Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 323 (2006) 11–17
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Relationship between drug dissolution and leaching of plasticizer for pellets coated with an aqueous Eudragit® S100:L100 dispersion

Hiroto Bando *, James W. McGinity

Drug Dynamic Institute, College of Pharmacy, University of Texas at Austin, Austin, TX 78712, USA

Received 26 September 2005; received in revised form 28 April 2006; accepted 23 May 2006
Available online 27 May 2006

Abstract

In order to investigate the relationship between drug dissolution and leaching of plasticizer, theophylline pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with different levels of triethyl citrate (TEC) were prepared. The influence of storage conditions on the dissolution profile of theophylline and leaching of TEC was determined.

Theophylline was found to dissolve completely from pellets coated with Eudragit® S100:L100 (1:1) plasticized with 50% TEC at pH 6.0 after 2 h. The shape of the pellets was maintained during dissolution testing. Cracks due to the leaching of TEC were observed in the scanning electron micrographs (SEMs) following dissolution testing at pH 6.0. Both the dissolution of theophylline and the leaching of TEC decreased during storage due to further coalescence of the acrylic polymers. The dissolution profiles of theophylline showed a biphasic pattern and the lag times were estimated as the time points at which a second, rapid release of theophylline was initiated. Subsequently, the percent of TEC leached at the lag time was calculated. While the lag time was increased by storage time and humidity, the percent of TEC leached at the lag time was unchanged as a function of storage condition and was dependent on the initial TEC levels in the films.

In conclusion, the plasticizer content in the film coating influenced the dissolution profile of theophylline from pellets coated with Eudragit® S100:L100 (1:1). A large amount of the TEC was leached from the enteric films before drug release was initiated and a TEC level of approximately 30% in the films, based on the polymer weight, was the critical amount of TEC for initiating drug release during dissolution testing at pH 6.0. While enteric films are more soluble and dissolve faster at higher pH values, the kinetics of plasticizer release was one of the important factors controlling the dissolution of drugs at pH 6.0, at which pH the enteric polymers were insoluble.

Keywords: Theophylline; Aqueous film coating; Eudragit® S100; Eudragit® L100; Triethyl citrate

1. Introduction

Polymeric film coatings have been used to control drug release from solid pharmaceutical dosage forms (McGinity, 1997). In the coating process, plasticizers are often required to reduce the brittleness of the polymeric films. An aqueous polymeric dispersion is generally preferred over solvent based solutions because of safety and environmental concerns and these systems exhibit a lower viscosity than organic-based solutions at the same solids content. The incorporation of plasticizers into the coating formulation reduces the minimum film formation temperature (MFT) and promotes film formation. Various studies regarding the influence of plasticizer concentration on the physicochemical properties of polymeric films and the dissolution properties of drugs from coated products have been reported in the scientific literature (Saettone et al., 1995; Ocarter and Singla, 2000; Lecomte et al., 2004). For example, higher levels of plasticizers in polymeric films was shown to decrease metoprolol release from pellets coated with Eudragit® RS 30D (Ocarter and Singla, 2000) and to improve the stability of theophylline release after storage of coated pellets (Amighi and Moës, 1996). Furthermore, the types of plasticizers have also been shown to affect the drug release rate. For example, release of propranolol from pellets coated with the mixture of ethylcellulose and Eudragit® L100-55 was faster when a hydrophilic plasticizer, triethyl citrate (TEC), was incorporated into the coating compared with a hydrophobic plasticizer, dibutyl sebacate (Lecomte et al., 2004). Other researchers have demonstrated that plasticizers can be

* Corresponding author. Present address: Takeda Pharmaceutical Company Ltd., Pharmaceutical Technology Research and Development Laboratories, Pharmaceutical Production Division, 17-85 Jusohonmachi2-Chome, Yodogawa-ku, Osaka 532-8686, Japan. Tel.: +81 6 6300 6375; fax: +81 6 6300 6717.
E-mail address: Bando_Hiroto@takeda.co.jp (H. Bando).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.05.043

leached from films during dissolution and this will influence both the mechanical and drug release properties (Bodmeier and Paeratakul, 1992, 1994a, 1994b; Frohoff-Hülsmann et al., 1999). Few reports on the relationship between drug release and leaching of the plasticizers during dissolution have been published for enteric polymers systems.

The methacrylic acid–methyl methacrylic acid copolymers including Eudragit® L100 and Eudragit® S100, which begin to dissolve at pH 6.0 and 7.0, respectively, are commonly used enteric polymers. Recent studies have focused on the combination of these acrylic enteric polymers to target drug delivery to the colon (Khan et al., 1999; Lecomte et al., 2004; Bando and McGinity, 2006). Since the MFT of these polymers is higher than normal coating temperatures (Lehmann, 1997), TEC levels of 50% and higher are recommended for aqueous dispersions. Despite the requirement of such high levels of TEC, few reports on leaching of the plasticizers from aqueous Eudragit® S100 and L100 films have been published. In our previous study (Bando and McGinity, 2006), leaching of TEC from cast films composed of Eudragit® S100:L100 (1:1) was reported to be dependent on the casting solvents, where the plasticizer diffused from aqueous based films more rapidly than from films prepared from organic solutions. In the current study, in order to investigate the relationship between drug dissolution and leaching of the plasticizer, theophylline pellets coated with 30% (w/w) Eudragit® S100:L100 (1:1) plasticized with different levels of TEC were prepared and the dissolution properties of theophylline and leaching of TEC from the film coating were simultaneously determined as a function of storage conditions.

2. Materials and methods

2.1. Materials

Theophylline as a model drug and lactose monohydrate as a diluent were purchased from Spectrum Chemical MFG. Corp. (Gardena, CA, USA). Nu-Pareil® (25/30) core pellets were supplied by CHR Hansen Inc. (Mahwah, NJ, USA) and Avicel® PH101 was donated by FMC Corp. (Newark, DE, USA). KLUCEL® (hydroxypropylcellulose, HPC-L) was supplied by Hercules Inc. (Wilmington, DE, USA). Eudragit® S100 (poly (methacrylic acid–methyl methacrylic acid) (MA-MMA) 1:2 copolymer) and Eudragit® L100 (MA-MMA 1:1 copolymer) were donated by Degussa Röhm America LLC (Piscataway, NJ, USA). Triethyl citrate (TEC) was donated by Morflex Inc. (Greensboro, NC, USA) and Altalc®500 USP (talc) as anti-tacking agent was supplied by Luzenac America (Englewood, CO, USA). Pharmacoat® 603 (hydroxypropylmethylcellulose, HPMC) was donated by Shin-Etsu Chemical Corp. Ltd. (Tokyo, Japan).

2.2. Preparation of theophylline core pellets

A 200 g batch of Nu-Pareil® (25/30) was transferred into a fluidized bed coater (Strea-1 Aeromatic-Fielder, Niro Inc., MD, USA) and theophylline pellets were prepared by layering a drug-binder dispersion (6.0% (w/w) theophylline, 6.0% (w/w) lactose monohydrate, 6.0% (w/w) Avicel® PH101, 2.0% (w/w) HPC-L, 80% (w/w) water). The inlet and outlet temperatures were 55 ± 2 °C and 35 ± 2 °C, respectively. The coating dispersion was applied at a rate of 2.0–2.5 g/min, and the pneumatic spray pressure was 1.5 bar. The coating dispersion was stirred continuously throughout the coating process to prevent sedimentation. Pellets were sieved after drying at 40 °C for 12 h, and the 16–20 mesh pellets were selected for further study.

2.3. Preparation of enteric coating dispersions

The dispersions of Eudragit® S100 and Eudragit® L100 were prepared separately and each acrylic polymer was partially neutralized by the addition of ammonia solution. The degree of neutralization was 15 mol% and 6 mol% for Eudragit® S100 and Eudragit® L100, respectively. The dispersions were stirred for 60 min prior to plasticization. After adding 50%, 70% or 100% TEC based on the polymer weight, polymer dispersions were stirred for an additional 60 min. Talc (50% based on dry polymeric weight) was previously dispersed in purified water using a POLYTRON (Brinkmann Instruments, Westbury, NY, USA) and the talc suspension was poured into the polymer dispersions. The final dispersions were prepared by adding the Eudragit® S100 slowly into the Eudragit® L100 dispersion.

2.4. Film coating

A 250 g batch of pellets (16–20 mesh) was transferred into a fluidized bed coater (Strea-1 Aeromatic-Fielder, Niro Inc., MD, USA), and the acrylic dispersions were applied until 30% (based on dry polymer weight) weight gain was achieved. The inlet and outlet temperatures were 55 ± 2 °C and 35 ± 2 °C, respectively. The coating dispersion was applied at a rate of 2.0–2.5 g/min, and the pneumatic spray pressure was 1.5 bar. The aqueous dispersion was stirred continuously throughout the coating process to prevent sedimentation. After application of the coating dispersion, the pellets were dried for an additional 10 min at 35 ± 2 °C in the fluidized bed unit, and then removed. An overcoat was added to prevent sticking of the pellets during storage. A HPMC solution including 50% talc based on HPMC weight (15% (w/w) solid) was used for this purpose (Harris and Ghebre-Sellassie, 1986) and was then applied to the pellets, resulting in an up to 5 wt.% gain as HPMC weight. Pellets were sieved after drying at 40 °C for 12 h, and the 12–16 mesh pellets were selected for further study. The coated pellets were stored at 40 °C in closed HDPE containers and 40 °C/75% RH in open containers for two months.

2.5. Dissolution of theophylline pellets

Dissolution testing of theophylline pellets was conducted using the USP 27 Apparatus II dissolution method (Paddle method, VanKel VK 6010; Cary, NC, USA) in 900 mL of media maintained at 37 °C with a paddle agitation rate of 50 rpm. The dissolution media included 0.1 N HCl or 50 mM phosphate buffered solutions (pH 6.0, 6.5 and 7.0). The pellets (ca. 400 mg)