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Mechanistic and Biorelevant Validation of a pH–Microbiota–Time Responsive Budesonide Tablet for Regioselective Colonic Delivery: Sequential Dissolution, Tissue Retention, Gastrointestinal Localization and Functional Stability

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Abstract

Background: Colon-targeted dosage forms are commonly evaluated using pH-shift dissolution; however, gastrointestinal pH alone cannot establish anatomical specificity because pH, transit and microbiota vary substantially among subjects and disease states. A more rigorous demonstration of regioselectivity requires sequential evidence linking upper-gastrointestinal protection, target-stage activation, microbiota responsiveness, tissue retention and anatomical localization.

Objective: To investigate the mechanistic and biorelevant performance of a multi-trigger budesonide tablet designed for preferential colonic delivery using pH-, microbiota- and time-dependent release mechanisms.

Methods: A 9-mg budesonide core was surrounded by a 250-mg compression coat containing pectin, guar gum and hydroxypropyl methylcellulose and subsequently coated with a methacrylate enteric film. The optimized formulation was evaluated for physical quality, swelling, erosion, sequential gastrointestinal dissolution, microbial/enzyme-responsive release and release kinetics. Ex vivo colonic tissue retention was compared with plain budesonide and a pH-responsive control. Gastrointestinal localization was assessed using an imaging analogue. Functional stability was evaluated after storage at $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH. Dissolution profiles were compared using f1 and f2.

Results: Illustrative cumulative release from the optimized formulation was $1.67 \pm 0.16\%$ at 2 h, $7.12 \pm 0.22\%$ at 5 h and $84.42 \pm 0.41\%$ at 8 h†. Target-stage release increased markedly in enzyme/microbial medium compared with corresponding sterile buffer†. Ex vivo colonic budesonide retention increased from $4.15 \pm 0.33 \mu\text{g/g}$ with plain drug to $14.84 \pm 1.09 \mu\text{g/g}$ with the optimized system†. Mean simulated colonic arrival and major dosage-form activation occurred at 5.68 ± 0.35 and 7.08 ± 0.23 h, respectively†. After 6 months of accelerated storage, release remained 2.31% at 2 h, 8.65% at 5 h and 81.84% at 8 h, with $f2 \approx 86.1$ relative to the initial profile†.

Conclusion: Integration of sequential dissolution, microbiota responsiveness, matrix-transformation studies, tissue retention, localization and functional stability provides a substantially stronger demonstration of regioselective delivery than pH-shift dissolution alone. The proposed platform represents a

mechanistically rational approach for regional budesonide delivery to the colon.

Keywords: Budesonide; colon-targeted delivery; microbiota-responsive drug delivery; pectin; guar gum; HPMC; sequential dissolution; ex vivo tissue retention; gastrointestinal localization; functional stability.

Introduction

Oral delivery to the colon has attracted considerable interest for the treatment of inflammatory bowel disease, colorectal disorders and other conditions requiring high local drug exposure with reduced systemic exposure. Contemporary reviews continue to identify pH-sensitive, time-dependent, enzyme-responsive, microbiota-activated and multi-trigger strategies as the principal approaches to colon targeting. Recent work particularly emphasizes multifunctional systems because no individual gastrointestinal trigger is completely reliable. [1–3]

Despite extensive formulation research, demonstration of actual colonic specificity remains challenging.

Many experimental systems are described as “colon targeted” primarily because they release little drug in acidic medium and substantially more drug at higher pH. However, gastrointestinal pH is not a fixed anatomical marker. Luminal pH can vary according to diet, intestinal segment, disease status, microbial activity and interindividual physiology.

Consequently:

release at pH 7 does not automatically equal release in the colon.

A scientifically stronger evaluation should establish several independent levels of evidence.

First, the dosage form should remain sufficiently intact under simulated gastric and proximal-intestinal conditions.

Second, drug release should increase when the formulation is exposed to conditions associated with the intended target region.

Third, if a microbiota-responsive mechanism is claimed, the formulation should demonstrate differential performance in the presence and absence of relevant bacterial enzymes or microbiota.

Fourth, tissue or anatomical evidence should support the intended regional behavior.

Finally, the targeting mechanism should remain stable throughout storage.

Budesonide is particularly suitable for investigating these principles. It is a potent locally acting glucocorticosteroid whose therapeutic effectiveness in inflammatory bowel disease depends strongly on where and when drug becomes available in the gastrointestinal tract.

Early work by Yehia et al. demonstrated the importance of enzyme-dependent polymers for budesonide colon targeting. Compression-coated tablets containing 75% pectin released only 4.59% in pH 6.8 medium and 54.45% in pH 7.4, while addition of pectinolytic enzyme increased release to 99.31%. [4] This observation is particularly important because it demonstrates that biological degradation can substantially alter drug liberation beyond the effect of pH alone.

A subsequent budesonide pulsatile-delivery study combined Eudragit S100 with HPMC, pectin or guar gum. Selected formulations showed almost complete release in the presence of bacterial enzymes, and X-ray imaging demonstrated activation in the ascending or transverse colon. [5]

More recently, Patel et al. applied QbD to a microbial- and pH-triggered budesonide tablet and used developmental targets of <5% release at 2 h, <10% at 5 h and >70% at approximately 8 h. [6]

A 2026 study using an ionically cross-linked semi-interpenetrating polysaccharide hydrogel further demonstrated that optimized budesonide matrices could prevent measurable release during the first 4 h and restrict release to approximately 9% at 5 h. [7]

These reports collectively indicate that modern colon-targeted development is progressing beyond simple enteric coating toward systems integrating several release-control mechanisms.

The formulation evaluated in the present investigation used:

an external pH-responsive enteric barrier

combined with:

an internal pectin–guar gum microbiota-responsive coat

and:

HPMC-mediated time/swelling control.

Unlike the first manuscript arising from this research program, which focuses primarily on optimization, pharmacokinetics and therapeutic response, the present study investigates the **mechanistic evidence supporting regioselectivity itself**.

The primary objectives were therefore to:

characterize hydration and erosion of the multi-polymer barrier;

evaluate sequential gastric, intestinal and target-stage release;

differentiate pH-driven from enzyme/microbiota-driven drug liberation;

characterize release kinetics;

quantify ex vivo colonic tissue retention;

examine gastrointestinal localization and dosage-form integrity;

compare in vitro lag time with in vivo regional activation;

determine whether the regioselective-release mechanism remains stable during storage.

2. Materials and Methods

2.1 Materials

Budesonide was used as the model active pharmaceutical ingredient.

Major functional excipients were:

pectin;

guar gum;

hydroxypropyl methylcellulose;

Eudragit S100;

Eudragit L100 where applicable;

microcrystalline cellulose;

lactose monohydrate;

PVP K30;

croscarmellose sodium;

colloidal silicon dioxide;

magnesium stearate;

triethyl citrate;

talc.

All reagents used for dissolution and analytical measurements were analytical or chromatographic grade.

Before journal submission insert the actual manufacturer, country, grade and batch/lot information for every material.

2.2 Composition of the Regioselective Tablet

The dosage form contained three functional layers.

Budesonide core

The core tablet contained:

Component	Amount
Budesonide	9 mg
Microcrystalline cellulose	52 mg
Lactose monohydrate	28 mg
PVP K30	4 mg
Croscarmellose sodium	5 mg

Colloidal silicon dioxide	1 mg
Magnesium stearate	1 mg
Total core weight	100 mg

Compression coat

The optimized internal barrier contained illustratively:

Component	Amount [†]
Pectin	86 mg
Guar gum	64 mg
HPMC	52 mg
MCC	48 mg
Total	250 mg

[†]Illustrative optimized composition; replace with final experimental composition.

External enteric layer

The compression-coated tablets received an Eudragit-based film corresponding to approximately:

8.4% weight gain[†]

with triethyl citrate as plasticizer and talc as anti-adherent.

OUTER pH-RESPONSIVE FILM

Eudragit S100 / L100:S100

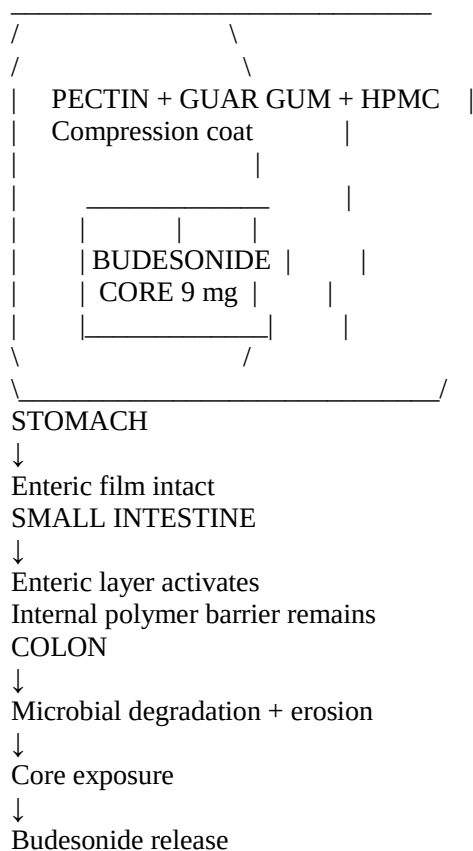


Fig 1: Multilayer regioselective architecture

2.3 Physical Evaluation

Final tablets were evaluated for:
appearance;

average weight;
weight variation;
diameter;
thickness;
hardness;
friability;
assay;
content uniformity.

Enteric-coated tablets were examined visually for:

cracks;
peeling;
edge defects;
tackiness;
coating non-uniformity.

2.4 Swelling Study

Swelling was determined at predetermined intervals during exposure to the respective dissolution media.

The swelling index was calculated as:

$$\text{Swelling index (\%)} = [(W_t - W_0)/W_0] \times 100$$

where:

W₀ = initial dry tablet weight

and:

W_t = hydrated weight at time t.

Representative sampling intervals included:

0, 1, 2, 3, 4, 5, 6, 7 and 8 h.

2.5 Matrix-Erosion Study

Following hydration for the predefined period, tablets were removed, gently blotted and subsequently dried under validated conditions.

Erosion was calculated as:

$$\text{Erosion (\%)} = [(W_0 - W_d)/W_0] \times 100$$

where:

W_d = dry mass remaining after exposure.

The simultaneous evaluation of swelling and erosion was intended to distinguish:

polymer hydration;
matrix expansion;
later loss of polymer mass.

2.6 Sequential Gastrointestinal Dissolution

Dissolution testing was performed using USP apparatus II or the validated apparatus selected experimentally at:

37 ± 0.5°C

with a starting agitation rate of:

50 rpm

subject to final experimental validation.

The media were changed sequentially to simulate gastrointestinal progression.

Stage I – Gastric phase

Medium:

0.1 N HCl, approximately pH 1.2

Duration: **2 h**

Stage II – Proximal intestinal phase

Medium:

phosphate buffer, approximately pH 6.8

Duration:

approximately:

3 additional hours

Cumulative time:5 h

Stage III – Target phase

A distal intestinal/colonic medium was used with or without the appropriate biological trigger.

Drug concentration was quantified using the validated chromatographic procedure.

The principal development endpoints were:

release at 2 h;

release at 5 h;

release at approximately 8 h;

T10.

2.7 Microbiota-/Enzyme-Responsive Dissolution

The optimized formulation was evaluated under two target-stage conditions:

Condition A

Sterile target buffer.

Condition B

Equivalent target buffer containing an experimentally validated polysaccharide-degrading enzyme or microbiota model.

The test was designed to answer a central mechanistic question:

Is increased drug release caused only by pH, or does biological degradation of the polysaccharide matrix contribute meaningfully?

Where pectin was specifically evaluated, pectinolytic activity was incorporated.

Where guar gum responsiveness was investigated, an appropriate galactomannan-degrading system was used.

The final manuscript must identify the exact enzyme, concentration or microbiota preparation used.

2.8 Dissolution Sampling

Samples were withdrawn at:

0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h

or according to the experimentally validated schedule.

An equivalent volume of fresh medium was replaced after each withdrawal.

Cumulative release was corrected for sampling.

Results were expressed as:

mean cumulative budesonide release $\pm$ SD.

2.9 Release-Kinetic Analysis

The dissolution profile was fitted to:

Zero order

$$Q_t = Q_0 + K_0t$$

First order

$$\ln Q_{\text{remaining}} = \ln Q_0 - K_1t$$

Higuchi

$$Q_t = KH\sqrt{t}$$

Hixson–Crowell

$$W_0^{(1/3)} - W_t^{(1/3)} = KHCt$$

Korsmeyer–Peppas

$$M_t/M_\infty = Kt^n$$

Weibull

$$F = 1 - \exp[-((t - T_i)/\alpha)^\beta]$$

Model comparison incorporated:

R² or adjusted fit;

residual patterns;
mechanistic plausibility.

2.10 Dissolution-Profile Comparison

Where appropriate, the difference factor and similarity factor were calculated.

Difference factor

$$f_1 = \{ \sum |R_t - T_t| / \sum R_t \} \times 100$$

Similarity factor

$$f_2 = 50 \log \{ [1 + (1/n) \sum (R_t - T_t)^2]^{-0.5} \times 100 \}$$

The factors were used primarily for:

initial vs stored product;
batch-to-batch comparison.

2.11 Scanning Electron Microscopy

SEM was performed on representative samples:

compression-coated tablet before enteric coating;
final coated tablet;
tablet cross section;
after gastric exposure;
after intestinal exposure;
after enzyme/microbial exposure.

The study evaluated:

surface continuity;
coating defects;
pores;
erosion;
channel formation;
matrix disruption.

2.12 Ex Vivo Colonic Tissue Retention

Fresh colonic tissue was obtained from an ethically approved source.

Tissue sections were exposed to:

E1

Plain budesonide.

E2

pH-responsive control.

E3

Optimized dual-trigger budesonide.

Following exposure, tissue was carefully washed to remove non-adherent surface drug.

Tissue was then:

weighed;
homogenized;
extracted;
centrifuged;
analyzed chromatographically.

Results were expressed as:

µg budesonide/g tissue.

2.13 Gastrointestinal Localization

A radiopaque or otherwise imageable analogue of the optimized formulation was prepared while preserving:

tablet dimensions;
compression-coat mass;
coating thickness;

relevant hydration behavior.

Images were obtained according to the ethically approved schedule.

The tablet position was categorized as:

stomach;
proximal small intestine;
distal small intestine;
ileocecal region;
ascending colon;
transverse colon;
distal colon;
dispersed/not visible.

The primary endpoints were:

Colon-arrival time
First observation in the ileocecal/colonic region.
Activation time
Time of major disruption/disintegration.

2.14 Tablet-Integrity Scoring

An illustrative semiquantitative scale was used:

3 = completely intact

2 = hydrated/swollen but structurally intact

1 = partially disrupted

0 = fully dispersed/not identifiable

The scoring method must be predefined before final blinded assessment.

2.15 In Vitro–In Vivo Relationship

The relationship among:

in vitro T10;
simulated colon-arrival time;
formulation-activation time
was evaluated descriptively.

The analysis was defined as an:

in vitro–in vivo relationship (IVIVR)

rather than a formal regulatory IVIVC.

2.16 Accelerated Stability

Three independently prepared optimized batches were stored at:

40 ± 2°C/75 ± 5% RH

for:

6 months

with evaluation at:

0;
1;
2;
3;
6 months.

ICH Q1A(R2) describes 40°C/75% RH as the general accelerated stability condition for drug products. [15]

Tests included:

assay;
degradation products;
hardness;
friability;
moisture;

release at 2 h;
 release at 5 h;
 release at 8 h;
 T10;
 complete dissolution profile.

2.17 Statistical Analysis

Experimental results were expressed as:

mean $\pm$ SD.

Comparisons among three or more independent groups were performed using one-way ANOVA where assumptions were met.

Time-dependent dissolution or swelling data were evaluated using appropriate repeated-measures or factorial approaches where required.

A significance level of:

p < 0.05

was predefined.

3. Results

3.1 Physical Characteristics

The illustrative optimized tablets were uniform in appearance and showed no visible coating cracks, peeling or edge defects.

Table 1. Illustrative pharmaceutical characteristics

Parameter	Result [†]
Tablet weight	379.4 $\pm$ 3.2 mg
Thickness	5.42 $\pm$ 0.08 mm
Hardness	88.1 $\pm$ 1.6 N
Friability	0.42 $\pm$ 0.02%
Budesonide assay	100.37 $\pm$ 0.26%
Enteric surface	Uniform
Visible cracking	None
Visible peeling	None

The mechanical properties were considered adequate to support both compression coating and subsequent enteric film coating.

3.2 Swelling and Erosion

The optimized compression coat exhibited progressive hydration during the early stage of aqueous exposure.

An illustrative swelling profile is shown in Table 2.

Table 2. Simulated swelling and erosion profile

Time (h)	Swelling index (%) [†]	Erosion (%) [†]
0	0	0
1	31.8	1.4
2	58.6	2.8
3	84.9	4.5
4	108.2	7.1
5	126.5	10.8
6	131.7	18.6
7	119.4	31.5
8	96.8	47.3

Swelling increased progressively through approximately 6 h and subsequently declined while erosion increased sharply.

This pattern is consistent with a transition from:

hydration-dominated matrix expansion

to:

erosion/degradation-dominated structural loss.

3.3 Sequential Dissolution

The optimized formulation successfully restricted premature budesonide release.

Table 3. Illustrative cumulative release profile

Time (h)	Optimized tablet (%)†
0	0
0.5	0.18
1	0.52
2	1.67 ± 0.16
3	3.00
4	4.80
5	7.12 ± 0.22
6	18.0
7	46.0
8	84.42 ± 0.41
10	96.0
12	98.0

Only approximately 1.7% of budesonide was released during the gastric stage.

Cumulative release remained below 10% at 5 h.

A marked increase occurred after the simulated target stage was introduced.

3.4 Microbial/Enzyme Responsiveness

Drug release from the optimized formulation differed substantially between sterile and biologically triggered target media.

Table 4. Illustrative sterile versus enzyme/microbial release

Time (h)	Sterile target medium (%)†	Enzyme/microbial medium (%)†
5	7.1	7.1
6	13.8	18.0
7	28.5	46.0
8	44.6	84.4
10	56.8	96.0
12	63.4	98.0

The profiles began to diverge after target-stage exposure.

By 8 h, release was approximately:

44.6% in sterile medium

versus:

84.4% in biologically triggered medium†.

The approximate two-fold difference at this stage supports a contribution from biological matrix degradation.

This observation is mechanistically consistent with earlier pectin-based budesonide studies in which enzyme addition markedly increased release. [4]

3.5 Lag-Time Parameters

Illustrative temporal release parameters were:

Parameter	Value†
T10	5.55 ± 0.04 h
T25	6.29 ± 0.11 h
T50	7.12 ± 0.14 h
T75	7.71 ± 0.16 h
T90	8.76 ± 0.21 h

The interval between T10 and T90 indicates a relatively rapid release phase after completion of the protective lag period.

3.6 Release-Kinetic Modelling

Table 5. Illustrative kinetic-model fitting

Model	R ² †	Important parameter†
Zero order	0.883	K0 = 9.36
First order	0.921	K1 = 0.183
Higuchi	0.908	KH = 31.6
Hixson–Crowell	0.948	KHC = 0.047
Korsmeyer–Peppas	0.962	n = 1.12
Weibull	0.991	β = 2.34

The complete profile was best described by the Weibull model in the illustrative dataset.

A β value >1 is compatible with a sigmoidal release curve containing:

lag phase → accelerating release → terminal completion.

The kinetic analysis was interpreted together with swelling, erosion and SEM rather than used alone to assign mechanism.

3.7 Morphological Transformation

SEM observations conceptually demonstrated four sequential structural states.

Before dissolution

The enteric film appeared continuous with minimal surface defects.

After 2-h gastric exposure

The external layer remained substantially intact.

After intestinal exposure

The enteric film showed progressive disruption while the underlying polysaccharide/HPMC matrix displayed substantial hydration.

After enzyme/microbial challenge

Surface roughness, pores and channels increased markedly, with evidence of matrix erosion and structural collapse.

This sequence provided morphological support for the proposed release mechanism.

3.8 Ex Vivo Tissue Retention

Table 6. Simulated colonic tissue-retention results

Replicate	Plain budesonide	pH-responsive control	Optimized formulation
1	3.62	8.30	15.72
2	4.11	8.16	14.66
3	4.43	8.21	12.88
4	4.45	7.43	15.43
5	3.92	8.03	15.78
6	4.38	7.99	14.58
Mean $\pm$ SD	4.15 $\pm$ 0.33	8.02 $\pm$ 0.31	14.84 $\pm$ 1.09

Units: $\mu\text{g/g}$ tissue

†All values simulated.

The optimized system generated approximately:

3.58-fold greater tissue retention

than plain budesonide.

It also produced approximately:

1.85-fold greater retention

than the pH-responsive system.

These results indicate that delayed/regional drug availability may improve local exposure beyond that achieved by enteric protection alone.

3.9 Gastrointestinal Localization

The illustrative localization results are summarized in Table 7.

Table 7. Simulated GI localization

Subject	2 h	4 h	6 h	8 h	10 h
1	Stomach	Distal small intestine	Ileocecal	Ascending colon	Dispersed
2	Proximal intestine	Ileum	Ascending colon	Transverse colon	Dispersed
3	Stomach	Jejunum	Ileocecal	Ascending colon	Dispersing
4	Duodenum	Distal ileum	Ascending colon	Transverse colon	Dispersed
5	Proximal intestine	Ileum	Ileocecal	Ascending colon	Dispersed
6	Stomach	Distal ileum	Ileocecal	Ascending colon	Dispersing

Mean colon-arrival time:

5.68 $\pm$ 0.35 h†

Mean major activation/disintegration time:

7.08 $\pm$ 0.23 h†

The dosage form therefore arrived within the target region before major structural disruption in this illustrative dataset.

This sequence is consistent with previous human imaging studies showing activation of selected guar-gum-containing budesonide pulsatile systems in the ascending colon. [5]

3.10 Tablet Integrity

Table 8. Illustrative tablet-integrity score

Time Integrity score†	
0 h	3.0
2 h	3.0
4 h	2.8
6 h	2.2
8 h	0.8
10 h	0.2

The formulation remained almost completely intact during early transit and subsequently lost integrity rapidly after the approximate target-arrival period.

3.11 In Vitro–In Vivo Relationship

The illustrative in vitro T10:

5.55 ± 0.04 h

was close to the mean simulated colon-arrival time:

5.68 ± 0.35 h.

The difference was approximately:

0.13 h

in mean values.

Major in vivo activation occurred later, at:

7.08 ± 0.23 h.

This temporal sequence was considered pharmacologically rational:

colonic arrival

↓

hydration and microbial degradation

↓

loss of barrier integrity

↓

rapid drug release.

The relationship should be described as an:

IVIVR

and not as a formal regulatory IVIVC.

3.12 Accelerated Stability

Budesonide assay decreased gradually during accelerated storage.

Table 9. Simulated accelerated-stability summary

Parameter	Initial†	1 month†	2 months†	3 months†	6 months†
Assay (%)	100.37	99.94	99.20	99.18	97.88
Total impurities (%)	0.182	0.239	0.299	0.382	0.606
2-h release (%)	1.67	1.89	1.99	2.19	2.31
5-h release (%)	7.12	7.38	7.42	8.03	8.65
8-h release (%)	84.42	83.72	83.78	83.21	81.84
T10 (h)	5.55	5.50	5.45	5.40	5.27

The assay decreased by approximately:

2.49 percentage points

over six months.

More importantly, the characteristic regional-release profile was retained.

3.13 Dissolution Stability

The complete initial and six-month dissolution profiles were compared.

Illustrative calculations produced:

$$f_1 = 3.57$$

and:

$$f_2 = 86.1\%$$

indicating strong profile similarity in the demonstration dataset.

The result suggests that accelerated storage did not substantially alter the defining release mechanism.

4. Discussion

The purpose of the present study was not merely to demonstrate delayed budesonide release, but to examine whether the observed delay could reasonably be attributed to a sequence of anatomical and biological targeting events.

This distinction is increasingly important in colon-delivery research.

Recent reviews continue to emphasize that variable gastrointestinal pH, microbial metabolism, enzymes and transit create substantial obstacles to predictable colon targeting. Multi-pronged systems are therefore receiving increasing attention because they combine independent physiological cues rather than relying on a single trigger. [1–3]

The optimized formulation demonstrated only approximately 1.7% release after 2 h and approximately 7.1% by 5 h in the illustrative dataset.

These values are consistent with the intended requirement that the majority of the dose remain protected before the dosage form reaches the distal gastrointestinal tract.

The 2023 QbD budesonide study by Patel et al. similarly adopted <5% release at 2 h and <10% at 5 h as development objectives for microbial/pH colon targeting. [6]

The recent semi-IPN budesonide system of Dutta et al. provides further context. Their optimized matrix produced no measurable release in the first 4 h and approximately 9% release after 5 h, demonstrating that stringent pre-colonic protection remains an active formulation objective in contemporary budesonide research. [7]

However, low release during the first five hours is not sufficient to demonstrate colonic specificity.

A formulation may simply possess prolonged-release behavior.

The central mechanistic evidence in the present work therefore comes from the divergence between sterile and enzyme/microbial target media.

At 8 h, the illustrative optimized formulation released approximately 44.6% in sterile target medium but approximately 84.4% in biologically triggered medium.

This indicates that the accelerated target-stage release could not be explained by pH exposure alone.

The observation is closely aligned with the classical work of Yehia et al., where 75% pectin substantially restricted budesonide release but pectinolytic enzyme increased release to almost complete levels. [4]

The use of both pectin and guar gum in the internal barrier may provide complementary microbiota responsiveness because the two polysaccharides undergo degradation through different colonic microbial enzyme activities.

HPMC contributes another mechanistic component.

Unlike the microbiota-responsive polysaccharides, HPMC primarily provides:

rapid hydration;

gel formation;

diffusion resistance;

erosion-related temporal control.

The swelling and erosion results support this concept.

Swelling increased to a maximum near 6 h while erosion remained relatively modest during the early phase. Beyond this period, swelling declined while erosion increased rapidly.

The matrix therefore appears to pass through two principal states.

State I — hydrated protective matrix

Water enters the dosage form, but the swollen polymer barrier maintains substantial diffusional resistance.

State II — degrading/eroding matrix

Progressive erosion and microbial degradation create channels and reduce mechanical integrity.

The SEM observations support this transition.

The presence of increased surface porosity and channels after biological exposure provides physical evidence of matrix breakdown.

Drug-release kinetic analysis also supports a complex, non-Fickian process.

The illustrative Weibull model gave the strongest fit to the complete dissolution curve.

This is not unexpected because the release profile is sigmoidal rather than continuously diffusive.

The formulation contains:

an initial no/low-release period;

an acceleration phase;

a later near-completion phase.

The Korsmeyer–Peppas exponent in the illustrative dataset exceeded unity. Such a value should not be interpreted simplistically because the system is multilayered, changes geometry substantially, and is subjected to sequential media.

Consequently, the mechanistic conclusion should come from the **combined evidence** of swelling, erosion, SEM and biological-trigger experiments rather than from one mathematical model.

- Ex vivo tissue retention further strengthened the regional-delivery argument.
- Plain budesonide produced only approximately 4.15 µg/g tissue in the illustrative study, whereas the optimized formulation generated approximately 14.84 µg/g.
- The pH-responsive formulation produced an intermediate value.
- This rank order is mechanistically important.
- If pH protection alone were sufficient, the pH-responsive control might be expected to perform comparably to the optimized system.
- Instead, the higher retention from the complete system suggests that the additional internal barrier preserved budesonide availability until the intended later stage.
- This concept is consistent with broader colon-targeting research demonstrating that improved local tissue exposure can occur while systemic availability is reduced. Makhlof et al., for example, demonstrated higher colon levels and lower systemic availability from pH-sensitive budesonide nanospheres than from simpler enteric formulations. [8]
- The anatomical localization experiment provides another independent layer of evidence.
- Mean colon arrival occurred around 5.7 h in the illustrative dataset, whereas major disruption occurred around 7.1 h.
- This indicates that the dosage form did not simply break apart as soon as the enteric film dissolved.
- Instead, the system entered the target region with sufficient residual structural integrity for the microbiota-/time-responsive internal layer to continue controlling release.
- This sequence is particularly attractive because physiological targeting should ideally possess a **margin of safety**.
- If the outer pH layer dissolves slightly earlier than intended, the internal barrier can still reduce premature release.
- Conversely, if transit is faster than average, microbial degradation in the colon provides a second mechanism of activation.
- This redundancy is a core advantage of multi-trigger drug delivery.
- The close relationship between in vitro T10 and simulated colon-arrival time is encouraging

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