Microscopy & Microtechniques Focus

EASING THE WAY FOR PAIN-FREE INSULIN INJECTIONS

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There are an estimated 194 million diabetics worldwide and at the present rate of growth, this figure will exceed 333 million by 2025 [1]. Since some 17 million of the 194 million suffer from Type 1 diabetes and rely on regular injections of insulin, there is continuous effort by manufacturers of insulin delivery devices and needles to minimise the pain associated with these vital injections.

Materials testing methods have an important role in ensuring that needles and needle assemblies meet the needs for safe handling and easy, pain-free injection.

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Diabetes is a condition in which the amount of glucose (sugar) in the body is too high because insufficient insulin is being produced. Insulin is a hormone which allows the cells in the body to absorb the glucose from the blood stream.

Insulin is produced in the pancreas, but for diabetic sufferers, either little or no insulin is produced, or the body cannot use its own insulin effectively. A build-up of glucose levels in the blood stream leads to hyperglycaemia, which can damage organs including the kidneys, eyes and nerves. It is also an important risk factor for coronary artery disease and other vascular diseases. There are two types of diabetes.

Type 1 diabetes develops if the body is unable to produce any insulin and is treated by insulin injections and diet. Type 2 diabetes develops when the body can still make some insulin, but not enough, or when the insulin that is produced does not work properly (known as insulin resistance).

Type 2 diabetes is treated with lifestyle changes such as a healthier diet, weight loss and increased physical activity. Tablets and/or insulin may also be required to achieve normal blood glucose levels. Diabetes can account for around 5-10% of a nation's healthcare budget.

INSULIN DELIVERY DEVICES

The most commonly used insulin delivery devices are the syringe and the more recently introduced insulin "pen". With the traditional syringe, the needle is inserted into the insulin phial and the required dose drawn up. Pens, however, are able to dispense pre-metered doses. The pen gets its name from its appearance *(Figure 1)* and uses an insulin cartridge rather than a vial and also uses disposable needles.

Pens are the most popular insulin delivery system in most parts of the world, except the United States, where syringes are the preferred method. Pens offer better dosing than syringes. Pen use is straightforward and is popular with children.

Some pens use replaceable insulin cartridges, and some pens use a non-replaceable cartridges and are then disposed of after use, All pens, however, use replaceable needles.

The smallest pen needles are very short and very thin (6 or 8 mm in length) and help minimise the discomfort of injection. In addition, the shorter length can help prevent accidental injection of insulin into muscle tissue.

Figure 1. Insulin pens from Novo Nordisk

NEEDLE TECHNOLOGY

With so many disposable needles being required on a daily basis, it is no wonder that insulin device and needle manufacturers have rigorous testing and quality control procedures. A key factor in needle technology is the development of thinner needles. Typically 30 and 31 gauge needles are now available. The thinner the needle, the less pain is experienced during the injection. Another important factor is the surface finish of the needle. Electropolishing and a surface coating with a material such as silicone can reduce friction, which is a major cause of injection site pain. As the overall diameter of the needle is reduced, the internal bore of the needle needs to be maintained large enough to ensure a good flow of insulin. The ultimate objective is to produce a needle as fine as possible yet with flow rates that will allow dose delivery times to be reduced. This leads to needles with thinner metal walls. There are a number of key issues that affect users of these needles:

- How easy is it to remove the needle from its protective packaging?
- How easy and safe is it to attach the needle to the pen
- Will the needle bend or break during the injection?
- Is the needle sharp enough for easy puncturing of the skin?

All of the above concerns can be addressed using conventional materials testing methods.

MATERIALS TESTING

Universal materials testing machines offer enormous versatility in making materials measurements. Equipped with the appropriate sample holding grips and test software, they can test for tensile strength, compression, flexure, friction, tear, peel, adhesion, shear, ductility, insertion and many other parameters. They can also be used to test throughout a product life cycle, from raw material to the finished product. A number of materials tests can be applied to insulin needles. These include 3-point bending tests, puncture strength, puncture resistance, torque tests and the measurement of separation and bond forces on the needle assemblies. The 3-point bend tests are carried out on the needle tubing material before assembly onto the needle cap. The sample is placed between two knife-edge points and a load is applied by the materials tester to the midpoint of the sample. This test allows bend strength of the needle tubing to be measured to ensure that it will not bend even if the syringe is twisted during an injection. The needles themselves are welded into an inner needle cap, which screws onto the insulin pen. A protective sheath fits over the needle to protect against needlestick injury. The whole assembly is supplied in a strong outer cap. The needle assembly is removed from the outer cap and the inner cap is screwed onto the pen. The sheath is then removed for the injection. The outer cap can also be replaced on the needle after use, which helps make it easier to remove the needle from the pen and dispose of it safely. By using the appropriate grips, the materials tester can be used to measure the tensile force required to remove the plastic sheath from the needle and also the tensile strength required to break the weld that secures the needle to the cap. These are important parameters for both for ease of use and for safety.

The instrument can also be set up to measure the torque required to screw on and unscrew the needle assembly from the pen. This not only ensures that the correct torque is required, but also checks that there is no flaw with the thread in the screw cap which could either allow air into the system or insulin to leak out, which would affect the actual dosed delivered.

In addition to the narrow gauge of the needle reducing pain of injection, the tip of the needle is profiled to ease puncturing of the skin. The sharpness of the needle can be measured by the materials tester using a puncture strength test *(Figure 2)*. Here the force required to penetrate a polymer film (chosen to simulate skin) is measured.

In addition, a puncture resistance test *(Figure 3)* can also be carried out. This test method determines the resistance of film to the needle at a single constant test speed, once the needle has punctured the membrane, and effectively measures how easily the needle slides into the skin layer.

APPLICATIONS IN PRODUCTION

Given the number of needles that must be manufactured for use on a daily basis, the effective adoption in a production environment of the tests described above requires batches of needles to be tested as part of the production process.

One of the leading manufacturers of insulin, needles and delivery devices, Novo Nordisk has invested heavily in materials testing technology at its manufacturing plant in Denmark. It now has three semi-automatic and three fully automatic testing systems.

These have each been built around a Lloyd Instruments' LRXPlus single column 5 kN universal materials testing system equipped with NEXYGEN™ measurement and control software, ONDIO™ application builder and batch tester, using robotics and both compressed air and servo motors for sample loading and retrieving. There are semi-automatic and fully automatic systems for measuring the separation and bond forces on the needle assemblies and semi-automatic and automatic systems for measuring the 'screw-on' and unscrew torque of the needles on to the pens.

Figure 3. A close up of the puncture resistance test

A semi-automatic system is used to measure needle sharpness and puncture resistance. The final automatic system is used for the 3-point bend test. For the semi-automatic systems, samples are loaded by hand, while the tests are carried out fully automatically.

For the fully automatic systems, samples are automatically selected from trays for testing and returned to pass or fail trays depending on the outcome of the test. Significant numbers of samples are tested. Batches of 500 needles are tested in the 3-point bend test and in total, around 130,000 samples have been tested over an 18-month period using semi-automatic systems and 500,000 samples per year using the automatic system.

Figure 2. Puncture strength test equipment

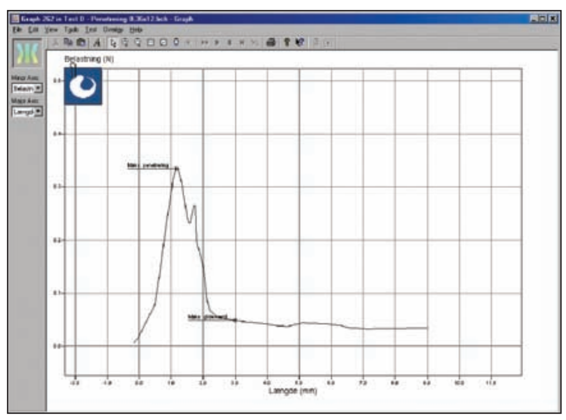

Figure 4. Pipetting aids together with serological pipettes are commonly used in bacteriological work.

MORE THAN PASS/FAIL

The measurements made are an integral part of the quality control procedure to ensure that only the highest quality product reaches the consumer. However, the data are also fed back into a statistical process control system. In this way, the manufacturing process can be continually improved and any trends showing deviation from the desired quality identified at an early stage so that the process can be refined before faulty product is produced.

This not only improves product quality but also improves productivity, streamlines the process and reduces wastage. Although the techniques employed here are an essential part of the production process they can also be applied in future research and development, as companies continue to strive to make insulin management as straightforward and pain-free as possible.

References [1] Facts and Figures, International Diabetes Federation, www.idf.org

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