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Review

Adhesion of polymeric films to pharmaceutical solids

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Abstract

The two major forces influencing polymer adhesion include the strength of the interfacial bonds between the polymeric film and the surface of the solid and the internal stresses within the film coating. While good adhesion between the polymer and the substrate is desirable for pharmaceutical products, the small size of the dosage form and the non-uniform surface roughness have created difficulties in assessing polymer adhesion. In this review, the experimental devices and procedures used to quantitate polymer adhesion are addressed. The affects of the physical and chemical properties of the substrate, including surface roughness and tablet hydrophobicity, on adhesion of a polymer to either tablets or capsules are discussed. The influence of the plasticizers, pigments, and solvents in film coating formulations on polymer adhesion, and the effects of aging of the coated solids on adhesion of polymers to tablets and capsules are also discussed.

Keywords: Polymer adhesion; Film coating; Internal stress; Surface roughness; Capsules; Plasticizers; Pigments; Aging; Review

1. Introduction

Good adhesion between a polymer and the surface of a solid is a major prerequisite for the film coating of pharmaceutical dosage forms [1–3]. Loss of adhesion may lead to an accumulation of moisture at the film-tablet interface, significantly affecting the stability of drugs susceptible to degradation by hydrolytic mechanisms [3]. Loss of adhesion may also compromise the mechanical protection that the film-coating provides to the solid substrate [4]. In addition, experiments on adhesion will be useful to the pharmaceutical scientist during preformulation studies to investigate the relationship between tablet excipients and polymeric film coating formulations [5].

The two major forces that have been found to affect polymer-tablet adhesion include the strength of the interfacial bond and the internal stresses within the film coating. For pharmaceutical products, hydrogen bond formation is the primary type of interfacial bonding mechanism between the tablet surface and polymer [6]. Dipole-dipole and dipole-induced dipole interactions also occur, however, to a lesser extent. Factors which affect the type or the number of bonds formed between the polymer and the solid surface will influence film adhesion.

The second major factor influencing polymer adhesion is the internal stresses within the film. When a polymeric solution or dispersion is applied to a substrate, an internal stress inevitably develops within the film [7]. The total stress within a film is the sum of all the stresses acting on the polymer, including stress due to shrinkage of the film on evaporation of the solvent, thermal stress due to the difference in thermal expansion of the film and the substrate, and volumetric stress due to the change in volume when a substrate swells during storage. Several researchers have developed equations to estimate the total stress within a film [7–10]. Eq. (1), recently developed by Okutgen et al. [11], includes contributions of volumetric changes of the tablet core in addition to the other well-established mechanisms.

$$P = \frac{E}{3(1-v)}\left[\frac{\Phi s - \Phi r}{1-\Phi r} + \Delta\alpha_{(cubic)}\Delta T + \frac{\Delta V}{V}\right] \quad (1)$$

In Eq. (1), P is the total internal stress in the film, E is the elastic modulus of the film, v is the polymer's Poisson's

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ratio, Φs represents the volume fraction of the solvent at the solidification point of the film, Φr is the volume fraction of solvent remaining in the dry film at ambient conditions, $\Delta\alpha_{(cubic)}$ is the difference between the cubical coefficient of thermal expansion of the film coat and the substrate, ΔT represents the difference between the glass transition temperature of the polymer and the temperature of the film during manufacturing and storage, ΔV is the volumetric change of the tablet core and V denotes the original volume of the tablet core. While this equation has been derived for polymeric solutions, the theory is applicable to polymeric dispersions as well. From Eq. (1), the total stress within a film is directly proportional to the elasticity of the polymer. Factors that influence the elastic modulus of the polymer will, therefore, affect the internal stress within the film.

A distinction must be made between 'fundamental' and 'practical' adhesion. 'Fundamental' or 'true' adhesion refers to the intermolecular interactions between the polymer and the substrate [12]. 'Practical' or 'measured' adhesion refers to the numerical value that results from a variety of testing methods including shear and tensile tests [13]. In addition to the interfacial interactions, other factors, such as stresses in the film and the adhesion measurement technique, will influence measured adhesion [10]. No methods used to quantitate polymer adhesion, however, can be directly used to measure fundamental adhesion.

Two types of failure, adhesive and cohesive, may occur during an adhesion test [3,14]. When the intermolecular bonding forces between the film and the tablet surface are stronger than those bonds between the powdered particles within the tablet, lamination of the tablet compact will occur during a butt adhesion test. This type of failure is known as cohesive failure and particles from the tablet are found on the surface of the film coating [15]. Adhesive failure of the film-coated tablets will result in the film coating being completely removed from the tablet surface with a minimal amount of powdered particles attached. In order to study film-tablet adhesion, the experimental parameters should be designed such that failure of the film is adhesive in nature [15,16]. Data from cohesive failure should not be compared to data from adhesive failure, due to the different forces that are involved in each of these processes.

2. Methods used to assess polymer adhesion

The small size of the tablet and the non-uniform surface roughness of the substrate have presented significant challenges to the pharmaceutical scientist in determining the adhesive properties of a polymer [1,16,17]. The earliest method for assessing adhesion of thin polymeric films to surfaces was the 'Scotch tape' test [18]. A piece of adhesive tape was applied to the film surface and then peeled off. The film either adhered to the solid surface or was removed with the adhesive tape. This method was qualitative and did not provide an accurate measurement of polymer adhesion.

Another method that has been used to provide qualitative information regarding adhesion of polymers to pharmaceutical solids is diametral compression of the coated substrate [19]. During the compression experiments, the total load will be distributed between the film coating and the solid substrate [4]. Fell et al. [20] suggested that the simultaneous fracture of the film coating and the tablet core was indicative of good adhesion between the polymer and the solid.

The first quantitative adhesion test was developed by Heavens in 1950 and was known as the 'Scratch test' [21]. Using this technique, the tip of a hard stylus was drawn across the surface of the film. The critical load required to completely detach the film from the substrate along the track of the scratch was determined and related to

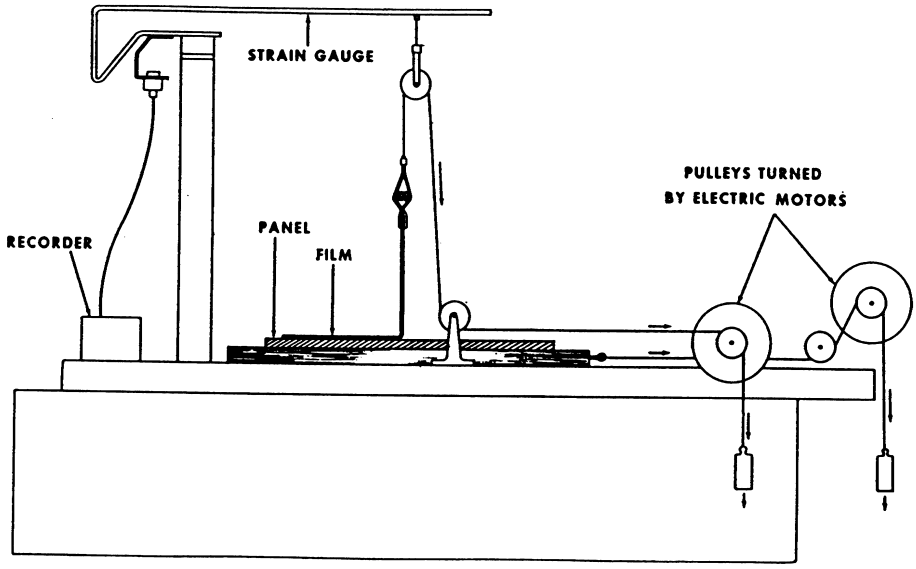

Fig. 1. Schematic diagram of a peel test apparatus used to determine polymer adhesion. Reproduced with permission from Ref. [41].

polymer adhesion. While used extensively to study adhesion of films cast onto metal surfaces, this method is unsuitable for pharmaceutical systems due to the relative rough surface of tablet compacts [22].

In the 1970's, the peel test was a popular method for the determination of film adhesion to tablet compacts. A schematic of the apparatus is shown in Fig. 1. The peel test used a modified tensile tester to peel the film from the surface of the tablet at a 90° angle [23]. The primary deficiency of this method was that the peel angle measured at the tablet surface was dependent on the elasticity of the film and the uniformity of adhesion, both of which will produce significant deviations in the data [13,16].

Several variations of the butt adhesion technique have been reported in the pharmaceutical literature over the past several years [15,16,24,25]. This method is similar to the peel test. However, the entire film is removed normal to the surface of the tablet, rather than sections of the film being peeled. The butt adhesion technique eliminates variations due to the elasticity of the film and is less influenced by the uniformity of adhesion. Fung and Parrott [5] used a modified analytical balance to perform butt adhesion experiments. A schematic of the apparatus is shown in Fig. 2. The film coating around the edge of the tablet was removed using a scalpel and the tablet was affixed to the lower, stationary platen using screw clamps. Double-sided adhesive tape was placed on the tablet surface and upper platen. Rubber backing was used due to the concave shape of the tablet. Weights were placed on the analytical balance until the film was separated from the tablet surface. A major disadvantage of this experimental design was that the rate of deformation of the film was not held constant. The rate of

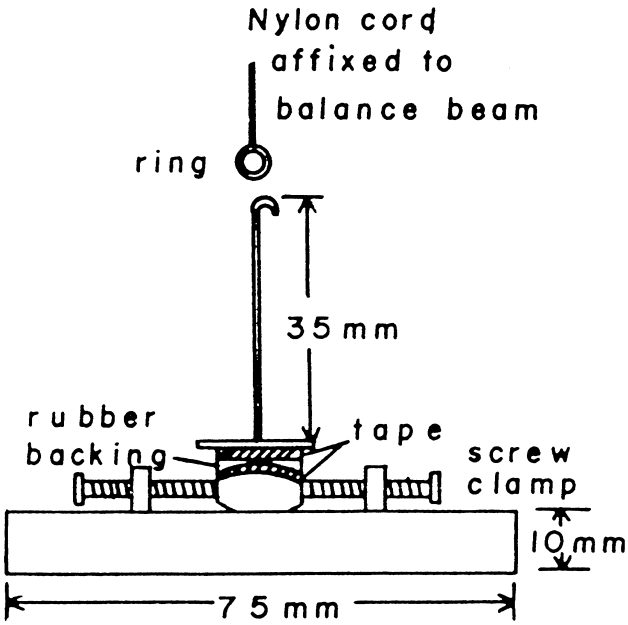

Fig. 2. Schematic diagram of the equipment employed by Fung and Parrott to quantitate polymer adhesion using a butt adhesion technique. Reproduced with permission from Ref. [5].

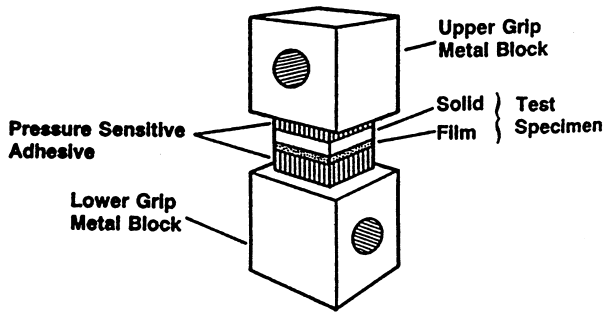

Fig. 3. Laminate structure of mounted test specimen employed by Johnson and Zografi to quantitate polymer adhesion using a butt adhesion technique. Reproduced with permission from Ref. [24].

application of stress has been reported to be an important variable in adhesion experiments [13,26,27].

In another study, Johnson and Zografi [24] used an Instron universal testing apparatus to perform butt adhesion experiments on cellulosic films. Rather than coat tablets, these researchers sprayed or cast polymeric films on well-defined solid substrates of polyethylene, poly(methyl methacrylate), or poly(ethylene terephthalate). After the films were formed, test specimens were cut and placed between two metal blocks using a pressure sensitive adhesive, as shown in Fig. 3. The force required to remove the polymeric films from the solid surfaces was determined. Although this apparatus provided a constant rate of deformation of the sample, this method required 9×12 mm square samples, making it unsuitable for use with film-coated tablets.

More recently, Felton and McGinity [15] used a Chatillon digital force gauge and motorized test stand to conduct butt adhesion experiments of tablets coated with an aqueous-based acrylic dispersion. The apparatus was connected to a personnel computer and force-deflection diagrams were constructed from the data, which permitted the visualization of the development of the force within the sample during the adhesion experiments. An example of a force-deflection diagram generated from this equipment is shown in Fig. 4. The profile is similar to a stress-strain diagram commonly generated in the tensile testing of free films. From the force-deflection diagrams, the elongation at adhesive failure, the modulus of adhesion, and the adhesive toughness of the polymer, in addition to the force of adhesion can be determined. The elongation at adhesive failure, analagous to the elongation at break obtained from tensile testing of free films, reflects the ductility of the polymer. The adhesive toughness is calculated as the area under the force-deflection diagram and is equal to the work required to remove the film from the surface of the solid.

An important factor to consider in the experimental design for investigating polymer adhesion is the shape of the tablet. In 1977, Rowe [28] compared the adhesive force between organic-based cellulosic films and either flat-faced or biconvex tablets. The force required to remove the film

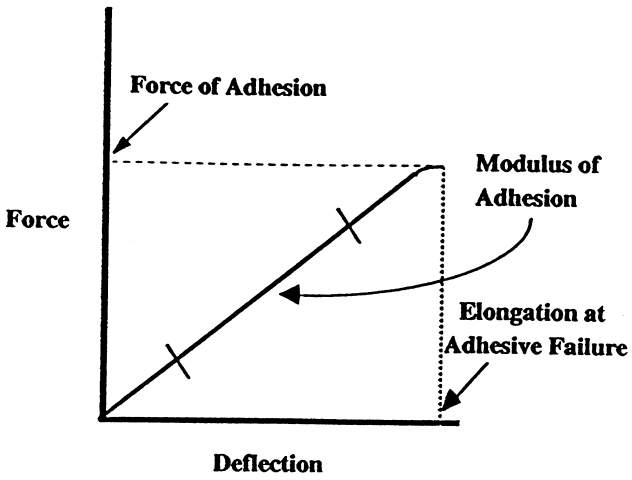

Fig. 4. Example of a force-deflection profile generated using a Chatillon digital force gauge and motorized test stand to quantitate polymer adhesion employing a butt adhesion technique. Reproduced with permission from Ref. [15].

from the surface of the biconvex tablets was lower than the same films coated onto flat-faced tablets. A direct relationship between the force of adhesion and the square of the diameter of flat-faced tablets was found, whereas a maximum force was reached with the biconvex tablets and no such correlation occurred. Interestingly, a direct relationship between the work required to remove the film from the tablet surface and the square of the diameter of the tablet was found for both flat-faced and biconvexed tablets. The author concluded that analysis of the work done to remove the film from the tablet surface provided a more accurate and quantitative measure of film-tablet adhesion for biconvex tablets than the direct force measurement, whereas investigation of either the adhesive force or the adhesive toughness would be useful in the study of adhesion involving flat-faced tablets.

The majority of research studies investigating adhesion of polymeric films to pharmaceutical solids has involved flat-faced tablets [15,16,25,28]. The sharp edge of the flat-faced tablets, however, may create difficulties during the coating process. Tablets may agglomerate in the coating pan apparatus during the coating process. Non-uniform adhesion of the polymer at the edge of the tablets has also been reported due to the high internal stresses within the film at the tablet edge [10,15,29]. In a study conducted by Felton and McGinity [15], flat-faced punches with a beveled edge were used to achieve a more uniform adhesion of the polymeric film. The beveled edge decreased the sharp angle at the edge of the tablet and lowered the internal stresses within the film.

The rate of application of stress and stress distribution are both important variables in adhesion testing [26]. In 1980, Rowe [27] investigated the rate effects in the measurement of the adhesion of film coatings to tablet surfaces. In that study, small increases in measured adhesion were found when the crosshead speed was increased from 0.1 to 1.5 mm/s, whereas decreased adhesion resulted when the deformation rates were increased above 1.5 mm/s, as shown in Fig. 5. Rowe concluded that higher rates of deformation result in uneven stress distribution, thus lowering the measured adhesion. Rates of deformation influence the rheological behavior of the different components in the system, including the adhesive tape, the foam padding, and the polymer itself, and, therefore, affect how the applied stress is transmitted and distributed at the film-tablet interface [27].

3. Substrate variables

The physical and chemical characteristics of the substrate can significantly influence the adhesive properties of polymeric films. The measured force of adhesion, for example, has been shown to be directly related to the square of the diameter of the tablet for flat-faced tablet compacts [16]. In addition, the size of the substrate may also affect the error in the data, with higher coefficients of variation in the adhesive force occurring when testing small tablets due to the difficulties involved in removing the film from around the edge of the tablets prior to testing [16].

In 1976, Fisher and Rowe [16] compared the force of adhesion of both the front and back surfaces of tablets and found no significant differences in polymer adhesion. Fung and Parrott [5] also found no significant differences in the measured force of adhesion of ten commercially available film-coated tablets as a function of front or back surfaces with one notable exception. One tablet formulation that

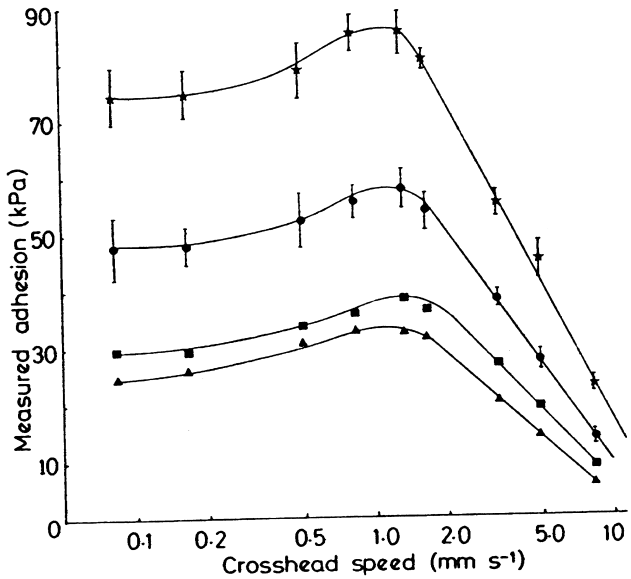

Fig. 5. The effect of crosshead speed on measured adhesion of an organic-based cellulosic film (filled star). Microcrystalline cellulose tablet core, 18 mm film thickness (Pharmacoat 606); (●) Microcrystalline cellulose tablet core, 70 mm film thickness (Pharmacoat 606); (■) Lactose tablet core, 35 mm film thickness (Pharmacoat 606); (▲) Lactose tablet core, 35 mm film thickness (Methocel E 50). Reproduced with permission from Ref. [27].

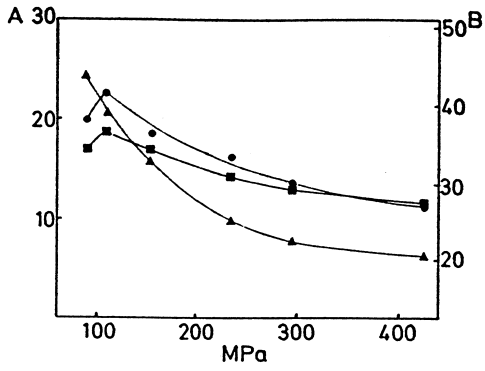

Fig. 6. The effect of compression pressure on the porosity (▲) and adhesion of film formulations containing low viscosity grade (●) and high viscosity grade hydroxypropyl methylcellulose (■). A-Porosity (%); B-Adhesion (kPa). X-Axis, Compression pressure (MPa). Reproduced with permission from Ref. [16].

these researchers investigated was a double-layered tablet and the authors attributed the difference in adhesion to the surface characteristics of the two tablet layers.

3.1. Surface roughness

The surface roughness of the tablet compact and the force of compression used during tableting will affect polymer adhesion, by altering the effective area of contact between the film coating and the surface of the solid. In a study conducted by Fisher and Rowe [16], the compressional force used during tableting was found to significantly influence adhesion of an organic-based cellulosic film, as shown in Fig. 6. Above the critical compression force of 108 MPa, increased compression pressure during the tableting process resulted in decreased adhesion. Below the critical compression pressure, cohesive failure of the tablet occurred, where the tablet laminated, rather than the film being separated from the tablet surface. The intermolecular forces holding the tablet compact together were weaker than the binding between the tablet surface and the film coating, thus resulting in cohesive failure.

Using a peel test, Nadkarni et al. [1] also found that the compressional force used during tableting influenced adhesion of poly(methyl vinyl ether/maleic anhydride) to tablet compacts. These researchers showed a relationship between the compressional load during tableting, surface roughness, wettability of the tablet surface, and peel strength. Using contact angles between the polymeric solution and the tablet surface, these researchers showed that rougher tablets were more readily wetted by the polymeric solution.

In another study, Lehtola et al. [25] determined the force of adhesion of aqueous-based hydroxypropyl methylcellulose (HPMC) to tablets as a function of compressional force. Contrary to other published studies, these researchers found that polymer adhesion to tablets containing the commercially available Cellactose®, a combination of lactose and cellulose, increased with increasing compression pressure. No theories, however, were discussed to explain these results.

In a recent study involving an aqueous-based acrylic polymeric dispersion, Felton and McGinity [15] demonstrated a relationship between tablet hardness and polymer adhesion. Force-deflection profiles, as seen in Fig. 7, show that as the tablet hardness was increased, the force of adhesion, elongation at adhesive failure, and the adhesive toughness of the acrylic polymer decreased. The softer tablets possessed a relatively rougher surface, as evidenced by an increase in the arithmetic mean and the root-mean-square roughness. The rougher surfaces provided greater interfacial contact between the polymeric film and the surface of the tablet, thus resulting in stronger polymer adhesion.

In addition to surface roughness, tablet porosity can influence polymer adhesion. During the coating process, penetration of the coating solution into the outer layers of the tablet surface is inevitable [16]. The rate and depth of polymer solution penetration will influence the interfacial contact between the polymer and the tablet, with the more porous tablet allowing faster penetration of the polymeric solution. Rowe [17] demonstrated a direct relationship between the arithmetic mean surface roughness and tablet porosity. In that study, the porosity of the tablet, which can be calculated from measurements of tablet weight, dimensions of the tablet, and the density of the tableting excipients, could be correlated with a complex surface characteristic.

3.2. Tablet excipients

Adhesion between a polymer and substrate is due to the intermolecular bonding forces. For pharmaceutical products, hydrogen bond formation is the primary type of interfacial contact between the film and tablet surface [6]. Excipients used in tablet formulations can alter the chemical

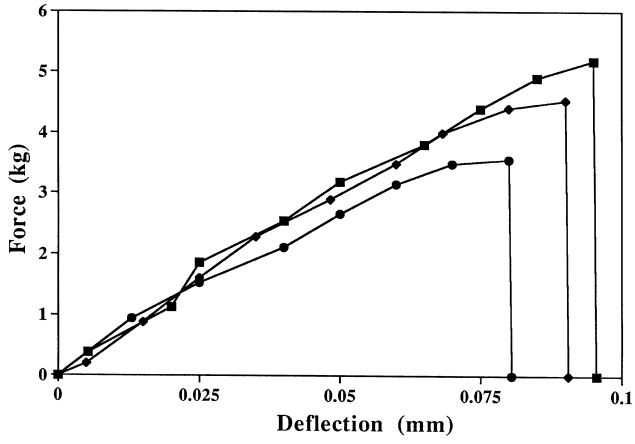

Fig. 7. Force-deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of tablet hardness. (■) 7 kg; (▲) 10 kg; (●) 14 kg. Reproduced with permission from Ref. [15].

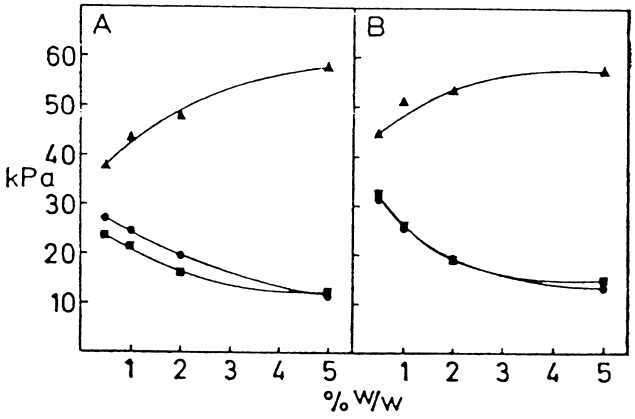

Fig. 8. The effect of lubricant concentration (% w/w) on the measured adhesion (kPa) of hydroxypropyl methylcellulose films. A-Pharmacoat 606; B-Methocel 60HG viscosity 50. (▲) Stearic acid; (●) Magnesium stearate; (■) Calcium stearate. Reproduced with permission from Ref. [2].

properties of the tablet surface, thus influencing polymer adhesion. Sustained-release wax matrix tablets, for example, are generally difficult to coat with aqueous polymeric dispersions due to the poor wettability of the hydrophobic tablet surface [30].

The influence of direct-compression filler excipients on adhesion of organic-based HPMC films was investigated by Rowe [2]. Polymer adhesion was found to be strongest when microcrystalline cellulose (MCC) was used in the tablet compacts. The interaction between the primary and secondary hydroxyl groups of HPMC and MCC was greater than with other excipients studied, including sucrose, lactose, and dextrose, due to the saturation of the tablet surface with hydroxyl groups [31]. In 1995, Lehtola et al. [25] found similar results with aqueous-based HPMC, where adhesion of the polymer was stronger to tablets consisting of MCC than to the lactose-containing tablets.

Lubricating agents used in tablet formulations may influence polymer adhesion by presenting surfaces consisting of mainly non-polar hydrocarbon groups and the extent of the effect is dependent on the nature and concentration of the lubricant. In 1977, Rowe [2] showed that increased concentrations of stearic acid, a commonly used lubricating agent which has a free polar carboxyl group, improved adhesion of an organic-based cellulosic polymeric film, as shown in Fig. 8A. When this group was combined with glycerol to form the glyceryl esters present in hydrogenated castor oil and vegetable stearin, polymer adhesion decreased, as seen in Fig. 8B. More recently, Felton and McGinity [15], investigating adhesion of an aqueous-based acrylic polymer, also found that adhesion decreased with increased concentration of hydrogenated castor oil in tablet compacts, as shown in Fig. 9.

The effects of the concentration of the hydrophobic lubricant magnesium stearate in the tablet formulation on adhesion of aqueous-based HPMC was investigated by Lehtola et al. [25]. Increasing the concentration of magnesium stearate in the tablet resulted in a decrease in the force of adhesion of HPMC films to MCC tablets compacts. For tablets containing primarily lactose, increased magnesium stearate concentrations had no significant affect on polymer adhesion. No mechanisms, however, were proposed by the authors to explain these results. The physical and chemical properties of the two tableting excipients may have caused differences in the surface characteristics of the tablets, including the surface roughness, wettability, or porosity.

3.3. Adhesion to capsules

Many difficulties have been reported in the film coating of hard gelatin capsule and have been attributed to the physical properties of the gelatin and the dosage form [32]. In addition to the capsule shell softening and becoming sticky during the coating process due to solubilization of the gelatin, poor adhesion of the polymer to the walls of the hard gelatin capsule may occur. Insufficient adhesion may result in splintering of the film coating. The capsule shell is relatively smooth and generally provides less surface area for interfacial contact between the polymer and the surface of the gelatin than tablet compacts [33,34]. The addition of polyethylene glycol 400 (PEG 400) and polyethylene glycol 6000 (PEG 6000) to the coating formulation has been used to improve adhesion of polymeric films to the gelatin shell [32]. An aqueous-alcoholic solution has also been shown to enhance polymer adhesion to the capsule shell [34].

In 1996, Felton et al. [19] conducted diametral compression experiments on film-coated soft gelatin capsules and found that adhesion of the aqueous-based acrylic polymer was dependent on the fill liquid of the capsule in conjunction with the plasticizer used in the coating formulation. Good polymer adhesion resulted, as evidenced by single-point failure during compression of the coated capsules [4,20], when triethyl citrate (TEC) was incorporated into the coating formulation, regardless of the fill liquid. When

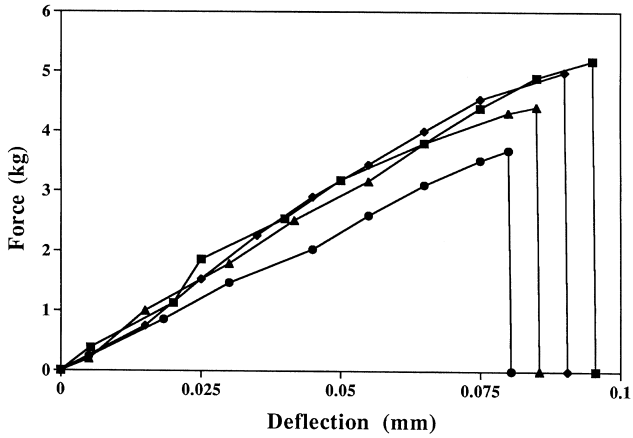

Fig. 9. Force-deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of the concentration (%w/w) of hydrogenated castor oil in the tablet compact. (■) 15%; (♦) 20%; (▲) 25%; (●) 30%. Reproduced with permission from Ref. [15].

the more hydrophobic plasticizer, tributyl citrate (TBC), was added to the coating formulation, polymer adhesion was dependent on the fill liquid of the soft gelatin capsule, with better adhesion occurring with the hydrophobic Miglyol® 812 fill liquid compared to the hydrophilic PEG 400.

4. Coating variables

Since the strength of adhesion between the film and tablet surface is dependent on the number and type of interfacial interactions, different polymers will exhibit different adhesive properties, depending on their chemical structures. In addition to the polymer itself, film coating formulations generally include a solvent, a plasticizing agent, an antiadherent, and a pigment, which may also influence polymer adhesion [35–40].

4.1. Solvents

Previous research on film-tablet adhesion has focused primarily on organic-based cellulosic films and several studies have been published on the affects of solvent systems used in the coating formulation on polymer adhesion. Wood and Harder [23] used contact angle measurements, as an indication of surface wettability, to predict polymer adhesion. An unusual phenomenon was reported, where the force of adhesion increased as the surface tension of the solution increased. Nadkarni et al. [1] conducted a further investigation and found that the relationship between contact angle and surface tension followed Zisman theoretical predictions for pure solvent-tablet systems. The polymeric material, however, adheres to the tablet surface and not to the solvent, which may account for the deviations from theory.

The solvent will interact with the polymer and affect the random coil structure of the polymer chains. It is generally accepted that the greater the polymer-solvent interaction, the greater the end to end distance, thus exposing more of the polymer which is capable of interacting with, and binding to the surface of the solid. Nadkarni et al. [1] suggested that the solubility parameter of the solvent be used as a qualitative measure of the extent of polymer solvation, with greater polymer solvation resulting in greater film-tablet adhesion. A good correlation between the cohesive energy density of the solvent and the peel strength of methyl methacrylate films coated on a tin substrate was found by Engel and Fitzwater [41]. In 1988, Rowe [42] developed equations using the solubility parameters of the tablet excipients and the polymer to predict trends in film-tablet adhesion.

Fung and Parrott [5] compared the force of adhesion of hydroxypropyl cellulose (HPC) films prepared from several solvent systems. Of the four solvents investigated, the force of adhesion varied twofold. In addition, the force of adhesion of films prepared from an aqueous-based system was 1/4 to 1/2 that of the organic-based films. Film coating technology today, however, has shifted towards aqueous-based systems due to environmental and economic concerns [43]. Only a few studies on film-tablet adhesion have focused on aqueous-based polymeric solutions and dispersions [15,25,44–46].

4.2. Additives in the coating formulation

4.2.1. Plasticizers

Plasticizers are included in coating formulations to improve the mechanical and film-forming properties of the polymers [39,47]. Several studies have focused on the effects of plasticizing agents on the adhesive properties of polymers. In 1961, Brantley [48] found a 50% reduction in the force of adhesion of nitrocellulose films to aluminum panels when the concentration of the plasticizer dibutyl phthalate was increased to 40%. Engel and Fitzwater [41] found similar results for methyl methacrylate films containing a variety of plasticizers coated onto metal surfaces. Fisher and Rowe [16] found only slight, insignificant decreases in the measured force of adhesion between organic-based HPMC films and tablet compacts when the concentration of propylene glycol was increased from 10 to 20%.

In a more recent study, Felton and McGinity [45] investigated the influence of plasticizers on the adhesive properties of an acrylic resin copolymer to hydrophilic and hydrophobic tablet compacts. Increasing the concentration of the plasticizer TEC in the coating formulation from 20 to 30% caused a slight, insignificant decrease in the force of adhesion. These results are in agreement with Fisher and Rowe [16]. Interestingly, Felton and McGinity [45] showed that increased plasticizer concentration also resulted in an increase in the elongation at adhesive failure and demonstrated a relationship between the adhesive and mechanical properties of the acrylic polymer. Furthermore, these researchers suggested that the elongation at adhesive failure and the adhesive toughness of the polymer in conjunction with the force of adhesion provided a more complete understanding of the mechanisms involved in polymer adhesion.

One of the two major forces influencing polymer adhesion is the internal stresses within the polymeric film [6]. The addition of plasticizing agents to coating formulations generally decreases the internal stress in the film by decreasing both the elastic modulus (E) and the glass transition temperature (Tg) of the film coating [10,49–51]. The measured force of adhesion, therefore, would be expected to increase with increased plasticization of the polymer. The contradictory results may be due to the interaction of the plasticizing agent with the polar groups of the polymer within the film structure. Further studies, however, are needed to investigate the effects of plasticizer concentration in the coating formulation on polymer adhesion.

Felton and McGinity [45] further investigated the effects of hydrophilic and hydrophobic plasticizers on polymer

Table 1

Influence of the plasticizer in the coating formulation on the force of adhesion and the glass transition temperature (Tg) of an acrylic resin copolymer to lactose-containing tablets

Plasticizer	Force of adhesion (SD)	Tg (SD)
Triethyl citrate	4.85 kg (0.27)	36.5°C (1.1)
Polyethylene glycol 6000	4.32 kg (0.25)	38.6°C (2.5)
Tributyl citrate	3.81 kg (0.30)	51.2°C (2.2)
Dibutyl sebecate	3.48 kg (0.33)	62.0°C (3.6)

adhesion. A relationship was found between polymer adhesion and the Tg of the film, with stronger adhesion occurring when the Tg of the film was lower, as shown in Table 1. The water soluble plasticizers, TEC and PEG 6000, lowered the Tg of the films to a greater degree than the hydrophobic plasticizers, TBC and dibutyl sebecate, and the films containing the hydrophilic plasticizers exhibited stronger adhesion. The researchers attributed these findings to the extent of the polymer-plasticizer interactions and the effectiveness of the plasticizing agent in lowering the internal stresses within the film coating. Plasticizers with a high degree of interaction with the polymer will decrease the Tg of the film to a greater extent than those agents which interact poorly with the polymer [52].

The influence of hydrophilic and hydrophobic plasticizers on the adhesion of the acrylic polymer to hydrophilic and hydrophobic tablet compacts was also investigated by Felton and McGinity [45]. Adhesion of the films plasticized with PEG 6000 was found to be significantly influenced by the hydrophobicity of the tablet surface, as shown in Fig. 10A. These findings are in agreement with previous research that showed increasing tablet hydrophobicity decreased adhesion of both cellulosic and acrylic polymers [2,15]. Interestingly, when TBC was incorporated into the coating formulation, no significant differences in the adhesive properties of the acrylic film were found, as seen in Fig. 10B. Furthermore, these findings were correlated with thermo-mechanical data, where the Tg of the films plasticized with PEG 6000 was dependent on tablet hydrophobicity while the amount of wax in the tablet core was not found to affect the Tg of the TBC-plasticized polymer.

4.2.2. Pigments and fillers

Conflicting reports have been published on the influence of fillers or pigments on polymer adhesion to various substrates. Adhesion of ethylcellulose films cast on aluminum surfaces decreased with the addition of chalk, whereas the incorporation of talc into the cellulosic film improved polymer adhesion [48]. The addition of titanium dioxide and ferric oxide to methyl methacrylate films sprayed onto polymeric and tin substrates had no affect on adhesion, while mica and talc were found to decrease polymer adhesion [41]. Okhamafe and York [3] suggested that the effects of additives in the coating formulations were dependent on the balance between their influence on the internal stress of the film coating and the strength of the film-tablet interface.

Several studies have investigated the influence of talc in coating formulations on adhesion of polymers to tablet compacts. Talc is a hydrophobic substance that is generally added to the coating formulation to reduce the tackiness of the lacquer during the coating process and has been found to decrease the dissolution rate of drugs [37,53]. Talc has also been found to decrease adhesion of polymers to tablet compacts [3]. The hydrophobic particles become embedded within the polymeric film and interfere with hydrogen bond formation between the tablet surface and the film coating. In addition, talc causes a stiffening of the film and increases the internal stresses within the polymer, as evidenced by an increase in the Tg of the film [54–56].

Pigments commonly used in pharmaceutical systems include aluminum lakes of water-soluble dyes, opacifiers such as titanium dioxide, and various inorganic materials including the iron oxides. Pigments differ significantly in their physical properties, including density, particle shape, particle size, and morphology, and these differences contribute to the complex relationship with aqueous film coatings [39,57,58]. In addition to affecting the mechanical properties of films [58,59], the incorporation of pigments into coating formulations has also been found to influence polymer adhesion. Fisher and Rowe [16], for example, found a 45% reduction in the force of adhesion of HPMC films with the addition of 10% titanium dioxide to the coating formulation. Okhamafe and York [54] showed that increased concentrations of titanium dioxide produced an increase in the Tg of HPMC films, which the authors attributed to the restriction in the mobility of the polymer chains by the presence of the additives.

Felton and McGinity [46] conducted a study that compared the adhesive properties of Opadry® and Opadry® II, two complete HPMC film coating systems commercially

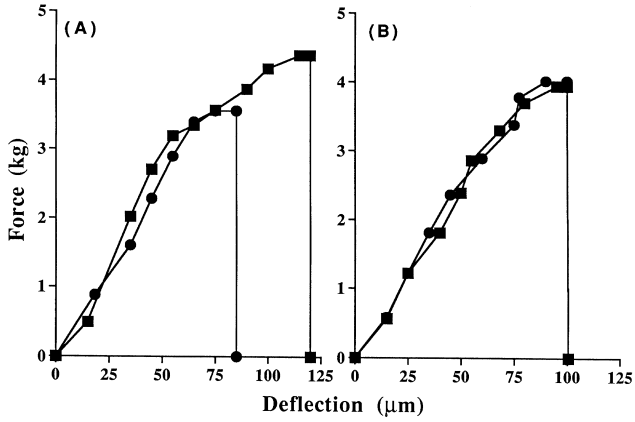

Fig. 10. Force-deflection profiles obtained from butt adhesion experiments of an aqueous-based acrylic resin copolymer as a function of plasticizer type and tablet hydrophobicity. (A) 20% (w/w) Polyethylene glycol 6000; (B) 20% (w/w) Tributyl citrate. (■) 0% Hydrogenated castor oil in tablet core; (●) 30% Hydrogenated castor oil in tablet core. Reproduced with permission from Ref. [45].

available from Colorcon (West Point, PA). The Opadry® II product contains maltodextrins and was formulated to achieve better adhesion, especially to hydrophobic substrates. The addition of the maltodextrins to the cellulosic coating system was found to enhance polymer adhesion to both hydrophilic and hydrophobic tablet compacts, as shown in Fig. 11.

4.3. Film thickness

Theoretically, film thickness should not affect the intrinsic adhesion at the film-tablet interface, with no influence on adhesion expected after the initial coverage of the substrate. Researchers, however, have found that polymeric film thickness will influence the measured force of adhesion. Rowe [17], for example, showed that increased film thickness resulted in decreased adhesion of an organic-based cellulosic polymer for films up to a thickness of 35 μm, while films greater than 35 μm in thickness exhibited increased adhesion with increased film thickness. In 1986, using aqueous- and organic-based HPC, Johnson and Zografi [24] also found decreased polymer adhesion to solid polymeric surfaces with increased film thickness up to 30 μm. More recently, Felton and McGinity [15] conducted a study involving aqueous-based acrylic polymeric coatings thicker than 35 μm and found that polymer adhesion increased with film thickness. Interestingly, in that study the elongation at adhesive failure increased significantly with increased film thickness, and demonstrated a relationship between the adhesive and mechanical properties of the polymer.

Rowe [17] suggested that the effect of film thickness on measured adhesion was a property of the test method and was due to changes in the stress distribution within the film during the adhesion experiment. During the adhesion test, these stresses will either augment or oppose the applied stress and, therefore, influence measured adhesion [26]. Extrapolation of the force of adhesion to a zero film thickness has been suggested by Reegen and Ilkka [60] as a method of minimizing the effects of residual stresses within a film. In most cases, however, a linear relationship between polymer adhesion and film thickness does not occur, and extrapolation of the force of adhesion to zero film thickness, therefore, would be difficult [17,24]. Furthermore, measured film thickness is a mean value and does not account for variations in film thickness that occur when the polymer is applied to the tablet using a spraying technique [17].

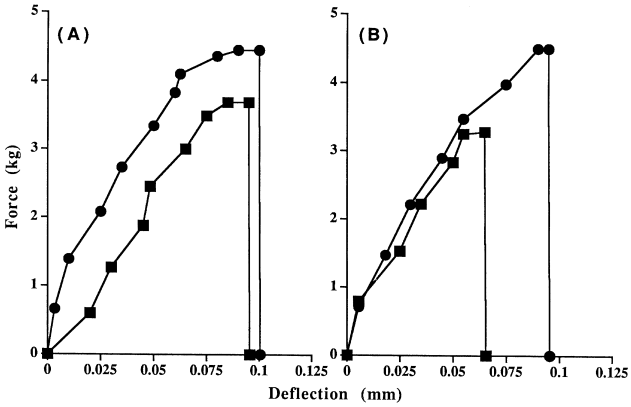

Fig. 11. Force-deflection profiles obtained from butt adhesion experiments of aqueous-based Opadry® and Opadry® II as a function of tablet hydrophobicity. (A) 0% Hydrogenated castor oil in tablet core; (B) 30% Hydrogenated castor oil in tablet core. (■) Opadry®; (●) Opadry® II.

4.4. Processing parameters and coating conditions

The magnitude of internal stresses that inevitably develop during the coating process is dependent upon the interrelationship between many parameters involving both the polymeric coating material and the core substrate [11]. These stresses include stress due to shrinkage of the film upon solvent evaporation, thermal stress due to the difference in the coefficient of thermal expansion of the substrate and polymer, and volumetric stress due to the swelling or contraction of the substrate [7]. Processing parameters may influence the development of these stresses. Okutgen et al. [61], for example, determined the dimensional changes in tablet cores as a function of temperature, simulating the temperature variations that tablets generally undergo during the coating process. Tablets containing Avicel®, maize starch, and Starch 1500 all contracted when exposed to elevated temperatures and expanded during the cooling phase, while Emcompress® tablets exhibited the opposite behavior. These dimensional changes in the tablet core will influence the internal stresses within the films of the final coated products, and may ultimately affect polymer adhesion. Selection of excipients used in the tablet core and polymeric coating materials that have similar coefficients of thermal expansion would minimize internal stresses within the film, and may improve polymer adhesion [10].

5. Influence of aging and storage conditions on polymer adhesion

Exposure of coated solids to various temperatures or relative humidities can influence the internal stresses within a film coating, and thus affect polymer adhesion. Okhamafe and York [3], for example, showed that adhesion of pigmented and non-pigmented cellulosic films decreased during storage at 37°C and 75% relative humidity. These findings were attributed to increased internal stresses in the polymeric films due to differences in the expansion coefficient of the polymer and tablet, and volumetric stresses due to the swelling of the tablet core.

In another study, two weeks of storage at high relative humidity (93% RH) caused a decrease in adhesion of an acrylic polymer to lactose tablets [45]. The authors attrib-

uted their findings to increases in the swelling-induced internal stresses at the film-tablet interface. While previous researchers have demonstrated that water functions to plasticize polymers [62,63], the swelling of the film and tablet core as water diffuses through the coating during storage caused the formation of new stresses within the polymer and weakened the film-tablet interface. Storage of tablets at high humidities for periods longer than two weeks resulted in cohesive failure, where the tablet laminated during the adhesion experiments, rather than the film being separated from the surface of the tablet. The cohesive failure of the coated tablets was due to a weakening of the tablet compacts by the sorption of moisture from the environment [64].

Felton and McGinity [45] also reported decreased polymer adhesion after three months of storage at 0% relative humidity. These findings were attributed to increased internal stresses within the film due to evaporation of residual water remaining in the polymeric film. Three months of storage at 40°C resulted in no significant change in the measured force of adhesion with only small decreases in the elongation at adhesive failure and adhesive toughness. The authors suggested that, since the tablets were stored at a temperature above the Tg of the film, the polymer chains were more mobile [65] and positioned themselves to minimize internal stresses.

In an earlier study conducted by Fung and Parrott [5], the effects of relative humidity on polymer adhesion were investigated. Some tablet formulations exhibited an increase in adhesion with increased humidity, whereas other coated tablets showed the opposite behavior. While the authors attributed their findings to variations in the coating material, solvent system, coating process, and substrates used, their results demonstrate the applicability of the butt adhesion technique in the study of polymer adhesion to tablet compacts.

Decreased adhesion between the polymeric film and the capsule shell has been reported to occur during storage of film-coated hard gelatin capsules at high humidity [32]. The film coating and the gelatin swell to varying degrees and affect the internal stresses within the film. In another study involving film-coated soft gelatin capsules [19], storage at high humidity was found to improve adhesion of an acrylic polymer plasticized with TBC to the capsule containing PEG 400 as the fill liquid. The authors theorized that the fill liquid from the capsule may migrate into the film coating, functioning to further plasticize the polymer and lower the internal stresses of the film. Unlike tablets, soft gelatin capsules are dynamic systems, where water molecules from the environment may permeate through the gelatin shell into the fill liquid and moisture from the gelatin shell may diffuse into the atmosphere [66–68]. The migration of the drug into the gelatin walls has also been reported [69]. Furthermore, the addition of PEG 400 in coating formulations has been shown to improve polymer adhesion to hard gelatin capsules [32].

6. Conclusions

While good adhesion between a polymer and the surface of a solid are desirable for a pharmaceutical product, limited research on polymer adhesion has been conducted involving systems of pharmaceutical interest. The small size of the dosage form and the non-uniform surface roughness have presented difficulties in assessing polymer adhesion to tablet compacts. Use of the butt adhesion technique to determine polymer adhesion to tablet compacts is the predominate method reported in the pharmaceteutical literature. The majority of the research that has been conducted on film-tablet adhesion has focused primarily on organic-based cellulosic films with few studies involving aqueous-based systems.

The physical and chemical properties of the substrate can significantly influence polymer adhesion. Rougher, more irregular surfaces are more readily wetted by the polymeric solution or dispersion and provided greater interfacial contact between the film and the tablet surface. Excipients used in the tablet core can also influence the wettability of the tablet surface and the extent of interfacial bonding between the polymeric film and the solid substrate. Additives in the coating formulation, including the solvent system, plasticizer, and pigments, can influence polymer adhesion. Processing parameters used during the coating process may affect polymer adhesion by influencing the internal stresses within the film coating. Finally, storage conditions can alter polymer adhesion by changing the internal stresses within the polymeric films.

Although many variables have been found to influence polymer adhesion and direct comparison of the numerical values from one study to another may not be practical, further experimentation involving adhesion of polymeric films to solid substrates will provide the pharmaceutical scientist a better understanding of the mechanisms involved in polymer adhesion.

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