Elemental Analysis for Pharmaceutical and Fine Chemical Manufacturing

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Elemental analysis for the elements Carbon, Hydrogen, Nitrogen, Sulphur and Oxygen have potential applications at several stages of the manufacturing process of pharmaceutical and chemical products. Prior to manufacturing CHNS analysis can be used to confirm the purity of ingredients and reagents. TOC (Total Organic Carbon) analysis can be used to validate the cleanliness of equipment and water used in manufacturing. Then throughout the process CHNS analysis can be used to confirm the purity of products at every stage to maintain a tight control on the production to maintain and document product quality.

Figure 1. Elemental analysis has potential applications at several stages of the manufacturing process of pharmaceutical and chemical products.

CHNS Analysis

The analysis of the elements Carbon, Hydrogen, Nitrogen and Sulphur, or CHNS analysis as it is commonly referred, is a staple technique within many industries. It allows a fast, accurate assessment of elemental composition to be made with minimal sample preparation. This enables it to be used as a quick screening test to check that a pure chemical is within a defined specification either prior to use or during manufacturing. If impurities are found more laborious techniques, such as LC-MS, may then be employed to identify the cause of the impurity.

The CHNS content of a sample is determined by weighing the sample and wrapping it in tin foil. High temperature combustion of the sample (1150°C for CHNS analysis) in an oxygen rich environment oxidises the sample, this is followed by controlled reduction of the gases formed during combustion. Through this process any carbon contained in the sample is converted to CO_2, hydrogen to H_2O, nitrogen to N_2 and sulphur to SO_2.

These compounds are mixed within a gas-stream and need to be separated to allow a non-specific detector such as a TCD (Thermal Conductivity Detector) to be used for the quantification of the element's concentration. Different techniques are employed for this gas separation, the most important considerations are the robustness of the separation and complexity of the instrument. Most systems that employ a chemical trap or GC column to retain and resolve the analyte gases allow the nitrogen to elute first followed by the carbon. Typically, a sample will contain much more carbon than nitrogen, this can often overwhelm the adsorption media causing the carbon to co-elute with the nitrogen signal causing a false reading for nitrogen. For this reason, it is preferable to have feedback control on the carbon elution to give maximum confidence in the results for nitrogen. This is less critical for hydrogen and sulphur as co-elution with these elements is less common unless liquid samples containing water are being analysed. Sulphur analysis has specific challenges which must be over-come to perform reproducible analysis.

Another way to determine the concentration of the gases associated with each element is to use a selective detector such as an IR detector. If this technique is employed no gas separation is required as a different wavelength detector can be used for each element (and a TCD for nitrogen). This can have a time saving benefit as separation increases analysis time. The downside is the much greater complexity of the instrument and overall higher cost both initially and ongoing.

As mentioned, Sulphur analysis can present more challenges than the other elements due to it being more difficult to combust, the highly corrosive nature of SO_2 and the relatively small amounts of sulphur in most compounds. To aid combustion of sulphur temperatures of above 1100 °C are used along with more expensive oxidation reagents. As SO_2 will readily form H_2SO_4 on contact with water it is essential to prevent any cold spots from forming in the instrument, this requires careful management of the gas flow path.

For all analyte gases it is essential to have good peak shape to give low detection limits and reproducible quantification. Sulphur is particularly challenging as it is present in relatively low abundance, so detection limits need to be very low. It is essential to provide adequate resolution between the analyte gases to guarantee correct analyte identification while allowing enough focusing to give sharp peaks. *Figure 2* shows a sample chromatogram for simultaneous CHNS analysis with a sulphur peak displaying excellent peak shape.

As sulphur is a less abundant element than CHN it is useful to be able to routinely switch an instrument to CHN only mode when sulphur is not of interest to reduce cost and complexity of the analysis.

Alternatives to CHNS analysis exist such as NMR and XRF. However, these techniques all tend to have worse accuracy for the elements CHN along with much greater purchase and operating costs. For this reason, CHNS elemental analysis remains the preferred technique when the organic element content of a sample is required.
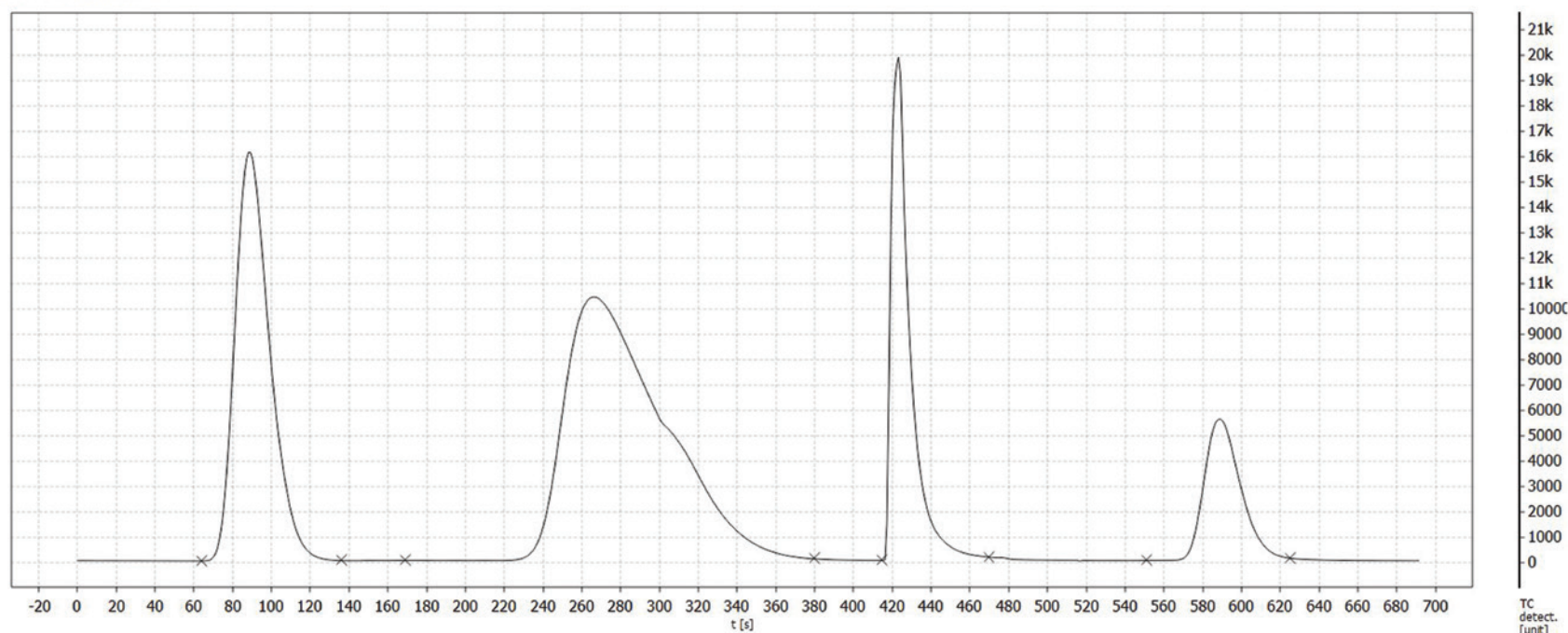
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Figure 2: Sample Chromatogram for simultaneous CHNS analysis. Peak elution order is Nitrogen, Carbon, Hydrogen and Sulphur. The sample is a 5 mg sulphanilamide standard used for calibration. Co-elution's are prevented by waiting for the previous peak to return to baseline before eluting the next peak. This is controlled by selective heating of the trap on which the elements are retained.

Oxygen Analysis

Oxygen can also be analysed by pyrolysis (heating in the absence of oxygen) of the sample which causes the oxygen in the sample to be converted to CO which is again detected using a TCD. The formation of CO occurs according to the Boudouard equilibrium and is more efficient at temperatures over 1250°C. As pyrolytic conditions are required for oxygen analysis it cannot be performed simultaneously with CHNS (which require oxygen for combustion) and so must be performed as a separate sample analysis.

Oxygen content is frequently calculated by subtraction. This involves subtracting the CHNS content and ash residue weight from a sample and assuming the remaining portion is oxygen. This method has been superseded in recent years as it contains accumulated errors and is so significantly less accurate than a direct measurement.

TOC Analysis

TOC analysis also has a vital role within the manufacture of pharmaceutical and fine chemical products. The main two uses are to validate that vessels used in the process are cleaned properly and do not contain contaminants and to confirm any water being used in the process is also free of contaminants. As with CHNS analysis TOC is often referred to as a screening test as knowing the TOC content hints at a samples ability to host microbial growth without identifying which organic carbon species are present in the sample. If a deeper understanding of the source of the TOC contained in a sample is required further techniques must be employed to identify these.

TOC analysis is performed in a similar way to CHNS analysis, however as only carbon is of interest a simplified system is used. As it is necessary to remove inorganic sources of carbon (TIC) from the sample the sample is acidified prior to analysis. For liquid samples acid is added directly to the sample and the sample purged with inert gas to remove the TIC as CO_2, this process is often performed by the instrument autosampler. For solid samples acid is manually added to the dried sample to again remove the TIC as CO_2.

For sample oxidation two methods can be used each of which is suited to certain sample types. Like with CHNS analysis the sample may be combusted to convert all the carbon in the sample to CO_2. Alternatively, the sample can be oxidised using UV light and the addition of a sodium persulfate solution to convert all carbon to CO_2.

The combustion method is better suited to higher TOC content samples or those containing solid particulate. This is because the maximum sample size for the combustion method is smaller than the UV-persulfate method giving higher overall detection limits, typically around 50 ppb. The combustion method can easily oxidise solid matter so can be used on samples containing precipitate and particles as well as purely solid samples.

The UV-persulfate method sometimes can't fully oxidise solid particles so isn't ideally suited to these analysing these samples types routinely. The larger sample size that can be analysed allows extremely low detection limits to be reached, about 2 ppb, making it ideal for clean water analysis and cleaning validation purposes.

With both methods the CO_2 generated from the sample is analysed by a NDIR (non-dispersive IR) detector. This detector is used as it is very sensitive, robust and stable. The choice of oxidation type largely depends on the application being employed and what detection limits are required.

One of the sample types that TOC analysis can struggle with is samples containing high levels of salts. This is because the combustion utilises catalysts to improve the efficiency of the oxidation. These catalysts are readily poisoned by salts, in addition to this the quartz glass tubes in which combustion occurs are readily degraded by salts. To help combat this poisoning and improve catalyst lifetime matrix separation can be used. This separates the sample for the catalyst so only the sample gases contact the catalysts isolating them from the salt residue. The use of sacrificial glass components also extends the lifetime of the combustion tubes. By using these approaches the routine analysis of saltwater samples can be successfully performed.

In the UV-persulfate method chlorides form chlorine gas which is damaging to the instrument. The persulfate may be omitted relying on the UV lamp alone to oxidise the sample. This isn't recommended for routine use so the combustion method is often more suited for routinely analysing high salt containing samples.

TOC analysis is classed as a non-selective method as opposed to selective methods like HPLC which allow compound identification and quantification. The benefit of using a non-selective technique is that no method alterations need to be made between sample types. With HPLC different methods must be employed and validated to identify each potential contaminant. TOC doesn't have any competing techniques within pharmaceutical and chemical manufacturing. Other techniques such as BOD and COD analysis are commonly used within environmental water analysis but due to the time taken for these techniques, they are not employed within manufacturing applications.

Applications

CHNS analysis gives the percentage composition of each element in a sample. This makes it useful either i f it is known what the target elemental composition should be, or if any element must be kept within specific limits or elements need to be within set ratios of each other. Impurities can easily be identified, or if a product is being synthesised it is clear if this has been successful. This makes it suited to a screening test of the final composition of an API or chemical prior to blending or further, more expensive, forms of analysis.

Due to the speed of analysis and ease of sample preparation CHNS analysis is suited to being performed during a manufacturing process to monitor the process. As the technique is not matrix specific no method amendments need to be made if the products being analysed change regularly. This makes it suited to contract manufacturing environments when products vary regularly.

TOC analysis has a very defined role within the pharmaceutical industry and is mandatory in many methods. The eluant from vessels is sampled during cleaning and analysed to check the TOC content is below set thresholds before the vessels can be reused. This is vital to maintaining the high-quality pharmaceutical product we all trust and rely upon.

In addition to this TOC testing is used to check the water being used in the manufacturing process of pharmaceutical and chemical products is of sufficient purity to give high quality products. Any impurities in the water used in the manufacturing may be present in the final product so this is an essential quality check.

Like CHNS, TOC analysis is matrix independent and thus suited to environments where potential contaminants may vary from batch to batch. Selective techniques such as HPLC would need different methods to be used to identify certain contaminants making them cumbersome to use when products change regularly. TOC doesn't need any method changes to be made regardless of the sample origin.