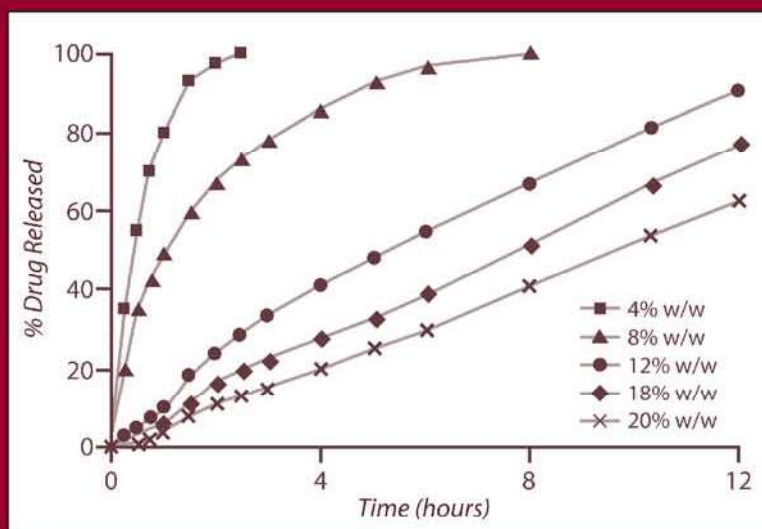


Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms

Third Edition



edited by

James W. McGinity
Linda A. Felton

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Mechanical Properties of Polymeric Films Prepared from Aqueous Dispersions

Linda A. Felton

*College of Pharmacy, University of New Mexico, Albuquerque,
New Mexico, U.S.A.*

Patrick B. O'Donnell

Neurocrine Biosciences, San Diego, California, U.S.A.

James W. McGinity

College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.

INTRODUCTION

Pharmaceutically acceptable polymers used in the film coating of solid dosage forms are primarily based on acrylic or cellulosic polymers. Many of these polymers have been formulated into aqueous colloidal dispersions (e.g., latexes or pseudolatexes) in order to overcome the high costs, potential toxicities, and environmental concerns associated with the use of organic polymer solutions (1–3). Film coating has been successfully utilized to control the release of active ingredients, prevent interaction between ingredients, increase the strength of the dosage form to maintain product integrity during shipping, and protect the dosage form from the environment (2,4–7).

Coating formulations usually contain many additives, in addition to the polymer, that aid in processing, appearance, and product performance. Most formulations contain plasticizers that impart flexibility to the films and reduce the incidence of crack formation (8,9). Pigments may be added to alter the appearance of the final product (10), and lubricants may be required to prevent agglomeration

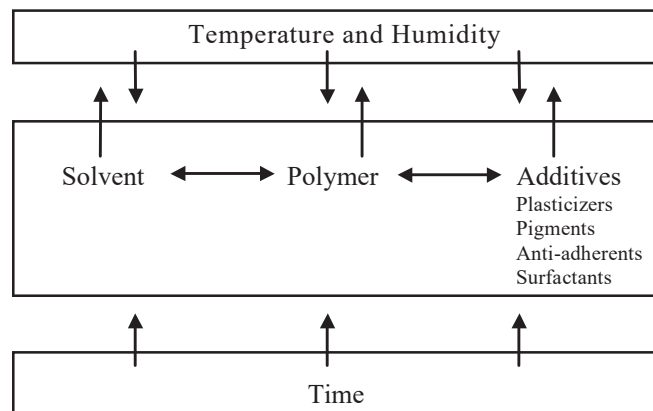


Figure 1 Factors affecting the mechanical properties of polymeric films.

of the coated substrates (11). Numerous polymer blends for controlled drug release have been investigated (4,5,12), and the release characteristics of these coated dosage forms are strongly dependent on certain properties of the film, e.g., permeability and mechanical strength (13–16). The amount and type of plasticizer in the film and the presence of other additives in the coating can significantly impact the film's mechanical properties (17–21). In addition, factors such as storage conditions and processing temperature will influence coalescence and film formation and thus product performance (22–24). Figure 1 illustrates the relationship between these factors.

FILM PREPARATION METHODS

Studies to investigate the mechanical properties of polymers may be conducted using free films or films applied to a substrate. Free films can be obtained by the casting method, where a polymeric solution or dispersion is cast onto a nonstick substrate and the solvent is evaporated (25–27). In formulations containing solid particles, however, sedimentation may occur during the drying stages, resulting in nonuniform films. The preparation of multilayered films by the cast method is also difficult because the solvent present when casting secondary layers may dissolve or interact with previous layers (28).

To avoid different film surfaces that may result from casting polymeric dispersions, a spray atomization technique may be employed. This type of spray box apparatus, shown in Figure 2, consists of a rotating drum inset into a box with heat introduced to facilitate solvent evaporation. The polymeric material is then sprayed onto the nonstick surface of the rotating drum (29,30). This technique better simulates coating processes and produces more uniform surfaces (28).

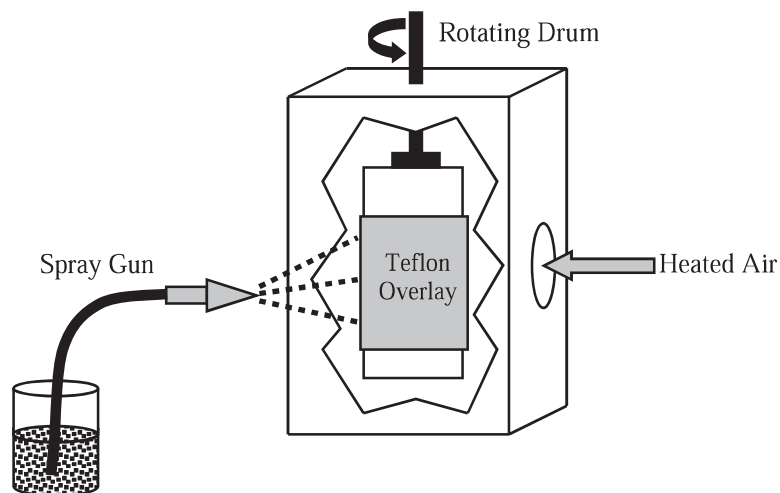


Figure 2 Schematic of a spray box apparatus used to prepare free films.

In contrast to the study of free films, the evaluation of applied films has recently gained in popularity (31–33). Applied films can be used to investigate substrate variables, processing parameters, storage conditions, and physical aging in addition to coating formulation factors. Since most solid dosage forms are designed to dissolve in water-based biological fluids and the majority of coating systems used today are aqueous-based, the dissolution of the outermost surfaces of the substrate occurs during the coating process, permitting physical mixing at the film–tablet interface, which could lead to migration of drug or excipient into the film (34). This physical mixing and migration of components into the coating can affect the mechanical, adhesive, and drug-release properties of the polymer film (35,36).

MECHANICAL TESTING TECHNIQUES

Stress–Strain Testing of Free Films

Stress–strain testing in the tensile mode has been a popular and widely used mechanical test for polymeric films. The tensile test is practical, and analysis of its data is relatively straightforward. The tensile test gives an indication not only of the elasticity and strength, but also of the toughness of the film. In the development of a film coating system, evaluation of the mechanical properties of free films can readily characterize the fundamental properties of the coating (37). However, polymers are viscoelastic, and their mechanical behavior is dependent on many factors, including environmental conditions and experimental testing parameters.

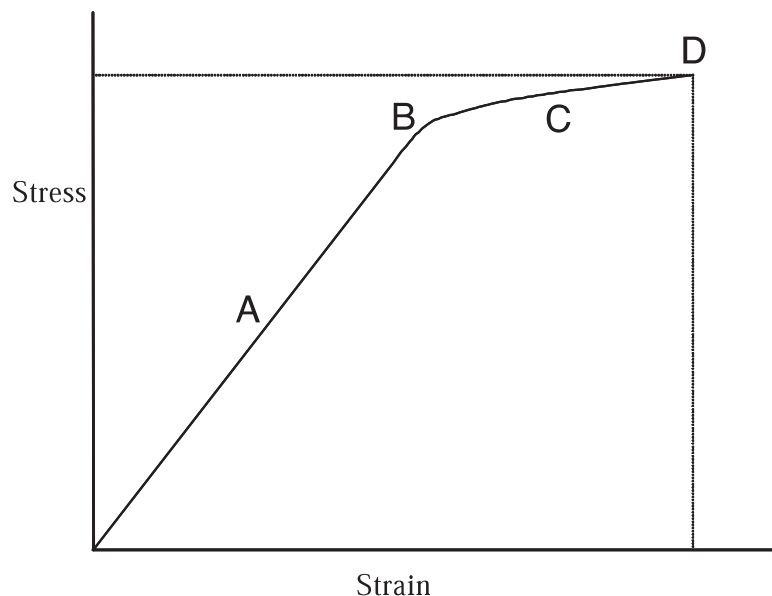


Figure 3 Example of a stress–strain profile generated from tensile testing of free films. (A) Region of elastic deformation, where stress is proportional to strain; (B) yield point; (C) region of plastic deformation, where polymer chains orient themselves; (D) film breaks.

A tensile-testing instrument such as an Instron (Norwood, Maine) or a MTS Systems Corp (Eden Prairie, Minnesota) mounted with a load cell may be used for the measurements. According to the American Society for Testing Materials (ASTM) guidelines, the data for tensile properties may be acquired in the form of a load–time (elapsed) profile or, more typically, a load–displacement or stress–strain profile, as shown in Figure 3. The data collected for a load–time or load–displacement profile can be converted mathematically to a stress–strain curve. Four mechanical properties, namely tensile strength, elongation, work of failure, and Young’s modulus, are then computed. The theory behind the computation of these parameters is well documented (21,38). The final equations that define each of these parameters are presented below.

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks (Fig. 3D). Tensile strength can be computed as the applied load at rupture divided by the cross-sectional area of the film, as described in Equation 1:

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Film thickness} \times \text{Film width}} \quad (1)$$

Tensile strength measurement alone is not useful in predicting the mechanical performance of films; however, higher values of tensile strength are indicative of abrasion resistance (27).

Strain

A film sample will stretch under applied stress, which is referred to as strain. Strain can be calculated as the deformation in the film divided by the original dimension of the sample. Strain is typically reported as percent elongation at fracture and is calculated using Equation 2:

$$\text{Percent elongation} = \frac{\text{Increase in length of film}}{\text{Initial length of film between the grips}} \times 100 \quad (2)$$

Elongation of a film will generally increase as the plasticizer level in the coating is increased (19,39).

Work of Failure

Work of failure is a function of work required to break the film specimen and represents the film toughness. It can be calculated from the area under the curve of the stress-strain diagram, cross-head speed, and the film dimensions, as described in Equation (3):

$$\text{Work of failure} = \frac{\text{Area under curve} \times \text{Cross-head speed}}{\text{Film thickness} \times \text{Film width}} \quad (3)$$

Young's Modulus

Young's modulus, sometimes referred to as elastic modulus, is the most basic and structurally important of all mechanical properties and is a measure of the stiffness of the film. It is the ratio of applied stress and corresponding strain in the region of approximately linear elastic deformation and can be computed using Equation 4:

$$\text{Young's modulus} = \frac{\text{Slope}}{\text{Film thickness} \times \text{Cross-head speed}} \quad (4)$$

Since most amorphous polymers behave as viscoelastic materials, their mechanical properties will depend on the temperature and the application rates of stress and strain. The profile in Figure 4 shows typical changes in polymer chain arrangement that occur during tensile testing of a free film. Initially, there is a linear portion in the stress-strain profile (Fig. 3A), where elongation is directly proportional to applied stress and polymer chains are randomly oriented (Fig. 4A). The slope of this straight line portion of the graph is used to calculate Young's modulus. The greater the slope of the curve, the higher the Young's modulus. As the stiffness and the strength of the film increase, more stress will be required to

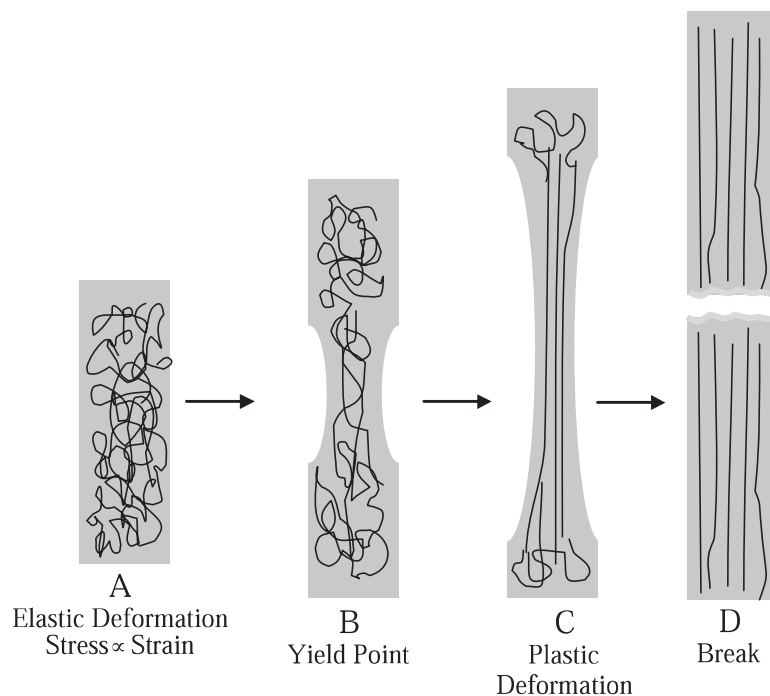


Figure 4 Schematic of the changes in polymer chain arrangement that occur during tensile testing of a free film.

produce a given amount of deformation. At the yield point (Figs. 3B and 4B), polymer chains begin to orient themselves to the applied stress and are completely aligned during the plastic deformation stage of stress-strain analysis (Figs. 3C and 4C). Finally, the film specimen fractures (Figs. 3D and 4D).

Not all polymers behave in a typical manner, and depending on the mechanical response of the polymer, a family of stress-strain profiles can be obtained to clearly define elasticity, tensile strength, and film elongation at the break of the plasticized polymer. Some examples are illustrated in Figure 5. Hard and brittle films exhibit a high tensile strength and Young's modulus with little elongation. In contrast, a soft and tough film will possess a low tensile strength but much greater elongation and a higher area under the curve (toughness).

Stress-Strain Testing of Applied Films

Compression testing of applied films is similar to tensile testing of free films in that uniform displacement rates are applied to a sample, and force and displacement values are recorded. The primary difference between the two techniques is in the direction of the applied stress. The substrate has been shown to significantly influence the mechanical strength of applied films (40,41). The affects of process-

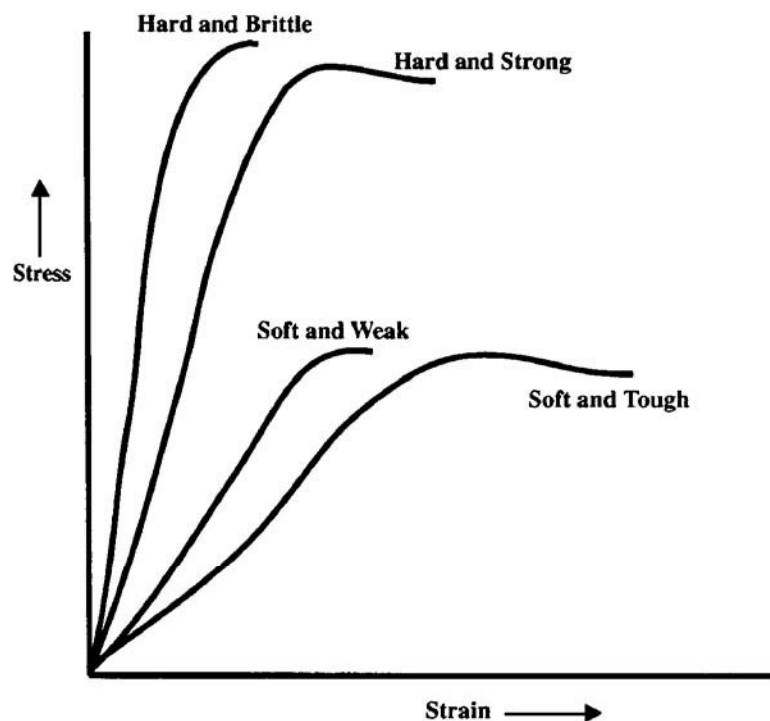


Figure 5 Examples of characteristic stress–strain profiles obtained from tensile testing of free films.

ing parameters, storage conditions, and physical aging of the applied film can be evaluated using compression testing (22,33). In addition, compression testing of applied films can provide qualitative information on adhesion of the coating to the substrate (6,41), with simultaneous fracture of the substrate and film indicating good adhesion.

Knowledge of the compression properties of applied films is critical if the coated substrate is to be tableted. If the compressional force exceeds the coating strength, the film will fracture and faster dissolution will result (32). The formation of matrix tablets when tableting coated pellets has also been reported, resulting in slower drug release as the polymer coatings fuse during compression (42). To reduce friction during compression and to prevent direct contact of the coating, readily compressible excipients are often blended with the coated pellets prior to tableting (43).

Glass Transition Temperature

The glass transition temperature (T_g) is the temperature at which the mechanical behavior of a film changes. Below this temperature, the polymer exists in a glassy

state that is characterized by a substructure in which there is minimal polymer chain movement. Above the T_g , the polymer is in a rubbery state, which is characterized by increased polymer chain movement and polymer elasticity. The T_g is typically measured using a differential scanning calorimeter (DSC), where a sample and reference pan are heated at a programmed rate, and thermal transitions, where more energy is absorbed or emitted, are determined. There are numerous examples in the literature of determining T_g values to evaluate polymer properties and interactions with excipients (44–46). The DSC instrument can also be used to determine melting temperature, detect polymorphism, study polymer miscibility, and investigate oxygen degradation (7,47–49). A number of variations in DSC testing have been developed, including a triple-cell system for more precise measurements of enthalpy, temperature-modulated units to separate reversing and nonreversing transitions, and high-sensitivity models (50,51).

Dynamic Mechanical Analysis

Dynamic mechanical analysis (DMA) is another type of test used to study the mechanical properties of polymeric films. In DMA testing, a free film is placed between two grips, one stationary and the other oscillatory. The free film is then deformed by torsion oscillation as a function of temperature. The storage modulus, loss modulus (dissipated energy), and damping coefficient (ratio of loss modulus to storage modulus) are determined. Several different modes are available, including fixed frequency, creep relaxation, and stress relaxation. DMA can be used to determine the T_g as well as other smaller, sub- T_g transitions that can provide some indication of polymer structure (52). Modifications to the instrument have permitted the mechanical properties of polymeric films applied to individual pellets to be determined (40).

EFFECTS OF PLASTICIZERS IN THE COATING FORMULATION ON MECHANICAL PROPERTIES

Many polymers used in film coating of pharmaceutical dosage forms display brittle properties at ambient temperature and humidity conditions, and the addition of a plasticizer is essential to achieve effective coatings without cracks or splitting defects (9). Plasticizers are added to polymeric solutions or dispersions to increase the workability or flexibility of the polymer and reduce brittleness, improve flow, and increase toughness and tear resistance of the films. These effects are the result of the plasticizer's ability to weaken intermolecular attractions and allow the polymeric molecules to move more easily. Several theories have been proposed to explain the mechanism by which the plasticizing agents impart flexibility to polymeric films (53). According to the lubricity theory, the plasticizer functions as an internal lubricant and facilitates movement of the polymer chains. The gel theory proposes that the unplasticized polymer exists as a three-dimensional gel and that the plasticizer functions by cleaving the intermolecular bonds within the gel. Finally, the free

volume theory states that plasticizers increase the free space around the polymer chains, providing a greater area for movement of the polymer molecules.

In addition to enhancing the flexibility of the film, plasticizers influence permeability and drug release (13,14,54). Many compounds can plasticize polymeric films, including water, drugs, and excipients (35,55). The selection of a plasticizer, therefore, is an important decision in the development of controlled-release pharmaceutical dosage forms. Ideally, the plasticizer level in the film should be optimized to reduce the brittle character of the film without adding excess plasticizer. Higher levels of plasticizer can cause sticking or agglomeration of the coated product during storage, which will compromise the release properties of the drug from such dosage forms (56).

The effectiveness of a plasticizing agent is dependent to a large extent on the amount of the plasticizer added to the coating formulation and the extent of polymer–plasticizer interactions. The interaction of a plasticizer with the polymer decreases the T_g of the film and is considered a common measure of plasticizer effectiveness, with the more effective plasticizers producing greater decreases in T_g . The influence of water-soluble and water-insoluble plasticizers on the T_g of Eudragit® L 100-55 is shown in Figure 6 (19). The presence of 10% plasticizer in

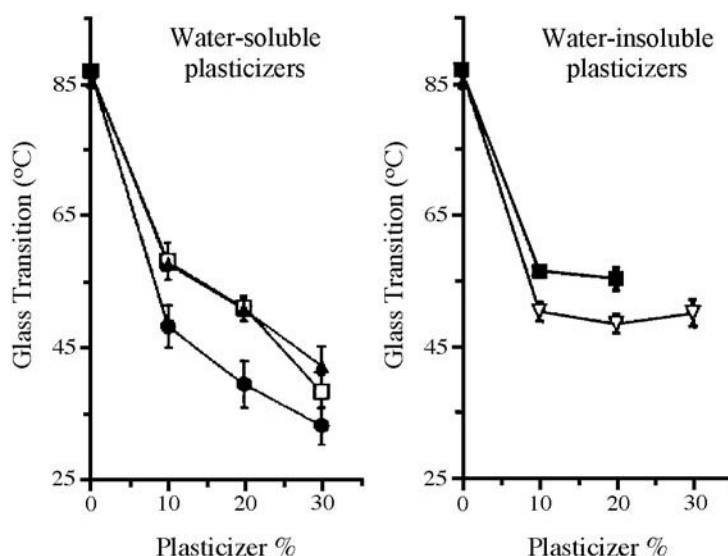


Figure 6 Effect of different levels of plasticizers on the glass transition temperature of Eudragit® L 100-55 films stored for 60 days at 23°C, 50% RH followed by 30 days at 23°C, 0% RH ($n = 5$). Water-soluble plasticizers: (●) TRI, triacetin (□) TEC, (▲) ATEC; water-insoluble plasticizers: (▽) TBC, (■) ATBC. Abbreviations: TRI; TEC, triethyl citrate; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; ATBC, acetyl tributyl citrate; RH, relative humidity. Source: From Ref. 19.