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Finding fakes – using Raman imaging to identify counterfeit medicines

Chemical sciences

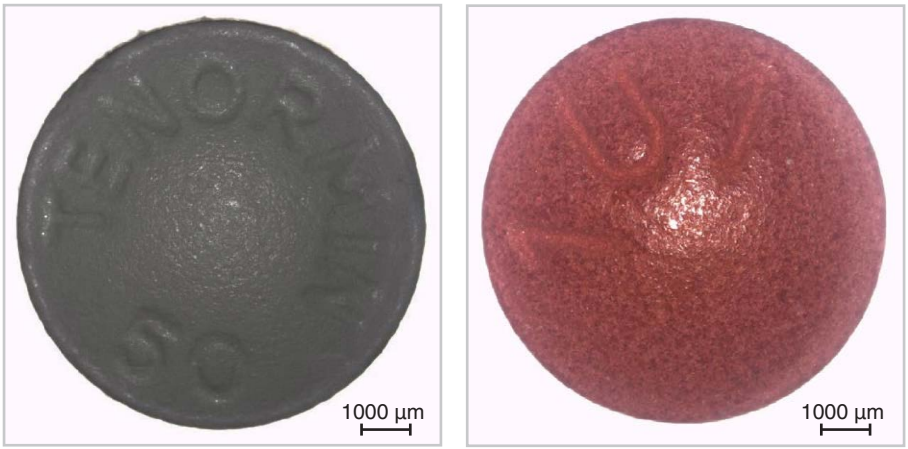
Combating counterfeits

Counterfeit medicines are on the rise.

Previously thought to be a problem limited to developing countries, the increasing number of online pharmacies and the demand for affordable medicines has meant that counterfeit drugs have become a menace to the developed world as well.

Counterfeit medicines offer little or no traceability and no guarantee of safety, efficacy or equivalence with the reference product. Such medicines are at best harmless placebos giving false hope to unsuspecting patients, at worst they carry significant health risks and have been implicated in patient deaths and health emergencies.

Identifying counterfeit drugs has become an area of increasing focus for regulatory authorities and also for pharmaceutical companies who are seeing their brand image tarnished and profits/margins eroded by poor quality counterfeits masquerading under their brand name.



Genuine Tenormin (left) and counterfeit Tenormin (right)

Why use Raman imaging for the identification of counterfeits?

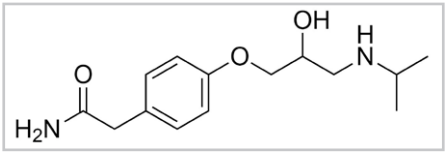
Raman spectroscopy is highly specific and can differentiate between materials with similar chemical structures - such as excipient grades and salt forms - even at low concentrations. This is often not possible using conventional techniques such as IR microscopy. This specificity makes Raman well-suited to identifying counterfeits which often use similar components to the reference product. The ability to accurately differentiate is key.

Raman imaging is a sensitive technique which can generate high-resolution (1 μm^2 per pixel) chemical maps of complex blends of material, such as tablets. Raman images or 'maps' allow users to study differences not only in chemical components but also the formulation's microstructure – an important facet in the identification of counterfeits.

Identifying counterfeit Tenormin tablets

Introduction

Renishaw, in conjunction with the Leicester School of Pharmacy, De Montfort University, UK, conducted a study on four different Tenormin tablets sourced from the UK, Saudi Arabia, Nepal and Pakistan.



Atenolol (Tenormin) molecular structure

Tenormin is the brand name of atenolol – a beta-blocker – used to treat cardiac disease. In common with the majority drugs, Tenormin is dangerous if taken in excessive quantities. Being a drug that acts on the cardiovascular system it is crucial for patient safety to ensure the correct dose is delivered; symptoms of overdose include hypotension-induced shock and acute heart failure.

In the pharmaceutical industry, medicines are required to undergo extensive testing throughout development and manufacturing to ensure that the correct dose is delivered to the patient consistently by each tablet in every batch. In the case of counterfeit drugs, there are no such guarantees as to the safety and efficacy of the products.

Results

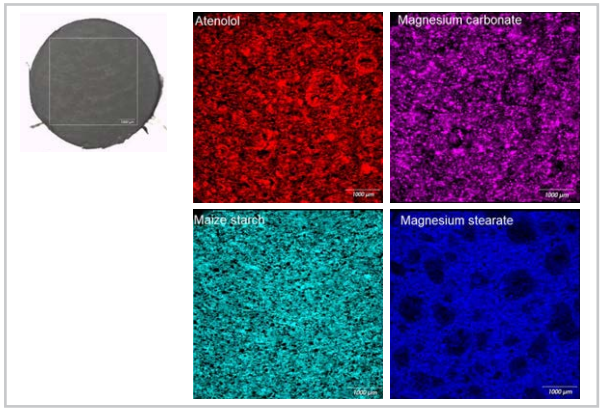
The four tablets were analysed using Renishaw's RA802 Pharmaceutical Analyser. The RA802 rapidly collected thousands of Raman spectra across milled cross-sections of the tablets' core.

The Renishaw RA802 Pharmaceutical Analyser

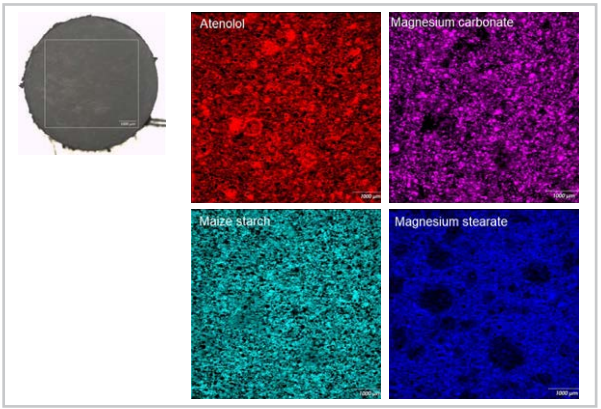
Once collected, the Raman spectra were analysed using statistical methods to isolate repeating spectral elements which recurred throughout the analysis area – these were assumed to be distinct chemical species. These isolated spectra were then compared to a reference database to identify the components within the tablets.

Once the components are identified, the software can render images of the individual components using false colour; each colour corresponding to a different formulation component. The software then uses the images to generate particle statistic data based on the images and semi-quantitative data on formulation concentration based on an assumed pure contribution from the reference spectra.

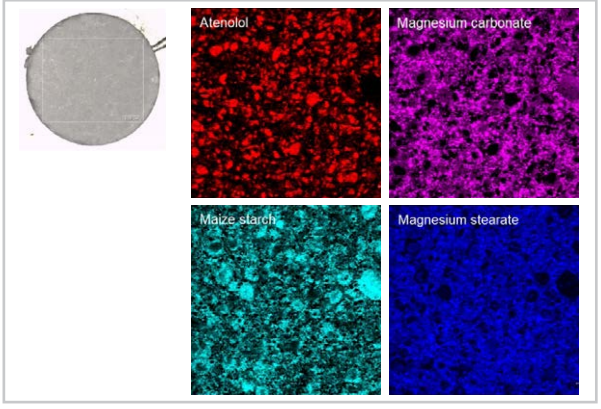
Tablet core



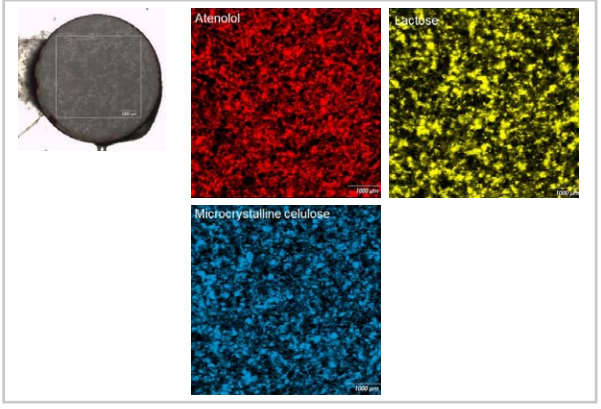
Saudi Arabia Tenormin



UK Tenormin



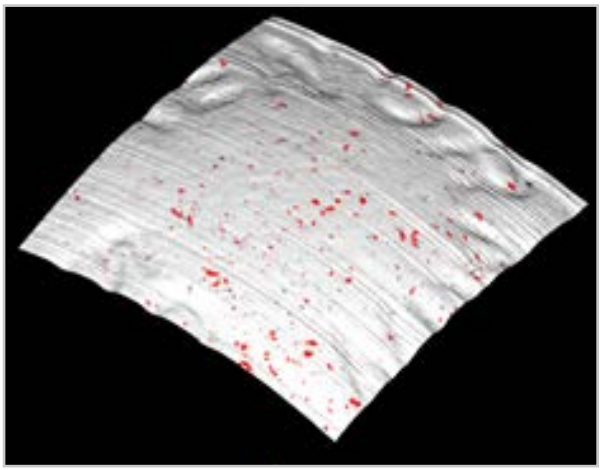
Nepal Tenormin



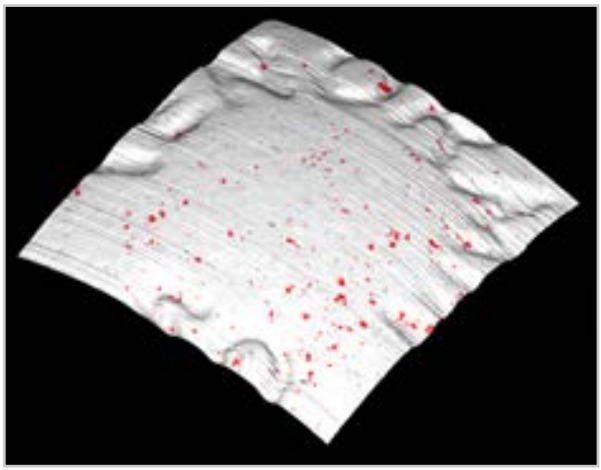
Pakistan Tenormin

Tablet Origin	Components	Concentration estimate (%)
Saudi Arabia	Atenolol	77.20
	Magnesium carbonate	15.43
	Magnesium stearate	2.98
	Maize starch	4.38
UK	Atenolol	76.47
	Magnesium carbonate	15.40
	Magnesium stearate	3.33
	Maize starch	4.80
Nepal	Atenolol	70.34
	Magnesium carbonate	19.51
	Magnesium stearate	4.50
	Maize starch	5.65
Pakistan	Atenolol	82.39
	Lactose	2.40
	Microcrystalline cellulose	15.21

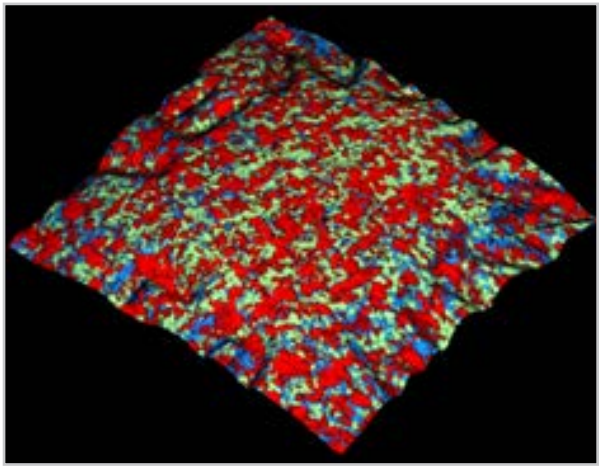
Tablet coating



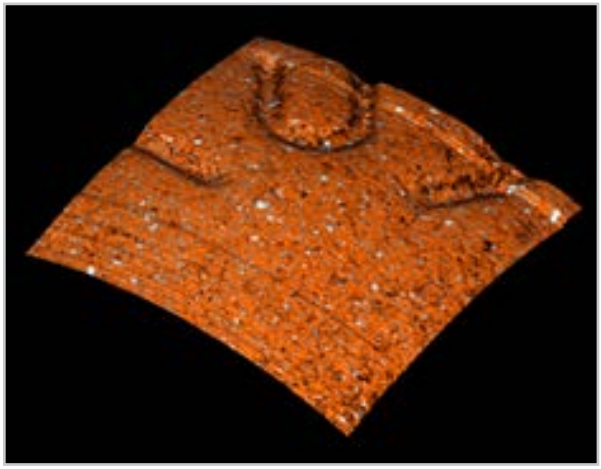
Saudi Arabia Tenormin



UK Tenormin



Nepal Tenormin



Pakistan Tenormin

Key: anatase – white, atenolol – red, maize starch – blue, $MgCO_2$ – light green, orange 2 – orange

Identified components			
Saudi Arabia	**UK**	**Nepal**	**Pakistan**
Anatase (titanium dioxide)	Anatase (titanium dioxide)	Atenolol	Anatase
Atenolol	Atenolol	Magnesium carbonate	Orange 2
		Maize starch	

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Discussion

UK and Saudi Arabia

Of the four Tenormin tablets, the UK and the Saudi Arabia tablets appear to be the most similar, qualitatively and quantitatively. The same components (atenolol, magnesium carbonate, maize starch and magnesium stearate) are present in similar concentrations (Table 1) determined from the Raman data. Even visually, the component images from each of the tablets look similar – there is a high degree of similarity in the microstructure of the formulation. The coatings also contain the same ingredients: Anatase and atenolol. From this we can infer that - although the Tenormin from the UK and Saudi Arabia may be made by different manufacturers - they are both following the same manufacturing process. Both tablets appear to be genuine.

Nepal

Although the Nepal Tenormin tablet does include the same ingredients as the UK and Saudi Arabia tablets, the concentration estimates of API (Table 1) appears to be around 7% lower in the Nepal tablet and the concentration of the three excipients (magnesium carbonate, maize starch and magnesium stearate) all appear to be proportionally higher. Furthermore, the microstructure is appreciably different from the UK and Saudi Arabia Tenormin. Except for the magnesium stearate component, which looks broadly similar, the atenolol, magnesium carbonate and maize starch components appear much less well distributed, forming larger aggregated clumps of material. The UK and Saudi Arabia tablets, by contrast, appeared to have a smaller particle size and were more uniformly distributed.

However, the most prominent indication that this tablet is a counterfeit is the tablet's coating, or the lack thereof. The tablet's surface contains the exact same components as the tablet's core, omitting only the magnesium stearate, which may just be too low concentration to be detected at the surface. It would appear that the powder blend has been compressed without any coating applied. If the coating has an effect on the release of drug, or in preventing decomposition, the lack of any coating may cause the drug to release differently or components to degrade which may, in turn, cause the incorrect dose being delivered to the patient.

Pakistan

The Pakistan Tenormin is the most obvious counterfeit. The tablet only contains two different excipients (lactose and microcrystalline cellulose) neither of which conform to any of the three excipients contained in the UK, Saudi Arabia and Nepal Tenormin (magnesium carbonate, maize starch and magnesium stearate). The concentration of atenolol (Table 1) is around 5% higher than that of the UK/Saudi tablets and the Pakistan Tenormin contains a relatively large quantity of disintegrant (15% microcrystalline cellulose) compared to the UK/Saudi tablets (≈ 5% maize starch). Furthermore the tablet coating is predominantly Orange 2 – an azo dye – and a minimal amount of anatase.

This tablet would be expected to perform differently on dissolution and may exhibit different bioavailability profiles to the reference product which could cause the wrong dose to be delivered. The packaging of the Pakistan Tenormin was also suspicious. The box carried the branding of AstraZeneca and ICI - raising further doubts as to the authenticity of the product.

Conclusions

The UK and Saudi Arabia tablets appeared to be genuine. The Nepal and Pakistan tablets were identified as likely counterfeits. A combination of qualitative and semi-quantitative data confirmed that the UK and Saudi Arabia Tenormin tablets were highly consistent, whereas the Nepal tablets showed differences in their microstructure and the Pakistan tablets in their composition. This white paper demonstrates the power of Raman imaging in the identification of counterfeit medicines.

Acknowledgements

Kind thanks to Rachel Armitage of Leicester School of Pharmacy, De Montfort University for providing samples and additional information.

Renishaw. The Raman innovators

Renishaw manufactures a wide range of high performance optical spectroscopy products, including confocal Raman microscopes with high speed chemical imaging technology, dedicated Raman analysers, interfaces for scanning electron and atomic force microscopes, solid state lasers for spectroscopy and state-of-the-art cooled CCD detectors. Offering the highest levels of performance, sensitivity and reliability across a diverse range of fields and applications, the instruments are designed to meet your needs, so you can tackle even the most challenging analytical problems with confidence.

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