Application Note
Pharmaceutical Testing and Research

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Pharmaceutical Packaging Materials Quality Control and USP Chapter <661.1> Compliance

Identification of packaging materials using the Agilent Cary 630 FTIR for quality control and detection of counterfeit pharmaceuticals

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Introduction

The composition and quality of packaging materials can have a critical impact on the performance, function, and production costs of pharmaceutical medications or drugs. Improper packaging can cause the active pharmaceutical ingredients (API) in medications to degrade faster and have shorter shelf lives. Detecting problems, impurities, or incorrect polymer compositions early in the packaging process or packaging material supply can prevent the costly recall of defective end-products from the consumer.

Mid-infrared FTIR spectroscopy has a long history of identifying the chemical composition of polymers, fillers, and additives used in the pharmaceutical, coatings, and chemical industries. The mid-infrared spectrum is often referred to as the chemical fingerprint of a material. This is because of the rich detail provided by the technique and its specificity in confirming a known composition. FTIR spectroscopy is a rapid and easily implemented technique that is widely used for the screening of polymers and other packaging materials.
FTIR spectroscopy can be used for:

- The qualification and identification of raw materials to be used for pharmaceutical packaging in accordance with regulations
- Quality assurance (QA) of materials during the manufacture of packaging
- The identification of suspected counterfeit pharmaceutical products by comparing the differences in the plastic packaging composition between a genuine product and a product of uncertain origin.

This application note focuses on the use of the Agilent Cary 630 FTIR spectrometer for the analysis of polymers used in pharmaceutical packaging. The application note provides information on:

- The differences in the FTIR spectra of name brand and generic packaging in over-the-counter cold and flu medications. Discrepancies observed from the spectra of polymers used in blister packs show how FTIR spectroscopy can help explain any packaging quality control (QC) issues.
- The detection of pharmaceutical counterfeits through the analysis of packaging materials. The access to high quality counterfeit drugs and their packaging is highly restricted. Therefore, the materials analyzed in this work are representative of the compositional differences that have been observed in the packaging of counterfeit and genuine products.
- The application of the Cary 630 FTIR to USP pharmaceutical packaging regulations outlined in chapter <661.1> Plastic Materials of Construction (*1*).

USP chapter <661.1>

USP chapter <661.1> Plastic Materials of Construction specifies test methods to determine if a plastic material is an appropriate candidate for the construction of a packaging system for pharmaceutical products (*1*, *2*).

The chapter requires identification of the plastic materials that are used to compose the drug product packaging systems using infrared spectroscopy (IR). The IR spectrometer must be able to measure in "transmission mode or be equipped with an internal reflection accessory" (*1*).

USP general chapter <854> outlines the instrument qualification requirements for mid-infrared spectrometers and describes attenuated total reflectance (ATR) spectroscopy as an internal reflection technique (*3*). Further, USP general chapter <197> accepts FTIR as suitable identification methodology and names it as the "most widely used methodology for chemical identification in compendial monographs" (*4*).

The Cary 630 FTIR spectrometer meets the performance specifications required by USP. It can be used to identify plastic materials of construction used in drug product packaging systems in accordance with USP chapter <661.1> (or USP chapter <661> if early adoption of chapter <661.1> is not implemented). USP chapter <661.1> becomes official on December 1, 2025. However, USP general chapter <659> permits the early adoption of chapter <661.1>. The requirements specified in chapter <661> apply until <661.1> is adopted (*5, 6*).

Instrumentation

An Agilent Cary 630 FTIR with KBr optics and equipped with a diamond ATR module was used in this work[a]. Agilent MicroLab FTIR software was used to collect the data and automatically compare the sample spectra with the spectra of standard polymers in the spectral library. The MicroLab software is easy-to-use software that guides users step by step through the analytical workflow using instructive images and an intuitive software design (Figure 1).

Figure 1. The MicroLab software for FTIR analysis automatically recognizes the attached sampling module and applies the correct parameters. The software navigates the user, step by step, through the analytical workflow using instructive pictures. Color-coded results, directly reported after data acquisition, make data review quick and intuitive.

MicroLab Pharma is an optional software package for the Cary 630 FTIR. The software supports users in regulated environments, providing tools to help achieve compliance with electronic record regulations such as 21 CFR Part 11 and EU Annex 11.

[a]*The Agilent Cary 630 FTIR with ZnSe optics also covers the spectral range of 3800-650 cm^{-1} specified in chapter <661.1>. It can also be used for the identification of plastic material of construction in accordance with the chapter.*

Materials and methods

Over-the-counter cold and flu liquid cap blister packaged medications were bought in a pharmacy. A total of five generic/store brand medications and four name brand medications were bought. The blister pack samples were measured on the inside and outside of the clear polymer blister (Figure 2A) and on the unprinted section of the outer foil (lidding), (Figure 2B).

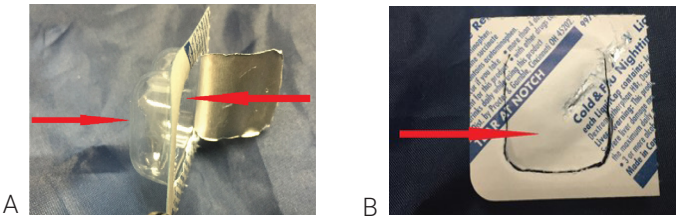

Figure 2. The blister pack areas of cold and flu liquid cap medications that were measured by FTIR: (A) the inside and outside of the clear polymer blister and (B) the unprinted region of the outer foil (lidding).

FTIR spectra of these samples were collected using the Cary 630 FTIR diamond ATR module with the following measurement parameters:

- Spectral range of 4000 to 650 cm^{-1}
- Each spectrum was the co-addition of 64 scans
- 4 cm^{-1} resolution

Results and discussion

Characterization of packaging materials

A comparison of the packaging used in a generic brand and name brand over-the-counter medicine was undertaken. The clear plastic material of a blister pack is often comprised of a polymer bilayer (Figure 2A). The lid or foil (Figure 2B) is glued to the plastic blister using adhesives to seal the product. The complete blister packaging provides a dry stable environment for the medicine. The composition of the bilayer polymers used in the blister has a significant impact on the water vapor permeability of the blister pack. The degree of water vapor permeability is measured as the water-vapor transmission rate (WVTR).

Identification of polyvinyl chloride (PCV)

Rigid polyvinyl chloride (PCV) is an industry standard blister pack material that has a low WVTR and has excellent thermoform characteristics. It was found in at least one layer in every blister pack tested. The most basic and lowest cost blister pack construction is a PVC/PVC bilayer, which was observed in one of the five generic cold medicines tested. As explained later in the study, polychlorotrifluoroethylene (PCTFE) was used as the outer blister layer for all the brand name products with PVC as the inner layer.

Figure 3 shows a comparison of the outer blister layer of a generic product (red) overlaid with the inner layer of a brand name blister product (purple). The blister polymer is PVC with ~2–3 % of a copolymer such a polyacrylate or polyvinylacetate as indicated by the presence of a weak ester carbonyl band at 1736 cm^{-1}. The concentration of this copolymer is variable from manufacturer to manufacturer, as shown in Figure 3. Therefore, the band at 1736 cm^{-1} could be used as a QC check or as confirmation of a genuine packaging material.

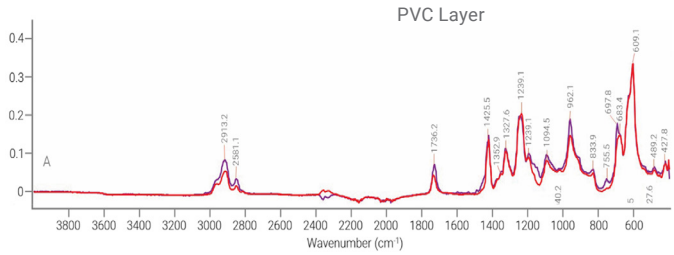

Figure 3. FTIR spectra of clear blister polymers from over-the-counter cold medicines collected on a Cary 630 FTIR with diamond ATR module. The outer blister layer of a generic product (red) is overlaid with the inner blister layer of a brand name product (purple). The band at 1736 cm^{-1} indicates the presence of ~2–3 % of a copolymer such a polyacrylate or polyvinylacetate.

Styrene-butadiene was identified as the copolymer in some of the PVC layers that were tested, with some variability in concentration between products (results not shown). Styrene-butadiene copolymers are often referred to as styrene-butadiene rubber (SBR) or styrene-butadiene-styrene (SBS). SBR is likely added to the PVC formulation to improve the thermoforming or physical performance characteristics of the blister pack.

In Figure 4 the spectrum of the interior PVC (red) of a different branded product is overlaid with the spectrum from the outside PVC (blue) of a generic product. Additional SBR absorbance bands in the red spectrum are observed at 3026 cm^{-1}, 2915 cm^{-1}, 2850.5 cm^{-1}, 1639 cm^{-1}, 1601 cm^{-1}, 1492 cm^{-1}, 964 cm^{-1}, 911 cm^{-1}, 755.5 cm^{-1}, and 698 cm^{-1}. The intensity of these absorbance bands is directly proportional to the concentration of SBR in the PVC. The concentration of SBR can be measured with high precision using the Cary 630 FTIR and MicroLab FTIR software.

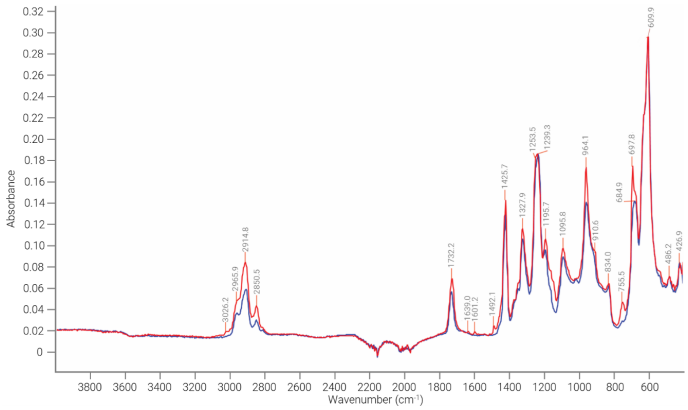

Figure 4. The FTIR spectral overlay of the PVC outer blister layer of a generic product (blue) overlaid with the inner blister layer of a name brand product (red), indicating PVC with additional SBR copolymer in the name brand material.

A MicroLab method that automatically calculates and reports the SBR content provides a quick and easy workflow for the routine analysis of SBR in copolymers. The software allows green, yellow, or red thresholds to be set to indicate the degree of difference of an unknown material to a known material. For a QA/QC or counterfeit analysis, warning levels can be set as "good," "marginal", or "critical" (Figure 5).

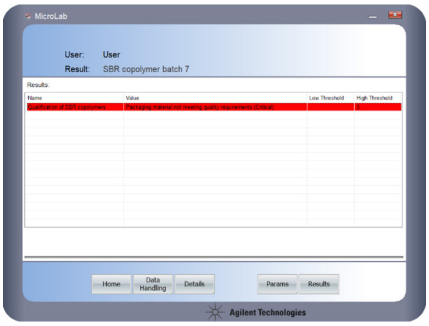

Figure 5. MicroLab software automatically calculates the SBR content of packaging material samples. Color-coded, actionable results are reported directly after data acquisition in line with the threshold settings of the method.

The ability of FTIR to detect a small amount of SBR copolymer in the blister polymer can be used as a counterfeit identification measure. For simple verification of packaging authenticity, compounds with specific infrared signatures could be added to the primary or secondary packaging of pharmaceutical products.

Identification of polyvinylidene chloride (PVDC)

Typically, PVC is used as the outside layer of generic blister packs and polyvinylidene chloride (PVDC) as the inside layer, facing the product and lidding. The layer of PVDC lowers the WVTR by a factor of 5 to 10 times (*7*), but it makes the blister packs more expensive to produce. Figure 6 shows the FTIR spectrum of a PVDC composition layer of one of the generic samples collected on a Cary 630 diamond ATR.

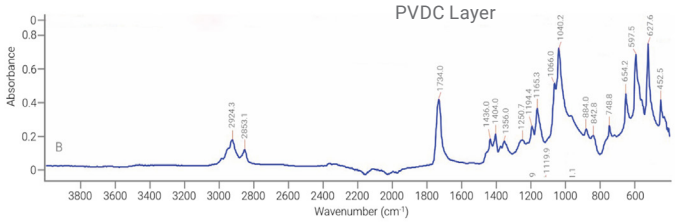

Figure 6. The FTIR spectrum of the inside facing layer of a clear generic blister pack identified as PVDC.

Contrary to expectations, one of the other generic blister packs was observed to have the PVDC coating on the outside layer, with PVC as the inside product facing layer. Differences in the blister pack composition could easily be overlooked in a counterfeit repackaging operation, so FTIR data could be used as evidence that a product is not genuine.

Identification of polychlorotrifluoroethylene

A third type of blister pack composition was used for all the branded cold medicines. As shown in Figure 7 (green spectrum), polychlorotrifluoroethylene (PCTFE) was used as the outer layer and PVC as the inner layer. PCTFE can lower the WVTR by a factor of 15 compared to PVC but is four to five times more expensive than a PVC/PVDC material with a comparable WVTR (*8*).

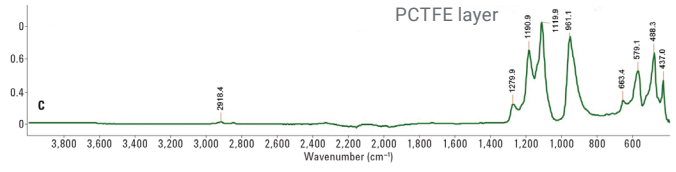

Figure 7. The FTIR spectrum of a clear blister identified as PCTFE.

Application of FTIR for identification of counterfeit packaging

One of the most important benefits of FTIR analysis is its ability to quickly measure multiple parts of a single sample. This capability allows for extra QA during manufacturing or provides evidence of tampering in counterfeit applications. An example of the identification of counterfeit packaging by FTIR is shown in Figure 8, following the analysis of the paper backing of blister packs. The backing of most blister packs, name brand or generic, use microcrystalline cellulose paper glued to an aluminum foil film (Figure 8 red). The IR analysis of one name brand blister pack (Figure 8 blue) indicated the use of a polymer backing material containing high concentrations of fillers.

The IR spectrum of the polymer backing material identified a styrene-acrylate copolymer (3060 cm^{-1}, 3026 cm^{-1}, 1729 cm^{-1}, etc.) with high levels of calcium carbonate (1420 cm^{-1}, 874 cm^{-1}) and kaolin clay (3690 cm^{-1}, 1026 cm^{-1}, 910 cm^{-1}, etc.). The detection of the relatively low levels of a styrene-acrylate copolymer is another indication of how effective the addition of IR-sensitive polymers can be to identify counterfeit blister packs.

The distinctive fingerprint-like FTIR spectra can quickly identify if packaging substitution has occurred. The Cary 630 FTIR with ATR sampling module allows both primary and secondary packaging to be measured and compared to known reference standards (*5*). Primary packaging is in direct contact with the product e.g. blister packs while secondary packaging is direct contact with the primary packaging component e.g. cold medicine box.

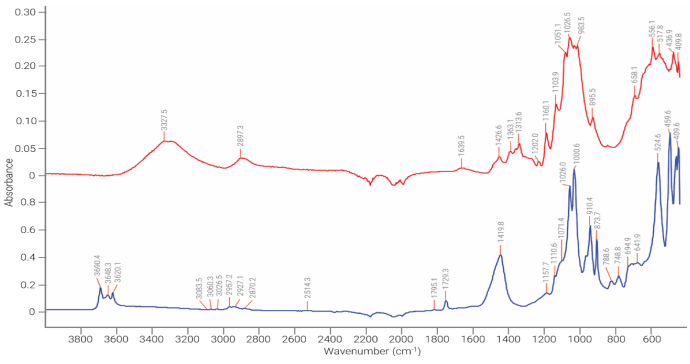

Figure 8. Overlaid FTIR spectra of the paper backing from cold medicine blister packs collected using an Agilent Cary 630 FTIR with diamond ATR module. Red: microcrystalline cellulose. Blue: styrene-acrylate copolymer. Most blister packs use the microcrystalline cellulose backing (red), however, one name brand product used the styrene-acrylate copolymer material (blue), which contains very strong bands for calcium carbonate and kaolin clay.

Agilent Cary 630 FTIR and USP chapter <661.1> compliance

USP chapter <661.1> recognizes that "the use of well-characterized materials to construct a packaging system is a primary means of ensuring that the packaging system is suited for its intended use." To consider plastic materials for construction, they need to be characterized in accordance with chapter <661.1>. The following characteristics must be established:

- Identity of polymers
- Biological reactivity
- General physicochemical properties
- Composition
- Extractable elements

Chapter <661.1> describes the identification of the following polymers by infrared spectroscopy:

- Cyclic olefins
- Polyamide 6
- Polycarbonate
- Polyethylene
- Polyethylene terephthalate
- Polyethylene terephthalate G
- Poly(ethylene-vinyl acetate)
- Polypropylene
- Polyvinyl chloride
- Polyvinyl chloride, plasticized

USP sells reference standards of these polymers that can be measured by FTIR. In the scope of chapter <661.1>, a sample is identified if the absorption spectrum of the sample is substantially equivalent to that of a USP reference standard material. Materials that are not part of the list are termed "unaddressed materials." Unaddressed materials must be characterized and meet acceptance criteria comparable to those for materials listed in chapter <661.1>.

USP chapter <197> allows the comparison of the spectrum of an unknown sample to a spectrum of the USP reference standard measured at the same time or to a stored spectrum of the USP reference standard. If a stored USP reference standard spectrum is used for comparison, the spectrum collected for the unknown should be obtained using equivalent instrumentation and operating conditions to those used to collect the spectrum of the reference material.

When using the Cary 630 FTIR, polymer identification is done by adding the FTIR ATR spectrum of the USP qualified standard polymer to a spectral library within the MicroLab software. The IR spectrum of the unknown polymer is then measured and searched against the USP chapter <661.1> library. The MicroLab software automatically overlays the IR spectrum of the unknown with the USP chapter <661.1> library spectrum, as shown in Figure 9.

The quality of the match is quantified automatically using an algorithm that provides a hit quality index between 0 to 1. A perfect match would be 1.000. However, identical polymers typically report a hit quality index >0.98.

The PVC sample measured in Figure 9 is from the interior blister polymer layer from a name brand cold medicine. The near perfect match index of 0.996 indicates a PVC and SBR copolymer. Small differences between the test sample and the reference standard, such as additives or copolymer formulations, will affect the hit quality index result. For example, a PVC blister pack polymer without SBR is shown as the second hit on the list, with a significantly lower hit quality index of 0.964.

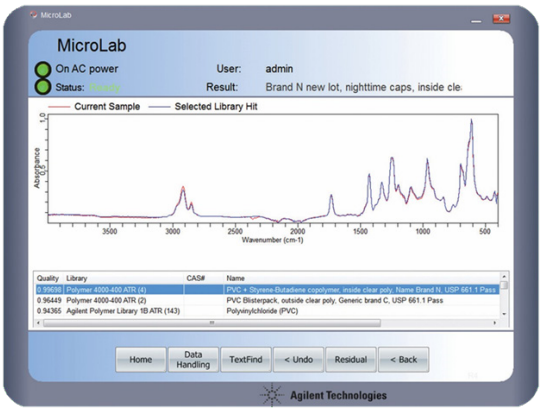

Figure 9. The FTIR ATR library search result from the Cary 630 FTIR MicroLab software. The unknown sample (red spectrum) is a blister polymer. A search was undertaken against a library of known USP chapter <661.1> polymers created from name brand and generic blisters. The top hit is a near-perfect match (quality 0.99698) to the library material, PVC and SBR copolymer (blue spectrum).

Conclusion

The Agilent Cary 630 FTIR equipped with a diamond ATR module can quickly and easily identify differences between blister pack materials from name brand and generic cold medicine products.

In this study, we observed that primary packaging used in name brand medicines comprises a more expensive blister polymer bilayer composition compared to the standard PCV used in generic blisters. Even similar PVC materials that were used in different name brand blisters incorporate different amounts of styrene-butadiene copolymer, which can be detected and measured precisely with the Cary 630 FTIR.

The polymer identification capability of the Cary 630 FTIR using library search methods in the MicroLab software was demonstrated for polymer screening as required by USP chapter <661.1>. The software automatically compared the FTIR spectrum of a polymer test sample to spectra contained in a library of the reference materials described in USP <661.1>, providing a hit-quality index value. The hit quality index value is an objective, quantifiable measure of how well the sample matches the USP polymer reference standard.

The spectral differences observed in this work are often subtle, but significant. They can identify unintentional differences in the polymer used in packaging, which can result in product quality problems and costly product recalls. They may also be indicative of counterfeit pharmaceuticals. If the packaging material is not consistent with the manufacturer's standard, then the drug may not be either.

The Cary 630 FTIR demonstrates the capability and flexibility to identify counterfeit pharmaceutical, QC, and USP chapter <661.1> compliance issues.

References

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2. USP 43-NF 38 General Chapter <1661>, Evaluation of Plastic Packaging Systems for Pharmaceutical Use and their Material of Construction
3. USP 34-NF 38 General Chapter <854>, Mid-Infrared Spectroscopy
4. USP 43-NF 38 General Chapter <197>, Spectrophotometric Identification Test
5. USP 43-NF 38 General Chapter <659>, Packaging and Storage Requirements
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