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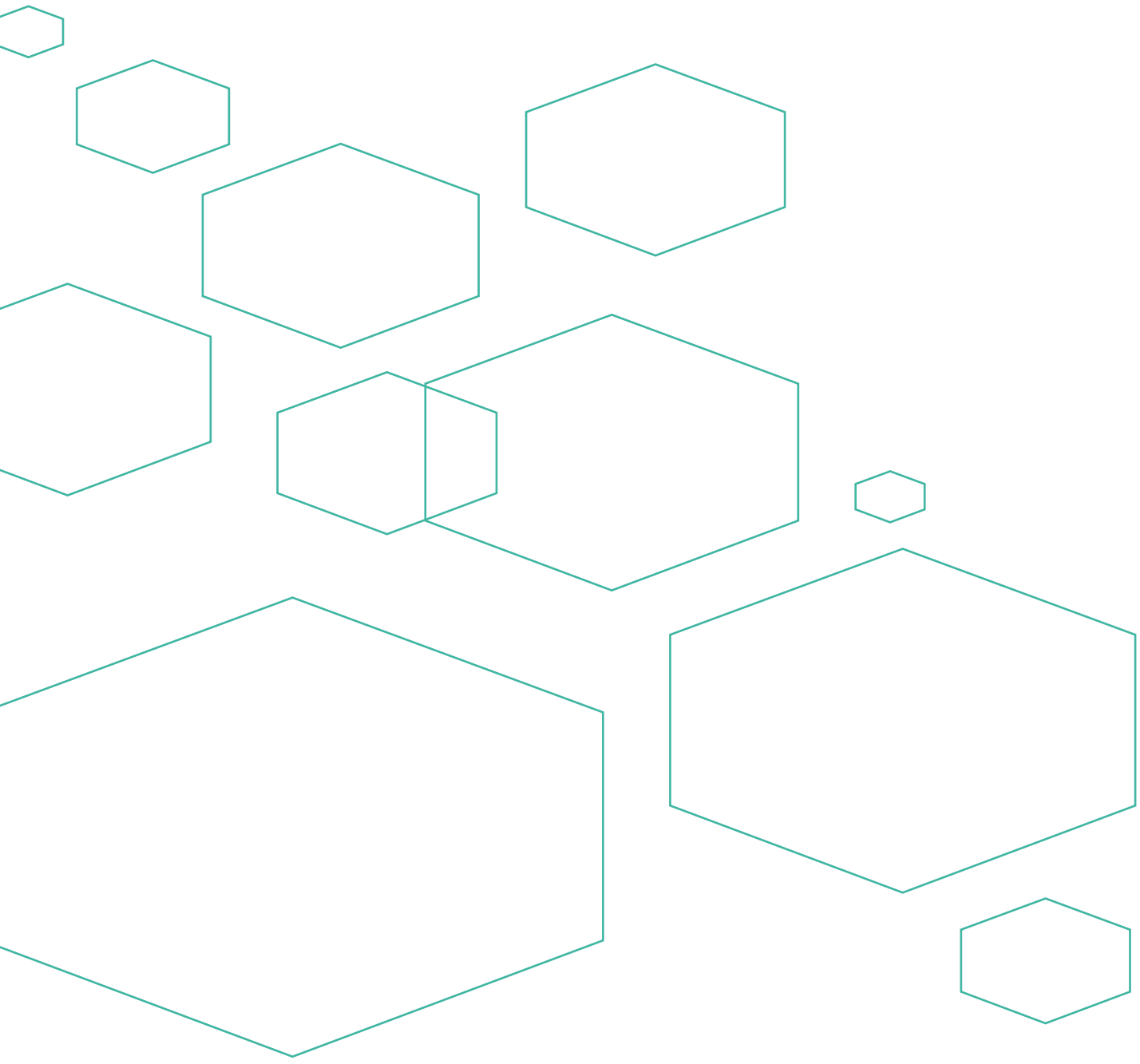
SOLUTIONS



PHARMACEUTICAL

APPLICATIONS

Applications of Raman spectroscopy in pharmaceutical analysis

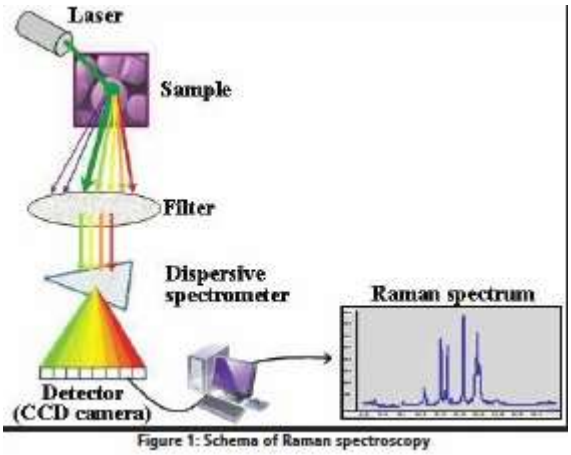
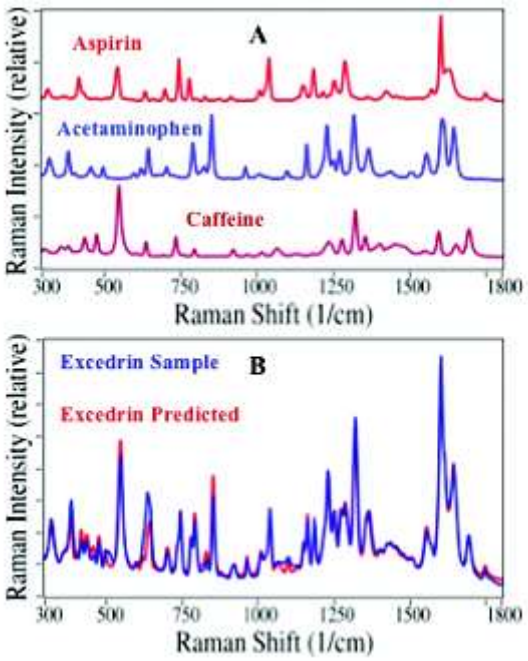


Figure 1: Schema of Raman spectroscopy

Raman spectroscopy is becoming one of the most popular analytical measurement tools for pharmaceutical applications ranging from verification of raw materials to process monitoring of drug production to quality control of products. Similar to an infrared spectrum, a Raman spectrum consists of a wavelength distribution of peaks corresponding to molecular vibrations specific to the sample being analyzed. Chemicals, such as drugs, can be identified by the frequency and quantified by the intensity of the peaks. In practice, a laser is focused into the sample, the inelastic scattered radiation (Raman) is optically collected and directed into a spectrometer, which provides wavelength separation, and a detector converts photon energy to electrical signal intensity. An attractive advantage to this technique is that samples do not have to be extracted or prepared, and the laser can simply be aimed at a sample to perform chemical measurements, which can often be accomplished in a minute or less.

Drug Development

Once a potentially new drug is identified, the method to synthesize the drug is developed. Raman spectroscopy is ideal for monitoring reactant, intermediate and product concentrations, determining pathways, kinetics, mechanisms, end-points, and yields for a variety of reaction types, such as Diels-Alder, Fischer esterification, Grignard, and hydrogenation.



Drug Quality

Quality-by-design in drug manufacturing begins with verification of the purity of raw materials and ends with the quality of the product. The latter requires assurance that the product, as a gel cap, tablet, etc., contains the correct amount of active, its polymorph (if appropriate), excipient and other additives (e.g. dyes). Raman spectroscopy can be used to monitor mixing in blenders, as well as to inspect individual products before shipment.

Product Authentication

Counterfeit drugs have become a significant problem during the past decade. The availability of such drugs has been made possible largely through purchases from fraudulent websites. The World Health Organization defines a counterfeit medicine as “one which is deliberately and fraudulently mislabeled with respect to identity and source”. Counterfeit drugs range from those employing incorrect ingredients, no actives (e.g. sugar pills), or insufficient actives. The latter are the most challenging since a simple compositional analysis may pass the sample as the genuine product.

Product Shelf Life

Drug formulations include additives and coatings to minimize degradation of the active ingredient due to heat, moisture and radiation, and thereby maximize product shelf-life. The shelf-life, or more specifically, the expiration date, is based on the time that a drug maintains greater than 90% potency. Most drugs fall into two categories, those that maintain potency for at least one year, and those that maintain potency for greater than two years from the time of manufacture. While most drug degradation products are benign and simply ineffective, acetaminophen, one of the most popular and effective drugs for pain relief, degrades into a poison, p-aminophenol, which can cause liver damage.

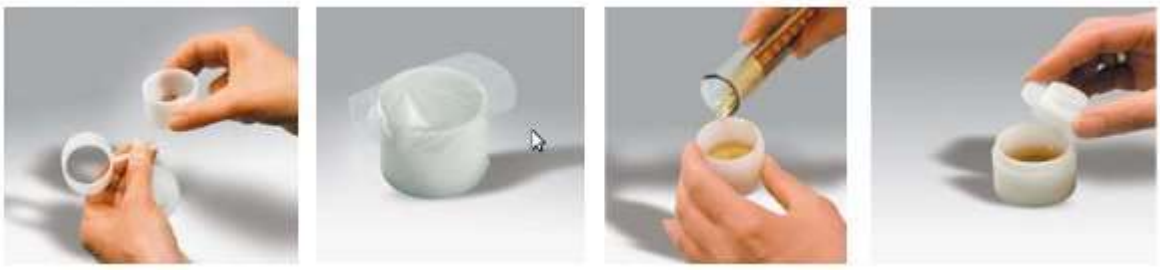
The Use of EDXRF for Pharmaceutical Material Elemental Analysis

The EDXRF technique is a robust, precise, sensitive and accurate method with the potential to analyze inorganic impurities in many types of pharmaceutical materials. The analysis of the elements Al, Sb, As, Cd, Cr, Co, Cu, In, Ir, Fe, Hg, Pb, Mg, Mn, Hg, Mo, Ni, Os, Pd, Pt, Rh, Ru, Ru, Se, Sr, Tl, Sn, W and Zn are all feasible by EDXRF. The EDXRF technique is capable of generating reporting limits that comply with current and proposed pharmacopeia limits for these metals.

One of the most common product safety related analytical tests is the quantification of inorganic impurities within a pharmaceutical product. This includes toxic heavy metals, such as As, Cd, Hg, and Pb. Other metals, such as Fe, Cr, Ni and Zn, are also of interest due to health risks. In addition, many Active Pharmaceutical Ingredients (APIs) may contain residual metal catalysts, such as Ru, Pt, and Pd. Since there are many potential sources of contamination, it may be of interest to measure raw materials, intermediates as well as final products. X-ray Fluorescence (XRF) technique is capable of performing elemental analysis of all of these pharmaceutical (liquid, powder and solid) materials with high sensitivity, precision and accuracy. Simple sample preparation, non-destructive analysis, a wide dynamic range and good to excellent detection limits across large parts of the periodic table are some of the advantages of this method.

Liquid samples

Liquid samples are poured in special sample cups, equipped with a supporting film. This film should be transparent to X-rays, chemically inert and free of contamination. Typical films are made from polypropylene and have thicknesses varying from 2.5 micrometers to 6 micrometers. The thinner films have higher transparency to X-rays (leading to higher intensities); the thicker films are more robust. These cells can also be used to analyze loose powders. Organic matrices (such as many pharmaceutical materials) exhibit relatively low X-ray absorption. To ensure that the X-ray intensities are determined only by the composition of the specimen and independent from the absolute mass, it is recommended to fill these cells to at least 1.5 cm in depth.



Powder and solid samples

Loose powder samples may be placed directly into a disposable sample cup. Coarse powders must be ground to a fine particle size. Powders can also be pressed into a solid pellet. This generally requires the addition of some binder. The resulting pellets can be analyzed without supporting film, and can also be analyzed in vacuum. The amount of binder added rarely exceeds 10% of sample mass, so the effect of the dilution is minimal. Advantages of pressing a sample are increased repeatability due to constant volume, enhanced light element reproducibility because air voids are removed which can absorb X-rays and the possibility to directly measure a pressed pellet without a supporting film resulting in greater sensitivity. Some materials such as lactose or cellulose do not require the addition of a binder, while other powders may require the addition of a suitable binder material, such as CEREOX. All non-homogenous solid samples such as coated tablets should be ground by means of mortar and pestle or a grinding device, such as a mill.

The simplified sample preparation technique which include direct liquid analysis without the concern of salt concentrations or acidity levels, direct loose powder or press pellet analysis, presents a great advantage over other analytical techniques. This represents a significant simplification in the analysis of pharmaceutical materials.

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