Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Bioequivalence and Relative Bioavailability of a Multiparticulate Apixaban Formulation Administered Intact or Dispersed in Yogurt

Mickaël Trémège
Laboratoires SMB SA
Romain Merlos
Laboratoires SMB SA
Jean-Michel Cardot
SAS Borvo
Ahmad Kamal Abdulkhaleq
Pharmaceutical Research Unit
Bruno Streel
Galephar MF
Sophie De Niet
sdeni@smb.be

Laboratoires SMB SA https://orcid.org/0000-0003-4393-2636

Research Article

Keywords: Bioequivalence, Pellets, Apixaban, Dysphagia

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11075574/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: The authors declare potential competing interests as follows: S.D.N., M.T. and R.M. are employees of Laboratoires SMB S.A. J.-M.C. serves as a consultant to Laboratoires SMB S.A. The other authors declare no competing interests.

Abstract

Two randomized, open-label, two-treatment, two-sequence crossover studies evaluated the pharmacokinetic characteristics of a multiparticulate pellet formulation of apixaban in healthy participants. Study 1 compared the apixaban 5 mg pellet formulation administered as an intact capsule with a reference apixaban 5 mg tablet under fasting conditions. Study 2 compared the pellet formulation administered as an intact capsule or dispersed in yogurt. Thirty-six participants were enrolled in each study. In Study 1, bioequivalence was demonstrated, with geometric mean ratios (90% confidence intervals) of 86.72% (81.41–92.38%) for Cmax and 92.20% (88.56–95.98%) for AUCt. In Study 2, yogurt administration resulted in an AUCt ratio of 115.37% (110.14–120.84%) and a Cmax ratio of 121.36% (113.30–129.99%), with median Tmax decreasing from 4.25 to 3.25 hours. The yogurt administration affected the rate of apixaban absorption more than its overall extent. A complementary handling assessment showed shorter preparation time (78.2% reduction when equipment rinsing was included) and more consistent direct dose recovery following capsule opening than reference tablet crushing (98.5% vs 96.5%).

1. Introduction

Apixaban is an oral direct factor Xa inhibitor widely used for the prevention and treatment of thromboembolic disorders. Because apixaban is frequently prescribed to older patients and patients with a history of stroke, swallowing difficulties may complicate administration of conventional tablets. Dysphagia is common in older adults and particularly prevalent following stroke, with objective instrumental assessments identifying dysphagia in approximately 64%–78% of patients managed in acute or long-term care settings after stroke.[1–3] Difficulties in swallowing solid oral dosage forms may result in medication avoidance or require manipulation of the dosage form to enable administration.[4–5] For patients unable to swallow intact tablets, medications may be crushed and dispersed in liquids or soft foods or administered through a feeding tube. However, tablet crushing introduces additional preparation and transfer steps and may result in incomplete dose recovery because of drug retention in crushing devices or preparation containers.[1] In addition, administration with food or other vehicles may alter drug dissolution or absorption. Alternative dosage forms that can be administered without tablet crushing may therefore facilitate administration while reducing manipulation of the medicinal product. Multiparticulate formulations provide one such approach because pellets can be released from a capsule and dispersed in an appropriate administration vehicle without a tablet-crushing step. A multiparticulate pellet formulation of apixaban 5 mg was developed to enable flexible oral administration.

The present investigation comprised two randomized crossover pharmacokinetic studies in healthy participants. Study 1 evaluated the bioequivalence of the apixaban 5 mg pellet formulation administered as an intact capsule and the reference apixaban 5 mg tablet under fasting conditions. Study 2 evaluated the relative bioavailability of the pellet formulation administered after dispersion in yogurt compared with administration as an intact capsule. In addition, a complementary in vitro handling assessment

compared preparation time and dose recovery following capsule opening with those following reference-tablet crushing.

2. Subjects and Methods

2.1. Pharmacokinetic Studies

2.1.1. Study Design and Ethics

The pharmacokinetic studies were open-label, randomized, two-treatment, two-sequence, two-period crossover with treatment periods separated by a washout period, calculated based on apparent terminal half-life, of at least 5 days. Participants were admitted to the clinical facility on day − 1 and remained at the clinical facility for the first 24 h of the study. On day 0, participants were randomly assigned to 1 of 2 treatment sequences.

Both studies were conducted at the Pharmaceutical Research Unit in Jordan in accordance with the Good Clinical Practice (GCP), the Declaration of Helsinki and applicable local regulations. The study protocols were reviewed and approved by the Independent Ethics Committee and the Institutional Review Board of the Pharmaceutical Research Unit (Study 1: approved May 6, 2024; Study 2: approved April 27, 2026). All participants provided written informed consent before undergoing any study-related procedures.

2.1.2. Study Population

Thirty-six healthy adults participated in each study. Healthy adults were defined as individuals without clinically significant abnormalities in their medical history, physical examination, ECGs, or laboratory tests. Women of childbearing potential had a negative serum pregnancy test result before starting the studies. Participants were excluded if they had a history of thrombosis, evidence of or risk factors for clinically significant bleeding or hepatic disease. The use of antiplatelet agents and other anticoagulant agents were not permitted during the studies.

The sample size for both studies was determined based on the conventional bioequivalence acceptance range of 80.00–125.00% for the 90% confidence interval of the geometric mean ratio (Test/Reference) of the primary pharmacokinetic parameters. An intra-subject coefficient of variation (CVw) of 22% for Cmax was assumed. Assuming a true Test/Reference difference not exceeding 10%, a two-sided significance level of 5% ($\alpha = 0.05$), and a statistical power of 80%, a minimum of 32 evaluable participants was estimated to be required to demonstrate bioequivalence. To account for potential dropouts and non-evaluable participants, the planned enrolment was increased to 36 participants.

2.1.3. Study Objectives

The primary objective of Study 1 was to demonstrate the bioequivalence between the apixaban 5 mg pellet formulation and the reference apixaban 5 mg tablet in fasting condition. The primary objective of

Study 2 was to assess the bioavailability of the apixaban 5 mg pellet formulation dispersed in yogurt compared with administration as an intact capsule.

In both studies, safety and tolerability of apixaban were assessed as secondary objectives.

2.1.4. Study Interventions

In Study 1, the apixaban 5 mg pellet formulation and the reference apixaban 5 mg tablet, were administered in fasting conditions with 240 ml of water. In Study 2, the apixaban 5 mg pellet formulation was administered in fasting conditions with 240 ml of water as intact capsule or dispersed in 15 g of yogurt with 240 ml of water. The investigational apixaban 5 mg pellet formulation was manufactured by Laboratoires SMB S.A. in accordance with applicable Good Manufacturing Practice requirements. Manufacturing, packaging, quality control, and release of the investigational product were performed under the pharmaceutical quality system of Laboratoires SMB S.A., ensuring compliance with predefined specifications for identity, strength, purity, and pharmaceutical quality prior to its use in the clinical studies. The reference apixaban 5 mg tablet (Eliquis®, Bristol-Myers Squibb) was sourced from the Belgian market. Prior to use in the clinical studies, the reference product was handled and released for clinical trial use by Laboratoires SMB S.A. in accordance with applicable procedures and regulatory requirements.

In both studies, participants were not permitted to drink any additional water within 1 hour before oral administration and 1 hour after the treatment administration.

2.1.5. Data Collection and Assessment

Study data were recorded in case report forms (CRFs) for each participant. Pharmacokinetic and safety data were collected according to predefined study procedures and assessment schedules. For pharmacokinetic assessment, blood samples were collected within 35 min before study drug administration (T0) and at 0.50, 1.00, 1.50, 2.00, 2.50, 2.75, 3.00, 3.25, 3.50, 3.75, 4.00, 4.25, 4.50, 5.00, 6.00, 8.00, 12.00, 24.00, 48.00, and 72.00 h post-dose in each treatment period. Safety and tolerability were assessed throughout both studies based on adverse events (AEs), vital signs, physical examinations, 12-lead electrocardiograms (ECGs), and clinical laboratory assessments performed at baseline and at predefined time points.

Plasma concentrations of apixaban were determined using validated ultra-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) methods following solid-phase extraction on 96-well plates. Human lithium-heparin plasma was used as the biological matrix, and stable isotope-labeled apixaban (^13C-d3-apixaban) was used as the internal standard. The bioanalytical methods were validated in accordance with the International Council for Harmonization (ICH) M10 guideline on bioanalytical method validation and study sample analysis. The lower limits of quantification were 1.0052 ng/mL for Study 1 and 1.0268 ng/mL for Study 2. Chromatographic separation was performed on a Kinetex C18 column (50 × 2.1 mm, 2.6 µm; Phenomenex) using 10 mM ammonium acetate and methanol (50:50, v/v) as the mobile phase at a flow rate of 0.4 mL/min. The injection volume was 5 µl,

and the total chromatographic run time was 2.5 minutes. Detection was performed using an API 5500 QTrap or API 6500 tandem mass spectrometer operated in positive ionization mode. Multiple-reaction monitoring transitions were m/z 460.1 → 199.1 for apixaban and m/z 464.1 → 203.1 for ^13C-d3-apixaban. The methods were validated over an apixaban concentration range of approximately 1–400 ng/mL using eight calibration levels. Calibration curves were fitted using weighted (1/x) quadratic regression. During pre-study validation, accuracy (bias) ranged from − 2.92% to − 0.72%, within-run precision ranged from 1.23% to 1.96% relative standard deviation (RSD), and between-run precision ranged from 1.61% to 2.22% RSD. During study sample analysis, 99.3% of quality-control samples were within 85%–115% of their nominal concentrations. Apixaban stability was demonstrated under the sample handling, storage, and analytical conditions applied during the studies.

2.1.6. Statistics

The pharmacokinetic parameters C_{max} and AUC_t were derived using non-compartmental analysis based on actual blood sampling times. Bioequivalence was concluded if the 90% confidence intervals (CIs) for the geometric mean ratios of C_{max} and AUC_t were entirely contained within the predefined acceptance range of 80.00–125.00%. Pharmacokinetic and biostatistical analyses were performed using the validated statistical software package Phoenix® WinNonlin® version 6.2.1. (Certara USA, Inc., USA).

Safety parameters, including adverse events, vital signs, electrocardiogram parameters, and clinical laboratory results, were summarized descriptively, as appropriate.

2.2. Handling and Dose Recovery Assessment

A complementary in vitro handling assessment was conducted to compare preparation procedures for the apixaban 5 mg pellet formulation and the reference apixaban 5 mg tablet. For the pellet formulation, preparation consisted of opening the capsule and transferring the pellets for administration. For the reference tablet, preparation consisted of crushing the tablet using a mortar and pestle and transferring the resulting material. Nine operators independently performed five replicate preparations of each formulation (45 preparations per formulation). Preparation time was measured from initiation of the procedure until the formulation was ready for administration. For the reference tablet, the preparation time was also calculated by including rinsing of the mortar to ensure complete recovery of the crushed tablet and minimize potential drug loss and summarized descriptively. Descriptive statistics, including mean, standard deviation (SD), minimum, and maximum, were calculated for each preparation procedure. As each operator performed both procedures, preparation times were evaluated on a paired basis at the operator level. The relative time reduction in preparation was calculated as [(mean tablet preparation time − mean capsule preparation time) / mean tablet preparation time] × 100. Inter-operator variability was assessed descriptively by comparing the range of operator-specific mean preparation times between the two procedures.

Dose recovery following preparation and transfer was also assessed for both procedures. Directly recovered apixaban was quantified after transfer of the prepared formulation and expressed as a

percentage of the nominal dose. For the tablet-crushing procedure, residual apixaban remaining in the preparation equipment was additionally quantified after rinsing of the mortar and pestle. For the capsule-opening procedure, the capsule was similarly rinsed and the rinsing solution was analysed for residual apixaban. Total dose recovery was calculated from the directly recovered and residual fractions, as applicable. Dose-recovery results were summarized descriptively using the mean, SD, minimum, and maximum.

3. Results

3.1. Pharmacokinetic Studies

3.1.1. Demographic Characteristics and Disposition of the Study Participants

Demographic characteristics of participants in both studies are shown in Table 1. A total of 72 healthy volunteers were enrolled, with 36 subjects in each study. Mean age was 31.06 ± 8.13 years in Study 1 and 26.75 ± 7.03 years in Study 2. The proportions of male subjects were 72.22% and 44.44%, respectively. Mean BMI was 25.67 ± 3.20 kg/m² in Study 1 and 25.92 ± 2.53 kg/m² in Study 2, with mean body weight and height ranging from 71.64 to 75.78 kg and from 166.11 to 172.03 cm, respectively. A total of 34 participants completed Study 1; one participant was excluded because of protocol noncompliance and one withdrew informed consent. All 36 participants completed Study 2.

Table 1
Subject Demographics and Baseline Characteristics

Age (years)		**Study 1**	**Study 2**
		N = 36	**N = 36**
	M ± SD	**31.06 ± 8.13**	**26.75 ± 7.03**
Gender			
- Male	N (%)	26 (72.22%)	16 (44.44%)
- Female	N (%)	10 (27.78%)	20 (55.56%)
Weight (kg)	m ± SD	75.78 ± 9.82	71.64 ± 9.23
Height (cm)	m ± SD	172.03 ± 8.66	166.11 ± 7.13
BMI (kg/m²)	m ± SD	25.67 ± 3.20	25.92 ± 2.53
m: mean; SD: standard deviation			

3.1.2. Pharmacokinetic and Bioavailability Assessments

As presented in Table 2, the apixaban 5 mg pellet formulation showed a bioequivalent rate and extent of exposure to the reference apixaban 5 mg tablet, after oral administration under fasting conditions with 240 ml of water. Specifically, the geometric ratio for C_{max} and AUC_t was 0.87 and 0.92 respectively, with the 90% confidence interval (CI) falling within the pre-defined bioequivalence range of 80–125%. The median T_{max} of apixaban was 3 hours for the apixaban 5 mg pellet formulation compared to 3.50 hours for the reference apixaban 5 mg tablet. These findings demonstrate bioequivalence between the apixaban 5 mg pellet formulation and the reference apixaban 5 mg tablet with respect to both rate and extent of exposure under fasting conditions. In Study 2, administration of the pellet formulation dispersed in yogurt resulted in a geometric mean ratio of 121.36% (90% CI, 113.30%–129.99%) for Cmax and 115.37% (90% CI, 110.14%–120.84%) for AUCt compared with the intact capsule. The median Tmax was 3.25 hours following administration with yogurt and 4.25 hours following administration as an intact capsule. The 90% CI for AUCt was within the conventional 80%–125% range, whereas the upper bound of the 90% CI for Cmax exceeded 125%. For descriptive visualization of the concentration–time profiles across studies, Study 2 concentrations were normalized using the ratio of the geometric mean AUCt for the apixaban capsule in Study 1 and Study 2 (0.8149) to account for the difference in overall exposure between the two study populations. (Fig. 1)

Table 2
PK Parameters and Statistical Analysis of Apixaban in Study 1 and 2

	C_{max} **Mean ± SD** **ng/ml**	**AUC_t** **Mean ± SD** **ng.h/ml**	**T_{max}** **Median (range)** **h**
Study 1 (N = 34)			
Apixaban 5 mg pellet (capsule)	108.76 ± 26.24	1046.76 ± 344.78	3.00 (2.50–4.50)
Apixaban 5 mg tablet	125.50 ± 30.32	1130.07 ± 355.27	3.50 (1.50–4.50)
GMR (90% CI)	86.72 (81.41;92.38)	92.20 (88.56;95.98)	-
Study 2 (N = 36)			
Apixaban 5 mg pellet (capsule)	121.55 ± 27.47	1256.15 ± 272.31	4.25 (2.00–6.00)
Apixaban 5 mg pellet (yogurt)	146.52 ± 30.78	1448.82 ± 322.27	3.25 (1.50–4.50)
GMR (90% CI)	121.36 (113.30;129.99)	115.37 (110.14;120.84)	-
SD: standard deviation; GMR: geometric mean ratio; CI: confidence interval			

3.1.3. Safety

No serious or severe adverse events were reported. No clinically significant differences in vital signs, ECG parameters or laboratory findings were observed between treatments.

3.2. Handling and Dose Recovery Assessment

Opening the capsule containing the apixaban pellet formulation required less preparation time than crushing the reference tablet. Across the nine operators, the mean ± SD preparation time was 33.38 ± 9.78 seconds for tablet crushing compared with 11.22 ± 3.80 seconds for capsule opening, corresponding to a mean reduction of 22.16 seconds and a relative reduction of approximately 66.4%. Operator-specific mean preparation times ranged from 17.0 to 50.2 seconds for tablet crushing (Table 3). When the time required to rinse the mortar and pestle was included in the tablet preparation procedure, the mean preparation time increased to 53.4 ± 10.0 seconds, corresponding to a mean difference of 42.16 seconds and a relative reduction of 78.2% compared with capsule opening (Table 4).

Table 3
Preparation Time following Capsule Opening and Reference-Tablet Crushing without mortar rinsing

Operator	**Apixaban tablet crushing Mean ± SD (s)**	**Apixaban pellet capsule opening Mean ± SD (s)**	**Mean difference (s)**	**Relative Reduction (%)**
A	50.2 ± 7	13.6 ± 2	36.6	72.9
B	42.4 ± 5	11.6 ± 2	30.8	72.6
C	35.2 ± 6	10.0 ± 2	25.2	71.6
D	34.4 ± 4	7.0 ± 1	27.4	79.7
E	30.0 ± 3	9.8 ± 1	20.2	67.3
F	31.8 ± 5	13.6 ± 6	18.2	57.2
G	17.0 ± 3	13.8 ± 6	3.2	18.8
H	28.4 ± 4	13.2 ± 3	15.2	53.5
I	31.0 ± 4	8.4 ± 1	22.6	72.9
Overall mean	33.38 ± 9.8	11.22 ± 3.8	22.2	66.4
S: seconds; SD: standard deviation				

Table 4
Preparation Time following Capsule Opening and Reference-Tablet Crushing with mortar rinsing

Operator	Apixaban tablet crushing Mean ± SD (s)	Apixaban pellet capsule opening Mean ± SD (s)	Mean difference (s)	Relative Reduction (%)
A	70.2 ± 7	13.6 ± 2	56.6	80.6
B	62.4 ± 5	11.6 ± 2	50.8	81.4
C	55.2 ± 6	10.0 ± 2	45.2	81.9
D	54.4 ± 4	7.0 ± 1	47.4	87.1
E	50.0 ± 3	9.8 ± 1	40.2	80.4
F	51.8 ± 5	13.6 ± 6	38.2	73.7
G	37.0 ± 3	13.8 ± 6	23.2	62.7
H	48.4 ± 4	13.2 ± 3	35.2	72.7
I	51.0 ± 4	8.4 ± 1	42.6	83.5
Overall mean	53.4 ± 10	11.2 ± 4	42.16 ± 10	78.2
S: seconds; SD: standard deviation				

Dose-recovery assessment showed a mean ± SD direct recovery of 98.5 ± 2.0% of the nominal apixaban dose following capsule opening and transfer, with individual values ranging from 95.5% to 104.3%. Following tablet crushing and transfer, direct recovery was 96.5 ± 3.0%, with a wider range of 84.7% to 99.4%. Rinsing of the mortar and pestle after tablet crushing recovered an additional 2.2 ± 1.0% of the nominal dose (range, 0.8%–7.1%), whereas apixaban concentrations in the capsule-rinsing solution were below the limit of detection. Total dose recovery was 98.5 ± 2.0% (range, 95.5%–104.3%) following capsule opening and 98.4 ± 3.0% (range, 88.2%–101.9%) following tablet crushing with subsequent equipment rinsing (Table 5).

Table 5
Apixaban Dose Recovery following Capsule Opening and Reference-Tablet Crushing (% of Nominal Dose)

Apixaban Recovery	Tablet			Capsule		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max
Direct recovery after preparation and transfer	96.5 ± 3	84.7	99.4	98.5 ± 2	95.5	104.3
Residual dose recovered by rinsing	2.2 ± 1	0.8	7.1	< LOD	< LOD	< LOD
Total dose recovery	98.4 ± 3	88.2	101.9	98.5 ± 2	95.5	104.3
SD: standard deviation; LOD: limit of detection						

4. Discussion

The present studies evaluated a multiparticulate apixaban formulation designed to facilitate administration in patients who experience difficulty swallowing conventional tablets. Three main findings emerged. First, the pellet formulation was bioequivalent to the reference apixaban 5 mg tablet under fasting conditions. Second, dispersion of the pellets in yogurt maintained the extent of apixaban exposure within the conventional 80%–125% range, although the rate of absorption was increased, as reflected by a higher Cmax and earlier Tmax. Third, capsule opening reduced preparation time compared with tablet crushing and resulted in more consistent direct dose recovery, without measurable residual apixaban in the capsule after rinsing.

Apixaban is widely used for the prevention and treatment of thromboembolic disorders because of its established efficacy and safety profile, with recent evidence further supporting its benefit–risk profile among direct oral anticoagulants.[6] Consequently, reliable administration in populations with swallowing difficulties, particularly older patients, remains clinically relevant. Yogurt administration resulted in faster apixaban absorption, with an approximately 21% higher Cmax and a median Tmax occurring approximately 1 hour earlier (3.25 vs 4.25 hours), while the extent of exposure, based on AUCt, remained within the conventional 80%–125% range. This pattern suggests that dispersion of the pellets in yogurt primarily affected the rate of absorption. This is pharmacologically plausible given that apixaban is predominantly absorbed in the small intestine and has an absolute oral bioavailability of approximately 50%.[7] Although apixaban pharmacodynamic activity is concentration-dependent, with anti-factor Xa activity showing a direct linear relationship with plasma concentrations, available pharmacokinetic and pharmacodynamic data provide context for the magnitude of the observed difference in peak exposure[7–8].

Apixaban has been studied across a range of exposures in single- and multiple-dose studies[9–10], and intrinsic and extrinsic factors may produce exposure changes of a similar magnitude: low body weight

has been associated with approximately 27% higher Cmax and 20% higher AUC, while diltiazem and clarithromycin increased Cmax by approximately 31% and 30%, respectively.[7] Inter-individual demographic differences may also contribute to variability in apixaban exposure across studies. In a dedicated age- and sex-effect study, Frost et al[11] reported Cmax and AUC∞ values approximately 18% and 15% higher, respectively, in female than in male participants, while AUC ∞ was approximately 32% higher in elderly than in younger participants. Despite these pharmacokinetic differences, corresponding differences in maximum mean international normalized ratio (INR), modified prothrombin time (mPT), and anti-factor Xa activity between demographic groups were small (< 15%), and no dose adjustment based on age or sex alone was considered necessary.[11] These findings illustrate that differences in apixaban exposure may occur as a consequence of intrinsic subject-related variability. Differences in demographic characteristics between the two study populations may therefore have contributed to the observed between-study variation in exposure; however, the present studies were not designed to formally evaluate the sources of this between-study variability. Exposure-response analyses provide additional context for the observed Cmax increase. In an analysis of 5,510 participants, Leil et al [12] found a relatively shallow relationship between apixaban exposure and bleeding, with a two-fold increase in exposure predicted to produce a modest increase in bleeding frequency. Moreover, population pharmacokinetic and exposure-response analyses in patients with venous thromboembolism found substantial overlap in AUCss, Cmax, and Cmin between patients with and without bleeding events and identified no clear exposure threshold predictive of bleeding; AUC rather than Cmax was the exposure metric significantly associated with bleeding risk.[7,12] Nevertheless, the present studies were not designed to evaluate clinical outcomes or establish the clinical relevance of the observed increase in Cmax following administration with yogurt. The finding should therefore be interpreted as a pharmacokinetic effect of the administration procedure.

Crushed apixaban tablets have been shown to provide bioequivalent exposure to intact tablets when suspended in water, including after nasogastric administration, whereas administration with applesauce resulted in a modest reduction in exposure that was not considered clinically meaningful.[13] Accordingly, apixaban tablets may be crushed and dispersed in appropriate vehicles. However, these procedures require tablet crushing, transfer, and adequate rinsing to optimize dose recovery. Under routine clinical conditions, variability in crushing techniques and devices may result in drug loss: medication losses of 1.9%–13.3%, and exceeding 40% with inadequate rinsing, have been reported, while underdosing related to powder loss was observed in up to 70% of crushing procedures in geriatric units.[1]

In the present handling assessment, opening the pellet-containing capsule reduced mean preparation time by approximately 66% compared with tablet crushing and by approximately 78% when mortar and pestle rinsing was included in the tablet-preparation procedure. The dose-recovery assessment provided complementary information regarding the two preparation procedures. Direct apixaban recovery was 98.5 ± 2.0% of the nominal dose following capsule opening compared with 96.5 ± 3.0% following tablet crushing, with ranges of 95.5%–104.3% and 84.7%–99.4%, respectively. Following tablet crushing, an additional 2.2 ± 1.0% of the nominal dose was recovered by rinsing the mortar and pestle, whereas

apixaban in the capsule-rinsing solution was below the limit of detection. Total recovery after tablet crushing and rinsing was similar to that observed following capsule opening. These findings indicate that tablet crushing required an additional rinsing step to recover residual drug, whereas direct transfer following capsule opening provided recovery close to the nominal dose without measurable residual apixaban in the capsule. Although preparation time and dose recovery are not clinical efficacy endpoints, these findings characterize practical differences between the two administration procedures that may be relevant when medication preparation is performed by healthcare professionals or caregivers.

The potential advantages of the apixaban pellet formulation may be relevant in geriatric, neurological, stroke rehabilitation, and long-term care settings, where dysphagia is common and reliable administration of anticoagulant therapy is important. However, several limitations should be acknowledged. Both pharmacokinetic studies were conducted after single-dose administration in healthy participants rather than in patients with dysphagia, and the studies were not designed to evaluate clinical efficacy or bleeding outcomes. The clinical relevance of the higher Cmax observed after administration with yogurt therefore cannot be established from these studies. In addition, the handling assessment involved nine operators under controlled conditions and did not assess medication errors, acceptability, palatability, or clinical outcomes in routine care. Further evaluation in patients requiring alternative administration of oral medications would be needed to establish the clinical and practical relevance of these findings.

5. Conclusions

The apixaban pellet formulation demonstrated bioequivalence to the reference apixaban 5 mg tablet when administered as an intact capsule under fasting conditions. Dispersion of the pellets in a small amount of yogurt maintained the extent of systemic exposure within the conventional 80%–125% range, although the rate of absorption was increased, resulting in a higher Cmax and earlier Tmax. The complementary handling assessment showed that capsule opening reduced preparation time compared with tablet crushing and provided more consistent direct dose recovery without measurable residual apixaban in the capsule after rinsing. These findings characterize the pharmacokinetic and administration properties of this multiparticulate formulation and support further evaluation in patients requiring alternative administration of oral medications to establish its clinical and practical utility.

Declarations

Author Contributions: Conceptualization, S.D.N. and M.T.; methodology, S.D.N. and M.T.; investigation, A.K.A.; formal analysis, M.T.; writing—original draft preparation, S.D.N., M.T., A.K.A., B.S. and R.M.; writing—review and editing, J.-M.C. All authors have read and agreed to the submitted version of the manuscript.

Funding: This research was funded by Laboratoires SMB S.A. The funder was involved in the study design, analysis of the data, and preparation of the manuscript through authors who are employees of

Laboratoires SMB S.A.

Institutional Review Board Statement: Study 1 was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Pharmaceutical Research Unit (protocol code APISD241; 6 May 2024). Study 2 was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Pharmaceutical Research Unit (protocol code APISD261; 27 April 2026).

Informed Consent Statement: Informed consent was obtained from all participants involved in the studies.

Data Availability Statement: The raw data supporting the conclusions of this article are available from the corresponding author upon reasonable request.

Competing Interests: S.D.N., M.T. and R.M. are employees of Laboratoires SMB S.A. J.-M.C. serves as a consultant to Laboratoires SMB S.A. The other authors declare no competing interests.

Acknowledgments: During the preparation of this manuscript, the authors used artificial intelligence (AI)-assisted tools for language editing, including spelling and grammar. The authors reviewed and edited the output and take full responsibility for the content of the manuscript.

References

1. Blaszczyk A, Brandt N, Ashley J, Tuders N, Doles H, Stefanacci RG. Crushed tablet administration for patients with dysphagia and enteral feeding: challenges and considerations. Drugs Aging. 2023;40:895-907. doi:10.1007/s40266-023-01056-y
2. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke. 2005;36:2756-2763. doi:10.1161/01.STR.0000190056.76543.eb
3. Fusco S, Cariati D, Schepisi R, et al. Management of oral drug therapy in elderly patients with dysphagia. J Gerontol Geriatr. 2016;64:9-20.
4. Badescu MC, Popescu D, Gosav EM, et al. The use of direct oral anticoagulants (DOACs) in the geriatric population—how to overcome the challenges of geriatric syndromes. J Clin Med. 2025;14:4396. doi:10.3390/jcm14134396
5. Yu N, Yang J, Katas H. Using status of secondary prevention medications in post-stroke dysphagia patients: time to raise awareness and develop special formulations. Sci Rep. 2024;14:15377. doi:10.1038/s41598-024-66407-0
6. Castellucci LA, Chen VM, Kovacs MJ, et al. Bleeding risk with apixaban vs rivaroxaban in acute venous thromboembolism. N Engl J Med. 2026;394:1051-1060. doi:10.1056/NEJMoa2510703
7. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: a clinical pharmacokinetic and pharmacodynamic review. Clin Pharmacokinet. 2019;58:1265-1279. doi:10.1007/s40262-019-00775-z

8. Byon W, Sweeney K, Frost C, Boyd RA. Population pharmacokinetics, pharmacodynamics, and exploratory exposure-response analyses of apixaban in subjects treated for venous thromboembolism. CPT Pharmacometrics Syst Pharmacol. 2017;6:340-349. doi:10.1002/psp4.12184
9. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol. 2013;75:476-487. doi:10.1111/j.1365-2125.2012.04369.x
10. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. Br J Clin Pharmacol. 2013;76:776-786. doi:10.1111/bcp.12106
11. Frost CE, Song Y, Shenker A, et al. Effects of age and sex on the single-dose pharmacokinetics and pharmacodynamics of apixaban. Clin Pharmacokinet. 2015;54:651-662. doi:10.1007/s40262-014-0228-0
12. Leil TA, Frost C, Wang X, Pfister M, LaCreta F. Model-based exposure-response analysis of apixaban to quantify bleeding risk in special populations of subjects undergoing orthopedic surgery. CPT Pharmacometrics Syst Pharmacol. 2014;3:e136. doi:10.1038/psp.2014.34
13. Song Y, Wang X, Perlstein I, et al. Relative bioavailability of apixaban solution or crushed tablet formulations administered by mouth or nasogastric tube in healthy subjects. Clin Ther. 2015;37:1703-1712. doi:10.1016/j.clinthera.2015.05.497

Figures

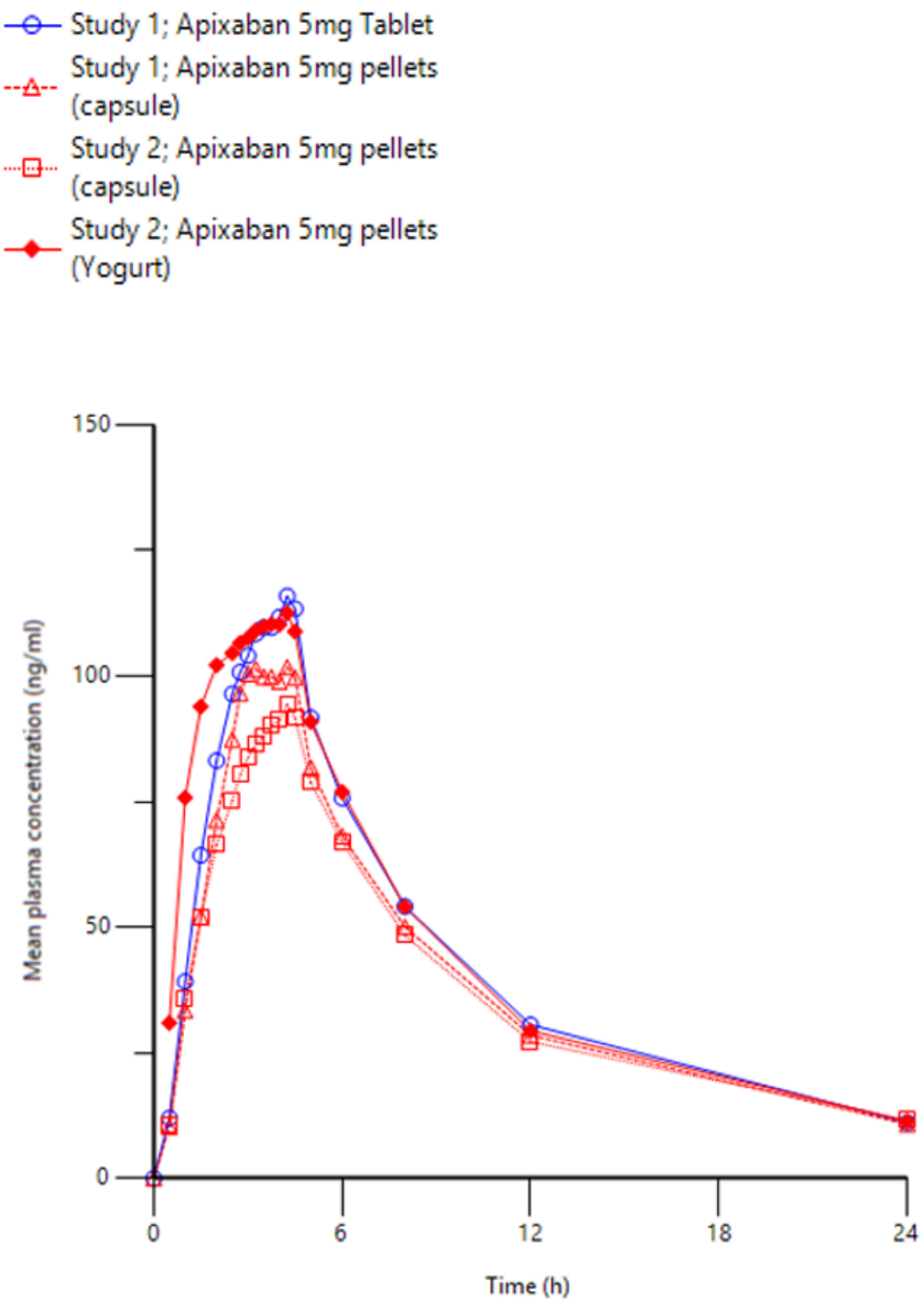


Figure 1

Mean plasma concentration–time profiles of apixaban 5 mg pellet and tablet formulations. For descriptive visualization across studies, Study 2 concentrations were normalized using the ratio of the geometric mean AUCt for the apixaban capsule in Study 1 and Study 2 (0.8149).