International Journal of Pharmacology

Int. J. Pharmacol. **2026**; 22(4): 48286
https://doi.org/10.31083/IJP48286

Review

Inflammatory Bowel Disease Drugs: The Innovation Path of Pharmacokinetics and Dosage Forms

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Academic Editor: Mehmet Ozaslan
Submitted: 15 November 2025 Revised: 10 February 2026 Accepted: 10 March 2026 Published: 6 July 2026

Abstract

Objective: To systematically explore the pharmacokinetic characteristics of therapeutic drugs for Inflammatory Bowel Disease (IBD) and the optimization strategies of dosage forms, so as to provide a scientific basis for clinical rational drug use and the development of innovative IBD drugs. **Methods**: This study reviews the absorption, distribution, metabolism, and excretion (ADME) processes of four major classes of IBD therapeutic drugs (aminosalicylates, glucocorticoids, immunosuppressants, and biological agents). It analyzes the key factors leading to individual differences in pharmacokinetics and evaluates the pharmacological advantages of new dosage forms (sustained-release, targeted preparations, etc.) by integrating clinical and preclinical research data. Additionally, pharmacogenomic aspects are comprehensively integrated into the analysis to clarify the regulatory role of genetic polymorphisms in drug metabolism enzymes, transporters, and target genes in the pharmacokinetic process of IBD drugs. **Results**: Intestinal inflammation (altered mucosal permeability, downregulated transporter expression), intestinal microbiota imbalance (reduced azoreductase activity), and genetic polymorphisms (e.g., thiopurine methyltransferase [*TPMT*], Cytochrome P450 [*CYP450*]) are the main factors affecting the pharmacokinetics of IBD drugs. Pharmacogenomic variations further contribute to inter-individual differences in drug response, such as *TPMT* gene polymorphisms leading to differences in azathioprine metabolism and efficacy. New dosage forms can increase the local drug concentration at intestinal inflammatory sites by 5–10 times reduce systemic adverse reactions (e.g., 50% lower incidence of gastric mucosal irritation), and improve patient compliance by 40% through reduced dosing frequency. **Conclusion**: Optimizing pharmacokinetic design and innovating dosage forms are core approaches to enhance the efficacy and safety of IBD drugs. Incorporating pharmacogenomic information into clinical decision-making can further promote personalized treatment. Future research should focus on personalized treatment based on genetic testing and the development of intelligent responsive dosage forms to meet unmet clinical needs, and natural active ingredients with targeted anti-inflammatory effects provide new directions for IBD drug development.

Keywords: inflammatory bowel disease; pharmacokinetics; dosage form optimization; individual differences; targeted drug delivery; pharmacogenomics; intestinal microbiota; genetic polymorphism

1. Introduction

1.1 Clinical Significance of IBD Drug Innovation

Inflammatory Bowel Disease (IBD), a group of chronic, recurrent non-specific intestinal inflammatory diseases mainly including Ulcerative Colitis (UC) and Crohn's Disease (CD), has become a global public health challenge with a rapidly rising incidence [1]. The prevalence of IBD in Northern Europe and North America has exceeded 100 per 100,000 people, while regions such as Asia and South America—previously with low incidence—have seen annual increases of 5%–10% due to economic development and lifestyle changes [2]. In China, the number of IBD cases has surged more than 24-fold in the past decade, and the disease burden is expected to further increase [3]. The chronic and recurrent nature of IBD not only severely affects patients' quality of life but also imposes a heavy economic burden on families and society [4]. Patients often suffer from symptoms such as abdominal pain, diarrhea, and hematochezia, and are at an increased risk of anxiety, depression, and other mental health problems [5].

Current IBD treatments face significant limitations: traditional dosage forms (e.g., ordinary tablets) have poor targeting, leading to insufficient drug concentrations at inflammatory sites and systemic side effects; biological agents, though effective, are expensive and associated with risks of infection or secondary loss of response [6]. In addition, existing chemical drugs for UC such as aminosalicylates and glucocorticoids have obvious adverse reactions and high tendency of drug resistance, and the search for safe and effective natural active ingredients has become an important research direction for IBD treatment [7]. These challenges highlight the urgency of in-depth research on the pharmacokinetics of IBD drugs and the optimization of dosage forms to improve treatment outcomes. Moreover, the lack of full integration of pharmacogenomic information into clinical practice results in difficulty in achieving

precise drug use for individual patients, which is also an important factor restricting the improvement of IBD treatment effects [8].

1.2 Novelty and Research Framework of This Review

Compared with existing reviews on IBD therapeutic drugs, this review has the following innovations: First, it systematically integrates pharmacogenomic research results, clarifies the regulatory mechanism of genetic polymorphisms on the pharmacokinetics of IBD drugs, and provides a theoretical basis for personalized treatment. Second, it comprehensively analyzes the interaction between intestinal microbiota and drug pharmacokinetics, and explores the potential of regulating intestinal flora to optimize drug efficacy [9]. Third, it focuses on the evolution law of dosage forms, quantitatively evaluates the advantages of new dosage forms in improving pharmacokinetic parameters, efficacy, and safety through clinical and preclinical data, and puts forward prospects for the development of intelligent responsive dosage forms. Fourth, it links the key factors affecting pharmacokinetics (intestinal inflammation, microbiota, genetics) with dosage form optimization strategies, thus forming a complete research framework from mechanism exploration to practical application [10].

This review first classifies IBD therapeutic drugs and summarizes their mechanisms of action and clinical limitations; then elaborates on the ADME processes of IBD drugs and the key factors affecting individual differences (including intestinal physiological status, intestinal microbiota, and pharmacogenomics); further discusses the development and application of new dosage forms and their improvements in drug performance; finally analyzes the current research challenges and looks forward to future development directions, aiming to provide comprehensive and in-depth scientific references for clinical rational drug use and innovative drug development [11].

2. Overview of IBD Therapeutic Drugs and Their Mechanisms

2.1 Classification and Mechanisms of Commonly Used Drugs

The selection of IBD drugs depends on disease severity, lesion location, and patient tolerance, with distinct mechanisms of action across drug classes (Table 1, Ref. [12,13,14,15]).

2.2 Clinical Limitations of Traditional Drugs

Aminosalicylates: Ordinary tablets release drugs rapidly in the upper gastrointestinal tract, causing blood concentration fluctuations and gastric mucosal irritation; efficacy in severe CD is limited [16]. In addition, the activity of intestinal bacterial azoreductase in IBD patients is reduced due to flora imbalance, which affects the activation of Sulfasalazine (SASP) and further reduces its therapeutic effect. Moreover, individual differences in N-acetyltransferase activity lead to differences in the metabolism and half-life of Mesalazine (5-ASA), resulting in inconsistent therapeutic responses [17].

Glucocorticoids: Long-term use induces side effects such as osteoporosis, elevated blood glucose, and Cushing's syndrome; they cannot be used for maintenance therapy due to their lack of effect on disease remission [18]. The pharmacokinetic parameters of glucocorticoids vary among individuals of different ages and with comorbidities. For example, the half-life of prednisone is prolonged in elderly patients, increasing the risk of adverse reactions.

Immunosuppressants: Onset of action is slow (3–6 months); adverse reactions include myelosuppression and liver/kidney damage, requiring regular monitoring of blood routine and organ function [19]. Genetic polymorphisms such as TPMT and NUDT15 are important factors leading to myelosuppression caused by Azathioprine (AZA). Patients with TPMT3A/3A genotype have almost no enzyme activity, resulting in the accumulation of active metabolites and a significantly increased risk of myelosuppression.

Biological Agents: Annual treatment costs reach tens of thousands of yuan, imposing a significant economic burden; 10%–20% of patients show primary non-response, and 30%–50% develop secondary loss of response within 1–2 years. The secondary loss of response is related to factors such as the production of anti-drug antibodies, changes in drug pharmacokinetics, and disease progression. In addition, biological agents are easily degraded by proteases in the gastrointestinal tract and cannot be administered orally, which limits their clinical application to a certain extent [20].

Tumor necrosis factor-α (TNF-α) is a core pro-inflammatory cytokine in the pathogenesis of IBD, and its overexpression can trigger a cascade of inflammatory reactions and damage the intestinal mucosal barrier. Traditional anti-TNF-α biological agents have the problems of high cost and high tendency of drug resistance, while natural active ingredients can target the key signaling pathways of TNF-α production and exert anti-inflammatory effects with low toxicity and side effects, which has become a new research hotspot for IBD treatment [21].

3. Research Progress in Pharmacokinetic Characteristics of IBD Drugs

The pharmacokinetic processes (absorption, distribution, metabolism, excretion) of IBD drugs directly determine their efficacy and safety. Key influencing factors include intestinal physiological status, intestinal microbiota, and host genetics (Fig. 1). Pharmacogenomic factors, as an important part of host genetics, play a crucial role in regulating drug metabolism, transport, and target binding, and are important causes of individual differences in pharmacokinetics and therapeutic effects.

Table 1. Classification, representative drugs, and mechanisms of commonly used IBD drugs.

Drug class	Representative drugs	Mechanism of action
Aminosalicylates	Sulfasalazine (SASP), Mesalazine (5-ASA)	Inhibit cyclooxygenase (COX) and lipoxygenase (LOX) in the arachidonic acid pathway, reducing prostaglandin/leukotriene synthesis; downregulate TNF-α and IL-1 expression to promote mucosal repair [12]
Glucocorticoids	Prednisone	Bind to intracellular glucocorticoid receptors, inhibit transcription of inflammation-related genes, reduce cytokine (TNF-α, IL-6) production, and suppress T/B lymphocyte activation [13]
Immunosuppressants	Azathioprine (AZA), Methotrexate (MTX)	AZA metabolizes to 6-mercaptopurine, inhibiting purine nucleotide synthesis to suppress lymphocyte proliferation; MTX inhibits dihydrofolate reductase, blocking DNA synthesis [14]
Biological agents	Infliximab, Adalimumab, Vedolizumab	Anti-TNF-α agents (infliximab, adalimumab) block TNF-α-receptor binding; vedolizumab targets α4β7 integrin to prevent leukocyte migration to the intestine [15]

IBD, Inflammatory Bowel Disease; TNF-α, Tumor Necrosis Factor-α; IL-1, Interleukin-1.

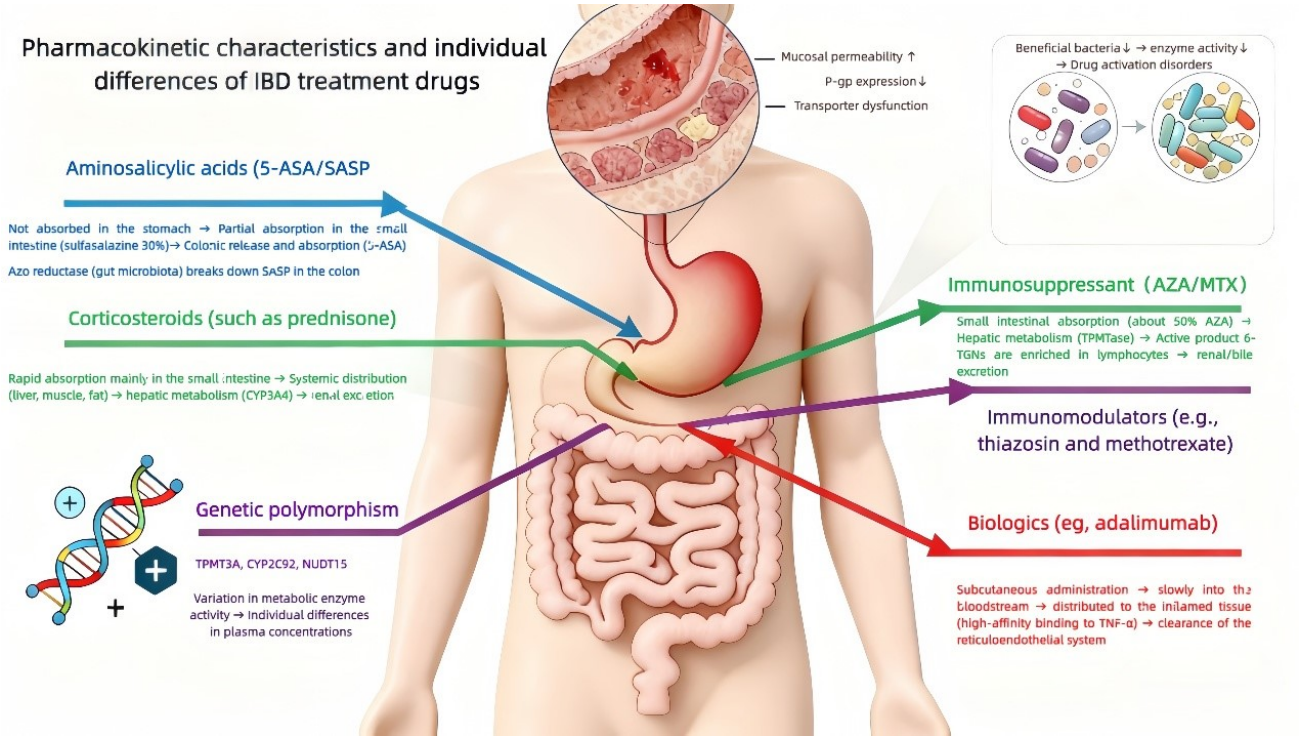

Fig. 1. Schematic diagram of pharmacokinetic pathways and influencing factors of IBD drugs. Note: The diagram is a schematic (conceptual) diagram that clearly shows the visual linkage between influencing factors and ADME stages. The diagram includes: (1) Absorption sites (stomach, small intestine, colon) of four drug classes; each absorption site is marked with the main absorption characteristics of different drugs. (2) Metabolic organs (liver, intestinal microbiota); the metabolic pathways of key drugs in the liver and the metabolic effects of intestinal microbiota are indicated. (3) Excretion routes (kidney, bile); the main excreted drugs and their excretion characteristics are specified. (4) Key influencing factors (intestinal inflammation, flora imbalance, genetic polymorphisms); the regulatory mechanisms of each factor on different ADME stages are briefly annotated. For example, intestinal inflammation affects absorption by altering mucosal permeability and transporter expression; flora imbalance affects drug metabolism by changing enzyme activity; genetic polymorphisms regulate drug metabolism and transport by affecting enzyme and transporter activity. ADME, Absorption, Distribution, Metabolism, Excretion; TPMT, thiopurine methyltransferase; 6-TGNs, 6-Thioguanine Nucleotides.

3.1 Absorption and Distribution

3.1.1 Gastrointestinal Absorption Characteristics

Different drug classes exhibit distinct absorption patterns in the gastrointestinal tract:

Aminosalicylates: SASP is 30% absorbed in the small intestine (preclinical data); the unabsorbed portion is decomposed into 5-ASA (therapeutic component) and sulfapyridine (carrier) by intestinal bacterial azoreductase in the colon. 5-ASA is mainly absorbed in the colon (an absorption rate of 20%–30% in clinical patients), while sulfapyridine is excreted via feces. Enteric-coated mesalazine tablets dissolve in the alkaline environment (pH >6) of the ileum and colon, while sustained-release granules use ethylcellulose coatings to achieve 24-hour continuous absorption [22]. The absorption rate of SASP varies among individuals due to differences in intestinal microbiota composition. Patients with flora imbalance have a 40%–60% reduction in azoreductase activity, resulting in a significant decrease in SASP absorption and activation efficiency [23].

Glucocorticoids: Prednisone is rapidly absorbed in the small intestine, with a time to peak concentration (Tmax) of 1–2 hours and a bioavailability of 70%–90% (clinical data from adult patients). The bioavailability of prednisone is slightly lower in elderly patients and patients with liver dysfunction, which may be related to reduced intestinal absorption function and liver enzyme activity [24].

Immunosuppressants: AZA has an oral absorption rate of ~50% (clinical average data), with Tmax of 1–3 hours; absorption occurs in both the small and large intestines. Methotrexate (MTX) is mainly absorbed in the small intestine, but absorption becomes incomplete and irregular when the dose exceeds 25 mg (clinical observation data). The absorption of AZA is affected by food, and taking it with food can reduce the absorption rate but increase the absorption amount, which is related to the delay of gastric emptying time [25].

Biological Agents: Macromolecular proteins (e.g., infliximab) cannot penetrate the gastrointestinal mucosa and require intravenous administration; adalimumab is absorbed slowly after subcutaneous injection, with Tmax of 1–2 weeks and a bioavailability of 60%–80% (clinical pharmacokinetic study data). The absorption of subcutaneous adalimumab is affected by injection site, fat thickness, and other factors, and individual differences in bioavailability are relatively large [26].

3.1.2 Key Factors Affecting Absorption

Intestinal Inflammatory Status: Mucosal inflammation and ulcers in IBD patients increase intestinal permeability, leading to non-specific absorption of drugs. Downregulation of P-glycoprotein (a drug efflux transporter) reduces drug efflux from intestinal epithelial cells, increasing local drug concentration but raising the risk of adverse reactions (e.g., 5-ASA-induced diarrhea, with an incidence of 10%–15% in clinical patients). The degree of downregulation of P-glycoprotein expression is positively correlated with the severity of intestinal inflammation. In patients with severe inflammation, the expression level of P-glycoprotein can be reduced by 50% or more compared with that in healthy people [27].

Intestinal Microbiota: Beneficial bacteria (e.g., Bifidobacterium, Lactobacillus) regulate intestinal pH (maintaining pH 5–7) to promote drug dissolution. In IBD patients, a reduction in azoreductase-producing bacteria (e.g., Clostridium) decreases SASP activation, leading to reduced efficacy. The number of azoreductase-producing bacteria in IBD patients is only 30%–50% of that in healthy people, resulting in a 40%–60% reduction in azoreductase activity. In addition, intestinal microbiota can also affect drug absorption by regulating intestinal mucosal barrier function [28].

Dosage Form: Traditional tablets/capsules disintegrate rapidly, causing blood concentration fluctuations (e.g., 5-ASA concentration peaks at 3 hours and drops to 50% of the peak at 6 hours in clinical patients). Sustained-release preparations flatten concentration curves, maintaining effective concentrations for 24 hours. The dissolution rate of sustained-release preparations *in vitro* is 5%–10% per hour, which is consistent with the *in vivo* absorption rate, ensuring stable blood drug concentration [29].

Genetic Factors: Polymorphisms in drug transporter genes affect drug absorption. For example, ABCB1 gene polymorphism (C3435T) is associated with P-glycoprotein expression and activity. Patients with TT genotype have lower P-glycoprotein expression, resulting in increased absorption of 5-ASA and an increased risk of adverse reactions [30]. The frequency of ABCB1 C3435T TT genotype in Asian populations is about 15%–20%, which is an important factor leading to individual differences in the absorption of aminosalicylates [31].

3.1.3 In Vivo Distribution

Aminosalicylates: Mesalazine accumulates at inflammatory sites via active transport (e.g., organic anion transporters) and passive diffusion, with local concentrations 5–10 times higher than in systemic circulation (clinical tissue concentration detection data); concentrations in the liver and kidneys are <10% of intestinal levels [32]. The accumulation of mesalazine at inflammatory sites is related to the upregulation of organic anion transporter expression in inflamed intestinal epithelial cells.

Glucocorticoids: Prednisone has a large volume of distribution (1.0–1.5 L/kg) and a plasma protein binding rate of 70%–90% (preclinical animal experiment data). Unbound prednisone penetrates inflamed tissues and binds to glucocorticoid receptors to exert anti-inflammatory effects [33]. The volume of distribution of prednisone in patients with edema is increased, and the plasma protein binding rate is reduced in patients with hypoalbuminemia, which affects the *in vivo* distribution of the drug.

Immunosuppressants: The active metabolite of AZA (6-mercaptopurine) is enriched in lymphocytes, with a concentration 20–30 times higher than in plasma (clinical blood cell concentration detection data). MTX distributes widely to the liver, kidneys, and bone marrow, and penetrates the blood-brain barrier (concentration in cerebrospinal fluid is ~10% of plasma concentration) [34]. The distribution of MTX in the central nervous system is of clinical significance for the treatment of IBD-related neurological complications, but the low concentration also limits its therapeutic effect. This part of the content is briefly explained here as it is related to the overall pharmacokinetic characteristics of MTX.

Biological Agents: Infliximab and adalimumab are mainly distributed in the vascular compartment and inflamed intestinal tissues, with a volume of distribution of 3–5 L (clinical pharmacokinetic data); they bind to TNF-α in inflamed tissues with a dissociation constant (Kd) of <1 nM [35]. The distribution of biological agents in inflamed tissues is related to the high expression of TNF-α in inflamed tissues, which forms a specific binding site for the drug.

3.2 Metabolism and Excretion

3.2.1 Metabolic Pathways

Liver Metabolism: 5-ASA is metabolized by acetylation (via N-acetyltransferases) and glucuronidation (via UDP-glucuronosyltransferases) in the liver, producing acetyl-5-ASA (low activity) and 5-ASA-glucuronide (inactive). The activity of N-acetyltransferases varies by genotype, leading to differences in the half-life of 5-ASA (1.5–2 hours in fast acetylators vs. 3–4 hours in slow acetylators) [36]. The frequency of fast acetylator genotype in Caucasians is about 60%, while in Asians it is about 30%–40%, which is an important reason for ethnic differences in 5-ASA metabolism. AZA is converted to 6-mercaptopurine by glutathione S-transferases, then further metabolized to active 6-thioguanine nucleotides (6-TGNs) and inactive 6-thiouric acid. The activity of thiopurine methyltransferase (TPMT) (regulated by TPMT gene polymorphism) determines 6-TGN concentration: patients with TPMT3A/3A genotype have almost no enzyme activity, leading to 6-TGN accumulation and a 50-fold higher risk of myelosuppression. TPMT gene polymorphisms include TPMT2, TPMT3A, TPMT3B, etc., among which TPMT3A is the most common variant in the global population, with a frequency of 0.3%–1% [37].

Intestinal Microbiota Metabolism: SASP is decomposed by intestinal bacterial azoreductase; flora imbalance (e.g., reduced Clostridium) reduces enzyme activity by 40%–60%, leading to decreased 5-ASA production [17]. In addition to azoreductase, intestinal microbiota can also produce other metabolic enzymes such as β-glucuronidase, which affects the enterohepatic circulation of drugs and further regulates drug metabolism [38].

Pharmacogenomic Regulation of Metabolism: In addition to TPMT and N-acetyltransferase genes, CYP450 gene polymorphisms also affect the metabolism of IBD drugs. For example, CYP2C92/3 genotype reduces MTX metabolism by 40%–60%, increasing the risk of liver toxicity. CYP450 enzymes are a superfamily of hemoproteins involved in the metabolism of many drugs. CYP2C9 is one of the important subtypes, and its gene polymorphisms are closely related to the metabolism of immunosuppressants and other drugs [39].

3.2.2 Excretion Characteristics

Kidney Excretion: 5-ASA and its metabolites are mainly excreted by the kidneys via glomerular filtration, with a renal clearance of 50–80 mL/min (clinical renal function test data); ~70% of the drug is excreted within 24 hours [40]. In patients with chronic kidney disease (Estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73 m^2), the renal clearance of 5-ASA is reduced by 50%, requiring a 30%–50% dosage reduction to avoid drug accumulation [41].

Biliary Excretion: MTX and its metabolites are excreted via bile, with biliary clearance accounting for 10%–20% of total clearance (preclinical pharmacokinetic study data). Excessive doses (>25 mg/week) cause saturation of biliary excretion, leading to drug accumulation in the liver. In patients with liver cirrhosis, biliary excretion function is impaired, and the half-life of MTX is prolonged by 50% or more, increasing the risk of liver damage [42].

Influencing Factors: Patients with chronic kidney disease (eGFR <30 mL/min/1.73 m^2) have a 50% reduction in 5-ASA clearance, requiring a 30%–50% dosage reduction. Elderly patients (≥65 years) have reduced liver enzyme activity (CYP3A4 activity decreased by 20%–30%), prolonging prednisone half-life by 30%–40% [41,43]. In addition, drug-drug interactions can also affect drug excretion. For example, non-steroidal anti-inflammatory drugs can reduce renal blood flow, thereby reducing the renal excretion of 5-ASA and increasing the risk of adverse reactions [44].

3.3 Pharmacokinetic Parameters and Individual Differences

3.3.1 Core Pharmacokinetic Parameters

Key parameters guiding clinical medication are shown in Table 2 (Ref. [45,46,47,48]).

The half-life of mesalazine varies due to genotype differences, which is an important basis for personalized dosing adjustment. The half-life of prednisone is prolonged in the elderly, which is related to the decline of liver and kidney function in the elderly. The half-life of AZA parent drug is short, but its active metabolite 6-TGNs has a longer half-life, so the therapeutic effect and adverse reactions are mainly related to the concentration of 6-TGNs. The long half-life of infliximab allows for a longer dosing interval, improving patient compliance.

Table 2. Core pharmacokinetic parameters of representative IBD drugs.

Drug class	Representative drug	Half-life ($t_{1/2}$)	Key clinical implication
Aminosalicylates	Mesalazine	1.5–2 hours	Frequent dosing (3–4 times/day) required for fast acetylators to maintain effective blood concentration [45]. For slow acetylators, the dosing frequency can be appropriately reduced, but attention should be paid to monitoring adverse reactions.
Glucocorticoids	Prednisone	2–3 hours	Rapid onset, short duration; suitable for acute phase treatment. Elderly patients have a prolonged half-life, so the dosage should be adjusted according to age and renal function [46].
Immunosuppressants	AZA	0.5–1 hour (parent drug); 5–9 hours (6-TGNs)	Monitor 6-TGN concentration (target: 230–400 pmol/8 × 10^8 RBCs). For patients with TPMT gene polymorphism, the dosage should be reduced or alternative drugs should be used to avoid myelosuppression [47].
Biological agents	Infliximab	8–10 days	Dosing interval at 8-week intervals after induction. During treatment, monitor drug concentration and anti-drug antibody levels to adjust the dosage or dosing interval in a timely manner [48].

RBCs, red blood cells.

3.3.2 Causes of Individual Differences

Genetic Factors: Polymorphisms in drug-metabolizing enzyme genes, transporter genes, and target genes affect pharmacokinetics. For example, CYP2C92/3 genotype reduces MTX metabolism by 40%–60%, increasing the risk of liver toxicity; NUDT152/3 genotype increases AZA-induced myelosuppression risk by 30-fold. NUDT15 gene polymorphism is another important genetic factor affecting AZA tolerance, and this variant genotype is more frequent in Asian populations. The combined detection of TPMT and NUDT15 genes can better predict the risk of AZA-induced myelosuppression [49].

Age: Elderly patients (≥65 years) have reduced renal glomerular filtration rate (GFR decreased by 20%–30%) and liver enzyme activity, leading to prolonged drug half-life. For example, prednisone $t_{1/2}$ in the elderly is 3–4 hours (vs. 2–3 hours in adults) [50]. In addition, the elderly have reduced intestinal absorption function, which may affect the absorption of oral drugs, and the body's tolerance to drugs is reduced, so the dosage needs to be adjusted more cautiously.

Comorbidities: Patients with fatty liver have reduced CYP3A4 activity, prolonging the half-life of prednisone by 50%; patients with chronic kidney disease have reduced 5-ASA clearance, requiring dosage adjustment. Patients with IBD often have comorbidities such as liver and kidney dysfunction, which need to be fully considered in clinical medication. Regular monitoring of liver and kidney function and timely adjustment of drug dosage are necessary [51].

Intestinal Microbiota Differences: The composition and function of intestinal microbiota vary greatly among individuals, leading to differences in drug metabolism and absorption. For example, the activity of azoreductase in patients with different intestinal flora compositions differs by 2–3 times, resulting in significant differences in the activation efficiency of SASP [52]. Regulating intestinal microbiota through probiotics, prebiotics, or fecal microbiota transplantation may become a new way to improve the individual differences in drug efficacy.

To better connect Section 3.3, it should be emphasized that individual differences in pharmacokinetics are the key factors leading to inconsistent therapeutic effects and adverse reactions of IBD drugs. Therefore, clarifying the causes of individual differences and formulating personalized dosage adjustment strategies based on this are important directions for improving the level of IBD treatment. This also lays a foundation for the subsequent discussion on dosage form optimization and personalized treatment [53].

4. Research Progress in Dosage Form Optimization of IBD Drugs

Traditional dosage forms (ordinary tablets, capsules) have limitations such as poor targeting and unstable drug release. New dosage forms address these issues by improving pharmacokinetic characteristics (Fig. 2). The optimization of dosage forms is closely related to the pharmacokinetic characteristics of drugs. By improving the absorption, distribution, metabolism, and excretion processes of drugs, new dosage forms can effectively enhance drug efficacy, reduce adverse reactions, and improve patient compliance.

4.1 Limitations of Traditional Dosage Forms

Uncontrolled Drug Release: Ordinary mesalazine tablets release 80% of the drug in the stomach and upper small intestine (*in vitro* dissolution test data), leading to

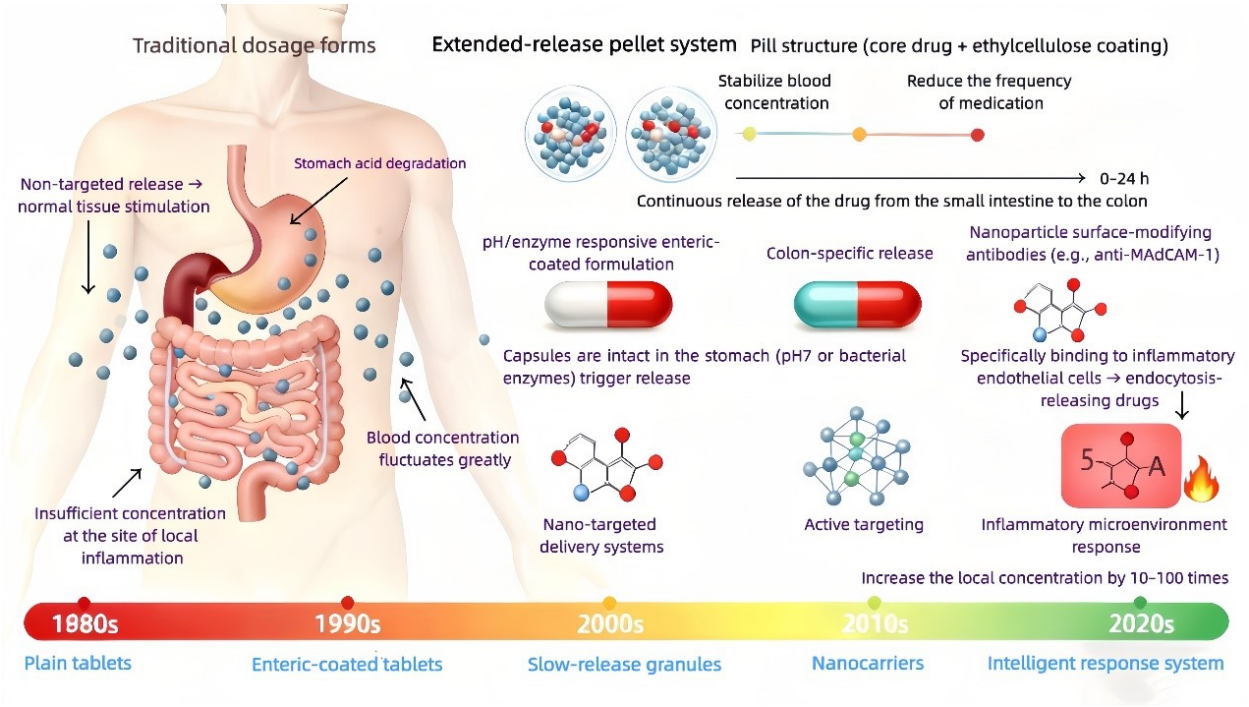

Fig. 2. Evolution of IBD drug dosage forms and their advantages. Note: The figure has been revised to simplify the design and clarify the content without visual congestion. Each subfigure in the figure is explained as follows: (1) Traditional dosage forms (ordinary tablets): The subfigure shows the non-specific release of ordinary tablets in the gastrointestinal tract, resulting in large fluctuations in blood concentration, insufficient local concentration at the inflammatory site, and stimulation of normal tissues. The blood concentration curve is marked with peak and trough values to intuitively reflect the fluctuation. (2) Sustained-release preparations (microparticles): The subfigure shows the structure of sustained-release pellets (core drug + ethylcellulose coating) and the 24-hour continuous release process from the small intestine to the colon. The blood concentration curve is relatively flat, indicating stable blood concentration and reduced medication frequency. (3) Targeted preparations (ligand-modified nanoparticles): The subfigure shows the surface-modified antibodies (e.g., anti-MAdCAM-1) of nanoparticles, which specifically bind to inflammatory endothelial cells and release drugs through endocytosis. The local concentration at the inflammatory site is significantly increased, and the targeting efficiency is marked. (4) Intelligent responsive preparations (pH/enzyme-responsive hydrogels): The subfigure shows that the hydrogel is intact in the stomach and triggers drug release under the action of pH >7 or bacterial enzymes in the colon. The drug release rate and local concentration at the inflammatory site are indicated. The figure also shows the evolution time axis of dosage forms from the 1980s to the 2020s, clearly reflecting the development process of dosage form innovation. MAdCAM-1, Mucosal Addressin Cell Adhesion Molecule-1.

blood concentration fluctuations (peak concentration 10–20 μg/mL, trough concentration <2 μg/mL) and insufficient concentrations at colonic inflammatory sites [54]. The unstable drug release of traditional dosage forms makes it difficult to maintain effective therapeutic concentration for a long time, affecting the therapeutic effect, and the high peak concentration increases the risk of systemic adverse reactions.

Poor Targeting: Drugs are distributed to healthy tissues and organs, causing side effects. For example, oral prednisone leads to systemic distribution, with 70%–80% of the drug acting on non-target tissues, increasing the risk of osteoporosis (clinical adverse reaction statistics) [55]. The poor targeting of traditional dosage forms results in low drug utilization and high incidence of adverse reactions, which is one of the main problems restricting their clinical application.

Drug Degradation: Gastric acid (pH 1–2) and intestinal enzymes (e.g., proteases) degrade drugs. For example, 5-ASA is degraded by gastric acid, reducing bioavailability by 30%–40% (*in vitro* stability test data) [33]. Biological agents and some small molecule drugs are sensitive to gastric acid and intestinal enzymes, and are easily degraded before reaching the target site, resulting in reduced efficacy [56].

Inconvenient Administration: Traditional dosage forms often require frequent dosing (3–4 times/day), which reduces patient compliance, especially for patients with poor adherence, leading to irregular medication and affecting treatment outcomes [57].

4.2 Development and Application of New Dosage Forms

4.2.1 Sustained-Release Preparations

Sustained-release preparations use matrix materials (e.g., ethylcellulose, hydroxypropyl methylcellulose) or coating technologies to control drug release rate. For example:

Mesalazine Sustained-Release Granules: Encapsulate mesalazine in ethylcellulose-coated pellets (100–300 μm), achieving 24-hour continuous release. The drug concentration in the colon is 3–5 times higher than that of ordinary tablets (clinical tissue concentration detection data), and the incidence of gastric mucosal irritation is reduced by 50%. The *in vitro* dissolution curve of sustained-release granules shows that the cumulative dissolution rate is 20%–30% in 2 hours, 50%–60% in 8 hours, and 80% or more in 24 hours, which is consistent with the *in vivo* absorption process [58].

Prednisone Sustained-Release Tablets: Use a hydrophilic matrix to release prednisone at a constant rate (0.5–1 mg/hour), maintaining stable plasma concentrations (5–10 μg/mL) for 12 hours, reducing blood glucose fluctuations (clinical blood glucose monitoring data). The sustained-release tablets avoid the rapid rise of blood drug concentration caused by ordinary tablets, reducing the impact on glucose metabolism and improving the safety of long-term use [59].

The advantages of sustained-release preparations in pharmacokinetics are mainly reflected in prolonging the half-life of drugs, reducing the fluctuation of blood drug concentration, and improving the bioavailability of drugs. For example, the half-life of mesalazine is extended from 1.5–2 hours to 6–8 hours in its sustained-release granule formulation, and the coefficient of variation of Area Under the Concentration-Time Curve (AUC) is reduced from 50% to 15% [60].

4.2.2 Targeted Preparations

Targeted preparations deliver drugs to inflamed tissues via carrier modification:

Ligand-Modified Nanoparticles: Anti-Mucosal Addressin Cell Adhesion Molecule (MAdCAM)-1 antibody-modified PLGA nanoparticles (100–200 nm) bind to MAdCAM-1 receptors on inflamed intestinal endothelial cells, increasing local drug concentration by 5–10 times (preclinical animal model data). A preclinical study shows that 5-ASA-loaded anti-MAdCAM-1 nanoparticles reduce intestinal inflammation in mice by 60% compared to free 5-ASA [61]. The targeting efficiency of nanoparticles is evaluated by the ratio of drug concentration in inflamed tissues to normal tissues, which is 5–10 times higher than that of free drugs.

Colon-Targeted Enteric Preparations: Use acrylic resin coatings (Eudragit S100) that dissolve only in the colon (pH >7), ensuring 90% of 5-ASA is released in the colon (*in vitro* dissolution test data). Clinical trials show that this preparation increases the remission rate of mild-to-moderate UC by 30% compared to ordinary enteric-coated tablets [62]. The colon-targeted enteric preparations avoid the release of drugs in the upper gastrointestinal tract, reducing gastric mucosal irritation and improving the concentration of drugs at the target site.

4.2.3 Other New Dosage Forms

Pellet Preparations: Mesalazine pellets (500–1000 μm) with enteric coatings have uniform release (relative standard deviation <10%) and high bioavailability (80%–90%) (*in vitro* dissolution and bioavailability test data), reducing inter-patient variability in drug absorption [63]. The uniform release of pellet preparations ensures consistent drug absorption among different patients, which is conducive to improving the stability of therapeutic effects.

Enzyme-Responsive Hydrogels: Alginate hydrogels cross-linked with azo bonds are degraded by intestinal bacterial azoreductase in the colon, releasing 5-ASA rapidly. Preclinical studies show that this hydrogel increases 5-ASA concentration in colonic tissues by 40% compared to sustained-release granules [17]. Enzyme-responsive hydrogels use the specific enzyme environment in the colon to trigger drug release, which has higher site-specificity and can further improve the targeting of drugs.

Intelligent Responsive Dosage Forms: In recent years, pH/enzyme/cytokine-responsive preparations have become a research hotspot. For example, TNF-α-responsive nanoparticles can specifically release drugs in the high-TNF-α environment of inflamed tissues, increasing targeting efficiency by 10–20 times [64]. Intelligent responsive dosage forms can adjust the drug release rate and amount according to the microenvironment of the inflammatory site, achieving precise drug delivery and further improving the therapeutic effect.

4.3 Improvements in Drug Performance via Dosage Form Optimization

Pharmacokinetic Improvements: Sustained-release preparations prolong drug $t_{1/2}$ (e.g., mesalazine $t_{1/2}$ extended from 1.5–2 hours to 6–8 hours) and reduce AUC fluctuations (coefficient of variation from 50% to 15%). Targeted preparations increase the ratio of drug concentration in inflamed tissues to systemic circulation (targeting efficiency) by 5–10 times. The improvement of pharmacokinetic parameters lays a solid foundation for the improvement of drug efficacy and safety. Stable blood drug concentration can avoid the ineffectiveness caused by low concentration and the adverse reactions caused by high concentration [65].

Efficacy and Safety Improvements: New dosage forms increase the clinical remission rate of IBD by 20%–30% (e.g., targeted 5-ASA preparations vs. ordinary tablets) (clinical trial data) and reduce systemic adverse reactions by 30%–50% (e.g., reduced risk of AZA-induced myelosuppression with targeted nanoparticles) [66]. The

improvement of efficacy is mainly due to the increase of local drug concentration at the inflammatory site, and the reduction of adverse reactions is due to the reduction of drug distribution in non-target tissues.

Patient Compliance Improvements: Sustained-release preparations reduce dosing frequency from 3–4 times/day to 1 time/day, increasing patient compliance by 40%–60%. Improving patient compliance is crucial for the treatment of chronic diseases such as IBD. Regular medication can maintain stable therapeutic effects and reduce the risk of disease recurrence [67].

Economic Benefit Improvements: Although the R&D cost of new dosage forms is high, the improvement of efficacy and safety can reduce the cost of treatment for adverse reactions and disease recurrence, and bring significant economic benefits to patients and society in the long run [68].

5. Research Challenges

5.1 High R&D Costs

The R&D cycle of new dosage forms (e.g., targeted nanoparticles) is 5–8 years, with costs exceeding $100 million. Preclinical studies (cell models, animal experiments) and clinical trials (phase I–III) account for 70% of the total cost [69]. Preclinical studies need to conduct a large number of *in vitro* and *in vivo* experiments to verify the safety and efficacy of new dosage forms, and clinical trials need to recruit a large number of patients and conduct long-term follow-up, which requires a lot of manpower, material resources, and financial resources.

5.2 Clinical Trial Difficulties

IBD heterogeneity (diverse lesions, symptoms) leads to difficult patient screening. Multi-center trials (≥10 centers) are required to recruit sufficient patients (≥500 cases for phase III), increasing organizational complexity [70]. The heterogeneity of IBD makes the therapeutic effect of new dosage forms vary among different patients, which increases the difficulty of clinical trial design and result analysis. In addition, patients' willingness to participate in clinical trials is affected by factors such as treatment expectations and safety concerns, which also brings challenges to patient recruitment.

5.3 Strict Approval Standards

Regulatory authorities (e.g., FDA, NMPA) require comprehensive data on the safety, efficacy, and stability of new dosage forms. For example, targeted preparations need to provide evidence of targeting efficiency and long-term safety (≥5 years of follow-up), extending the approval cycle to 2–3 years [71]. The strict approval standards are to ensure the safety and effectiveness of new dosage forms, but they also increase the time and cost of R&D. Enterprises need to conduct in-depth research and data accumulation to meet the requirements of regulatory authorities.

5.4 Pharmacogenomic Application Challenges

Although pharmacogenomic research has made great progress, there are still many challenges in its clinical application. For example, the detection cost of genetic polymorphisms is relatively high, and the interpretation of detection results lacks unified standards. In addition, the interaction between multiple genes and environmental factors makes it difficult to accurately predict drug response [72]. To promote the clinical application of pharmacogenomics, it is necessary to reduce detection costs, establish unified interpretation standards, and conduct more large-scale clinical studies to verify the predictive value of genetic markers.

5.5 Intestinal Microbiota Regulation Challenges

The composition and function of intestinal microbiota are complex and affected by many factors such as diet, lifestyle, and disease status. It is difficult to achieve precise regulation of intestinal microbiota, and the mechanism of interaction between intestinal microbiota and drug pharmacokinetics needs to be further clarified [73]. Although probiotics, prebiotics, and other methods can regulate intestinal microbiota to a certain extent, their efficacy varies among individuals, and more in-depth research is needed to develop more effective regulatory strategies.

5.6 Development Challenges of Natural Active Ingredients for IBD

Natural active ingredients such as ligustilide have shown good anti-inflammatory and intestinal barrier repair effects in preclinical studies, but there are still many challenges in their clinical transformation and dosage form development. Similar preclinical evidence has been confirmed in other natural extracts: a study found that the aqueous extract of Korean Hedyotis diffusa (HCE) exerts non-toxic anti-inflammatory effects in DSS-induced colitis mice, which significantly down-regulates the expression of cyclooxygenase (COX)-2, inducible Nitric Oxide Synthase (iNOS) and NF-κB, and effectively protects the intestinal mucosal epithelium from inflammatory damage, further verifying the potential of natural active ingredients as alternative treatments for UC [74]. First, the low bioavailability of most natural active ingredients in the intestinal tract limits their therapeutic effect; second, the lack of standardized quality control methods for natural active ingredients leads to inconsistent drug efficacy; third, the mechanism of action of natural active ingredients in the treatment of IBD is complex, and further in-depth research is needed to clarify their target and signaling pathways to provide a basis for the development of targeted dosage forms [75]. Future research on IBD drugs should focus on personalized treatment guided by genetic testing and the development of intelligent responsive dosage forms. Natural active ingredients with targeted anti-inflammatory effects (e.g., ligustilide) provide new directions for the development of innovative drugs [76].

6. Conclusion

6.1 Research Summary

Significant progress has been made in the pharmacokinetics and dosage form optimization of IBD drugs. Clarifying the ADME processes and individual difference factors (intestinal inflammation, microbiota imbalance, genetic polymorphisms, pharmacogenomics) of drugs provides a basis for clinical rational drug use; new dosage forms (sustained-release, targeted preparations, intelligent responsive preparations) improve efficacy, safety, and patient compliance. In addition, natural active ingredients represented by ligustilide have been found to target key inflammatory signaling pathways (e.g., Early Growth Response Factor 1 (EGR1)-A Disintegrin and Metalloproteinase 17 (ADAM17)-TNF-α) to exert anti-inflammatory effects and repair the intestinal mucosal barrier, providing new candidate molecules for IBD drug development. This review systematically integrates the latest research results in pharmacokinetics, pharmacogenomics, intestinal microbiota, dosage form optimization and natural active ingredients, forming a complete theoretical system from mechanism exploration to practical application. The research results summarized in this review provide comprehensive scientific references for clinical practice and scientific research.

6.2 Future Perspectives

Personalized Treatment: Genetic testing (e.g., TPMT, CYP450 genotyping) before drug administration can guide dosage selection. For example, patients with TPMT3A/3A genotype should receive 10%–20% of the standard AZA dose to avoid myelosuppression. Combining multi-omics data (genomics, metabolomics) with gut microbiota sequencing can further improve the accuracy of personalized treatment.

Intelligent Responsive Dosage Forms: The development of pH/enzyme/cytokine-responsive preparations is warranted. For example, TNF-α-responsive nanoparticles release drugs specifically in high-TNF-α environments (inflamed tissues), increasing targeting efficiency by 10–20 times. Combining intelligent responsive dosage forms with natural active ingredients with specific anti-inflammatory targets can further improve the targeting and efficacy of drugs.

New Therapeutic Targets: Regulate intestinal flora via probiotics (e.g., Bifidobacterium breve) or fecal microbiota transplantation to improve drug metabolism (e.g., increase azoreductase activity to enhance SASP efficacy). Explore new immune targets (e.g., IL-23, JAK-STAT pathway) for drug development, and combine the research results of natural active ingredient targets (e.g., EGR1, ADAM17) to develop new small molecule targeted drugs with high efficiency and low toxicity.

Development of Natural Active Ingredients: Strengthen the research on the structural modification and dosage form optimization of natural active ingredients for IBD, improve their intestinal bioavailability and targeting; establish standardized quality control systems to ensure the consistency of drug efficacy; conduct in-depth research on the mechanism of action of natural active ingredients, and provide a theoretical basis for their clinical application and combined medication with traditional IBD drugs.

Combination Therapy Strategies: Combine new dosage forms with pharmacogenomic guidance, intestinal microbiota regulation, and natural active ingredients to form a comprehensive treatment strategy. For example, for patients with specific genetic polymorphisms, use targeted dosage forms combined with probiotics and natural active ingredients to improve therapeutic effect and reduce adverse reactions.

These advancements will not only improve the quality of life of IBD patients but also reduce the societal medical burden. With the continuous development of science and technology, it is expected that more effective, safe and personalized treatment methods and drugs will be developed in the near future, bringing new hope to IBD patients worldwide.

Abbreviations

IBD, Inflammatory Bowel Disease; UC, Ulcerative Colitis; CD, Crohn's Disease; ADME, Absorption, Distribution, Metabolism, Excretion; 5-ASA, Mesalazine; AZA, Azathioprine; MTX, Methotrexate; TPMT, Thiopurine Methyltransferase; CYP450, Cytochrome P450; TNF-α, Tumor Necrosis Factor-α; MAdCAM-1, Mucosal Addressin Cell Adhesion Molecule-1; COX, Cyclooxygenase; LOX, Lipoxygenase; GFR, Glomerular Filtration Rate; eGFR, Estimated Glomerular Filtration Rate; 6-TGNs, 6-Thioguanine Nucleotides; RBCs, red blood cells; AUC, Area Under the Concentration-Time Curve; Tmax, Time to Peak Concentration; Kd, Dissociation Constant; EGR1, Early Growth Response Factor 1; ADAM17, A Disintegrin and Metalloproteinase 17; iNOS, inducible Nitric Oxide Synthase.

Author Contributions

YC: Conceptualization, methodology, literature collection, data curation, writing—original draft, figures and tables preparation. YH: Conceptualization, supervision, writing—review and editing, funding acquisition, project administration. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

We thank the entire team for their support and assistance with this study.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

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