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Science Behind the Strip: An Engineer's Guide to Designing Blood Glucose Test Strips for Accuracy.

3M Medical Materials and Technologies

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INTRODUCTION

You create lifesaving technology. The blood glucose test strips you design enable those living with diabetes to make life-sustaining decisions while maintaining their independence and active lifestyles.

Blood glucose test strip accuracy is paramount, and it all starts with flawless design. Each layer within the strip has a critical function and needs to be able to do its job and work together without interference from other layers or external contamination.

Regardless if you've designed blood glucose test strips before or are new to the process, understanding the importance of each layer's role, effects, and reactions of different materials and design process considerations will help you provide the reliable results people depend on. Confidence in the materials used in the strip design allows the design engineer to focus on other factors known to contribute to bias in glucose measurements such as temperature, enzyme performance, and patient factors.

ANATOMY OF A TYPICAL TEST-STRIP

The magic of at-home blood glucose testing comes to life when each layer functions appropriately in combination with other layers to generate an accurate test result. When there is inconsistent bonding between layers, fluid flow can be impeded or allow sample to leak into unintended areas of the test strip. Let's break a typical test strip down¹ and look at it layer by layer to examine common intended features and potential problems.



The face side of the test strip

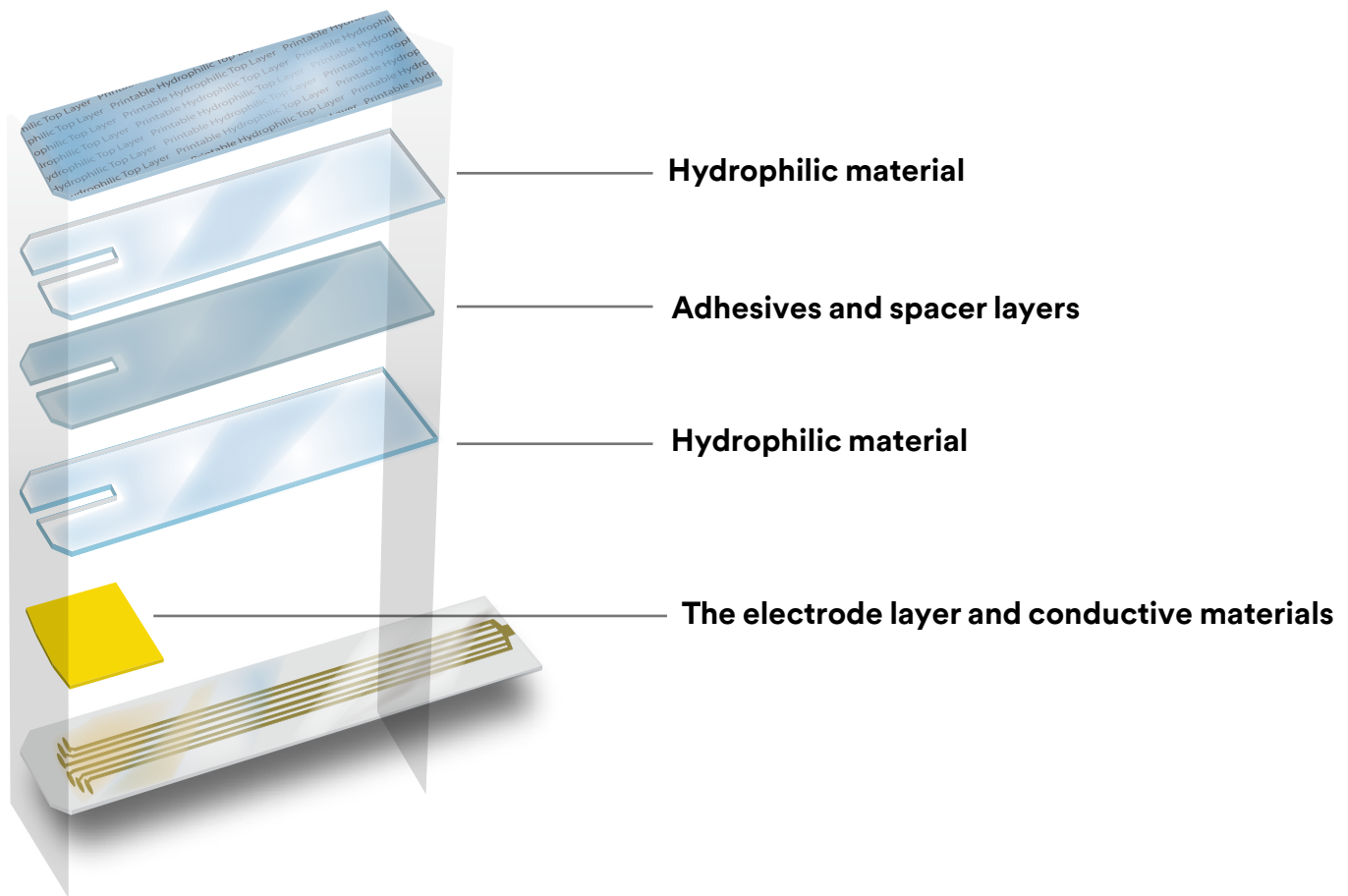
Protects the inside layers from the outside world and may also allow for branding insignia or other helpful artwork. The top layer is not always made of the same material along the length and width of the test strip and may incorporate features to promote fluid flow to the desired areas of the test strip. A hydrophilic film is typically used at the biological sample end of the test strip. Commonly an air gap is provided via die cutting, molding or laser drilling to allow air to be expressed when

fluid enters the capillary test chamber. Test-strip designers may use a selectively coated hydrophilic film to help ensure that the small amount of blood provided for sampling goes where intended for measurement.

The blood sample chamber

The chamber is typically made up of at least three material layers combined to promote fluid flow into a consistent test chamber geometry.

THE ANATOMY OF A TEST STRIP



The layers working together ensure a repeatable sample is presented for analysis.

Hydrophilic material – Promotes fluid flow from the chamber entrance to where the blood glucose measurement is made via the system sensor(s). The hydrophilic top layer is usually transparent to allow the user to see that blood has filled the chamber making for easy visual verification that the test is in progress. A consistent hydrophilic structure is crucial to ensure that the blood fills the chamber entirely and within the expected time for the measurement system design requirements. Imperfections in the hydrophilic structure can lead to systems errors and contribute to inaccuracies in measurements.

Adhesives and spacer layers – Provide attachment to the hydrophilic top layer film and the bottom conductive layer containing the test-strip electrodes and reagent coating. Features of these bonding layers critical to performance are its thickness and composition. Adhesives must not contain chemicals that may interact with either blood or reagents negatively. The composition of adhesives and any sacrificial liners used in production must be demonstrated to be compatible with the reagents used for blood glucose measurement. The manufacturing process used and the quality system deployed by the material supplier will ensure conformance of the material for the intended use over the life of the product. Not all designs will utilize

adhesives in the same way and the material supplied may have different constructions and properties desired for best performance. Tight thickness control is critical for spacer layers as the spacer provides the elevation in the capillary chamber. Thickness variation may cause variable sample volume that can introduce errors in measurement. The chamber's overall geometry, determined by the test-strip manufacturer, ensures the required sample volume is controlled for assay.

The enzyme layer

Once the blood fills the capillary channel, electrochemical measurements can be made utilizing a specialized enzyme layer that uses glucose to generate an electrical charge. Each manufacturer will likely have a custom recipe for the enzymatic layer that is designed to generate consistent results for a given concentration of glucose within the blood. The enzyme layer generally covers the entire capillary channel to maintain consistent measurement area. This reduces the potential for variation in the enzyme coverage. Typically, the enzyme is present in excess relative to the available glucose to minimize the introduction of measurement errors; more importantly, a change in the enzyme area covering the electrode can result in significant test-strip performance issues².

Materials used in the construction of test strips, therefore, need to maintain adhesion and prevent leakage due to construction de-bond or defects

in adhesive coverage. Leakage caused by these defects can allow sample migration away from the designed test site and cause measurement errors. Potential interferents create other sources of measurement error. Device designers need to ensure that their chemistry is robust for common blood-borne substances or may be stipulated interferents on the device labelling³. It is essential that suppliers of materials used in the construction of diagnostic devices have process controls in place to minimize the chance that contaminants may be introduced. Examples of common strategies for process controls to limit contaminants at the material supplier are robust tier-two supplier management, effective cleaning procedures during process change-over, and analytical testing of product composition.

Electrode layer and conductive materials

The electrochemical response signal at the enzyme test site travels through the test-strip circuitry to the glucose meter. The meter calculates the amount of glucose based off one or more signals presented by the test strip to the meter for analysis. Environmental effects such as capillary blood oxygenation at various altitudes, temperature effects on blood circulation or, meter circuitry bias among other influences may cause system inaccuracies². The use of noble metals for electrodes is fairly common in test-strip designs to minimize variation in conductivity due to environmental effects or test-strip aging. Conductive materials need to adhere to the supporting film layer following deposition,

during the test-strip manufacturing process, and throughout the life of the strip. Besides the signal used to determine glucose concentration in the blood sample, some test-strip manufacturers may use additional circuits to provide system corrections to increase accuracy.

WHAT MALFUNCTIONS CAN OCCUR?

Issues can arise during the design and manufacturing phases, as well as during the test strip's shelf life. Below are problems you might face, as well as potential solutions to help mitigate complications.

Contaminants or Leeching: Materials that are not stable or that contain components that may be dissolved by blood could migrate and contaminate the sample and interfere with the test result. Contaminants may be introduced via material suppliers, during strip assembly or as a result of degradation from storage conditions as the strip ages before use.

How to mitigate: Careful choice of materials that are stable and compatible with the assay design is critical. Measurement and certification of incoming material purity and composition from material suppliers provide assurance. Expectations of supply chain management by tier-one suppliers to properly manage their suppliers and provide evidence that process and design controls are in place to help minimize the risk of unintended contaminants.

Stability and aging effects: Material stability or aging is a complex subject as shelf life studies are both time consuming, expensive to undertake, and should consider environmental factors such as temperature and humidity². In addition to the expiration date that is set by test-strip manufacturers, the material suppliers used in test-strip constructions should also perform stability studies. Some materials may lose performance over time, especially at elevated temperatures or material may degrade chemically. Degradants could contaminate the blood sample and interfere with the test result. The loss of performance such as de-bonding of an adhesive may cause the test-strip to fail and impact accuracy.

How to mitigate: Choose materials that are stable across the range of temperatures they will experience. Material suppliers should demonstrate stability testing has been accomplished under conditions appropriate for your device. Lot analysis and certification of materials that may encounter sample or reagents are a desirable component of the supplier management process. Process validation studies and process controls should be used to ensure that materials are consistent lot to lot. Shop floor management is important to ensure that equipment is adequately maintained, is in calibration, and that proper cleaning procedures for equipment are applied before production of materials.

Adhesives and spacer layers: Control of material thickness, sometimes called caliper, is important in devices that rely on die-cutting operations used to create microfluidic channels. An inconsistent volume in the channel can potentially cause measurement errors as reagents may not be present in quantities sufficient for the device design. Incomplete coverage, coating voids, or adhesive streaks can also result in leakage of the blood from fluidic channels to unintended areas causing measurement errors.

How to mitigate: Choose an adhesive supplier that can ensure a uniform thickness, coverage, and minimal coating defects. Suppliers should have adequate detection methods in place. Methods such as gauges and optical defect detection to provide their films, adhesives and other coated substrates consistently and uniformly. It should be noted that test-strips and point-of-care diagnostics devices are generally quite small and that many material suppliers will use industrial sized production equipment. The differences in scale across production methods between devices and material suppliers can cause challenges in defect detection. Quite small defects such as streaks and voids in a coating can impact device performance and are often difficult to measure at a larger industrial scale.

Downstream processing of films: Fractures, slitting shards, and other debris generation along with slit edge quality can affect the risk of contamination, and microfluidic obstructions.

How to mitigate: Process conditions need to be optimized for slitting, die cutting, laminating and other functions concerning heat, speed, and pressure. Choosing materials with properties that allow efficient processing during converting operations and will produce clean and consistent parts. Careful choice of a qualified converter and converting methods are required for optimal device assembly. Edge quality and straightness can be critical to operations such as lamination and registration of multiple layers into a finished device. To leverage roll-to-roll processing techniques, (the inherent efficiencies) engineers need to manage process settings such as web tensions, speeds, steering, and lamination conditions to produce a device meeting design performance criterion.

Special considerations for roll-to-roll

operations: Wrinkling, curling, banding, and other roll formation issues, combined with the need for liner stripping and consistent lamination conditions, are all potential pitfalls capable of causing equipment stoppages and downtime.

Manufacturing issues

Adhesive build-up: The slitting and die-cutting of adhesives can result in adhesive build up on machine blades over time.

How to mitigate: Choose an adhesive that has sufficient stiffness to resist deformation and transfer to cutting equipment while still having adequate adhesion to the other materials used in your device.

Damage to substrates and coatings: Scratching and other damage to components during assembly can produce a device that does not function properly. If optical methods are used for assay detection, scratches produced during manufacturing can cause surface defects and may create measurement errors.

How to mitigate: Process and machine designs should be selected that minimize the potential for damage. When possible, choose materials capable of resisting scratching and other damage.

The best way to avoid the above issues is to ensure you're choosing the right materials for the device design. When you work with suppliers that have the capability and technology to measure and mitigate these issues it can help you avoid expensive problems and streamline your device development process.

HOW DO I CHOOSE THE RIGHT MATERIAL?

When choosing materials, it is important to consider material compatibility, as not every material works well with other materials. Lack

of compatibility can cause the test strip to fail under use conditions. Here are some considerations for best results:

Composition of materials

Certain adhesives stick better to some materials than others. Properties such as surface energy, roughness, and process conditions can influence bond strength considerably. It may be important to consult an expert and work together to select the best materials. It is possible to alter the surface properties of substrates by using treatments to functionalize surfaces, resulting in improved bonding to adhesives.

Device design and construction

The need for a specific sample volume may dictate the thickness of one or more layers of your device. Careful selection of the materials for these layers is required if they are to be of optimal stiffness for processing. Strategic use of materials and the total number of layers required for a design may also create unique challenges for lamination and registration. Pattern printing of materials may be used to aid processing such as registration or could be required for the device for deposition of reagents. Films may also be structured with embossed patterns or textures to produce features such as lensing elements or optical pathways.

Biocompatibility with assay

As with other products that come into contact with biological fluids, all materials selected must be compatible with the assay and not interfere with the test sample. Be wary of materials that are unstable and may outgas, or may be reactive. Uncured or reactive compounds can change properties over time or introduce contaminants into the sample.

Adhesion properties

Two simple measurements reveal an adhesive's properties: peel force and liner release. Peel force measures the strength of an adhesive's bond to an opposing surface. It's an indication of how well an adhesive will stick to the materials it is bonding. Liner release is similar – it measures the bond between an adhesive and liner – but because the liner needs to be removed, a balance in bond strength is needed. The liner needs to stay on the material before processing, but must be removed easily, cleanly and consistently during the manufacturing process. Other factors affecting adhesion are surface roughness of the opposing surface and bonding conditions such as temperature, pressure, and dwell time.

TELL ME MORE ABOUT HYDROPHILIC MATERIAL SELECTION.

Hydrophilic materials and coatings play an undeniable role in the success of a test strip's reliability. It's what guides the sample to the test chamber for blood glucose measurement. The wettability or hydrophilicity is an essential property of the selected material so that it can move the intended amount of blood to the test chamber at the right speed. Coatings are generally used to raise the surface energy of plastic films, and a robust coating is desired to withstand manufacturing processes and function during the entire duration of the device shelf life.

To select the right material for your application, consider the following:

It is important to understand how hydrophilicity is measured to choose the right material for your application. Hydrophilicity may be measured in several different ways such as contact angle and wet index. Additionally, flow speed measurements may be used to help ensure fluids arrive in time for reaction. The wet index is a measure of how much a liquid spreads out on a material as a drop size assessment. A high numeric wet index (drop size) or low contact angle would both correlate to better hydrophilicity. Flow speed measurements are more difficult to accomplish and usually require measurements on finished devices, as many factors can impact how well a channel design wicks fluid. Materials and design work together to move

fluids to their intended locations at a certain speed to allow for the test to be completed within the allotted time.

Make sure your film's surface energy, or degree of hydrophilicity, is suitable for your application.

Few materials are hydrophilic enough for use in test strips and these are easily compromised due to moisture, so be sure to follow proper storage conditions when processing hydrophilic films. For instance, bare polyester doesn't have enough surface energy to promote fluid flow but can be functionalized by various surface treatments, such as plasma or chemical top coatings, to create a hydrophilic surface. Some treatments tend to be more durable than other treatments, and some treatments potentially may solubilize when exposed to the test sample. Test-strip manufacturers should get test compatibility studies.

Know your test strip's shelf life.

To make sure your material is suitable for your application's intended shelf life, ask yourself, "Will the chosen materials maintain their properties and function in their intended storage and use environment for the intended shelf life? Do any of the materials selected have shelf life considerations and could properties change during storage?" Materials you choose in your design generally will have a stated expiration date. The expiration date indicates the supplier has knowledge that the

material properties will meet performance specifications for the duration of the shelf life provided storage guidelines are followed. It is the device developer's responsibility to confirm that the test strip will meet performance criteria once assembled.

Be aware of variables capable of damaging the material.

Some processes, environmental and manufacturing conditions could impact a test strip's overall performance. Some factors may not immediately compromise performance and may only exhibit during stability testing. For example, contaminants may require time to migrate within a device and as such may delay compromising durability or stability of the device only after a period of time. Biologically inert materials that are stable when exposed to other processes are ideal. Materials that are properly stored, used as intended, and are produced and consumed in carefully managed processes will likely avoid many situations that could cause problems for strip manufacturers.

Many engineers ask if it's possible to improve hydrophilic material stability and shelf life.

If you're unsure of a hydrophilic material's specifications and which film would be best for your project, talk with a knowledgeable material supplier.

CONCLUSION

Blood glucose test strips are small but mighty. What they're able to accomplish aids in critical health decisions, and with such an important task, every test-strip must be constructed so that each layer seamlessly works together.

To ensure the success of your blood glucose test strip – and your medical device as a whole – partner with a knowledgeable supplier that will support your development efforts, work to understand your specific design requirements and provide the appropriate technical competence and analytical skills. Having a partner that will help to troubleshoot challenges as they occur can be the difference between a reliable, accurate blood glucose test strip and one that fails.

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