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REVIEW ARTICLE

Techniques to assess film coatings and evaluate film-coated products

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Abstract

Background: Polymeric film coatings have been applied to pharmaceutical solids for decorative, protective, or functional purposes. The application process is quite complex, with variables related to the coating formulation, substrate properties, processing parameters, and interactions thereof, all of which can affect product performance. *Objective*: This article describes a number of experimental techniques used to determine the physical, mechanical, adhesive, thermal, and permeability properties of free and applied films. These analytical tools can be used to optimize product performance, advance our knowledge of the film formation process, and investigate interactions between the coating and the solid surface. *Conclusion*: Through a better understanding of film-coating processes, the cause of problems that arise during manufacturing, defects observed in the coating, and changes in performance upon subsequent storage may be more quickly and accurately resolved.

Key words: *Analysis; film coating; film structure; gloss; mechanical properties; microscopy*

Introduction

Polymeric film coating can be used for decorative, protective[1–3], and functional purposes[4–7]. Generally, the polymer is dissolved or dispersed in a solvent and applied to the solid dosage forms using a spray atomization process. The polymer-containing droplets impinge on the solid surface, spread, and, upon solvent evaporation, form the film. The coating process is considered complex, with variables related to the coating formulation, the substrate properties, the processing parameters, and the interactions thereof. A schematic of the coating process and variables that affect film coating is shown in Figure 1.

The properties of free films are often characterized to evaluate coating formulations. Traditionally, free films are prepared from solutions or suspensions of the coating materials in either a suitable organic solvent (or organic solvent mixture) or water. Most coating formulations used in the pharmaceutical industry today are applied as aqueous-based systems. The use of water as the solvent is less expensive than organic materials, requires no solvent recovery system, and is environmentally friendly. Moreover, the potential toxicities associated with residual solvents in the product are eliminated. When preparing free films, an aliquot of the coating solution or dispersion is applied to a suitable substrate, such as glass, polytetrafluoroethylene, or other useful material. A casting knife is used to spread the liquid into a thin sheet, which is then dried in an oven at a suitable temperature. Preparation of the film samples is not a trivial matter, because defects introduced during preparation can overwhelm the significance of the results.

Casting of polymeric dispersions has been shown to result in nonuniform film surfaces because of sedimentation of solids within the formulation[8]. This problem is further confounded when pigmented coating formulations are cast. An alternative to casting is a spray atomization technique where a spray box apparatus is used[9,10]. Such a system consists of a rotating drum with a nonstick surface and a heat source to facilitate solvent evaporation. The polymeric material is then atomized with air and sprayed onto the drum.

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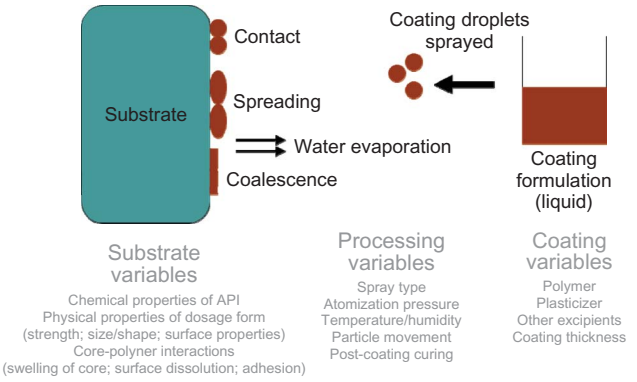

Figure 1. Schematic of the film-coating process.

This technique simulates the coating processes typically used in the pharmaceutical industry and can produce more uniform film surfaces[8]. In addition to the cast and sprayed free films, properties of applied films can be determined to investigate substrate, processing, and storage variables as well as coating formulation considerations.

The purpose of this article is to describe a number of experimental techniques used to characterize film coatings and evaluate coated products. Many of these methods can be used during the formulation development phase to optimize product performance. Moreover, these techniques allow the process of film formation and the interactions between the coating and the solid surface to be investigated. Through a better understanding of film-coating processes, the cause of problems that arise during manufacturing, defects observed in the coating, and changes in performance upon subsequent storage may be more quickly and accurately resolved.

Mechanical assessment techniques

Stress analysis

Stress analysis, performed on sections of isolated films, provides the formulator with a simple, relatively quick means of assessing the mechanical properties of film coatings. Because many polymeric film formulations are hydrophilic in nature, the film samples are generally dried and stored under environmentally controlled conditions before testing. This controlled approach avoids variable moisture content in the films, as residual water can plasticize the coating. Such a general technique has been described by Porter[11]. Experimental variability can be further increased when testing films with defects and those that are inherently fragile.

Tensile stress analysis

Tensile stress analysis is usually performed using a stress–strain analyzer. Fundamentally, films are cut into strips and clamped into the platens of the device. The film is then stretched at a uniform rate until it breaks. The stress–strain curve (a typical example of which is shown in Figure 2) is recorded. From the stress–strain plot, a number of mechanical parameters for the sample can be determined, including the following:

- ultimate tensile strength, which is the highest value for stress recorded before fracture;
- elastic modulus, which is the slope of the 'linear' portion of the stress–strain profile (note: Because polymer films are generally viscoelastic, rather than being perfectly elastic, the so-called linear portion of the stress–strain curve will typically have some degree of curvature to it, and thus will not be perfectly linear);
- strain at failure, which is the fractional increase in film length up to the point of failure;
- work of failure or toughness, which is the area under the stress–strain curve; and
- tensile strength/Young's modulus ratio, which is a measure of crack resistance (higher values are indicative of a lower tendency to crack[12]).

Although these parameters are determined from examining isolated films, which may not be structurally identical to that which can be achieved on an actual coated tablet, the data so derived will almost certainly provide a useful guide to formulators charged with the responsibility of designing a suitable film-coating formulation. By way of example, some typical data indicating the effect of changing the plasticizer levels in a coating are shown in Table 1. Results from such an analysis have been reported[10,11,13,14].

Puncture stress analysis

Generally, the mechanical properties of films are determined while in a dry state. However, in vivo performance may differ as the film becomes hydrated. First, water can function as a plasticizer, thus altering the mechanical properties of the film. In addition, leaching of plasticizers upon exposure to gastrointestinal fluid can occur[15]. Mechanical properties in the hydrated state are especially significant for osmotic pump systems that must maintain physical integrity during exposure to high-osmotic pressures. Understanding the mechanical properties of films in the wet or hydrated state is also important for systems that rely on rupturing of the coating for drug release[16].

To assess the mechanical properties of hydrated polymeric films, a puncture strength test has been reported[17], where a film is placed in a holder and submerged in an appropriate fluid. A puncture probe

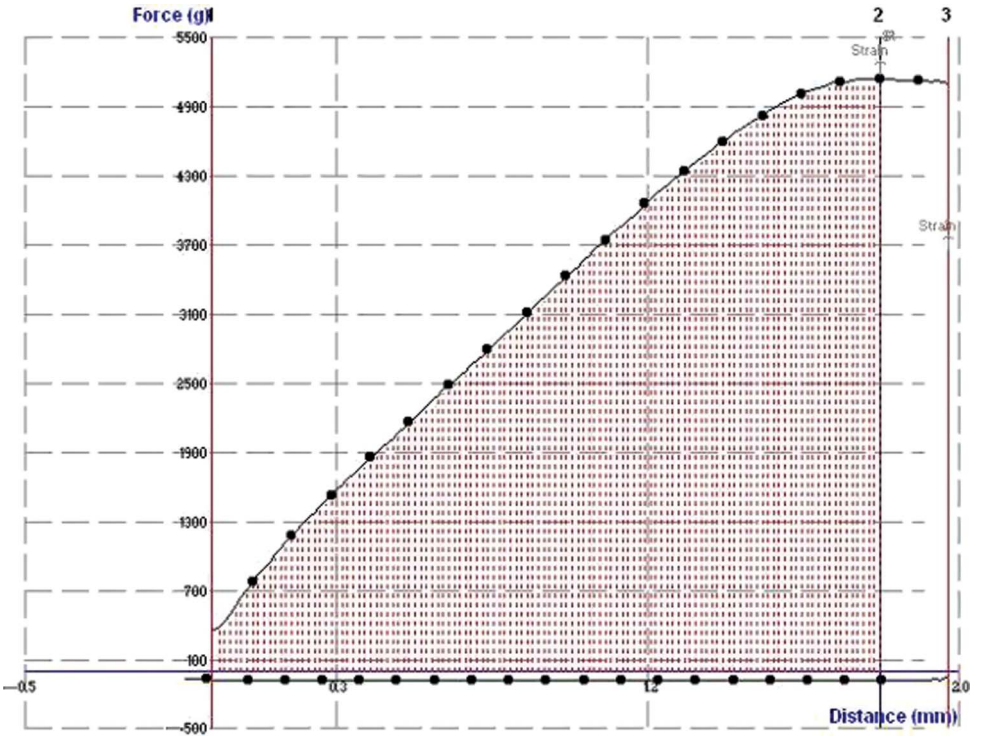

Figure 2. Example of a stress–strain curve.

Table 1. Influence of plasticizer level on the mechanical properties of a film coating.

	Formulation details			Mechanical properties		
Formulation	Polymer content (%, w/w)	Plasticizer content (%, w/w)	Pigment content (%, w/w)	Tensile strength, σ (MPa)	Elastic Modulus, E (GPa)	Ratio $\sigma/E \times 10^{-2}$
1	94.0	0.0	6.0	46.60	2.17	2.15
2	86.0	8.6	5.4	32.72	1.64	1.99
3	79.0	15.8	5.2	15.40	0.81	1.90
4	73.0	21.9	5.1	7.98	0.42	1.92

attached to a load cell is then driven into the hydrated film. Data determined from this experimental setup include

- puncture strength (calculated as the force required to puncture the film divided by the cross-sectional area of the dry film) and
- percent elongation at puncture.

Several publications have reported the use of such a puncture test to compare the properties of wet and dry films[18–20].

Film adhesion

Good adhesion of film coatings to the surfaces of solid dosage forms is a criterion of significant importance, for several reasons. Simple flaking or peeling of a functional film from the substrate will obviously adversely affect drug release or product stability. Shear stresses that develop at the surfaces of the tablets during tumbling in a coating process can cause the coating to be rubbed off if coating robustness and adhesion are inadequate. Today, with the need to provide clear on-product identification of the final dosage form, many tablets are intagliated, where an identification mark is debossed into the tablet face using engraved tablet punches. Lack of good adhesion of the film combined with the internal stresses that develop within the coating on drying (for further explanation, see Rowe[21]) can make legibility of the intagliation difficult (see Figure 3).

Polymer adhesion is related to (i) the type and number of film–substrate interfacial interactions and (ii) the internal stresses within the film. Internal stresses arise due to shrinkage of the film upon solvent evaporation, thermal stress due to the difference in thermal expansion of the substrate and film, and volumetric stress as

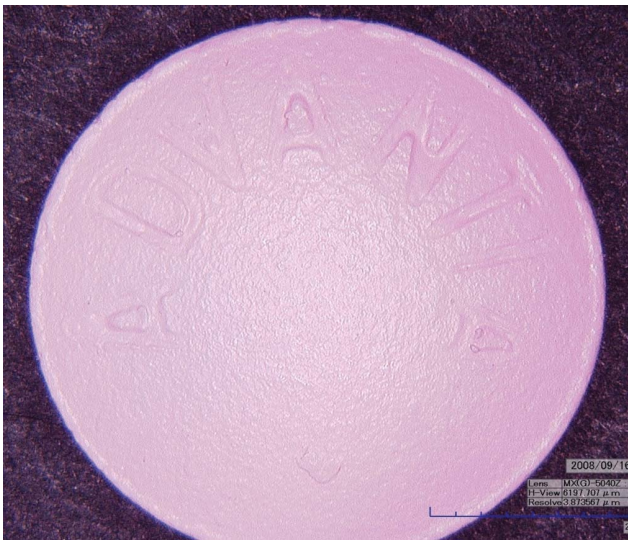

Figure 3. Picture of a bridged intagliation.

the substrate swells upon storage. Equation (1) has been used to estimate total internal stress (P) within a film coating[14,22–24], where E is the elastic modulus of the film, ν is Poisson's ratio, Φ_s is the volume fraction of solvent at the solidification point of the film, Φ_r is the volume fraction of solvent in an air dried film, $\Delta\alpha_{cubic}$ is the difference in coefficient of thermal expansion between the film and substrate, ΔT is the difference between the glass transition temperature of the film and the temperature during manufacturing and storage, ΔV is the volumetric change of the substrate, and V is the original volume of the substrate core.

$$P = \frac{E}{3(1-\nu)}\left[\frac{\Phi_s - \Phi_r}{1-\Phi_r} + (\Delta\alpha_{cubic}\Delta T) + \left(\frac{\Delta V}{V}\right)\right] \quad (1)$$

Adhesion testing is a useful tool in designing an appropriate coating because film adhesion can vary from one product to another, especially for tablets that are quite hydrophobic or have low porosity. Rowe[25] has published extensively in this area. Contact angles between the coating formulation and substrate surface provide information regarding substrate wettability, where the more wettable surface produces greater interfacial interactions and thus, generally, stronger adhesion. A modified tensile tester has been used to peel the film from a tablet surface at a 90° angle. The peel strength, however, is dependent on the elasticity of the film and the uniformity of adhesion[26]. The most widely accepted methodology to determine polymer adhesion is the butt adhesion test, where the entire film is removed normal to the surface of the tablet. This technique eliminates

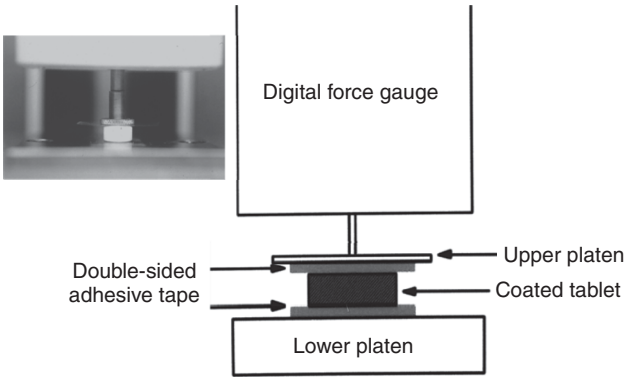

Figure 4. Schematic of a butt adhesion test. Adopted from Felton and McGinity[27].

variations because of the elasticity of the film and is less influenced by the uniformity of adhesion.

Available stress–strain analyzers, essentially of the type used for performing tensile stress analysis of free films, have been adapted for butt adhesion testing. A schematic of the experimental setup is shown in Figure 4. One of the platens is modified to allow for gripping of a coated tablet, whereas the other platen provides a flat surface to which the film coating on the upper tablet surface is attached with double-sided adhesive tape. Once the tablet has been appropriately located in the lower platen, and the adhesive tape is affixed to the upper platen, the other platen is lowered so that the adhesive becomes firmly bonded to the exposed surface of the coating. Reversal of the direction of movement of the upper platen allows the coating to be removed from the tablet surface, and the force required to do so, generally expressed as the force per unit area, is recorded. To facilitate removal of the coating from the tablet surface, the test sample is usually a flat-faced tablet where the coating has been removed from the sidewalls of that tablet. This is done so that the force being recorded is simply that required for adhesive failure and not that required also for tearing the film at the edges of the tablet. Although conventional convex tablets can be used, the use of flat-faced tablets simplifies the test and increases the chances that the coating will be removed completely from the exposed surface of the tablet. Felton and McGinity[26] have provided a thorough review of polymer adhesion to pharmaceutical solids.

An example of a force–deflection profile obtained from a butt adhesion test is shown in Figure 5. The figure is similar to a stress–strain profile obtained from tensile testing of free films. Graphing the force–deflection data enables the force that develops within the sample during the experiment to be visualized. The force of adhesion is the force at which the film is removed from the substrate surface. Elongation at

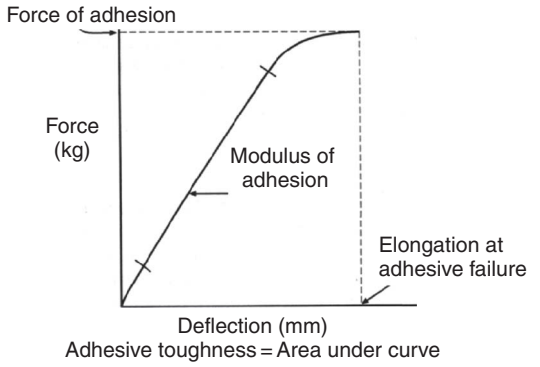

Figure 5. Schematic of a force–deflection profile obtained from a butt adhesion test. Adopted from Felton and McGinity[28].

Table 2. Results obtained by undertaking adhesion test to show how an improved coating formulation can resolve the logo bridging problems.

	Measured adhesion (kPa)	
Tablet cores	Film-coated tablets showing the adhesion problem	Tablets coated with improved coating formulation
Placebo tablets	30	>128
Ibuprofen tablets	15	220

adhesive failure is the distance the platen moved at film removal and reflects the ductility of the film. The modulus of adhesion is analogous to the Young's modulus in the tensile testing of free films and is the slope from the linear region of the force–deflection diagram. And, finally, work of adhesive failure is the area under the curve. Some typical adhesion data, used in the resolution of the bridging of intagliation problem shown in Figure 3, are provided in Table 2.

Surface micro- and nanoindentation testing

Although stress analysis of free films has been a primary means of conducting mechanical tests on film coatings, the testing of isolated films that are structurally different from those deposited on the surface of a solid often poses questions about the value of the data obtained. Thus, conducting analyses on applied films can provide a potentially useful alternative.

The principle of micro- or nanoindentation techniques involves forcing an indenter (often, but not always, spherical) under the influence of a measured load, into the surface of the applied coating. From the initial penetration, the resistance to surface deformation, or surface hardness value, can be determined. From the recovery obtained after the load has been removed, it is possible to calculate the elastic modulus of the coating. Such a technique has previously been described[10,29,30].

More recently developed mechanical devices, often called nanoindentation testers, use an established method where an indenter tip with a known geometry is driven into the surface of the test material by applying an increasing normal load. When reaching a preset maximum value, the normal load is reduced until partial or complete relaxation occurs. This procedure is performed repetitively; at each stage of the experiment, the position of the indenter relative to the sample surface is precisely monitored with a differential capacitive sensor. For each loading/unloading cycle, the applied load value is plotted with respect to the corresponding position of the indenter. The resulting load/displacement curves provide data specific to the mechanical nature of the coating being examined. Established models are used to calculate quantitative hardness and modulus values from the data obtained.

A typical load/displacement curve is shown in Figure 6. From this graph, the compliance C ($1/S$, which is the inverse of the contact stiffness) and the contact depth h_c are determined after correction for thermal drift. A simple linear fit through the upper one-third of the unloading data intersects the depth axis at h_t. The stiffness, S, is given by the slope of this line. The contact depth, h_c, is then calculated using Equation (2):

$$h_c = h_m - \varepsilon(h_m - h_t) \qquad (2)$$

where ε depends on the material being tested. Young's modulus, E, can then be calculated, and from it, surface hardness is determined. Some typical data obtained for film-coated tablets are shown in Table 3.

Thermal analysis

Determination of the glass transition temperature

Most polymers used in pharmaceutical film-coating processes are amorphous and hence the mechanical properties of the material change as a function of temperature.

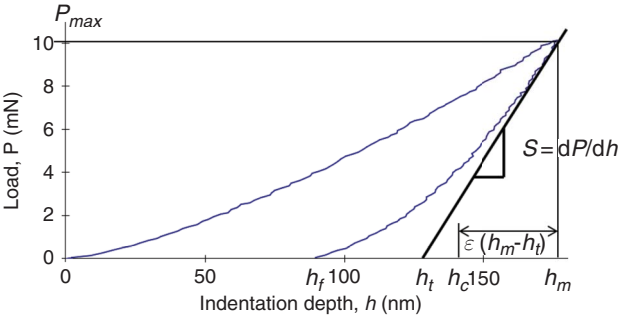

Figure 6. Load–displacement profile from a Microindenter.

Table 3. Mechanical properties of applied film coatings determined using a surface nanoindentation tester.

Sample	$\underline{H}_v$ [Vickers]	H [MPa]	E [GPa]	Δd [mm]
1	27.47	290.7	6.42	9.08
2	25.82	273.3	6.65	9.25
3	24.26	256.7	6.11	9.57
4	19.58	207.2	5.48	10.53
5	26.49	280.3	6.71	9.15
Average	24.72	261.64	6.27	9.52
Std dev	2.78	29.38	0.45	0.53

The glass transition temperature (T_g) of such polymeric films is the temperature at which the mechanical properties change from stiff and brittle to soft and elastic. At temperatures below the T_g, polymer chain movement is restricted and the film is rigid. In contrast, an increase in the mobility of the polymer chains at temperatures above the T_g allows the film to behave as a flexible material. The most common technique used to determine the T_g is differential scanning calorimetry (DSC). Using DSC, a sample of the film is heated at a controlled rate. Thermal transitions, where more energy is absorbed or emitted by the sample in comparison to the reference (typically an empty pan), are determined. Appropriate analytical software allows for quick determination of the onset and midpoint of the transition. Modifications to conventional DSC testing include the triple-cell system that allows for more precise measurements of enthalpy and temperature-modulated units that separate reversing transitions, such as melting or glass transition temperature, from nonreversing events, such as evaporation or degradation.

There are numerous examples in the literature of using the T_g to evaluate polymer properties and interactions with excipients in the coating formulation[31–33]. In particular, the effectiveness of plasticizers in polymeric films is often evaluated in this manner, with agents that produce the greatest decrease in T_g being considered more effective plasticizers, as the intermolecular interactions between the polymer chains are reduced[34–36].

DSC is also used to study polymer miscibility[7,20,37]. The blending of polymers to achieve desired mechanical properties is a practice that is becoming more commonplace and polymer–polymer miscibility is an important consideration. Polymers that are miscible will exhibit a single glass transition temperature, somewhere between the two individual materials. In contrast, two distinct T_g values will be observed for immiscible films. In addition, DSC can be used to determine melting points and detect polymorphs[38] and to investigate oxidative degradation[39,40].

Determination of the minimum film-forming temperature

The minimum film-forming temperature (MFFT) is the minimum temperature necessary to cause coalescence of a polymeric dispersion to form a film. At temperatures below the MFFT, an opaque or white powdery material is formed upon solvent evaporation, whereas clear, transparent films result at temperatures equal to or greater than the MFFT. Knowledge of the MFFT is critical in film-coating processes, because the bed temperature in the coating process must be above this temperature. The MFFT can be determined experimentally by pouring the polymeric material onto a temperature gradient plate. Drying air is then blown across the surface. The lowest temperature at which a transparent film is visually observed is considered the MFFT. In some cases, the MFFT for a given polymer may be below room temperature[5]. Plasticizers and other excipients in the coating formulation can affect this parameter[41,42].

Microscopy analytical techniques

Digital imaging for surface analysis of film-coated products

Oftentimes, the visualization of the surface characteristics of film-coated tablets and the identification of surface defects can only be achieved through high-power imaging techniques. Although a number of classic techniques, including conventional microscopy, can be usefully employed for these purposes, digital imaging can provide an opportunity not only for visualizing surface characteristics, but also for accurately storing image files. Focusing at different depths of field allows the final image to be reconstructed in a three-dimensional format, thus allowing key defects, structure, and other attributes of the surface to be recorded and stored electronically (Figure 7).

Scanning electron microscopy

One of the most commonly employed microscopic techniques is scanning electron microscopy (SEM). This instrument images the sample surface by scanning a high-energy beam of electrons in a raster scan pattern. The electrons interact with atoms at or near the surface of the sample to produce high-resolution images. The SEM micrographs are three-dimensional in appearance and provide useful information regarding the surface topography of the sample. In conventional imaging, samples must be electrically conductive at the surface and electrically grounded to prevent accumulation of electrostatic charge at the surface. A thin layer of gold,

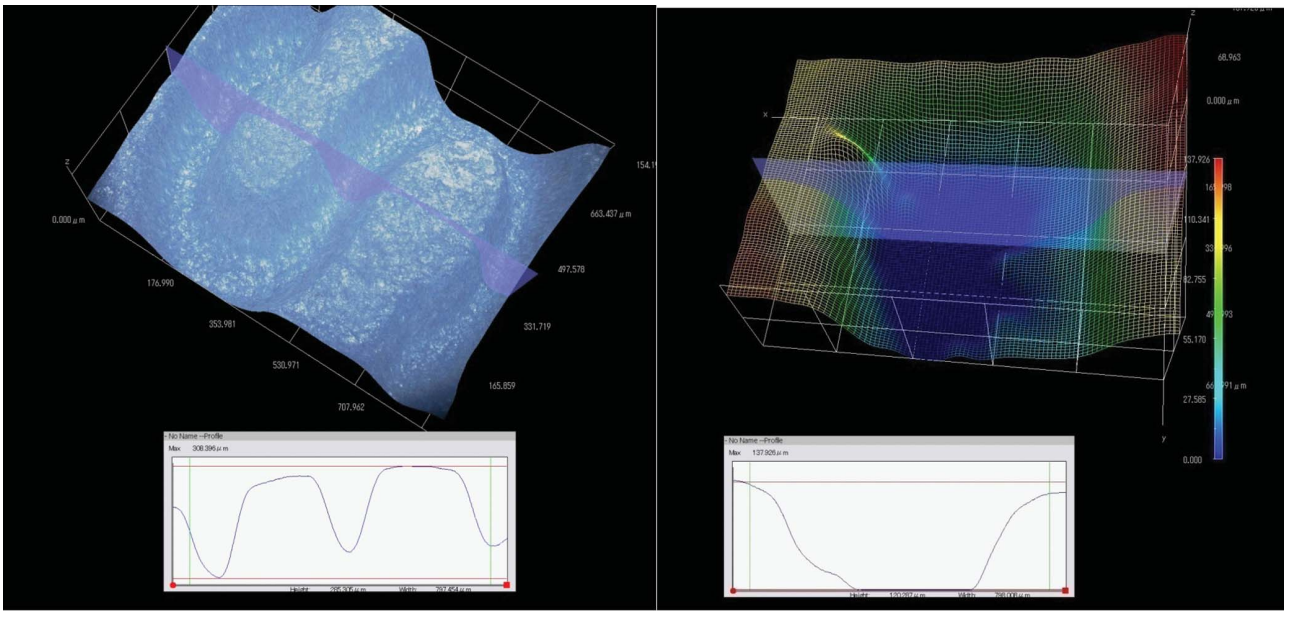

Figure 7. Example of data obtained from a digital imaging experiment.

gold/palladium, or other appropriate material is generally deposited on the surface of nonconductive samples using sputter coating or high-vacuum evaporation techniques. Coating even conductive samples can enhance spatial resolution. SEM can be combined with energy-dispersive X-ray spectroscopy for the elemental analysis of the surface of the sample. This technique analyzes X-rays emitted from the sample during the electron scan and relies on the principle that each element has a unique atomic structure. This technique can be used to identify, inter alia, the migration of ingredients from the core [such as the active pharmaceutical ingredient (API)] into the coating.

Atomic force microscopy for determining coating surface and roughness characteristics

Several techniques for assessing surface roughness of both coated and uncoated products have been reported in the literature (see 'Determination of surface roughness of film-coated tablets' in the next section). Conventional SEM has been used to provide qualitative information regarding surface morphology and the appearance of the coating whereas profilometric methods can be used to quantitatively measure surface roughness. Another technique that has been shown to be useful to quantify roughness is atomic force microscopy (AFM). With this technique, a microscale cantilever with a sharp tip is scanned across a relative small area of the solid. The tip interacts with the sample to cause the cantilever to deflect and thus measures the mechanical contact force. Three-dimensional images can be obtained with AFM.

The tip of a conventional AFM unit can be replaced with a thermal probe and this instrumentation is known as scanning thermal microscopy. The power required to maintain the temperature of the tip is monitored, thus allowing for the simultaneous gathering of topographical and thermal data. Local thermal events, such as melting temperature, T_g, and water loss, and multiphase polymer systems can be investigated with this system[43].

Confocal microscopy

Confocal laser scanning microscopy (CLSM) is an optical imaging method that has been used in the biological sciences for many years. This technique has only recently been used to investigate systems of pharmaceutical interest[44–47]. With this system, a laser beam is passed through an aperture where it is then focused by an objective lens onto a sample. This process occurs in a raster scan pattern to create the images. Reflected light not coming from the focal plane and out of the focus light is blocked to allow imaging of planes at different depths. Thus, CLSM has the ability to depth profile in a nondestructive manner. However, a major limitation to the use of CLSM is that a fluorescent compound must be used. As is common in the biological sciences, fluorescent dyes can be added to the coating formulation and/or the tablet to investigate systems of interest.

Techniques for assessing the surfaces of film-coated tablets

Coating gloss measurement

The measurement of gloss transcends many industries, and techniques to quantify glossiness have been described more than half a century[48]. The determination of gloss measurement for pharmaceutical film-coated tablets has been described by Rowe[49,50]. Fundamentally, incident light falling onto a surface (in our case, a coated tablet surface) can be reflected in a number of ways. Two extremes are specular reflection and diffuse reflection (Figure 8). Specular reflection, or that which will be reflected from a perfectly mirrored surface, is characterized by the angle of incident light being exactly the same as that of the angle of reflected light. Diffuse reflection occurs with light being reflected from a very uneven or granular surface so that the incident light is scattered in many directions. In simple terms, a glossy film will be more likely characterized by a high component of specular reflection, whereas a matte film will produce almost completely diffuse reflection. The measurement of the general appearance (i.e., color) of a film-coated tablet essentially involves the determination of diffuse reflectance, because pigment particles dispersed in a polymeric film will cause much of the reflected light to be scattered.

The reflectance characteristics of coated surfaces can be measured instrumentally using reflectance spectrophotometers using a technique known as goniophotometry[48]. Specialized instruments, often called gloss meters, are used to determine the magnitude of the specular reflectance component and thus facilitate the quantification of gloss.

When considering pharmaceutical film-coated tablets, although the nature of the coating formulation can have a significant impact on gloss, much of the derived gloss is related in a substantial way to the actual coating process conditions used. For example, in the response surfaces shown in Figure 9, the gloss values for the two systems shown are very similar. In the case of the copovidone-based coating, the gloss is primarily due to the production of a smoother coating (i.e., a processing issue), whereas the gloss is primarily a characteristic of the polymer used (i.e., a formulation issue) for the coating based on poly(vinyl alcohol) (which is inherently rougher).

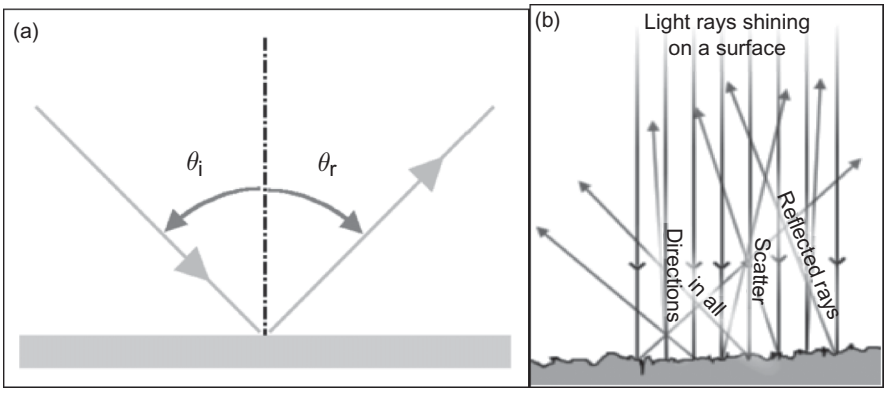

Figure 8. (a) Specular reflectance and (b) diffuse reflectance.

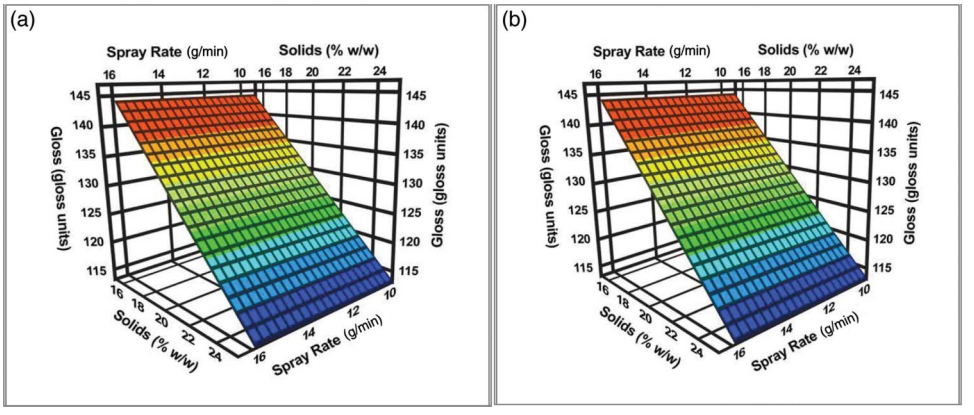

Figure 9. Example of a gloss–response surface. (a) Copovidone-based coating system. (b) Poly(vinyl alcohol)-based coating system.

Determination of surface roughness of film-coated tablets

Pharmaceutical film coatings are applied under very dynamic conditions, where atomized droplets of the coating solution or dispersion, after a very short distance of flight from the spray nozzle to the surface of the dosage form being coated, are required to impinge with that surface, wet the surface, and coalesce into a dried film before adjacent tablets touch each other (which would otherwise allow the adhesive nature of the coating to cause tablets to stick together). Hence, film coating is a process where it is critical to strike a careful balance between

- the need for the coating to remain liquid long enough for a high-quality, coherent film to be formed and
- the need for the coating to dry almost instantaneously so that tablets do not stick together.

Spray rate and drying time are major variables that influence the smoothness of the coated surface. Atomized droplets of coating liquid can dry before they have had a chance to coalesce into a smooth coating. The result is a problem commonly termed 'orange peel', where the profile of the original droplets is clearly evident in the surface structure of the final coating. In contrast, overwetting of the solid can result in surface dissolution and potential migration of material from the tablet into the film[51,52].

Accepting that some degree of such a surface defect will always be evident in film-coated tablets, the goal of the formulation scientist and process engineer is to keep the problem to a minimum. The availability of a suitable means to quantify the degree of surface roughness thus becomes an invaluable tool in the ability to optimize film-coating formulations and coating processes. Over the last 40 years or so, a number of such tools have been used. Earlier approaches to assess roughness tended to rely mainly on mechanical techniques, whereas, more recently, there has been growing reliance on using laser and/or light-scanning techniques for such quantification.

Mechanical profilometry as a means of determining coating surface roughness

Mechanical profilometry techniques, when utilized for quantifying the surface roughness of pharmaceutical dosage forms, were first described by Nadkarni et al.[53] These researchers used a device similar to that described earlier by Schwartz and Brown[54] to quantify the roughness of pharmaceutical tablets and its impact on adhesion of a film coating to those tablets. Subsequently, Rowe[29,55] used mechanical profilometers quite prolifically to quantify the roughness of both tablet surfaces and those of film-coated tablets.

Mechanical profilometers, in a manner similar to the needle on an old phonograph machine, use a stylus to map the surface characteristics of the material in question. The stylus is drawn across a surface under a light load to maintain good contact in a manner that allows the peaks and valleys of that surface to be recorded. Once the surface profile has been recorded, the results can be mathematically treated to allow mean roughness values to be calculated.

Laser/light-scanning profilometry to determine coating surface roughness

Mechanical profilometers potentially suffer from several drawbacks. First, there is a risk of the stylus modifying the surface structure when the coating is soft. These mechanical profilometers are only able to carry out measurements on tablet surfaces that are very flat because of the linear motion of the device. In addition, only a thin strip of the surface, dependent on the size of the stylus, can be measured. To overcome these particular limitations, there has been growing reliance in recent years on the use of noncontacting profilometers that use either a focused laser or a light beam to scan the surface of the specimen. One such device, called a Nanovea Light Scanning Profilometer, uses a source of white light and employs axial chromatism, where light passes through an objective lens with a high degree of chromatic aberration. The refractive index of the objective lens will vary in relation to the wavelength of the light. In effect, each separate wavelength of the incident white light will refocus at a different distance from the lens (different height). When the measured sample is within the range of possible heights, a single monochromatic point will be focalized and form the image. Because of the confocal configuration of the system, only the wavelength in focus will pass through the spatial filter with high efficiency, thus causing all other wavelengths to be out of focus.

For a test sample composed of several layers, each layer will reflect light of a different wavelength, and the spectrum of detected light will be composed of a series of spectral peaks. The chromatic aberration technique allows all layers to be detected and their positions to be measured simultaneously. The spectral analysis is accomplished using a diffraction grating, which causes each wavelength to deviate at a different position intercepting a line of a charge-coupled device; this in turn indicates the position of maximum intensity and allows direct correspondence to the Z height position. From this, a profile of surface roughness can be extracted and a three-dimensional image can be reconstructed.

Noncontacting profilometers can be programmed to scan a defined area of the surface in question, allowing

Table 4. Various roughness parameters that can be determined from noncontact profilometry surface scans.

Symbol	Roughness term	Definition of term
Sq	Root mean square height	SD of the height distribution, or RMS surface roughness. Computes the standard deviation for the amplitudes of the surface
Ssk	Skewness	Skewness of the height distribution. Third statistical moment, qualifying the symmetry of the height distribution
Sku	Kurtosis	Kurtosis (or relative flatness/peakedness) of the height distribution. The fourth statistical moment, qualifying the flatness of the height distribution
Sp	Maximum peak height	Height between the highest peak and the mean plane
Sv	Maximum pit height	Depth between the mean plane and the deepest valley
Sz	Maximum height	Height between the highest peak and the deepest valley
Sa	Arithmetic mean height	Mean surface roughness, computing the mean distances between the peak heights and valley depths in comparison to the mean plane

any one of a number of mean surface roughness values (as shown in Table 4) to be computed. The use of light-scanning profilometers has been described by Drefko et al.[56], who have used the technique to aid in optimizing a process for applying delayed-release coatings to aspirin tablets, and Hadfield et al.[57], who used the same technique to study the influence of superdisintegrants on the surface roughness of film-coated tablets.

Film-structural analysis techniques

Terahertz analysis

Terahertz analysis is a totally nondestructive and rapid imaging technique that operates in the far-infrared (10–120 cm^{-1}) region of the electromagnetic spectrum. The principles of operation are similar to that of sonar, where the signal that bounces back off a sample is modified based on the sample it contacted. The usefulness of this technique for analyzing film-coated products stems from the fact that terahertz radiation can penetrate through most pharmaceutical excipients. In addition, polymers used in film-coating formulations appear either completely transparent or semitransparent to terahertz radiation.

Terahertz analysis, more specifically terahertz pulsed imaging, has been shown to be a very useful technique for

- quantifying the amount of coating deposited on coated tablets and the thickness of the applied film[58,59],
- examining the interaction between different layers in a multilayered coated product[60,]
- visualizing the variation in coating thickness across the surface of enteric-coated tablets that have intagliations[56], and
- explaining inconsistencies in drug release (5-aminosalicylic acid) from delayed-release coated tablets at pH values below 7.2[61].

Using a modified technique involving terahertz electric field peak strength, Ho et al.[59] were able to identify the causes for differences in drug release from tablets coated with a modified-release coating. In that study, drug release was shown to be dependent on the structure of the film, specifically coating density.

X-ray photoelectron spectroscopy

As mentioned earlier, polymeric coatings are generally applied to solid substrates using the spray atomization technique, where polymer-containing solutions or dispersions are atomized with air and delivered to the substrate surface as fine droplets. These droplets spread across the surface and solvent evaporation causes polymer chain coalescence and film formation. Because most solid dosage forms are designed to dissolve in water-based biological fluids and the majority of coating systems used today is aqueous-based, dissolution of the outermost surfaces of the substrate can occur during the coating process, permitting physical mixing at the film–tablet interface and allowing for the potential migration of drug or excipient into the film[51,52]. This physical mixing and migration of components into the coating can affect the mechanical, adhesive, and drug release properties of the polymer film.

One technique that can be used to investigate the film–tablet interfacial region is X-ray photoelectron spectroscopy (XPS). XPS is a surface-sensitive technique that has been used to determine both elemental analysis and chemical structure of materials of pharmaceutical interest[62–64]. In a preliminary study, XPS was combined with intermittent ion bombardment to depth profile and quantify film–tablet interfacial thickness[51]. Drawbacks to this technique included the requirement to use unique, identifiable components in both the film coating and the substrate and the need for tedious sample preparation. More recently, XPS was combined with a classification method that permitted the evaluation of the interface for any system containing carbon and eliminated complicated sample preparation[52].

Assessment of material transfer across film coatings

Water vapor permeability

The interaction of water vapor with pharmaceutical materials represents an area of broad interest, because the phenomenon provides insight into potential changes that can take place, including solid-state transitions and the stability of APIs. Oftentimes, conducting studies involving the interaction of moisture with materials of interest can be a very time-consuming undertaking. Film coatings can be used to slow water vapor permeation and thus extend the stability and hence the shelf life of drugs that degrade by hydrolytic mechanisms[65,66]. Analytical techniques can quantify the effectiveness of both free films and applied films as barriers to water vapor permeability.

Water vapor transmission through free films

To assess water vapor permeability, a free film is placed across the top of a glass or aluminum container such that water vapor can only flow either into or out of the transmission cell through the film. Inside this cell, a known vapor pressure is created using a saturated salt solution. The transmission cell is then placed in another chamber at a different vapor pressure, thus creating the vapor pressure gradient necessary for water movement. The transmission cell is weighed at specified time intervals and the change in weight is plotted versus time. The slope of the line from this graph calculated using linear regression is the water vapor transmission rate. The permeability constant (P_{erm}) of the film can then be calculated using Equation (3):

$$P_{\text{erm}} = \frac{WVTR \times L}{A \times \Delta P} \tag{3}$$

where L is the film thickness, A is the area of the exposed film, and ΔP is the vapor pressure gradient. A number of variables have been shown to influence water vapor permeability, including film composition, film thickness, and film preparation technique[2,7,67,68].

Dynamic vapor sorption analysis to assess moisture permeability of applied films

Dynamic vapor sorption (DVS) is a tool that quantifies water vapor permeability of applied polymeric films. A schematic for a typical DVS apparatus is shown in Figure 10. Essentially, DVS facilitates the rapid, accurate determination of moisture. Using an ultrasensitive recording microbalance, measurements are made inside a chamber, that is, under dynamic environmental control. The sample under test is exposed to varying conditions of moisture and temperature, and the response of the sample, with respect to a reference sample, is measured gravimetrically.

DVS is a tool that has become utilized across a broad range of industries. In pharmaceutical applications, DVS has been used to

- examine moisture sorption on chewable tablet blends[69],
- investigate the stability of prednisone and diphenylhydantoin[70],
- study the recrystallization of amorphous lactose[71], and
- examine the interaction of water with ethyl cellulose, especially with respect to particle size of the polymer[72].

Data from DVS combined with that from DSC experimentation have been shown to be useful in determining mechanistic differences in water vapor permeabilities between various moisture barrier film coatings[73].

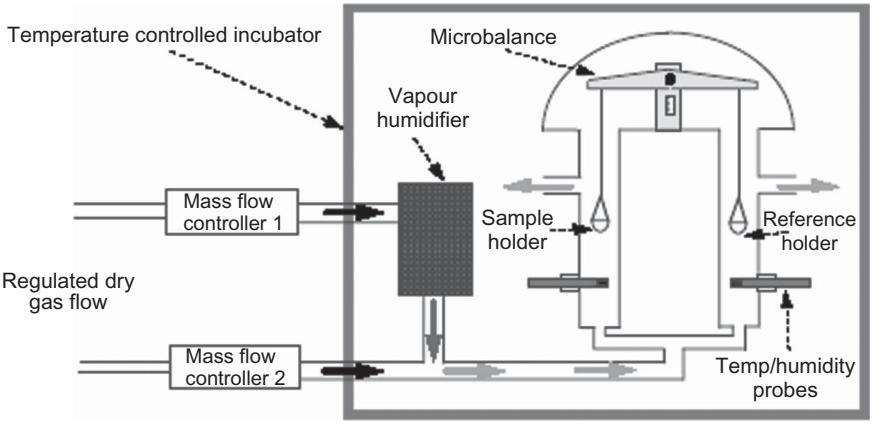

Figure 10. Schematic of a dynamic vapor sorption experimental setup.

Oxygen transmission

The rate of oxygen permeation is a measure of the effectiveness of the coating material as a barrier to oxygen and is especially important when working with APIs that degrade by oxidative processes. Film composition and film thickness have been shown to significantly influence oxygen vapor transmission[74,75].

Oxygen permeability of free films

Unlike water vapor transmission determinations, the assessment of oxygen transmission across free films is more complex because of the analytical techniques required to detect oxygen (water vapor permeation can often be determined by simple gravimetric means). The majority of published work has been focused on assessing oxygen permeation of free films, where a test specimen is placed between two chambers, as shown in the schematic in Figure 11. Permeation of oxygen molecules across the film-coating sample is determined by exposing one side (the donor) to pure oxygen; the distal side of the film (representing the receptor compartment) is exposed to nitrogen. As oxygen molecules permeate through the film, the concentration of oxygen in the nitrogen-rich compartment increases and the level can be detected by means of a coulometric sensor.

The use of such a technique has been demonstrated, *inter alia*, by

- Butler et al.[76], who studied how the permeability of chitosan films was affected by both composition and storage conditions;
- Gulian et al.[75], who studied the oxidative protection of ibuprofen tablets coated with film coatings based on poly(vinyl alcohol); and
- List and Kassis[74], who examined the effects of coating composition on the permeability of various tablet coatings to both water vapor and oxygen.

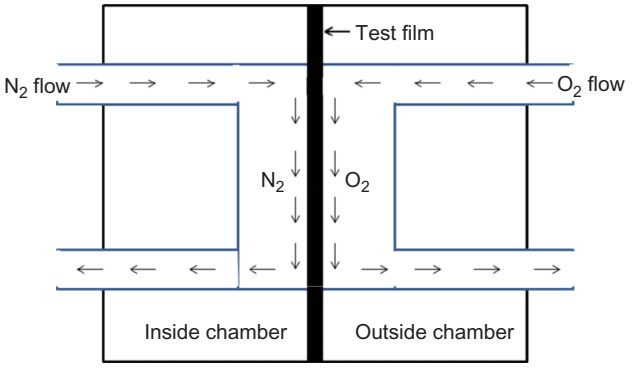

Figure 11. Schematic of an oxygen transmission cell for the determination of oxygen permeability of free films.

Oxygen permeability of applied films

The oxygen permeability of applied films can be determined using a nondestructive electron paramagnetic resonance spectroscopic technique described by Felton and Timmins[3]. This method involves the insertion of an oxygen-sensitive lithium phthalocyanine crystal inside the dosage form and is based on that reported by Liu et al.[77] The peak-to-peak linewidth of the first derivative of the electron paramagnetic resonance spectra of this lithium-based crystal is directly proportional to the partial pressure of oxygen (pO_2). The pO_2 can be plotted versus time and linear regression can be used to calculate the slope of the line to obtain the oxygen permeation rate. The rate of oxygen permeation through an applied film has been shown to be significantly slower than through uncoated tablets[3].

Permeability of gastric fluid across applied enteric coatings

Enteric coatings are used to protect drugs that degrade in the presence of the acidic environment or gastric enzymes in the stomach as well as to protect the stomach from exposure to irritating drugs. The United States Pharmacopoeia (USP) disintegration test has been extensively used to assess the performance of enteric-coated systems. However, it is often of interest to be able to quantify enteric performance in a more quantitative measure than simply pass or fail. One technique that has been reported in the literature to quantify the permeability of the film to gastric fluid involves a modification to the conventional USP disintegration test. This so-called 'modified disintegration test' requires individual coated tablets to be accurately weighed before exposure to the acidic media. Tablets are next placed in the baskets of the USP disintegration tester and exposed to simulated gastric fluid for a period of time (usually 2 hours). A modification of this technique involves placing 500–1000 tablets in a shallow tray, covering them with simulated gastric fluid and allowing them to soak in the solvent, also for 2 hours. In either test, at the end of the prescribed time, the coated tablets are retrieved, blotted dry, and reweighed. The weight gain, equivalent to the amount of gastric fluid absorbed, is then calculated. If the coated product disintegrates before termination of the experiment, the unit is said to have 100% absorption. Cunningham et al.[78] used this technique to investigate the effects of tablet shape on the performance of an enteric film coating.

Conclusions

This article describes a number of analytical tools available to the pharmaceutical scientist that enable the

properties of film coatings and film-coated products to be investigated. Although this is by no means an all-inclusive list, techniques in common practice have been included. It is to be expected that techniques from other industries will continue to be applied to pharmaceutical systems, whereas new analytical capabilities will also be developed. The intent of this article is simply to describe some very useful analytical methods that may prove useful in gaining a further understanding of both the film-coating and film-formation processes. At the same time, it is expected that these techniques may aid the formulation scientist in the development of film-coating systems, especially with a view to achieving complete optimization of such systems.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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