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A Novel Approach in the Assessment of Polymeric Film Formation and Film Adhesion on Different Pharmaceutical Solid Substrates

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ABSTRACT

The purpose of this study was to evaluate the nature of film formation on tablets with different compositions, using confocal laser scanning microscopy (CLSM), and to measure film adhesion via the application of a novel "magnet probe test." Three excipients, microcrystalline cellulose (MCC), spray-dried lactose monohydrate, and dibasic calcium phosphate dihydrate, were individually blended with 0.5% magnesium stearate, as a lubricant, and 2.5% tetracycline HCl, as a fluorescent marker, and were compressed using a Carver press. Tablets were coated with a solution consisting of 7% hydroxypropyl methylcellulose (HPMC) phthalate (HP-55), and 0.5% cetyl alcohol in acetone and isopropanol (11:9). The nature of polymer interaction with the tablets and coating was evaluated using CLSM and a designed magnet probe test. CLSM images clearly showed coating efficiency, thickness, and uniformity of film formation, and the extent of drug migration into the film at the coating interfaces of tablets. Among the excipients, MCC demonstrated the best interface for both film formation and uniformity in thickness relative to lactose monohydrate and dibasic calcium phosphate dihydrate. The detachment force of the coating layers from the tablet surfaces, as measured with the developed magnet probe test, was in the order of MCC>lactose monohydrate>dibasic calcium phosphate dihydrate. It was also shown that the designed magnet probe test provides reliable and reproducible results when used for measurement of film adhesion and bonding strength.

KEYWORDS: Film coating, film formation, confocal laser scanning microscopy (CLSM), adhesion test, magnet probe test

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INTRODUCTION

The application of coatings to pharmaceutical solids has been practiced for over 150 years. Coating has been used in a variety of pharmaceutical products such as tablets, beads, pellets, granules, capsules, and drug crystals.[1] It offers many benefits, namely, improving the aesthetic qualities of the dosage form, masking unpleasant odor or taste, easing ingestion, improving product stability, and modifying the release characteristics of the drug, for example, in enteric coating, colonic delivery systems, controlled release systems, and osmotic pump systems.

Film coating is a complex and multistep process involving the application of thin polymer-based layers to a substrate under conditions that permit parallel computations between the addition rate of the coating liquid and drying, uniformity of distribution of the coating liquid across the surface of the substrate, and optimization of quality of the process and final coat.[1,2]

Film layers may be formed from either polymeric solution (organic-solvent- or aqueous-based) or aqueous polymeric dispersion (commonly called latex). In the majority of film-coating formulations, polymer is the main ingredient; it may be from different origins, including cellulosics, acrylics, vinyls, and combination polymers. Thus, viscosity, chemical structure, molecular weight, film modifiers, and molecular weight distribution of the polymers play a critical role. Polymers used in film coating are mostly amorphous in nature; therefore, glass transition temperature (T_g) plays an important role in formation of the coat layer and its stability. Below T_g polymer is brittle, while it becomes rubbery and flexible above T_g, which indicates an increase in the temperature coefficient of expansion. Many polymers used in film coatings have high T_gs; for instance, the T_g of hydroxypropyl methylcellulose (HPMC) is 170°C to 180°C. To lower T_g and impart flexibility, plasticizers (eg, polyethylene glycol, triacetin, glycerol) are added. The magnitude of their effect is dependent on the compatibility or degree of interaction of the plasticizer and the polymer.[1]

Many factors may affect the film formation and the interaction between the film and the substrates as well as the stabil-

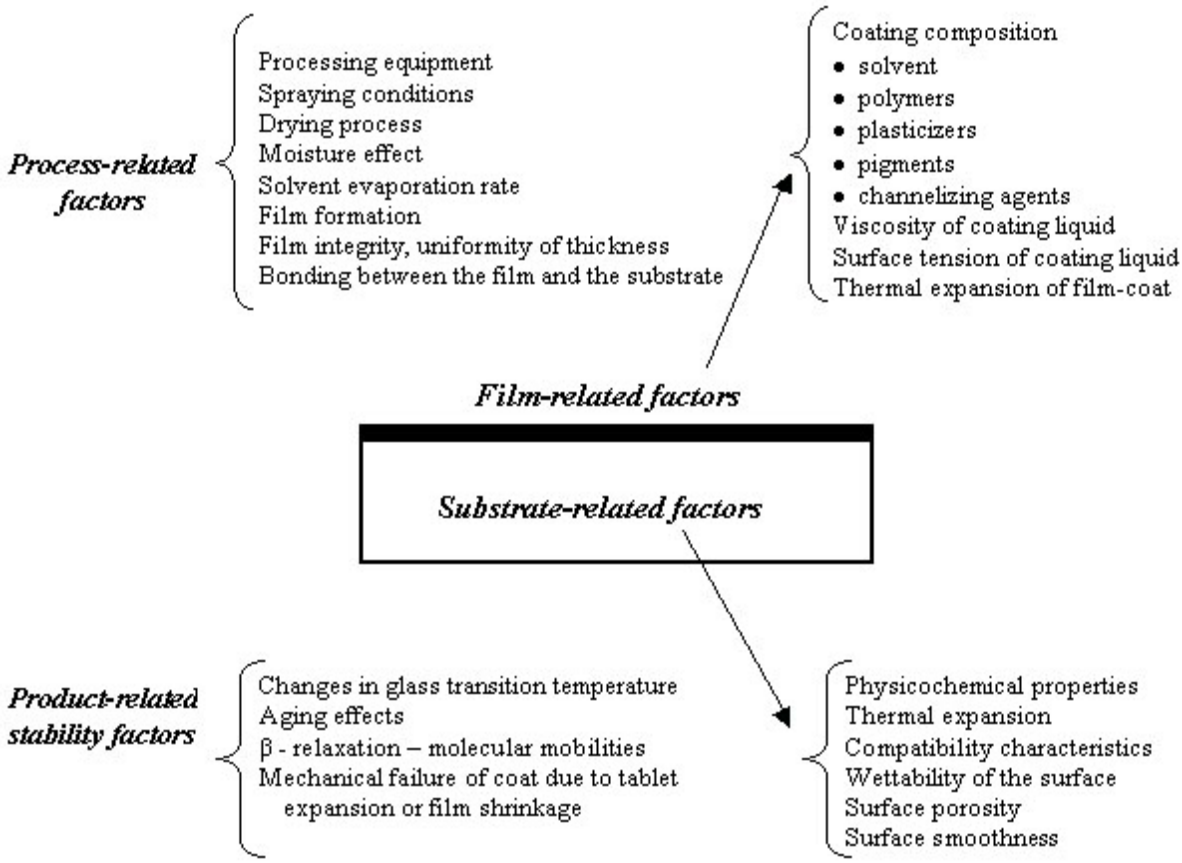


Figure 1. Factors involved in the typical film-coating process and film stability.

ity of the film upon aging, as shown in Figure 1. These factors are substrate related, film related, and process related. Substrate-related factors include formulation components' physicochemical properties, thermal expansion, compatibility characteristics, wettability of the surface, and surface porosity.[3-5] Factors related to the polymeric film and process include coating composition (solvent, polymers, plasticizers, pigments, channelizing agents), viscosity and surface tension of the coating liquid, thermal expansion of film coat and thermal stresses due to different thermal properties of the film coat and the core, the processing equipment, spraying conditions, drying process and moisture effect, solvent evaporation rate, film formation, film integrity, uniformity of thickness, type of film, and bonding between the film and the substrate.[1,2,6,7]

Given the complexity of coating, various problems may be encountered in the process, such as twinning, picking, orange peel (roughness), film cracking, film peeling, bridging of logos (intagliations), and edge wear (chipping). Another major problem is physical aging of the polymers that happens below T_g where chain mobility is decreased to the point that an equilibrium cannot be reached in terms of conformation, and over time this causes hardening of the film layer and affects the drug release kinetics and stability of the coated product. In most film-coating processes, there is exposure to increased temperatures for various time periods to remove water or solvent from the product (thermal treatment or annealing). This can affect the properties of the final product as well.[1,2] These factors can affect the stability, dissolution behavior and overall in vitro/in vivo performance of the coated products, and if not controlled properly, may eventually lead to unpredictable product behavior, with various regulatory implications.

The mechanisms involved in film formation are not fully understood, which makes film coating an important area of research. Over the last 30 years, significant advances have been made in coating technology, with improvements in materials and processing equipment as well as methods of film-coating evaluation.[8,9] Control and understanding of such a complex process becomes more critical as, PAT (Process Analytical Technology), which provides for in-process measurements of quality in real time, is gaining support among pharmaceutical manufacturers and the US Food and Drug Administration.

In the present study, different methods are discussed to help better understand the mechanism of film formation and film

adhesion to various compacts, with 2 objectives: evaluating the nature of film formation on different tablet cores using confocal laser scanning microscopy (CLSM), and assessing the adhesion propensity of film coatings to the tablets by studying the detachment behavior of film from different substrates.

CLSM is known for its ability to produce images of high resolution, free from out-of-focus fluorescent light. It permits visualization and identification of different compounds and structures, provided the material is sufficiently labeled with a fluorescent marker. Furthermore, CLSM can be used noninvasively and without prior sample preparation,[10,11] so it offers several advantages when compared with traditional optical microscopy.[12] CLSM has been extensively used in cell biology and is finding more applications in the evaluation and characterization of solid dosage forms, including determining drug release processes within controlled release preparations,[13] quantifying differential expansion within hydrating hydrophilic matrices,[14] and characterizing particle deformation during compression.[15] CLSM also has been used in material science to evaluate the microstructure of pigmented coating[10] and to measure the topography of the top surface of the coating.[16] However, there are no reports in the literature regarding its application in the characterization of pharmaceutical coatings. This work was therefore undertaken to highlight the usefulness and application of CLSM in the pharmaceutical process of film coating.

In general, the performance and stability of film-coated dosage forms mainly depend on good adhesion between the film layer and the surface of the solid substrate. There are 2 main factors that influence the film–substrate adhesion: the internal stress within the film layer, and the strength and number of bonds at the film–substrate interface. The limited surface area of various substrates and the roughness of their surfaces pose considerable challenges in assessing the adhesion and formation of the film layer to the solid substrates as well as potential drug migration and chemical interaction at the substrate interface. Several qualitative and quantitative methods have been studied and proposed in the literature to assess this property.[7,17] These methods include the Scotch tape test, diametral compression of the coated solid, the scratch test, the peel test, and the butt adhesion technique. Because of high variability, several different designs for the latter method have been reported in the literature (Table 1).[7-9] To overcome the lack of reproducibility and reliability, a novel approach has been presented in this work to assess the film adhesion more efficiently.

MATERIALS AND METHODS

For the purposes of this study, 3 commonly used excipients were chosen as substrate models, each exhibiting different physicochemical properties and solid characteristics: microcrystalline cellulose (MCC; Avicel PH 101, FMC Corp, Philadelphia, PA); lactose monohydrate NF, spray-dried (Foremost #316 Fast-flo, Foremost Farms USA, Baraboo, WI); and dibasic calcium phosphate dihydrate USP (Amend Drug and Chemical Co, Irvington, NJ).

Preparation of Film-Coated Tablets

Each excipient was individually blended with 0.5% magnesium stearate USP, as a lubricating agent, and 2.5% tetracycline HCl USP, as a fluorescent marker. The blends were directly compressed on a Carver Laboratory Press (Fred S Carver, Wabash, IN) using a matching 16-mm diameter, flat-faced punch and die. One planar surface of each compact was then coated manually using a Preval spray gun system (Valve Corporation, Yonkers, NY) with an organic coating solution consisting of 7% (wt/vol) hydroxypropyl methylcellulose phthalate (HP-55), and 0.5% (wt/vol) cetyl alcohol in the mixture of acetone-isopropanol (11:9). Each tablet was coated individually with 2 mL of the coating solution by spraying in a sequential manner, with intermittent periods of 10-minute drying. Every attempt was made to perform the coating procedure under identical conditions to ensure consistency and uniformity of application.

CLSM

An inverted Olympus IX70 microscope equipped with FluoView 2.1 for CLSM image processing (Olympus America Inc, Melville, NY) was used to observe the interfacial boundary of the film layer and the tablet core. To view the sample under the microscope, a thin cross-section was removed from each film-coated tablet using a sharp scalpel and placed individually on a cover glass. Different locations of the sample were then scanned with 2 interchangeable incident wavelengths (488 nm/568 nm) using an argon-krypton laser line. Tetracycline, incorporated into the tablets, served as a fluorescent marker in this study. The confocal fluorescence pictures were taken with a 40× objective, and the sequential images were stored as a 512 × 512 pixel box with 8-bit resolution.

Film Adhesion Studies

The extent of coating adhesion was studied using the modified texture analyzer, TA.XT2*i* (Texture Technologies Corp, Scarsdale, NY), equipped with a 5-kg load cell and Texture Expert software (version 2.56). For adhesion testing, 2 methods of textural analysis were developed and evaluated: peel test and magnet test. The latter was regarded as a novel method. In the peel test, one planar surface of the tablet was

Table 1. Methods Reported in the Literature for Film Adhesion Assessment

Method and Reference	Type of Method	Description	Disadvantage
Scotch tape (Strong 1935)[18]	Qualitative	This is the earliest method. A piece of tape is applied to the film surface and then peeled off.	There is no measurement of the adhesion force.
Diametral compression (Felton et al 1996)[19]	Qualitative	Total pressure is distributed between film and core during compression; simultaneous rupture of film and core indicates good adhesion.	There is no measurement of the adhesion force.
Scratch test (Heavens 1950)[20]	Quantitative	A scratch is caused using a stylus across the surface of the film. Adhesion force is the force required to detach the film from the core along the scratch.	The test is not suitable for solid pharmaceuticals because of their rough surfaces.
Peel test* (Wood and Harder 1970)[21]	Quantitative	With the aid of a modified tensile tester, a section of film is peeled off the tablet surface at a 90º angle.	The peel angle at the tablet surface depends on uniformity of adhesion and film elasticity.
Butt adhesion method (Fung and Parrott 1980)[22]		This is similar to the peel test, but the entire film layer is pulled off normal to the tablet surface with the aid of double-sided adhesive tape.	The deformation rate of the film layer is not held constant.
(Johnson and Zografi 1986)[23]	Quantitative	Instron universal testing apparatus along with pressure-sensitive adhesives are used for butt adhesion test on cellulosics films.	Instead of regular tablets, 9 ×12 mm square samples are used; therefore, this is not suitable for film-coated solids.
(Felton and McGinity 1999)[17]		Chatillon digital force gauge and motorized test stand are used to perform the butt adhesion test using acrylic aqueous dispersion. Force–deflection diagrams allow the visualization of the development of force within the solid sample during the adhesion test.	

*In the present study, a modification of the peel test has been performed; however, the results proved not to be reproducible. To overcome the deficiencies of the existing methods, a novel magnet test has been proposed.

coated, along with one end of a rectangular piece of paper with the dimensions of 16 mm × 50 mm. After drying, the tablet assembly was then fixed on the lower platform of the texture analyzer with the aid of double-sided adhesive tape (Acrylic Glass-Tac tape, Glass-Tac). The free end of the paper was attached to the probe of the analyzer. A section of film layer and the paper were then peeled off the tablet surface, and the lift-up force required for this detachment was recorded. The peel angle was kept at 90° while the film layer was being peeled.

In the magnet method, the tablet core was coated along with a galvanized iron disk placed on the top surface of the tablet and allowed to dry. The disk dimensions were selected so that its thickness was 420 μm and its area was equivalent to 40% of the surface area of the substrate. The tablet assembly was then affixed to the lower platform of the texture analyzer using double-sided adhesive tape, as shown in Figure 2. The magnet probe, upon coming into contact with the coated metal disk on the sample and attaining the trigger force of 30 g, was raised at a constant speed of 1 mm/s. The adhesion force required to remove the film along with the metal disk from the tablet surface was recorded. For each model substrate, at least 6 coated tablets were selected with a weight gain of 4% ± 0.2%, considering the original tablet weight as zero.

In both methods, a personal computer generated and recorded the development of the force (g)– displacement (mm) profiles at the interface of the film and the tablet core.

RESULTS AND DISCUSSION

CLSM images showed that the coat–substrate (tablet) interface was not uniform for all tablets, as depicted in Figures 3A and 3B. MCC demonstrated the best substrate for both film formation and uniformity in thickness. The compacts of lactose monohydrate and dibasic calcium phosphate dihydrate demonstrated the presence of entrapped air within the film layers; this was more prevalent in dibasic calcium phosphate dihydrate. Lack of uniformity of film formation might be attributed to the physicochemical nature of the

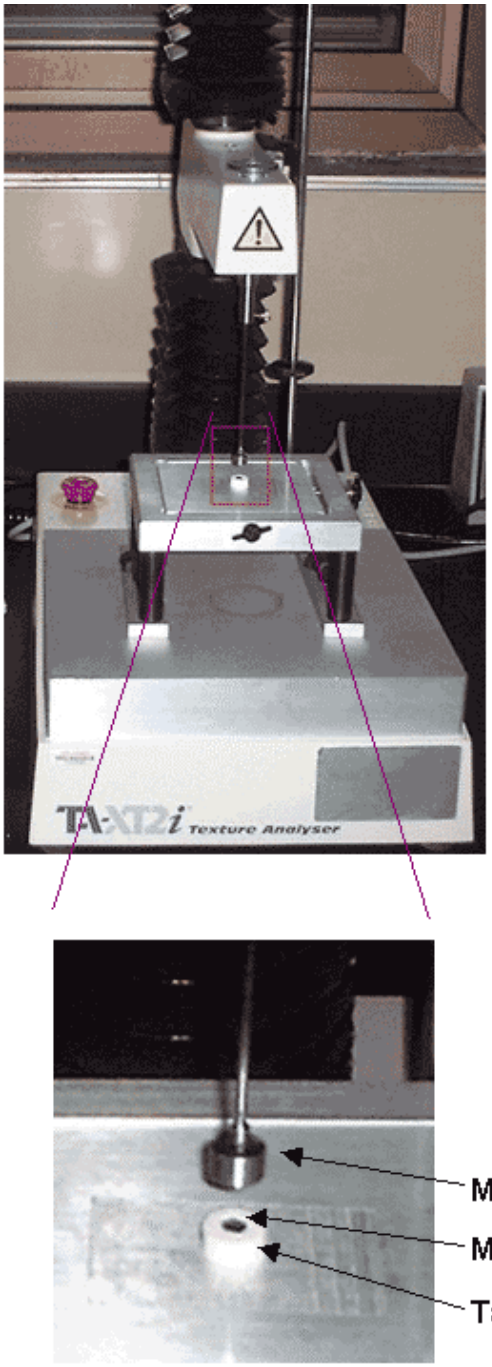


Figure 2. The modified texture analyzer, TA.XT2*i*, used for performing the magnet test on film-coated tablets.

substrates, such as the degree of hydrophilicity/hydrophobicity, which influences the interaction of the polymer solution with the substrate and the formation of the film layer. This is due to the unfavorable surface tension and surface characteristics, which cause the difference in wettability of the surface, and spreadability of the coating solution on the surface of each compact, as has been described in Figure 1. When the coating solution is sprayed onto each compact, the contact angle formed between the atomized droplets and the surface of the substrate may vary depending on the factors cited above. The higher the angle, the lower the spreading of the coating solution on the surface, which further results in a noncoherent and nonuniform film layer.

Among the excipients in this study, MCC has an average particle size of 50 µm and a specific surface area of 1.18 m^2/g, and is practically insoluble in water (1 mg/mL at 25°C). Lactose monohydrate has a particle size range of 100 to 250 µm and is soluble in water (1 in 4.63 at 25°C). Dibasic calcium phosphate dihydrate has a particle size range of 100 to 200 µm, with a specific surface area of 1 to 2 m^2/g, and it is insoluble in water.[24]

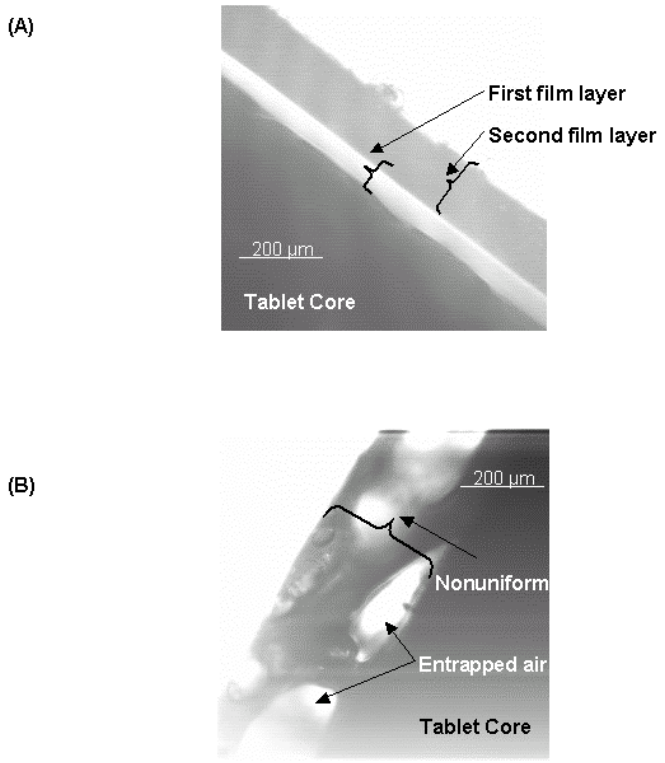


Figure 3. CLSM images of the interfacial boundary of the film layer on the substrates representing the difference in morphology of coatings: (A) microcrystalline cellulose compact, showing consistent film layers; (B) lactose monohydrate compact, demonstrating a nonuniform film layer with entrapped air pockets.

In addition to the substrates' physicochemical properties, the nature of the particulate system and its consolidation behavior may also contribute to the difference in surface morphology of each substrate, and hence the uniformity of the film layer. MCC is a viscoelastic material and undergoes plastic deformation, while both lactose monohydrate and dibasic calcium phosphate dihydrate consolidate by fragmentation (brittle-fracture).

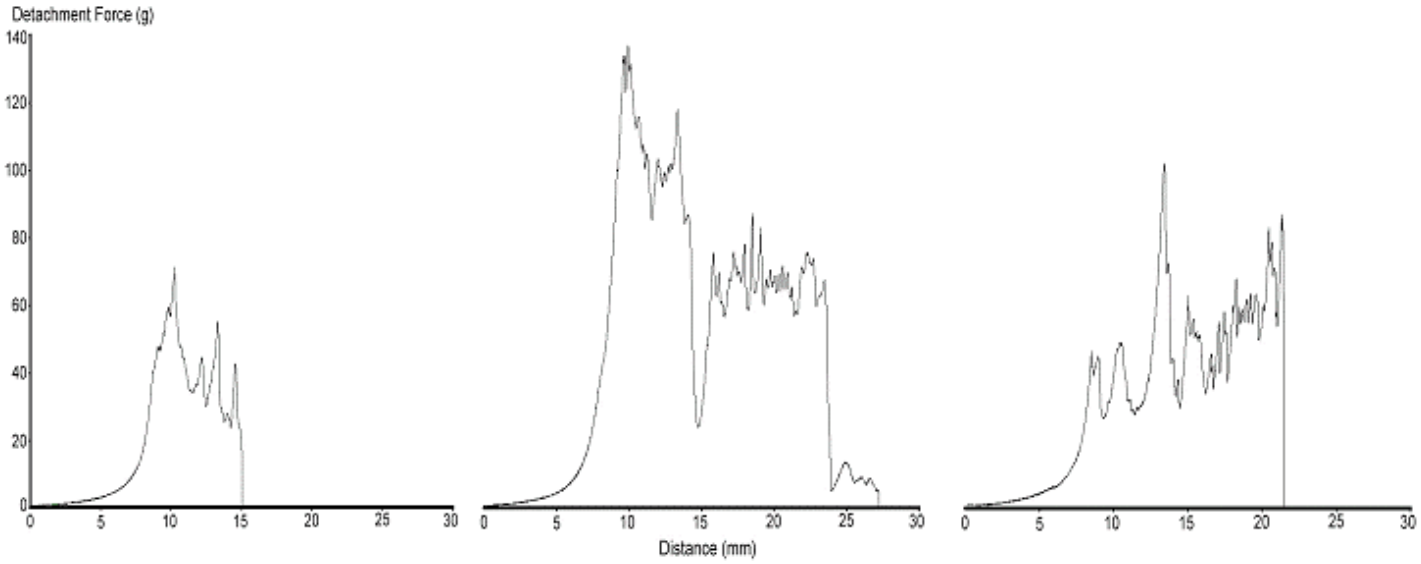


Figure 4. Typical force–distance profile acquired for 3 microcrystalline cellulose tablets, employing the peel test method.

Scans acquired by CLSM also revealed slight and variable drug migration into the polymeric film on all substrates, which was evident at the interfaces; however, the degree of migration did not appear to be significantly different among the tablets. The drug migration, however, provided a clear picture of the film boundary on the substrate and the uniformity of film formation, as shown in Figure 3.

In the adhesion assessment test, the detachment of the coating layers from the substrate cores is expressed as the maximum force required to remove the film layer from the surface of each compact under the given conditions. No attempt was made to prepare free films by casting and evaluating mechanical properties such as elongation at break and tensile strength. Figure 4 shows typical force–distance profiles attained for MCC tablets employing the peel test similar to the literature reports.[21] As demonstrated, this method proved unreliable because of the presence of variable jagged profiles and lacked reproducibility. It is noteworthy that the measured peel angle in a peel test depends on the film elasticity and the uniformity of adhesion to the tablet surface, which are often difficult to standardize and may result in a large deviation in the results.[17]

The proposed magnet test, however, showed acceptable reproducibility for different substrates throughout the experiment. Figure 5 demonstrates the reproducibility of the profiles for MCC performed on 6 coated compacts. The cited detachment force peaks correspond to the maximum detachment force required to lift the film layer from the top surface of the tablet. The pattern to reach peak force values is the focus in evaluation and comparison of the respective profiles. The descending portion starting immediately after the peak force (approximately after 0.4 mm) demonstrates the force–displacement profile associated with postpeak removal of the entire film.

Figure 6 depicts the comparative maximum detachment force–distance profiles for all 3 substrates, obtained with the magnet test. As seen, MCC exhibits the highest detachment force (ie, greatest adhesion strength), followed by lactose monohydrate and dibasic calcium phosphate dihydrate. This is due to the strong interaction between the film layer and MCC substrate as compared with the other excipients. The result is consistent with the uniformity of film observed in CLSM images acquired for this substrate. The strong interaction between MCC and the applied polymer is due to intermolecular bonding forces, mainly hydrogen bond formation, uniform surface morphology due to high plastic flow, and solvent interaction at the interface. Lactose monohydrate also possesses hydroxyl groups that, although less prevalent than for MCC, may engage in forming hydrogen bonds with the film layer. Dibasic calcium phosphate dihydrate, on the other hand, does not possess such groups on its structure. Both lactose monohydrate and dibasic calcium phosphate dihydrate fragment during compression, which may result in formation of new surfaces and add to the complexity of surface morphology with different density domains.

Therefore, the results obtained from both techniques confirm that the physicochemical properties as well as the different consolidation behavior of each substrate should be

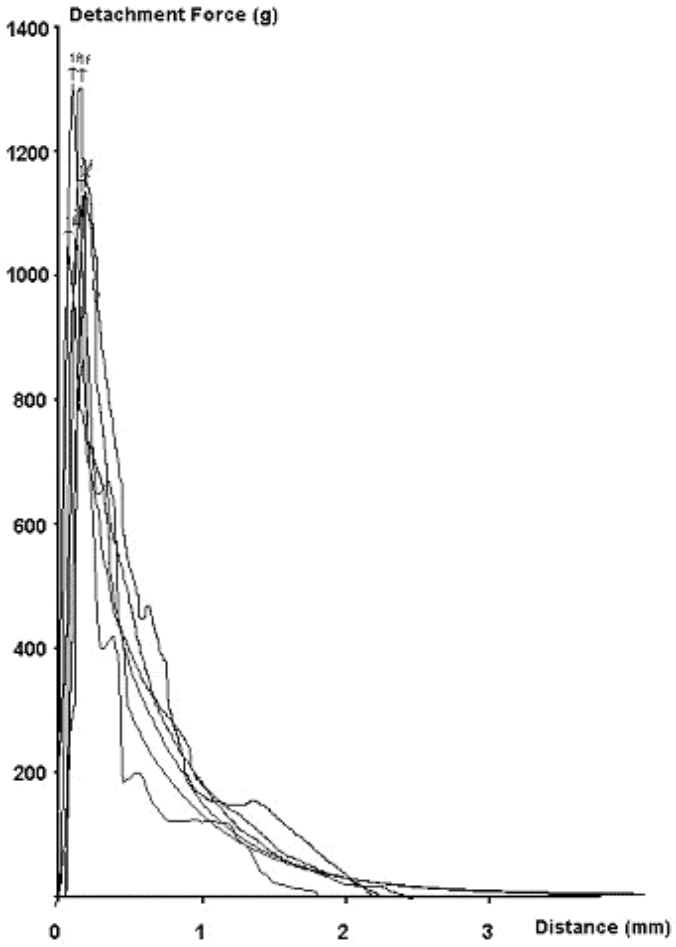
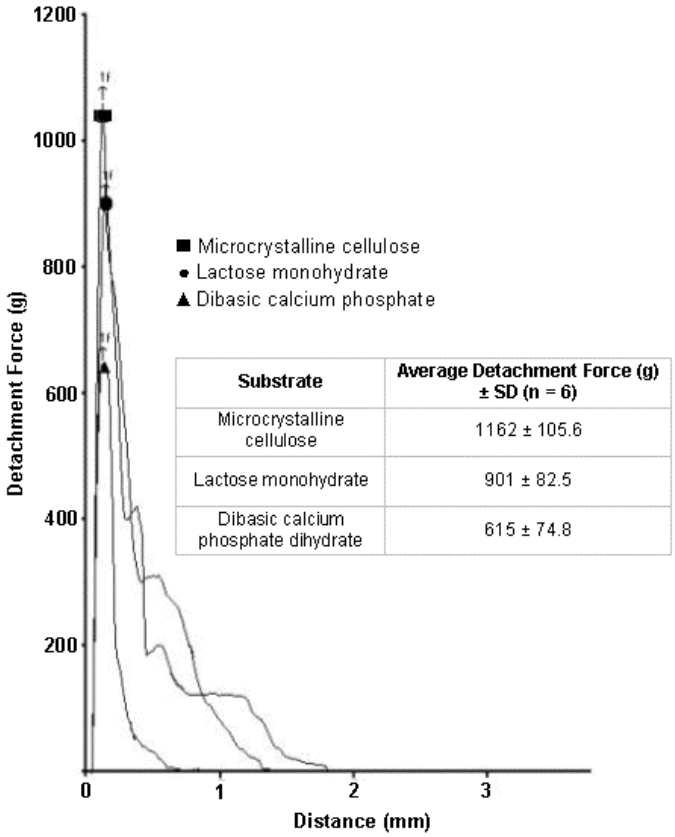


Figure 5. Typical force–distance profiles demonstrating the reproducibility of the magnet test for microcrystalline cellulose (n = 6). The maximum detachment force values (g) achieved for each compact are 1059.7, 1132, 1161.7, 1284.3, 1288.4, and 1045.9.

taken into account prior to their selection as part of tablet formulation.

CONCLUSION

The mechanical nature of the substrates along with their respective physicochemical properties play a critical role in film formation together with the process and composition of coating solution, as clearly assessed by CLSM images. The strongest bond formation was associated with tablets made of MCC compared with lactose monohydrate and dibasic calcium phosphate dihydrate. This study also confirms that plastically deforming excipients such as MCC may provide a smooth and ideal substrate for film formation and minimize difficulties posed during film coating.



Substrate	Average Detachment Force (g) ± SD (n = 6)
Microcrystalline cellulose	1162 ± 105.6
Lactose monohydrate	901 ± 82.5
Dibasic calcium phosphate dihydrate	615 ± 74.8

Figure 6. Comparative force–distance profiles for microcrystalline cellulose, lactose monohydrate, and dibasic calcium phosphate dihydrate tablets, using the proposed magnet test. The symbols represent the peak force for each substrate.

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