# Is it what it says on the packet? ATR FTIR provides a rapid answer to counterfeit tablet formulations

G Lawson, E Turay, R Armitage, L Goodyer and S Tanna

**1. Introduction**

How many people would question the reliability of a packet of paracetamol or even atenolol bought whilst away on holiday?

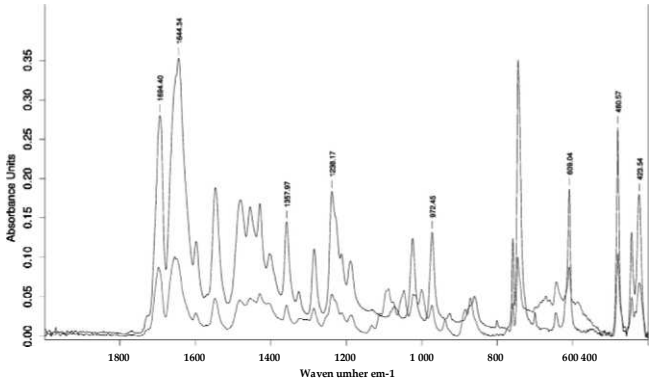
Counterfeiting of medicines is a global phenomenon that affects both developed and developing countries and especially in medicines sourced via the internet.[1] In the UK the level of counterfeit medicines is thought to be between 1 and 2% whilst elsewhere in the world figures as high as 40% are cited by the WHO. A counterfeit medicine is a medicine which is deliberately and fraudulently mislabelled in regards to identity and source which apply to both branded and generic products. Products may or may not have the correct excipients, exclusion of active pharmaceutical ingredient (API) or insufficient quantities of API or fraudulent packaging. The effects of counterfeit medicines on patients can range from the difficult to detect and quantify to an important cause of unnecessary morbidity, mortality and loss of public confidence in medicines and the health systems. In recent years more and more incidents of deaths resulting from sub-standard or counterfeit medicines have been reported. Recently in Pakistan, for example, more than 400 deaths were thought to have resulted from counterfeit cardiovascular medication. The identification of these materials causes problems for the regulatory authorities both in the Healthcare Supply Chain and also for Border Agency staff. The problem with international visitors is particularly acute for countries like Saudi Arabia, where large numbers of pilgrims often bring excess medicines with them which need to be rapidly assessed.

Rapid assessment implies a screening process rather than the time consuming in depth analyses offered by conventional laboratory equipment such as GC-MS or NMR.[2] The first step is a visual assessment of barcodes or more frequently now the use of two dimensional barcodes read by smart phones. This provides rapid communication between supplier, importer and the border agency but is however only limited to assessing the packaging rather than the con-tents. Chemical test kits are limited to specific active ingredients, a problem not faced by a portable Raman spectroscopy system which is being trialled in this area and can be programmed for many APIs.[3] Costs and concerns about the robustness of the system have raised some concerns.

In this paper an alternative spectroscopic system Fourier Transform Infra-Red (FTIR) spectroscopy utilising Attenuated Total Reflection (ATR) sampling[4] has been investigated. FTIR systems form the basis of compound identification in the British Pharmacopoeia (BP)[5] and the combination with the ATR sampling system removes the need for any prior solvent extraction to separate the API from the excipients. A tablet formulation would simply be finely powdered and a small sample of the API + excipients powder placed on the ATR window and the resultant spectrum produced. As can be seen from Figure 1 the spectrum obtained for caffeine from the tablet formulation is virtually indistinguishable from the spectrum obtained from the reference material.

This approach therefore appears to provide a 'fingerprint method' to rapidly assess if the expected API is present in the dose format being tested. An assessment of the API dose level may also be made from the intensity of the peaks characteristic of the API of concern. This determination would be dependent on the detection capabilities of the ATR FTIR system and very low dosage levels may not be currently detectable.

**Figure 1**
*Comparison of reference (red top) and tablet samples for Caffeine.*




**Experimental**
Alpha system equipped with a platinum diamond single reflection sampling station. Spectra of each sample were collected at a resolution of 2cm$^{-1}$ over the range 400 - 4000cm$^{-1}$. Replicate spectra, a minimum of three, were collected for all calibration and trial samples. The BP based analyses were run on a Thermo Electron Helios Omega UV/Vis instrument using Vision Lite

2.2 software.

*2.2 Chemicals and sample preparation* The reference samples: caffeine, atenolol and para-etamol were > 99% analytical grade, whilst the excipients used to prepare the calibration mixtures were all pharmaceutical grade. The excipients used included hydroxymethyl cellulose, titanium dioxide and magnesium stearate.

Reference spectra of the authentic APIs were produced from finely ground samples placed on the ATR sample station. The FTIR system was zeroed prior to each sample series.

For the quantitative calibration samples several single excipients were used for individual experiments since the excipients in the test samples would be unknown. Powder quantitative calibration and val-idation samples were prepared by mixing suitable amounts of the API and excipient to cover the nor-mally encountered dosage range. These calibration samples are expressed as a percentage by weight of the API in the excipient. The anticipated ranges were:
Paracetamol 30-80% w/w and Atenolol 10-40% w/w
based on the tablets studied. After mixing using a pestle and mortar to ensure homogenisation powder samples were placed on the ATR station and replicate spectra were recorded. This process was repeated for several different samples taken from the calibration mixture to ensure reproducibility. Quantitative data was obtained from the Opus 6 software for spectral peaks characteristic of the target APIs to produce calibration data for the subsequent analyses.

Samples for the BP analyses were prepared as detailed in the British Pharmacopoeia 2010 modified for single tablet analysis.

Strips of tablets of both paracetamol and atenolol were obtained adventitiously from pharmacies in the UK, Pakistan, and India. These trial samples were identified as follows:

- Paracetamol - UK: 4 x 500mg and India: 5 x 500mg
- Atenolol - UK: 3 x 50mg, Pakistan 3 x 50mg + 1 x 100, India 2 x 50mg + 1 x 25mg

**3. Results and Discussion**
*3.1 Identification of the API*
The overlay spectra in Figures 2 and 3 comparing the spectrum of the neat API with that obtained from a typical pill formulation, show that the anticipated API can be readily identified to be present. The correlation between the spectra confirms that no other API is present at significant levels.

*3.2 Determination of the dosage level*

ATR measurements are affected by the degree of surface contact between the sample and the sampling diamond and a fine powder sample is therefore important for reproducible data. Furthermore, as seen by Mazurek,[3] increasing the number of samples analysed will improve the data as shown in Table 1 where the $r^2$ regression coefficient from different calibration diagrams demonstrates these effects.

**Table 1**

*Methods to improve reproducibility*

| Mixing Time | No Spectra | $r^2$ Value |
|---|---|---|
| Short | 1 | 0.8 |
| Short | 3 | 0.9 |
| Long | 3 | >0.95 |

**Figure 2**

*ATR-FTIR spectrum in absorbance mode of UK tablet (blue) and pure Paracetamol reference (red)*

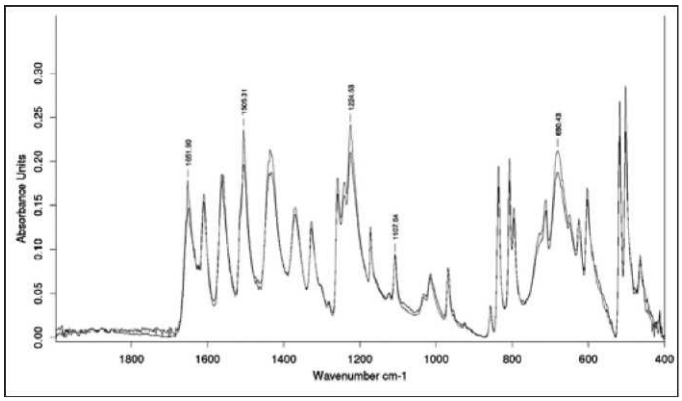
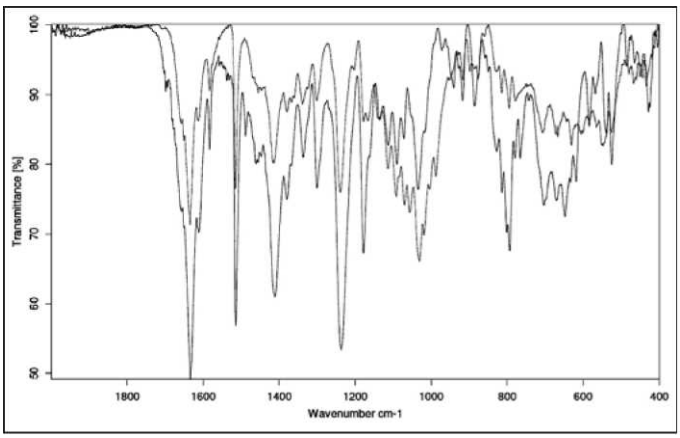



**Figure 3**

*ATR-FTIR spectrum in transmission mode of UK tablet (red) and pure Atenolol reference (blue)*



Once suitable calibration data has been obtained the percentage level in the tablet formulation can be derived and the actual dosage level calculated from the mass of the pill.

The results derived from this investigation are shown in Table 2.

Once the calibration data has been prepared the identification and quantification of the target API is generally available within 5 minutes of opening the tablet packet. As can be seen the results for the UK tablets show good agreement. Two of the paracetamol samples from India are not as expected, one with a low dose 438mg vs 500 and more surprisingly one at 628 vs 500mg. The measured doses in all the atenolol samples from Pakistan were lower than stated on the packet and these samples were analysed using the BP method to confirm these findings. The results obtained for the Pakistan atenolol samples were #A 34mg and #B 61mg confirming the ATR data.

**Table 2**

*Quantitative analysis results*

| | | Paracetamol | | | Atenolol | |
|---|---|---|---|---|---|---|
| Dose | | Expected | Measured | | Expected | Measured |
| UK | *m* | BOO | 523 | #A | SO | 45 |
| | *1-2* | 500 | 490 | *HB* | 100 | 104 |
| | #3 | 500 | 505 | #C | 100 | 96 |
| | #4 | 500 | *5* 12 | | | |
| India | n | 500 | 438 | ɑA | 25 | 20 |
| | #2 | 500 | 502 | #8 | 50 | 42 |
| | nj | 500 | 525 | nC | 50 | 45 |
| | #4 | 500 | 485 | 80 | 50 | 30 |
| | *US* | 500 | 628 | #E | 50 | 30 |
| Pakistan | | | | #A | SO | 40 |
| | | | | KG | 100 | 58 |

*Note all results subject to a 10% error.*

### 3.3 Discussion

The results demonstrate the potential of the ATR FTIR approach to rapidly assess the actual components of a medicine against those stated. This approach provides a regulatory authority with the means to rapidly identify a suspect material using only bench top analytical equipment with no consumables other than electricity. Further analysis would be required to confirm the presence of either a substandard or counterfeit material.

The cardiovascular tablets were obtained from Pakistan shortly after the problems in this area were reported and the measured low levels of atenolol may be related to these incidences.

The substandard levels of paracetamol and atenolol may well be the results of poor mixing at the production stage and it is unlikely that these tablets would provide therapeutic levels of the relevant drug under the prescribed conditions.

The elevated paracetamol level found in one set of samples from India would be of concern for people prescribed 8 or more tablets a day where the total dose would be around 5024 mg rather than the 4000 expected.

This work provides further evidence regarding the poor quality of some of pharmaceuticals available in many developing countries.[6] It is quite likely that this is due to issues relating to poor quality control of the manufacturing processes and the impact on the health of the population in such countries is hard to quantify. For the traveller visiting such areas this data serves as a warning that wherever possible medicines should be purchased before departure, including items such as paracetamol used to treat minor conditions.

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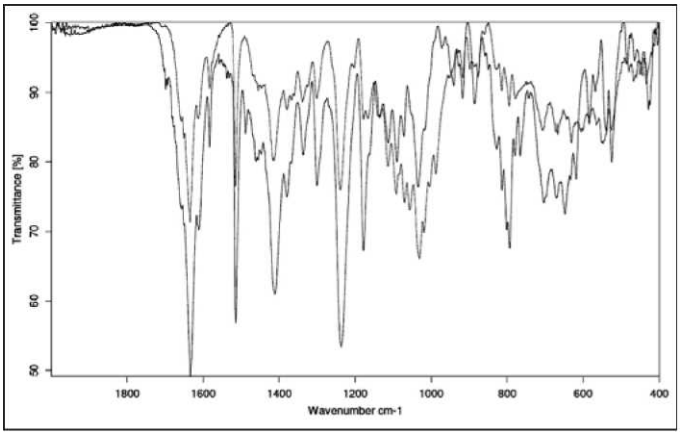
**Figure 3**
*ATR-FTIR spectrum in transmission mode of UK tablet (red) and pure Atenolol reference (blue)*