0.039
25	Blister_MVTR_25C_65-0RH [mg/day]	0.055	0.031
26	Blister_MVTR_25C_60-0RH [mg/day]	0.047	0.025
27	Blister_OTR_23C_100RH [mm3/day]	1.624	1.624

Figure 6: Analysis of thinning, MVTR, and OTR rates for two candidate films.

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Lines 1 through 10 of the table give the moisture vapor transmission rate (MVTR) for the unformed film (FlatSheet) at various temperatures (30C, etc.) and relative humidities (75RH, etc.). Line 11 gives a figure for oxygen transmission (OTR). Line 12 gives the pre-formed thickness of the two films. Note that FILM 2 is the thicker candidate. Lines 13-16 give the key parameters for the provisional cavity design. They are the same because both films are being evaluated for their performance in the same cavity design. Lines 18 through 27 show the software's calculation of the MVTR and OTR that will be achieved by this cavity design for each film. The blue highlighted figures show that FILM 1 fails at high temperature and humidity to achieve the target MVTR of less than .5 mg/day.

With this degree of data specificity, simple software tools can be developed for visualizing the performance of particular films in particular applications. Combining information about the moisture vulnerability of the pharmaceutical with the performance capabilities of the film, engineers can produce an uptake plot that charts the amount of moisture absorbed by the pharmaceutical over time. Figure 7 shows one example of an uptake plot.

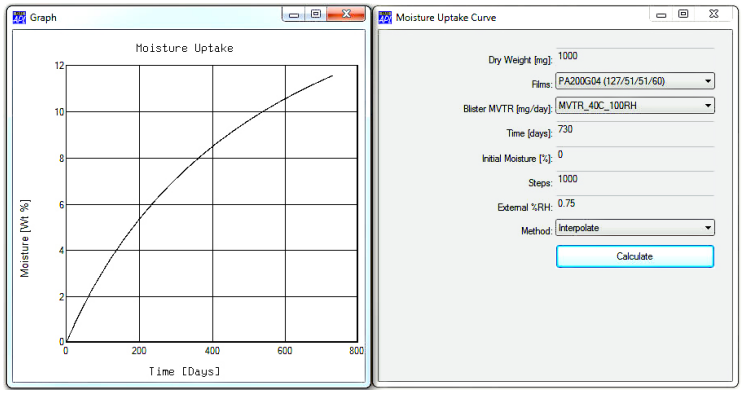

Figure 7: MVTR uptake plot for a sample pharmaceutical, with inputs on the right.

The software accepts inputs for a number of variables. This allows engineers to specify initial moisture present, to select various films and environmental conditions, and to vary the time scale of the display. As another tool for modeling film performance, the uptake curve is only one of several vital steps in a rapid process of iteration and evaluation that takes place before any physical prototype is built.

THE VALUE OF VIRTUAL PROTOTYPING

Failure of a virtual prototype is actually a good result that helps speed the blister development process. BlisterPro® allows designers to model package performance with great accuracy, and to adjust package geometry and materials to achieve the performance that the product requires. This means that only the most promising and most likely to succeed designs will be built into physical prototypes and tested, thus greatly reducing time and cost.

According to Steve Warakomski, Technical Manager for Pharmaceutical Films with kp: "We value the ability to work through package designs virtually before getting into the physical details and tasks. The tools within the BlisterPro® services allow us to very often steer clear of pitfalls that may have not been obvious, and also to clearly define failure points. This virtual component of our service complements the real process component nicely and allows us to be more effective in optimizing performance and incorporating safety factors. We wouldn't want to go back to working without these types of tools and techniques."

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