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Research Paper

A case study exploring the impact of an oxygen barrier coating on formulation stability, in-vitro dissolution and bioperformance

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Abstract

Objectives The impact of a carmellose sodium (sodium carboxymethycellulose)-based coat (Opaglos 2) on the stability of an oxygen-sensitive compound A and in-vitro dissolution and bioperformance of compound B has been investigated.

Methods Tablets containing compounds A and B were coated with various weight gains of Opaglos 2 and a comparative elegance coating (poly(vinyl alcohol)-based Opadry II). Film-coated tablets were assessed for oxidative degradation under accelerated stability conditions (30°C/65% RH and 40°C/75% RH).

Key findings An apparent rank order of restriction of oxygen (O_2) permeability afforded by the coatings was observed, with only higher Opaglos 2 coating weight gains (6 and 8% w/w) providing adequate oxidative degradation stability for up to 52 weeks. Improved stability at the higher coating weight gains was attributed to incomplete polymeric film formation at lower coating weight gains. The 6% and 8% w/w Opaglos 2 formulations showed dissolution retardation compared with elegance-coated formulations in USP dissolution apparatus II, predicting significant impact on formulation bioperformance. However, pharmacokinetic studies in Beagle dogs showed similar bioperformance for all formulations.

Conclusions The Opaglos 2 coating system evaluated in these studies afforded adequate protection from oxidative degradation with no negative impact on bioperformance as compared to elegance coating. However, further studies are needed using several compounds to assess the broader applicability of these coatings.

Introduction

Within the pharmaceutical industry, achieving adequate stability for pharmaceutical actives through various formulation strategies is critical in the development of new dosage forms and successful formulation commercialization. One key development barrier for oral dosage forms is controlling oxidative chemical stability for the duration of shelf-life. In the competitive environment of pharmaceutical drug development, there is a key business driver to find cost-effective and efficient methodologies of controlling the potential instability of active pharmaceutical ingredients from oxidative and other chemical degradation.

A number of approaches have been documented for improving chemical stability and prolong the product shelf-life of pharmaceutical and food products susceptible to oxidation. With respect to packaging materials, oxygen barrier layers typically consist of expensive synthetic barrier polymers including ethylene vinyl alcohol (EVOH) copolymers, polyvinylidene chloride (PVDC), polyethylene terephthalate (PET), and polyamide-6 (nylon), which are commonly used in the form of coextruded or laminated films and coatings. As a viable alternative, excellent barrier properties have been obtained through disposition of aluminum vapour or by plasma-assisted deposition of inorganic layers such as silicon oxide on common polymeric films.[1–3] However, surface modifications require significant technical effort (e.g. vacuum or plasma) and expensive materials. Despite the availability of a variety of excellent synthetic oxygen barriers, the disadvantage of any such composite polymeric structures is primarily due to problematic recycling. The existing composite films contain layers of different plastic materials, which cannot be recycled because typically only single component plastics are recyclable. Owing to these significant issues with the currently

available oxygen barrier packaging materials, there is an increasing interest within the pharmaceutical and food industry in the development of biodegradable polymers (i.e. biopolymers) for specific coating applications of the products.

Sustainable biopolymers can be formed into either coatings for solid dosage forms or stand-alone films. The key functional properties, as well as potential practical uses of biopolymer films and coatings based on polysaccharides, proteins, and lipids from numerous plant and animal sources, have been reviewed previously.[4,5] Among the various biopolymers used in pharmaceutical applications, the extremely low oxygen permeability of carmellose sodium (sodium carboxymethylcellulose) films, in addition to good gloss and mechanical properties, makes it potentially useful as a transparent coating material for improving the stability of oxygen-sensitive pharmaceutical actives.

The aims of this study were to assess the impact of O_2 barrier coating on the formulation stability of compound A, which was highly susceptible to oxidative degradation, the in-vitro dissolution of compound B, and bioperformance of compound B. Due to the complex pharmacokinetics of compound A, as well as lack of in-vitro–in-vivo relationship, compound B was used to assess the in-vitro and in-vivo performance of the formulations. Since both compounds A and B had comparable in-vitro dissolution and were contained within the same granulation in all the tablet formulations, it was reasonable to assume that the pharmacokinetics of compound B was indicative of the overall bioperformance of the formulations. The novelty of this study lies in the in-vivo assessment of an O_2 barrier coating, which showed oxidative protection of a drug susceptible to oxidative degradation via electron transfer to molecular oxygen. In addition an in-vitro assessment of the coating effect on dissolution was evaluated during the in-vivo study. Despite being an established technology the current published literature in this area has been sparse.

Materials and Methods

Materials

An oxygen-sensitive model Biopharmaceutics Classification System (BCS) class II drug (compound A) and BCS class II compound B, both with pH sensitive solubility profiles were used as received. Microcrystalline cellulose (Avicel PH 102) was obtained from FMC Biopolymer (Philadelphia, PA, USA), lactose monohydrate (Fast Flo 316) from Foremost Co. (Baraboo, WI, USA) and magnesium stearate (Type 2255) from Mallinckrodt Specialty Co (St Louis, MO, USA). The proprietary film coating systems Opadry II Brown 85F96652 (poly(vinyl alcohol) PVA based) and Opaglos 2 97A19243 (carmellose sodium based) were obtained from Colorcon (Sodium CMC, Dartford, UK). The structures of PVA and carmellose sodium are shown in Figure 1. All reagents were of analytical grade and used as received from Sigma-Aldrich (Dorset, Poole, UK). Pentagastrin was obtained Sigma-Aldrich (St Louis, MO, USA). The packaging materials used for the stability study were high density polyethylene (HDPE) plastic bottles with 33 mm Clik-Lok induction sealable caps.

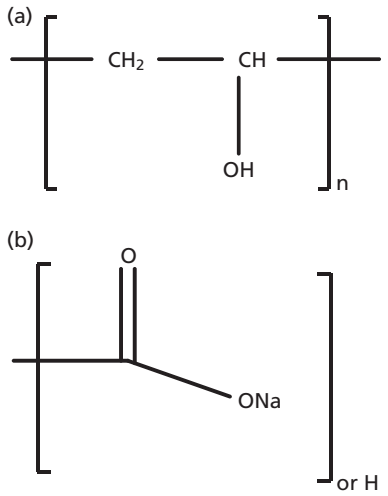

Figure 1 Structures of the polymers used in the coatings in this study. (a) Poly(vinyl alcohol) and (b) carmellose sodium.

Tablet manufacture

Compounds A and B were dry granulated together with excipients on an Alexanderwerk WP120 (Alexanderwerk, Remscheid, Germany) with 25 mm rolls. Subsequently, bilayer tablets containing compounds A and B within the same tablet layer were compressed using a Riva Piccola press at 2.3 kN tamping force and 30 kN main compression force. A bilayer used as a third active was present in the other layer. These core tablets were coated with either Opaglos 2 (2–8% w/w of the total tablet weight) or Opadry II (2% w/w of the total tablet weight) depending on the arm of the in-vivo study.

Coating mixture preparation

The Opaglos 2 coating suspension was prepared by adding 200 ml water to the Opaglos 2 formulation to make an 8% w/w suspension and stirring at 200 rev/min for 30 min using a Silverson Mixer. The Opadry II coating suspension was produced by mixing 15% solids with aqueous fluids using a Silverson mixer for 200 rev/min for 30 min.

Coating process

Film coating was carried out in an O'Hara LabCoat II (Freund Industrial Co., Tokyo, Japan) coating pan equipped with a Masterflex computerized drive (Barnant Co., Barrington, IL) pump. The inlet and outlet temperatures were 60–65°C and

48–50°C, respectively. The spray rate was approximately 10 g/min. The pan speed was maintained at 17°rev/min, the atomized air pressure was 1.5°Bar and the batch size was 1.75 kg. Owing to the limited availability of active bilayer tablets, microcrystalline cellulose-based placebo tablets were added as pan filler in a ratio of 1 : 2 for the coating operation. The active bilayer tablets could be easily identified and collected owing to the differences in size and shape to the placebo tablets.

The tablets were preheated to 38°C for 30 min before coating. Initially, the polymer mixture flow rate was maintained at 1 ml/min for 20 min to allow sealing of the tablets and prevent moisture permeation into the tablet core. Subsequently, flow rate was gradually increased to 2.5 ml/min and maintained throughout the coating process. The coating thickness ranged from 30 to 150 μm for 2% and 8% w/w Opaglos 2 formulations, respectively. The coated tablets were air dried (25°C and 55 ± 5% RH) for 48–72 h, packed into 75-ml HDPE bottles containing 1 g of desiccant, induction sealed and then placed under accelerated condition for an oxidative stability assessment.

Oxidative stability assessment

Samples were stressed at 40°C/75% RH closed with desiccant for 13 weeks and 30°C/65% RH closed with desiccant for a total of 52°weeks. Samples were extracted and then analysed by HPLC-UV using a validated stability indicating assay. Oxidative degradation levels were assessed by a summation of all reportable oxidative degradates greater than 0.1% by label claim.

In-vitro dissolution testing

Dissolution studies of compounds A and B were performed using USP II Apparatus (XXVIII edition, 2005) in a Vankel VK 7025 dissolution tester equipped with a VK8000 autosampler (Varian Inc., Palo Alto, CA, USA). The dissolution medium was 900 ml pH 6.8 phosphate buffer, which was kept at a constant temperature of 37 ± 0.5°C, with the paddles rotating at 75 rev/min. Samples were taken at timed intervals and the drug dissolution profile was obtained by performing a HPLC-UV analysis using Agilent 1100 HPLC (Agilent Technologies, Stockport, UK).

Animal study and pharmacokinetic analysis

Nine male Beagle dogs (Marshall Farms) were used for this study. A 3-period full crossover study was conducted under a protocol approved by the Merck Institutional Animal Care and Use Committee (IACUC). After an overnight fast, all dogs were treated with intramuscular injection of pentagastrin (0.006 mg/kg) approximately 30 min before dosing to reduce gastric pH to a value more representative of a fasted human.[6] Subsequently, dogs were dosed orally with the formulations, immediately followed by 3.5 ml/kg water via oral gavage. Water was restricted for 1 h following dosing while food was returned at 4 h after dosing. Blood was drawn from a catheter placed into the cephalic vein at 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h after dosing. The plasma was separated by centrifugation and analysed by a validated liquid chromatography-tandem mass spectrometry method. All studies were conducted under a protocol approved by Merck IACUC. Area under the curve ($AUC_{0-24\,h}$), observed maximum plasma concentration (C_{max}), and time of C_{max} (T_{max}) were calculated using the linear trapezoidal, noncompartmental model in WinNonLin v5.2. Plasma concentration values below lower limit of quantitation were set at zero for pharmacokinetic calculation purposes.

Statistical analysis

The relative bioavailability (arithmetic mean ratio) of the test formulations i.e. oxygen barrier-coated tablets to the reference elegance-coated tablets was compared to assess the difference in bioperformance of these formulations in dogs.

Results

Assessment of oxidative stability

Table 1 shows the extent of oxidative degradation of compound A for each coating configuration. Protection from oxidative degradation was not immediately afforded by any weight gain of the carmellose sodium coatings. There was a noticeable 'burst' of degradation occurring across all formulations of approximately 0.3–0.5% at the four-week time-point of the 40°C/75% RH condition. However, at the more stressed eight-week 40°C/75% RH condition, formulations exhibited little growth above the 5% w/w coating threshold. Longer term data for the 30°C/65% RH condition (26 and 52 weeks) showed the same trends, with an obvious degradative growth plateau at approximately 0.6–0.8% by label claim in oxidative degradation for the 6% and 8% w/w coatings.

A total oxidative degradate variability assessment showed that as coating weight gain decreased, the oxidative degradates increased. The data indicated that below the 6% w/w coating threshold, the coating process was sub-optimal for oxidative protection, with an inherent variability associated with the coating process. Based on this data, the 6% and 8% w/w coating formulations were assessed for an in-vitro dissolution and pharmacokinetic impact *in vivo*.

Assessment of in-vitro dissolution impact

Although some O_2 protection was afforded by lower weight gain carmellose sodium coatings, a clear oxidative degradation plateau with respect to time was not observed except at

Table 1 Total reportable oxidative degradation as % label claim of formulations of compound A at increasing Opaglos II coating at varying stability conditions vs an elegance-coated Opadry II formulation of compound A

Condition		40°C/75% RH			30°C/65% RH		
Formulation/time on station	Initial	4-week	8-week	13-week	26-week	32-week	52-week
Elegance coat (Opadry II)	0.2	–	–	–	–	2.0 (4.0)	–
2% w/w (Opaglos II)	0.2	0.7 (10.9)	–	–	1.7 (18.0)	–	–
3% w/w (Opaglos II)	0.2	0.7 (18.4)	–	–	1.1 (0.0)	–	–
4% w/w (Opaglos II)	0.2	0.6 (3.9)	0.9 (1.6)	0.9 (10.0)	1.4 (13.7)	–	1.6 (3.9)
5% w/w (Opaglos II)	0.2	0.5 (4.6)	0.6 (13.1)	0.8 (0.9)	0.7 (17.1)	–	0.7 (3.2)
6% w/w (Opaglos II)	0.2	0.5 (1.5)	0.6 (2.6)	0.6 (NA)	0.7 (2.1)	–	0.7 (2.2)
7% w/w (Opaglos II)	0.2	0.5 (2.9)	–	–	0.8 (0.0)	–	–
8% w/w (Opaglos II)	0.2	0.6 (2.3)	0.6 (0.0)	0.8 (18.0)	0.7 (2.1)	–	0.7 (2.2)

Values are mean (% RSD). $n = 10$ tablets. NA, not available; RH, relatively humidity.

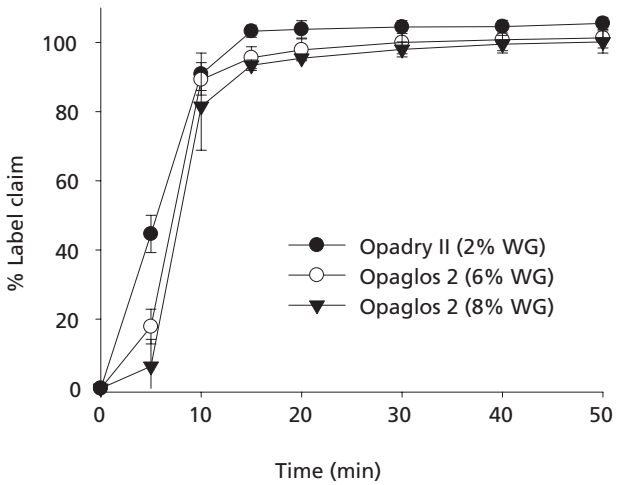

Figure 2 Compound A dissolution profile from formulations with different coatings. Coatings were 2% Opadry II, 6% Opaglos 2 or 8% Opaglos 2. USP II at 75 rev/min in 900 ml pH 6.8 phosphate buffer. $n = 6 \pm 1$ SD.

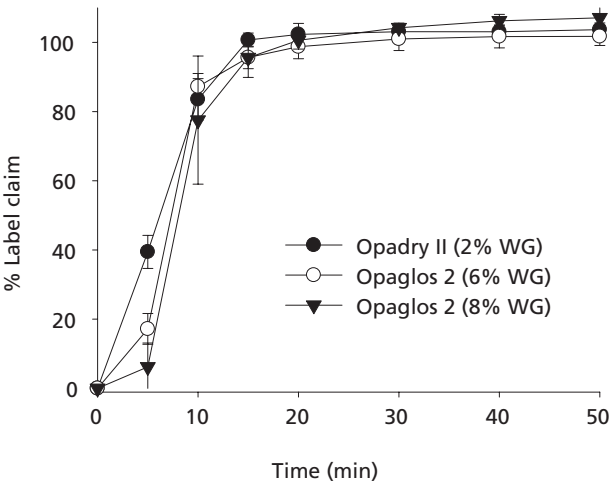

Figure 3 Compound B dissolution profile from formulations with different coatings. Coatings were 2% Opadry II, 6% Opaglos 2 or 8% Opaglos 2. USP II at 75 rev/min in 900 ml pH 6.8 phosphate buffer. $n = 6 \pm 1$ SD.

the higher weight gains (6% and 8% w/w). This suggested the requirement of a minimum coating thickness to restrict gas permeability sufficiently to afford O_2 protection. These formulations were comparatively evaluated against the elegance-coated formulation with respect to in-vitro dissolution performance in USP apparatus II. Figures 2 and 3 show that this dissolution data exhibited a reduction in the rate of dissolution of compounds A and B release at the initial (5 min) time-point from the 6% and 8% Opaglos formulations compared with the elegance coating. By 30 min, the 6% Opaglos and elegance-coating formulations reached 100% release for both actives but the 8% Opaglos formulation showed less than 100% release up to 50 min. A critical observation of this in-vitro behaviour is that the impact on dissolution appeared primarily in affording a lag to the initial drug release; the subsequent release rate post-coating rupture appeared unaffected.

Assessment of in-vivo impact

The dog studies were designed to assess the relative bioavailability of the O_2 barrier coatings as compared with the elegance coating. Owing to the limited number of dogs used, these studies could not assess statistical significance in the observed differences. Hence, a rank-ordering of the formulations have been shown here. The in-vivo results (Table 2 and Figure 4) showed that the $AUC_{0-24\,h}$ and C_{max} of compound B were similar between the O_2 coatings and elegance coating. The arithmetic mean ratios relative to the elegance coating were 0.96 and 0.99 (6% Opaglos 2), and 0.81 and 0.92 (8% Opaglos 2) for the AUC and C_{max}, respectively. This suggested that the initial dissolution differences for compound B between formulations did not impact the overall bioperformance in dogs and hence it might be concluded that bioperformance of these formulations would be similar in humans.

Table 2 Pharmacokinetic parameters of compound B following oral administration of tablets with different film coating in fasted pentagastrin-treated male beagle dogs

Formulation	$AUC_{0-24\,h}$ (nM*h)	C_{max} (nM)	T_{max} (h)[a]	AUC ratio relative to Opadry II	C_{max} ratio relative to Opadry II
6% Opaglos 2	5930 ± 968	1700 ± 288	0.5 (0.3–2.0)	0.96	0.99
8% Opaglos 2	5000 ± 655	1580 ± 227	0.5 (0.5–2.0)	0.81	0.92
2% Opadry II	6170 ± 977	1710 ± 300	0.5 (0.3–2.0)	–	–

[a]For T_{max} median and range are reported. Values are mean ± SE, $n = 8$ or 9. AUC_{0-24}, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time of C_{max}.

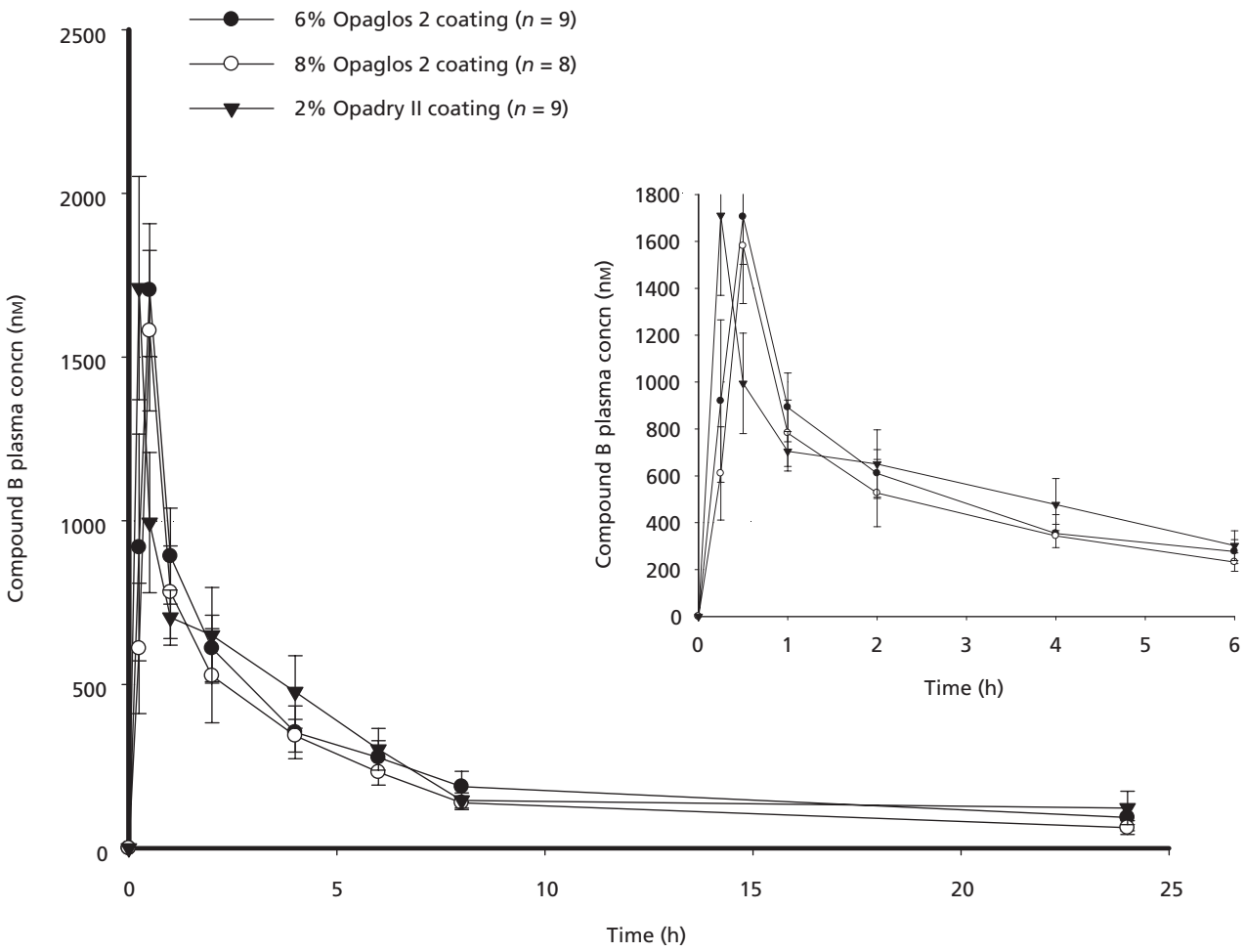

Figure 4 Plasma concentration profile of compound B following oral administration of tablets with different film coating in fasted pentagastrin-treated male beagle dogs. Values are mean ± SE.

Good agreement was observed between the in-vitro dissolution and in-vivo data in terms of formulation rank-order, as the $AUC_{0-24\,h}$ and C_{max} shifted directionally lower with increase in coating weight gain (i.e. 6% vs 8%) as predicted by the dissolution data. The lower value of $AUC_{0-24\,h}$ for the 8% coating was consistent with the dissolution data, as this formulation showed the slowest release compared with 6% weight gain and elegance coatings.

Discussion

Oxidative protection afforded by carmellose sodium-based coatings

It could be concluded that a carmellose sodium-based coating would provide adequate stability to oxidation for compound A in this formulation. There may be several critical reasons for the impact of coating weight gain in achieving

oxidative degradation control. These could include the formation of micro-cracks in the coating film structure at lower weight gains. Owing to incomplete film formation, oxygen can penetrate through to the tablet core resulting in increased degradation. In addition, full film formation may not occur at the lower weight gains. It should be noted that the tablet cores were not coated under nitrogen flushed conditions. Oxygen could permeate into the dosage form before the formation of the film coating structure. Once coated, oxygen gas would have been free to redistribute within the dosage form through diffusion-driven processes but unable to escape to the external environment owing to the restrictive coat permeability to oxygen. This could explain the degradative burst at the early stability time-point. This was unlikely based on a calculation of the molar volume of oxygen that could potentially be trapped within the tablet microstructure and comparing with the levels of oxidative degradation seen before the plateau (data not shown). The calculation of the volume of trapped oxygen was only one aspect of determining the potential impact. The calculation informed of the total asymptotic % degradation assuming all oxygen was consumed, but was not indicative of the rate since this was proportional to oxygen partial pressure (0.21 for air).

Polymeric film coat curing phenomena have been reported extensively in the literature (e.g. Amighi and Moës[7], Bodmeier and Paeratakul[8], and Hill[9]). We speculated that this may have played a significant role in the results observed with the carmellose sodium-based coat. It was possible that restrictive O_2 permeability of the carmellose sodium-based coat was not achieved until the polymer had undergone complete thermoplastic deformation. Film coat curing was the final stage of film formation when polymer particles coalesced and polymer chains inter-diffused to form a homogeneous, fully dense, and continuous film. Consequently, the extent of film formation could affect the drug release rate. Thus, film coat curing was critical to coating quality, product ageing (particularly with respect to the drug release stability) and overall product performance. In this work, it appeared that the polymeric film coating may have been critical in achieving full gaseous impermeability.

The variability generally observed for the weight gains below 6% were indicative of sub-optimal coats owing to coat imperfections of individual tablets included in the main assay value. Imperfections and variations which reduce the effectiveness of the coating system are a major concern.

Large variability for the reported stability degradates was observed at the 8% w/w formulation at 13 weeks (40°C/75% RH). Visually, heavier weight gains appeared more susceptible to physical damage such as chipping during handling and shipping. It is hypothesized that the higher coat weight gain was more cohesive than adhesive to the tablet core surface or an issue of plasticizer level in the coat. This made it more likely to show chipping or coat fracture. Ultimately, this suggested that there may be an optimum coating thickness to provide acceptable stability while affording concurrent robustness to withstand typical processing, handling and shipping.

In-vitro and in-vivo impact of carmellose sodium film coatings

The data shown in Figure 2 and Table 2 suggested little impact of either the coating type or coating weight gain on formulation bioperformance of compound B. This apparent discrepancy between the dissolution and pharmacokinetic data could be owing to several key differences in the USP II dissolution and in-vivo luminal conditions such as: fluid hydrodynamics; hydrodynamic forces; pH; composition; and luminal motility.[10,11] Of these factors, the differences in fluid hydrodynamics and luminal forces between the in-vitro and in-vivo environment were probably the primary reasons for the discrepancy between the USP II and dog data. Computational fluid dynamic studies have shown significantly higher agitation rates, fluid velocities and mixing pattern in the gastrointestinal lumen than in USP II apparatus.[10,12] In addition, imaging studies have shown significantly stronger axial forces in the stomach, particularly during the gastric emptying process and erratic movement during gastrointestinal transit.[13,14] These phenomena are difficult to reproduce in dissolution studies. The greater agitation and higher forces in-vivo were most likely responsible for more effective rupture of the coat and drug release, thus showing no difference in exposure between the formulations *in vivo*.

In addition, our previous studies of this system, in the absence of an oxygen barrier coat, had highlighted a clear disconnect between the predicted bioperformance from USP II dissolution apparatus and the human pharmacokinetic data for an elegance-coated system.[15] A clear rank ordering was achieved through the use of sophisticated in-vitro technology (e.g. the dynamic gastric model), which suggested similar in-vitro tools could have potential utility in this case. However, this lack of in-vitro–in-vivo agreement for compound B, which is a low solubility and high permeability (BCS class II) molecule, cannot be generalized at this time, since in-vitro–in-vivo correlation has been explored and established for other BCS class II molecules.[16,17] Further to this, the lack of human data makes it difficult to draw conclusions on the relevance of these preclinical data with respect to bioperformance in humans.

The advantages offered by an carmellose sodium coating – an industrial perspective

There are several commercial advantages to using an oxygen impermeable coating system vs packaging system to control electron-mediated oxidative degradation. These include the

associated high cost of a packaging option, the elegance of the final pharmaceutical product, the removal of the need for adequate recycling and the flexibility of providing in-use O_2 protection over and above the limited scope of protection afforded by a packaging option once a package is opened to the environment. This work has suggested that an additional benefit is the lack of an in-vivo impact of the oxygen barrier coating which may have represented a significant hurdle for the utilisation of this technology. The process of coating of pharmaceutical tablets and pellets is a widely established and mature process that could easily be utilised to provide a protective oxygen barrier. A key development area would be the identification of in-vitro tools that are predictive of the lack of impact on bioperformance, e.g. the dynamic gastric model.

Conclusions

The evaluation of a carmellose sodium coating revealed several mechanistic phenomena with respect to protection from O_2-mediated degradation, an impact on in-vitro dissolution performance and influence on bioperformance. The coating system appeared to afford good protection from electron transfer-mediated oxidative degradation when an adequate coating thickness had been achieved. Despite an apparent reduction in the rate of dissolution in USP II at the initial time-points, the 6% and 8% Opaglos 2-coated formulations exhibited similar in-vivo bioperformance to the elegance coating. However, data for multiple compounds with a variety of physicochemical and biopharmaceutical properties will have to be generated to understand the broader applicability of these coatings. This data suggested that investigation of alternative in-vitro methods to assess the performance of O_2 barrier products may be necessary in future product development involving these systems.

Declarations

Conflict of interest

The Authors are employees of Merck Sharpe & Dohme Corporation. The Authors declare that they have no conflicts of interest.

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