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REVIEW

Influence of Insoluble Excipients on Film Coating Systems

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ABSTRACT

Insoluble excipients are added to polymeric film coating solutions and dispersions to improve the physical appearance of dosage forms, enhance the stability of photolytic drugs, and aid in processing. These insoluble additives, however, may significantly affect the physical, mechanical, adhesive, and drug-release properties of the films. In this review, the theories of the interactions between polymer and insoluble excipient are addressed. This article also discusses the influence of the concentration, particle size, morphology, and surface chemistry of insoluble excipients on the various polymer properties.

Key Words: *Adhesion; Drug release; Film coating; Mechanical properties; Pigments; Talc*

INTRODUCTION

Polymeric materials have been used to coat pharmaceutical solid dosage forms for decorative, protective, and functional purposes (1–9). Many polymers of pharmaceutical interest exhibit brittle properties and require the addition of a plasticizing agent to obtain an effective coating that is free of cracks and other defects. Plasticizers function by weakening the intermolecular attractions between the polymer chains and play a critical role in the performance of polymeric films (10–12). In addition to the plasticizer, film coating formulations often include auxiliary components, such as pigments, anti-adherents, antifoaming agents, and surfactants. These additives, both water-soluble and insoluble in nature, may improve the appearance of the final dosage form, facilitate the processing of the material, and promote spreading of the solution or dispersion on the solid substrate (13–15).

Insoluble excipients are often included in polymeric film coating formulations to prevent or reduce agglomeration of the solids during the coating process (16,17). Talc, a hydrophobic,

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water-insoluble compound, is one of the most commonly used anti-adherents employed in film coating formulations. As with most excipients, the quality and the physical characteristics of talc, such as particle size, may vary depending on suppliers (18–21). Other insoluble additives that have been used to reduce the tackiness of polymeric film coating formulations include glycerol monostearate (GMS), magnesium stearate, silicon dioxide, and kaolin (22–25).

Pigments commonly used in pharmaceutical systems include the aluminum lakes of water-soluble dyes, opacifying agents such as titanium dioxide, and various inorganic materials including the iron oxides. The use of water-soluble dyes in pharmaceutical products has been curtailed due to reports of color migration and stability concerns. Pigments are generally added to polymeric solutions and dispersions to provide easy product identification and to present a more pharmaceutically elegant dosage form. In addition, titanium dioxide has been incorporated into film coating formulations as an opacifying agent to improve the stability of light-sensitive drugs (2,26). Pigments differ significantly in their physical properties including density, particle size, and morphology, as seen in Table 1. These characteristics may vary depending on the supplier (27,28).

The addition of pigments and anti-adherents in polymeric solutions and dispersions is common, and in many instances necessary, for the production of film-coated pharmaceutical products. The inclusion of these insoluble additives in coating formulations may affect processing parameters, the physical appearance of the final product, the mechanical strength of the film, polymer adhesion, the permeability of the film, and even the dissolution characteristics of the coated solid. The relationship between polymeric materials and insoluble excipients is extremely complex, being influenced by the powder properties of the additive as well as the degree of dispersion in the film, and the extent of polymer–filler interaction (29). The concentration, particle size, morphology, and surface chemistry of the filler will affect the extent to which insoluble solids influence polymer properties. This article will address the various polymer properties that may be influenced by the addition of insoluble powder particles to the coating formulation and will discuss how the characteristics of the additive can be used to predict the behavior in the final film coating.

CRITICAL PIGMENT VOLUME CONCENTRATION

The critical pigment volume concentration (CPVC) is an important concept in understanding the relationship between polymeric film coatings and insoluble excipients. As the concentration of an insoluble powder in film coating formulations is increased, the amount of polymer necessary to

Table 1

Physical Properties of Several Pigments

Pigment	Morphology[a]	Density[b]	Particle Size[a]	Surface Area[c]
Titanium dioxide	Rounded[d]	3.78[e]–4.08[d]	0.2[f]–1[d]	36.98[g], 7.60[f]
Yellow iron oxide	Acicular	4.53[d,f]	0.5–1[f], 5[d]	13.07[f]
Red iron oxide	Spherical	5.41[f]–5.42[d]	0.32[f], 15[d]	7.56[f]
Black iron oxide	Cubical	4.98[f]	0.5–1[f]	3.84[f]
Aluminum lakes				
Blue No. 1	Irregular	1.84[d]–1.85[e]	30[d]	—[h]
Yellow No. 6	Irregular	1.80[f]	—[h]	93.10[f]

[a] Determined visually using microscopic techniques.
[b] Determined using helium pycnometry.
[c] Determined using BET.
[d] Felton and McGinity (60).
[e] Rowe (28).
[f] Gibson et al. (32).
[g] Maul and Schmidt (80).
[h] No published data available.

completely surround the particles in the dry film increases. At a specific concentration, known as the CPVC, insufficient polymer is present to surround all the filler particles. Once the CPVC has been exceeded, marked changes occur in the mechanical properties, the appearance, and the permeability of the film (29–31). The CPVC is a characteristic of specific polymer–filler combinations and theoretical determinations of this value are practically impossible.

Gibson et al. (32) determined the CPVC of hydroxypropyl methylcellulose (HPMC) using a gloss measurement technique and the data are reported in Table 2. While the surface areas are similar, the CPVC range for titanium dioxide is much greater than that found for the red iron oxide pigment. The authors proposed that the differences in CPVC were due to interactions between the polymer and pigment and that titanium dioxide adsorbs to and interacts with the cellulosic polymer to a greater extent.

The morphology and packing characteristics of the pigments contribute to the differences in the CPVC for the iron oxides. As shown in Table 2, the CPVC for the films containing the cubical-shaped black iron oxide is much lower than the value reported for the cellulosic polymer pigmented with the acicular yellow iron oxide. Gibson et al. (32) suggested that the black iron oxide particles aggregate within the film and trap a significant portion of the polymer, leaving less polymer available for film formation. The acicular yellow iron oxide particles also aggregate, however, a more open structure is formed and less polymer is entrapped.

Table 2

Critical Pigment Volume Concentrations of HPMC Films as Determined by Gloss Measurements

Pigment	CPVC (% v/v)
Black iron oxide	7.0–8.5
Red iron oxide	8.5–10.0
Yellow iron oxide	10.0–12.0
Titanium dioxide	13.5–15.0
Aluminum lake yellow No. 6	12.0–13.5
Talc (surface area 2.99 $\mathrm{m^2/g^a}$)	12.0–15.0
Talc (surface area 14.33 $\mathrm{m^2/g^a}$)	25.0–35.0

[a] Determined by BET nitrogen adsorption.
Source: Ref. 32.

The CPVC range of HPMC containing the aluminum lakes or talc is high in comparison to the iron oxide pigmented films, as seen in Table 2. The aluminum lakes are highly aggregated pigments, requiring a great deal of energy to disperse the particles (33). While these pigments have a high surface area, the aggregation of the particles limits the external surface available to the polymer, leading to the relatively high CPVC value. In contrast, rather than aggregating, the platelet-like talc particles tend to align themselves parallel to the planar structure within the polymeric film. This alignment of the filler particles is thought to contribute to the relatively high CPVC values of the cellulosic films (32). Interestingly, differences in the CPVC ranges of HPMC films were noted for the two talcs investigated and may be related to the surface area or the morphology of the particles.

INTERNAL STRESSES WITHIN POLYMERIC FILMS

Internal stresses within a film inevitably develop when polymeric solutions or dispersions are applied to solid substrates (34). These stresses include stress 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 the substrate swells upon storage. The total stress within a film is the sum of all the stresses and is given by Eq. (1):

$$P = \frac{E}{3(1-\nu)}\left[\frac{\phi_\mathrm{s}-\phi_\mathrm{r}}{1-\phi_\mathrm{r}} + \Delta\alpha_\mathrm{cubic}\Delta T + \frac{\Delta V}{V}\right] \qquad (1)$$

where P is the total internal stress in the film, E is the elastic modulus of the film, ν is the Poisson ratio of the polymer, ϕ_s represents the volume fraction of the solvent at the solidification point of the film, ϕ_r is the volume fraction of the solvent remaining in the dry film at ambient conditions, $\Delta\alpha_\mathrm{cubic}$ is the difference in 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 (35–37).

The addition of insoluble excipients to film coating formulations can influence the internal stresses in the film. The total stress within the film is directly proportional to the elastic modulus of the film. Any additives to the coating formulation that influence the modulus of elasticity will directly affect the internal stresses within the film. In addition, excipients in film coating formulations may alter the glass transition temperature of the polymer, thus affecting the degree of thermal stress in the film. The relationship between insoluble additives in film coating formulations and internal stresses within polymeric films will be discussed throughout this article.

PROCESSING

Due to the tackiness of polymeric materials, agglomeration of coated substrates may occur during processing, resulting in picking, sticking, and other imperfections in the coating surface. The minimum film-forming temperature (MFT) of a polymer has been used as a measure to predict tackiness, with lower MFT values indicative of a higher degree of stickiness. Furthermore, tackiness has been shown to occur more readily at high bed temperatures and at high plasticizer concentrations (17). Insoluble additives have been incorporated into film coating formulations to reduce the tackiness of the film. The most common material used to reduce sticking and agglomeration of the tablet bed is talc. However, the high levels of talc (up to 100% w/w, based on dry polymer weight) required to reduce the stickiness of the film may result in clogging of the spray nozzle and sedimentation. Additional solvents may be used to reduce the overall solids content, although processing times may be prolonged. Glyceryl monostearate has been used as an alternative to talc (24). Wesseling et al. showed that 5% GMS was as effective as 50% talc at reducing the tackiness of several acrylic polymeric films (17).

While insoluble materials may be incorporated into film formulations to reduce the stickiness, these solids may have detrimental effects on the stability of polymeric dispersions. An incompatibility or chemical interaction between the polymer and insoluble additives may result in coagulation or flocculation of the coating formulation. Polymethacrylate latexes are sensitive to both pH changes and the presence of electrolytes in the polymeric dispersions, and are incompatible with water-soluble dyes that contain sulfonic acid groups. When these dyes are adsorbed onto alumina substrates to form insoluble lakes, interaction with the polymeric dispersion is decreased and good compatibility is generally observed. Lakes of poor quality, however, may contain small amounts of the soluble dyes and coagulation may still occur. Coagulation may also result with higher quality lakes when the concentration in the coating formulation is extreme (22). Furthermore, pigments may interact with and bind to stabilizing compounds within the polymeric dispersion.

In a recent study, the stability of pigmented Eudragit L 30 D-55 dispersions was enhanced when the pH was increased to 5.2, presumably due to electrostatic repulsion stabilization resulting from ionization of the weakly acidic polymer (38). Interactions between insoluble excipients and cellulosic polymers have also been reported. The addition of iron oxide pigments to HPMC solutions, for example, has resulted in the precipitation of the cellulosic polymer and strong agitation is required during the coating process to prevent sedimentation (39).

The rheological behavior of cellulosic solutions has been reported to change from newtonian to pseudoplastic with the addition of insoluble agents to film coating formulations (40). These changes have been attributed to the disturbances in the flow pattern caused by the solids and the orientation of asymmetrical particles as the shear rate increases. A greater deviation from newtonian behavior would be expected with the addition of platelet-like particles such as talc, whereas incorporation of more spherical particles such as titanium dioxide in cellulosic solutions would be predicted to exhibit less deviation.

The viscosity of polymeric solutions and dispersions may be increased with the incorporation of insoluble agents to the coating formulation. The spreadability of the polymeric material across the tablet surface, for example, may be reduced as the viscosity of the coating formulation is increased and tablets may appear rougher (41). The extent to which the viscosity increases is dependent on the nature of the additive and the concentration in the polymeric solution (40).

PHYSICAL APPEARANCE

The inclusion of insoluble excipients in film coating formulations can change the physical appearance of the final coated dosage form, affecting the color, opacity, and glossiness of the polymeric film. While the addition of pigments to film coating formulations offers no therapeutic advantage, altering the color of the final product may provide a more pharmaceutically elegant and easily identifiable product (1,30) and improve the stability of photolytic drugs (2,42,43).

While pigments may be included in coating formulations to mask flaws in tablet cores, these colorants can also create imperfections in the films. The pigment must be thoroughly dispersed in the polymeric material to achieve uniform color distribution in the final film coating. The presence of agglomerates in the polymeric solution or dispersion may lead to mottling in the film, where the color of the coating is not consistent (44). Although more common with water-soluble dyes, color migration in the film may occur when insoluble lakes are incorporated into coating formulations, as the dye becomes desorbed from the alumina substrate. Once separated from the insoluble substrate, the dye may dissolve in the plasticizer and migrate in the film, creating mottled tablets. This behavior is more common with lower quality lakes and lakes with low bleed thresholds (44).

Refractive Indices of Pigments

The refractive index is a physical property of particles and is of fundamental importance in determining the appearance of polymeric films containing insoluble additives. The capacity of a film coating to reflect light and hide imperfections in the tablet core is dependent on the refractive indices of the dispersed solids and the polymer. The refractive indices of several insoluble additives and polymers are shown in Table 3. Several of the excipients possess more than one refractive index and the appearance of films containing these additives is dependent on the orientation of the materials within the film coating.

At each polymer–additive interface, a certain amount of incident light is reflected. The amount of light reflected at this interface is given by Eq. (2):

$$R = \left[\frac{n_1 - n_2}{n_1 + n_2}\right]^{1/2} \tag{2}$$

where R is the amount of light reflected at the polymer–additive interface, n_1 is the refractive index of the additive, and n_2 is the refractive index of the polymer film former (45). When no insoluble additives are used in the coating formulation, the resulting film is generally transparent and light is reflected from the core surface with little or no distortion.

Table 3

The Refractive Indices of Several Insoluble Excipients and Polymeric Materials

Compound	Refractive Indices
Aluminum lakes	1.50–1.54[a]
Talc	α 1.539, β 1.589, γ 1.589
Kaolin	α 1.558, β 1.564, γ 1.565
Titanium dioxide (anatase)	ε 2.493, ω 2.554
Red iron oxide	ε 2.493, ω 3.22
Yellow iron oxide	α 1.94, β 2.20, γ 2.51
Methylcellulose	1.50
Ethyl cellulose	1.47
Hydroxypropyl cellulose	1.56
Hydroxypropyl methylcellulose	1.49
Acrylic resins	1.48

[a]Values of the aluminum lakes will vary depending on the dye content of the lake.

Source: Ref. 45.

Opacity of the Film

The capacity of a film coating to hide imperfections in the tablet core is dependent on the opacity of the insoluble excipients added to the coating formulation. When the refractive index of the polymer is equal to that of the additive, the R value in Eq. (2) becomes zero and the film is transparent (45). Greater amounts of light will be reflected at the polymer–additive interface as the difference between the refractive indices of the additive and the polymer increases. In addition, the insoluble particles must be finely dispersed throughout the film so that the number of polymer–filler interfaces is large in order for the coating to appear opaque.

Since the refractive index of the aluminum lakes is similar to the values reported for most polymers, as seen in Table 3, films containing aluminum lakes alone are generally transparent in nature and exhibit little hiding capability. Red iron oxide and titanium dioxide, however, are considered good opacifying agents (45). These pigments are regarded as uniaxial anisotropic compounds, each possessing two relatively high refractive indices, as shown in

Table 3. The orientation of these particles within the structure of the film to produce an opaque coating is irrelevant, since both values of the refractive indices are similar for each of the compounds.

In addition to the refractive indices of the insoluble excipients, the degree of opacity of a film is also dependent on the particle size and volume concentration of the pigment or filler, and the thickness of the polymeric coating (43,45). Furthermore, the crystalline form of titanium dioxide incorporated into coating formulations may influence the opacity of the resulting film (46).

Glossiness of the Film

Gloss is the specular reflection of light by a film coating to create a surface that is shiny in appearance. The addition of pigments to coating formulations generally decreases the glossiness of the film of the final dosage form. The magnitude of the decrease in gloss is dependent on the particle size and the concentration of the pigment in the film (47). In the paint industry, little change in gloss was reported when pigment particles were less than 0.4 μm in diameter (48). A rapid decrease in gloss was noted when the diameter of the insoluble particles was increased to 5 μm (48,49), while the addition of pigment particles with a diameter greater than 10 μm was found to produce films with a matte finish (49).

Orientation of Insoluble Particles

The alignment or orientation of insoluble particles within a polymeric film may significantly influence the appearance of the final dosage form. In the paint industry, for example, yellow iron oxide has been reported to orient during brushing, a phenomenon known as silking (45). Stripes or streaks in the film may appear lighter or darker than the surrounding surface, depending on the direction from which the film is viewed. Several insoluble excipients in pharmaceutical systems have been shown to orient themselves within the structure of the film. Utilizing an ion beam etching technique, Gibson et al. (50) found that larger talc particles aligned themselves parallel to the plane of the film, whereas small talc particles were more randomly distributed.

Many pigments and other insoluble additives exhibit optical anisotropic properties, where the particles possess different refractive indices dependent on their orientation, as shown in Table 3. If these compounds orient themselves to the lowest refractive index, the resulting films are generally transparent, whereas films may appear opaque if the particles orient themselves to the highest refractive index. Random orientation of anisotropic compounds within the polymer also results in opaque coatings (45). The degree of opacity for films containing anisotropic particles, therefore, provides some indication of the extent of particle orientation (51).

Calcium carbonate and talc particles exhibit optical anisotropy. These particles generally orient themselves within the film equivalent to the lowest refractive index, resulting in a fairly transparent film. When coatings containing these additives are sprayed over the intaglios of tablet compacts, the insoluble particles orient randomly and result in an opaque white film (45). Rowe (51) proposed several possible theories to explain the alignment of these insoluble additives, including the minimization of internal stresses in the film. While no hypothesis has been proven, the pharmaceutical scientist can utilize this unique behavior to produce interesting effects in tablet compacts. When these insoluble additives are included in film coating formulations and sprayed onto colored substrates, for example, the intaglios become highlighted in white, with no visible changes in the remainder of the tablet compact.

Effect of Insoluble Particles on Crack Formation in Polymeric Films

In addition to altering the color, opacity, and glossiness of the film, insoluble excipients may alter the internal stresses within the film coating and crack formation in the film may result. Internal stresses in polymeric films were discussed in detail previously. Cracking or splitting of the coating will generally occur when the internal stresses in the film approach or exceed the cohesive strength (52). Cracks in the film may diminish the elegant appearance of the dosage form and compromise the functionality of the coating.

The incidence of edge splitting or cracking of a polymeric film has been shown to be influenced by the concentration and morphology of insoluble excipients incorporated in the coating formulations (53). Rowe (44) added talc, calcium carbonate, and magnesium carbonate to film coating formulations

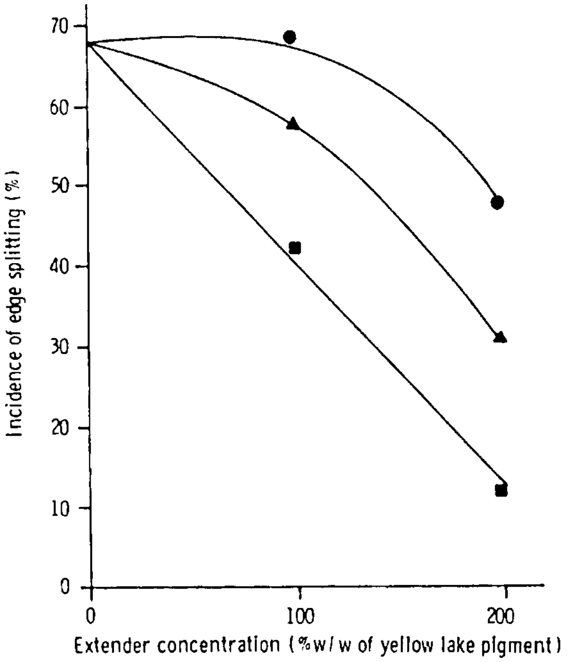

Figure 1. The effect of insoluble additives on the incidence of edge splitting of a cellulosic polymer containing 5% (w/w) yellow lake pigment. (●) Calcium carbonate; (▲) magnesium carbonate; (■) talc. (From Ref. 44.)

to reduce or minimize the incidence of cracking of the film or edge splitting, as shown in Fig. 1. These platelet-like particles align themselves parallel to the surface of the substrate, causing restraint in volume shrinkage upon solvent evaporation and minimizing internal stresses within the film.

MECHANICAL PROPERTIES

The mechanical testing of polymeric films has been used to predict the performance of the coating (54) and the incidence of film defects in the coated tablets, including edge splitting and bridging of intaglios (52). These mechanical data have also been used to evaluate the effectiveness of plasticizing agents (55), as well as to estimate the long-term stability of film-coated solid dosage forms (56,57). While the addition of insoluble excipients in coating formulations may be beneficial in improving the aesthetic appearance of films, these filler materials may be detrimental to the mechanical properties of the polymer (30).

Glass Transition Temperature

The glass transition temperature (T_g) is probably one of the most commonly reported physical characteristics of amorphous polymeric materials. At temperatures below T_g, the polymer generally behaves as a hard and brittle glass, whereas the mechanical properties of the polymer change to soft and flexible at temperatures above T_g. The inclusion of insoluble additives, such as pigments and antiadherents, in coating formulations has been shown to modify the T_g of polymeric films. Changes in the T_g of the polymer will directly affect the internal stresses within the film and, potentially, the incidence of crack formation in the coating (37,58).

Okhamafe and York (31) studied the effects of talc and titanium dioxide concentration on the T_g of HPMC films. Increased concentrations of both excipients produced an increase in the glass transition temperature, as shown in Fig. 2. The authors

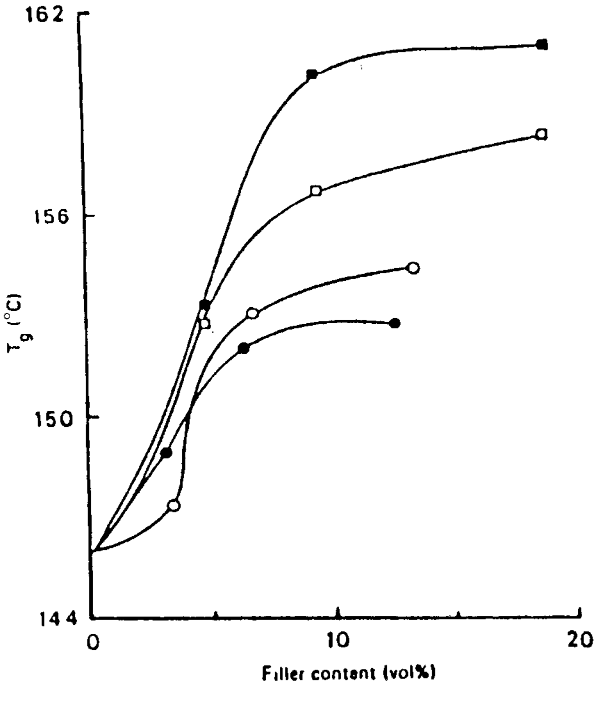

Figure 2. Influence of filler concentration on the glass transition temperature of HPMC films. (□) Talc, coarse platelet particles, specific surface area 1.34 m²/g. (■) Talc, fine platelet particles, specific surface area 1.81 m²/g. (○) Titanium dioxide, spherical, anatase form, specific surface area 7.89 m²/g. (●) Titanium dioxide, spherical, rutile form, specific surface area 8.42 m²/g. (From Ref. 31.)

attributed their findings to the restriction in the mobility of the polymer chains. It is interesting to note that increasing the concentration of the talc or titanium dioxide beyond 10% in the coating formulation did not produce additional increases in the T_g of the polymer. Similar findings for an acrylic film and titanium dioxide were reported by Felton (59).

Felton and McGinity (60) determined the T_g of an acrylic polymer containing various pigments and the data are presented in Table 4. The addition of the insoluble additives resulted in an increase in the T_g of the polymer, with larger particles causing greater increases in the T_g of the film when the coating was applied to the hydrophilic substrate. Only small changes in the T_g were found with the addition of the pigments to the film applied to the more hydrophobic tablet compacts. These data demonstrate that the hydrophobicity of the tablet core also influences the T_g of the polymer.

Tensile Properties

The addition of pigments to polymeric materials generally reduces the tensile strength and elongation and increases the elastic modulus of free films (1,13,58,61). In other words, polymeric films become more brittle upon the addition of pigments to the coating formulation. The extent of the changes in the tensile properties of the polymer is dependent on hydrodynamic effects, including the size, morphology, concentration, and orientation of the filler particles, and on reinforcing effects, such as physical or chemical bonding of the insoluble material to the polymer matrix (29).

Concentration

Aulton and Abdul-Razzak (1) determined the tensile properties of HPMC films as a function of titanium dioxide concentration. The stress–strain diagrams, depicted in Fig. 3, clearly show that the cellulosic films became more brittle as the concentration of the pigment was increased, as evidenced by the decrease in elongation and the increase in Young's modulus. More recently, Hsu et al. (62) showed that the addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength.

Okhamafe and York (63) determined the toughness index of HPMC films as a function of the concentration of both anatase and rutile forms of titanium dioxide, and the data are presented in

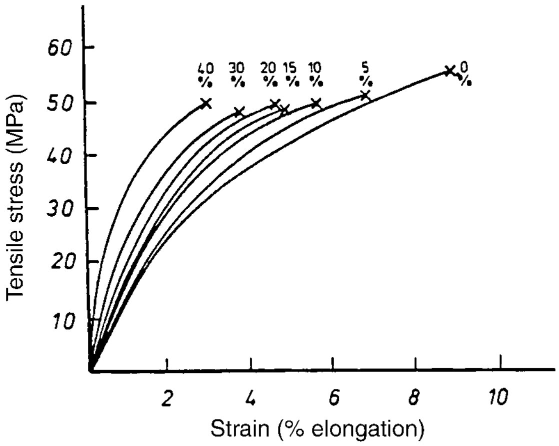

Figure 3. Influence of titanium dioxide concentration (% w/w) in the dried polymer on the stress–strain curves of HPMC films. (From Ref. 1.)

Table 4

Influence of Pigments In Film Coating Formulations on the Glass Transition Temperature of an Acrylic Resin Copolymer

	Glass Transition Temperature (SD)	
Pigment (10% v/v)	0% Wax Tablet Core	30% Wax Tablet Core
Unpigmented	36.5°C (1.5)	49.3°C (0.8)
Yellow iron oxide	41.8°C (0.2)	50.4°C (0.2)
Red iron oxide	38.5°C (0.8)	50.0°C (0.1)
Aluminum lake blue No. 1	46.9°C (1.2)	49.9°C (0.1)
Surface-treated mica	51.2°C (1.2)	50.3°C (0.2)

Source: Ref. 60.

Table 5

Influence of Titanium Dioxide Concentration on the Toughness Index of HPMC Films

Titanium Dioxide (% wt)	Toughness Index (kJ/m^3) × 10^3			
	HPMC Alone	HPMC/PVA	HPMC/PEG 400	HPMC/PEG 1000
Unpigmented	8.14	7.56	5.64	4.67
Anatase				
10	3.31	4.83	4.08	5.24
20	2.11	3.19	2.01	2.11
30	1.73	2.85	1.59	1.91
40	1.72	2.42	1.23	1.34
50	1.32	1.73	0.99	1.08
Rutile				
10	3.68	4.46	4.63	4.23
20	2.25	2.32	1.34	2.14
30	2.78	2.51	1.53	1.78
40	1.54	1.57	1.19	1.10
50	1.17	1.18	0.96	0.80

Source: Ref. 63.

Table 5. The toughness index represents the resistance to crack formation and is given by Eq. (3):

$$T_{\mathrm{d}} = \frac{\sigma\varepsilon}{2} \tag{3}$$

where T_{d} is the toughness index, σ is the tensile strength of the film, and ε is the elongation. These researchers then related the toughness index to the incidence of edge splitting, where edge splitting became more prevalent as the toughness index of the polymer decreased.

Increased concentrations of other insoluble excipients in film coating formulations have also been found to affect the mechanical properties of polymeric films. Aulton and Abdul-Razzak (1) demonstrated that increasing the concentration of an aluminum lake caused HPMC films to become more brittle. In another study, Okhamafe and York (58) showed that increased concentrations of talc in HPMC films resulted in an increase in the Young's modulus of the polymer. The authors proposed that the decrease in the elasticity of the polymeric film was probably due to the filler particles physically impeding the mobility of the polymer phase, or the filler–polymer interaction stiffening the molecular chains of the polymer and reducing segmental mobility.

Porter (30) determined the diametral crushing strength of film-coated tablets containing various pigments and the data are presented in Fig. 4. Increasing the concentration of the pigments in the coating formulation caused a decrease in the crushing strength of the film-coated tablet, indicating that the tablet compact became weaker. In fact, the coated tablet was weaker than the uncoated tablet cores when the concentration of the aluminum lake was sufficiently high.

The change in the mechanical properties of polymers to more brittle materials with the addition of greater amounts of filler may be related to the internal stresses within polymeric films. Polymer chain mobility may be decreased due to polymer–filler interactions, which results in an increase in stress. From Eq. (1), the elastic modulus of the film is directly proportional to the internal stresses within the film. As the concentration of the insoluble excipient in the coating is increased, polymer chain mobility is further reduced and the elastic modulus of the film increases, thus causing an increase in the total stress within the polymer.

Particle Size

Researchers have theorized that stress locations or flaws in the film coating occur at the filler–polymer interface and these flaws can ultimately lead to failure of the coating (33,58). Flaws in the films may be related to the particle size of the additives

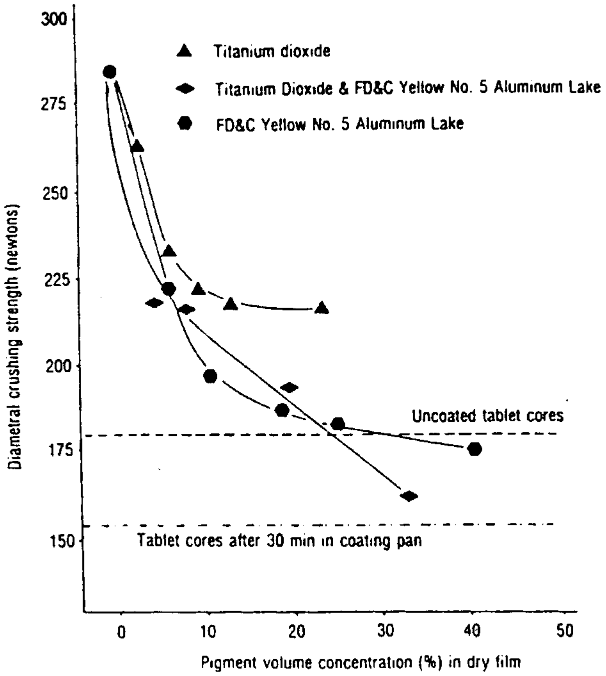

Figure 4. Influence of pigment concentration on the diametral crushing strength of placebo tablet cores coated with HPMC. (▲) Titanium dioxide; (◆) titanium dioxide and FD&C yellow No. 5 aluminum lake; (●) FD&C yellow No. 5 aluminum lake. (From Ref. 30.)

in the film coating formulation. Van Krevelen (64) proposed a mathematical model to predict stress in polymeric films. The stress at the tip of a flaw, such as the filler–polymer interface, is multiplied by $(L/r)^{1/2}$, where L is the length of the flaw and r is the tip radius. The Van Krevelen flaw term, L, is a function of particle size, with larger particles possessing higher L-values. This proposed model indicates that the platelet-like talc particles would create more stress in the films than spherical titanium dioxide. The results reported by Okhamafe and York (58) are in agreement with this proposed theory, where films containing larger talc particles exhibited a higher modulus, indicative of a more brittle film, than when smaller talc particles were incorporated into the film coating formulation.

Particle Morphology

The morphology of the insoluble excipients incorporated into the film coating formulations may influence the mechanical properties of polymeric films. Okhamafe and York (65), for example, reported that the Brinell hardness and Young's modulus for HPMC films containing platelet-like talc particles were greater than for coatings containing the more rounded titanium dioxide particles. The authors attributed these differences to the particle morphology and the extent of polymer–filler interaction. No comment, however, was made regarding the differences in the specific surface areas of the compounds ($1.81\,m^2/g$ talc; $8.42\,m^2/g$ titanium dioxide).

Gibson et al. (61) found that the increase in the Young's modulus of the polymer was dependent on the particle morphology of the fillers added to the coating formulation. The greatest increase in the modulus occurred with the addition of talcs and yellow or black iron oxide, whereas the addition of aluminum lakes to film coating formulations resulted in small changes in the elasticity of the film. From the data, the authors suggested that the morphology of the filler particle could predict the magnitude of the increase in the elastic modulus, with lamellar shapes causing the greatest increase, followed by acicular-shaped particles, cubic particles, and finally spherical particles. Rowe (28) also predicted that the inclusion of more irregular-shaped particles in film coating formulations would cause greater increases in the elastic modulus of the polymer than with the incorporation of spherical particles into the coating.

Surface Chemistry

Few studies have investigated the effect of surface chemistry of insoluble additives on the tensile properties of polymeric films. Aulton and Abdul-Razzak (1) investigated the mechanical characteristics of cellulosic films containing three different aluminum lakes of similar particle size and size distribution. The stress–strain diagrams for these films were nearly identical, as shown in Fig. 5. In the same study, researchers compared high-tinting (HT) and regular lake pigments. Only small differences in the work of rupture were noted, with the HT grade being slightly tougher at all concentrations investigated. The authors suggested that the mere presence of the insoluble compound in the film was important, not the surface chemistry of the material. Since the concentration, particle size, and morphology of insoluble excipients in film coating formulations have been shown to produce significant changes in the tensile properties of polymeric films,

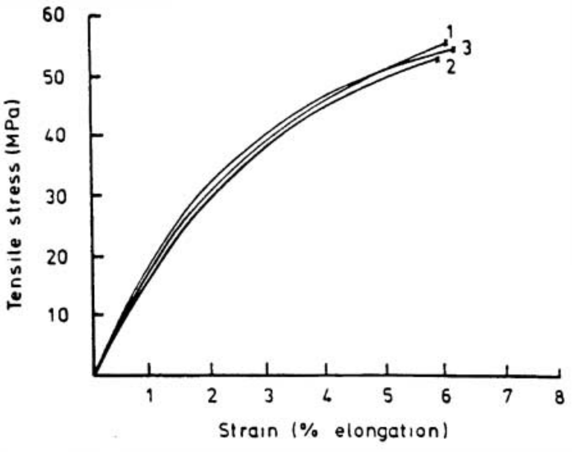

Figure 5. Stress–strain diagrams of HPMC films containing various aluminum lakes. (1) Brilliant blue FCF lake; (2) erythrosine lake; (3) tartrazine lake. (From Ref. 1.)

it seems plausible that the chemistry of the insoluble compounds would also affect polymer properties. Further studies are necessary to explore the mechanisms by which the surface chemistry of insoluble excipients may influence the tensile properties of polymeric films.

ADHESION OF POLYMERIC FILMS TO SOLID SUBSTRATES

Good adhesion between a polymeric film and the surface of a solid is desirable for a pharmaceutical product. Insoluble additives in coating formulations, however, may hinder adhesion of the polymeric film to solid substrates. Polymer adhesion is dependent on a balance between the internal stresses within the film and the strength of the film–tablet interface. In addition to increasing the internal stress within the film, these insoluble particles are thought to embed themselves within the film and interfere with the intermolecular bonding at the film–tablet interface. The extent to which excipients incorporated into film coating formulations may affect polymer adhesion is dependent on the particle size, concentration, and morphology of the insoluble agents in the coating.

Particle Size

The particle size of insoluble additives in film coating formulations has a direct effect on polymer adhesion. Pigment particles embed themselves within the polymeric film and at the film–tablet interface and disrupt interfacial contact between the film and the tablet surface (66). Felton and McGinity (60) investigated the effects of pigments in an acrylic film on polymer adhesion. These researchers found that adhesion was strongest when the small yellow iron oxide pigment was incorporated into the film coating formulation, whereas the presence of the larger mica particles in the acrylic dispersion resulted in significantly poorer film–tablet adhesion, as seen in Fig. 6. The authors theorized that larger particles disrupt the interfacial bonding between the polymer and the surface of the tablet to a greater extent than smaller particles.

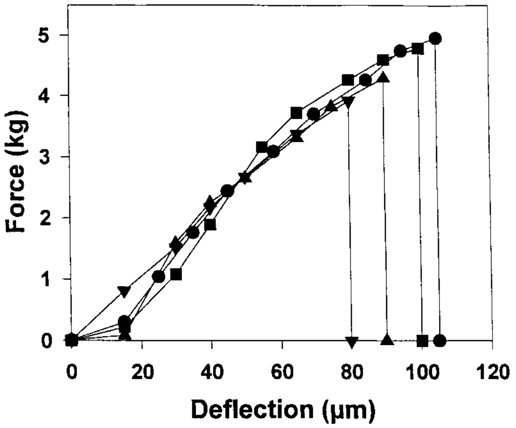

Figure 6. Force–deflection profiles obtained from using a butt adhesion technique of an acrylic polymer containing various insoluble pigments. (●) Yellow iron oxide; (■) red iron oxide; (▲) blue aluminum lake; (▼) surface-treated mica. (From Ref. 60.)

Particle Morphology

Few studies have investigated the relationship between particle shape and film–tablet adhesion. A study conducted by Rowe (67) showed that measured adhesion was strongest when talc, a platelet-shaped filler, was incorporated into HPMC films, whereas the coating containing an irregular-shaped aluminum lake exhibited the poorest film–tablet adhesion, as seen in Table 6. While these findings indicate a relationship between particle morphology and polymer adhesion, no information was given with respect to the size of the insoluble excipients and the data, therefore, may be misleading.

Table 6

The Effect of Particle Morphology on the Measured Adhesion of Pigmented HPMC Films Coated onto a Placebo Tablet Substrate (Pigment Concentration 25% w/w)

Pigment	Particle Morphology	Measured Adhesion (kPa)
Unpigmented	—	28.5
Aluminum lake yellow No. 5	Irregular	22.5
Black iron oxide	Cubic	24.6
Red iron oxide	Spherical	26.0
Yellow iron oxide	Acicular	28.1
Talc	Flake or platelet	29.5

Source: Ref. 67.

Furthermore, while the densities of pigments and fillers vary significantly, as seen in Table 1, the concentration of pigment in the coating formulations in that study was based on weight fractions.

There is indirect evidence that the morphology of the excipients may influence polymer adhesion. The shape of insoluble additives has been found to influence the internal stresses within polymeric films, with irregular-shaped structures causing a greater increase in stress than platelet-like excipients (36). Felton and McGinity (68,69) demonstrated a relationship between the mechanical properties of polymers and film–tablet adhesion. Furthermore, film–tablet adhesion is a balance between the internal stresses within the film and the strength of the film–tablet interface. It stands to reason, therefore, that the morphology of insoluble additives may influence polymer adhesion to some extent (58,67).

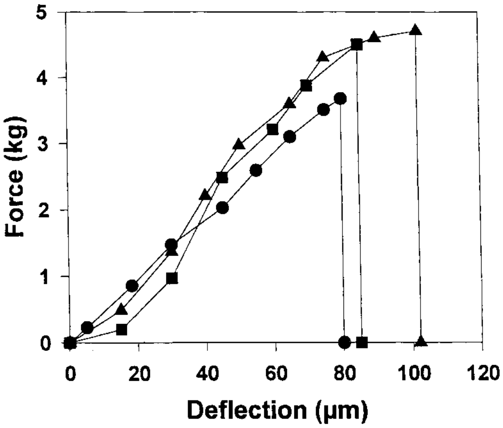

Figure 7. Influence of titanium dioxide concentration (% v/v) in an acrylic dispersion on film–tablet adhesion. (●) 0%; (■) 10%; (▲) 20%. (From Ref. 60.)

Concentration

The concentration of insoluble additives in film coating formulations has been shown to influence polymer adhesion. Lehtola et al. (70) found that film–tablet adhesion increased as the concentration of titanium dioxide in HPMC films was increased. Felton and McGinity (60) also found stronger adhesion with increasing amounts of titanium dioxide, as shown in Fig. 7. The adhesive toughness, or area under the force–deflection profile, increased as the concentration of titanium dioxide increased, indicating that more work was required to remove the film from the surface of the tablet compact. These findings were attributed to the extent of the interfacial interaction between the polymeric material and the surface of the tablet. The opacifying agent was thought to strengthen the film–tablet interface through the formation of a larger number of hydrogen bonds, with minimal increases in the internal stresses, thus improved adhesion resulted. The increased strength of the film–tablet interface may be due to the presence of adsorbed water on the pigment particles, as reported by Gibson et al. (61). The improvement in the adhesive characteristics of the cellulosic and acrylic polymers with increased concentration of titanium dioxide is rather unexpected since the addition of pigments and other insoluble excipients to film coating formulations generally causes an increase in the internal stresses within the film. Other pigments added to polymeric materials may not exhibit behavior similar to that of titanium dioxide. Further studies are necessary to fully understand the relationship between the concentration of insoluble particles in film coating formulations and polymer adhesion.

PERMEABILITY

Insoluble excipients in film coating formulations may function as a barrier to moisture permeation and thus provide greater protection for drugs that degrade through hydrolytic mechanisms (30). The addition of filler particles to film coatings may increase the tortuosity of the diffusion pathway initially, resulting in a decrease in the permeability of the film (71). The extent to which insoluble particles affect the permeability of polymeric films is dependent on the surface chemistry, particle size, concentration, and morphology of the filler, as well as the degree of filler–polymer interaction (29,72).

Particle Size

The particle size of insoluble additives in film coating formulations will influence the permeability of the final film to water vapors. Parker et al. (72) investigated the effects of two talcs, Italian talc and USP talc, with median particle sizes of 20.5 and 12.5 μm, respectively. Films containing the larger particles exhibited slower rates of water vapor transmission, whereas the inclusion of the smaller-sized particles in the coating resulted in the films being more permeable to moisture. In another study, Okhamafe and York (29) investigated the effects of the surface area of talc and titanium dioxide on the diffusion of water through polymeric films. Incorporation of fillers with the larger surface area caused the polymeric films to be less permeable than when the excipients with a smaller surface area were included in the coating formulation.

Particle Morphology

Few studies have been published that address the effects of particle morphology on the permeability of polymeric films. In unpublished work by Felton and Torres (73), the water vapor permeability for an acrylic polymer containing various pigments was determined. Films containing the irregular-shaped aluminum lake particles were extremely brittle and were unable to be tested. Films containing the acicular yellow iron oxide pigment exhibited a higher permeability than films containing spherical red iron oxide. These findings, however, may be due to the particle size of the additive rather than the morphological structure of the pigments.

Surface Chemistry

The surface chemistry of the insoluble excipient incorporated into coating formulations may influence the permeability of the film. The inclusion of talc in aqueous dispersions of an acrylic polymer was found to reduce water vapor permeability, whereas titanium dioxide in the coating formulation resulted in an increase in the permeability of water through the film (3). These differences were attributed to the surface characteristics of the particles. Talc is a hydrophobic compound, whereas the anatase form of titanium dioxide is hydrophilic and has a strong affinity for water. The increased permeability of the films containing titanium dioxide may be due to the presence of interfacial moisture (29). Water at the polymer–pigment interface has also been shown to influence the permeability of paint films (74,75).

In another study, Okhamafe and York (29) determined the diffusion coefficient of cellulosic films containing different forms of titanium dioxide. The pigments investigated had a similar surface area, yet differed in their surface chemistry. The surface of the rutile titanium dioxide is hydrophobic, whereas the anatase form of titanium dioxide is hydrophilic. Interestingly, the diffusion coefficient was higher when the HPMC films contained the hydrophobic opacifying agent. The authors attributed these findings to inadequate filler–polymer interaction of the rutile titanium dioxide as a consequence of the surface treatment, which led to voids at the interface through which moisture rapidly diffused.

Concentration

The permeability of polymeric films has been shown to be influenced by the concentration of insoluble additives incorporated into the coating formulations. Increased concentrations of titanium dioxide resulted in a corresponding increase in the water vapor permeability (3,62). These results may be attributed in part to the surface chemistry of the pigment and the presence of water adsorbed onto the filler particles. In contrast, increasing the concentration of the hydrophobic compound talc in film coating formulations decreased the permeability of both cellulosic and acrylic films, presumably through increasing the tortuosity of the diffusional pathway (3,71,72).

Porter and Ridgway (76) investigated the effects of red iron oxide on the permeability of two enteric polymers, cellulose acetate phthalate (CAP) and polyvinyl acetate phthalate (PVAP). Increased concentrations of the pigment in PVAP films resulted in little change in water vapor permeability. The permeability of CAP films was initially decreased, and higher concentrations of the inorganic pigment resulted in increased permeability. The authors proposed that the tortuosity of the diffusional pathway was increased at low concentrations of red iron oxide, in accordance with the Chatfield principle (71). As the concentration of the insoluble filler surpassed the CPVC, however, the binding capacity of the polymer was exceeded and the moisture permeability of the film increased.

DISSOLUTION OF FILM-COATED SOLIDS

Dissolution is the process by which a drug passes from the solid state into solution. A drug must first dissolve before it can be absorbed through the biological membranes to exert its therapeutic effect. The addition of various excipients to film coating formulations may alter the dissolution properties of coated solids. Previously, researchers demonstrated that plasticizers and surfactants added to coating formulations influence the dissolution or disintegration rate of film-coated solids (12,77–79). The size, morphology, surface polarity, and concentration of insoluble excipients incorporated into polymeric coating formulations may also affect drug release from film-coated solids.

Particle Size

The particle size of insoluble additives incorporated into film coating formulations may influence the dissolution properties of coated solids, where larger particles in the polymer slow drug release to a greater extent than smaller particles present in the film. Maul and Schmidt (80) compared the dissolution properties of bisacodyl pellets coated with the enteric acrylic dispersion Eudragit L 30 D-55 as a function of particle size of pigments added to the coating formulation. Incorporation of large platelet-like surface-treated mica particles in the film coating resulted in slower drug release compared to formulations that contained smaller titanium dioxide pigment. Since the mica pigments were treated with titanium dioxide, the authors attributed their findings to the particle size of the pigments, rather than surface chemistry. These findings are in agreement with the permeability data published by Parker et al. (72) and Okhamafe and York (29).

Particle Morphology

Several researchers have suggested that the platelet structure of fillers may function as a barrier, where the particles are arranged in a roof tile-like manner, lengthening the diffusion pathway of water through the films and leading to slower drug release (30,81). This theory is supported by the data published by Maul and Schmidt (80,82), who found that platelet-shaped pigments or fillers, irrespective of their chemical constitution or surface chemistry, reduced drug release from film-coated solids.

Acicular-shaped yellow iron oxide and spherical titanium dioxide have been reported to produce films more permeable than when the platelet-shaped pigments are incorporated into the film coating formulation (80,83). Several theories have been proposed to account for these findings. Lippold et al. (84) suggested that pigment particles cause the formation of pores in the film coating during dissolution. List and Kassis (3), on the other hand, indicated that the surface chemistry of the insoluble additive accounted for the differences in the dissolution characteristics. Maul and Schmidt (80) tended to support this theory, proposing that titanium dioxide particles aggregate within the polymeric film and act as wicks due to their highly hydrophilic surfaces, thus leading to faster drug release. Although none of the theories that have been proposed to explain the influence of particle shape on drug release have been widely accepted, it is clear that the addition of insoluble excipients in film coating formulations alters the dissolution characteristics of the coated solid. The morphology of the pigments may be of importance in selecting insoluble excipients to be employed in coating formulations.

Surface Chemistry

Maul and Schmidt (82) used similar-sized excipients with different surface polarities to investigate the effect of surface chemistry of insoluble additives in polymeric systems on the release of theophylline from coated pellets. The drug release rates from pellets coated with Eudragit RS 30 D or Aquacoat are shown in Figs. 8 and 9, respectively. Drug release was faster when the polymeric films contained pigments with a more hydrophobic surface. The authors suggested that the more polar pigments formed tighter films than when the hydrophobic talc was incorporated into the coating. In another study by Wan and Lai (85), diphenhydramine hydrochloride release from methylcellulose-coated granules was found to be more rapid when hydrophobic anti-adherent excipients were included in the coating. These authors proposed that in addition to the more extensive voids at the filler–polymer interface, the hydrophobic materials agglomerated within the film, causing uneven swelling upon exposure to water.

In addition to the surface chemistry of the pigments, drug release from the coated pellets was also found to be influenced by the plasticizer in the coating formulation, as shown in Figs. 8 and 9. The rate of drug release was much slower when the acrylic polymer was plasticized with triethyl citrate than when dibutyl phthalate was used as the plasticizing agent. Drug release from the cellulosic coating was also found to be influenced by the plasticizing agent, although to a lesser extent than the acrylic films. The rate of drug release from the pellets coated with the titanium dioxide-pigmented cellulosic film was nearly identical to the unpigmented formulation when triethyl citrate was used as the plasticizing agent, as seen in Fig. 9A. Maul and Schmidt (82) proposed that some type of interaction

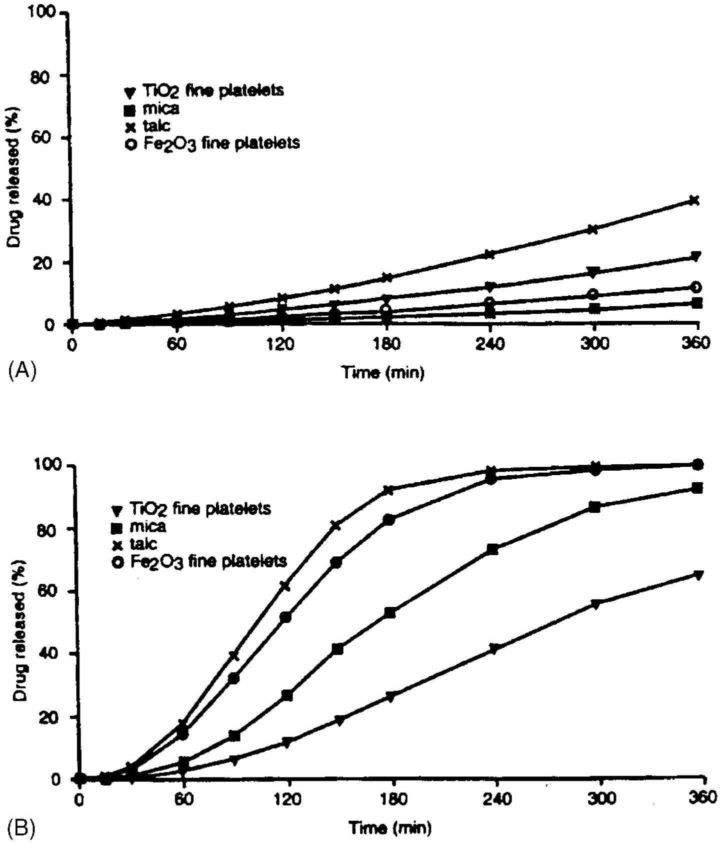

Figure 8. Influence of surface chemistry of pigments incorporated into Eudragit RS 30 D films on theophylline drug release from coated pellets as a function of plasticizer. All pigments were platelet-like structures of comparable size. (A) Triethyl citrate; (B) dibutyl phthalate; (▼) titanium dioxide; (■) mica; (×) talc; (○) red iron oxide. (From Ref. 82.)

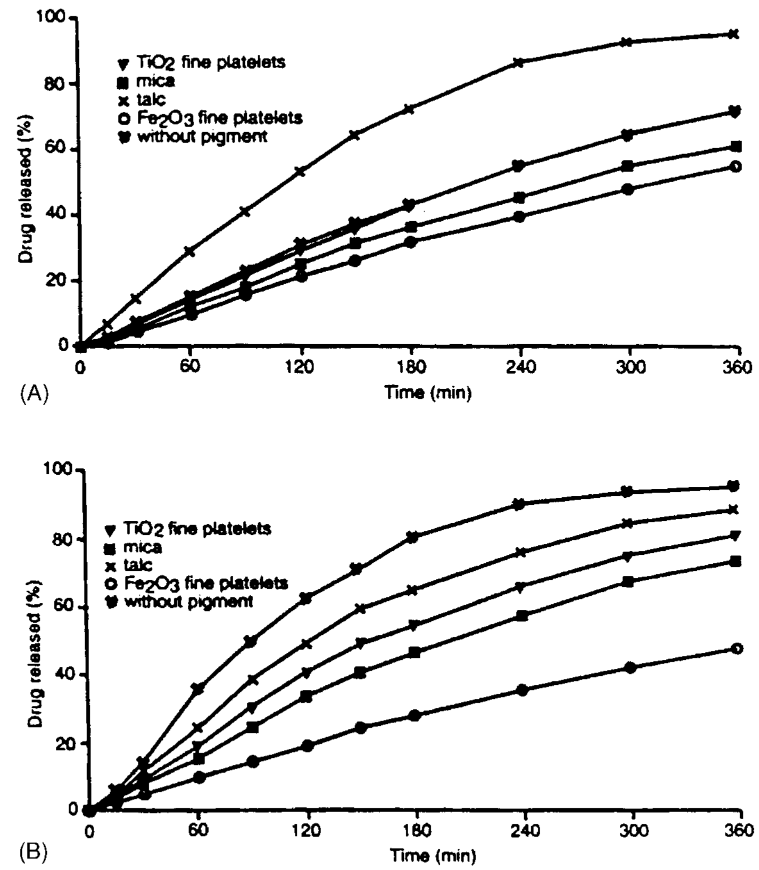

Figure 9. Influence of surface chemistry of pigments incorporated into Aquacoat ECD 30 films on theophylline drug release from coated pellets as a function of plasticizer. All pigments were platelet-like structures of comparable size. (A) Triethyl citrate; (B) dibutyl phthalate; (▼) titanium dioxide; (■) mica; (×) talc; (○) red iron oxide; (✱) no pigment. (From Ref. 82.)

between the plasticizer and the pigment may occur within the film, thus influencing drug release. Further research is required to understand possible interactions between pigments and plasticizers and their influence on drug release from polymeric films.

Concentration

Ghebre-Sellassie et al. (25) showed that increasing the concentration of kaolin in an acrylic film resulted in a decrease in the lag time and faster drug release. In another study, Wan and Lai (85) found that increasing the concentration of magnesium stearate in methylcellulose films increased the rate of drug release, as shown in Fig. 10. The authors proposed several theories to explain these results. Firstly, the particles may agglomerate in the film, rather than be homogeneously dispersed, thus causing higher internal stresses within the polymer. Secondly, and possibly more importantly, at such high concentrations of the insoluble excipient the CPVC may be exceeded and the polymer matrix may be unable to bind all the insoluble additive particles.

The addition of other excipients in polymeric solutions and dispersions, however, has been shown to exhibit a retarding effect on drug release. Li et al. (16) found that increasing the concentration of talc in an acrylic polymer resulted in decreasing the dissolution rate of theophylline granules. These findings are in agreement with the permeability data published by Parker et al. (72) and List and Kassis (3), where the permeability of both cellulosic and acrylic films was decreased as the concentration of talc in the coating formulation was increased. The insoluble platelet particles are thought to increase the tortuosity of the diffusional pathway, thus slowing the penetration of water to the solid core and, correspondingly, decreasing drug release.

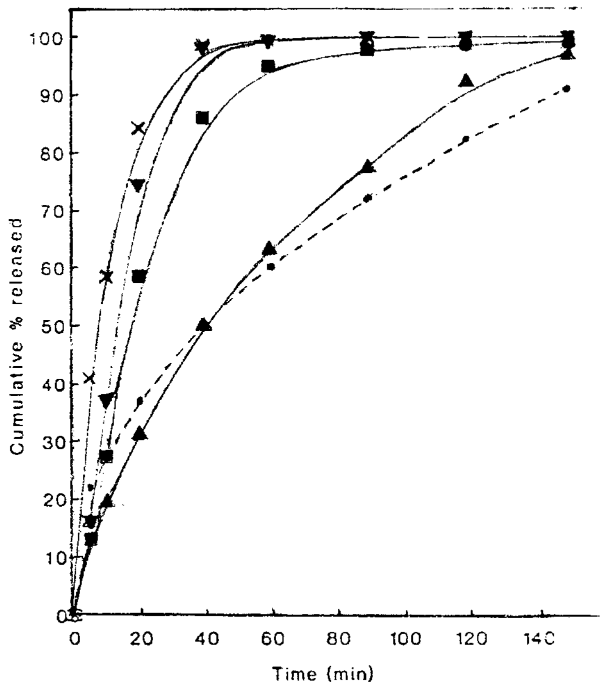

Figure 10. Influence of the concentration of magnesium stearate in the film coating formulation on the release of theophylline from granules coated with methylcellulose. (X) Drug powder; (•) uncoated granules; (▲) 20% w/w; (■) 50% w/w; (▼) 80% w/w. (From Ref. 85.)

Maul and Schmidt (80,82) also found that increasing the concentration of pigments in coating formulations could significantly retard drug release. As shown in Fig. 11, release of theophylline decreased as the concentration of titanium dioxide was increased. Interestingly, the dissolution rate was dependent on the plasticizer incorporated in the film coating formulation, with more dramatic changes in drug release occurring when the polymer was plasticized with dibutyl phthalate. In addition to interacting with the polymer, these findings suggest that the filler may interact with other excipients in the film coating formulation, such as plasticizers, and further demonstrates the complex behavior of insoluble additives in film coating formulations.

CONCLUSIONS

The addition of insoluble excipients to film coating formulations can improve the appearance of the film, enhance the stability of photolytic drugs, and aid in processing. However, these insoluble additives may significantly affect the physical, mechanical, adhesive, and drug-release properties of the films. The extent to which insoluble particles in film coating formulations affect polymer properties may be related to the particle size, morphology, surface chemistry, and concentration of the insoluble excipient. In addition to the polymer, these insoluble additives may also interact with other excipients in the coating. Understanding the mechanisms by

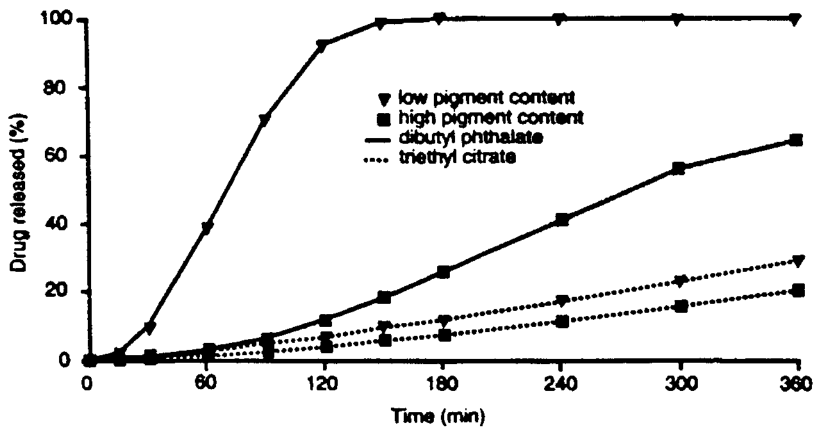

Figure 11. Release of theophylline from pellets coated with Eudragit RS 30 D plasticized with (—) dibutyl phthalate or (····) triethyl citrate as a function of titanium dioxide concentration. (▼) Low pigment concentration ($1\,cm^3/15\,g$ dry latex). (■) High pigment concentration ($3\,cm^3/15\,g$ dry latex). (From Ref. 80.)

which these insoluble materials influence polymer properties will allow the pharmaceutical scientist to predict behavior and exploit the use of these compounds to achieve desired effects.

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