Section: Miscellaneous

Original Research Article

# PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODELLING FOR MESALAMINE SACHET FORMULATIONS: PREDICTION OF IN VIVO PERFORMANCE AND COMPARISON AMONG FORMULATIONS AVAILABLE IN INDIA

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ABSTRACT

**Background:** Mesalamine is a first-line agent used for treatment of ulcerative colitis. This study aims to evaluate mesalamine concentrations in different parts of the gastrointestinal tract, especially the colon, from four brands including test products. For this purpose, physiologically based pharmacokinetic modelling (PBPK) was used for determination of mesalamine concentration in GIT and colon.

**Materials and Methods:** Four commercially available mesalamine (1g and 2 g) sachets (Brand P, Vegaz OD, Brand M, and Brand R) were modelled. A physiologically based biopharmaceutics model (PBBM) was applied for determination of mesalamine concentration, total dose of mesalamine in colon from different sachet (1/2g) formulations. The dissolution conditions used were 0.1 N HCl for 2 hours, pH 6.4 phosphate buffer for 1 hour, and pH 7.2 phosphate buffer for 24 hours. The model was validated with in vivo plasma concentration time profiles in fasting condition, obtained from in-house bioequivalence study (2x500mg) for reference product Brand P capsule. Further, the validated PBBM was used to compare various brands of mesalamine to predict local concentrations in various parts of gastrointestinal tract. Mesalamine concentration (i.e. Cmax, concentrations), in vivo release in various parts of intestine together with colon concentration and T/R ratios in colon for various formulations in fasting and fed conditions were simulated.

**Results:** Similar luminal and enterocytic concentrations of mesalamine between Vegaz OD and Brand P in the colon were achieved with both 1g and 2g Vegaz OD sachets in a fasting state whereas for other brands, lower concentrations were observed. In fed state, concentrations in colon for Vegaz OD were equivalent or higher than Brand P and other two brands. In vivo release and concentrations of mesalamine in Vegaz OD is similar to Brand P and other two brands exhibited lower release.

**Conclusion:** Vegaz OD sachet had total mesalamine levels similar to brand P and thus this generic formulation is equivalent to branded innovator formulation.

**Keywords:** Mesalamine, Pentasa, Vegaz, colon, PBBM.

## INTRODUCTION

The United States Food and Drug Administration (FDA) has approved mesalamine, also known as 5-aminosalicylic acid (5-ASA), primarily for the treatment of inflammatory bowel disease. The release mechanism of 5-ASA varies based on its formulation,

allowing it to be released at different locations within the gastrointestinal tract.[1]

Mesalamine, classified as a class IV medication by the Biopharmaceutics Classification System, is commonly used to treat inflammation associated with conditions affecting the colon, such as Crohn's disease and ulcerative colitis.[2] The delivery system should enable the medication to be released in the colon while protecting it and delaying its release in the upper gastrointestinal tract, including the small intestine and stomach.[3] Although the exact mechanism of action remains unclear, it is theorized that mesalamine reduces the production of prostaglandins and leukotrienes by modulating the inflammatory response derived from the cyclooxygenase and lipoxygenase pathways. Another hypothesis suggests that mesalamine interferes with the production of inflammatory cytokines by reducing the activity of nuclear factor-κB (NF-κB) and inhibiting tumor necrosis factor (TNF), as well as affecting the cellular functions of mucosal lymphocytes, macrophages, and natural killer cells. Additionally, mesalamine has been proposed to act as an antioxidant and a free radical scavenger.[4,5]

To effectively treat inflammatory bowel diseases, there has been a significant focus on the ongoing development and enhancement of colon-specific mesalamine delivery systems. There are several formulations of mesalamine available, including extended-release capsules/tablets/granules and delayed release tablets. These formulations are primarily differentiated by their mechanisms for delivering active mesalamine to the colon.[6] Various strategies, including time-dependent, pH-responsive, prodrug, and enzymatic/microbial-responsive mechanisms, have been utilized to develop colonic delivery systems for mesalamine. Most oral mesalamine formulations employ a pH-dependent coating that delays the release of 5-ASA in the stomach, allowing it to be released at a higher intestinal pH. This targeted administration of mesalamine to the colon has garnered significant attention as it aims to enhance therapeutic efficacy while reducing potential adverse effects.[2]

PBBM (Physiologically Based Biopharmaceutics Modelling) is an in-silico tool that integrates physicochemical, pharmacokinetic and physiological processes to simulate in vivo performance of the active pharmaceutical ingredient. PBBM has demonstrated significance in both generic and innovator product development with plethora of applications. One of critical model input in the PBBM is in vitro dissolution, as it can govern in vivo performance of orally administered solid dosage forms.[7] An in vitro dissolution, that is mimicking the pH, duration and volumes of gastrointestinal tract becomes powerful tool that can enable prediction of in vivo performance.[8] In the present case, PBBM coupled with biorelevant dissolution is used to predict in vivo performance of mesalamine of various brands available in market. The developed PBBM was validated for its predictive performance by comparing the predicted vs observed pharmacokinetic behavior of reference formulation. The PBBM also enabled prediction of local concentrations of mesalamine in colon allowing to correlate with possible efficacy and comparison of various brands. The PBBM coupled with biorelevant dissolution enabled successful comparison of various dosage forms and paved a way for selection of formulation that exhibited closer performance to the innovator branded formulation.

Vegaz OD sachets contain modified release pellets that are coated with Eudragit and ethyl cellulose, facilitating sustained and targeted release of Mesalamine through diffusion, swelling, and erosion. This study aims to evaluate the local concentrations of Mesalamine in various parts of the gastrointestinal tract (GIT), particularly in the colon, released from Vegaz OD sachet (Dr. Reddy's Laboratories Ltd., India). Additionally, it compares these concentrations against other competitor brands such as using in-silico modelling.

## MATERIALS AND METHODS

A physiologically based biopharmaceutics model (PBBM) was developed using Brand P capsule (2 × 500 mg) fasted plasma profile and dissolution profile (0.1 N HCl for 2 hours, followed by pH 6.4 phosphate buffer for 1 hour, followed by pH 7.2 phosphate buffer for 24 hours) of Brand P sachet. The model was validated using an in-house pilot fed bioequivalence study of 1 g Brand P Capsule (2 × 500 mg Capsules). The validated PBBM was then used to determine various output parameters, such as the concentration and in vivo release of mesalamine throughout the intestine, the concentration of mesalamine, and the total dose of mesalamine in the colon, for comparison of commercially available mesalamine sachets.

Dissolution media: A change in dissolution media was chosen for the dissolution of Brand P and three other generic sachet formulations. The selected dissolution media included 0.1N HCl, followed by pH 6.4 phosphate buffer, and then pH 7.2 phosphate buffer using USP I apparatus maintained at 100 rpm rotation speed. This selection was based on the pH levels of the gastrointestinal tract (GIT) and the time points were determined by the drug's transit time through different sections of the GIT. Overall, the dissolution condition mimicked the transfer of dosage form in various parts of GIT through the following mechanisms:

- Stomach has a pH range of 1.0 to 2.0 and the transit time was estimated to 2 hrs (range 1.5 to 3.0 hrs)[9] 0.1N HCl provides a pH of 1.0, which simulates the drug dissolution in stomach. The volume used for this condition was 750 mL, with sampling time points of 1 and 2 h.
- Duodenum has a pH range of 5.8 to 7.0 and the transit time is approximately 1 hr. Phosphate

buffer with pH 6.8 mimics the duodenum. The volume used for this condition was 950 mL, with sampling time points of 1 h.

- Large intestine (specifically Colon) has a pH in the range of 7.0 to 8.0 and the transit time ranges from 10 to 40 hrs. phosphate buffer with pH of 7.2 mimics the drug dissolution in colon. The volume used for this condition was 960 mL, with sampling time points of 1, 2, 4, 6, 8, 12, 16, 24 h.

**PBBM modelling and simulations approach**

**GastroPlusTM**

GastroPlus version 9.8 (Simulations Plus, Inc.) was used as an in-silico tool to build a PBBM for mesalamine in both fasted and fed conditions. GastroPlus simulates intravenous, gastrointestinal, ocular, nasal, and pulmonary absorption, pharmacokinetics, and optionally, pharmacodynamic effects for drugs dosed in humans and animals. The software interface has five main tabs: Compound (drug info and database calculations), Physiology (permeabilities and model parameters), Pharmacokinetics (PK parameters, observed values, metabolism/transport scale factors), Simulation (single simulation, population simulation, parameter sensitivity analysis), and Graph (plots).

Model development: The physicochemical and biopharmaceutical properties of Mesalamine were defined using a combination of literature-based inputs or optimized inputs for simulations and are presented in [Table 1]

**Table 1: Key physicochemical and biopharmaceutical parameters for Mesalamine used in GastroPlus simulations**

| Property | Value used | Remarks |
|---|---|---|
| Molecular wt. | 153.135 | [17] |
| Dose | 1000 mg | NA |
| pKa | 2.30, 5.69, 13.9 | [18] |
| Log P | 0.11 | [18] |
| Solubility (mg/mL) at pH 1.2 | 8.47 | In house generated |
| Human permeability [Peff (cm/s × 103)] | 1.8 | Optimized value to fit the in vivo data |
| Particle size (µ) | Radius – 25 | Default value in GastroPlus |
| Mean precipitation time (sec) | 900 | Default value in GastroPlus |
| CL (L/h) | 24.609 | Calculated after fitting intravenous plasma profile using PK Plus module |
| Vd (L/Kg) | 0.29076 | Calculated after fitting intravenous plasma profile using PK Plus module |
| Administration | CRU: Dispersed | NA |

Wt.: Weight; pKa: Acid Dissociation Constants; Log P: Logarithm of the Partition Coefficient; Solubility (mg/mL): Solubility in Milligrams per Milliliter; Human permeability [Peff (cm/s × $10^3$)]: Human Effective Permeability (in centimetres per second × $10^3$); (µ): Micrometres; Sec: Seconds; CL (L/h): Clearance in Liters per Hour; Vd (L/Kg): Volume of Distribution in Liters per Kilogram of Body Weight; NA: Not applicable.

**Dissolution data input:** Dissolution data of Brand P, Vegaz OD, Brand M, and Brand R are used as dissolution input as '.crd files in Gastroplus and time scaling was utilised. To match the Tmax accurately, a time scaling factor was utilized. Time scaling factor was subsequently used for other Mesalamine formulations to simulate the in vivo behavior. The time scaling equation is as follows:

Fasting and fed condition: In vivo time (h) = 0.5 × in vitro time (h)

**Elimination parameters:** To determine elimination parameters, intravenous infusion data (500 mg, 5 min) from literature,[7] was used. These parameters predicted oral plasma concentration time profiles of Brand P Capsules in fasted and fed states and for fasted and fed states the bioavailability was corrected through liver first pass extraction (%FPE). The calculated elimination parameters were defined through 2-compartmental model and yielded acceptable prediction errors for Brand P Capsule.

**Physiology:** For the simulation of mesalamine behavior in the fasted and fed states, the 'Human - Physiological - Fasted' and 'Human - Physiological - Fed' states under the 'Gut physiology' tab were selected, respectively. The absorption scaling factor (ASF) model employed was the Opt Log D Model SA/V 6.1. The oral mechanistic absorption model developed measured only passive diffusion (paracellular and transcellular). The ADMET PredictorTM predicted permeability (Human Peff: 0.74 × 10─4 cm/sec), which was initially used and subsequently optimized to 1.8 × 10─4 cm/sec to match the in vivo Tmax and used for all simulations.

**Model Validation:** For the purpose of model validation, the plasma concentration time profile pertaining to pilot Brand P Capsule 1 g (2 × 500 mg) plasma profile under fed condition was utilized in order to understand basic model's predictability utilising single simulation.

The physiologically based biopharmaceutics model (PBBM) was developed under both fasted and fed states. Ultimately, the in vivo fasted plasma profile of Brand P Capsule was predicted using the developed PBBM, and the prediction errors (%PE) for pharmacokinetic parameters (Cmax and AUCs) were calculated using the specified formula. Simulations were deemed acceptable if the %PE was less than 25%.

$\%\ PE = (Predicted\ value - Observed\ value / Observed\ value) \times 100$.

**Model Application:** After the validation of the developed PBBM against in house fed pilot BE outcome, the model was utilized for the following applications.

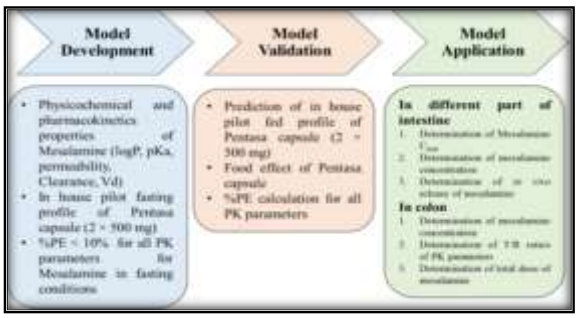



**Figure 1: Flow chart for the modelling and simulation**

**Determination of Mesalamine Cmax throughout intestine for different formulations in Fasted and Fed states**

Previous studies suggested that luminal as well as enterocyte concentrations of mesalamine are critical to achieve the therapeutic efficacy of mesalamine.[10,11] Thus, enterocytic and luminal concentration of mesalamine (maximum concentration) in each part of intestine were determined. The validated model was utilized to predict local concentrations of all the four formulations of mesalamine in lumen and in enterocytes of intestine to determine therapeutic equivalence amongst them under both fasted and fed states.

**Determination of mesalamine concentration in different parts of intestine under Fasted and Fed state**

The concentration of mesalamine in different parts of intestine were determined using the validated model for all sachet formulations. It was predicted using the validated model and the volume of fluid present in different parts of intestine. In the "Physiology tab" section of GastroPlus software as default, the volume of fluid present in different compartments of GIT were defined in both fasted and fed state.

**Determination of in vivo release of mesalamine in different parts of intestine under Fasted and Fed state**

It was calculated for the sachet formulations using validated model, which was utilized to predict amount of mesalamine dissolved, amount in portal vein, amount absorbed, amount in systemic circulation from each sachet formulations. The amount of mesalamine dissolved in different part of GIT was accounted as in vivo release of mesalamine in different parts of intestine under fasted and fed states.

**Determination of mesalamine concentration in Colon under Fasted and Fed state**

Previous reports suggested that luminal as well as enterocyte concentrations of mesalamine are critical to achieve the therapeutic efficacy of the mesalamine.[11] Thus, the enterocytic and luminal concentration of mesalamine in colon was determined under fasted and fed states using the validated model.

**Determination of T/R ratios of PK parameters in Colon under Fasted and Fed state**

To predict the bioequivalence of generic sachet formulations (Vegaz OD, Brand M, and Brand R) against mesalamine sachet Brand P the T/R ratios for PK parameters (Cmax and AUCt) in colon were determined. PK parameters for all the sachet formulations in colon (enterocyte and lumen) were predicted using validated model and further T/R ratios were calculated considering Brand P sachet. As all the generic sachet formulations are indicated for ulcerative colitis and the local concentrations of mesalamine in colon govern the pharmacological effect hence, T/R ratios were only calculated for PK parameters in colon under both fasted and fed states.

**Determination of total dose of mesalamine in Colon under Fasted and Fed state**

To understand the effectiveness of the sachet formulations to treat ulcerative colitis, the total dose of mesalamine in colon was predicted using the validated model. The total dose of mesalamine in colon was calculated from % absorption of mesalamine in colon when 1 g / 2 g sachet of Mesalamine formulations were dosed under both fasted and fed states. Subsequently, based on the % absorption, the amount of dose was calculated accordingly.

**Determination of rate of release of Mesalamine from different formulation**

To understand linear release of Vegaz OD as compared to other sachet formulations the rate of release of mesalamine from different formulations were determined separately. The rate of release of mesalamine from all sachet formulations were calculated and plotted against time.

## RESULTS

The results of dissolution study indicated that the release of mesalamine from Vegaz OD is similar to innovator formulation whereas other two studied brands have exhibited lower dissolution. At the end of dissolution testing in colon, the % release was only 80% for these brands indicating incomplete release and thereby possible loss of efficacy. Whereas Vegaz OD and innovator branded formulation have released complete drug thereby confirming the similarity in vivo behavior and thus possible therapeutic equivalence.

[Table 2] represents the calculated %PE for Cmax and AUC parameters for Brand P Capsules (1000 mg) were less than 10% thereby confirming the validity of the model. The PBBM was validated using in house fed BE study data of Brand P Capsules 1000 mg. The model predicted PK parameters (Cmax, AUCt, and AUCinf) were predicted well with <20% prediction error.

**Table 2: Predicted PK parameters of 1000 mg Brand P Brand P Capsules under fasted and fed state**

| PK Parameters | Observed | Predicted | %PE |
|---|---|---|---|
| Fasted state | | | |
| $C_{max}$ (ng/mL) | 1120.3 | 1203 | 7.38 |
| $AUC_{0\text{-}inf}$ (ng-h/mL) | 5079.4 | 5343.9 | 5.21 |
| $AUC_{0\text{-}t}$ (ng-h/mL) | 5079.4 | 5326.5 | 4.86 |
| Fed state | | | |
| $C_{max}$ (ng/mL) | 287.8 | 267.63 | -7.01 |
| $AUC_{0\text{-}inf}$ (ng-h/mL) | 1604.3 | 1281.9 | -20.10 |
| $AUC_{0\text{-}t}$ (ng-h/mL) | 1583.8 | 1278.7 | -19.26 |

%PE: Percent Prediction Error (%), Cmax (ng/mL): Maximum plasma concentration of the drug in nanograms per milliliter; $AUC_0$-inf (ng·h/mL): Area under the plasma concentration-time curve from time zero to infinity (nanograms per hour per milliliter); $AUC_0$-t (ng·h/mL): Area under the plasma concentration-time curve from time zero to the last measurable time point (nanograms per hour per milliliter).

**Determination of T/R ratios of PK parameters in Colon under Fasted and Fed state**

The T/R ratios of PK parameters in colon for three generic mesalamine sachets are presented in [Table 3] both under fasted and fed state. The T/R ratios for Cmax and AUCt for all three generic mesalamine sachets, including Vegaz are observed within 80 – 125% range.

**Table 3: T/R ratios of PK parameters in Colon under Fasted and Fed state**

| **Fasted state** | | | |
|---|---|---|---|
| T/R ratio (Brand P 1 g as R) | Vegaz OD 1 g | Brand M 1g | Brand R 1g |
| Enterocyte $C_{max}$ | 100 | 97 | 95 |
| Enterocyte $AUC_t$ | 98 | 94 | 91 |
| Luminal Cmax | 100 | 99 | 95 |
| Luminal $AUC_t$ | 98 | 94 | 91 |
| T/R ratio (Brand P 2 g as R) | Vegaz OD 2 g | Brand M 2 g | Brand R 2 g |
| Enterocyte $C_{max}$ | 100 | 99 | 97 |
| Enterocyte $AUC_t$ | 99 | 102 | 88 |
| Luminal Cmax | 100 | 100 | 100 |
| Luminal $AUC_t$ | 98 | 102 | 88 |
| Fed state | | | |
| T/R ratio (Brand P 1 g as R) | Vegaz OD 1 g | Brand M 1g | Brand R 1g |
| Enterocyte $C_{max}$ | 99 | 96 | 93 |
| Enterocyte $AUC_t$ | 98 | 94 | 91 |
| Luminal Cmax | 100 | 97 | 90 |
| Luminal $AUC_t$ | 98 | 94 | 91 |
| T/R ratio (Brand P 2 g as R) | Vegaz OD 2 g | Brand M 2 g | Brand R 2 g |
| Enterocyte $C_{max}$ | 99 | 100 | 95 |
| Enterocyte $AUC_t$ | 97 | 103 | 85 |
| Luminal Cmax | 100 | 100 | 100 |
| Luminal $AUC_t$ | 97 | 104 | 85 |

T/R ratio: Test-to-Reference ratio; g: gram; R: Reference; Cmax: Maximum concentration of the drug; AUCt: Area under the drug concentration-time; Vegaz-OD; Vegaz-Once Daily.

**Determination of Mesalamine luminal concentration in Colon under Fasted state**

Mesalamine luminal concentration in colon under fasted state obtained from different mesalamine sachet formulations (1g) are predicted using validated PBBM and presented in [Figure 2A] and obtained from different mesalamine sachet formulations (2g) are presented in [Figure 3A]. 1g Vegaz OD and 1g Brand P sachets showed similar luminal mesalamine concentrations in the colon. In contrast, 1g Brand M and 1g Brand R sachets had slightly lower concentrations. Both 2g Vegaz OD and 2g Brand P sachets resulted in comparable mesalamine levels, while 2g Brand M sachets produced higher concentrations than 2g Vegaz OD under fasted conditions.

**Determination of Mesalamine enterocytic concentration in Colon under Fasted state**

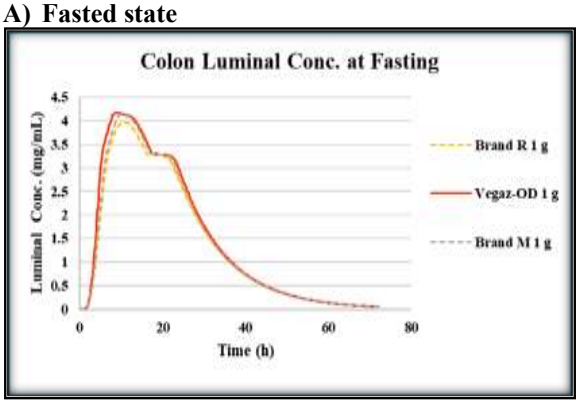
Further, enterocytic concentration in colon under fasted state obtained from different mesalamine sachet formulations (1g) are predicted using validated PBBM and presented in [Figure 4A] and obtained from different mesalamine sachet formulations (2g) are presented in [Figure 5A]. It was observed that enterocytic concentration of Vegaz OD 1 g is similar to Brand P sachet 1 g under fasted state, but Brand R and Brand M sachets showed lower enterocytic concentration than Vegaz OD 1g. Further, 2g Vegaz OD and 2g Brand P sachets resulted in similar enterocytic concentration of mesalamine in colon. Whereas other generic sachet Brand M 2g resulted higher enterocytic concentration of mesalamine in colon than Vegaz OD 2g sachet under fasted state.

**Determination of Mesalamine luminal concentration in Colon under Fed state**

Mesalamine luminal concentration in colon under fed state obtained from different mesalamine sachet formulations (1g) are presented in [Figure 2B] and obtained from different mesalamine sachet formulations (2g) are presented in [Figure 3B]. Similarly, under fed state Vegaz OD (both 1g and 2g)

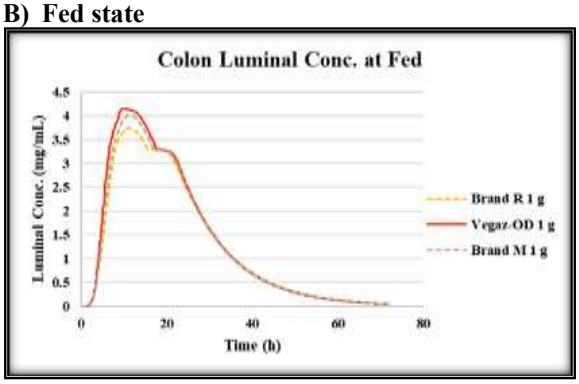
sachets showed similar luminal concentration in colon to both 1g and 2g Brand P sachets. Both 1g generic sachet formulations showed lower luminal concentration in colon than 1g Vegaz OD, whereas 2g Brand M sachet showed higher and 2 g Brand R sachet showed lower luminal concentration in colon than Vegaz OD 2g sachet.

**A) Fasted state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Luminal Conc., mg/mL): Luminal concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

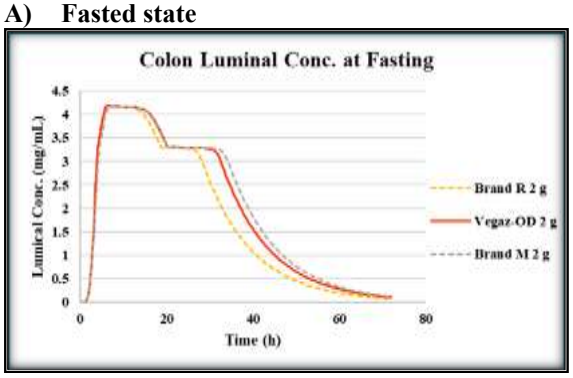
**B) Fed state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Luminal Conc., mg/mL): Luminal concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

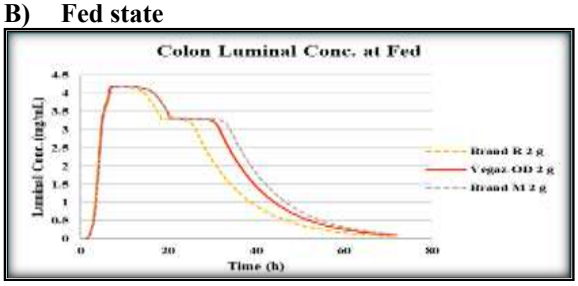
**Figure 2: Colonic concentration of mesalamine in fasting and fed models with Vegaz OD, Brand M, and Brand R Sachet formulations (1 g)**

**A) Fasted state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Luminal Conc., mg/mL): Luminal concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

**B) Fed state**



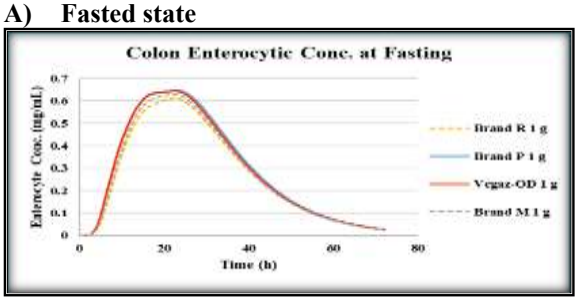

**X-axis (Time, h): Time in hours after drug administration; Y-axis (Luminal Conc., mg/mL): Luminal concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

**Figure 3: Colonic concentration of mesalamine at Lumen from Vegaz OD, Brand M, and Brand R Sachet formulations (2 g)**

**Determination of Mesalamine enterocytic concentration in Colon under Fed state**

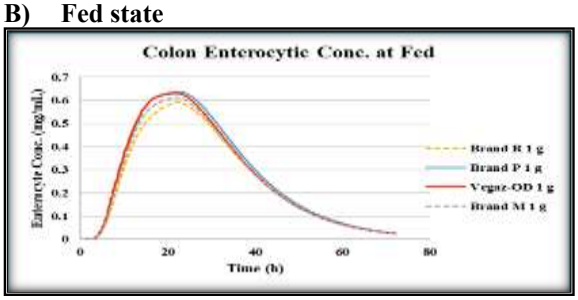
Further mesalamine enterocytic concentration in colon under fed state obtained from different mesalamine sachet formulations (1g) are presented in [Figure 4B] and obtained from different mesalamine sachet formulations (2g) are presented in [Figure 5B]. Vegaz OD (both 1g and 2g) sachets showed similar enterocytic concentration in colon to both 1g and 2g Brand P sachets. However, 1g generic sachet formulations showed lower enterocytic concentration in colon than 1g Vegaz OD. Whereas 2g Brand M sachet showed higher and 2g Brand R sachet showed lower enterocytic concentration in colon than Vegaz OD 2 g sachet.

**A) Fasted state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Enterocytic Conc., mg/mL): Enterocytic concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

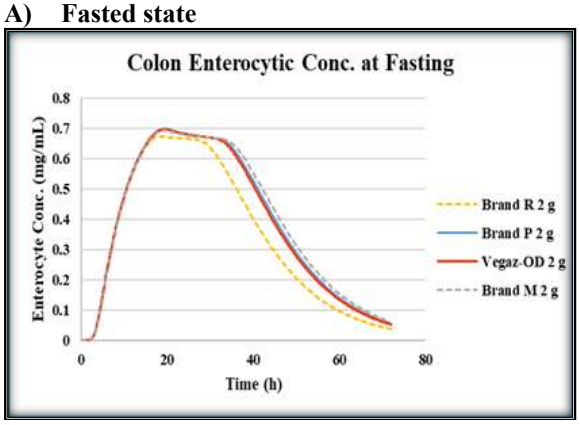
**B) Fed state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Enterocytic Conc., mg/mL): Enterocytic concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

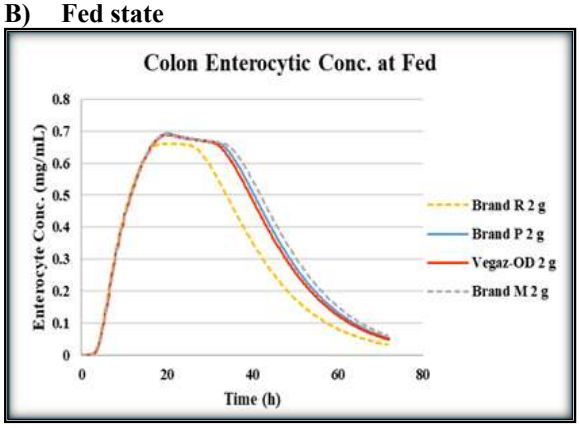
**Figure 4: Colonic concentration of mesalamine at Enterocyte from different Sachet formulations (1 g) under fasted and fed state**

**A) Fasted state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Enterocytic Conc., mg/mL): Enterocytic concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

**B) Fed state**




**X-axis (Time, h): Time in hours after drug administration; Y-axis (Enterocytic Conc., mg/mL): Enterocytic concentration in milligrams per milliliter; Vegaz-OD; Vegaz-Once Daily.**

**Figure 5: Colonic concentration of mesalamine at Enterocyte from different Sachet formulations (2 g) under fasted and fed state**

## DISCUSSION

In silico modelling is crucial in pharmaceutical research. Physiologically Based Pharmacokinetic (PBPK) models are utilized to enhance clinical trial efficiency. Regulatory bodies like the FDA and EMA recognize its value due to its practical representation.[12] Recognizing the potential of Physiologically Based Biopharmaceutics Modelling (PBBM), regulatory guidelines have been established to outline its applications across various clinical scenarios. The European Medicines Agency's (EMA) Physiologically Based Pharmacokinetics (PBPK) guidance, effective since 2018, emphasizes the use of PBPK modelling in new drug submissions, encompassing drug-drug interaction studies, first-in-human dose estimations, and other related applications. Similarly, the US Food and Drug Administration's (USFDA) PBBM guidance, introduced in 2020, centers on the manufacturing and quality aspects of pharmaceutical formulations from a biopharmaceutics standpoint. This guidance has facilitated the adoption of PBBM for purposes such as enabling biowaivers, establishing clinically relevant dissolution specifications, broadening dissolution specifications, and waiving specific bioequivalence studies in the development of both generic and new drug products.

The use of physiologically based biopharmaceutics modelling (PBBM) to predict in vivo drug performance and support formulation development is becoming more prevalent.[13] Previous studies have showcased the use of GastroPlus, an in silico tool for IVIVC simulation of gastrointestinal bioavailability, in the formulation development of Biopharmaceutical Classification System (BCS) class II drugs.[12,14] GastroPlus is a physiologically based modeling tool that facilitates exposure predictions across different scenarios, such as fasting, fed states, and physiological changes associated with specific disease conditions. In this study, we utilized GastroPlus-based PBBM to evaluate and compare the performance of various mesalamine formulations available in the Indian market. Vegaz OD, a generic mesalamine sachet formulation intended for the treatment of ulcerative colitis, is designed to release mesalamine in the colon for effective therapy. This generic formulation was considered equivalent to the innovator product, and an innovative PBBM approach was applied to assess its superiority over other brands. Since PBBM accurately reflects physiological gastrointestinal conditions, it enables predictions of mesalamine availability and concentrations in various regions of the gastrointestinal tract. Notably, this tool provided a comparative analysis of different brands, supporting the correlation between anticipated therapeutic equivalence and efficacy. (citation) From the perspective of in-silico modelling, the randomized crossover study conducted by Corey et al. (1990) provides critical pharmacokinetic data that can be simulated to gain deeper insights into drug behavior.[15] Participants received 800 mg of mesalamine as two enteric-coated tablets and 2,000 mg of sulphasalazine as four 500 mg tablets, administered at 12-hour intervals with a 14-day washout period between treatments. Using physiologically based biopharmaceutics modelling (PBBM), the observed mean area under the curve (AUC) values, indicating systemic drug exposure at steady state, can be modeled. For mesalamine, the mean plasma AUC was 13.71 µg/ml·h (range: 5.02–29.64 µg/ml·h), while for sulphasalazine, it was 11.59 µg/ml·h (range: 1.78–26.09 µg/ml·h). Such in-silico approaches allow for precise simulation of drug absorption, distribution, and availability, enabling predictions of therapeutic outcomes under various physiological conditions. In the current study, it was observed that for all three generic mesalamine sachets, including Vegaz OD, the T/R ratios for Cmax and AUCt were within the 80–125% range. This concluded that all the generic mesalamine sachets are bioequivalent with Brand P sachet under

both fasted and fed conditions. However, for Vegaz OD 1 g and 2 g sachets, the T/R ratios were approximately 100%, indicating that Vegaz OD sachets are more similar to Brand P sachets compared to the other two generic sachets.

In another open-label, randomized, crossover bioequivalence study conducted on thirty-four healthy volunteers, the test product mesalamine 400 mg by APL Research Centre-Hyderabad, India, was compared with Brand M 400 mg tablets. The maximum concentration for the test product was 849.41 ng/mL, whereas for the reference product, the maximum concentration reached was 719.92 ng/mL.[16] The clinical findings relate with the observations of the current study. In our study, the T/R ratios of PK parameters in the enterocytic region of the colon under a fasted state for Vegaz OD 1 g and 2 g were 100%. In the fed state, the maximum enterocytic concentration for 1 g of Vegaz OD, Brand M, and Brand R was 99%, 96%, and 93%, respectively. This indicates that the maximum concentration reaching the colon was for Vegaz OD in the fasted state. Additionally, in the fed state, the luminal concentration was 100% for both 1 g and 2 g doses.[16] From the study results, it is evident that the Vegaz OD yielded significant and equivalent concentrations of mesalamine in colon both from maximum concentration and significant concentrations throughout the course of action. Further, the in vivo release of mesalamine from Vegaz OD is comparable to branded innovator and superior to other two formulations. Further, the Vegaz OD is closer to innovator in terms of local Cmax and AUC as compared to other brands. Overall, this study has provided significant conclusions that Vegaz OD is equivalent to innovator formulations, localizes in colon to a greater extent as compared to other brands thereby conforming superiority in efficacy in ulcerative colitis.[17,18]

The study design included an in-silico method to predict the behavior of systems under various conditions, allowing researchers to anticipate potential outcomes before conducting expensive or lengthy experiments. This approach aided in predicting outcomes without human inclusion, thereby simplifying the process. Nevertheless, many in-silico models may not fully replicate tissue-specific or organ-specific behaviors. Future studies might integrate genetic data to forecast bioavailability in patients with specific genetic variations that affect drug absorption, metabolism, or elimination. In-silico models can be increasingly validated by real-world data, including clinical trial outcomes and post-market surveillance.

## CONCLUSION

The prediction results suggested that the total dose of mesalamine obtained from Vegaz OD sachets is similar to that of Brand P sachets with respect to dissolution and PK profile. Additionally, Vegaz OD resulted in comparable or better total mesalamine compared to two other generic sachet formulations. Therefore, it can be concluded that Vegaz OD sachet formulation is similar to Brand P sachet and comparable to the other two competitor sachet brands (Brand M and Brand R).

## REFERENCES


1. B. Barberio, J. P. Segal, M. N. Quraishi, C. J. Black, E. V. Savarino, and A. C. Ford, "Efficacy of Oral, Topical, or Combined Oral and Topical 5-Aminosalicylates, in Ulcerative Colitis: Systematic Review and Network Meta-analysis," Journal of Crohn's and Colitis, vol. 15, no. 7, pp. 1184–1196, Jul. 2021, doi: 10.1093/ecco-jcc/jjab010.
2. M. F. Bayan and R. F. Bayan, "Recent advances in mesalamine colonic delivery systems," Futur J Pharm Sci, vol. 6, no. 1, p. 43, Dec. 2020, doi: 10.1186/s43094-020-00057-7.
3. R. Mehta, A. Chawla, P. Sharma, and P. Pawar, "Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system," J Adv Pharm Technol Res, vol. 4, no. 1, p. 31, 2013, doi: 10.4103/2231-4040.107498.
4. S. Garud and M. A. Peppercorn, "Review: Ulcerative colitis: current treatment strategies and future prospects," Therap Adv Gastroenterol, vol. 2, no. 2, pp. 99–108, Mar. 2009, doi: 10.1177/1756283X09102329.
5. J. Meier and A. Sturm, "Current treatment of ulcerative colitis," World J Gastroenterol, vol. 17, no. 27, pp. 3204–3212, Jul. 2011, doi: 10.3748/wjg.v17.i27.3204.
6. J. Nakashima, P. Patel, and C. V. Preuss, "Mesalamine (USAN)," in StatPearls, Treasure Island (FL): StatPearls Publishing, 2024. Accessed: Dec. 07, 2024. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK551714/
7. M. Ibarra, A. Schiavo, and L. J. Lesko, "Physiologically Based Biopharmaceutics Modeling (PBBM)," in The ADME Encyclopedia, Cham: Springer International Publishing, 2021, pp. 1–6. doi: 10.1007/978-3-030-51519-5_170-1.
8. Y. Lu, S. Kim, and K. Park, "In vitro-in vivo correlation: perspectives on model development," Int J Pharm, vol. 418, no. 1, pp. 142–148, Oct. 2011, doi: 10.1016/j.ijpharm.2011.01.010.
9. R. K. Goyal, Y. Guo, and H. Mashimo, "Advances in the physiology of gastric emptying," Neurogastroenterology Motil, vol. 31, no. 4, p. e13546, Apr. 2019, doi: 10.1111/nmo.13546.
10. P. H. Layer, H. Goebell, J. Keller, A. Dignass, and U. Klotz, "Delivery and fate of oral mesalamine microgranules within the human small intestine," Gastroenterology, vol. 108, no. 5, pp. 1427–1433, May 1995, doi: 10.1016/0016-5085(95)90691-6.
11. L. Staerk Laursen, M. Stokholm, K. Bukhave, J. Rask-Madsen, and K. Lauritsen, "Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion.," Gut, vol. 31, no. 11, pp. 1271–1276, Nov. 1990, doi: 10.1136/gut.31.11.1271.
12. S. Choi, C.-Y. Kang, B.-J. Lee, and J.-B. Park, "In Vitro-In Vivo Correlation Using In Silico Modeling of Physiological Properties, Metabolites, and Intestinal Metabolism," CDM, vol. 18, no. 11, pp. 973–982, Jan. 2018, doi: 10.2174/1389200218666171031124347.
13. E. Eckernäs and C. Tannergren, "Physiologically Based Biopharmaceutics Modeling of Regional and Colon Absorption in Dogs," Mol. Pharmaceutics, vol. 18, no. 4, pp. 1699–1710, Apr. 2021, doi: 10.1021/acs.molpharmaceut.0c01201.
14. T. da S. Honório et al., "In vitro-in vivo correlation of efavirenz tablets using GastroPlus®," AAPS PharmSciTech, vol. 14, no. 3, pp. 1244–1254, Sep. 2013, doi: 10.1208/s12249-013-0016-4.
15. A. E. Corey, G. M. Rose, and J. D. Conklin, "Bioavailability of Single and Multiple Doses of Enteric-Coated Mesalamine

and Sulphasalazine," J Int Med Res, vol. 18, no. 6, pp. 441–453, Nov. 1990, doi: 10.1177/030006059001800601.
16. K. Mala, N. Hwisa, C. RAO, and P. Katakam, "An open-label, randomized, crossover bioequivalence study of mesalamine 400 mg tablets in Indian healthy volunteers under fasting conditions," Der Pharmacia Lettre, vol. 5, pp. 465–471, Jun. 2013.
17. National Center for Biotechnology Information (2024), "PubChem Compound Summary for CID 4075, Mesalamine." [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/Mesalamine.
18. USFDA, "Center for Drug evaluation and Research and Environmental Assesssment for Asacol (mesalamine) Delayed Release Tablet, 800 mg."