Comparison of the dissolution profile of Nefecon with three other commercially available oral formulations of budesonide: Implications for interchangeability

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INTRODUCTION

- **Nefecon**, a novel oral formulation of the corticosteroid budesonide, is specifically designed to target release in the **Peyer's patch-rich distal ileum**, a major source of Gd-IgA1 overproduction[1]
- Nefecon has been approved by the FDA and EMA for adult patients with **primary IgAN** at risk of rapid disease progression[2,3]
- Three other **oral budesonide formulations** are available commercially: Entocort, Budenofalk, and Cortiment[4-6]
  - They are used for the treatment of **inflammatory bowel diseases** such as Crohn's disease and ulcerative colitis
  - Each formulation is designed to **selectively target** a specific disease and, hence, the relevant part of the gastrointestinal tract
- The **aim of this study** was to compare the dissolution of budesonide from the four formulations to ascertain their interchangeability

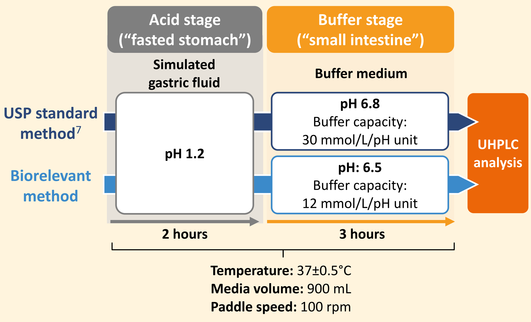
Table 1: Summary of commercially available oral formulations of budesonide

	Nefecon	Budenofalk	Entocort	Cortiment
Indication[2-6]	IgAN	Crohn's disease; autoimmune hepatitis; microscopic colitis	Crohn's disease; microscopic colitis	UC; microscopic colitis
Target tissue[2-6]	Peyer's patch-rich distal ileum	Ileum and ascending colon	Ileum and ascending colon	Colon
Enteric coat	Eudragit L&S	Eudragit L&S	Eudragit L55	Eudragit L55 & S
What is enteric coated?	Capsule shell	Beads	Beads	Tablet
Nominal pH of enteric coating	Proprietary information*	6.4 (RMS AR)	5.5 (FDA)	7 (FDA)
Capsule material	HPMC	Gelatin	Gelatin	Not applicable
What sustains release?	Ethylcellulose-based coating on beads	Eudragit RS	Ethylcellulose	MMX (stearic acid/ HPC matrix)

METHODS

- **Dissolution experiments** were performed to compare the release of budesonide from each formulation
- Products were subjected to an **acidic environment** for 2 hours, representing maximum residence time in a fasted stomach
  - This was followed by exposure for 3 hours to a **buffer environment**, representing passage through the small intestine
- Two sets of experiments were performed:
  - **Standard USP** quality control design conditions (Method B),[7] with a pH of 6.8 in the intestinal phase
  - A **biorelevant method**, with a pH of 6.5 in the intestinal phase and using a lower concentration of buffer to better reflect the *in vivo* intestinal environment
- Samples were analyzed using **ultra-high-performance liquid chromatography**
- The f_2 **statistic**, which tests for similarity between dissolution profiles, was calculated using Nefecon as the reference product

Figure 1: Summary of standard USP and biorelevant methods



RESULTS

- **No formulation** released significant amounts of budesonide in the **acid (gastric) phase** of the experiment; therefore, only data for the buffer (intestinal) phase are shown
- For Nefecon, capsule disintegration and onset of budesonide release occurred **1 hour** after entering the buffer phase
  - Budesonide was **released over a relatively short period**, starting at ~1 hour and completing by 3 hours
  - This release pattern corresponds to a **localized release** of budesonide to the **Peyer's patch-rich ileum**
- Entocort started releasing budesonide **almost immediately** upon entering the buffer phase due to the low nominal pH of its enteric coating
  - Its release lasted over 3 hours, with almost 80% released in the first hour, indicating it would mostly be released in the **proximal small intestine**
- Budenofalk **did not release budesonide** in the biorelevant method medium over the 3-hour test period
  - In the higher pH standard USP buffer, Budenofalk released budesonide after a **2-hour delay**
  - This would be consistent with some budesonide release in the terminal ileum, but with **transfer of a substantial amount to the colon**
- Cortiment **failed to release** budesonide in the intestinal phase with either method, suggesting that release starts in the colon in accordance with its UC indication
- All f_2 **values were <50**, failing to meet the criterion for similarity between dissolution profiles by a wide margin

Figure 2: Budesonide release profiles in the buffer (intestinal) phase according to standard USP and biorelevant methods

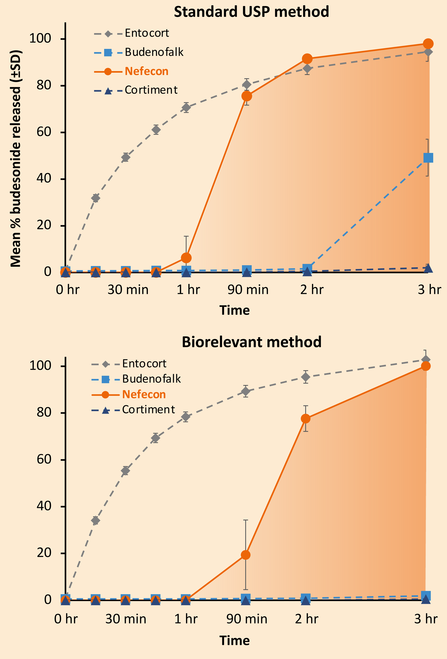
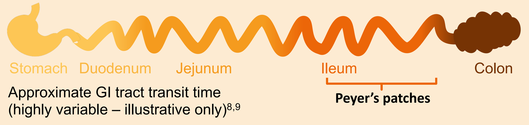


Table 2: f_2 values comparing the dissolution profiles of Entocort, Budenofalk, and Cortiment with Nefecon

	Entocort	Budenofalk	Cortiment
f_2 **value (standard USP method)**	18.1	16.0	15.8
f_2 **value (biorelevant method)**	11.7	16.1	15.8



Approximate GI tract transit time (highly variable – illustrative only)[8,9]

CONCLUSIONS

- The doses, dosing conditions, and approved indications of the four budesonide products differ widely, and this study demonstrates that each formulation has a distinct dissolution profile consistent with its individual therapeutic goals
  - The rapid release of budesonide from Nefecon after 1 hour in intestinal conditions is expected to result in a localized release of budesonide to the Peyer's patch-rich ileum, the target tissue for downregulation of Gd-IgA1 production
- The f_2 analysis demonstrates strongly dissimilar release profiles, showing that there is no basis for the budesonide formulations to be considered pharmaceutically or therapeutically interchangeable

Scan to view Nefecon presentations, posters, and materials

REFERENCES

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ABBREVIATIONS

EMA, European Medicines Agency; FDA, US Food and Drug Administration; Gd-IgA1, galactose-deficient immunoglobulin A1; GI, gastrointestinal; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methylcellulose; IgAN, immunoglobulin A nephropathy; pH, potential of hydrogen; RMS AR, Reference Member State Assessment Report; rpm, revolutions per minute; SD, standard deviation; UC, ulcerative colitis; UHPLC, ultra-high-performance liquid chromatography; USP, US Pharmacopeia.

DISCLOSURES

JD reports no disclosures. **RP** is an employee of Calliditas Therapeutics. **JB** is a consultant to Calliditas Therapeutics and reports grants, consultancy, and personal fees from STADA Arzneimittel AG, Everest Medicines, and Calliditas Therapeutics.

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*Calliditas Therapeutics has confirmed that the nominal pH of the enteric coating of Nefecon is between that of Entocort and that of Budenofalk.