Drugs R D (2015) 15:211–215
DOI 10.1007/s40268-015-0097-5

SHORT COMMUNICATION

Dissolution of Commercially Available Mesalamine Formulations at Various pH Levels

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Published online: 27 June 2015
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Abstract

Introduction Mesalamine (5-aminosalicylic acid; 5-ASA) is recommended first-line therapy for mild-to-moderate ulcerative colitis. Many mesalamine formulations employ a pH-dependent release mechanism designed to maximize drug release in the colon. This study compared the in vitro release of 5-ASA from six commercially available mesalamine formulations at pH levels similar to those typically encountered in the human gastrointestinal tract.

Methods The release of 5-ASA from six mesalamine formulations [Mesalazin-Kohlpharma (Kohlpharma, Germany), Mesalazin-Eurim (Eurimpharm, Germany), Mesalazina-Faes (Faes Farma, Spain), Mesalazine EC (Actavis B.V., Netherlands), Mesalazine EC 500 PCH (Pharmachemie B.V., Netherlands); multimatrix mesalamine (Shire US Inc., USA)] was monitored separately at three different pH levels [1.0 (2 h), 6.4 (1 h), and 7.2 (8 h)] using United States Pharmacopeia dissolution apparatus II. The dissolution percentage was calculated as a mean of 12 units for each formulation.

Results At pH 1.0 and 6.4, <1 % of 5-ASA release was observed for each of the mesalamine formulations tested. At pH 7.2, complete release of 5-ASA occurred within 1 h for Mesalazine EC and Mesalazine EC 500 PCH, and within 2 h for Mesalazin-Kohlpharma, Mesalazin-Eurim, and Mesalazina-Faes; complete release of 5-ASA from multimatrix mesalamine occurred within 7 h. Little variability in rate of 5-ASA dissolution was observed between tablets of each formulation.

Conclusion At pH 7.2, 5-ASA release profiles were variable among the commercially available mesalamine formulations that were tested.

Key Points

This study examined mesalamine (5-aminosalicylic acid; 5-ASA) release from six commercially available mesalamine formulations in simulated physiological pH conditions.

At pH 1.0 and pH 6.4, <1 % 5-ASA release was observed for each of the mesalamine formulations tested.

At pH 7.2, 5-ASA was completely released within 1 h for Mesalazine EC and Mesalazine EC 500 PCH, and within 2 h for Mesalazin-Kohlpharma, Mesalazin-Eurim, and Mesalazina-Faes; complete release of 5-ASA from multimatrix mesalamine occurred within 7 h.

1 Introduction

Ulcerative colitis (UC), a chronic mucosal inflammatory condition that affects the colon and rectum, is characterized by symptoms of abdominal pain, diarrhea, and rectal bleeding, and is typically diagnosed through endoscopic biopsy [1]. Mesalamine (5-aminosalicylic acid; 5-ASA) is a topical, anti-inflammatory compound that acts locally within the colonic mucosa to reduce inflammation, and is recommended first-line treatment for patients with active mild-to-moderate UC [2]. While both oral and rectal formulations of 5-ASA are available

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to patients, rectal formulations are associated with leakage and abdominal bloating, and patient compliance to prescribed dosing regimens of rectal formulations remains poor [3]. Consequently, oral formulations of 5-ASA have become the mainstay treatment option for mild-to-moderate UC [3].

When mesalamine is administered orally via an unprotected delivery system, the active drug is quickly absorbed in the upper gastrointestinal (GI) tract, resulting in the systemically absorbed drug having little clinical effect [4, 5]. In order to achieve stable delivery of 5-ASA to the mucosa of the terminal ileum and colon, numerous formulations have been developed that aim to delay the release of the active drug during passage through the GI tract. For example, protective enteric coatings are used in some mesalamine formulations to control or delay the release of the active drug [4, 6–9]. In particular, many of these mesalamine formulations use a pH-dependent release mechanism designed to minimize active drug release at acidic pH levels, such as those observed higher in the digestive tract (e.g., pH $\sim$2 in the stomach and pH $\sim$6 in the small intestine), and maximize drug release at more basic pH levels, such as those observed in the colon (pH 7–8) [10]. The colonic pH in patients diagnosed with UC has been observed at levels lower than pH 7 due to reduced mucosal bicarbonate secretion, increased mucosal and bacterial lactate production, and impaired short-chain fatty acid absorption and metabolism [11, 12].

The objective of the study was to compare the in vitro dissolution profiles of mesalamine from commercially available products in Europe indicated for the treatment of UC. The mesalamine formulations included in this set of dissolution experiments were selected based upon two criteria: (1) They were among the most widely clinically used mesalamine formulations in Europe at the time of the study (IMS Health Monthly MIDAS Data, October 2012); and (2) With the exception of multimatrix mesalamine, the selected formulations had not been included in an initial set of dissolution experiments conducted by our laboratory [13]. This in vitro study compared 5-ASA release at physiologically relevant pH conditions from the following commercially available, controlled-release mesalamine formulations: Mesalazin-Kohlpharma (Kohlpharma, Germany), Mesalazin-Eurim (Eurimpharm, Germany), Mesalazina-Faes (Faes Farma, Spain), Mesalazine EC (Actavis B.V., Netherlands), Mesalazine EC 500 PCH (Pharmachemie B.V., Netherlands), and multimatrix mesalamine (Shire US Inc., Wayne, PA, USA).

2 Methods

Dissolution experiments were conducted with the following mesalamine formulations: Mesalazin-Kohlpharma 500 mg tablets, Mesalazin-Eurim 500 mg tablets, Mesalazina-Faes 500 mg tablets, Mesalazine EC 500 mg tablets, Mesalazine EC 500 PCH 500 mg tablets, and multimatrix mesalamine 1.2 g tablets. United States Pharmacopeia (USP) apparatus II (paddle) was used for the dissolution study (Sotax AT7^{TM} dissolution tester; Sotax Corporation, Horsham, PA, USA) [14].

In order to investigate the effect of simulated GI conditions on the release of active 5-ASA, dissolution testing was performed in an experiment across different physiologically relevant pH levels. Tablets of each formulation were individually exposed to the dissolution medium in an acid stage (pH 1.0) for 2 h, an initial buffer stage (pH 6.4) for an additional hour, and in a subsequent buffer stage (pH 7.2) for 8 h, simulating anticipated pH environments to be encountered after ingestion in the stomach, small intestine, and colon, respectively (Table 1) [12]. The composition of the dissolution media used during each stage is listed below.

- Acid stage pH 1.0 (0.1 N HCl): dilution of hydrochloric acid 37 % with purified water.
- Phosphate buffer pH 6.4 (0.2 M Na_3PO_4): 0.2 M Na_3PO_4 solution with 0.1 N HCl (if needed, pH adjusted with 2 N NaOH or 2 N HCl).
- Phosphate buffer pH 7.2 (0.2 M Na_3PO_4): pH 6.4 buffer with 2 N NaOH (if needed, pH was adjusted with 2 N NaOH or 2 N HCl).

Sink conditions were maintained. The solubility of mesalamine in phosphate buffers at pH 6.0 and 7.2 was approximately 1.2–5.5 mg/mL, respectively. Buffer capacity has been evaluated according to USP as the quantity of acid or base needed to change the buffer pH expressed as Eq/L per unit pH. The buffer capacity at pH 6.4 in our study was 0.02 Eq/L per unit pH for either addition of 1 N HCl or 1 N NaOH; at pH 7.2, the buffer capacity was 0.02 Eq/L per unit pH for addition of 1 N HCl and 0.01 Eq/L per unit pH for addition of 1 N NaOH. A paddle speed of 100 rpm was selected to ensure adequate mixing as well as completion of dissolution in a reasonable time period.

The dissolution bath was maintained at a mean [±standard deviation (SD)] temperature of 37 °C (±0.5°), and the quantitative determination of 5-ASA released was measured by ultraviolet-visible (UV-Vis) spectrophotometry at wavelengths of 301 nm at pH 1.0, and 330 nm for

Table 1 Experimental conditions for the study of 5-ASA release from mesalamine tablets (USP II method)

Conditions	Acid stage	Buffer stage 1	Buffer stage 2
Dissolution media	750 mL, 0.1 N HCl	950 mL, 0.16 M phosphate buffer	960 mL, 0.16 M phosphate buffer
pH	1	6.4	7.2
Duration (h)	2	1	8
Sample time (h)	2	1	1
Rotation speed (rpm)	100	100	100

5-ASA 5-aminosalicylic acid, *USP* United States Pharmacopeia

both pH 6.4 and 7.2 (PerkinElmer Lambda 25™; PerkinElmer Life and Analytical Sciences, Inc., Waltham, MA, USA). The dissolution percentage was calculated as a mean of 12 units for each formulation.

3 Results

In the acid stage and first buffer stage, <1 % of 5-ASA combined release was observed for each of the mesalamine formulations tested. However, some variability in 5-ASA dissolution profiles was observed between the mesalamine formulations at buffer stage 2 (pH 7.2), after the initial exposure to pH 1.0 for 2 h and pH 6.4 for 1 h (Fig. 1). Mesalazine EC and Mesalazine EC 500 PCH demonstrated complete release of 5-ASA within 1 h at pH 7.2, while Mesalazin-Kohlpharma, Mesalazin-Eurim, and Mesalazina-Faes exhibited complete release within 2 h. Multimatrix mesalamine demonstrated complete 5-ASA release over a period of 7 h (Fig. 1). Analysis of the pill-to-pill variability in mesalamine tablet dissolution within each formulation revealed minimal variability between tablets (Table 2).

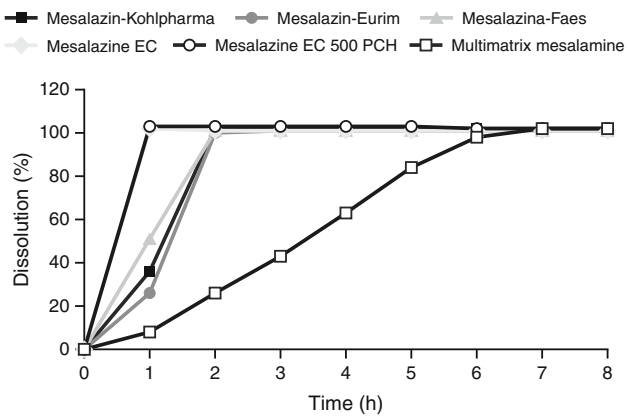

Fig. 1 Release of 5-ASA from mesalamine formulations at pH 7.2 over 8 h

4 Discussion

This study evaluated the 5-ASA dissolution profiles of various mesalamine formulations across different pH levels. In order to delay the release of 5-ASA until the drug reaches the colonic mucosa, many mesalamine formulations employ pH-dependent release mechanisms that limit drug release in acidic environments [10]. As expected, all mesalamine formulations tested in our study released little to no drug at acidic pH conditions. However, at pH 7.2, some variability in the dissolution profiles of mesalamine formulations was observed. Mesalazin-Kohlpharma, Mesalazin-Eurim, Mesalazina-Faes, Mesalazine EC, and Mesalazine EC 500 PCH released 5-ASA within 1 or 2 h, while multimatrix mesalamine released the active drug within 7 h. Results for multimatrix mesalamine were consistent with previous observations of 5-ASA release from multimatrix mesalamine under similar conditions [6, 13, 15, 16].

A recently published study by Goyanes et al. [17] also examined the dissolution profiles of several commercially available mesalamine formulations. In this study, a novel technology, the Auto pH System™, was used to mimic human GI parameters in vitro, including pH, ionic strength, and buffer capacity. The system allowed for dissolution testing at seven different pH conditions from 5.6 to 7.4. A bicarbonate-based buffer was also used, which more closely resembled the ionic composition and buffer capacity of in vivo intestinal fluids, compared with the phosphate buffer used in the current experiment. As the methods used in the Goyanes study were substantially different, it is difficult to directly compare their results to those of the current study. The Goyanes et al. study, nevertheless, also demonstrated that different commercial mesalamine formulations showed different release profiles and could also be attributed at least partially to a pH-dependent release mechanism.

A prior study by Fadda et al. [18] demonstrated that dissolution results from the same mesalamine formulation may vary depending on the type of buffer used. In that study, multimatrix mesalamine was exposed to pH 1.2 (0.1 M HCl) for 2 h, then transferred to pH 7.4 in either a

Table 2 Average and pill-to-pill variability in mesalamine tablet dissolution at pH 7.2

Formulation	Mean (SD) dissolution (%)							
	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
Mesalazin-Kohlpharma 500 mg	36.21 (11.68)	101.74 (2.44)	101.90 (2.37)	101.88 (2.36)	101.87 (2.32)	101.80 (2.32)	101.79 (2.3)	101.75 (2.28)
Mesalazin-Eurim 500 mg	25.56 (9.52)	100.25 (3.80)	101.07 (4.06)	101.17 (4.07)	101.11 (4.07)	101.12 (4.05)	101.10 (4.06)	101.13 (4.05)
Mesalazina-Faes 500 mg	50.59 (6.57)	100.84 (2.03)	100.90 (2.07)	101.27 (2.07)	101.03 (2.03)	101.05 (2.06)	101.12 (2.07)	101.16 (2.08)
Mesalazine EC 500 mg	101.64 (1.43)	101.33 (1.06)	101.36 (1.04)	101.26 (1.04)	101.22 (1.03)	101.15 (1.06)	101.13 (1.08)	101.11 (1.04)
Mesalazine EC 500 PCH 500 mg	103.01 (1.25)	102.55 (1.22)	102.57 (1.22)	102.53 (1.23)	102.50 (1.19)	102.48 (1.22)	102.41 (1.22)	102.39 (1.22)
Multimatrix mesalamine 1.2 g	8.05 (1.26)	25.72 (2.14)	43.47 (3.84)	63.01 (5.3)	83.82 (5.68)	98.30 (3.97)	101.65 (1.08)	101.57 (1.06)

SD standard deviation

phosphate buffer or Krebs bicarbonate buffer. In the phosphate buffer, the zero-order, slow drug release was observed, and the drug started to release after about 30 min at pH 7.4, reaching <80 % release after 9 h. In the bicarbonate buffer, both the lag times and drug release profiles were different from the phosphate buffer. The zero-order, slow drug release was no longer apparent, and the drug started to release approximately 3 h after exposure to pH 7.4, reaching 90–100 % release after 8 h. Drug release in both media suggested release of 5-ASA over many hours. Our study also exposed mesalamine formulations to an intermediary buffer stage of pH 6.4 for 1 h prior to exposure at pH 7.2.

While different formulations of mesalamine may reveal variations in dissolution rates in vitro, it remains to be determined if these differences correlate with 5-ASA delivery at the colon. Additionally, while physiologically relevant pH conditions were used in our study, the phosphate buffer used may not be physiologically relevant, limiting the ability to correlate results with in vivo performance [18]. Further studies will be needed to determine if the findings of our study, as well as those of other dissolution studies, are clinically relevant.

Acknowledgments The author would like to acknowledge Myo Kyaw for his contribution to the study interpretation. Research was funded by the sponsor, Shire Development LLC. Cosmo Pharmaceuticals received funding from Shire Development LLC for assistance with data collection and data analysis. Under the direction of the authors, writing and editorial support was provided by Jason Jung, PhD, of MedErgy. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by MedErgy. Shire Development LLC provided funding to MedErgy for support in writing and editing this manuscript. Srini Tenjarla, PhD, is an employee of Shire, and holds stock and/or stock options at Shire.

Ethical standards statement This manuscript does not contain clinical studies or patient data.

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