

Infrared Spectroscopy

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Analysis of Pharmaceutical Packaging Materials – USP 661.1

Introduction

Packaging is defined as a means of providing protection, identification and containment of a product during storage and transport until it is consumed. As such, materials used in the packaging of pharmaceuticals must have suitable

physical, chemical and biological properties to ensure the integrity of the product.¹ As of 2015, the pharmaceutical packaging industry has an estimated value of \$68.7 billion.² The United States Pharmacopoeia (USP) chapter 661.1 pertains to the characterization of plastic materials used in the packaging of pharmaceuticals. This specifies various biological, chemical and physicochemical tests which must be carried out on plastic materials which will come into direct contact with therapeutic products. A key part of this specification is the determination of the infrared spectrum between 3800 and 650 cm^{-1} .

There are currently six different plastic materials approved for use in pharmaceutical packaging due to their physical, chemical and biological properties. The chemical structures of these materials are shown in Figure 1.

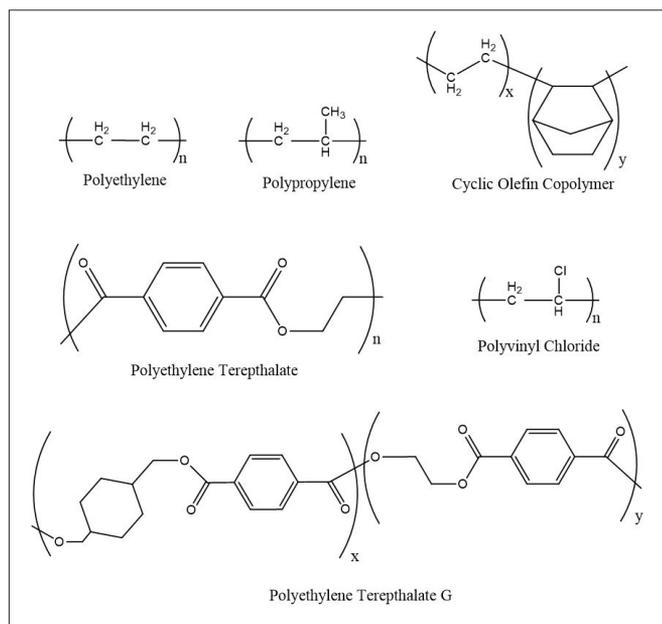


Figure 1. Chemical structures of the materials approved for the packaging of pharmaceuticals.

Of these six materials, the most commonly used in drug blister packs is polyvinyl chloride (PVC).³ In addition, several plastic additives are also approved for each material by USP 661.1. Common examples include Dioctylphthalate (DOP), phenolic and nonphenolic antioxidants, amides and stearates. These additives function as plasticizers and stabilizers. In the case of PVC, known as rigid PVC in the absence of plasticizers, additives or other layers may be included to improve the high water vapour transmission (WVTR) rate.

USP chapter 661.1 allows for either transmission or attenuated total reflectance (ATR) measurements to be used in the collection of the infrared spectrum of the unknown material. In this application, ATR is used to collect spectra of packaging materials as this requires far less sample preparation than transmission measurements, thus offering a more efficient method of sample analysis. ATR also allows the analyst to individually measure the materials used to produce the inside and the outside of pharmaceutical blister packaging in the case of multilayer films.

Experimental

Spectra of both the inside and outside layers of six different blister packs were collected using the PerkinElmer Spectrum Two™ FT-IR spectrometer with Universal Attenuated Total Reflectance (UATR) accessory (Figure 2).



Figure 2. PerkinElmer Spectrum Two FT-IR with UATR accessory.

For this application, the experimental parameters shown in Table 1 were used.

Table 1. Experimental parameters used in the measurement of spectra of packaging materials.

Parameter	Value
Wavenumber Range	4000 – 450 cm ⁻¹
Number of Scans	4
Spectral Resolution	4 cm ⁻¹
Atmospheric Correction	Yes

In order to determine the legitimacy of the packaging, spectra were collected and searched against a library containing spectra of known USP certified polymer samples.

Results and Discussion

An interesting aspect of this USP documentation is that it allows for variation between packaging spectra and the reference spectrum so long as it can be explained by natural compositional and/or physical variations between polymers of the class. This is known as substantial (rather than exact) equivalence and is particularly important in the case of PVC as it can contain a variety of plasticizers and other additives to give it more favourable properties. An example of this is shown in Figure 3.

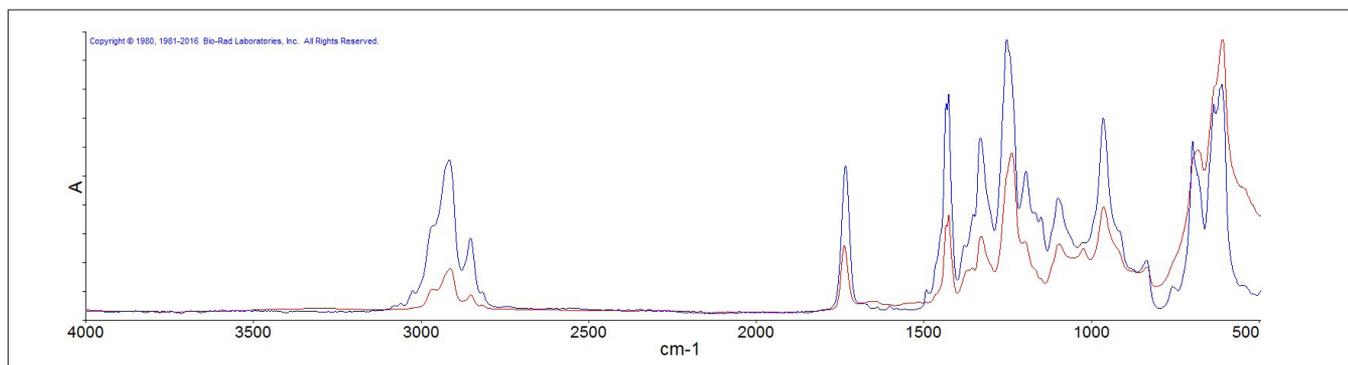


Figure 3. Overlaid spectra from inside layer of branded blister packaging (red) and a reference spectrum (blue).

Despite the obvious variation between the two spectra, this can be explained by natural compositional and/or physical variations. Firstly, all peaks present in the sample spectrum are also present in the reference spectrum at a higher absorbance. A particular point of interest is the sharp peak at 1734 cm^{-1} . This corresponds to a C=O stretch in a carbonyl which will likely arise from the presence of di(2-ethylhexyl)phthalate (commonly referred to as dioctylphthalate or DOP) as a plasticizer. USP chapter 661.1 allows for any quantity of DOP up to 20 mg/g (2%). This explains the variation in absorbance at 1734 cm^{-1} . Other materials are also permitted in PVC used in pharmaceutical packaging. These include N'N''-diacylethylenediamines, epoxidized soya oil, epoxidized linseed oil and vinyl chloride. Vinyl chloride is not an intended additive although the United States Pharmacopeia requires its level is monitored as it may be present as a residual monomer.

An example spectrum of the inside of a generic blister pack is shown overlaid with a reference spectrum in Figure 4.

Unlike the branded packaging, the IR spectrum of the generic packaging contains peaks which are not present at all in the reference spectrum. This may be due to use of different plasticizers or possibly co-polymers of PVC.

Materials consisting of several layers are also used to package pharmaceuticals. Regulations set out in USP 661.1 only refer to to packaging which is in direct contact with the drug. An example of this was found in the packaging of a branded dispersible aspirin product. The inside layer, which was in contact with the drug, was determined to be USP compliant PVC. However, the packaging consisted of two other layers, polyamide on the outside and aluminum foil as the middle layer. Overlaid spectra of the outer layer of the packaging and the best hit from the search library are shown in Figure 5.

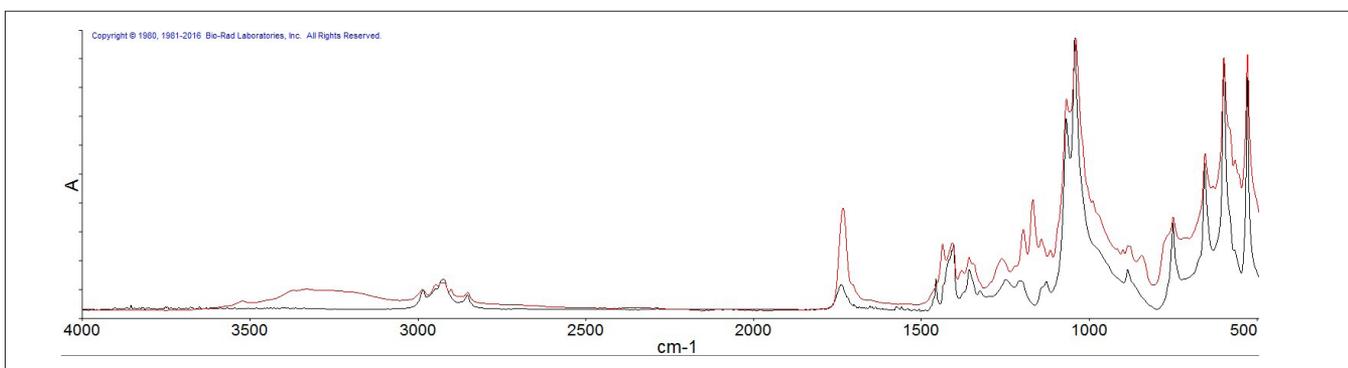


Figure 4. IR spectra of generic packaging (red) and a reference, USP certified PVC material (black).

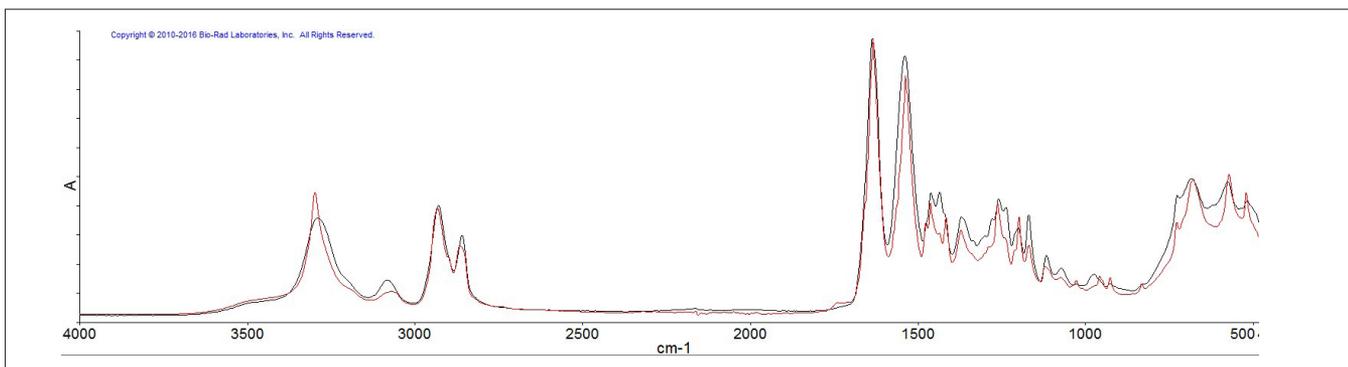


Figure 5. IR spectrum of outside layer of multilayer packaging (red) overlaid with best hit (Nylon-6, black).

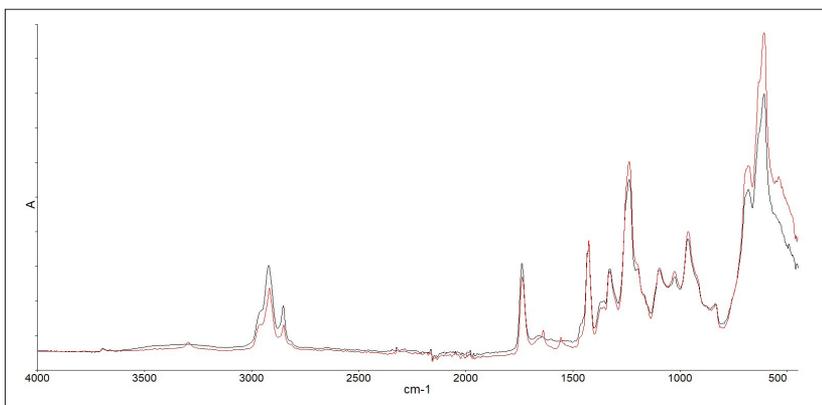


Figure 6. Overlaid spectra of the inside of packaging measured as received (black) and after heat pressing into a thin film (red).

USP Chapter 661.1 specifies that samples may either be measured as received, or heat pressed into thin films. To determine which method offered better results, a piece of packaging was measured, as received, then pressed into a thin film and measured again. The overlaid spectra from this experiment are shown in Figure 6.

An interesting aspect of the thin film spectrum is the two peaks present between 1500-1700 cm^{-1} . These are not present in the spectrum of the untreated material and may arise from material formed as a result of the high temperatures used to press the thin films.

Conclusion

The PerkinElmer Spectrum Two FT-IR spectrometer with UATR accessory provides a fast and robust method for determination of pharmaceutical packaging material. Furthermore, when used in conjunction with Spectrum 10™ Enhanced Security (ES), packaging can be easily analyzed while fulfilling the requirements of 21 CFR part 11 compliance.

References

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2. <https://www.alliedmarketresearch.com/pharmaceutical-packaging-market> (Accessed 11/06/19)
3. P. D. Bairagi, A. B. Darekar, S. B. Gondker, R. B. Saudagar, World Journal of Pharmacy and Pharmaceutical Sciences, 2018, 7, 482-510