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

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.\textsuperscript{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.\textsuperscript{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 $T_g$s; 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.\textsuperscript{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.

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 stability.