Variability in Content of Hydrocortisone Sodium Succinate

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RAPID COMMUNICATION

Abstract

SOLU-CORTEF® Sterile Powder is a type of anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as its active ingredient. It can be administered intravenously or intramuscularly, and comes in several packages including 100 mg plain vials without diluent. The diluent, which is part of the ACT-O-VIAL system, contains only Water for Injection and no preservatives. The pH of each formula is adjusted with sodium hydroxide to ensure it falls within the specified range of 7 to 8 after reconstitution.

Intralot variability was detected in lot GA6092. Measuring in the PC subspace using just PCs 4, 5 and 6, vial 12 plots 4.2 BEST SDs from the center of the cluster, and vial 7 is 3.7 SDs from the center. Vial 18 appears 3.1 SDS from the center of the cluster (3/18, 17%). Interlot variability was also found in the spectral library (lots GA6092, GK7048, GM6839, GR8925, FL8062, FN6860, FR1914, and FR5098) containing the spectra of 126 hydrocortisone sodium succinate vials.

Introduction

The University of Kentucky's (UK) Drug Quality Study was established in August of 2019 to engage in consumer-level quality assurance screening for drugs used within UK HealthCare's pharmacies (Isaacs, 2023a). DQS currently screens medications using Fourier transform near-infrared spectrometry (FTNIR) and Raman spectrometry for potential quality defects indicated by variability in absorbance peak intensities and locations. Through years of continuous monitoring, DQS has assembled a spectral library containing medications typically used in a health system setting. Statistical analyses using DQS' spectral library are performed to identify potential intra-lot and inter-lot variability in medications under review. Using Medwatch and publications in the scientific literature, DQS reports its findings in an effort to hold manufacturers accountable for GMP requirements and to improve patient outcomes by providing information on quality to augment the information on price that is already available. The increasing transparency is designed to improve the pharmaceutical supply chain.

Drug Product

SOLU-CORTEF® Sterile Powder is a type of anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as its active ingredient. It can be administered intravenously or intramuscularly, and comes in several packages including 100 mg plain vials without diluent. The diluent, which is part of the ACT-O-VIAL system, contains only Water for Injection and no preservatives. The pH of each formula is adjusted with sodium hydroxide to ensure it falls within the specified range of 7 to 8 after reconstitution.

Hydrocortisone sodium succinate has the same metabolic and anti-inflammatory effects as hydrocortisone, and is equally biologically active when given parenterally at equimolar quantities. Its highly water-soluble nature makes it useful for quickly administering high doses of hydrocortisone through intravenous injection with small volumes of diluent. Effects of the drug are typically evident within an hour of administration and last for a period of time. The body typically eliminates the administered dose within 12 hours.

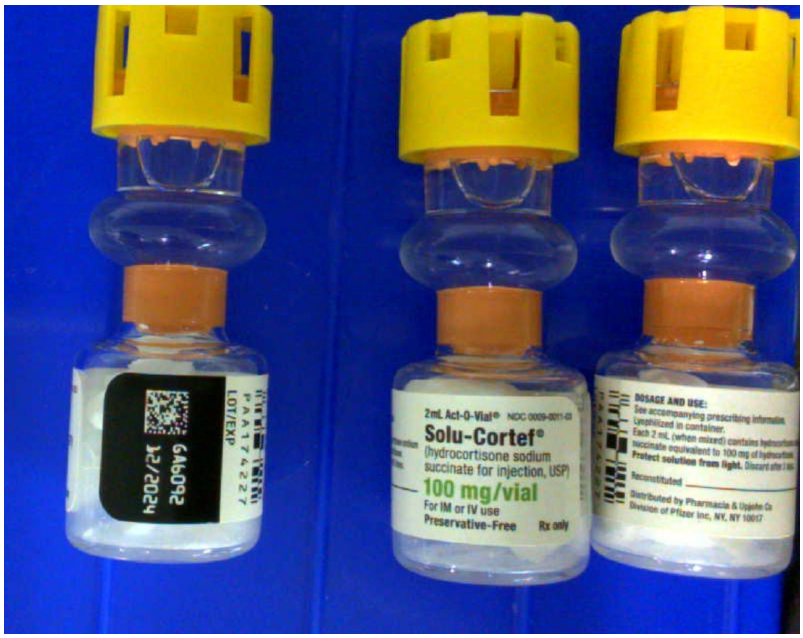

Figure 1. Vials of hydrocortisone sodium succinate from lot GA6092. The drug appears as a white powder.

Figure 1 is a photo of the hydrocortisone sodium succinate drug product. The drug appears as a white powder.

The lot initially under examination was lot GA6092. The lot numbers making up the spectral library were GA6092, GK7048, GM6839, GR8925, FL8062, FN6860, FR1914, and FR5098.

Background

One area of current research involving hydrocortisone sodium succinate is in treating sepsis and septic shock. Sepsis is a life-threatening condition that can lead to long-term cognitive impairment, psychological problems, and functional decline. Sepsis can also lead to septic shock, or hemodynamic instability secondary to infection. There are conflicting results on the utility and outcomes of glucocorticoid use in septic shock. A 2018 meta-analysis found no short-term mortality benefit with the addition of glucocorticoids in septic shock, while the 2021 “Surviving Sepsis” Guidelines make a weak recommendation for the addition of glucocorticoids in patients requiring vasopressor therapy (Zhou, 2018)(Evans, 2021). Adding hydrocortisone sodium succinate as an adjunct pharmacotherapy for patients in septic shock requiring high doses of vasopressor or multiple vasopressors is common in many critical care units.

The VICTAS (Vitamin C, Thiamine, and Steroids in Sepsis) trial was a randomized controlled trial that evaluated the effects of vitamin C, thiamine, and hydrocortisone sodium succinate on long-term cognitive, psychological, and functional outcomes in sepsis survivors (Roberson, 2023). The VICTAS trial included 213 participants who were randomized to either the intervention group (received vitamin C, thiamine, and hydrocortisone) or the control group (received placebo). The trial found that treatment with vitamin C, thiamine, and hydrocortisone

did not improve or had worse cognitive, psychological, and functional outcomes at 6 months compared with patients who received placebo. The intervention group received intravenous vitamin C (1.5 g), thiamine hydrochloride (100 mg), and hydrocortisone sodium succinate (50 mg) every 6 hours for 96 hours or until death or intensive care unit discharge.

The intervention group had lower immediate memory scores and higher odds of posttraumatic stress disorder than the control group. There were no other statistically significant differences in cognitive, psychological, and functional outcomes between the two groups. These findings challenge the hypothesis that antioxidant and anti-inflammatory therapy during critical illness mitigates the development of long-term cognitive, psychological, and functional impairment in sepsis survivors.

Pfizer recalled 8 lots of hydrocortisone sodium succinate for injection in 2016 due to a labeling error (Pfizer, 2016). The text on the side panel of the carton indicated that the reconstituted product contained 125 mg/mL of hydrocortisone, when it actually contained 50 mg/mL. This could have led to a potential dosing error, and hydrocortisone is a powerful medication that can have serious side effects if not administered correctly. The drug is indicated for the treatment of multiple diseases, disorders, and medical conditions, including medical emergencies such as shock secondary to adrenocortical insufficiency. The drug can be administered by intravenous injection, intravenous infusion, or by intramuscular injection. The preferred method for initial emergency use is intravenous injection. The recall was issued as a precautionary measure to ensure that patients receive the correct dose of hydrocortisone.

In March 2023 Pfizer announced a supply shortage of Pfizer's Solu-Cortef® (hydrocortisone sodium succinate for injection, USP) 100 mg/2 mL (50 mg/mL) ACT-O[1]VIAL™ Single Dose Vials and provided guidance on how to access product reserved for patient specific emergency needs (Pfizer, 2023). All hydrocortisone sodium succinate for injection inventory is available from Pfizer through direct order only, and Pfizer is allocating limited quantities to institutions with a history of product purchases. Pfizer provides guidance to clinicians for utilizing the emergency request process for obtaining the medication. The disruption was expected to exist until June 2023. There was a Notification of Emergency Date Extension for Solu-Cortef® (hydrocortisone sodium succinate for injection, USP) 100 mg/2 mL (50 mg/mL) ACT-O-VIAL™ Single Dose Vial. There are 32 lots listed in the table included at the end of the letter from Pfizer that have been extended by five months beyond the labeled 36-month expiration date by the FDA. The estimated recovery date is December 2023.

FDA Medwatch

An FDA Form 3500 Medwatch describing the findings of this Rapid Communication was filed.

Methods

FTNIR (Fourier Transform Near-Infrared) Spectrometry

Using nondestructive analytical techniques, FTNIR spectra were collected from inventory belonging to 4 lots as part of routine medication quality screening. A representative sample of 30 individual vials were selected for screening from lots 0Y0272, BY0349, BY0351, and BY0484 and noted to be stored under the conditions required by the manufacturer in their original packaging. FTNIR spectra were collected noninvasively and nondestructively through the bottom of the vials using a Thermo Scientific Antaris II FTNIR Analyzer (Waltham, MA, USA)(Isaacs, 2023b).

Smoothing

Data smoothing is a technique used to remove noise from data. This can be done by fitting a smooth curve to the data, such as a cubic spline. Cubic splines are piecewise cubic polynomials that are continuous and have continuous first and second derivatives. This makes them very smooth and resistant to noise. Cubic splines can be easily fitted to data using least squares (Matlab, 2023)(Pollock, 1998).

Multiplicative Scatter Correction (MSC)

Multiplicative scatter correction (MSC) is a widely used spectrometric normalization technique. Its purpose is to correct spectra in such a way that they are as close as possible to a reference spectrum, generally the mean of the data set, by changing the scale and the offset of the spectra (Isaksson, 1988).

BEST (Bootstrap Error-Adjusted Single-sample Technique)

The BEST calculates distances in multidimensional, asymmetric, nonparametric central 68% confidence intervals in spectral hyperspace (roughly equivalent to standard deviations)(Dempsey, 1996). The BEST metric can be thought of as a "rubber yardstick" with a nail at the center (the mean). The stretch of the yardstick in one direction is therefore independent of the stretch in the other direction. This independence enables the BEST metric to describe odd shapes in spectral hyperspace (spectral point clusters that are not multivariate normal, such as the calibration spectra of many biological systems). BEST distances can be correlated to sample composition to produce a quantitative calibration, or simply used to identify similar regions in a spectral image. The BEST automatically detects samples and situations unlike any encountered in the original calibration, making it more accurate in chemical investigation than typical regression approaches to near-IR analysis. The BEST produces accurate distances even when the number of calibration samples is less than the number of wavelengths used in calibration, in contrast to other metrics that require matrix factorization. The BEST is much faster to calculate as well (O(n) instead of the $O(n^3)$ required by matrix factorization.

Principal Components (PCs)

Principal component analysis is the process of computing the principal components of a dataset and using them to execute a change of basis (change of coordinate system) on the data, usually employing only the first few principal components and disregarding the rest (Joliffe, 2016). PCA is used in exploratory data analysis and in constructing predictive models. PCA is commonly utilized for dimensionality reduction by projecting each data point onto only the first few principal components to obtain lower-dimensional data while preserving as much of the original variation in the data as possible. The first principal component is the direction that maximizes the variance of the projected data. The second principal component is the direction of the largest variance orthogonal to the first principal component. Decomposition of the variance typically continues orthogonally in this manner until some residual variance criterion is met. Plots of PC scores help reveal underlying structure in data.

Subcluster Detection

In typical near-infrared multivariate statistical analyses, samples with similar spectra produce points that cluster in a certain region of spectral hyperspace. These dusters can vary significantly in shape and size due to variation in sample packings, particle-size distributions, component concentrations, and drift with time. These factors, when combined with discriminant analysis using simple distance metrics, produce a test in which a result that places a particular point inside a particular cluster does not necessarily mean that the point is actually a member of the cluster. Instead, the point may be a member of a new, slightly different cluster that overlaps the first. A new cluster can be created by factors like low-level contamination, moisture uptake, or instrumental drift. An extension added to part of the BEST, called FSOB (Fast Son of BEST) can be used to set nonparametric probability-density contours inside spectral clusters as well as outside (Lodder, 1988), and when multiple points begin to appear in a certain region of cluster-hyperspace the perturbation of these density contours can be detected at an assigned significance level using r values, and visualized using quantile-quantile (QQ) plots. The detection of unusual samples both within and beyond 3 SDs of the center of the training set is possible with this method. Within the ordinary 3 SD limit, however, multiple instances are needed to detect unusual samples with statistical significance.

Artificial Intelligence Tools

Artificial intelligence (AI) tools, principally used for background information, include Bard (Google LLC) and GPT-4 (OpenAI). AI can be used in a variety of ways, including to brainstorm, organize thoughts, develop arguments, and edit.

Results and Discussion

Intralot analysis

Routine screening using FTNIR suggested that lot GA6092 required closer examination. The spectra of 18 vials from lot GA6092 appear in Figure 2 below. The spectra all appear similar to the naked eye except for some small variations around the water absorbance band at 5150 cm^{-1} and around 4500 cm^{-1}.

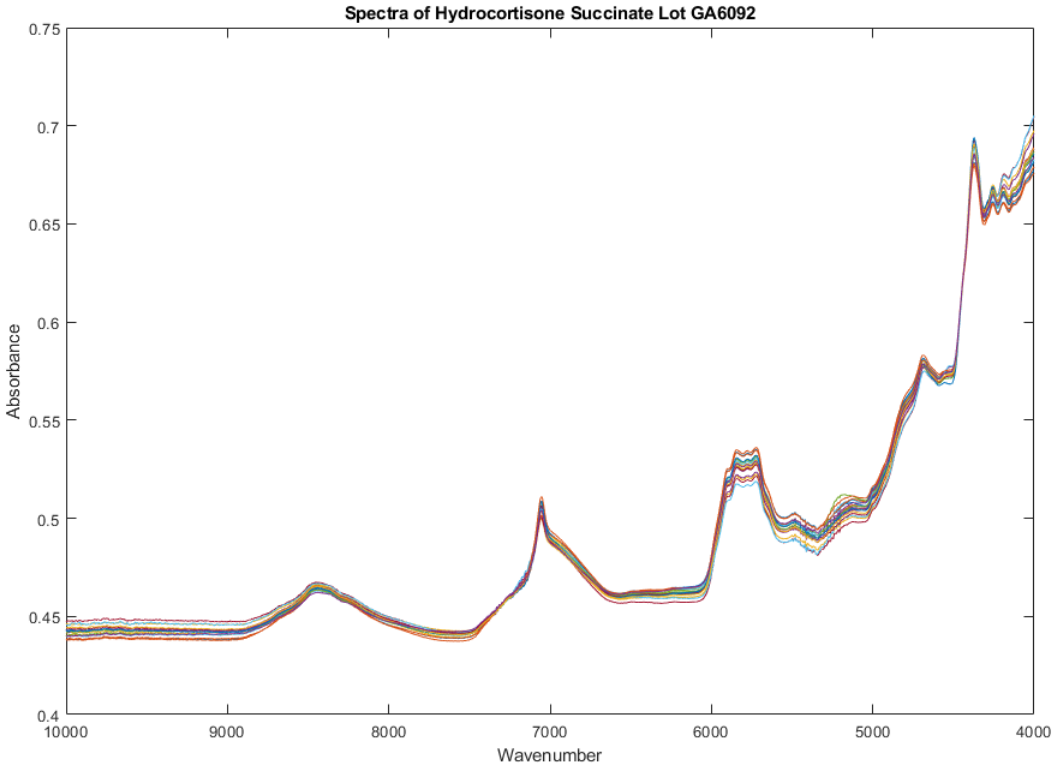

Figure 2. The spectra of 18 vials of hydrocortisone sodium succinate sampled from lot GA6092.

Principal components 1, 2, and 3 of the 18 spectra in Figure 2 are plotted in Figure 3. On the first three PCs the spectra appear to be fairly homogeneous, with only vial 7 and perhaps vial 13 plotting out at the edges. However, none of the spectra fell beyond the three BEST standard deviation limit on cluster membership in this PC space.

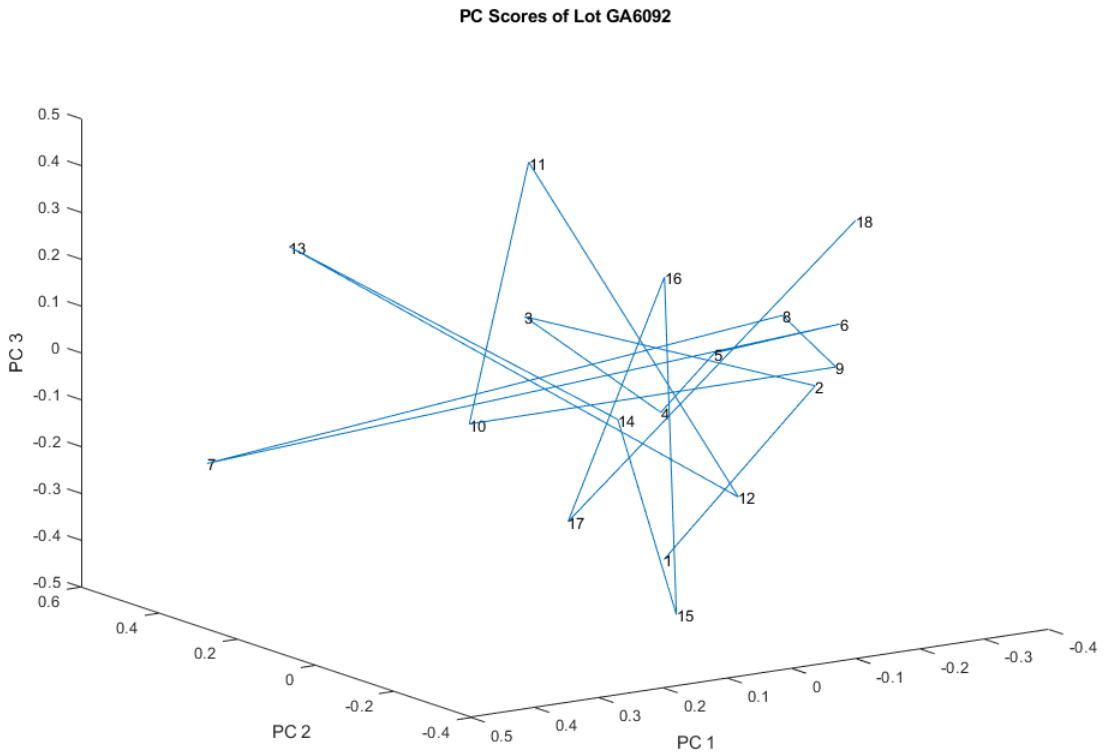

Figure 3. Principal components 1, 2, and 3 of the 18 spectra from lot GA6092 shown in Figure 2. None of the spectra fell beyond the three BEST standard deviation limit on cluster membership in this PC space.

When the PC scores for PCs 4, 5, and 6 of the 18 spectra from lot GA6092 are plotted, however, vial 12 appears to lie farther away from the center of the cluster (see Figure 4). Using a full spectrum BEST SD vial 12 appears 2.5 SDs away from the center of the cluster. However, measuring in PC space using just PCS 4, 5 and 6, vial 12 plots 4.2 BEST SDs from the center of the cluster, and vial 7 is 3.7 SDs from the center. Vial 18 appears 3.1 SDS from the center of the cluster. A table of variations accounted for by each of the principal components of the spectra of lot GA6092 appears in Table 1. The majority of the variation appears on the first PC, as is typical in the well-controlled production of small molecule therapeutics. By the sixth PC over 99% of the cumulative spectral variation has been accounted for by the model.

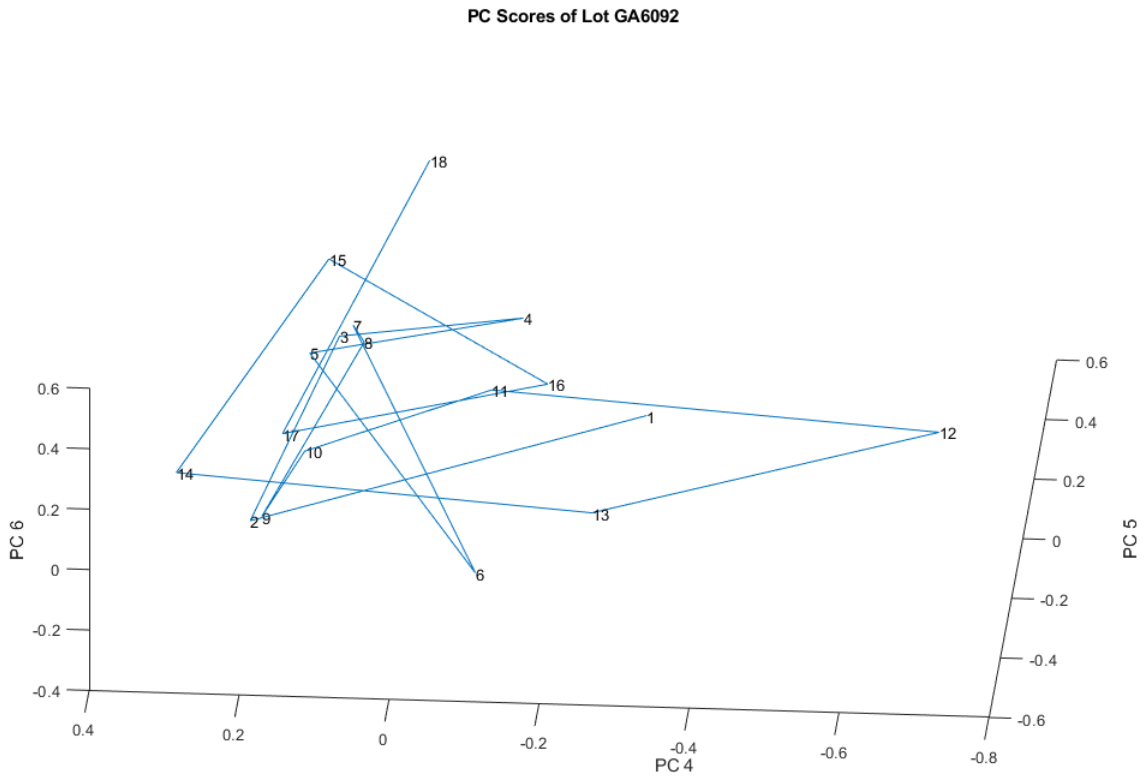

Figure 4. Principal components 4, 5, and 6 of the 18 spectra from lot GA6092. Vial 12 plots 4.2 BEST SDs from the center of the cluster measuring in PC space using just PCs 4, 5 and 6.

Table 1: Variation Accounted for by Each of the Principal Components of the Spectra of Lot GA6092 of Hydrocortisone Sodium Succinate

PC Number	Variation in this PC	Cumulative PC Variation
1	0.7890	0.7890
2	0.0950	0.8841
3	0.0552	0.9393
4	0.0241	0.9634
5	0.0195	0.9828
6	0.0113	0.9941

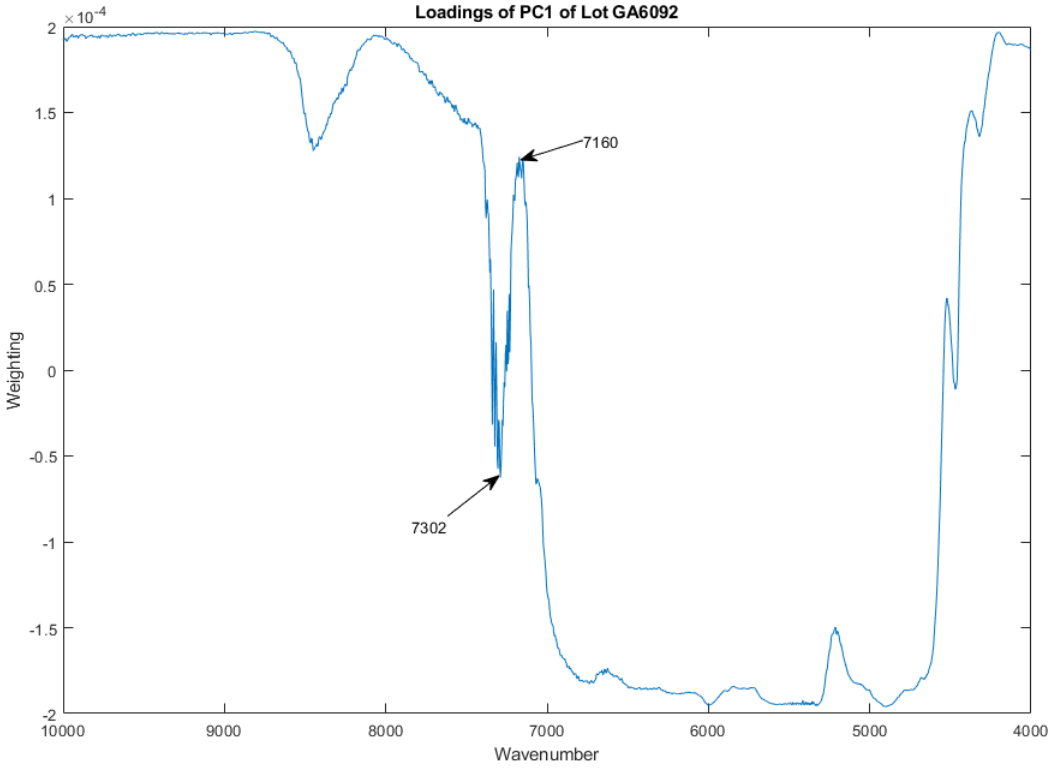

Figure 5. The loadings spectrum for the first principal component of lot GA6092. Distinguishing spectral features are marked at 7160 and 7302 cm^{-1}.

The loadings spectrum for the first PC of lot GA6092 appears in Figure 5. As is typical for most small molecule therapeutics, the major variation is baseline variation after multiplicative scatter correction. Distinguishing spectral features are marked at 7160 and 7302 cm^{-1}.

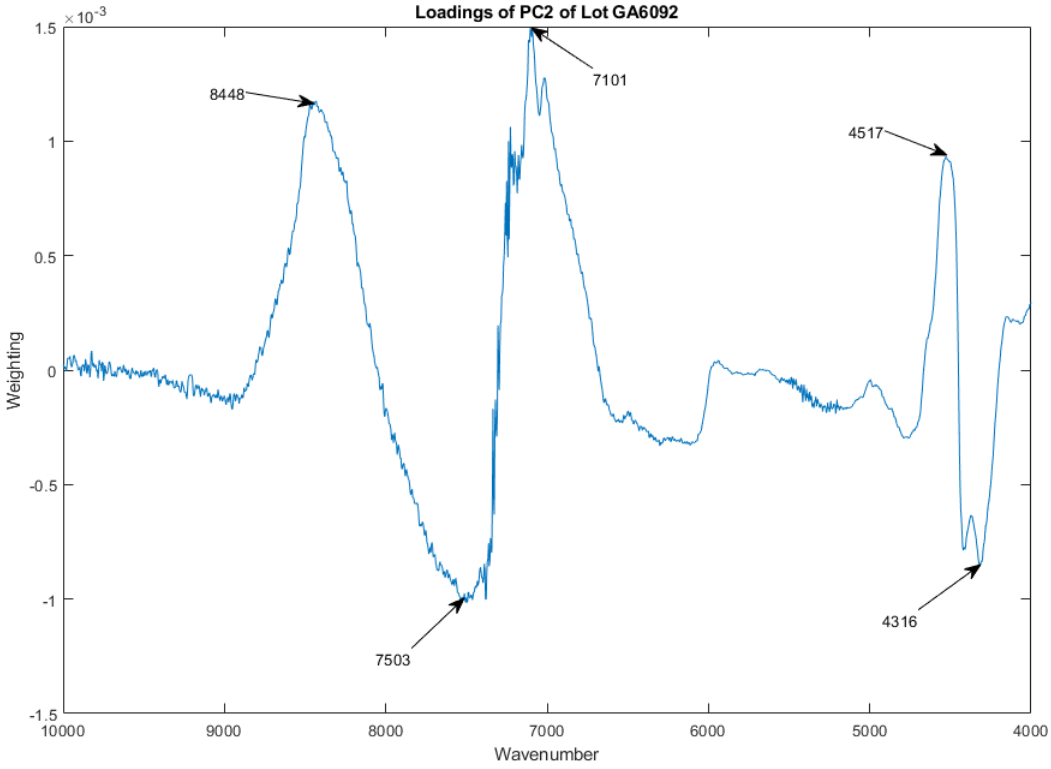

Figure 6. The loadings spectrum for the second principal component of lot GA6092. Distinguishing spectral features are marked at 4316, 4517, 7101, 7503, and 8448 cm^{-1}.

The loadings spectrum for the second PC of lot GA6092 appears in Figure 6. Distinguishing spectral features are marked at 4316, 4517, 7101, 7503, and 8448 cm^{-1}. In the unsmoothed spectra noise begins to creep in from the visible light end of the spectrum (10,000 cm^{-1}) in the second principal component.

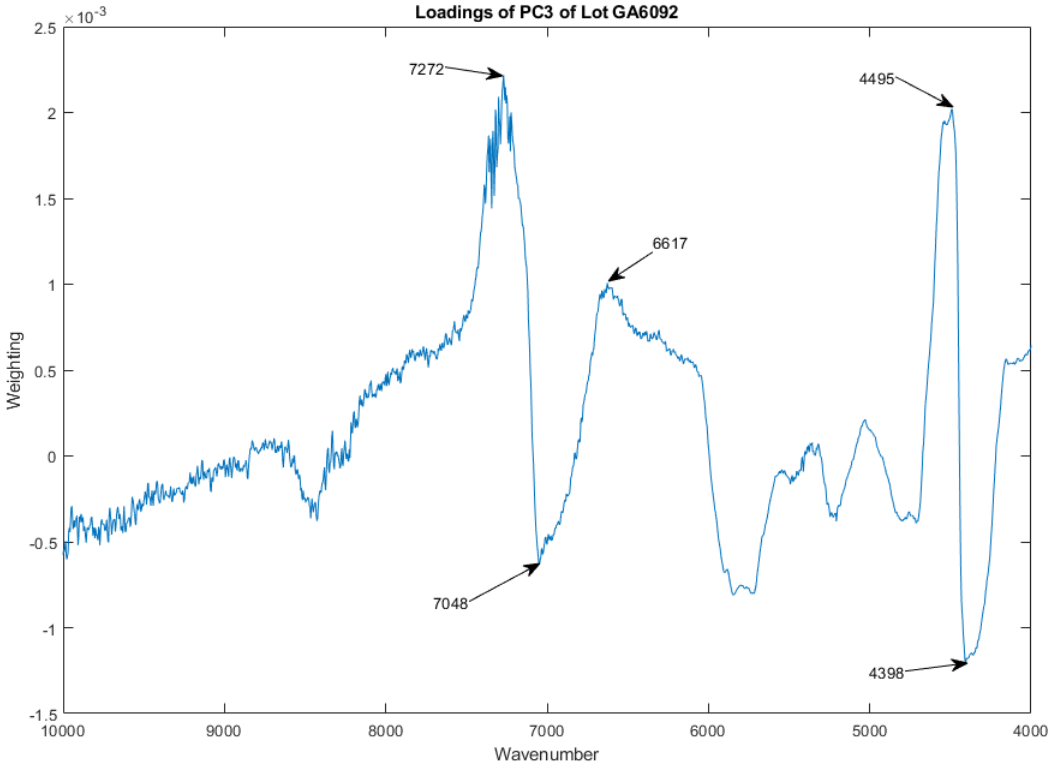

Figure 7. The loadings spectrum for the third principal component of lot GA6092. Distinguishing spectral features are marked at 4398, 4495, 6617, 7048, and 7272 cm^{-1}.

Figure 7 depicts the loadings spectrum for the third principal component of the 18 vials in lot GA6092. Distinguishing spectral features are marked at 4398, 4495, 6617, 7048, and 7272 cm^{-1}.

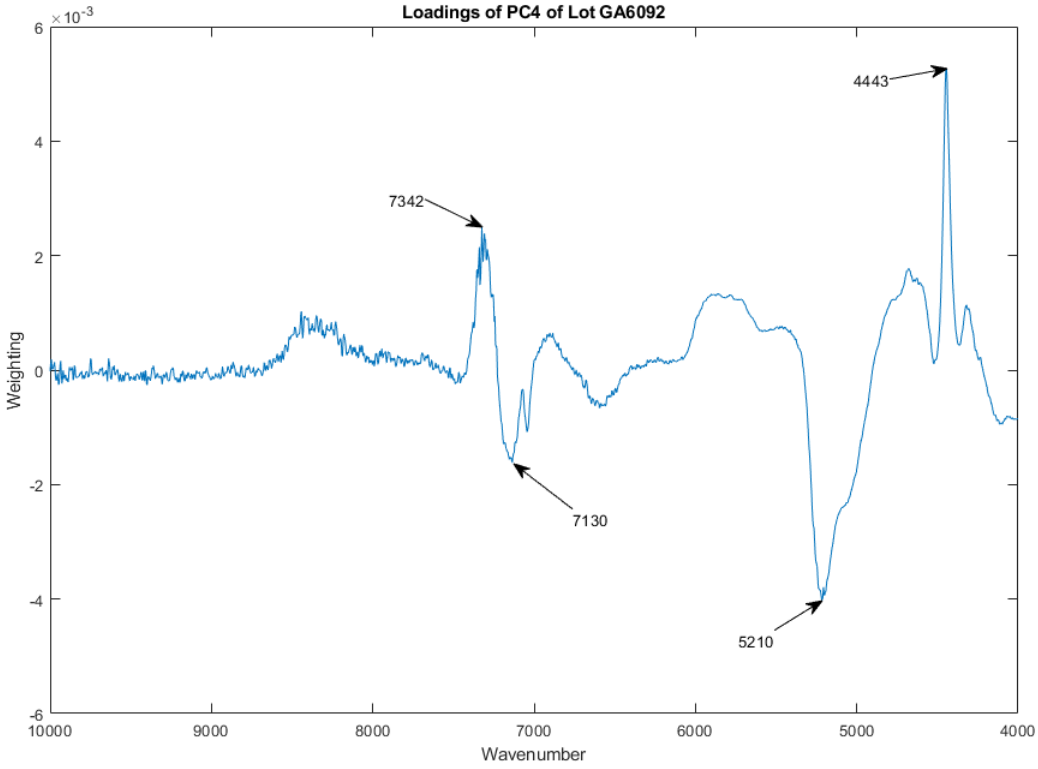

Figure 8. The loadings spectrum for the fourth principal component of lot GA6092. Distinguishing spectral features are marked at 4443, 5210, 7130, and 7342 cm^{-1}.

Figure 8 graphs the loadings spectrum for the fourth principal component of the spectra of the vials in lot GA6092. Distinguishing spectral features are marked at 4443, 5210, 7130, and 7342 cm-1.

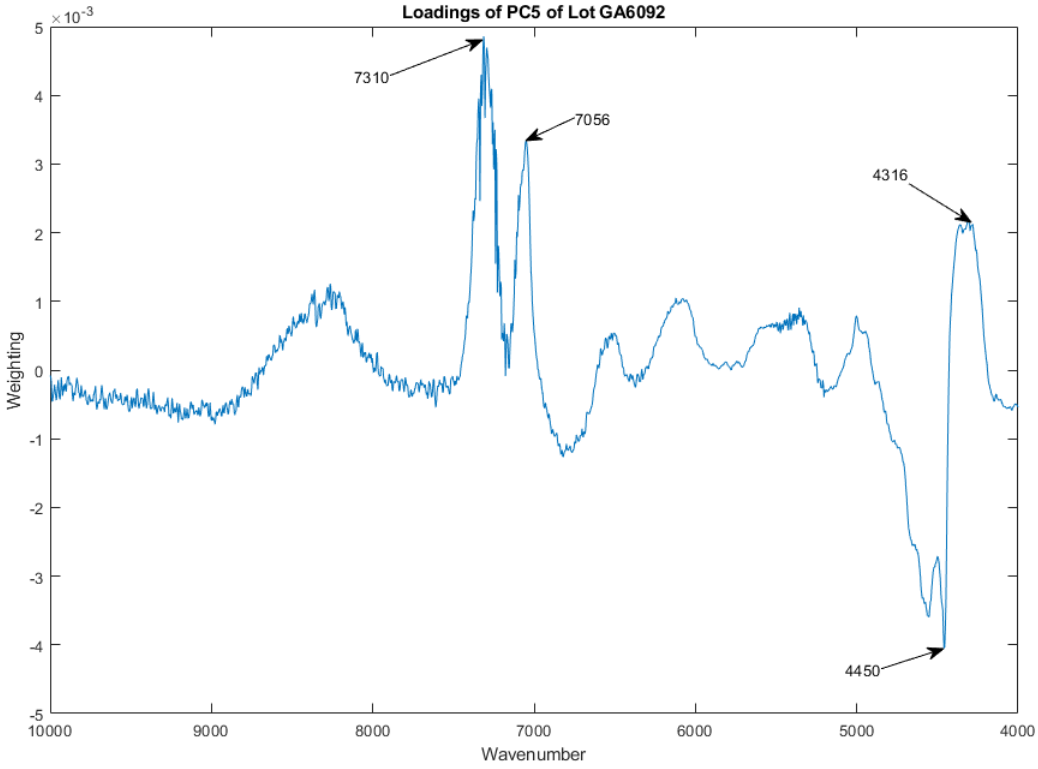

Figure 9. The loadings spectrum for the fifth principal component of lot GA6092. Distinguishing spectral features are marked at 4316, 4450, 7056, and 7310 cm^{-1}.

Figure 9 is a graph of the loadings spectrum for the fifth principal component of the vial spectra of lot GA6092. Distinguishing spectral features are marked at 4316, 4450, 7056, and 7310 cm^{-1}.

The loadings spectrum for the sixth principal component of lot GA6092 is shown in Figure 10. Distinguishing spectral features are marked at 4473, 6699, and 7048 cm^{-1}.

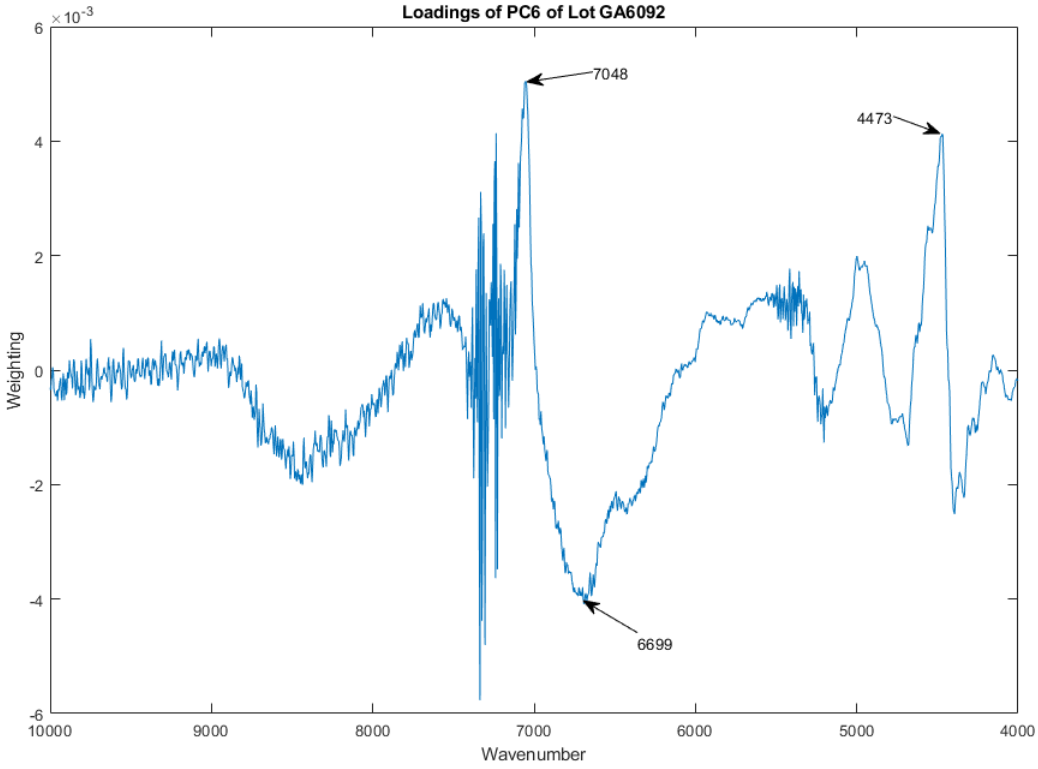

Figure 10. The loadings spectrum for the sixth principal component of lot GA6092. Distinguishing spectral features are marked at 4473, 6699, and 7048 cm^{-1}.

Interlot analysis

The outliers in lot GA6092 suggested a closer examination of the spectral library of hydrocortisone sodium succinate (composed of the spectra of all lots of the drug made by the same manufacturer). The smoothed spectra of the complete library (lots GA6092, GK7048, GM6839, GR8925, FL8062, FN6860, FR1914, and FR5098) containing the spectra of 126 hydrocortisone sodium succinate vials is shown in Figure 11. The spectra all appear similar except for some minor variations around the water absorbance band at 5150 cm^{-1} and around 4500 cm^{-1}.

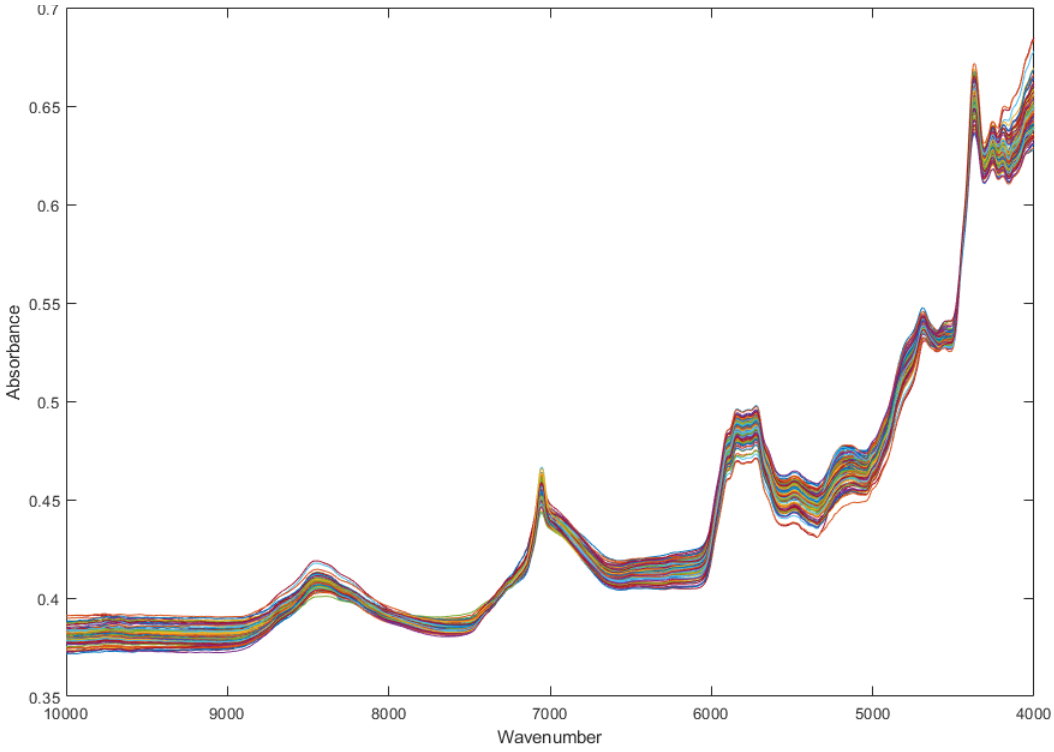

Figure 11. Smoothed spectra of the complete library (lots GA6092, GK7048, GM6839, GR8925, FL8062, FN6860, FR1914, and FR5098) of 126 hydrocortisone sodium succinate vials.

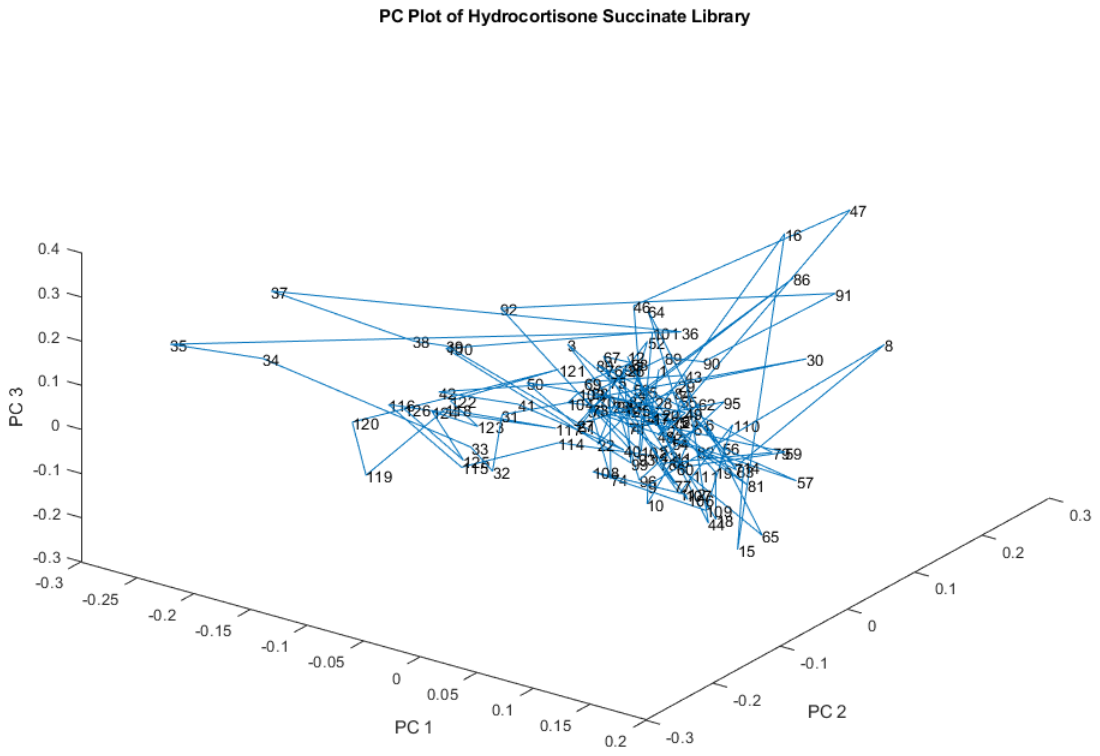

Figure 12. Scores of the spectra in Figure 11 on PCs 1-3. There may be a small subcluster (12 vials, or 9.5%) to the left of the main cluster along with several outliers (e.g., vials 34, 35, and 37).

Figure 12 is a plot of the PC scores of the smoothed spectra in Figure 11 on PCs 1, 2, and 3. There may be a small subcluster to the left of the main cluster containing 12 vials (12/126, or 9.5% of the library), and also several outliers. Vial 34 is 5.0 BEST SDs from the center of the cluster on PCs 1, 2, and 3. However, it is only 2.1 SDs away from the center on PCs 4 through 6. Vial 35 is 5.3 SDs from the center on PCs 1 through 3, and only 3.4 SDs with the full-spectrum BEST. Vial 37 is 3.8 SDs away from the center on PCs 1 through 3, and 1.7 SDs on PCs 4 through 6. Vial 37 is 3.2 SDS away from the center using the full spectrum BEST. Vial 47 is 4.5 SDS away from the center on PC's 1 through 3, and 4.9 SDS using the full spectrum BEST. Vial 16 is 3.9 SDS away from the center on PCs 1 through 3 as well as using the full spectrum BEST. Figure 13 plots the scores of the spectra in Figure 11 on PCs 4-6.

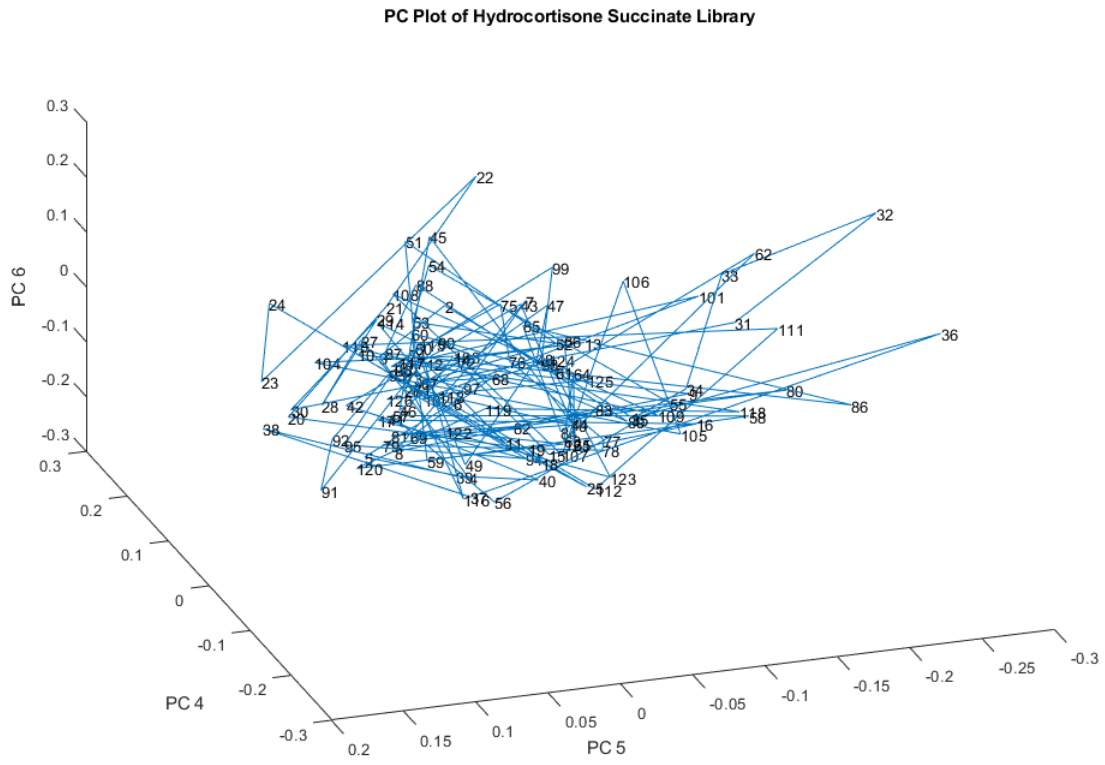

Figure 13. Scores of the spectra in Figure 11 on PCs 4-6.

Table 2 is a table of variations accounted for by each of the principal components of the spectra of 126 vials across 8 lots in the library of hydrocortisone sodium succinate.

Table 2: Variation Accounted for by Each of the Principal Components of the Spectra of 8 Lots in the Library of Hydrocortisone Sodium Succinate

PC Number	Variation in this PC	Cumulative PC Variation
1	0.7276	0.7276
2	0.1297	0.8573
3	0.0834	0.9408
4	0.0229	0.9637
5	0.0156	0.9793
6	0.0111	0.9904

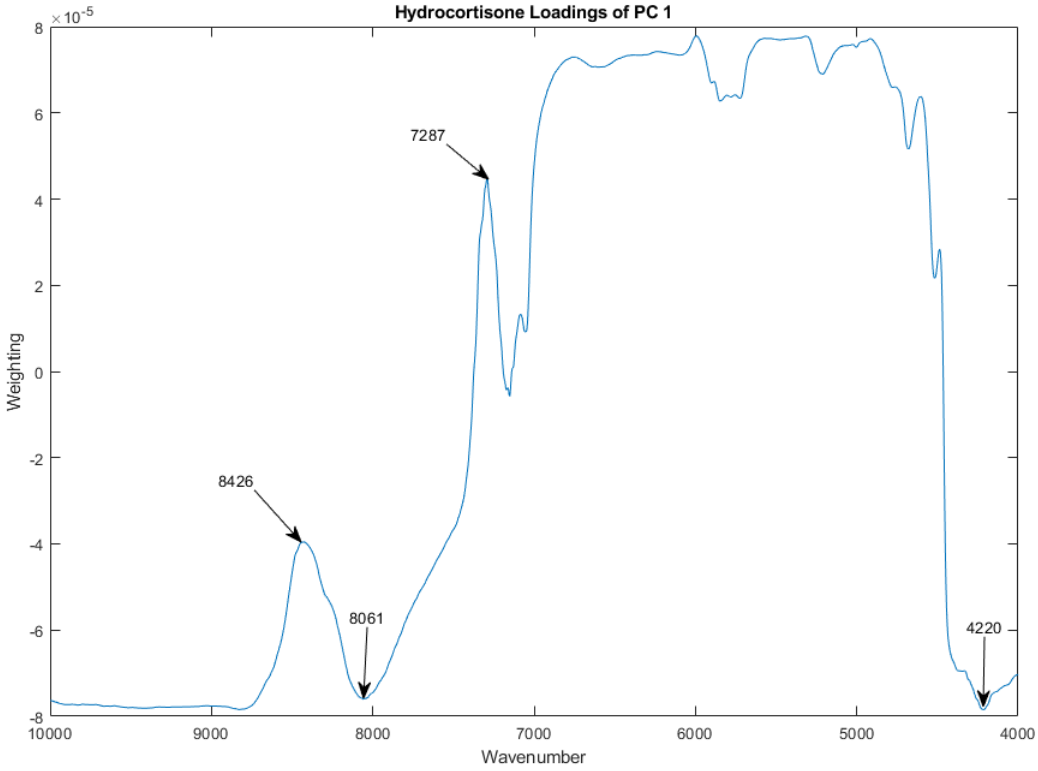

Figure 14. The loadings spectrum for the first principal component of the smoothed spectral library of 126 vials from 8 lots of hydrocortisone sodium succinate. Distinguishing spectral features are marked at 4220, 7287, 8061, and 8426 cm^{-1}.

Figure 14 presents the loadings spectrum for the first principal component of the smoothed spectral library of 126 vials from 8 lots of hydrocortisone sodium succinate. Distinguishing spectral features are marked at 4220, 7287, 8061, and 8426 cm^{-1}. As in Figure 5, the major variation is baseline variation after multiplicative scatter correction.

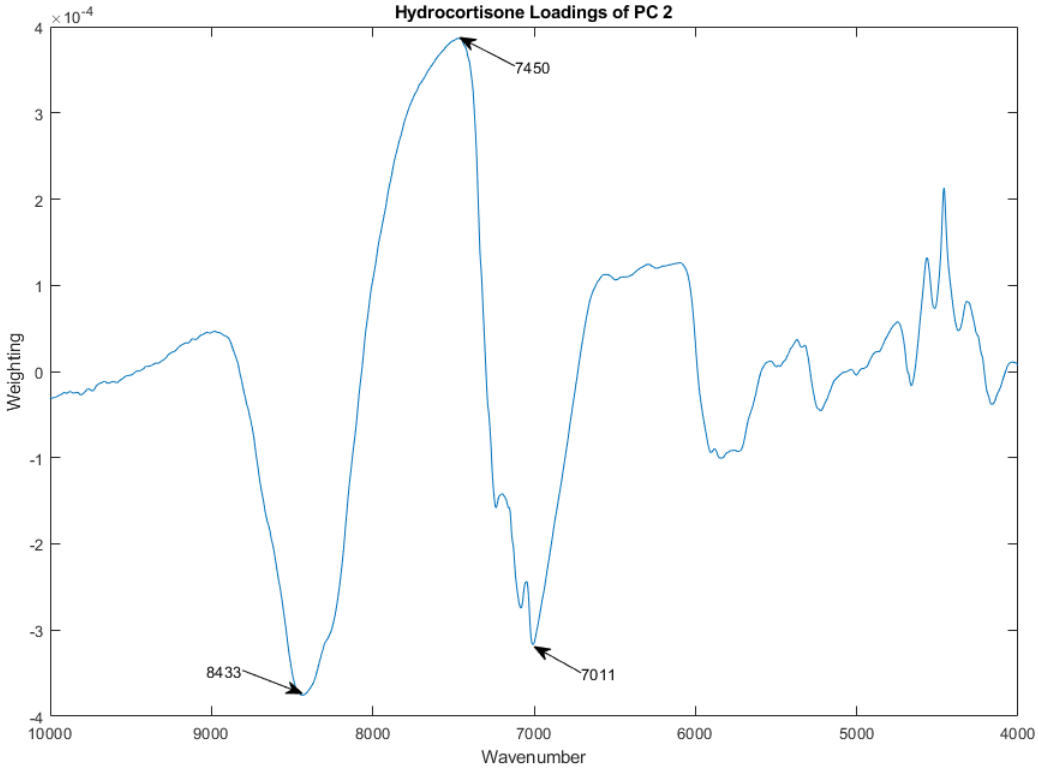

Figure 15. The loadings spectrum for the second principal component of the smoothed spectral library of 126 vials from 8 lots of hydrocortisone sodium succinate. Distinguishing spectral features are marked at 7011, 7450, and 8433 cm^{-1}.

Figure 15 depicts the loadings spectrum for the second principal component of the smoothed spectral library of 126 vials from 8 lots of hydrocortisone sodium succinate. Distinguishing spectral features are marked at 7011, 7450, and 8433 cm^{-1}.

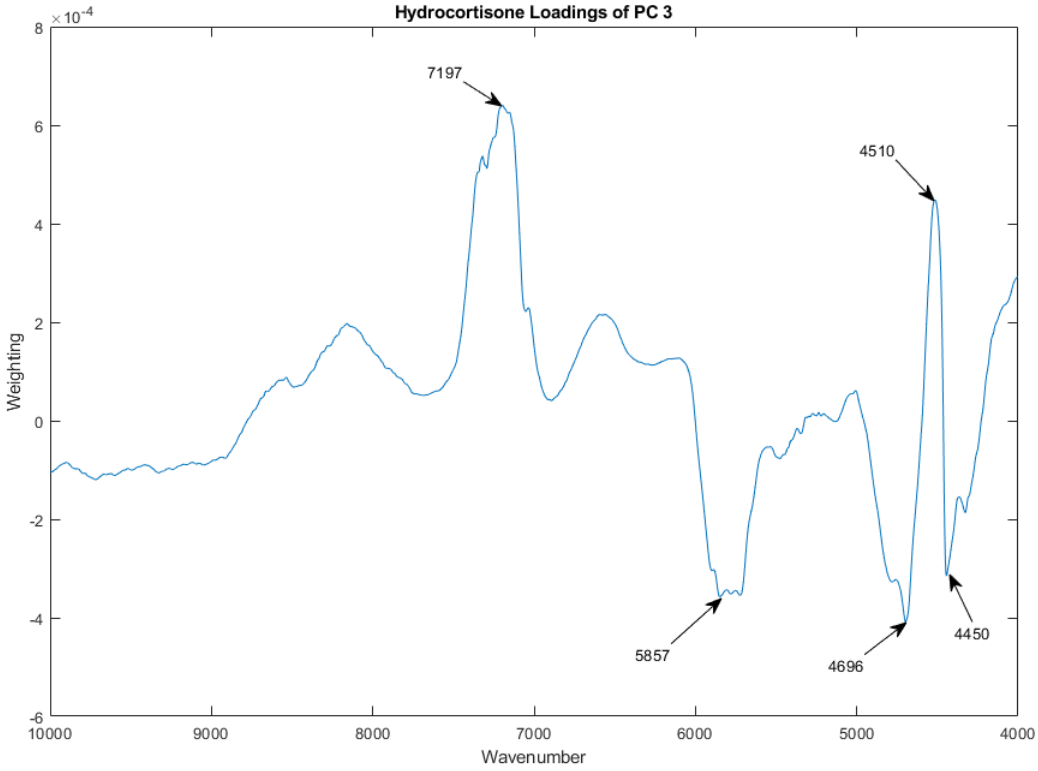

Figure 16. The loadings spectrum for the third principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4450, 4510, 4696, 5857, and 7197 cm^{-1}.

Figure 16 is a graph of the loadings spectrum for the third principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4450, 4510, 4696, 5857, and 7197 cm-1.

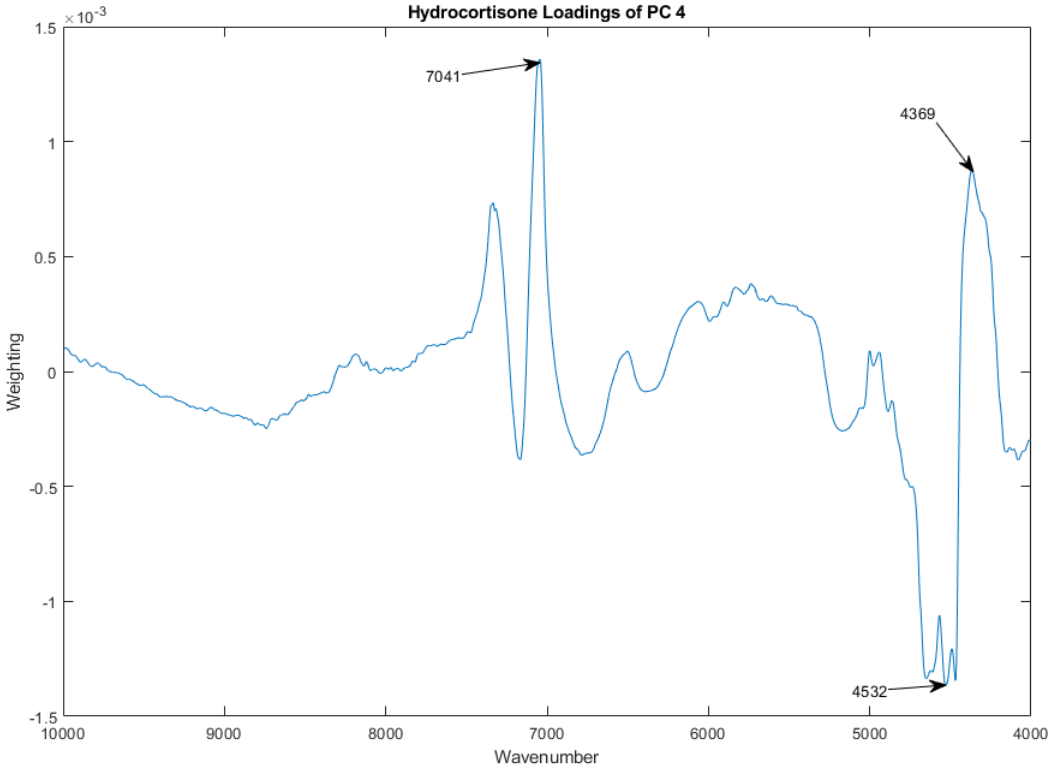

Figure 17. The loadings spectrum for the fourth principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4369, 4532, and 7041 cm^{-1}.

Figure 17 presents the loadings spectrum for the fourth principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4369, 4532, and 7041 cm^{-1}.

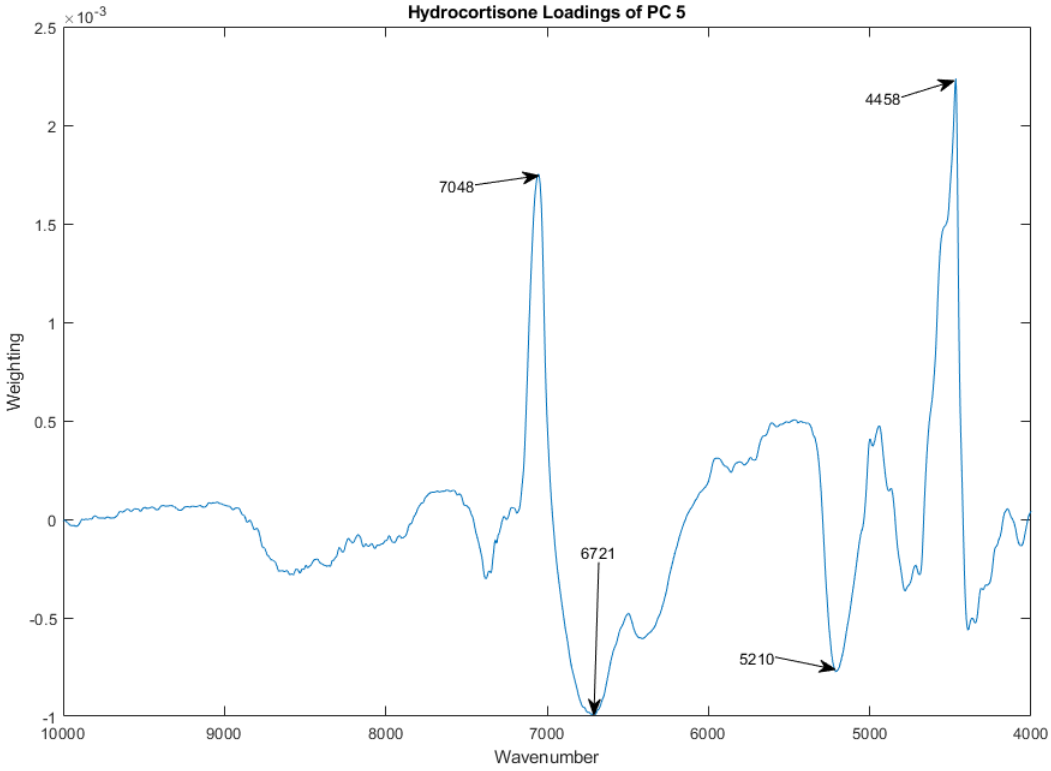

Figure 18. The loadings spectrum for the fifth principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4458, 5210, 6721, and 7048 cm^{-1}.

Figure 18 is a graph of the loadings spectrum for the fifth principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4458, 5210, 6721, and 7048 cm^{-1}.

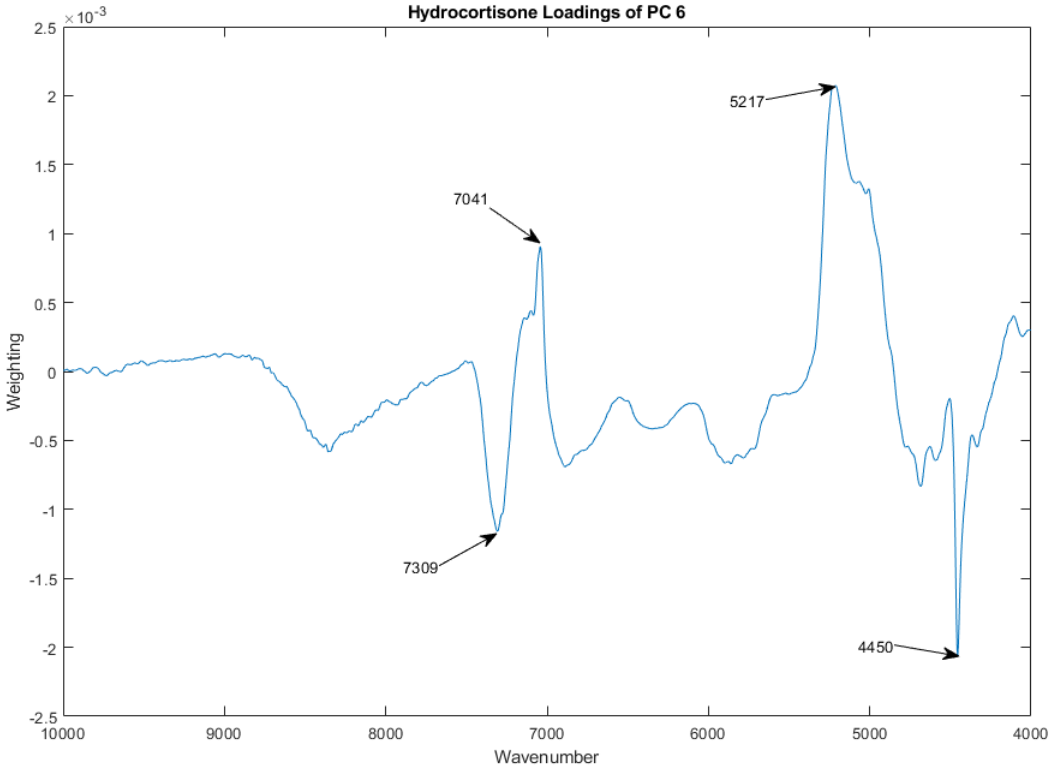

Figure 19. The loadings spectrum for the sixth principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4450, 5217, 7041, and 7309 cm^{-1}.

Figure 19 is a plot of the loadings spectrum for the sixth principal component of the smoothed spectral library. Distinguishing spectral features are marked at 4450, 5217, 7041, and 7309 cm^{-1}.

Conclusion

SOLU-CORTEF® Sterile Powder is a type of anti-inflammatory glucocorticoid that contains hydrocortisone sodium succinate as its active ingredient. It can be administered intravenously or intramuscularly, and comes in several packages including 100 mg plain vials without diluent. The diluent, which is part of the ACT-O-VIAL system, contains only Water for Injection and no preservatives. The pH of each formula is adjusted with sodium hydroxide to ensure it falls within the specified range of 7 to 8 after reconstitution.

Hydrocortisone sodium succinate has research uses as well as clinical uses. The drug was recently tested in treatment of sepsis in the VICTAS trial. In 2016 Pfizer recalled 8 lots of hydrocortisone sodium succinate for injection due to a labeling error. In March 2023, Pfizer

announced a supply shortage of Pfizer's Solu-Cortef® (hydrocortisone sodium succinate for injection, USP) 100 mg/2 mL (50 mg/mL) ACT-O[1]VIAL™ Single Dose Vials and provided guidance on how to access product reserved for patient specific emergency needs. According to the FDA, 62-67% of drug shortages over the past decade are the result of quality problems (Shukar, 2021)(FDA, 2023).

Intralot variability was detected in lot GA6092. Measuring in the PC subspace using just PCs 4, 5 and 6, vial 12 plots 4.2 BEST SDs from the center of the cluster, and vial 7 is 3.7 SDs from the center. Vial 18 appears 3.1 SDS from the center of the cluster (3/18, 17%). Interlot variability was also found in the spectral library (lots GA6092, GK7048, GM6839, GR8925, FL8062, FN6860, FR1914, and FR5098) containing the spectra of 126 hydrocortisone sodium succinate vials. A small subcluster containing 12 vials (12/126, or 9.5% of the library) may exist in the library, and this will be monitored as additional purchases are made.

These spectrometric results do not prove an excess level of impurities or adulteration. However, they suggest that the manufacturing process may have been occasionally operating outside of a state of process control. Additional investigation is needed.

Acknowledgements

The project described was supported in part by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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