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Review

Physical aging in pharmaceutical polymers and the effect on solid oral dosage form stability

Shawn A. Kucera[a,*], Linda A. Felton[b], James W. McGinity[c]

[a] Merck KGaA, Frankfurter Strasse 250, Darmstadt 64293, Germany
[b] College of Pharmacy, University of New Mexico Health Sciences Center, Albuquerque, NM 87131, United States
[c] College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, United States

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ABSTRACT

The application of a polymeric film to a solid oral dosage form can be an effective technique to modify drug release. Most polymers used for such purposes are amorphous in nature and are subject to physical aging. This physical aging phenomenon has been shown to cause changes not only in the mechanical and drug release properties of polymeric films, but also the permeability of these films due to a densification and decrease in free volume of the polymer as the material relaxes to an equilibrated thermodynamic state. Temperature, humidity, and additional excipients in the coating formulations have been shown to influence the aging process. This review article discusses the process of physical aging in films prepared from aqueous dispersions, describes various analytical techniques that can be used to investigate the aging process, and highlights strategies to prevent such aging.

Contents

1. Introduction

The coating of oral pharmaceutical dosage forms with a polymer is an effective means of modifying the drug release rate. The mechanism of drug release can be such that the polymer dissolves

* Corresponding author. Tel.: +49 6151 72 58055; fax: +49 6151 72 23478.
E-mail addresses: shawn.a.kucera@gmail.com, shawn.kucera@merckgroup.com (S.A. Kucera).

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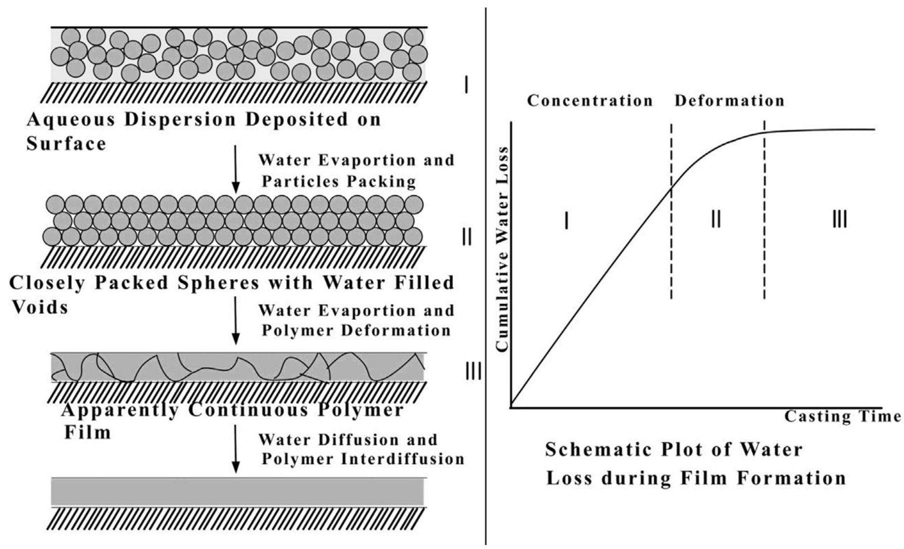

Fig. 1. The formation of thin films from polymeric lattices occurs with the simultaneous evaporation of water (McGinity and Felton, 2008).

as a function of gastrointestinal fluid pH or by diffusion through a semi-permeable or permeable membrane. With the strict requirements of environmental and regulatory bodies regarding the use of organic solvents in production facilities, there has been an increasing trend to move from solvent-based coating systems, in which the polymer is fully dissolved, to aqueous latex or pseudolatex polymeric systems.

It has been previously reported that the formation of a thin, transparent film from latex or pseudolatex dispersions occurs with the simultaneous evaporation of water (Lin and Meier, 1995; Lippold and Pages, 2001), as demonstrated in Fig. 1 (McGinity and Felton, 2008). Stage 1 of film formation occurs during the coating process as the latex or pseudolatex particles are applied to the substrate and water is removed at a constant rate. As water evaporates, capillary forces cause the particles to be drawn closer to each other (stage 2). During this time, the rate of water evaporation decreases. Stage 3 is characterized by a plateau in the rate of water evaporation and the formation of the film is generally considered to be complete; however, it is during stage 3 that changes in the drug release rate may occur due to physical aging or further gradual coalescence of the polymeric film.

1.1. The origin of physical aging

Physical aging, or enthalpy relaxation, is not a new concept but is a phenomenon that has been known by polymer scientists for many years. All amorphous polymers exhibit physical aging, which can be characterized by an increase in the rigidity, brittleness, and density of a polymer film (Greiner and Schwarzl, 1989). In his text "Physical Aging in Amorphous Polymers and Other Materials", Struik (1978) cited the early work of Simon (Simon, 1931) who showed that amorphous materials were not in thermodynamic equilibrium at temperatures below their glass transition temperature (T_g). This unstable state is the result of a material possessing a greater volume, enthalpy, and entropy than that found in the equilibrium state, as shown in Fig. 2. The transport mobility of particles, or in this case polymer chains, in a tightly packed system, as defined by the free volume concept, is primarily dependent on the degree of packing, and thus the "free volume" of said system. Once the polymer is cooled to a temperature below its T_g, the free volume is greater than it would be at equilibrium and the volume will decrease slowly over time (Guo, 1999; Struik, 1978). This contraction is accompanied by a decrease in the polymer chain mobility, which leads to a densification of the polymer. Changes in both porosity and tortuosity in the film can significantly impact drug release (Guo, 1999; Zheng et al., 2005).

1.2. The effect of physical aging on diffusion-based drug release

The diffusion of drug through a thin permeable or semi-permeable membrane can be described mathematically by Fick's first law of diffusion:

$$Q = \frac{K \times D \times S \times (C1 - C2) \times t}{h} \tag{1}$$

where Q (the quantity of drug to diffuse through the film over time, t) is a function of h, the film thickness; S, the surface area available for diffusion; C_1, the concentration of drug in the donor compartment; C_2, the concentration of drug in the acceptor compartment, D, the diffusion coefficient of the drug; and K, the partition coefficient of the drug with respect to the membrane separating the donor and acceptor compartments. The Iyer Equation (Eq. (2)) shows that

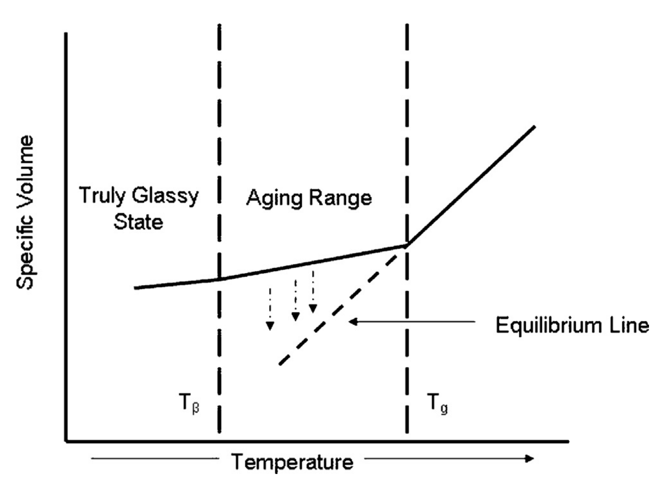

Fig. 2. Graphical representation of the origin of physical aging. T_g is the glass transition temperature of the polymer and T_β is the temperature of the highest secondary transition (Struik, 1978).