Content Uniformity (CU) analysis is a mandated test for releasing drug product, ensuring that the dosage is uniform across a production batch. Typically, the analytical method used is high-pressure liquid chromatography (HPLC), which is a resource-intensive and expensive technique. Transmission Raman Spectroscopy (TRS) is an alternative with a 5-10x lower cost per test, which requires fewer resources and less laboratory space.

Content Uniformity Analysis

For drug product release a Uniformity of Dosage Units (UDU) test is required. This is defined by the United States Pharmacopoeia in, e.g., USP<905>; content uniformity is an applicable test for UDU testing. To pass a content uniformity test for tablets 10 individual tablets are assayed and the samples demonstrated to be within a calculated acceptance value. Traditionally HPLC is used as the CU method.

The cost of testing could be reduced significantly by replacing HPLC with a faster non-destructive method that requires fewer laboratory instruments. Alternative techniques include near-infrared spectroscopy, but this method can be cumbersome for creating and maintaining suitable and stable analytical models. However, CU analysis by Transmission Raman spectroscopy takes seconds per tablet, is less susceptible to the issues of model-building encountered in NIR and offers significant cost savings in regulated batch-testing. Technical details of TRS can be found elsewhere.

Simple operation for TRS analysis: insert test samples into the tray, load into TRS100 and run the test. Results are outputted automatically in a customisable report ready for QC sign-off.
Transmission Raman Spectroscopy

Transmission Raman spectroscopy (TRS) enables quantitative pharmaceutical analysis of intact coated tablets and capsules. TRS uses the rich information derived from Raman spectroscopy with the high sampling volume of a transmission technique to quantify the bulk content of intact tablets and capsules. In TRS analysis a quantitative analysis model is created first using calibration tablets to enable the prediction of CU in future samples. Once validated, the model can be used for batch releases without any sample preparation. This leads to several benefits for batch testing summarised in the context of TRS and HPLC analysis in Table 1.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>HPLC</th>
<th>TRS100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed</td>
<td>Many hours per batch test – multiple systems often required</td>
<td>Typically &lt;5 minutes per batch test. Can replace multiple HPLC instruments/operators</td>
</tr>
<tr>
<td>Consumables</td>
<td>Solvents and disposal costs, columns and glassware</td>
<td>No consumables</td>
</tr>
<tr>
<td>Skills requirements</td>
<td>Skilled in preparation and analysis</td>
<td>No sample preparation or data analysis required</td>
</tr>
<tr>
<td>for routine use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorph quantification</td>
<td>Physical state information is not preserved</td>
<td>Quantification of polymorphic content possible to &lt;0.5%w/w</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>Potential for variations and bias between operators/instruments</td>
<td>Excellent reproducibility, no operator bias</td>
</tr>
</tbody>
</table>

Table 1: Comparison between HPLC and the TRS100 instrument for routine CU analysis.

Costs of Operating HPLC vs. TRS100

The total cost analysis will naturally differ between companies and individual testing requirements. A summary of costs is provided here based on the data used in this document. The raw data, such as salaries, overheads, equipment costs, servicing, HPLC analysis times, etc., are surveyed from US and UK companies and presented in US dollars. In all of the analyses it is assumed that the HPLC instruments are used at 90% of their capacity, i.e. are modern instruments maintaining a high throughput, and that the TRS100 is utilised for 50-75% of its time as the analysis typically takes <5 minutes per measurement run. The cost of the instruments was depreciated over 10 years and full service contracts were maintained.

<table>
<thead>
<tr>
<th>Metric</th>
<th>HPLC</th>
<th>TRS100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per test of batch</td>
<td>$208</td>
<td>$33</td>
</tr>
<tr>
<td>Cost for 40 batches per week</td>
<td>$8,308</td>
<td>$1,320</td>
</tr>
</tbody>
</table>

Table 2: Cost comparison for HPLC and TRS batch tests.
Cost per Batch Test

Table 2 summarises the total costs for a batch test of tablets averaged over a year of testing. The higher cost of HPLC is strongly influenced by the resource costs of the analysts, number of HPLC instruments and the consumables cost. A much larger number of HPLC instruments is required for an equivalent throughput compared with the TRS100. For this calculation an average cost of the HPLC and technician is used, i.e. the resource is an average from a much larger pool of resource, which is representative of a company that has many HPLC instruments. The cumulative total cost per test is 6x lower for TRS than HPLC when spread over 40 batches per week.

For a lab running 8 batches per day the saving is over $1,400 per day, which, for a working year means more than $300K per year of cost savings are possible.

Cost Breakdown

This scenario is for replacing an existing routine batch test currently performed by HPLC, filed as an alternative method. The TRS method is developed using the existing HPLC reference method. The cost of a single product method development for HPLC and TRS is similar at $13,200. For the TRS method the cost of the original HPLC method is not considered as this would typically already exist.

The costs are calculated based on the total cost of ownership of the instruments per annum, taking into account the depreciation over 10 years and the need for multiple HPLC instruments. The instruments are run by a scientist (FEC $84,300) and a team of technicians (FEC $54,600 each). One technician is required per TRS100 instrument but between half and one per HPLC instrument is required, depending on the test.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>HPLC</th>
<th>TRS100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch tests per instrument</td>
<td>500 per instrument, pa</td>
<td>4,000 per instrument, pa</td>
</tr>
<tr>
<td>Solvent costs, inc. disposal</td>
<td>$6,100 per instrument, pa</td>
<td>$0</td>
</tr>
<tr>
<td>Cost of owning instrument</td>
<td>$15,700pa</td>
<td>$40,770pa</td>
</tr>
</tbody>
</table>

Table 3: Cost differences for owning, maintaining and using HPLC and TRS100 instruments.

Eight batches per day represents approximately 2,000 batches per year. For an equivalent output it is calculated that 4 technicians would be required to operate the 8 HPLC instruments. Note that this scenario is the case where each HPLC method is different rather than running many tests using the same method. This would be more typical of a multi-product manufacturing plant.

Resource savings per annum in replacing HPLC, assuming 2,000 tests per year, would be:

- 3 technicians at $163,800
- $84,900 instrumentation costs (including $48,750 solvent savings)

Other savings unaccounted for include bench/lab space and costs of HPLC repeats due to operator error. In some laboratories several (perhaps 2-3) runs might be stacked up for HPLC. This is also possible for the TRS100, which can hold up to 200 tablets on a single tray, so has not been considered here. There is also a negligible time penalty for the TRS100 in testing more than 10 samples per batch, enabling better statistics with a more representative batch analysis.
Cost Savings per Test in a Year

For a laboratory that is introducing transmission Raman as a replacement for HPLC a reasonable scenario is that HPLC tests are replaced over time. Figure 1 shows the cost savings as a function of the number of tests replaced and the rate at which the tests are replaced by TRS. This analysis does not take into account utilisation rates, i.e. the proportion of time that the equipment sits unused when not testing. This is a worst case scenario for the TRS100 cost saving as the TRS100 analysis time is so much quicker than HPLC. With these parameters the savings start during year 1 as the TRS instrument is introduced and models are created for routine testing. In year 2 there are $55,000 of savings at 600 tests per annum, or 12 tests per week.

![Cost Savings Graph](graph.png)

Figure 1: Cost savings as a function of the number of tests. The numbered points show how many tests are done by TRS in year 1-9.

Conclusions

Transmission Raman is a compelling technique for content uniformity testing that provides a significant cost saving for batch-release testing in pharmaceutical manufacturing plants. The return on investment for a well-utilised TRS100 can exceed the capital outlay in a year when the instrument is operating at less than 50% capacity. The cost per test can be more than 6x lower than the equivalent HPLC test.