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An investigation into moisture barrier film coating efficacy and its relevance to drug stability in solid dosage forms

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ABSTRACT

Barrier coatings are frequently employed on solid oral dosage forms under the assumption that they prevent moisture sorption into tablet cores thereby averting premature degradation of moisture-sensitive active ingredients. However, the efficacy of moisture barrier coatings remains unproven and they may actually accelerate degradation. This study aimed to investigate the barrier performance of four coating systems following application onto a low hygroscopic tablet formulation containing aspirin as a model moisture sensitive drug. Tablets were prepared by direct compaction and coated with aqueous dispersions of Eudragit® L30 D-55, Eudragit® EPO, Opadry® AMB and Sepifilm® LP at the vendors' recommended weight gains. Moisture uptake was studied by dynamic vapor sorption at 0 and 75% RH (25 °C). Accelerated stability studies were undertaken at 75% RH/25 °C for 90 days and HPLC assay was used to determine aspirin content. Uncoated tablet cores equilibrated rapidly and took up very little water (0.09%). The mean water uptake for coated cores was higher than for the uncoated formulation and varied as follows: 0.19% (Eudragit® L30 D-55), 0.35% (Opadry® AMB), 0.49% (Sepifilm® LP) and 0.76% (Eudragit® EPO). The level of aspirin decreased in all the samples such that by the time the study was terminated, the mean aspirin recovered was as follows: uncoated cores 80.0%; Eudragit® L30 D-55 coated cores 78.8%; Opadry® AMB coated cores 76.2%, Sepifilm® LP coated cores 76.0% and Eudragit® EPO coated samples 66.5%. From these results, it is concluded that the efficacy of moisture barrier polymer coatings on low hygroscopic cores is limited, and application of these coatings can, instead, enhance drug degradation in solid dosage forms.

1. Introduction

Many physico-chemical properties of pharmaceutical substances are significantly modified following exposure to water vapor (Dawoodbhai and Rhodes, 1989), and there is a potential risk of premature drug degradation in pharmaceutical products (Carstensen, 1988). Raw materials may come into contact with water during product processing, and moisture may be retained within the final dosage form as a result. Adverse storage conditions, either during manufacture, post-production or even when in use by the patient can contribute to dosage form moisture exposure and compromise the integrity and shelf life of the drug product: Hence, preventing water uptake is crucial for maintaining product viability.

There are many ways that can be used to minimize water uptake into dosage forms and/or prevent its interaction with active drug substances that are susceptible to hydrolysis. Some of the most commonly used approaches today include the careful selection of excipients that are able to bind or repel water, inclusion of desiccant in the product container, as well as the rational selection of packaging materials (Ahlneck and Zografi, 1990; Alvarez-Lorenzo et al., 2000; Zografi and Kontny, 1986). Increasingly, the application of moisture barrier coatings to the primary solid dosage form unit is undertaken.

An ideal moisture barrier coating should exhibit low permeability to water vapor without compromising its dissolution functionality. Such a coating should have an ability to sequester any sorbed moisture and prevent it from reaching the core. It is also important that any time-dependent, moisture stress-induced relaxation and ageing of the polymer coating is minimal to disallow the sustained uptake that is usually seen upon repeated exposure to moisture (Mwesigwa et al., 2008). The ubiquity of

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water coupled with its high reactivity (due to the large dipole moment of the O—H bond) means that any attempt at preventing contact between water molecules and the barrier coating is a challenging proposition. Moreover, there is a whole spectrum of additional effects that sorbed water may produce. As an example, sorbed water may interact with excipients or active substance either at the surface interface or in the substance's matrix, resulting into plasticization, deliquescence, dissolution, hydrate formation, or even polymorphic transformations (Buckton and Darcy, 1996; Zografi, 1988), further impairing functionality of the applied coating. Obviously, the outcome of these interactions depends not only on the chemical and physical properties of the polymer, excipient or drug substance in question, but also on the prevailing conditions of temperature and relative humidity (Zografi, 1988).

It is widely acknowledged that excipient selection is central to achieving stability of moisture sensitive actives. Some excipient types, while taking up more moisture, may actually stabilize moisture sensitive drugs better than those that are non-hygroscopic (Du and Hoag, 2001; Heidemann and Jarosz, 1991; Waterman and Adami, 2005). For example, it has been argued that hygroscopic excipients bind moisture through hydrogen bonding and thereby lower the water activity within the core, rendering it less available to participate in hydrolytic reactions (Höckerfelt and Alderborn, 2014). In a series of papers from our laboratory, we reported on the permeability characteristics of moisture barrier coatings in order to correlate them with the ability to protect a typical hydrolysable drug (aspirin) in a model hygroscopic tablet formulation (Mwesigwa et al., 2008; Mwesigwa et al., 2005). Our results showed that coatings exhibited complex sorption behaviors, achieving a net reduction in moisture uptake over uncoated cores. However, when the stability of aspirin was evaluated, it was found that the levels of degradation were higher in the coated cores (despite lower moisture uptakes) when compared with that in uncoated cores. Clearly, although moisture barrier coatings reduced water uptake by coated cores, neither their sorption and/or permeability characteristics correlated with their protective functionality after application onto hygroscopic tablet cores. This led us to conclude that the hygroscopic formulation did not adequately prevent aspirin hydrolysis as expected.

Thus, it was necessary to investigate the effect of tablet formulations having a lower hygroscopicity. Therefore, the purpose of the current study was to investigate whether the same moisture barrier coatings applied onto a much lower hygroscopic tablet formulation (based on dibasic calcium phosphate dihydrate and stearic acid) offers better protection and ensures the stability of a hydrolysable active drug substance. As a model hydrolysable drug, aspirin is a well-studied molecule and its degradation kinetics are widely reported (Ball, 1994; Carstensen et al., 1985; Edwards, 1950; Leeson and Mattocks, 1958). To maintain the claimed barrier performance, the manufacturers' recommended application guidelines and coating weight gains were followed and are hereby used as the basis for comparison.

2. Materials and methods

2.1. Materials

Poly(methacrylic acid ethyl acrylate) copolymer (Eudragit® L30 D-55, Evonik, Darmstadt, Germany), poly((butyl methacrylate) 2-dimethylaminoethyl) methacrylate methyl methacrylate copolymer (Eudragit® EPO, Evonik), a polyvinyl alcohol (PVA)-based coating system (Opadry® AMB, Colorcon, Dartford, UK); and a hypromellose-based coating system (Sepifilm® LP 014, Seppic, Paris, France) were free samples from respective vendors. Dibasic calcium phosphate dihydrate (Emcompress®, JRS Pharma, Rosenberg, Germany) was purchased from JRS Pharma. Aspirin (USP Grade), triethyl citrate, talc, titanium dioxide, poly ethylene glycol (PEG) 6000, stearic acid, magnesium stearate, sodium lauryl sulphate, and carboxy methylcellulose sodium were all purchased from Sigma–Aldrich (Poole, Dorset, UK).

2.2. Methods

2.2.1. Tablet preparation and coating

Multiple batches ($n \geq 3$) of tablet cores were obtained by direct compression and were based on aspirin (30%), dibasic calcium phosphate dihydrate (69.5%) and stearic acid (0.5%). To manufacture tablet cores, all the required ingredients were weighed and blended together in a planetary mixer for a total of seven minutes and compressed on a single stage tablet press (Manesty, Merseyside, UK) to yield cores with a target weight of 135 mg and a breaking strength of ≥70N. Coating was undertaken in a laboratory-scale fluidized bed coater (Aeromatic-Fielder AG, Switzerland) at 40 °C. The coatings vendors' recommended guidelines were followed to achieve theoretical dry weight gains of 1.8 % (Eudragit® L30 D-55), 6.4% (Eudragit® EPO), 4% (Opadry® AMB), and 3% (Sepifilm® LP). All coated and uncoated samples cores were thoroughly dried in a vacuum oven (for six hours at 40 °C) to remove residual moisture and thereafter stored in tightly closed bottles over phosphorous pentoxide desiccant pending further tests. The amount of aspirin post-coating was determined and the level of degradation in coated samples was found to insignificant (less than 0.1%).

2.2.2. Equilibrium moisture sorption studies

Moisture sorption profiles of uncoated and coated tablet cores were studied in a dynamic vapor sorption apparatus (DVS 1, Surface Measurement Systems, London, UK). The RH was programmed to expose samples at 0% RH and then automatically switch to 75% RH upon equilibration with the set condition. The equilibration condition for each RH stage was set at a mass change rate of 0.001%/min between two consecutive measurements. All experiments were performed at 25 °C. The results of water uptake are reported as the per cent dry basis (db) versus exposure time (minute) and are based on a minimum of three experimental runs.

2.2.3. Aspirin stability studies

Stability studies were undertaken at 75% RH/25 °C in sealed glass desiccators, which were placed in a thermostat-controlled incubator (Sanyo-Gallenkamp, Loughborough, UK). This condition was chosen to minimise temperature-mediated effect on aspirin degradation. The 75% RH condition was provided by a NaCl slurry. Aspirin tablets were placed in open glass containers and topped with loose cotton wool to prevent condensation from directly contacting the samples. From each container, 20 tablets were removed at day 15, 30, 45, 60, 75 and 90, allowing the degradation of aspirin (retained acetylsalicylic acid content as a% of the original dose) to be determined as described in Section 2.2.4.

2.2.4. HPLC assay

The amount of aspirin remaining in tablets following exposure to moisture stress was determined as follows: 12 tablets were coarsely ground in a mortar and transferred into a 100 ml volumetric flask. A portion of extraction solvent (i.e., acetonitrile-methanol (92:8) acidified with phosphoric acid) was then added. The mixture was sonicated for 15 min, made to volume, and a portion removed for centrifugation at 10,000 rpm. The supernatant was filtered using 0.45 μm syringe filters and transferred into 1 ml HPLC glass vials. A previously validated HPLC method (Fogel et al., 1984) was used (with minor modifications) to assay the retained strength of aspirin within the tablets. The HPLC system