The Pharmacokinetics of Single-Inhaler Triple Therapy: A Systematic Reviews

ABSTRACT

Background: Single inhaler triple therapy (SITT), combining an inhaled corticosteroid, a long-acting β_2-agonist, and a long-acting muscarinic antagonist, is recommended for patients with chronic obstructive pulmonary disease (COPD) who remain symptomatic or experience recurrent exacerbations. Although its clinical benefits are well established, pharmacokinetic evidence across healthy subjects and patients with COPD remains fragmented and requires systematic evaluation. **Methods:** This systematic review was conducted in accordance with the PRISMA 2020 guidelines. Electronic databases were systematically searched to identify clinical and population pharmacokinetic studies evaluating SITT in healthy volunteers and patients with COPD. Studies were selected based on predefined eligibility criteria. Risk of bias was assessed using standardized appraisal tools, and findings were synthesized narratively, focusing on key pharmacokinetic parameters. **Results:** Included studies consistently reported maximum plasma concentration, area under the concentration–time curve, and time to reach maximum concentration for individual SITT components. Overall, systemic exposure of inhaled corticosteroids, long-acting β_2-agonists, and long-acting muscarinic antagonists administered as SITT was comparable to that observed with dual- or single-component inhaled therapies. No clinically meaningful accumulation was identified with repeated dosing. Variability in pharmacokinetic profiles was primarily associated with population characteristics, disease status, and inhalation technique. **Conclusion:** Current evidence indicates that SITT demonstrates predictable pharmacokinetic behavior with limited systemic exposure in both healthy subjects and patients with COPD. These findings support its clinical use as a pharmacokinetically stable and effective therapeutic option.

Keywords: Chronic obstructive pulmonary disease; Single inhaler triple therapy; Pharmacokinetics; Systematic review

ABSTRAK

Latar Belakang: *Single inhaler triple therapy* (SITT) yang mengombinasikan kortikosteroid inhalasi, agonis β_2 kerja panjang, dan antagonis muskarinik kerja panjang, direkomendasikan bagi pasien penyakit paru obstruktif kronis (PPOK) yang tetap bergejala atau mengalami eksaserbasi berulang. Meskipun manfaat klinisnya telah terbukti dengan baik, bukti farmakokinetik SITT pada individu sehat dan pasien PPOK masih tersebar dan memerlukan evaluasi sistematis. **Metode:** Ulasan sistematis ini dilakukan sesuai dengan pedoman PRISMA 2020. Basis data elektronik ditelusuri secara sistematis untuk mengidentifikasi studi farmakokinetik klinis dan populasi yang mengevaluasi SITT pada relawan sehat dan pasien PPOK. Studi diseleksi berdasarkan kriteria inklusi dan eksklusi yang telah ditetapkan sebelumnya. Risiko bias dinilai menggunakan alat penilaian metodologis standar, dan hasil disintesis secara naratif dengan fokus pada parameter farmakokinetik utama. **Hasil:** Studi yang disertakan secara konsisten melaporkan konsentrasi plasma maksimum, luas area di bawah kurva konsentrasi–waktu, dan waktu pada konsentrasi puncak dari masing-masing komponen SITT. Secara keseluruhan, paparan sistemik kortikosteroid inhalasi, agonis β_2 kerja panjang, dan antagonis muskarinik kerja panjang yang diberikan sebagai SITT sebanding dengan terapi inhalasi tunggal atau kombinasi ganda. Tidak ditemukan akumulasi sistemik yang bermakna secara klinis pada penggunaan berulang. Variabilitas farmakokinetik terutama berkaitan dengan karakteristik populasi, status penyakit, dan teknik inhalasi. **Kesimpulan:** Bukti yang tersedia menunjukkan bahwa SITT memiliki profil farmakokinetik yang dapat diprediksi dengan paparan sistemik yang terbatas pada individu sehat maupun pasien PPOK. Temuan ini mendukung penggunaan SITT sebagai pilihan terapi yang stabil secara farmakokinetik dan efektif secara klinis.

Kata kunci: Penyakit paru obstruktif kronis; Inhaler tunggal tiga komponen; Farmakokinetika; Ulasan sistematis

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition marked by enduring airflow restriction and chronic airway inflammation, and it continues to be a primary cause of morbidity and mortality globally (Agustí et al., 2023). Patients who persist with symptoms or recurrent exacerbations despite dual inhaled therapy should escalate to inhaled triple therapy, which includes an inhaled corticosteroid (ICS), a long-acting β_2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), as per international guideline (Suissa et al., 2022). Extensive clinical trials have shown that triple therapy improves pulmonary function and reduces the likelihood of exacerbations compared with dual regimens (Lipson et al., 2017). The development of single-inhaler triple therapy (SITT) formulations, such as fluticasone furoate/umeclidinium/vilanterol, budesonide/glycopyrronium/formoterol, and beclomethasone dipropionate/formoterol/glycopyrronium, aims to optimize treatment and improve adherence while maintaining efficacy (Young et al., 2025). The combination of three medicines with distinct pharmacological characteristics in a single inhaler raises significant questions about their pharmacokinetic behavior.

COPD affects approximately 10.3% of the global population, corresponding to nearly 392 million individuals worldwide, creating a substantial demand for effective long-term inhalation therapies (Di Marco et al., 2025). Within this context, SITT represents 28.2% of triple-therapy initiations in France and 21.9–35.8% of triple-therapy users in Spain, while approximately 10.5% of diagnosed COPD patients receive triple therapy overall (Alcázar-Navarrete et al., 2022; Deslee et al., 2023; Di Marco et al., 2025). Across epidemiological cohorts, SITT users are typically older adults (mean age 67–75 years) and predominantly male (63–74%), with moderate (≈62%) to severe (26.5–37%) airflow limitation, and approximately 84% of initiations occur following escalation from dual therapy (Alcázar-Navarrete et al., 2022; Deslee et al., 2023). Real-world data further indicate 12-month persistence rates of 62–64%, compared with 52–54% for multiple-inhaler triple therapy, alongside 32–35% lower risk of moderate-to-severe exacerbations and approximately 33% lower all-cause mortality (González-González et al., 2025).

Inhaled therapies aim to administer medications directly to the lungs while reducing systemic exposure; however, detectable plasma concentrations of ICS, LABA, and LAMA components are consistently noted (Brealey et al., 2015). Clinical and population pharmacokinetic studies in healthy individuals and COPD patients have assessed parameters including maximum concentration (C_{max}), area under the concentration–time curve (AUC), and time to reach maximum concentration (t_{max}) for SITT components. These trials indicate that systemic exposure from SITT parallels that of the same medications used in monotherapy or dual therapy, with no clinically significant accumulation with prolonged usage (Dunn et al., 2020). Pharmacokinetic variability may arise from variations in illness severity, lung function, and inhalation technique, thereby affecting both efficacy and safety (Bourbeau et al., 2021).

A comprehensive synthesis of existing pharmacokinetic research is essential to facilitate clinical and regulatory decision-making. This systematic review seeks to synthesize clinical pharmacokinetic data on single-inhaler triple therapy in healthy volunteers and COPD patients, emphasizing systemic exposure to ICS, LABA, and LAMA components and variations across populations. This review aims to assess the relationship between the pharmacokinetic properties of SITT and its therapeutic efficacy and safety in the management of COPD, in accordance with PRISMA recommendations, thereby providing a succinct scientific foundation for improved, personalized treatment regimens.

METHODS

Study Protocol and Eligibility Criteria

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in the execution and documentation of systematic reviews. The primary objective was to identify, evaluate, and synthesize clinical evidence on the pharmacokinetics of triple inhaler therapy, specifically the combination of inhaled corticosteroids (ICS), a long-acting β2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA). The eligibility criteria were defined using the PICOS framework. We included studies involving adult patients with or without Chronic Obstructive Pulmonary Disease (COPD). The intervention of interest was single-inhaler triple therapy (SITT), such as fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), budesonide/glycopyrronium/formoterol (BGF), and beclomethasone dipropionate/formoterol/glycopyrronium (BDP/FF/GB). Studies were eligible if they compared these interventions against multiple-inhaler triple therapy (MITT), dual therapies (LABA/LAMA or ICS/LABA), or monotherapies. The outcomes focused on key pharmacokinetic parameters, including maximum plasma concentration (C_{max}), area under the curve (AUC), and time to reach maximum concentration (t_{max}). The study designs included randomized controlled trials (RCTs), crossover trials, and clinical pharmacokinetic studies. Conversely, studies were excluded if they met any of the following criteria: patients diagnosed with primary asthma or Asthma-COPD Overlap (ACO); preclinical research, including in vitro models or animal studies; non-original research articles, such as case reports, literature reviews, editorials, and conference abstracts with insufficient data; and studies published in languages other than English where no official translation was available.

Search Strategy and Study Selection

A comprehensive systematic search was performed across electronic databases, including PubMed, ScienceDirect, and Scopus, from inception to December 2025. To ensure a maximum retrieval of relevant studies and considering the limited volume of existing literature on this topic, no restrictions were applied regarding the year of publication. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords: ("Pulmonary Disease, Chronic Obstructive" OR

"COPD") AND ("Triple Therapy" OR "Single Inhaler" OR "Fixed-dose combination") AND ("Pharmacokinetics" OR "Bioavailability" OR "Lung Deposition") AND ("Clinical Efficacy" OR "Safety"). To ensure literature saturation, the reference lists of retrieved articles and relevant review papers were manually screened. After removing duplicates using reference management software, two independent reviewers screened the titles and abstracts. Full-text versions of potentially eligible studies were then independently assessed for final inclusion. Any disagreements between the reviewers were resolved through discussion.

Data Extraction and Quality Assessment

Data extraction was performed by two independent reviewers using a standardized electronic data collection form. Discrepancies were resolved through consensus. The extracted data were categorized into two primary domains. First, general study characteristics were recorded, including the primary author, year of publication, country of origin, study design, sample size, outcome measures, comparator groups, and specific dose regimens. Second, pharmacokinetic parameters were systematically tabulated to capture dose-specific data, including peak plasma concentration (C_{max}), area under the curve (AUC), and time to reach $_{max}$imum concentration (t_{max}). This dual-structured extraction approach ensured a comprehensive overview of both the clinical context and the technical pharmacological profile of single-inhaler triple therapy.

The methodological quality assessment of the included studies was rigorously evaluated using the Critical Appraisal Skills Programme (CASP) checklists. Depending on the study design, the appropriate CASP tool (CASP Randomized Controlled Trials Checklist and CASP Cohort Study Checklist) was applied. Each study was assessed across key domains, including the clarity of the research objective, the appropriateness of the study design, recruitment strategy, minimization of bias, and the precision and applicability of the results. The quality of each study was then categorized as high, medium, or low based on its compliance with the CASP criteria. This assessment was used to determine the strength of the evidence and to inform the narrative synthesis of the pharmacokinetic and therapeutic findings.

Data Synthesis and Analysis

The synthesis of evidence was conducted using a systematic narrative approach, focusing on integrating study characteristics and quantitative pharmacokinetic data. Given the expected variability in study designs and reporting formats, data were synthesized based on two primary domains: general study characteristics and clinical pharmacokinetic parameters. In the first phase of the analysis, a descriptive synthesis of general characteristics was performed. Studies were categorized by author, year, and country of origin to identify geographical trends in research. We further analyzed the distribution of study designs, sample sizes, and specific dose regimens. Comparator groups were evaluated to distinguish between studies comparing Single-Inhaler Triple Therapy (SITT) against dual therapy or

multiple-inhaler regimens. The second phase involved a specialized synthesis of pharmacokinetic (PK) parameters. Quantitative data for each component of the triple therapy (ICS, LABA, and LAMA) were extracted and compared. The analysis focused on systemic exposure metrics, specifically peak plasma concentration (C_{max}), area under the curve (AUC), and time to reach maximum concentration (t_{max}). Parameters were summarized using mean values and standard deviations or geometric means and coefficients of variation, as reported in the original studies. To address the study's objective, we performed a comparative analysis of these PK parameters across different dose regimens and populations. Due to the technical nature of pharmacokinetic data and the anticipated heterogeneity in sampling timeframes and analytical methods, a narrative synthesis supported by detailed summary tables was utilized to illustrate the pharmacological behavior of SITT formulations.

RESULTS AND DISCUSSION

Study Selection Process and General Characteristics

The search and study selection process is conducted systematically across three central electronic databases: Scopus, ScienceDirect, and PubMed. The study selection followed a systematic approach across three databases (Scopus: n=46; ScienceDirect: n=11; PubMed: n=46). Initial searches yielded 103 records, which were refined to 98 records after applying 'research article' and 'open access' filters. After removing 52 duplicate records, 46 unique records remained and were included in the screening stage. During the title and abstract screening, 33 studies were excluded (n=20 due to irrelevant topics; n=13 due to being review articles), leaving 13 studies for full-text assessment. At the full-text assessment, 5 additional studies were excluded: one (n=1) because the outcomes did not align with the study objectives, and four (n=4) because the study design did not meet the inclusion criteria. Finally, 8 studies met all criteria and were included in this systematic review.

A complete flowchart is presented in Figure 1, which comprehensively shows the stages of identification, screening, eligibility, and inclusion of the study.

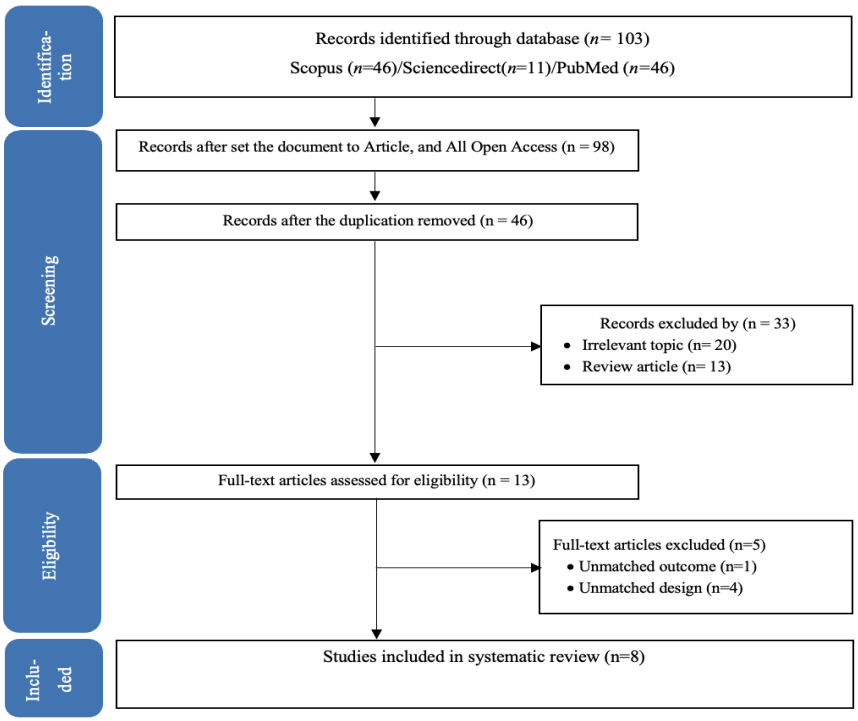

Figure 1. PRISMA Flowchart

All studies (n=8) that met the inclusion criteria were analyzed in this systematic review (Table 1), including phase I, phase III, and phase IV trials conducted in various geographic regions, including the United States, China, Europe, and Japan. The studies evaluated the pharmacokinetic profiles of three different single-inhaler triple therapy (SITT) formulations. For the combination of Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI), pharmacokinetic evidence is supported by phase I trials in healthy volunteers by Brealey et al. (2015) and Li et al. (2018). The evaluation of the Budesonide/Glycopyrronium/Formoterol (BGF) formulation included six studies, consisting of phase I trials on healthy subjects by Chen et al. (2019), Darken et al. (2018), Dorinsky et al. (2020), and Maes et al. (2019), as well as pharmacokinetics substudies in COPD patients by Dunn et al. (2020) and pooled analysis by Huang et al. (2020).

Table 1. Main characteristics of the included trials on the triple inhaler

Author (Year)	Country (s)	Study Design	Sample Size (Condition)	Problem Statement	Main Finding(s)	Consistency vs Dual/Single Therapy	Repeated Dose Accumulation
Budesonide/Glycopyrrolate/Formoterol Fumarate (BUD/GLY/FOR)							
Chen et al. (2019)	China	Phase I, RCT, DB, parallel	96 (Healthy)	Need to ensure adding budesonide does not change LAMA/LABA disposition in Chinese subjects	Triple combination is PK stable; high subject variability is a standard hurdle in this population	CONSISTENT: Budesonide's PK is comparable to Western & Japanese populations; no DDI glycopyrronium-budesonide	MODERATE ACCUMULATION: RAC budesonide 1.5, glycopyrronium 3.0–3.3 (day-8)
Darken et al. (2018)	USA	Phase I, RCT, SD, crossover	84 (Healthy)	Bioequivalence of co-suspension MDI vs. traditional MDI	Budesonide bioequivalence achieved; healthy subjects are more sensitive for detecting formulation differences	CONSISTENT: Bioequivalent of BUD/FORM DPI for budesonide; no PK interaction between components	
Maes et al. (2019)	USA	Phase I, RCT, SD, crossover	72 (Healthy)	Reliability of co-suspension MDIs vs. flow-dependent DPIs	DPIs show higher variability than MDIs; MDIs are more robust for patients with inconsistent breath patterns	CONSISTENT: BGF≈BFF for budesonide & formoterol; confirmation of no DDI glycopyrronium-budesonide	
Dorinsky et al. (2020)	USA	Phase I, OL, SD, crossover	56 (Healthy)	Whether spacers cause dangerous over-exposure or merely stabilize drug delivery	Spacers help subjects with poor technique reach standard exposure levels without safety risks	TECHNIQUE VARIABILITY: Spacer increases budesonide exposure by 1.3–1.5×; glycopyrronium 2.4× (Cmax)	
Dunn et al. (2020)	USA	Phase III, Randomized, DB, parallel group	202 (COPD)	Uncertainty if COPD lung obstruction changes drug absorption vs. healthy subjects	Steady-state PK is consistent regardless of COPD severity, validating safety models using healthy subjects	CONSISTENT: PK budesonide in COPD ≈ other dual/triple therapies in KRONOS (GMR 96–109%)	HIGHER ACCUMULATION: RAC AUC budesonide 1.26; glycopyrronium 1.79; Formoterol 1.43
Huang et al. (2020)	China, Japan, Western (2)	Post-hoc analysis of 4 pooled RCTs	264 (Healthy)	Lack of unified cross-ethnic data to classify BGF MDI as ethnically insensitive	Ethnic exposure differences are statistically present but clinically irrelevant; global standardized dosing is safe	MINOR ETHNIC DIFFERENCES: Asia's glycopyrrolate Cmax is 30–47% lower than Western; budesonide & formoterol are comparable	
Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI)							
Brealey et al. (2015)	USA	Phase I, RCT, SD, crossover (DB/OL)	88 (Healthy)	Unknown PK profile for FF/UMEC/VI; standard sampling missed rapid Vilanterol peaks	Triple and dual therapies are equivalent; 3-compartment modeling corrected initial C_{max} underestimations	CONSISTENT: Exposure of FF, UMEC, VI is comparable to dual therapy; Cmax VI difference is clinically meaningless	
Li et al. (2018)	China	Phase I, OL, SD, and RD	16 (Healthy)	Need for local bridging data due to potential Chinese metabolic differences	Chinese data aligns with global profiles; body size, not ethnicity, drives fluticasone furoate exposure	CONSISTENT: PK profiles were comparable to Caucasian mono/dual therapy data; Ro Cmax FF = 1.99	MEDIUM ACCUMULATION: RAC Cmax FF 1.99; UMEC 1.67; VI 1.63

Note: SD: Single Dose; RD: Repeated Dose; DPI: Dry Powder Inhaler; MDI: Metered Dose Inhaler;; OL: open label; DB: double blind; RCT: Randomized Controlled Trial.

Quality Assessment

The methodological quality assessment of the included studies was conducted using the Critical Appraisal Skills Program (CASP) instrument for Randomized Controlled Trial (RCT) and cohort designs. Overall, the analyzed RCTs demonstrated strong internal validity, with almost all studies formulating clear research questions and randomly assigning participants to minimize selection bias. Studies by Brealey et al. (2015), Chen et al. (2019), Darken et al. (2018), and Maes et al. (2019) demonstrate full compliance with blinding procedures for participants, investigators, and outcome assessors alike. Specifically for Maes et al. (2019), despite limitations in reporting the research question formulation, this study demonstrates methodological strengths in operational aspects, including complete participant accountability and precise estimation of effect sizes. However, there are variations in the blinding element in some other studies. For example, the survey by Dorinsky et al. (2020) did not use any blinding procedure, whereas Dunn et al. (2020) used only partial blinding (i.e., yes). Despite differences in concealment techniques, all of these RCT studies remained accountable by reporting all participants through the end of the research. They presented the intervention effects comprehensively, with precise estimates of precision.

Consistent with the findings of the RCTs, the assessment of the cohort studies by Huang et al. (2020) and Li et al. (2018) indicates high methodological standards. Both studies successfully recruited cohorts and measured exposure and outcomes accurately, minimizing bias. The most significant thing is the researchers' ability to identify and account for confounding factors in both the design and analysis of their research. The results of this cohort study provide compelling evidence of similar pharmacokinetic profiles between Asian and Western subjects, supporting the clinical application of interventions without the need for ethnic-based dose adjustments. Collectively, the low risk of bias across most domains in all reviewed studies strengthens the validity of the findings in this systematic review. However, caution should still be exercised when interpreting subjective outcomes from non-blinded studies.

The consistency of findings across the RCT and cohort studies provides a strong foundation for the validity of this systematic review's results. In the RCT group, the similarity of baseline characteristics between study groups and equivalent treatments outside the experimental intervention ensures that observed differences in outcomes are truly the effect of the intervention administered. For example, the success of studies such as Brealey et al. (2015) and Chen et al. (2019) in maintaining strict blinding procedures indicates that performance bias and detection bias have been minimized. On the other hand, findings from cohort studies by Huang et al. (2020) and Li et al. (2018) strengthen clinical evidence by comprehensively identifying confounding factors, making the results regarding pharmacokinetic (PK) profiles reliable and relevant to a broader population.

Individual Study Results and Data Synthesis

A total of 8 studies were analyzed to evaluate the pharmacokinetic parameters of SITT. Statistical summaries for the main PK parameters of the key studies are presented in the pharmacokinetics summary Table 2 below.

Table 2. Pharmacokinetics parameters of included trials on the triple inhaler

Study	Model	Drug (Total doses in mcg)	C_{max} (pg/mL)	AUC (h.pg/mL)	t_{max} (h)	Vd/F (L)	CL/F (L/h)
Budesonide/Glycopyrrolate/Formoterol Fumarate (BUD/GLY/FOR)							
Chen et al. (2019)	NCA	BUD (320)	626.4	2510 (AUC_{0-12})	0.333	NR	NR
		GLY (14.4)	11.30	69.49 (AUC_{0-12})	0.333		
		FOR (10)	16.13	81.94 (AUC_{0-12})	0.100		
Darken et al. (2018)	NCA	BUD (320)	472.04	1612.21 (AUC_{0-12})	0.67	NR	NR
		GLY (14.4)	8.28	10.82 (AUC_{0-12})	0.08		
		FOR (10)	10.55	53,66 (AUC_{0-12})	0.33		
Maes et al. (2019	NCA	BUD (320)	528.9	1762.5 (AUC_{0-12})	0.33	NR	207.3
		GLY (14.4)	7.36	19.73 (AUC_{0-12})	0.03		NR
		FOR (10)	9.36	42.86 (AUC_{0-12})	0.67		204.8
Dorinsky et al. (2020)	NCA	BUD (320)	702.3	1934 ($AUC_{0-t\ last}$)	0.33	918.5	150.1
		GLY (36)	47.7	74.3 ($AUC_{0-t\ last}$)	0.03	3028	712.9
		FOR (9.6)	18.1	35.9 ($AUC_{0-t\ last}$)	0.10	1137	152.0
Dunn et al. (2020)	NCA	BUD (320)	654.4	2573 (AUC_{0-12})	0.97	NR	NR
		GLY (18)	19.8	83.1 (AUC_{0-12})	0.08		
		FOR (9.6)	10.5	61.9 (AUC_{0-12})	0.63		

Huang et al. (2020) (*Chinese*)	NCA	BUD (320)	459.3	1747.9 (AUC_{0-12})	NR	NR	NR
		GLY (18)	4.9	29.4 (AUC_{0-12})			
		FOR (9.6)	9.7	47.8 (AUC_{0-12})			
Huang et al. (2020) (*Japanese*)	NCA	BUD (320)	639.5	2165.5	NR	NR	NR
		GLY (18)	11.2	29.5			
		FOR (9.6)	13.2	56.3			
Huang et al. (2020) (*Western*)	NCA	BUD (320)	455.0	1632.6	NR	NR	NR
		GLY (18)	9.0	22.1			
		FOR (9.6)	9.6	48.80			
Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI)							
Brealey et al. (2015)	NCA; 3-Comp (VI)	FF (400)	79.4	882 (AUC_{0-t})	0.2	NR	NR
		UMEC (500)	1189	885 (AUC_{0-t})	0.1		12 (CL)
		VI (100)	639	522 (AUC_{0-t})	0.1		NR
Li et al. (2018)	NCA	FF (100)	27.32	276.96 (AUC_{0-t})	0.875	NR	NR
		UMEC (62.5)	241.35	117.19 (AUC_{0-t})	0.083		
		VI (25)	196.78	101.12 (AUC_{0-t})	0.083		

Note: NCA: non-compartmental analysis; comp: compartment; C_{max}: maximum observed plasma concentration; AUC: area under the plasma drug concentration-time curve; t_{max}: time to C_{max}; Vd/F: volume of distribution; CL/F: apparent total body clearance; NR: not reported

Systemic Absorption Pattern of Triple Inhaler Components

Cross-study analysis revealed consistent absorption patterns across drug classes. Inhaled corticosteroids (ICS) showed the highest C_{max} among the three components, with the highest values in beclomethasone dipropionate (790 pg/mL) and the lowest in fluticasone furoate (27.32-79.4 pg/mL). These differences indicate significant systemic absorption variability between different ICS molecules.

Long-acting muscarinic antagonists (LAMAs) exhibit extensive C_{max} variability, ranging from 4.9 pg/mL (glycopyrrolate in Huang et al., 2020) to 1189 pg/mL (umeclidinium in Brealey et al., 2015) This extreme variability is likely due to differences in absolute doses, formulations, and devices used.

Long-acting beta2-agonist (LABA) exhibits relatively consistent systemic absorption in the low to moderate range. Formoterol fumarate from the BUD/GLY/FOR combination showed C_{max} 7.4-18.1 pg/mL, while vilanterol from the FF/UMEC/VI combination showed higher values (196.78-639 pg/mL).

Absorption Time Profile

Although systemic exposure (Cmax and $AUC_{0–12}$) of budesonide is consistently higher in patients with COPD than in healthy subjects, the tmax parameter shows a distinct pattern. The tmax values for budesonide, glycopyrronium, and formoterol in COPD patients reported by Dunn et al. (2020) (0.97 hours, 0.08 hours, and 0.63 hours, respectively) are similar to those observed in healthy subjects across all included studies (budesonide: 0.33 hours; glycopyrronium/umeclidinium: ≤0.33 hours; formoterol/vilanterol: 0.083–0.67 hours). This consistency suggests that airway obstruction in COPD does not substantially delay the peak absorption rate of SITT components. Therefore, while COPD pathophysiology appears to increase the amount of drug absorbed systemically, as indicated by higher Cmax and AUC values, it does not affect the rate of attainment of peak concentrations. These findings support the hypothesis that increased systemic exposure in COPD is primarily influenced by post-absorptive factors, such as reduced clearance and altered metabolism, rather than by changes in initial lung deposition and absorption kinetics.

Direct comparison of tmax values across studies is constrained by variability in sampling schedule designs. In a subsequent study, Brealey et al. (2015) incorporated additional sampling points at 3, 7, 10, and 12 minutes post-dose and observed that the tmax of vilanterol occurred earlier (approximately 5 minutes) compared to estimates from the initial study, which employed less frequent sampling. This finding demonstrates that tmax is highly sensitive to the resolution of the blood sampling schedule, as it is directly determined by the available sampling points. Consequently, numerical differences in tmax between studies should be interpreted in light of differences in sampling design, rather than as true biological variation.

Distribution and Clearance Parameters

Data on distribution volume (Vd/F) and clearance (CL/F) are only reported on a limited basis. Dorinsky et al. (2020) reported the most complete data for the BUD/GLY/FOR combination, showing varied Vd/F: budesonide 918.5 L, glycopyrrolate 3028 L, and formoterol 1137 L. Large distribution volumes for glycopyrrolate indicate extensive tissue distribution.

The reported apparent clearance (CL/F) shows considerable variability. For budesonide, the CL/F ranges from 150.1 to 207.3 L/h, indicating significant first-pass hepatic clearance. Glycopyrrolate exhibits a very high CL/F (712.9 L/h), consistent with the characteristics of quaternary ammonium compounds

that have extensive renal and hepatic clearance. Formoterol shows CL/F in the range of 152.0-204.8 L/h.

General Interpretation of Results in the Context of Other Evidence

This systematic review identified and synthesized pharmacokinetic evidence from 9 studies evaluating three triple inhaler combinations for COPD therapy. The main findings showed that all triple inhaler combinations exhibited rapid systemic absorption profiles, with t_{max} less than 1 hour for each component, indicating efficient pulmonary deposition and rapid onset of action. This pharmacokinetic profile fundamentally supports the rationale for the use of triple therapy in the management of COPD, particularly for patients with persistent symptoms or recurrent exacerbations despite having received dual treatment.

The findings regarding the variability of C_{max} between drug components are consistent with known physicochemical and pharmacological characteristics. Inhaled corticosteroids exhibit the most significant systemic absorption, which is clinically relevant given the potential systemic side effects of corticosteroids, especially with long-term use.

The differences in pharmacokinetic profiles between fluticasone furoate and budesonide reflect fundamental differences in the physicochemical properties of the two molecules. Fluticasone furoate showed a lower C_{max} (27.32-79.4 pg/mL in Brealey et al., 2015; Li et al., 2018) compared to budesonide (459.3-702.3 pg/mL), indicating higher pulmonary deposition and lower systemic absorption. This is consistent with the high lipophilicity of fluticasone furoate, which facilitates retention in the lungs and minimizes systemic exposure, potentially reducing the risk of systemic side effects.

The pharmacokinetic profile of the LAMA shows the most significant variability among the three drug classes. Umeclidinium in the FF/UMEC/VI combination showed a much higher C_{max} (241.35-1189 pg/mL in Brealey et al., 2015; Li et al., 2018) compared to glycopyrrolate in the BUD/GLY/FOR combination (4.9-47.7 pg/mL). This difference is likely due to differences in absolute dose: umeclidinium is administered at 62.5-500 mcg, while glycopyrrolate is administered at 14.4-36 mcg. However, these differences do not necessarily reflect differences in clinical efficacy, given the differences in intrinsic potency and receptor affinity between the two molecules.

The large volume of distribution for glycopyrrolate (3028 L in Dorinsky et al., 2020) indicates extensive distribution to peripheral tissues, consistent with the characteristics of quaternary ammonium compounds. Despite this, the large distribution volume does not compromise the efficacy of local bronchodilation, as the main action of LAMA is on airway muscarinic receptors.

Long-acting beta2-agonists exhibit the most consistent and predictable pharmacokinetic profile. Formoterol fumarate exhibits C_{max} in the range of 7.4-19.4 pg/mL with a very fast t_{max} (0.08-0.67 hours), consistent with the clinically known fast-acting onset of formoterol. Vilanterol exhibits a higher C_{max}

(196.78-639 pg/mL in Brealey et al., 2015; Li et al., 2018), which is likely associated with higher doses (25-100 mcg) than formoterol (9.6-12 mcg).

The findings of this systematic review are consistent with the existing literature on the pharmacokinetics of individual components of triple inhalers. No significant pharmacokinetic interactions were identified when these components were administered in fixed combinations, indicating that the absorption, distribution, and elimination of each component were not substantially affected by the presence of the others. This supports the pharmacological rationale of using fixed-dose combinations to simplify the therapy regimen and improve patient adherence.

The Influence of Ethnicity on Pharmacokinetics of SITT

The cross-ethnic analysis conducted by Huang et al. (2020), which included data from 264 subjects (64 Chinese, 31 Japanese, and 169 Western), revealed that the AUC_{0-12} and Cmax parameters for budesonide and formoterol were consistent across ethnic groups, with most GLSM ratios ranging from 0.92 to 1.22. In contrast, the glycopyrrolate component demonstrated significant inconsistency: Cmax in Asian subjects was lower than in Western subjects, although the AUC_{0-12} remained comparable. This finding contrasts with the results of Li et al. (2018), who reported that in a Chinese population receiving FF/UMEC/VI, the Cmax of UMEC was higher compared to historical Western population references.

Budesonide is metabolized primarily by CYP3A4 and CYP3A5 in the liver. Polymorphisms in these genes, which differ in prevalence between ethnicities, can affect budesonide clearance. Differences in allele frequencies across ethnic groups suggest that Asian populations, with a higher prevalence of the CYP3A5*3 allele, may exhibit reduced first-pass budesonide metabolism compared to Caucasian populations. This could result in higher bioavailability and potentially different therapeutic outcomes (Roy et al., 2005).

Asian populations generally have lower BMIs but higher body fat percentages than Western populations at the same BMI. Differences in body composition, such as higher visceral adipose tissue in specific populations, can influence drug distribution and metabolism (Li et al., 2019). Lipophilic drugs like budesonide are distributed in body fat, and the amount and distribution of adipose tissue can influence their pharmacokinetics. Higher body fat can increase the volume of distribution and potentially alter the clearance rates of lipophilic drugs (Goto et al., 2017).

Although all subjects in Huang et al. (2020) are healthy, minor differences in lung capacity, airway geometry, or inter-ethnic breathing patterns can affect pulmonary deposition and subsequent absorption. The significantly higher inter-ethnic variability of glycopyrrolate compared with budesonide or formoterol suggests that ethnic factors influence the pharmacokinetics of LAMAs more substantially. The clinical implications of these findings are that dose optimization for triple inhalers may need to consider ethnic factors, particularly in populations with consistently higher or lower systemic exposures. However, it should be noted that intra-ethnic variability remains substantial, and personalization based

on individual patient characteristics (renal function, body weight, comorbidities) may be more relevant than generalizations based solely on ethnicity.

Pharmacokinetics in COPD Patients Compared to Healthy Subjects

A direct comparison between studies in healthy subjects and the investigation by Dunn et al. (2020) in patients with COPD demonstrates clinically discrepancies. In healthy subjects administered BGF MDI 320 µg (Darken et al., 2018; Maes et al., 2019; Chen et al., 2019; Huang et al., 2020), the maximum plasma concentration (Cmax) of budesonide ranged from 455 to 528.9 pg/mL. In contrast, COPD patients in the KRONOS sub-study (Dunn et al., 2020) exhibited a Cmax of 631 to 663 pg/mL, exceeding the upper limit observed in healthy subjects by 19 to 46%. A similar trend was observed for the area under the concentration-time curve from zero to twelve hours (AUC_{0-12}): 1.612 to 1.762 h·pg/mL in healthy subjects compared to 2,516 to 3,005 h·pg/mL in COPD patients.

These results challenge the prevailing assumption that airway obstruction in COPD reduces pulmonary deposition and consequently lowers systemic exposure. Several mechanisms may account for this observation: redistribution of drug deposition from peripheral to central airways, which could enhance systemic absorption; potential reductions in drug clearance due to comorbidities in older COPD patients; and changes in CYP3A4 metabolic enzyme expression associated with chronic inflammation. However, this interpretation warrants methodological caution, as the KRONOS sub-study utilized a parallel-group design rather than a crossover design, so differences in exposure between groups may be confounded by patient characteristics.

Airway obstruction in COPD can shift deposition from peripheral to central airways, where systemic absorption may be more efficient due to greater vascularization (Rafael & Andrade, 2024; Zhou & Yan, 2023). COPD patients often have comorbidities (cardiovascular disease, kidney disorders) or concomitant drug use that can affect budesonide clearance (Rizvi et al., 2012). Reduced clearance will result in a higher AUC at the same dose. COPD is a chronic inflammatory condition that can affect the expression or activity of metabolic enzymes and transporters, potentially altering pharmacokinetics (Berg et al., 2014). COPD patients in Dunn et al. (2020) likely have a diverse spectrum of severity. Patients with more severe COPD may have different pharmacokinetic patterns than those with mild COPD. These findings have important implications for safety monitoring. If COPD patients experience systemic exposures comparable to or higher than those of healthy subjects, then the risk of systemic side effects of corticosteroids needs to be monitored closely, especially in long-term use.

Consistency of Systemic Exposure of SITT Compared to Dual and Single Therapy

Five studies that directly compared systemic exposure to single-inhaler triple therapy (SITT) with dual- or single-component therapy—including Brealey et al. (2015), Darken et al. (2018), Maes et al. (2019), Chen et al. (2019), and the KRONOS sub-study in Dunn et al. (2020)—collectively indicate that the single-inhaler formulation does not alter the pharmacokinetic profiles of the individual components

compared to separate therapies. The confidence in this conclusion depends on the methodological quality of the included studies. Four of these studies employed a double-blind crossover design (Brealey et al., Darken et al., Maes et al., Chen et al.), whereas the KRONOS substudy used a parallel-group design.

The findings of Brealey et al. (2015), who initially reported a 46% higher Cmax of vilanterol in triple therapy compared to FF/VI, were not replicated in their subsequent study, which implemented a more frequent sampling schedule. Post-hoc analysis indicates that the observed difference was most likely attributable to an underestimation of Cmax in the dual-therapy arm due to limitations in the original sampling schedule, rather than a true formulation effect. This case illustrates how methodological design, particularly sampling strategy, can directly influence the validity of pharmacokinetic findings.

Consistency of Accumulation Patterns with Repeated Dosing

Three studies evaluating the pharmacokinetics (PK) of repeated dosing—Li et al. (2018) in healthy Chinese subjects with FF/UMEC/VI, Chen et al. (2019) in healthy Chinese subjects withe subjectswidthe subjectswidth BGin COPD patients with BGF MDI—provide an informative comparative overview of accumulation patterns patterns paThe accumulation ratio (RAC) of budesonide demonstrates good consistency: Li et al. reported an Ro Cmax of 1.99 for,99 untuk FF; Chereported aelaporkan for RAC Cmax buof 1.4–1.5; and–1,5; dan Dunreported aelaporkan for RAC Cmax buof 0.95 (indicating no significant accumulation at Cmax), but a RAC $AUC_{0–12}$ of 1.26. This pattern—minimal accumulation at Cmax but more apparent at AUC—is consistent with the pharmacokinetics of budesonide, which is characterized by a long half-life and rate-limited absorption from the lungs.

In contrast, the RAC of glycopyrronium shows greater variability: Chen et al. reported a RAC $AUC_{0–12}$ of 3.0–3.3 in healthy Chinese subjects, compared to a RAC $AUC_{0–12}$ of 1.79 in COPD patients in the study by Dunn et al. This difference may reflect variations in renal function between populations (COPD patients are older with potentially reduced GFR), rather than a direct effect of disease on pulmonary pharmacokinetics—considering that glycopyrronium is primarily eliminated via the kidneys. Nevertheless, both studies agreed that glycopyrronium accumulation did not result in clinically meaningful adverse effects at the dosages used.

Limitations of the Evidence Included in the Review

Not all studies report a complete set of pharmacokinetic parameters. Distribution parameters (Vd/F) were reported by only one study, and clearance (CL/F) was reported by only two studies. The absence of these data hinders a comprehensive understanding of drug disposition and the identification of factors influencing variability. This selective reporting may not be due to methodological limitations (these parameters can be readily calculated from time-concentration data), but rather to editorial decisions or space constraints, which raise concerns about selective reporting bias.

Substantial heterogeneity in dose regimens, AUC definitions (AUC_{0-12} vs. AUC_{0-t} vs. $AUC_{0-\infty}$), and outcome reporting prevented quantitative pooling of data and calculation of summary effect estimates with confidence intervals. The narrative synthesis in this review, although comprehensive, is inherently more subjective and does not yield objective precision estimates.

Although the study was conducted in several countries (the US, China, Japan, and the UK), there was a notable absence from other regions, such as Europe (excluding the UK), Latin America, Africa, and the Middle East. Pharmacokinetic variability may exist across different geographic areas due to genetic, dietary, environmental, or healthcare practice differences that have not been captured in this evidence base.

Implication for Future Practice and Policy

The findings of substantial variability in systemic exposure, particularly in the glycopyrrolate and LAMA components, suggest that the one-size-fits-all dosing approach is not optimal for all patients. Clinicians should consider a variety of factors influencing exposure: ethnicity (the Japanese population experiences 40% higher exposure than that of Chinese or Westerners), renal function (patients with creatinine clearance <60 mL/min require dose adjustment), extreme body weight, and polypharmaceuticals, especially with CYP3A4 inhibitors that can increase budesonide exposure by up to 4 times. Given the substantial systemic exposure of budesonide, systematic safety monitoring is essential, including testing of adrenal function, bone health screening with DEXA scanning, ophthalmological screening for cataracts and glaucoma, and vigilance against infectious complications. In addition, selecting appropriate inhalation devices and techniques, including the use of spacers with MDI formulations, significantly affects lung deposition and systemic exposure, requiring regular technique training and reassessment at each clinic visit.

Evidence from this systematic review may inform formulary decisions, as substantial differences in systemic exposure across different triple combinations suggest that automatic substitution policies may not be appropriate without clinical reassessment. The findings of heterogeneity and data limitations indicate an urgent need for the development of regulatory guidance that includes: standardized PK study design requirements, including evaluation of target populations with uniform AUC reporting, and mandatory evaluation in specific populations (age >75 years, kidney/liver disorders, different ethnic groups) before approval.

CONCLUSION

This systematic review synthesizes current evidence on the clinical pharmacokinetics of single inhaler triple therapy in healthy subjects and patients with COPD. The findings indicate that systemic exposure to individual components remains comparable to established inhaled regimens and does not result in clinically relevant accumulation. Pharmacokinetic variability appears to be influenced by patient-related and technical factors rather than formulation-specific limitations. These results reinforce the therapeutic

reliability and safety of SITT in routine clinical practice. Continued integration of pharmacokinetic data in clinical decision-making may further optimize individualized COPD management.

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CONFLICT OF INTEREST

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