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Comparative Dissolution of Budesonide from Four Commercially Available Products for Oral Administration: Implications for Interchangeablity

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ABSTRACT

Budesonide is a corticosteroid regularly used in oral formulations to treat various inflammatory diseases in the gastrointestinal tract, such as Crohn's disease and ulcerative colitis. Budesonide has also been formulated to be effective against immunoglobulin A (IgA)-related nephropathy. This study aimed to compare the release of budesonide from four oral formulations under discriminating dissolution conditions to ascertain if they are interchangeable. Each product had a unique dissolution profile along with differences in indications, doses, and dosing conditions. As such, there is no basis for considering the tested products to be pharmaceutically or therapeutically interchangeable.

KEYWORDS: Budesonide, oral products, dissolution, release profile, interchangeability

INTRODUCTION

Budesonide is a corticosteroid regularly used in oral formulations to treat various inflammatory diseases in the gastrointestinal (GI) tract, such as Crohn's disease and ulcerative colitis. Because these inflammatory conditions affect different parts of the GI tract, different formulations have been introduced over the years to deliver budesonide selectively to inflamed tissue.

Entocort EC is indicated for treatment of active mild to moderate Crohn's disease at a daily dose of 9 mg (three 3-mg capsules once daily) or 6 mg (two 3-mg capsules in the morning) to maintain patients in remission (*1*). The equivalent European product, Entocort has similar indications, with the addition of microscopic colitis (*2*). Although Entocort is approved for treatment of the disease in both the ileum and ascending colon, the capsules consist of beads with an enteric coating (Eudragit L55, Evonik GmbH, Germany) designed to dissolve at pH 5.5 and above, so budesonide release likely starts proximally in the small intestine. Once the enteric coating on the beads is dissolved, an ethylcellulose component provides sustained release of budesonide.

Budenofalk (currently marketed in Europe but not available in the USA) is indicated for induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon at a daily dose of 9 mg (either three 3-mg capsules in the morning or one capsule in the morning, one at midday, and one in the evening). Budenofalk has also been approved for the treatment of microscopic colitis and autoimmune hepatitis (*3*). Like Entocort EC, the oral formulation consists of enterically coated beads housed in a capsule, but the coating is a mixture of Eudragit L and Eudragit S. The combination of Eudragit L and S in the coating formulation has a higher nominal pH of release (pH 6.4) than that of Eudragit L alone, so budesonide release from Budenofalk likely begins more distally in the small intestine than from Entocort EC (*4*). Once the enteric coating components on the bead dissolve, prolonged release of the active component is provided by Eudragit RS.

Cortiment 9-mg prolonged-release tablets are approved for induction of remission in patients with mild to moderate active ulcerative colitis (UC) in cases where 5-aminosalicylic acid (ASA) treatment is not sufficient, as well as to induce remission in adult patients with active microscopic colitis. Tablets are taken with or without food in the morning, taking care not to break, crush, or chew the tablet, because the film coating is intended to ensure a prolonged release (*5*). However, because the

coating is a mixture of Eudragit L and S with a release pH of 7, it serves more as a delaying rather than a prolonging component. Prolonged (extended) release of budesonide is ensured by embedding the drug in a multimatrix (MMX) formulation. The applications of MMX formulations have been described (*6*).

Nefecon (TARPEYO in US; Kinpeygo in UK) 4-mg delayed release capsules are another oral product containing budesonide. Unlike the other commercially available formulations, Nefecon is indicated to reduce urine protein levels in adults with primary immunoglobulin A (IgA) nephropathy who are at risk of rapid disease progression (*7*). Nefecon is formulated to target the release of budesonide to gut-associated lymphoid tissue, in particular the Peyer's patches (*8*). Four capsules are taken in the morning 1 hour before food intake. Instead of enterically coated beads, the capsule itself is coated. The beads containing budesonide are housed in the capsule, and release from the beads is regulated by an ethylcellulose-based coating.

The aim of this study was to compare release of budesonide from these four products under discriminating dissolution conditions to ascertain if they are interchangeable in terms of delivering budesonide to the same location within the GI tract.

METHODS

Materials

Four commercially available, orally administered, delayed-release budesonide products were compared with respect to their release characteristics:

- Entocort (Batch #32448, Tillot's Pharma)
- Budenofalk (Batch #L21017A, Dr. Falk Pharma)
- Cortiment (Batch #P152, Ferring Pharma)
- Nefecon/Tarpeyo (Batch #3193032, Calliditas Therapeutics)

The pharmaceutical characteristics of these products are summarized in Table 1.

All materials used for ultra high-performance liquid chromatography (UHPLC) analysis were of analytical grade.

Dissolution Studies

The release of budesonide from the four commercial products was compared using the same USP apparatus 2 (paddle) dissolution tester (VK 7000, VanKel) under two sets of experimental conditions.

In the first set of experiments, the products were studied according to *United States Pharmacopeia* (USP) general chapter <711> Dissolution, following the two-stage experimental design (method B) for delayed-release oral products, but with 900 mL per vessel (instead of 1000 mL) and $n = 3$ (*9*). Media were prepared according to *USP* directions for simulated gastric fluid (SGF) and simulated intestinal fluid (SIF), which has a buffer capacity of 30 mmol/L/pH unit.

In the second set of experiments, a biorelevant method with reduced buffer capacity in the intestinal phase was used to capture the essential aspects of release from enteric-coated products in vivo. Each product was subjected to an acidic environment (SGF, pH 1.2) for 2 hours to represent the maximum gastric residence time of the product when administered on a fasted stomach, followed by exposure to an almost neutral environment (pH 6.5) to represent pH conditions in the small intestine. Media were prepared with fasted-state simulated intestinal fluid version 1 (FaSSIF v1) buffer concentrate from Biorelevant.com (London, UK). After dilution according to the manufacturer's instructions, this buffer had a pH of 6.5 and a capacity of 12 mmol/L/pH unit (*10*). The tests with the biorelevant method were conducted with $n = 6$.

Enteric coatings are polymeric acids, so dissolution is highly dependent on both pH and buffer capacity of the

Table 1. Pharmaceutical Characteristics of Delayed-Release Budesonide Oral Formulations

Parameter	Nefecon	Budenofalk	Entocort	Cortiment
Enteric coating material and component	Eudragit L and S on capsule shell	Eudragit L and S on beads	Eudragit L55 on beads	Eudragit L55 and S on tablet
Nominal pH of enteric coating	Proprietary information[a]	pH 6.4 (RMS Assessment Report)	pH 5.5 (FDA)	pH 7 (FDA)
Capsule material	HPMC	Gelatin	Gelatin	N/A
Sustained-release component	Ethylcellulose-based coating on beads	Eudragit RS	Ethylcellulose	MMX (stearic acid/HPC matrix)

[a]*Nominal pH is between that of Entocort and Budenofalk (written communication, Calliditas Therapeutics).*
RMS: Regulatory Management System of the Medicines and Healthcare Products Regulatory Agency (MHRA), UK; HPMC: hydroxypropyl methylcellulose; MMX: multimatrix formulation; HPC: hydroxyproplycellulose.

dissolution media. Ozturk et al. demonstrated that when the buffer capacity at a given pH is reduced, the acidic enteric coating counteracts buffer ions approaching the coating surface more effectively, thus maintaining lower pH at the dissolving surface of the coating and decreasing the rate of dissolution (*11*). Likewise, Markopoulos, Andreas et al. reported that pH and buffer capacity are the two key factors required to achieve biorelevance in dissolution testing of products with enteric coatings (*10*). Therefore, in the intestinal phase of the test, the concentration of the buffer species (buffer capacity) was lowered to correspond more closely to the in vivo environment in the small intestine.

For all dissolution studies, the media volume was 900 mL, the paddle speed was 100 rpm, and the temperature was 37 + 0.5 °C. Samples (10 mL) were filtered through 25-mm Whatman filters (6890-2507 GD/X). The first 8 mL of filtrate was discarded, and the last 2 mL were retained for UHPLC analysis.

Ultra High-Performance Liquid Chromatography (UHPLC) Analysis

Analysis of all dissolution samples was conducted using a Vanquish UHPLC system (Dionex Softron GmbH, Germering, Germany), including a binary pump H (VH-P10-A) powered by Smart Flow, fitted with an Acquity UPLC BEH C18 column (1.7 µm, 2.1 × 50 mm). The mobile phase solution consisted of 2.70 g sodium acetate trihydrate in 1 L water in a ratio of 420:580 (v/v) with acetonitrile. The operating temperature was 40 °C. These conditions resulted in a run time of 1 minute, with elution of budesonide as a single peak between 0.46 and 0.53 minutes.

The lowest concentration used for the calibration curve was 40 ng/mL, corresponding to 1% dissolution from a 4-mg capsule. The correlation coefficient for the calibration curve was 0.999 or higher in each run. Mean recovery of budesonide was 99% for standard solutions in gastric media and 102% in phosphate buffer.

The method development for this analytical procedure is described in laboratory journal 21E2197 (RI.SE AB, Sweden).

Statistical Analysis

Dissolution results are presented as mean percent of drug release with standard deviation. The data are also presented in tabular form in the Supplementary Material (available online). The f_2 statistic (similarity factor) was calculated using Nefecon (Tarpeyo) as the reference product to compare with the other products. Statistics were calculated with Microsoft Excel.

RESULTS

USP Method

Drug release profiles using the general USP methodology are shown in Figure 1. None of the products released an appreciable amount of budesonide in the acid (gastric) phase of the experiment (pH 1.2 for 2 hours), so only results in the buffer (intestinal) phase are shown.

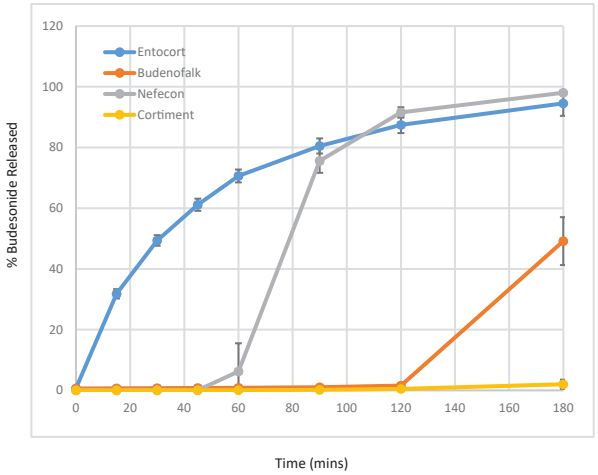

Figure 1. Dissolution profiles (mean ± SD % release) of four delayed-release budesonide oral formulations using the USP <711> method B. Only the buffer (intestinal) phase is shown; no appreciable release of budesonide was observed in the acid (gastric) phase.

The four products displayed clearly different dissolution profiles under the USP test conditions. As expected from its Eudragit L55 coating (nominal pH of release is pH 5.5), the Entocort product started to release budesonide immediately in the pH 6.8 dissolution medium, then budesonide release was sustained over approximately 3 hours. By contrast, the Cortiment product released a minimal amount of budesonide within the 3-hour test period, reflecting a higher nominal pH of 7.0 for initiation of release, which, together with the MMX used to sustain release after the enteric coating dissolves, minimizes release at pH 6.8. Budenofalk, with a nominal pH of 6.4 for initiation of release, started to release after 2 hours of exposure to the pH 6.8 medium. The sustained-release component (Eudragit RS) in Budenofalk limited release to approximately 50% between the 2- and 3-hour mark. Nefecon had yet another distinct dissolution profile, with little or no release in the first 60 minutes of exposure to the pH 6.8 dissolution medium, followed by a modestly sustained-release pattern, with most of the release occurring during the second hour of the intestinal phase of the test.

Biorelevant Method with Reduced Buffer Capacity

Drug release profiles in the FaSSIF v1 buffer (intestinal phase) are shown in Figure 2.

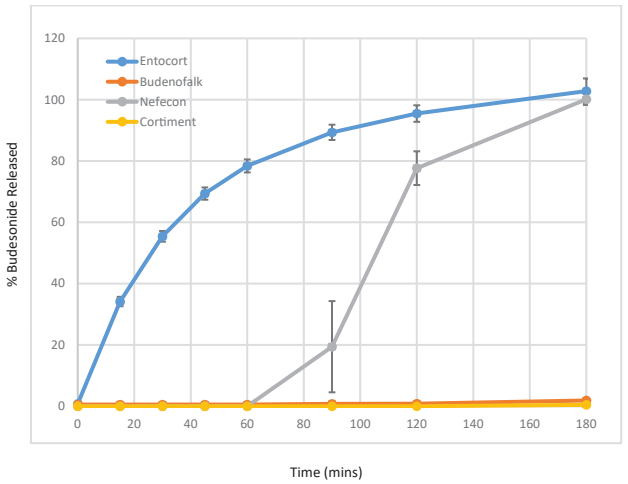

Figure 2. Dissolution profiles (mean ± SD % release) of four delayed-release budesonide oral formulations using the biorelevant method with reduced buffer phase. Only the buffer (intestinal) phase is shown; no appreciable release of budesonide was observed in the acid (gastric) phase.

Large differences in budesonide dissolution profiles were observed among the four products. For Budenofalk, the release was more delayed more under biorelevant conditions compared with *USP* <711> conditions, most likely because the pH of the dissolution medium was adjusted to pH 6.5, which is close to the nominal pH of release from this product. With lower buffer capacity in the dissolution medium, the pH at the surface of the enteric coating is expected to remain lower, curbing the onset of release (*11*).

Table 2 shows the f_2 values for comparison of Nefecon with the other products. An f_2 value of 50 or greater is required to demonstrate similarity of the profiles (*12, 13*). In line with the visual inspection of the release profiles, all f_2 values failed to meet this criterion for similarity by a very wide margin.

Table 2. Similarity Factor (f_2) Analysis for Comparison of Dissolution Profiles

	Nefecon	Entocort EC	Budenofalk	Cortiment
f_2 value (USP)	Reference	18.1	16.0	15.8
f_2 value (biorelevant)	Reference	11.7	16.1	15.8

DISCUSSION

The selection of dissolution test conditions for these studies was based on *USP*, FDA, and EMA guidelines. The first round of tests was run essentially under USP <711> Method B conditions for oral delayed release products, the only variations being a dissolution volume of 900 mL rather than 1000 mL and a more granular sampling schedule. With a pH of 6.8, these conditions conform to one of the conditions in the FDA's Product Specific Guidances (PSG) for delayed-release budesonide products (*14–16*). The PSGs call for dissolution at several pH values ranging from 4.5 to 7.5. As the aim of the study was to discriminate among the formulations with respect to onset and rate of budesonide release, dissolution at pH 4.5 (at which no release is expected because pH < pKa of the Eudragit coatings) and pH 7.2 and 7.5 (at which 100% release is expected because pH > pKa of the Eudragit coatings) was not studied. Instead, the focus was on pH values that are most likely to be discriminating for enteric coatings, i.e., pH 6.5 and 6.8. The EMA guideline on studies for demonstrating therapeutic equivalence for locally applied, locally acting oral products suggests investigating the effect of various physiological factors on release, including buffer strength and intraluminal pH (*17*). Therefore, the experimental conditions used in this study were based on these guidances combined with considerations from Ozturk et al. and Markopoulos, Andreas et al. (*10, 11*).

Under both experimental conditions, the release profile of budesonide differed widely among the four commercial products. None of the f_2 comparisons demonstrated similarity. Thus, the release profiles for the tested products are considered strongly dissimilar and not pharmaceutically equivalent.

The Nefecon release profile in biorelevant conditions showed that 1) capsule disintegration and onset of release are delayed until approximately 1 hour after switching from the acid (gastric) phase to the FaSSIF v1 buffer (intestinal) phase, 2) the majority of drug release subsequently occurs within 2 hours, and 3) complete budesonide release is reached within 3 hours in the intestinal phase. The comparatively short period of release under intestinal conditions is expected to result in a more localized release compared with the other products. Since the passage time through the small intestine is typically 3.5–4.5 hours, the Nefecon release pattern is commensurate with the stated target of Nefecon therapy, which is to deliver budesonide selectively and specifically to the ileum (*18–20*).

By comparison, Entocort starts releasing budesonide almost immediately upon exposure to intestinal conditions, irrespective of the buffer conditions. This can be attributed to the formulation with Eudragit L55, an enteric coating that starts to release at a comparatively low pH of 5.5. Thereafter, release is sustained over a period of about 3 hours, with almost 80% released in the first hour of exposure to intestinal conditions. As a result,

it is expected that most of the budesonide in Entocort is delivered to more proximal regions of the small intestine.

In contrast to Entocort, Budenofalk only releases budesonide at small intestinal pH under highly buffered (*USP*) conditions. Furthermore, the release starts after 2 hours of exposure to these conditions, consistent with Budenofalk's therapeutic objective of releasing budesonide to the distal ileum and the caecum, whereby a substantial amount of budesonide is delivered into the colon (*2*). Differences in release profiles for Entocort® and Budenofalk have been previously reported by Klein et al. (*21*).

Cortiment failed to release significant amounts of budesonide under either lightly or highly buffered conditions at intestinal pH levels, which is in line with its target of releasing budesonide to the colon to treat ulcerative colitis (*5*).

When considering interchangeability among these budesonide products, one must also consider further aspects of their characteristics, such as the indications for which they are approved, the dose strengths available, and the recommended dosing conditions. Of the four products, only Nefecon specifies that the dosage form must be taken 1 hour before food in the morning. The other three products have no limitation on food intake, and for Budenofalk there is the possibility to split the dosing up over the day. Given that Cortiment contains 9 mg of budesonide, the only product that could be substituted from a dosage point of view is Budenofalk. The prescriber information for Entocort specifies two 3-mg capsules per day (i.e., maximum of 6 mg) for maintenance therapy or three 3-mg capsules per day for active inflammation, while Nefecon capsules contain 4 mg of budesonide, making it impossible to match the dose of any of the other three products, except at 12 mg, a dose that is not approved for any of other products. Uniquely, and because of the higher dose (four 4-mg capsules per day), dose tapering is additionally recommended when discontinuing therapy with Nefecon.

Finally, the indications for which the products are approved differ substantially. Entocort and Budenofalk are both approved for the treatment of mild to moderate Crohn's disease and to maintain patients with this disease in remission. Budenofalk is also approved for the treatment of microscopic colitis and autoimmune hepatitis. Unlike the anti-inflammatory indications for Entocort and Budenofalk, Cortiment is approved for the induction of remission in patients with mild to moderate active UC if 5-ASA treatment is not sufficient. Cortiment is also approved to induce remission in adults with active microscopic colitis, but (unlike Budenofalk) it is not approved for autoimmune hepatitis. Nefecon is the only product of the four that is approved to reduce urine protein levels in adults with primary IgA nephropathy who are at risk of rapid disease progression.

Because the doses, dosing conditions, approved indications, and dissolution profiles of the four budesonide products studied differ so widely, substituting one of these products for another cannot be either scientifically or medically justified.

CONCLUSION

The dissolution data reported herein support the therapeutic goals of each product tested (Entocort EC for Crohn's disease, Budenofalk for Crohn's and UC, Cortiment for UC, and Nefecon for IgA nephropathy). Given the substantial differences in drug release patterns, widely divergent therapeutic aims, and differences in doses and dosing conditions of the four products, they cannot be regarded as either pharmaceutically or therapeutically interchangeable.

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CONFLICT OF INTEREST

The author disclosed no conflict of interest related to this article.

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