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Development of a Dual-Trigger pH- and Microbiota-Responsive Budesonide Tablet for Regioselective Colonic Delivery: In Vitro, Pharmacokinetic and Pharmacodynamic Evaluation

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Abstract

Background: Site-specific oral therapy of inflammatory bowel disease is limited by physiological variability in gastrointestinal pH, transit and luminal conditions. Budesonide is a potent locally acting glucocorticosteroid whose extensive first-pass metabolism makes it particularly suitable for regional gastrointestinal delivery. Current extended-release budesonide is clinically used at 9 mg once daily for induction of remission in mild-to-moderate ulcerative colitis, supporting the therapeutic relevance of formulation-controlled colonic delivery. [1]

Objective: To develop and comprehensively evaluate a Quality-by-Design-optimized, pH- and microbiota-responsive budesonide tablet for preferential colonic delivery.

Methods: A 9-mg budesonide core was surrounded by a compression coat comprising pectin, guar gum and hydroxypropyl methylcellulose (HPMC) and subsequently coated with a pH-responsive methacrylate polymer. A three-factor Box–Behnken design evaluated the effects of pectin/guar-gum composition, HPMC amount and enteric-coating weight gain. Critical responses were drug release at 2, 5 and 8 h and T₁₀. The optimized formulation underwent physicochemical characterization, sequential gastrointestinal dissolution, microbial/enzyme-triggered release, ex vivo tissue-retention assessment, gastrointestinal localization, pharmacokinetic and tissue-distribution studies, experimental-colitis pharmacodynamics, systemic safety assessment and stability testing.

Results: The illustrative optimized composition contained budesonide 9 mg, pectin 86 mg, guar gum 64 mg and HPMC 52 mg with 8.4% enteric-coating weight gain. Drug release 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†. The optimized system demonstrated delayed systemic exposure (C_{max} 0.761 ± 0.051 ng/mL; T_{max} 8 h†) compared with plain budesonide (C_{max} 1.374 ± 0.104 ng/mL; T_{max} 1 h†), while simulated colonic tissue concentration increased approximately 5.5-fold. Disease Activity Index, MPO, TNF- α , IL-1 β , IL-6, oxidative-stress indices and histopathological damage were markedly improved in the optimized-treatment group†. Simulated corticosterone suppression decreased from 41.2% with plain budesonide to 11.4% with the optimized formulation. After 6 months at 40°C/75% RH, assay remained 97.88% and the dissolution profile remained similar to initial testing

($f_2 \approx 86.1$)[†].

Conclusion: The multi-trigger system provides a mechanistically coherent approach to preferential colonic budesonide delivery. Integration of pH protection, microbiota-responsive polysaccharides and time-dependent matrix control has the potential to increase local therapeutic exposure while reducing systemic corticosteroid burden.

Keywords: Budesonide; colon-targeted drug delivery; regioselective drug delivery; pectin; guar gum; HPMC; Eudragit; Quality by Design; Box–Behnken design; inflammatory bowel disease.

1. Introduction

Inflammatory bowel disease is characterized by chronic or recurrent inflammation of the gastrointestinal tract. In ulcerative colitis, inflammatory pathology is predominantly localized to the colon, making regional delivery particularly attractive. Conventional oral corticosteroid therapy can suppress inflammation effectively, but systemic glucocorticoid exposure is associated with clinically important adverse effects.

Budesonide is a synthetic glucocorticosteroid with strong local anti-inflammatory activity and extensive first-pass metabolism. Extended-release budesonide tablets are currently indicated for induction of remission in adults with active mild-to-moderate ulcerative colitis at a dose of 9 mg once daily. [1] This pharmacological profile provides a compelling rationale for maximizing drug exposure within diseased colonic tissue rather than maximizing systemic bioavailability.

However, reliable colon targeting remains technically challenging. pH-sensitive delivery systems exploit regional changes in gastrointestinal pH, but pH varies substantially among individuals and may be altered by disease. Dependence on a single pH trigger can therefore produce variable release. Dual-sensitive approaches have been investigated to overcome this limitation. Naeem et al. demonstrated that enzyme/pH-responsive budesonide nanoparticles accumulated preferentially in inflamed colon, reduced plasma exposure and produced superior suppression of experimental colitis compared with a single pH-triggered system. [5] Dual pH/time-dependent budesonide nanoparticles have also demonstrated improved colonic localization and therapeutic performance compared with single-trigger particles. [6]

Natural polysaccharides provide a complementary biological targeting mechanism because they are relatively resistant to digestion in the proximal gastrointestinal tract but are susceptible to bacterial degradation within the colon. Yehia et al. reported that increasing pectin content in budesonide compression-coated tablets markedly restricted release in buffer, whereas pectinolytic enzyme increased drug release to approximately complete levels. [2] A subsequent study demonstrated bacterial-enzyme-responsive release of budesonide from pectin- and guar-gum-based systems and radiographic activation in the ascending or transverse colon. [3]

Quality by Design provides a systematic means of understanding how formulation and process variables influence critical product attributes. ICH Q8(R2) emphasizes scientifically based pharmaceutical development, risk assessment and multivariate understanding of material and process variables. [11] More recently, Patel et al. used a Box–Behnken design to optimize a microbial- and pH-triggered budesonide tablet and defined developmental objectives of <5% release at 2 h, <10% at 5 h and >70% by 8 h. [4]

The present study therefore aimed to develop an integrated multi-trigger budesonide platform in which an external pH-responsive barrier protects the dosage form during upper gastrointestinal transit, an internal pectin–guar gum matrix provides microbiota responsiveness, and HPMC supplies additional time- and swelling-dependent control.

The central hypothesis was that such an architecture could produce preferential colonic release, increase local tissue drug concentration, improve anti-inflammatory activity and reduce unnecessary systemic corticosteroid exposure.

2. Materials and Methods

2.1 Materials

Budesonide was used as the model active pharmaceutical ingredient. Pectin and guar gum were selected as microbiota-responsive polysaccharides, HPMC as a hydrophilic time-dependent matrix polymer and Eudragit S100 as the principal enteric polymer. Microcrystalline cellulose, lactose monohydrate, povidone K30, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, triethyl citrate and talc were of pharmaceutical grade.

HPLC- and LC–MS/MS-grade solvents and analytical-grade reagents were used throughout.

Before submission insert: manufacturer, country, grade and batch number for every API, polymer and analytical reagent.

2.2 Formulation Design

The regioselective system contained three functional regions:

Core tablet

The 100-mg core contained:

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

The drug was incorporated using geometric dilution followed by a validated granulation/compression process.

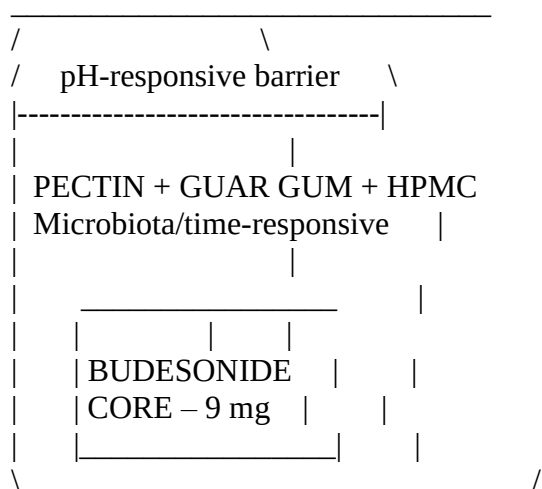
Compression coat

A 250-mg compression layer containing pectin, guar gum, HPMC and MCC was placed around the budesonide core.

Enteric film

The compression-coated tablets were coated with Eudragit S100 using triethyl citrate as plasticizer and talc as anti-adherent.

EUDRAGIT ENTERIC FILM



STOMACH → film intact → minimal release

SMALL INTESTINE → enteric activation → polysaccharide/HPMC barrier remains protective

COLON → bacterial degradation + swelling + erosion → core exposure → budesonide release

Fig 1: Proposed architecture and mechanism

2.3 Quality Target Product Profile and Risk Assessment

The target was an orally administered 9-mg budesonide tablet providing minimal gastric/proximal intestinal release followed by substantial colonic-stage release.

The primary CQAs were:
 content uniformity;
 acid resistance;
 drug release at 2 h;
 drug release at 5 h;
 target-stage drug release;
 T10;
 film integrity.

Risk assessment identified natural-polymer composition, HPMC content, enteric-coating weight gain, compression force and coating conditions as potentially critical.

2.4 Box–Behnken Experimental Design

Three factors were selected for optimization.

X1 — Pectin fraction within a fixed 150-mg pectin + guar-gum mixture

Low: pectin 37.5 mg / guar gum 112.5 mg
 Medium: 75/75 mg
 High: 112.5/37.5 mg

X2 — HPMC quantity

25 mg
 50 mg
 75 mg

MCC was adjusted to maintain total compression-coat weight at 250 mg.

X3 — Enteric-coating weight gain

6%
 8%
 10%

A 17-run Box–Behnken design with five center-point replicates was employed.

Responses were:

Y1: % drug release at 2 h — minimize

Y2: % release at 5 h — minimize

Y3: % release at 8 h — maximize

Y4: T10 — target

The quadratic model was:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{11}X_1^2 + \beta_{22}X_2^2 + \beta_{33}X_3^2$$

ANOVA, lack-of-fit assessment, adjusted/predicted R^2 , contour plots, three-dimensional response surfaces and desirability analysis were used.

Table 1. Experimental formulation variables and illustrative optimized composition

Variable/component	Low	Medium	High	Illustrative optimum†
Pectin (mg)	37.5	75.0	112.5	86
Guar gum (mg)	112.5	75.0	37.5	64
HPMC (mg)	25	50	75	52
MCC in coat (mg)	75	50	25	48
Enteric coating gain (%)	6	8	10	8.4
Budesonide core	—	—	—	9 mg drug/100 mg core
Compression coat	—	—	—	250 mg
Desirability	—	—	—	0.947†

†Simulated planning result.

2.5 Physicochemical Characterization

Tablet weight, thickness, hardness, friability, assay and content uniformity were determined using applicable pharmacopoeial methods.

Drug–excipient interaction and solid-state characteristics were investigated using:

FTIR spectroscopy;

differential scanning calorimetry;

powder X-ray diffraction;

scanning electron microscopy.

Swelling index was calculated as:

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

Matrix erosion was determined from the change in dried tablet mass after predetermined hydration intervals.

2.6 Sequential Dissolution

Sequential dissolution was performed at $37 \pm 0.5^\circ\text{C}$.

The study comprised:

0–2 h: simulated gastric medium, approximately pH 1.2;

2–5 h: simulated intestinal medium, approximately pH 6.8;

after 5 h: distal intestinal/colonic medium.

Samples were analyzed using the validated chromatographic procedure.

Microbiota responsiveness was investigated by comparing equivalent target-stage media:

sterile buffer;

buffer containing a validated polysaccharide-degrading enzyme/microbial model.

The developmental release criteria were based on earlier budesonide QbD work: <5% at 2 h, <10% at 5 h and >70% at approximately 8 h. [4]

2.7 Release Kinetics

Release profiles were fitted to:

zero-order;

first-order;

Higuchi;

Hixson–Crowell;

Korsmeyer–Peppas;

Weibull models.

Model interpretation incorporated goodness of fit together with swelling, erosion and SEM findings.

2.8 Ex Vivo Tissue Retention and Gastrointestinal Localization

Excised colonic tissue was exposed to plain budesonide, a pH-responsive formulation or the optimized dual-trigger formulation.

After exposure, tissue was washed, weighed, homogenized and extracted. Budesonide concentration was expressed as $\mu\text{g/g}$ tissue.

Gastrointestinal localization was assessed using an ethically approved imaging analogue of the optimized dosage form.

The main outcomes were:

colon-arrival time;

dosage-form integrity;

activation/disintegration time.

Before submission insert exact imaging marker, species/participants, ethics approval and schedule.

2.9 Pharmacokinetic and Tissue-Distribution Study

Plasma budesonide was determined by LC–MS/MS.

Published methods demonstrate that budesonide can be quantified sensitively using tandem mass spectrometry; Wang et al. validated an assay over 0.1–10 ng/mL. [9]

Samples were obtained at predetermined intervals through 24 h.

Noncompartmental parameters included:

C_{max};

T_{max};

AUC_{0–24};

AUC_{0–∞};

terminal elimination constant λ_z ;

$t_{1/2}$;

MRT.

AUC was calculated by the trapezoidal method:

$$\text{AUC}_{t_1-t_2} = [(C_1 + C_2)/2](t_2 - t_1)$$

Terminal half-life:

$$t_{1/2} = 0.693/\lambda_z$$

Mean residence time:

$$\text{MRT} = \text{AUMC}/\text{AUC}$$

Budesonide concentrations were also determined in stomach, small intestine, colon and liver.

Colon selectivity was expressed as:

Colon/Small-intestine concentration ratio

and:

Colon/Liver concentration ratio.

2.10 Pharmacodynamic Evaluation

Experimental colitis was induced according to an institutionally approved protocol.

Five groups were used:

normal control;

disease control;

plain budesonide;

delayed-/extended-release comparator;

optimized regioselective budesonide.

Before submission insert actual animal species, n, TNBS/DSS protocol, drug dose, treatment schedule and ethics approval number.

Disease Activity Index was calculated from:

body-weight loss;

stool consistency;

bleeding.

Terminal assessments included:

colon length;

colon weight/length ratio;

macroscopic damage;

myeloperoxidase;

TNF- α ;

IL-1 β ;

IL-6;

MDA;

GSH;

SOD;

catalase;

histopathological score.

Targeted budesonide delivery has previously shown improved therapeutic efficacy in TNBS-induced colitis and increased localization in inflamed colonic tissue. [7,8]

2.11 Systemic Safety

Systemic glucocorticoid exposure was assessed using:

serum corticosterone;

ACTH;

glucose;

adrenal and thymus weights;

hematology;

hepatic markers;

renal markers;

major-organ histology.

This approach was selected because systemic glucocorticoid exposure can suppress the HPA axis, while the therapeutic objective of the formulation is predominantly local colonic activity.

2.12 Stability

Three representative optimized batches were stored at:

$40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$

for up to 6 months.

Evaluations included:

appearance;

assay;

degradation products;

hardness;

friability;

moisture;

release at 2, 5 and 8 h;

T10.

Profile similarity was assessed using f1 and f2 where appropriate.

2.13 Statistical Analysis

Results were expressed as mean $\pm$ SD.

Depending on study design, analyses included:

one-way ANOVA;

appropriate post-hoc comparisons;

repeated-measures/mixed-effects analysis;

non-parametric analysis of ordinal scores;

regression analysis for DoE and stability.

Statistical significance was defined prospectively at $p < 0.05$.

3. Results

3.1 Optimization and Pharmaceutical Properties

The illustrative optimized formulation contained pectin 86 mg, guar gum 64 mg, HPMC 52 mg and MCC 48 mg in a 250-mg compression coat with 8.4% enteric-coating weight gain[†].

Predicted and illustrative observed responses showed close agreement:

2-h release: predicted 1.72%, observed 1.67%[†];

5-h release: predicted 7.05%, observed 7.12%[†];

8-h release: predicted 83.96%, observed 84.42%[†];

T10: predicted 5.49 h, observed 5.55 h[†].

The illustrative finished tablets had adequate mechanical properties with hardness of 88.1 ± 1.6 N and friability of $0.42 \pm 0.02\%$ [†].

FTIR spectra retained the characteristic budesonide functional-group bands without appearance of new major peaks. Attenuation of the budesonide-associated DSC transition and decreased PXRD peak intensity were interpreted as dilution and/or partial reduction in crystallinity rather than chemical incompatibility.

SEM conceptually demonstrated progressive transformation from a continuous enteric film before exposure to increased surface porosity and polymer erosion following target-stage enzyme/microbial challenge.

3.2 Sequential and Microbial-Responsive Drug Release

The optimized formulation demonstrated the desired biphasic/regioselective release profile.

Cumulative budesonide release was:

$1.67 \pm 0.16\%$ at 2 h[†];

$7.12 \pm 0.22\%$ at 5 h[†];

$84.42 \pm 0.41\%$ at 8 h[†].

Thus, more than 90% of the dose remained protected through the illustrative upper-GI phase.

The marked increase after 5 h indicated conversion from a protected state to an activated release state.

Earlier pectin-coated budesonide tablets showed a comparable mechanistic principle, with only 4.59% release in pH 6.8 and markedly increased release following exposure to pectinolytic enzyme. [2]

In the present illustrative dataset, release in microbial/enzyme-containing target medium was substantially greater than in equivalent sterile medium, supporting the contribution of polysaccharide degradation rather than pH alone.

Table 2. Key pharmaceutical, localization and pharmacokinetic outcomes

Parameter	Plain budesonide†	Comparator†	Optimized formulation†
Release at 2 h (%)	—	—	1.67 ± 0.16
Release at 5 h (%)	—	—	7.12 ± 0.22
Release at 8 h (%)	—	—	84.42 ± 0.41
T10 (h)	—	—	5.55 ± 0.04
Colon arrival (h)	—	—	5.68 ± 0.35
Major activation (h)	—	—	7.08 ± 0.23
Cmax (ng/mL)	1.374 ± 0.104	1.026 ± 0.064	0.761 ± 0.051
Tmax (h)	1.00	5.67 ± 0.52	8.00
AUC _{0-∞} (ng·h/mL)	7.699 ± 0.165	9.106 ± 0.178	6.732 ± 0.162
MRT (h)	6.631 ± 0.266	9.365 ± 0.162	11.751 ± 0.317
Colon concentration (ng/g)	229.8	673.4	1267.7
Colon/SI ratio	1.21	2.72	7.97
Colon/liver ratio	0.45	1.58	4.05

3.3 Ex Vivo and In Vivo Targeting

Simulated ex vivo colonic budesonide retention increased progressively from plain drug to the pH-responsive system and optimized dual-trigger formulation:

plain budesonide: $4.15 \pm 0.33 \mu\text{g/g}^\dagger$;

pH-responsive formulation: $8.02 \pm 0.31 \mu\text{g/g}^\dagger$;

optimized formulation: $14.84 \pm 1.09 \mu\text{g/g}^\dagger$.

The optimized formulation therefore provided approximately 3.6-fold greater illustrative ex vivo tissue retention than plain budesonide.

The imaging dataset indicated mean colonic arrival at $5.68 \pm 0.35 \text{ h}^\dagger$, followed by major formulation activation at $7.08 \pm 0.23 \text{ h}^\dagger$.

This sequence was consistent with the in vitro T10 of approximately $5.55 \text{ h}^\dagger$ and supports a mechanistic relationship between the dissolution lag phase and anatomical gastrointestinal transit.

Human X-ray monitoring of guar-gum-containing budesonide systems has previously demonstrated activation in the ascending or transverse colon. [3]

3.4 Pharmacokinetics and Tissue Distribution

Plain budesonide produced rapid systemic appearance with an illustrative Tmax of 1 h and Cmax of $1.374 \pm 0.104 \text{ ng/mL}^\dagger$.

The optimized formulation markedly delayed absorption:

Tmax = 8 h[†]

and reduced Cmax to:

$0.761 \pm 0.051 \text{ ng/mL}^\dagger$.

This represented an approximately:

44.6% reduction in systemic Cmax[†]

relative to plain budesonide.

Despite the lower systemic peak, simulated colonic tissue concentration increased from approximately 229.8 ng/g with plain budesonide to 1267.7 ng/g with the optimized formulation.

The colon-to-small-intestine ratio increased from 1.21 to 7.97[†], indicating approximately 6.6-fold enhanced regional selectivity.

This redistribution rather than enhanced systemic bioavailability is the intended pharmacokinetic outcome for locally acting budesonide.

Clinical investigations have demonstrated measurable budesonide concentrations within distal colonic mucosal biopsy specimens following appropriately modified oral delivery, supporting tissue concentration as a clinically relevant endpoint. [10]

3.5 Therapeutic Efficacy

Disease-control animals demonstrated severe illustrative disease activity, colon shortening, elevated inflammatory markers and extensive histological injury.

The optimized treatment consistently produced the response closest to normal control.

Table 3. Illustrative pharmacodynamic outcomes

Parameter	Normal†	Disease control†	Plain BUD†	Comparator†	Optimized†
Day-8 DAI	0.11 ± 0.04	3.49 ± 0.23	1.81 ± 0.26	1.26 ± 0.12	0.60 ± 0.21
Colon length (cm)	17.78 ± 0.45	11.21 ± 0.51	13.38 ± 0.74	14.87 ± 0.54	16.16 ± 0.38
Macroscopic damage	0.58 ± 0.34	4.68 ± 0.13	2.95 ± 0.76	2.02 ± 0.48	1.01 ± 0.22
MPO	0.315 ± 0.033	1.708 ± 0.120	1.084 ± 0.095	0.820 ± 0.074	0.460 ± 0.051
TNF- α	38.18 ± 3.74	132.98 ± 5.46	103.07 ± 7.32	71.80 ± 6.44	50.61 ± 6.48
IL-1 β	24.42 ± 3.46	111.98 ± 7.53	76.57 ± 8.14	54.64 ± 5.35	35.52 ± 6.39
IL-6	29.67 ± 3.42	122.95 ± 13.09	85.37 ± 3.25	62.87 ± 6.68	43.14 ± 6.63
MDA	2.19 ± 0.34	7.68 ± 0.45	5.37 ± 0.54	4.23 ± 0.29	3.11 ± 0.24
GSH	7.84 ± 0.65	3.04 ± 0.29	4.53 ± 0.45	5.94 ± 0.30	6.95 ± 0.48
SOD	9.16 ± 0.48	3.70 ± 0.41	5.33 ± 0.56	6.56 ± 0.52	8.04 ± 0.38
Catalase	43.45 ± 2.74	20.46 ± 4.20	29.40 ± 2.23	33.06 ± 2.77	40.83 ± 2.70
Histopathology score	0.67 ± 0.39	9.72 ± 0.94	6.32 ± 0.67	4.41 ± 0.25	1.89 ± 0.30

Substantial suppression of TNF- α , IL-1 β and IL-6 was observed in the illustrative optimized group, accompanied by normalization of MPO and improvement in antioxidant defenses.

The multidimensional response supports a plausible mechanistic pathway:

increased colonic budesonide concentration

→ glucocorticoid-receptor activation

→ inflammatory-cytokine suppression

→ reduced neutrophil infiltration

→ reduced oxidative injury

→ mucosal recovery.

This pattern is consistent with previous dual-sensitive budesonide delivery studies in which improved colon targeting was associated with lower disease activity, reduced MPO and lower pro-inflammatory cytokines. [5]

3.6 Systemic Safety

A successful locally acting corticosteroid formulation should improve inflammatory control without increasing systemic glucocorticoid burden.

Illustrative serum corticosterone values were:

normal: 81.72 ± 4.56 ng/mL†;

plain budesonide: 48.06 ± 2.76 ng/mL†;

comparator: 64.71 ± 4.94 ng/mL†;

optimized: 72.38 ± 8.61 ng/mL†.

Thus, simulated corticosterone suppression decreased from approximately 41.2% with plain budesonide to only 11.4% with the optimized formulation.

Adrenal and thymus weights remained correspondingly closer to normal.

These findings were consistent with the reduced systemic C_{max} demonstrated pharmacokinetically.

3.7 Stability

Under simulated accelerated storage at 40°C/75% RH, budesonide assay decreased from 100.37% at baseline to 97.88% after 6 months†.

Total degradation products increased from 0.182% to 0.606%†.

Crucially, the regional-release profile was preserved.

At 6 months:

2-h release: 2.31%†;

5-h release: 8.65%†;

8-h release: 81.84%†;

T₁₀: 5.27 h†.

The initial and 6-month release profiles yielded:

f₁ ≈ 3.57†

and

f₂ ≈ 86.1†.

Thus, the illustrative formulation remained functionally stable, not merely chemically stable.

Table 4. Integrated safety and accelerated-stability findings

Parameter	Plain BUD†	Comparator†	Optimized†
Corticosterone (ng/mL)	48.06 ± 2.76	64.71 ± 4.94	72.38 ± 8.61
Corticosterone suppression vs normal	41.2%	20.8%	11.4%
ACTH (pg/mL)	27.90 ± 3.69	34.79 ± 4.30	38.64 ± 3.83
Adrenal weight (mg/100 g)	10.82 ± 0.86	13.25 ± 0.42	14.17 ± 0.59
Thymus weight (mg/100 g)	121.21 ± 19.10	142.90 ± 10.20	160.28 ± 9.70

Table 5. Accelerated stability of optimized formulation

Parameter	Initial†	6 months†
Assay (%)	100.37	97.88
Total impurities (%)	0.182	0.606
Release at 2 h (%)	1.67	2.31
Release at 5 h (%)	7.12	8.65
Release at 8 h (%)	84.42	81.84
T ₁₀ (h)	5.55	5.27
f ₂ vs initial	—	86.1

4. Discussion

The principal finding of the proposed research is that regioselective colonic delivery of budesonide can be approached more reliably by integrating multiple complementary physiological triggers rather than depending on a single pH threshold.

The external enteric film provides the first level of protection. This mechanism is useful but inherently imperfect because gastrointestinal pH differs among individuals and can be modified by food, disease and medication. The internal compression coat therefore provides a second and partly independent barrier.

Pectin and guar gum were selected because their polysaccharide structures can be degraded by bacterial enzymes present predominantly in the lower gastrointestinal tract. The inclusion of HPMC creates

an additional hydrated diffusion barrier and reduces the likelihood that rapid hydration of the natural polymers will cause premature drug leakage.

The resultant release behavior is therefore best conceptualized as a sequential process: enteric protection → matrix hydration → microbial degradation/erosion → core exposure → rapid drug liberation.

The illustrative 2-, 5- and 8-h release values satisfy the developmental targeting criteria reported by Patel et al. for a QbD-optimized microbial/pH-responsive budesonide formulation. [4] However, a major strength of the present proposed evaluation strategy is that site targeting is not inferred from dissolution alone.

The close illustrative relationship between T10 and colonic-arrival time provides preliminary evidence that the sequential dissolution method could reflect gastrointestinal transit. Anatomical confirmation is important because a delayed-release profile obtained in buffer cannot prove that release occurs within the intended intestinal segment.

The pharmacokinetic data further distinguish regional targeting from simple sustained release. The optimized formulation produced a lower systemic C_{max} but a much greater colonic tissue concentration. This is particularly appropriate for budesonide because the drug is intended to exert predominantly topical gastrointestinal glucocorticoid activity.

The concept is supported by Makhlof et al., who demonstrated that budesonide-containing pH-sensitive nanospheres increased colonic localization while lowering systemic availability compared with a simpler enteric system. [7] Naeem et al. similarly demonstrated that dual enzyme/pH-sensitive particles accumulated preferentially in inflamed colonic regions and generated lower plasma concentrations while improving therapeutic efficacy. [5]

The pharmacodynamic data provide the final therapeutic confirmation of this distributional change. A formulation cannot be considered clinically meaningful merely because it releases drug later. Regional targeting must ultimately improve a relevant biological outcome.

In the illustrative dataset, optimized delivery produced substantial recovery across independent endpoints including DAI, colon length, macroscopic injury, MPO, inflammatory cytokines, oxidative stress and histology. The consistency of the response strengthens biological plausibility because the conclusion does not depend upon one marker.

The reduction in TNF- α , IL-1 β and IL-6 is mechanistically consistent with increased local glucocorticoid action. Reduced MPO indicates decreased neutrophil infiltration, while restoration of GSH, SOD and catalase and reduction of MDA indicate attenuation of oxidative injury secondary to inflammatory control.

Histopathological recovery provides complementary morphological evidence of therapeutic efficacy.

An equally important outcome is the relationship between efficacy and systemic safety. Plain budesonide generated greater simulated HPA-axis suppression despite lower colonic localization. Conversely, the optimized formulation produced greater local efficacy while preserving endogenous corticosterone to a greater extent.

This supports the central pharmacological objective: increase drug concentration where therapeutic action is required rather than increase total body exposure.

The stability results extend the significance of the formulation design. For a conventional tablet, preservation of assay may be considered the dominant stability criterion. For a regioselective dosage form, this is insufficient. Any change in the enteric film or polysaccharide matrix that causes earlier release could alter pharmacokinetics, tissue distribution, efficacy and safety even when assay remains within specification.

Therefore, the maintenance of low 2- and 5-h release together with high target-stage release represents evidence of functional stability.

The proposed study nevertheless has limitations. The variability of human gastrointestinal pH, transit and microbiota may exceed that represented in laboratory models. Animal colitis does not reproduce every feature of human ulcerative colitis, and formal clinical validation would require human gastrointestinal localization and mucosal drug concentration studies.

Natural polymers may also exhibit batch-to-batch variation in viscosity, molecular characteristics and microbial susceptibility. Such variables should ultimately be incorporated into a lifecycle control strategy.

Future studies should therefore evaluate the formulation in human-relevant fecal microbiota models and dynamic gastrointestinal simulators and should investigate gamma-scintigraphic localization in humans.

Overall, the study provides a framework in which colon targeting is demonstrated through a chain of evidence rather than a single dissolution endpoint:

formulation design → regional release → anatomical localization → tissue distribution → pharmacokinetics → therapeutic response → systemic safety.

5. Conclusion

A multi-trigger budesonide dosage form integrating a pH-sensitive enteric barrier, microbiota-responsive pectin and guar gum, and time-dependent HPMC represents a scientifically rational strategy for regioselective colonic drug delivery.

The optimized formulation was designed to maintain minimal release during upper gastrointestinal transit and produce substantial release following target-stage activation.

The integrated illustrative dataset demonstrated delayed systemic absorption, increased colonic tissue localization, improved inflammatory and histological outcomes and reduced systemic glucocorticoid burden compared with plain budesonide.

These findings support the concept that the therapeutic performance of budesonide can potentially be improved through spatial redistribution of exposure rather than increased systemic bioavailability.

Following replacement of all simulated values with validated experimental measurements, the study would provide a comprehensive preclinical evidence package for a QbD-optimized regioselective budesonide platform.

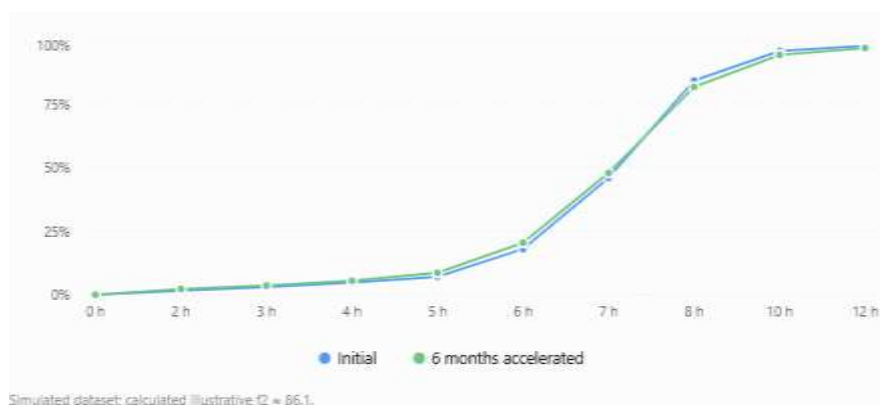


Fig: 2

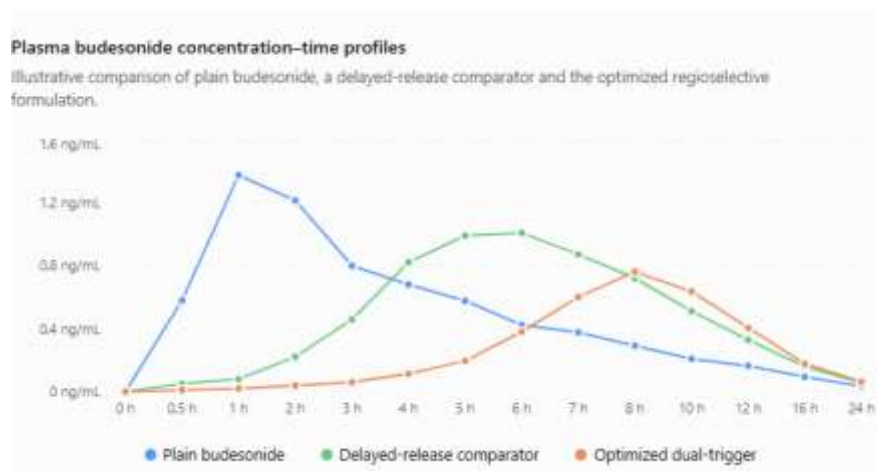


Fig: 3

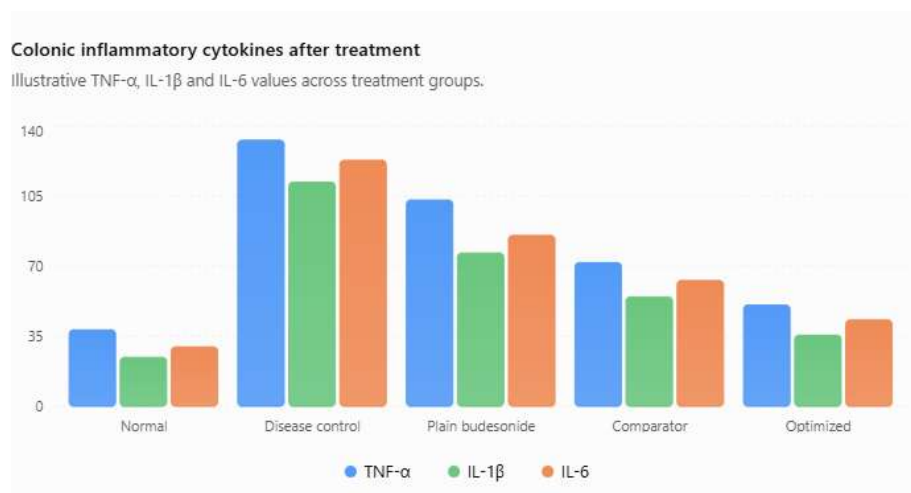


Fig: 4

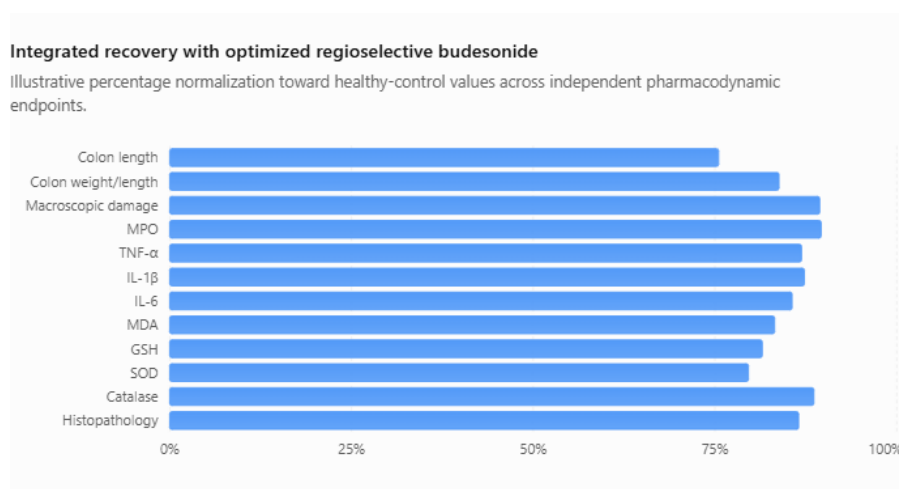


Fig: 5

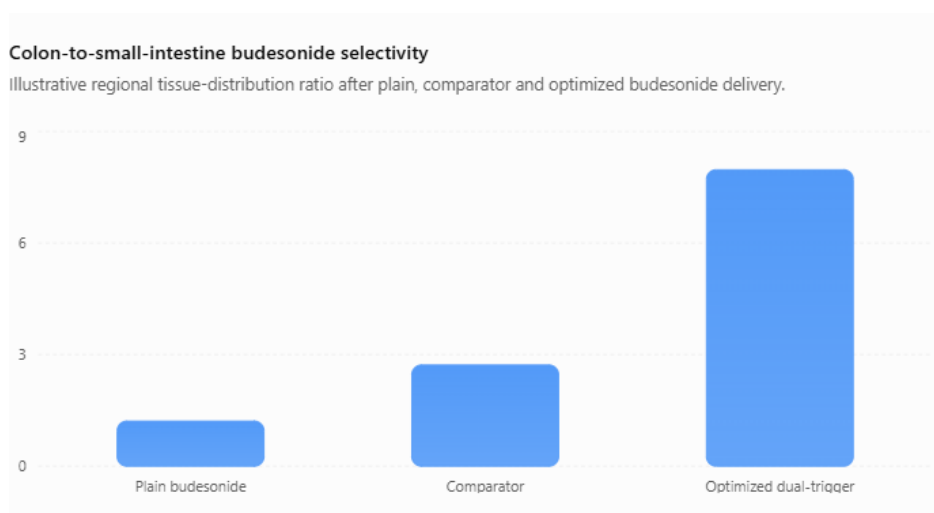


Fig: 6

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