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Identifying pharmaceutical manufacturing equipment's surface roughness and mitigating robustness concerns when using specular reflectance Fourier-transform infrared (FTIR) spectroscopy for rapid cleaning verification

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ABSTRACT

Preventing cross-contamination during manufacturing is a regulatory requirement in the pharmaceutical manufacturing industry. One element of measures to prevent cross-contamination is the validation of cleaning processes for manufacturing equipment by assessing the surface contamination prior to manufacturing the next product. Several analytical techniques are used by the pharmaceutical industry, such as swab and rinse, followed by laboratory-based analytical techniques for analysis. While these are well-accepted techniques, a real-time analytical technique is a long-term desire by the industry. The FTIR technique is proven to be an effective measurement system for real-time analysis. However, in its early development, this technique requires many rigorous studies to implement in GMP manufacturing. In this study, the effect of the surface roughness, excipients, measurement distance, and the impact of the environmental temperature was investigated as part of the robustness testing as per the ICH guidelines. In addition, this investigation aimed to identify the surface roughness or surface type using the FTIR before the measurement and use the appropriate calibration model for the surface measurement. It was found that the FTIR could be used to identify the surface type and surface roughness of the pharmaceutical manufacturing equipment. This study also demonstrated that the surface finish# could impact the chemical prediction by approximately 28%. However, if the method described in this investigation is followed precisely, the FTIR would be capable of measuring surface cleanliness with a high degree of accuracy.

Introduction

The prevention of cross-contamination is critical for pharmaceutical and biopharmaceutical manufacturing processes, and it is also equally important for medical device manufacturing processes, especially when the devices are introduced inside the human body [1,2]. The detection and quantification of the surface contaminants on pharmaceutical, biopharmaceutical, food, and medical device manufacturing equipment are currently accomplished using a traditional analytical method such as swab or rinse and subsequence laboratory testing [3]. With the development of advanced technology and newly developed analytical techniques, the industry has an interest in the cleaning verification method to shift towards a more real-time and at-line measurement technique using Process Analytical Technology (PAT). These techniques are non-destructive, rapid, and in some cases, the accuracy of the analysis improves significantly compared to the traditional swab and rinse technique [4]. The investigation outlined in this paper was performed in the laboratory to calibrate and simulate the pharmaceutical manufacturing plant environment. The ultimate goal of this experiment is to use the portable hand-held Fourier-transform infrared (FTIR) on the production floor and use the equipment to measure the manufacturing equipment surface cleanliness directly, thus acquiring results in real-time.

The recent development of the Fourier-transform infrared (FTIR) technology to quantify the surface contaminant for cleaning verification is an example of the advancement of the analytical technique. These techniques do not only produce the results in real-time but also improve the analytical accuracy significantly. Although the technique has proven

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to be effective, it must be robust to use this method in the Good Manufacturing Practice (GMP) manufacturing facility. Therefore, interference from the surface and other potential sources must be rigorously tested before implementation [5–11]. This study was focused on the potential sources of interferences that may impact the result of the FTIR during routine use.

With FTIR, the measurement is performed directly on the surface. Therefore, it is crucial to understand the effects of the different surface types used in the pharmaceutical manufacturing plant. It is well known that most pharmaceutical manufacturing equipments are stainless steel. However, the surface roughness of this manufacturing equipment can vary depending on the product and the guidance provided by the regulatory authority [12,13]. In most cases, the manufacturing equipment is made using highly reflective (finish# 7 or finish# 8) stainless steel as this steel is easy to clean, and the product will not stick to the surface to the same degree as an equivalent rough surface. However, some equipment may have a highly polished surface initially, but the equipment surface finishes may change over time due to the use.

The technique used to measure the surface contaminant using FTIR is known as reflective measurement. The fundamental of this methodology is to detect the amount of IR incidence reflecting back to the instrument detector. Therefore, it is expected that the FTIR signal would be impacted by the surface roughness as the rough surface will scatter some light, and the total reflective light will be lower than a smooth surface. Similarly, if the surface is dull, less amount of light will reflect back to the detector. Therefore the surface roughness and shininess will have some effect on the overall FTIR signal [14–16].

FTIR is a high-sensitive analytical technique, and the specular reflective FTIR measurement system measures chemical signature at a fixed distance, also known as the focal distance. The FTIR is designed to operate at the fixed incidence and reflection angle, as well as fixed distance. Any deviation from the fixed angle and distance could also result in a poor quality spectrum [17]. Therefore, care should be taken to fine-tune the spectral accusation parameter prior to collecting the spectra. Collecting spectra with the optimal distance and angle will undoubtedly improve spectral stability, reproducibility, and quality [18].

Chemical interference is a well-known phenomenon in FTIR measurements. The presence of an alternative chemical on the sample/surface other than the analyte could interfere with the FTIR peak if both chemicals are structurally similar. During a routine cleaning verification study, interference from the excipients is expected. Therefore excipient interference must be tested prior to the FTIR method validation [18–20].

The temperature effect on the FTIR spectra or detector is well-known to all spectroscopy users. The temperature correction for the FTIR spectra is important in order to minimize the temperature effect on the collected spectrum during routine cleaning verification [21–23].

In this investigation, the specular reflective FTIR technique was evaluated to quantify the effects of the roughness and shininess of the stainless steel surface on the FTIR signal. The experiment was divided into two parts; (a) use a blank coupon to identify the surface type using an FTIR, (b) deposit API on the coupon, and quantify the effect on the actual API to simulate the real-life scenario. This surface identification technique was validated using several independent coupons, and the effects on the API prediction were established by depositing the same amount of the API on the coupon with a variable surface finish#. A previously developed calibration model was used to predict the amount of residue present on the surface, and the predicted value was compared with the control coupon.

The strategy of identifying the surface roughness of the manufacturing equipment using the FTIR will be particularly important as it will allow the user to use the correct calibration model suitable for the surface type. In addition, this surface identification technique will allow the analyst to replace the less accurate surface meter, which requires a flat surface and a larger space to measure surface roughness.

In addition to the surface roughness study, the effects of other potential sources of the interference, such as temperature, measurement distance & angle to the surface, and chemical interference, have been studied in detail. Measuring the chemical interference on the surface contamination is challenging as it needs to simulate the real-life situation. Designing an experiment for temperature, distance, and angle study is similarly challenging, especially when the measurement is performed on a surface using a specular reflective FTIR.

A number of innovative approaches have been applied in this study, such as spraying the excipient on the coupon and adding water to the coupon with an ultrasonic spray; control distance between the surface and the FTIR interface using an O-ring; and control measurement error using the instrument operating software. A mechanism was identified where the software would use the collected data to determine whether the scan was collected with an optimum distance and angle. The experiments performed in this investigation are critical and should be considered prior to validate the FTIR technology in a GMP manufacturing facility for rapid cleaning verification.

Experimental

According to the ICH guideline, robustness testing is one of the critical components of analytical method validation in pharmaceutical manufacturing facilities. In this investigation, the robustness of the FTIR and the analytical steps were tested using a number of critical experimental parameters, which could potentially impact the analytical result during routine cleaning verification. The primary goal of this investigation was to perform the measurement on the equipment surface directly. Therefore the surface roughness or finish# was identified as the primary source of the variable. A number of other sources were also tested, such as interference from other potential chemicals, such as excipients. The measurement distance, angle, and temperature were also investigated as potential sources that can impact the FTIR signal.

The experiment was designed to answer the following robustness question:

- Investigate how the different surface roughness or finish# can be identified by using FTIR rather than the use of a surface meter which may not be as accurate as FTIR and is challenging to use.
- How much effect does surface roughness has on the API prediction when using FTIR?
- Are the measurement distance and angle have an effect on FTIR spectra?
- Identify the best approach to study excipient interference on the FTIR spectra for cleaning verification.
- Investigate the environmental temperature impact on the FTIR data.
- Provide suggestions based on the results of the experimental plan to overcome the robustness challenges.

Material and instrumentation

The experiments were performed using finish# 4, 5, 6, 7, and 8 stainless steel coupons or plates are shown in Fig. 1. The coupons used for this experiment were 5*5 cm. These coupons were sourced from Laser Technology, Dublin, Ireland. HPLC-grade water and ethanol were purchased from Sigma- Aldrich (Ireland), which was used to clean the coupon and for standard preparation. The API was provided by the Pfizer manufacturing network. The Chem-Cal microdot printer from Photon System Inc. (PSI, Covina, California, USA) was used to deposit known amounts of the targeted APIs uniformly onto stainless steel coupons. Gilson P200 and P1000 microliter pipettes were used to dilute the stock solutions, and a Mettler Toledo XSR105DU analytical balance was used for weighing the solid compounds. These instruments were used as per vendor guidelines.

The Agilent 4300 Hand-held Mid-IR system (Agilent Technologies, Santa Clara, California, United States) with a specular reflectance

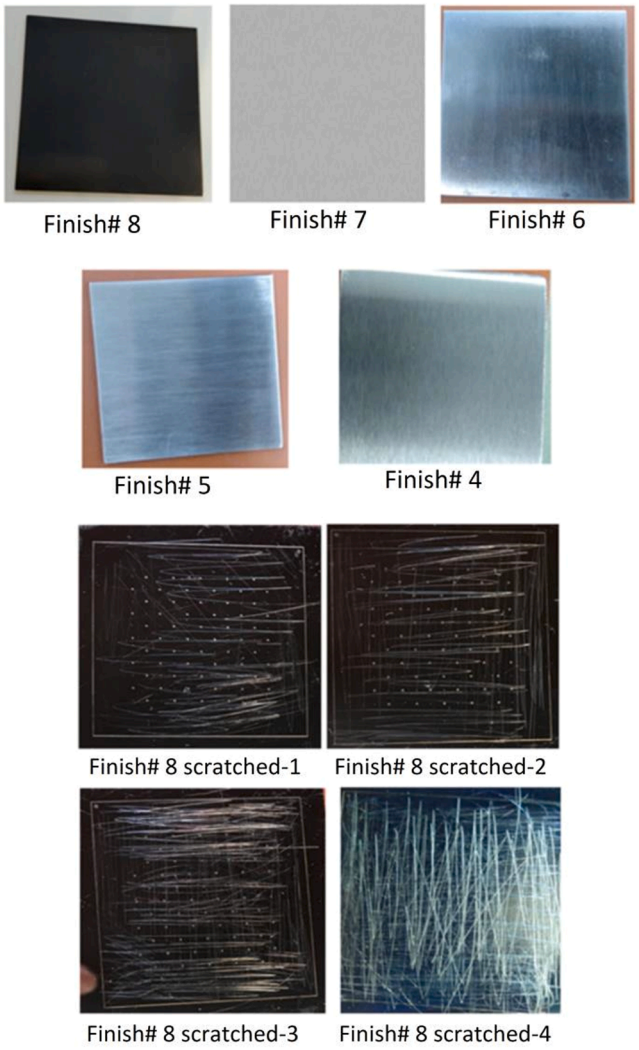


Fig. 1. Visual representation of different coupon types with varying levels of surface scratches. Each of these coupons are 5*5 cm. top 5 coupons represent the fresh coupon when they are new, and the bottom four coupons are finished # 8. These coupons were scratched at varying degrees to simulate the wear and tear due to overuse.

interface was used in this study. The Mid- IR system was equipped with a 450 specular reflectance interface with a 1.76 mm^2 spot size. The instrument was controlled using Agilent's Micro-lab software (version V5.3.1748). The Mid-IR system was configured to collect data over a wide wavelength range (650–5000 cm^{-1}). The instrument is capable of performing non-destructive testing, providing instant feedback via the onboard computer display. VTSYIQI Surface Roughness Meter (manufactured by Vetus Instruments) was used to identify the surface finish# of the coupons used for this investigation at the time of the experiment. The generic ultrasonic moisture generator was sourced from an e-commerce website.

Description of the method

Surface roughness effect on the FTIR

This experiment was performed (a) using a blank coupon and (b) using API on the surface to quantify the surface effect.

Experiment with blank coupons

Twenty-five or more evenly spaced scans were collected from each of the five clean coupons with surface finish# 4, 5, 6, 7, and 8. Four additional finish# 8 coupons were scratched with different levels of scratches. At least twenty-five evenly spaced scans were also collected on the scratched coupons using the hand-held FTIR. In addition, The coupons were measured using the surface meter, and a standard surface measuring guidance (Table 1) was followed to identify the surface finish#. Normally, the surface roughness is determined by measuring the average of the surface heights and depths across the surface. This measurement is generally expressed as 'Ra' for 'Roughness Average'.

Surface effects experiment with API

A Standard solution was prepared using API and the appropriate solvent. The target concentration of the API was kept at 3.19 μg cm^{-2}. Seven microliters of each standard were deposited on the surface of each of the coupons using the 'Chem-Cal' dot printer. The deposition area and volume are recorded to calculate the final surface concentration. A finish# 8 non-scratched coupon was identified as a control coupon. All coupons were scanned using the FTIR, and the result was compared to the finish# 8 control coupon.

Excipient interference

Coupon preparation

Each coupon was printed using the Chem-cal printer with the targeted API. Immediately after printing, the coupons were scanned with the FTIR. The average of the 30 scan results was recorded, and this result was treated as the baseline result. The excipient was then deposited on the coupon using an air spray; the technique is shown in Fig. 2A. The coupon was rescanned, and the results were compared with the initial result.

Water was then sprayed onto the coupon after the excipient deposition, as shown in Fig. 2B. The water is added using a moisture generator to ensure that the water is added to the surface without washing the coupon surface (Fig. 2B). The coupon was scanned after the water addition, and the result was compared with the initial result.

Angle and distance

In order to investigate the effect of the distance from the Instrument measuring head, measurements were performed on coupons at variable distances ranging from 0–1.7 mm to the surface. Similarly, the effects of the measurement angle were identified by taking the measurement at different angles ranging from 90–102.5°.

Temperature effects

The instrument was allowed to reach the operating temperature (55 °C). A coupon was printed with the targeted API, and the first scan was taken at 55 °C. The surrounding temperature was then increased using a heater that allowed the inner temperature of the instrument to increase up to 64 °C. The coupon was then scanned repeatedly in the same location as the temperature was increasing without moving the instrument and the coupon.

Table 1
Reference surface roughness value (Ra) for each finish# type.

Surface Finish#	Common Name	Ra (μ-inch)
Finish# 4	Biotech Finish#	25–30
Finish# 5	Biotech Finish#	20–24
Finish# 6	Biotech Finish#	15–19
Finish# 7	Biotech Finish#	8–12
Finish# 8	Mirror Finish#	4–7

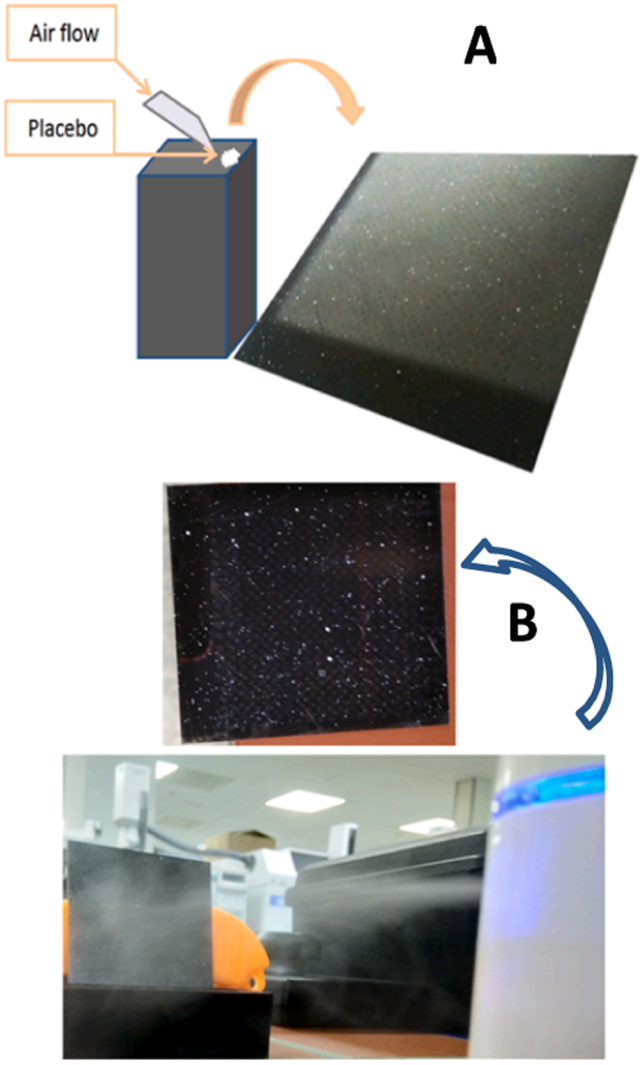


Fig. 2. (A) schematic of how the placebo of the excipient was deposited using an air spray. (B) Moisture addition to the coupon with placebo and the API.

Data collection parameters

The data collection parameters of the Mid-IR were selected by investigating the collected spectra for each API and experiment setup and its chemical signature. The spectral resolution was set at 4 cm^{-1} for all the experiments in this investigation. The spectral range was set from 650–4000 cm−1. A minimum of 25 acceptable spectra was collected using a specular reflectance FTIR data collection interface from each coupon analyzed. All the data collected for the PCA model development was acquired at the optimum equipment distance and angle to the surface. The average of the 25 acceptable spectra was used to develop the PCA model for better visibility. It is recommended that all 25 spectra from each surface should use without averaging in the PCA model when the FTIR is used in the manufacturing plant.

Results and discussion

The impact of surface roughness on the blank coupon

Five different types of stainless-steel coupons were selected with a surface finish# of 4 to 8. The finish# 8 coupon was scratched using a stainless steel pin in order to simulate the reasonable sign of used equipment over time. The top five images in Fig. 1 replicate the different types of stainless steel used in the pharmaceutical industry with different surface finish# types. The bottom four images of Fig. 1 illustrate similar surface roughness with reasonable wear and tear.

Each of the coupons was scanned using the surface roughness meter in order to verify the surface roughness, and it was found that when the coupon was not used, the meter reads the coupon type as described by the manufacturer. When the coupon was scratched to simulate the sign of use, it was found that minor scratches do not affect the surface roughness meter reading and overall finish#. The moderate scratch does change the surface roughness slightly, where Finish# 8 coupon was measured as a finish# 7. When the surface was scratched significantly, the surface roughness reading (Ra) was between 25–30 μ-inch, indicating that the finish# 8 coupon was measured to approximately finish# 4 (Table 2). The moderately scratched coupon (scratched-3) was expected to read lower on the surface meter, but the actual reading was finish# 7 (Table 2). One potential reason could be that the surface meter scans a very small amount of area to measure the surface roughness and could miss the scratched area, thus generating a result that may not represent the actual surface roughness.

Use of FTIR to identify surface type

A number of parameters were carefully monitored during the scanning of the blank coupon, including the angle and the distance of the FTIR from the surface of the coupons. The background spectra were collected from the standardized reference stainless steel, and a new background was frequently collected during the experiment to minimize the environmental effects on the collected spectra.

Each of the coupons were scanned using the FTIR a minimum of 25 times at the same distance and angle. The collected spectra from different surface types, including the coupons with different degrees of scratches, are shown in Fig. 3. The spectra shape and baseline differed significantly depending on the surface roughness and the surface shininess. It was observed that due to the surface roughness, the baseline of the spectra shifted upward at the region of the 4000 cm^{-1} and formed a curvature shape in the spectrum (Fig. 3).

Development of a model to identify surface type

In order to identify the surface finish# using the FTIR, a principle component analysis (PCA) model was developed using the reference spectra collected from each surface. From the PCA model (Fig. 4), it was observed that finish# 7 and 8 overlapped each other; hence, no significant difference was observed in the spectra for finish# 7 and 8. In addition, the minor and medium scratched coupons were also overlapping with finish# 7 and 8 coupons. However, the heavily scratched coupon separated from the finish# 7 and finish# 8 coupons (Fig. 4). The finish# 4, 5, and 6 coupons are visually rough-looking. The surface is not smooth when compared to finish# 7 and finish# 8, which are polished, and the surface is very smooth. The finish# 4, 5 & 6 coupons are dull compared to finish# 7, and the finish#8 surface is smooth and mirror-like.

The overarching goal of this experiment was to use raw spectra to

Table 2
Surface roughness meter reading for all coupons used.

Experiment	Surface finish# at the time of purchase	Surface finish# at the time of the experiment
Blank Coupon	Finish# 4	4
	Finish# 5	5
	Finish# 6	6
	Finish# 7	7
	Finish# 8	8
Finish# 8 Scratched coupon (1-4)	Finish# 8 (1)	8
	Finish# 8 (2)	8
	Finish# 8 (3)	7
	Finish# 8 (4)	4

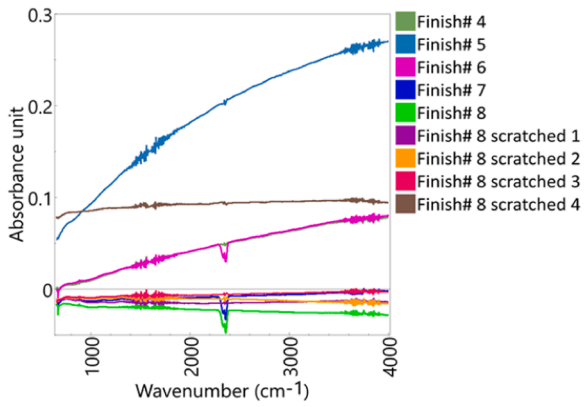


Fig. 3. Each spectrum represents an average of 25 or more spectra for each surface finish# and scratches; all the spectra were collected from blank coupons.

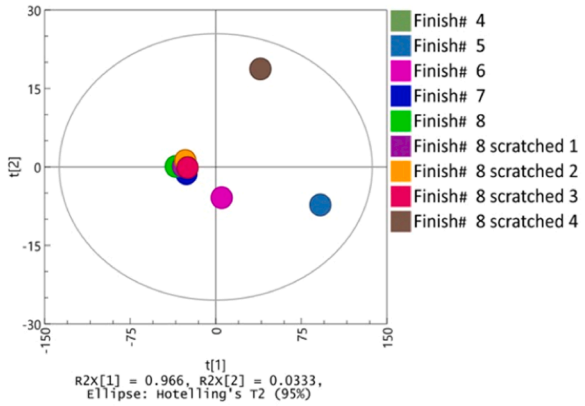


Fig. 4. The Principal Component Analysis (PCA) model shows how the surface roughness and different level of scratches affect the spectra. Finish# 7, 8, and minor scratched coupons are clustered together, while the finish# 4, 5, 6, and heavily scratched coupons are separated from finish#7 and 8. The model was developed using these differences in the spectral feature to identify the surface type.

develop a PCA model to identify the surface type. Typically, the pre-treatment, such as derivative and/or baseline correction, is used to minimize the baseline shift. In this investigation to develop the PCA model, pre-processing was not used because the spectra were collected from the blank surface, and the background was also collected from the blank stainless steel reference cap. Therefore, no chemical spectral features are present in the spectrum that can be used to differentiate the coupon surface type as all the surfaces are stainless steel. The surface identification is truly based on the spectral shape and baseline shift affected by the different surface roughness. Removing those effects from the spectra using the pre-processing would affect the performance of the PCA model to predict the surface type accurately.

Typically, the surface roughness is measured using a surface meter which is not only highly variable but also impractical to use in a production environment. The use of an FTIR for surface roughness measurement investigated in this study is a noble concept. The spectral signature of the surface roughness was used to identify the surface using a PCA model.

Validation of the PCA model by identifying the surface type

The principal component analysis (PCA) model in Fig. 4 was validated by identifying the independent coupons targeted surface type. A number of coupons with known surface (finish# 4 to #8) types were scanned using the FTIR, and the PCA model was used to predict the surface type. In each case, The PCA model was capable of identifying the primary source of the variance in the spectra collected from the different surfaces and accurately predicted the surface type.

Experiment using the API

The overall goal of this experiment was to test the effects of the surface finish# and shininess of the manufacturing equipment when an FTIR is used to quantify the API on the surface. Therefore, the targeted API was printed on each surface type as well as the coupons with different levels of scratches that were generated as described earlier. The printed coupons were scanned with the FTIR to evaluate the effects of the surface finish# and the scratches on the surface. The finish# 8 coupon was used as the control coupon as the calibration model was developed using the finish# 8 coupons. Therefore, the new finish# 8 coupon's predicted value was set to 100% (3.21 μg/cm^2), and the predicted results for each coupon are shown in Table 3. A previously built calibration model was used to predict the amount of API on the surface. (The details of the calibration model development can be found in the previously published article cited in reference [2])

All other results were compared to the finish# 8 coupon to calculate the percentage prediction. The results suggest that surface finish# 7, 8, and the minor scratched coupons (Finishe# 8 scratched' 1, 2, and 3) have minimal or no effects on the API prediction. However, if a finish# 8 surface is overused and the surface is completely damaged from overuse or extremely scratched, the prediction would be similar to the finish# 4 and 5. The result indicates that finish# 4, 5, and 6 are approximately 28% (average) lower compared to the finish# 8 control coupon. This effect also depends on the shininess of the surface. The shininess of the coupon for the finish#4 coupon was slightly higher than the finish# 5 and 6 (Fig. 1). Therefore, it was concluded that two different calibration models would require to measure all types of surface finish used in pharmaceutical manufacturing.

Angle and distance impact on FTIR spectra

The impact of the distance and the angle on the API collected spectra were assessed by collecting the spectra at different distances and angles. Fig. 6 shows the overall effects of the distance and angle on the instrument energy and absorbance value. Fig. 5 shows the distance effects on the overall peak shape and the quality of the spectra.

The spectral feature in Fig. 5 was carefully observed, and it was noticed that the peak shape and peak height in Fig. 5A,D were not very clear compared to the 5C, and the 5B was slightly better than 5A and 5D. Although all four spectra were collected from the same sample and location of the coupon, the difference between the spectral peak shape and height is clearly visible. The only variable in these spectra was the

Table 3
Surface roughness or finish# effects on API prediction.

Surface Finish	Surface concentration predicted by the model(μg/cm2)	Percent prediction of the controlcoupon (%)
Finish# 4	2.54	79.13
Finish# 5	2.17	67.60
Finish# 6	2.19	68.22
Finish# 7	3.09	96.26
Finish# 8*	**3.21**	**100.00**
Finish# 8 scratched 1	3.25	101.25
Finish# 8 scratched 2	3.31	103.12
Finish# 8 scratched 3	3.24	100.93
Finish# 8 scratched 4	2.33	72.59

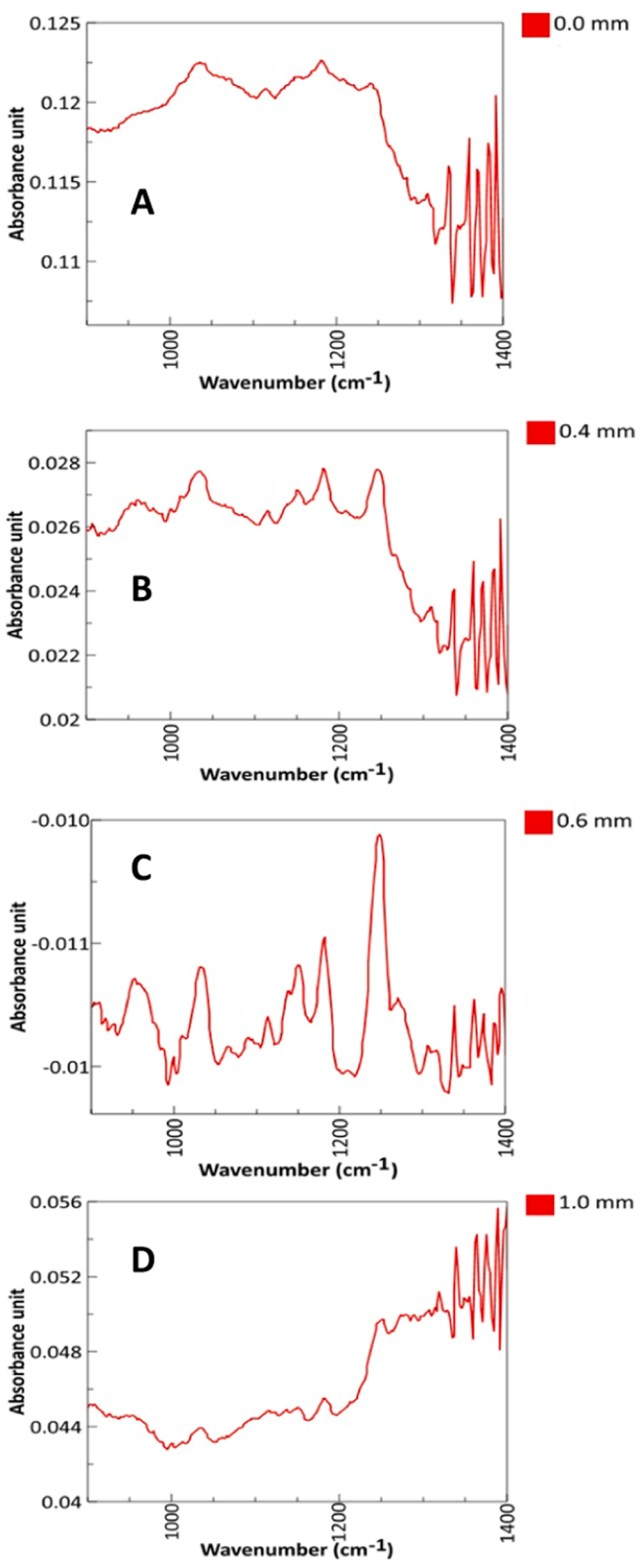


Fig. 5. Distance effects on the overall FTIR peak shape and size. (A) The spectrum was collected too close to the surface; there is no clear visible peak. (B) the spectrum was collected near to the optimum distance; the prominent peak is visible, but the sample peak is not clearly visible. (C) The spectrum was collected at an optimum distance; all peaks are clearly visible, and peaks are sharper (D). The spectrum was collected too far from the surface, and the spectrum lost most of its peak features.

distance of the measurement. After analyzing the data in Fig. 6A, it was concluded that the collected spectra in Fig. 5A were too close to the FTIR data collection interface, and the 5D spectra were collected too far from the data collection interface. The spectra in Fig. 5C were collected at the optimum distance. These experimental results suggest that to obtain good shape spectra with a clear visible peak; the instrument needs to operate at optimum maximum energy; the instrument produces maximum energy only at an optimum distance. The optimum distance for the measurement was identified to be between 0.55 and 0.65 mm from the surface (Fig. 6A).

The angle of the measurement to the surface was also investigated, and it was found that it had a similar impact as distance. The incidence angle was carefully monitored, and it was noticed that when the measurement is collected at an angle greater than 90^0 it creates a gap between the surface and the instrument's interface. Therefore it was concluded that if the instrument operated at an angle, the impact would be similar to the distance. If the instrument is held at a surface other than 90^0 angles, that creates a distance, and if the angle is increased greater than 93°, that affects the absorbance of the measurement. However, if the instrument is operated at 95° or less to the surface, the effect is minimal (Fig. 6B).

Therefore, it is recommended that the instrument should be operated at an angle below 93° to the surface.

The operating distance and angle of the instrument to the surface are critical and must be controlled accurately. In the laboratory, the

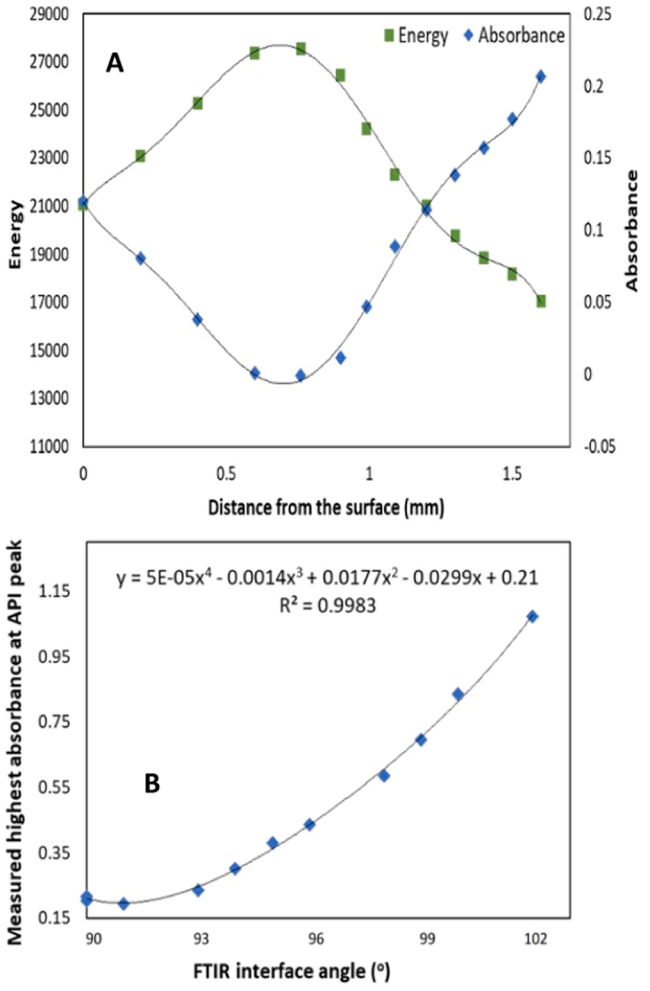


Fig. 6. (A) Impact of the measurement distance on the absorbance and energy of the FTIR. (B) The impact of the measurement angle on the absorbance value on the main peak on the API.

instrument distance and angle can be controlled by placing the instrument at a fixed distance or on an XYZ stage, which holds the instrument at a constant distance and angle while the measurement is performed. However, in the manufacturing plant, this will not be easy to control, and the angle could differ slightly. It is important that the angle of the instrument is less than 95° to the surface, and the distance is at 0.6 mm. A rubber O ring may be attached as a spacer to the interface to maintain the distance at 0.6 mm.

This optimum operating distance from the targeted surface is minimal, and it is 0.5–0.7 mm when the rubber O-ring is not in use. If the rubber O-ring is in use, the interface of the Agilent 4300 must be gently pressed to the targeted surface.

In order to control the data collection at an incorrect distance and angle, an experimental method should be developed using various component algorithms present in the currents micro lab software, which will notify the operator that the collected data was collected outside the defined angle and distance.

Excipient effect on API prediction

For the excipient study, a placebo of the chosen drug product was prepared with all the excipients required for a typical tablet formation. The placebo method described in the experimental section was used instead of individual excipients, as this approach simulates a similar process to the manufacturing environment. The amount of excipient deposited on the surface to see a comparable effect on the spectra was critical because an excessive amount of excipient will mask the signal from the API completely. Therefore, in this experiment, the API was deposited on the surface uniformly using the Chem-Cal coupon printer. The amount of excipient deposited on the coupon was determined by the guidance of the swab and visual inspection. According to the swab testing guidelines, a visual inspection must be performed prior to collecting the swab. If the visual inspection fails, no swab should be collected, and the manufacturing equipment must be cleaned again. Therefore the amount of excipient deposited was limited to a visual level. It was ensured that the excipient was visible but not completely covering the coupon. This method is considered as a worst-case scenario where a visual inspection provides a false negative result.

The experimental data in Table 4 shows a 1.32% API prediction difference after excipient addition to the coupon. Even after water addition, there were no significant effects observed in most cases. However, hotspots of the excipient were observed when an excessive amount of excipient was used. Some of the excipients were dissolved on the surface after water addition. In those cases, the dissolved excipients cover the API signal, which had up to 15% difference in the API prediction. However, Fig. 2 shows that the amount of excipient used in this study is very visible. If the visual inspection is performed properly and the API is not visible to the naked eye, then the interference from the excipient would be minimal.

Therefore the analytical method would pass the interference study where in most cases, the specification of passing the interference study for cleaning verification is approximately 15–20% of the actual value. However, if the amount of excipient is above the visible limit, the signal from the excipient may cover the API signal and could therefore influence the prediction of the targeted API. Thus, the visual inspection must be performed prior to scanning the manufacturing surface using the FTIR.

Table 4
Predicted API concentration of a targeted coupon before and after excipient addition on the surface.

Description	Predicted API surface concentration (μg/cm^2)	% difference
No excipient	7.61	1.32
After Excipient Addition	7.51	

Temperature

The temperature of the FTIR detector was closely monitored, and it was noticed that the temperature of the detector increased as the atmospheric temperature increased, as outlined in the experimental section. Additionally, it was found that internal instrument temperature has an effect on the collected spectra. Therefore it is very important to control the instrument temperature in order to minimize the temperature effect on the collected spectra. Fig. 7A shows the temperature effect on the overall spectra, and Fig. 7B shows the actual effects on the model region for the specific API used in this study.

The temperature has a linear relationship with the absorbance value for any region of the spectra, especially around the region 1200 to 1800

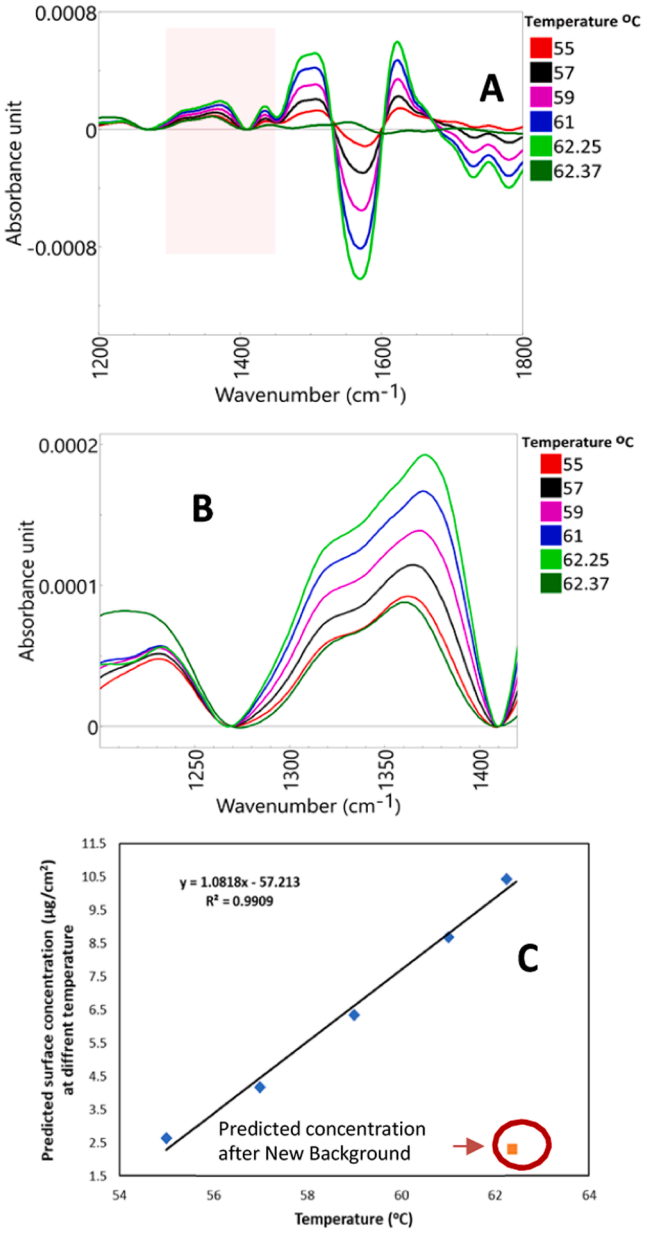


Fig. 7. (A) The temperature effects on the overall spectra. The high-lighted region of the spectra represents the region of interest for the calibration model (B) Zoomed image of the model region (C) linear relationship of the environmental temperature and the PAI predicted by the model. the red circle is a data point with a new background.

cm^{-1}. Control of this effect is critical to measure the API accurately on the surface as the manufacturing area may not be temperature controlled. Therefore the FTIR reading may not be reliable if the temperature effect can not be controlled.

After performing further experiments, it was found that if a background is collected every 10–15 min, the temperature effect can be minimized significantly or, in some cases, can be eliminated completely. The results in Fig. 7C show that as the detector temperature increases, the API predicted concentration also increases proportionately. However, once the new background is collected, the absorbance and predicted concentration value returned to the normal range (Fig. 7B, the spectra of 62.37 °C and Fig. 7C data point in the circle).

The result shown in Fig. 7 confirms that a frequently taken new background is critical to minimize the temperature effects on the collected spectra. If there is a concern, the environmental temperature could vary. In addition, the regular background will also help to reduce noise from the environmental carbon dioxide and other instrumental noise that may be present in the instrument.

Conclusion

Although this technology demonstrated its ability to verify equipment cleanliness, a number of factors need to be considered in order to routinely collect reliable results when using the FTIR. Incorporating the mitigation demonstrated in this investigation are critical such as measuring the surface roughness using the FTIR before measurement using a PCA model. Based on the API prediction results outlined in Table 3, using FTIR in all stainless steel surfaces used in pharmaceutical manufacturing will require two different calibrations models. The entire range of the stainless steel surface type used in pharmaceuticals can be divided into two groups, namely (a) finish# 4, 5, and 6 with badly scratched surface and (b) finish# 7 and 8 with minor scratches. The use of two different calibration models can significantly improve the robustness and accuracy of the measurement.

In solid oral dose manufacturing facilities, where most of the swab analysis is performed, the most commonly found chemical contamination that could interfere with the API measurement is an excipient. The study of the excipient interference on the specular reflective FTIR spectra is complex as most of the excipient does not dissolve in solvent or water. Therefore it is not suitable to dissolve the excipient and API together and deposit them on the surfaces. In addition, dissolving the excipient and API in a solvent does not simulate the real-life scenario of the manufacturing process. During the routine cleaning, the excipient will be washed away. Therefore the most probable scenario is that some excipient may stick to the equipment wall. The excipient surface addition technique used in the study did produce an acceptable result however, further optimization of the excipient deposition will enhance the confidence in the experiment. The key takeaway of the excipient interference study is that the manufacturing equipment must be visually cleaned prior to analysis.

The instrument investigated in the study has a very tight operating distance and angle. The ideal instrument should have a self-control mechanism where an integrated sensor would control the distance and angle, whereby the measurement would only perform when the distance and angle to the measuring surface are optimum. This will eliminate human error completely. Until such a system is developed, the mitigation would be, using an O-ring or some other type of spacer to control the distance between the surface and FTIR data collection interface so that the data would be collected from too close to the surface. Then, use the FTIR spectral alignment check functionality in the MicrolabPC software to prevent collecting data far from the surface.

The temperature effect on the instrument is also significant, and there may be a requirement to regularly collect a background when the instrument is used in an uncontrolled temperature environment. A useful development involves an algorithm being developed and built into the software whereby the FTIR will automatically compensate for the temperature effect, which is possible with the system used in these studies

Although the rapid cleaning verification method using the FTIR can be validated using the guidance outlined in this paper and the previous publication by the author [2], a comparability study to swab testing will be required prior to using the technology in a Good Manufacturing Practice (GMP) regulated pharmaceutical manufacturing environment. The success of this technology has the potential to be a game-changer for cleaning verification practices. However, the size of the current instrument and the collection interface remain significant challenges and will limit the use of the instrument for this application. The current size of the instrument and interface are very large and cannot be accessed to most of the small manufacturing equipment. Smaller compact FTIR and the collection interface are critical for the technology to succeed in the pharmaceutical cleaning verification sector.

Declaration of Competing Interest

Dear Sir/Madam,

We have no conflicts of interest to disclose.

Please address all correspondence concerning this manuscript to me at e.moore@ucc.ie.

Thank you for considering this manuscript.

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