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AN OVERVIEW OF CEFIXIME TRIHYDRATE & POTASSIUM CLAVULANATE FIXED-DOSE COMBINATION AND ITS DIFFERENT ANALYTICAL METHOD

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ABSTRACT

Cefixime trihydrate and potassium clavulanate combination dosage form are widely used for the treatment of bacterial infections caused by susceptible and β-lactamase-producing microorganisms. Cefixime, a third-generation cephalosporin antibiotic, was first approved by the CDSCO in 1993, while clavulanic acid, administered as potassium clavulanate, was approved in combination with β-lactam antibiotics in the early 1980s. The fixed-dose combination of cefixime and potassium clavulanate was subsequently developed to enhance antibacterial efficacy and overcome resistance mediated by β-lactamase enzymes, receiving formal CDSCO approval in 2006. Owing to the extensive clinical use of this combination, reliable analytical methods are required for quality control and routine analysis. A review of the literature indicates that very limited analytical methods have been reported for the simultaneous estimation of cefixime trihydrate and potassium clavulanate in tablet dosage forms. To date, no validated UV spectrophotometric method has been published for this combination, whereas only a few RP-HPLC methods employing phosphate buffer and methanol in different ratios as mobile phases have been reported. Therefore, there is a critical need for the development of simple, economical, accurate, and validated analytical methods for the routine Pharmaceutical analysis of this combination dosage form.

KEYWORDS: Cefixime trihydrate, Potassium clavulanate, Fixed-dose combination, Tablets, RP-HPLC, UV spectrophotometry, Method development, Validation.

INTRODUCTION

Antimicrobial resistance (AMR) remains one of the most formidable challenges to global public health, severely compromising the efficacy of established antibiotic regimens. Among the diverse resistance mechanisms, the bacterial production of β –lactamase enzymes represents the primary defense mechanism against β-lactam antibiotics, rendering conventional therapies ineffective. To counter this threat, the clinical strategy of pairing a potent antibiotic with a -lactamase inhibitor has gained immense traction. A premier example of this synergistic approach is the fixed-dose combination (FDC) of **Cefixime** and **Potassium Clavulanate**.

Therapeutic Profile and Clinical Significance[1,2,3,4]

- **Cefixime:** A broad-spectrum, third-generation oral cephalosporin antibiotic. It exerts its bactericidal activity by binding to penicillin-binding proteins (PBPs), thereby disrupting bacterial cell wall synthesis. It exhibits robust activity against a wide array of Gram-positive and Gram-negative pathogens.
- **Potassium Clavulanate:** A "suicide" β-lactamase inhibitor structurally related to penicillins. While it possesses negligible intrinsic antibacterial activity, it inactivates β-lactamase enzymes by binding to them irreversibly. This protects Cefixime from

enzymatic degradation and restores its full therapeutic spectrum against resistant strains.

This combination is widely prescribed for treating moderate-to-severe bacterial infections, including.

- Upper and lower respiratory tract infections (e.g., bronchitis, sinusitis)
- Urinary tract infections (UTIs)
- Skin and soft-tissue infections
- Otitis media

Regulatory Context and Quality Challenges

Recognizing the escalating threat of multi-drug resistant pathogens, the **Central Drugs Standard Control Organization (CDSCO)** of India formally approved this specific fixed-dose combination in **2006**. Since its introduction, its market presence has grown exponentially, bringing an essential need for rigorous quality control frameworks.

The co-formulation of an inherently moisture-sensitive and unstable β -lactamase inhibitor like potassium clavulanate with a cephalosporin presents distinct pharmaceutical stability hurdles. Minor variations in manufacturing or storage environments can alter drug stability, impacting therapeutic outcomes and risking toxicity. Consequently, establishing precise, reliable, and reproducible analytical methodologies for simultaneous estimation is mandatory for routine quality control and regulatory compliance.

OBJECTIVE OF THE REVIEW

While extensive literature details the clinical pharmacokinetics and efficacy of this FDC, a comprehensive, comparative critique of its analytical estimation remains fragmented. This review addresses that gap by synthesizing and evaluating the primary analytical techniques utilized for the simultaneous estimation of Cefixime and Potassium Clavulanate in both bulk and pharmaceutical dosage forms.

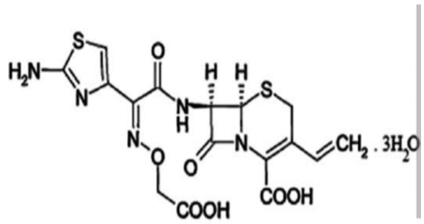
We specifically focus on a comparative analysis between.

1. **Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC):** Examined for its superior specificity, resolution, accuracy, and stability-indicating properties.
2. **Ultraviolet-Visible (UV-Vis) Spectrophotometry:** Critiqued for its cost-effectiveness and rapidity, with a focus on advanced mathematical modifications like **first-order derivative spectroscopy** required to overcome overlapping absorbance peaks.

DRUG PROFILE[1,2,3,4]

1. Drug: cefixime trihydrate

2. Molecular Structure



3. Molecular Formula: $C_{16}H_{21}N_5O_{10}S_2$

4.IUPAC Name: (6R,7R)-7-[[(2Z)-2-(2-amino-1, 3-thiazol-4-yl)-2-(carboxymethoxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclooct-2-ene-2-carboxylic acid trihydrate.

5. Molecular weight: 507.50 g/mol

6. Bioavailability.: Cefixime trihydrate is a third-generation cephalosporin antibiotic with an oral bioavailability of approximately 40% to 50%. It is well-absorbed from the gastrointestinal tract, and its absorption is not significantly affected by food. The drug has a half-life of 3 to 4 hours, and about 50% of the absorbed dose is excreted unchanged in urine within 24 hours

7. Protein binding: 65 %

8. Melting point: 218℃ - 225 ℃

9. Solubility: Cefixime trihydrate is a BCS Class II/IV drug with poor aqueous solubility, leading to low oral bioavailability. It is highly soluble in methanol, dimethyl sulfoxide, glycerin, and propylene glycol, but only partially or sparingly soluble in ethanol, acetone, and water. Solubility is improved via methods like solid dispersion.

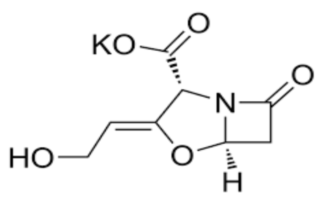
10. Category: Cefixime trihydrate is a third-generation cephalosporin antibiotic, used primarily to treat bacterial infections (e.g., respiratory tract, urinary tract, gonorrhea). It belongs to the beta-lactam class of antibiotics and is effective against both gram-positive and gram-negative bacteria. It is a prescription-only, broad-spectrum medication

11. Mechanism of action: Cefixime is a third-generation, broad-spectrum cephalosporin antibiotic that kills bacteria (bactericidal) by inhibiting bacterial cell wall synthesis. It binds to specific penicillin-binding proteins (PBPs) on the bacterial cell membrane, halting the final transpeptidation step of peptidoglycan synthesis, causing cell lysis and death.

12. Side effects: diarrhea (which may be severe), nausea, vomiting, abdominal pain, and flatulence.

1. Drug: potassium clavulanate

2. Molecular Structure



3. Molecular Formula: $C_8H_8KNO_5$
4. IUPAC Name: potassium (2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate.
5. Molecular weight: 237.25 g/mol
6. Protein binding: It has a relatively low serum protein binding, with approximately 25% bound to human serum proteins.
7. Melting point: 160℃ - 180 ℃
8. Solubility: highly water-soluble and soluble in methanol and DMSO /DMF
9. Category: beta-lactamase inhibitor
10. Mechanism of action: Clavulanic acid contains a beta-lactam ring in its structure that binds in an irreversible fashion to beta-lactamases, preventing them from inactivating certain beta-lactam antibiotics, with efficacy in treating susceptible gram-positive and gram-negative infections.

Table 1: Comparative Physicochemical Properties of Cefixime Trihydrate and Potassium Clavulanate.[1,2,3,4]

Property	Cefixime Trihydrate	Potassium Clavulanate
IUPAC Name	(6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-(carboxymethoxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trihydrate	Potassium (2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate
Molecular Formula	$C_{16}H_{15}N_5O_7S_2$. $3H_2O$	$C_8H_8KNO_5$
Molecular Weight	507.50 g/mol (Anhydrous: 453.5 g/mol)	237.25 g/mol
Physical Appearance	White to light-yellow crystalline powder	Pale yellow to light-brown solid powder
Melting Point	218 °C – 225 °C (with decomposition)	>160 °C (with decomposition)
Solubility Profile	Freely soluble in methanol and dimethyl sulfoxide (DMSO); slightly soluble in water insoluble in ethyl acetate.	Freely soluble in water; slightly soluble in ethanol (96%); very slightly soluble in acetone.
Ionization Constant (pKa)	~ 2.10 (carboxylic acid) and 7.3 (amine)	~ 2.7 (clavulanic acid)
Partition Coefficient (Log P)	-0.4 to -0.7 (H ydrophilic/Lipophilic balance)	Highly hydrophilic (Log P < 0)
BCS Classification	Class IV (Low solubility, low permeability)	Class I / III (High solubility)
Stability & Storage	Moderately hygroscopic; susceptible to degradation in highly acidic or alkaline media.	Extremely hygroscopic and moisture-sensitive; highly prone to hydrolytic ring cleavage.

Analytical Implications of Physicochemical Properties

1. Solubility Discrepancies

The most pronounced analytical challenge in simultaneous estimation is the opposing solubility of the two compounds. Potassium clavulanate is highly water-soluble, whereas cefixime trihydrate is poorly aqueous-soluble. Consequently, analytical methodologies (particularly UV spectrophotometry and RP-HPLC) must employ optimized co-solvent systems-often utilizing methanol or specifically buffered aqueous-organic mixtures to ensure complete dissolution and extraction from complex tablet matrices without precipitating either active ingredient.

2. pH Dependency and Mobile Phase Selection

Both compounds are acidic in nature due to the presence of carboxylic acid functional groups. Cefixime possesses multiple ionizable sites, resulting in pH-dependent peak tailing and retention time variations in liquid chromatography. To maintain both drugs in a unified, non-ionized state for sharp, symmetrical chromatographic resolution, mobile phases must be strictly buffered (frequently utilizing phosphate or acetate buffers between pH 3.0 and 6.8).

3. Hydrolytic Degradation

The β-lactam ring inherent to both structures is highly susceptible to hydrolysis, a vulnerability exponentially exacerbated in potassium clavulanate. Ambient moisture or elevated temperatures rapidly induce structural cleavage. Therefore, analytical sample preparations must be conducted rapidly, utilizing anhydrous or low-water solvents where possible, and auto-sampler environments should be maintained at lower temperatures (e.g., 4 °C to 8 °C) to preserve sample integrity during extended analytical runs.

Mechanism of Action and Synergistic Pharmacodynamics[5,6,7]

The therapeutic superiority of the cefixime and potassium clavulanate fixed-dose combination (FDC) relies on a highly synchronized, dual-action pharmacodynamic profile. This co-formulation strategically pairs the bactericidal lethality of a third-generation cephalosporin with the protective enzymatic blockade of a β-lactamase inhibitor, deliberately engineered to neutralize the primary defense mechanisms of resistant pathogens.

1. Cefixime: Inhibition of Cell Wall Synthesis

Cefixime functions as the primary antibacterial agent by fundamentally disrupting the structural integrity of the bacterial cell wall, which is essential for pathogen survival in hypotonic host environments.

- **Receptor Binding:** Upon reaching the site of infection, cefixime penetrates the bacterial envelope and covalently binds to specific Penicillin-Binding Proteins (PBPs) located on the cytoplasmic membrane.
- **Transpeptidase Blockade:** These PBPs are crucial transpeptidase enzymes responsible for synthesizing the peptidoglycan matrix. Cefixime's binding halts the terminal cross-linking of peptidoglycan chains.
- **Cellular Lysis:** The failure to construct a competent cell wall triggers the activation of autolytic enzymes (autolysins) within the bacteria, leading to irreversible osmotic instability, cellular swelling, and ultimate bactericidal lysis.

2. Potassium Clavulanate: Suicidal Enzyme Inhibition

While cefixime is highly potent, it remains susceptible to hydrolytic cleavage by β-lactamase enzymes secreted by resistant bacterial strains. Potassium clavulanate is incorporated exclusively to neutralize this threat.

- **Structural Mimicry:** Possessing a β-lactam-like core, clavulanate exhibits exceptionally high affinity for the active sites of both plasmid- and chromosomally-mediated β-lactamases.
- **Irreversible Inactivation:** It operates as a "suicide inhibitor." Clavulanate binds irreversibly to the catalytic center of the β-lactamase enzyme, forming a stable acyl-enzyme complex. This permanently deactivates the enzyme, effectively sacrificing the clavulanate molecule in the process.

3. The Synergistic Clinical Effect

The combination of these two agents creates a profound synergistic effect. By irreversibly binding and neutralizing the defensive β-lactamase enzymes, potassium clavulanate acts as a molecular shield for cefixime. It prevents the enzymatic degradation of cefixime's active β-lactam ring, allowing the antibiotic to reach its PBP targets unimpeded. Consequently, this synergy not only restores but significantly broadens the antimicrobial spectrum of cefixime, re-establishing its efficacy against previously refractory, β-lactamase-producing strains of *Escherichia coli*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*.

Clinical Administration, Dosage Formulations, and Therapeutic Profile[8,9,10]

The fixed-dose combination of cefixime trihydrate and potassium clavulanate is engineered primarily for systemic oral administration. Clinically, this synergistic formulation provides enhanced antibacterial efficacy and is extensively prescribed to manage moderate-to-severe respiratory tract, urinary tract, otorhinolaryngological (ENT), and skin and soft-tissue infections driven by resistant, β-lactamase-producing bacterial pathogens.

Formulation Strategies and Dosage Regimens To accommodate diverse patient demographics and mitigate the distinct physicochemical vulnerabilities of the active ingredients, the combination is commercially available in several optimized formats.

- **Film-Coated and Dispersible Tablets:** Standard adult therapeutic regimens typically prescribe a twice-daily (every 12 hours) oral dose of 200 mg cefixime paired with 125 mg potassium clavulanate. Because potassium clavulanate is exceptionally hygroscopic and rapidly degrades upon exposure to gastric acidity, the specialized polymeric film coating serves as a critical Pharmaceutical safeguard. It preserves the structural integrity of the β-lactamase inhibitor during harsh stomach transit, facilitating targeted release and absorption within the alkaline environment of the small intestine.
- **Dry Powder for Oral Suspension:** Formulated specifically for pediatric populations where dosage is meticulously calculated based on body weight (mg/kg) and geriatric patients experiencing dysphagia. To prevent the premature hydrolytic degradation of both the cephalosporin ring and the clavulanate core, this formulation is dispensed as an anhydrous powder. It necessitates reconstitution with sterile water immediately prior to the first use and carries a strictly limited post-reconstitution shelf-life, typically restricted to seven days under continuous refrigeration.

Pharmacokinetic Considerations and Patient Guidelines Clinical administration protocols recommend swallowing the intact tablet with a full glass of water to maintain adequate hydration during therapy. The formulation is ideally administered adjacent to meals (post-prandial administration). While the baseline bioavailability of cefixime (approximately 40–50%) remains unaffected by gastric contents, co-administration with food significantly enhances the gastrointestinal absorption profile of potassium clavulanate. Furthermore, post-prandial consumption effectively minimizes the gastrointestinal distress such as nausea or antibiotic-associated diarrhea frequently linked to clavulanic acid. From a clinical safety perspective, dose modifications are requisite for patients presenting with severe renal impairment, and the therapy must be administered with stringent caution in individuals documenting a history of hypersensitivity to cephalosporins or penicillins.

Implications for Analytical Quality Control The sophisticated nature of these clinical delivery systems poses distinct challenges for pharmaceutical quality control. The necessary incorporation of robust binding agents, polymeric film coatings, flavoring compounds, and suspending agents results in a highly complex sample matrix. Consequently, during routine batch release and stability testing, analytical methodologies-particularly reverse-phase high-performance liquid chromatography (RP-HPLC) must demonstrate extraordinary specificity. This ensures the precise isolation and simultaneous estimation of both active pharmaceutical ingredients, successfully resolving them from heavy excipient interference to guarantee the patient receives the exact, degradation-free clinical dose.

Clinical Therapeutics, Spectrum of Indications, and Pharmacological Advantages[13,14]

The clinical utility of the cefixime and potassium clavulanate fixed-dose combination (FDC) is rooted in its potent, broad-spectrum bactericidal activity. This formulation is specifically engineered to overcome the defensive mechanisms of β-lactamase producing, multidrug-resistant (MDR) pathogens, thereby broadening the clinical application of cefixime far beyond its original, isolated capabilities.

Primary Therapeutic Indications

The FDC is extensively utilized to manage moderate-to-severe bacterial infections across multiple domains:

- **Respiratory and Otorhinolaryngological (ENT) Infections:** The combination is highly efficacious in managing upper and lower respiratory tract infections, serving as a frontline choice for acute and chronic bronchitis exacerbations, community-acquired pneumonia, and lower respiratory infections. In ENT applications, it is a definitive targeted therapy for acute otitis media, sinusitis, pharyngitis, and severe tonsillitis, effectively eradicating resistant strains of *Haemophilus influenzae* and *Moraxella catarrhalis*.
- **Urinary and Gynecological Infections:** It is frequently prescribed for both uncomplicated and complicated genitourinary conditions, including cystitis and pyelonephritis. The synergistic mechanism critically restores drug susceptibility against Extended-Spectrum β-Lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. It is also utilized to treat specific bacterial infections of the female reproductive tract.
- **Gastrointestinal Infections (Enteric Fever):** The combination demonstrates profound clinical clearance rates in managing typhoid fever and other enteric infections caused by susceptible, multidrug-resistant *Salmonella typhi*, offering a robust alternative in regions with endemic fluoroquinolone resistance.
- **Skin and Soft-Tissue Infections (SSTIs):** It is successfully deployed to rapidly resolve localized cutaneous bacterial infections, including severe cellulitis, skin abscesses, and post-operative wound infections mediated by resistant staphylococcal and streptococcal strains.
- **Gonococcal Infections:** The formulation serves as a critical intervention tool for infectious disease specialists in treating uncomplicated gonorrhea driven by β-lactamase-producing *Neisseria gonorrhoeae*.

Clinical and Pharmacological Advantages

The widespread adoption of this combination therapy is driven by several distinct pharmacological advantages:

1. **Extended Antimicrobial Spectrum:** The addition of potassium clavulanate successfully protects the cephalosporin core from hydrolytic degradation, conferring robust activity against previously refractory mixed and resistant bacterial populations.
2. **Mitigation of Antimicrobial Resistance:** By neutralizing the primary bacterial defense mechanism (β-lactamase enzymes), the FDC actively reduces the trajectory of bacterial resistance to cefixime.
3. **Enhanced Patient Compliance:** The formulation provides a highly effective, definitive treatment for severe infections via convenient oral administration, circumventing the need for intravenous antibiotic therapy in outpatient settings.

Analytical Relevance of Widespread Clinical Utility

The pervasive prescription of this FDC across such diverse and critical clinical indications underscores the absolute necessity for uncompromising pharmaceutical quality. Because patient outcomes rely entirely on the precise ratio and chemical stability of these two active ingredients, deploying rigorously validated analytical techniques such as RP-HPLC and UV derivative spectroscopy is mandatory. These analytical frameworks ensure dosage uniformity, detect hydrolytic degradation impurities, and guarantee that commercially available formulations consistently meet stringent regulatory standards to ensure patient safety.

Adverse Effect Profile of the Solid Oral Formulation[13,14]

The fixed-dose combination (FDC) tablet of cefixime and potassium clavulanate introduces an amplified adverse effect profile compared to cefixime monotherapy, driven primarily by the β-lactamase inhibitor.

- **Gastrointestinal (GI) Toxicity (Most Common):** Potassium clavulanate acts as a local gastric irritant. Ingestion frequently induces nausea, vomiting, dyspepsia, and flatulence. The broad-spectrum eradication of gut flora also triggers antibiotic-associated diarrhea, carrying a severe idiosyncratic risk of *Clostridioides difficile*-induced pseudomembranous colitis.
- **Hepatic Impairment (Most Significant Systemic Risk):** While cefixime is hepatically safe, the addition of clavulanic acid introduces a cumulative risk of cholestatic jaundice, hepatitis, and elevated transaminases (AST/ALT). This toxicity predominantly affects elderly males following prolonged therapy (>10 days).

- **Hypersensitivity Reactions:** Because both drugs share a β-lactam ring, cross-reactive immunological responses are a critical concern. Reactions range from common cutaneous eruptions (pruritus, maculopapular rash) to rare, life-threatening events like IgE-mediated anaphylaxis and Stevens-Johnson syndrome (SJS).

Clinical Safety Profile, Tolerability, and Pharmacological Precautions[13,14]

The fixed-dose combination (FDC) of cefixime trihydrate and potassium clavulanate generally exhibits a favorable safety profile and is well-tolerated across diverse demographic groups. The availability of oral suspension formulations specifically enhances compliance and therapeutic outcomes in pediatric populations, maintaining a safety profile comparable to adult cohorts. However, the integration of a β-lactamase inhibitor inherently introduces specific pharmacological risks that necessitate careful clinical vigilance and stringent Pharmaceutical quality control.

1. Absolute Contraindications and Hypersensitivity

The formulation is strictly contraindicated in patients presenting with a documented history of severe hypersensitivity, anaphylaxis, or severe cutaneous adverse reactions (SCARs) to any cephalosporin, penicillin, or other β-lactam antibiotics, due to the high risk of potentially fatal immunological cross-reactivity. Furthermore, administration is contraindicated in individuals who have previously experienced clavulanate-associated cholestatic jaundice or hepatic dysfunction.

2. Tolerability and Monitoring in Special Populations

To optimize patient outcomes, therapeutic regimens must be carefully calibrated for physiologically vulnerable populations.

- **Renal Impairment:** Because both active pharmaceutical ingredients undergo primary elimination via the renal route, strict dose adjustments are imperative for patients presenting with moderate-to-severe renal impairment (creatinine clearance < 60mL/min). Failure to adjust dosages can lead to systemic drug accumulation, escalating the risk of neurotoxicity and rare interstitial nephritis.
- **Hepatic Impairment and Geriatrics:** While mild and transient elevations in liver enzymes (AST/ALT) are noted, significant hepatotoxicity including hepatitis and cholestatic jaundice is driven almost exclusively by the cumulative effects of potassium clavulanate. Elderly patients are particularly susceptible to both this hepatic risk and gastrointestinal distress. Consequently, routine monitoring of hepatic function is strongly recommended if therapy extends beyond 10 days.
- **Pregnancy and Lactation:** Classified under Pregnancy Category B, the combination lacks teratogenic evidence in animal models but should be prescribed during pregnancy only following a rigorous risk-benefit evaluation. Cautious administration is advised during lactation, as trace amounts of the drug are excreted in human breast milk.

3. Significant Pharmacokinetic Interactions

Concurrent administration of the FDC with specific therapeutic agents requires proactive clinical management to prevent adverse drug-drug interactions:

- **Anticoagulants:** Co-administration with coumarin derivatives (e.g., warfarin) may significantly prolong prothrombin time (PT) and the International Normalized Ratio (INR), escalating hemorrhagic risks.
- **Uricosuric Agents:** Drugs such as probenecid competitively inhibit the renal tubular secretion of cefixime. This interaction precipitates elevated and abnormally prolonged serum antibiotic concentrations, requiring dosage recalibration.
- **Neurological Agents:** The FDC may elevate systemic carbamazepine levels, necessitating therapeutic drug monitoring to prevent drug-induced toxicity.

Pharmacodynamic Profile and Synergistic Mechanism of Action[5,6,7]

The therapeutic efficacy of the cefixime trihydrate and potassium clavulanate fixed-dose combination (FDC) is rooted in a highly synchronized, dual-action pharmacodynamic profile. This strategic co-formulation is engineered specifically to neutralize the primary enzymatic resistance mechanisms of multidrug-resistant (MDR) bacterial pathogens, thereby restoring and dramatically expanding the antimicrobial spectrum of the cephalosporin.

1. Cefixime: Time-Dependent Bactericidal Activity

Cefixime functions as the primary antibacterial agent. As a third-generation cephalosporin, it exhibits time-dependent bactericidal pharmacodynamics; its clinical efficacy correlates directly with the duration that its serum concentration remains above the Minimum Inhibitory Concentration (T > MIC) of the target pathogen.

- **Target Receptor Binding:** Cefixime penetrates the bacterial cell envelope and covalently binds to specific Penicillin-Binding Proteins (PBPs) primarily PBP-3 and PBP-1 located on the inner cytoplasmic membrane.
- **Inhibition of Transpeptidation:** By blocking these critical transpeptidase enzymes, cefixime halts the terminal cross-linking of the peptidoglycan matrix. This action critically compromises the structural integrity of the bacterial cell wall.
- **Cellular Lysis:** The inability to construct a competent cell wall triggers the activation of

endogenous autolytic enzymes, culminating in rapid bactericidal lysis. In the absence of resistance mechanisms, this action is highly effective against native Gram-positive and Gram-negative pathogens, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Proteus mirabilis*.

2. Potassium Clavulanate: Suicidal Enzyme Inhibition

Despite its potent PBP affinity, cefixime's structural β-lactam ring remains highly vulnerable to hydrolytic cleavage by bacterial β-lactamase enzymes. Potassium clavulanate is integrated exclusively to neutralize this enzymatic threat.

- **Structural Mimicry and Affinity:** Possessing a β-lactam-like core, clavulanic acid exhibits minimal intrinsic antibacterial activity. However, it demonstrates an exceptionally high binding affinity for the catalytic active sites of both plasmid- and chromosomally-mediated β-lactamases (particularly Ambler Class A and certain Class D enzymes).
- **Irreversible Inactivation:** Clavulanate operates as a "suicide inhibitor." It binds irreversibly to the β-lactamase enzyme to form a highly stable, covalent acyl-enzyme complex. This reaction permanently deactivates the enzyme, effectively destroying the clavulanate molecule while neutralizing the bacterial defense.

3. Synergistic Pharmacodynamics and Clinical Significance

The pharmacodynamic synergy of this FDC is profound. By sacrificing itself to irreversibly deactivate defensive enzymes, potassium clavulanate acts as a molecular shield. It protects cefixime from enzymatic degradation, allowing the cephalosporin to reach its target PBPs unimpeded. Consequently, this interaction dramatically lowers the MIC breakpoints for cefixime, reducing the likelihood of treatment failure and aggressively broadening its clinical spectrum to eradicate previously refractory, β-lactamase-producing strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.

Pharmacokinetic Profile and Disposition Kinetics[11,12]

A comprehensive understanding of the distinct absorption, distribution, metabolism, and excretion (ADME) profiles of cefixime and potassium clavulanate is essential for optimizing clinical dosing regimens. Despite being co-formulated in a single fixed-dose combination (FDC) to achieve synergistic antibacterial activity, these two active pharmaceutical ingredients exhibit highly divergent pharmacokinetic trajectories, functioning independently without significant pharmacokinetic drug-drug interactions.

1. Gastrointestinal Absorption and Systemic Bioavailability

Following oral administration, both drugs are rapidly absorbed from the gastrointestinal tract, though their systemic bioavailability and responses to gastric contents differ significantly.

- **Cefixime Trihydrate:** Cefixime exhibits steady gastrointestinal absorption, achieving an absolute oral bioavailability of approximately 40% to 50%. Peak plasma concentrations (*Cmax*) are typically reached within 2 to 6 hours (*Tmax*). While the presence of food may delay the absorption rate, it does not significantly alter the total extent of absorption.
- **Potassium Clavulanate:** Conversely, clavulanic acid is absorbed extremely rapidly, reaching *Cmax* within 1 to 2 hours with a higher oral bioavailability of 60% to 75%. Crucially, the systemic absorption of potassium clavulanate is significantly enhanced when administered concurrently with a lipid-rich meal, underpinning the clinical recommendation for post-prandial administration.

2. Systemic Distribution and Protein Binding

Once in systemic circulation, both compounds readily penetrate well-perfused tissues and fluids, achieving highly effective therapeutic concentrations in respiratory tract tissues, tonsils, middle ear effusions, and the genitourinary tract:

- **Cefixime:** Exhibits moderate binding to human plasma proteins (predominantly albumin), with a bound fraction of approximately 65% to 70%. Its steady-state volume of distribution ensures adequate penetration into the extracellular fluid compartments where bacterial colonization occurs.
- **Potassium Clavulanate:** Demonstrates a highly un-ionized state at physiological pH and exhibits remarkably low plasma protein binding (20% to 30%). This low binding affinity facilitates rapid tissue diffusion, ensuring the inhibitor arrives at the site of infection concurrently with, or slightly preceding, the cephalosporin.

3. Metabolism and Routes of Elimination

The metabolic fate and elimination half-lives (*t*~1/2~) of the two compounds represent their most significant pharmacokinetic divergence.

- **Cefixime (Minimal Metabolism):** Cefixime undergoes virtually no hepatic biotransformation. It is eliminated primarily as the unchanged, biologically active drug via renal excretion (glomerular filtration and tubular secretion), with a portion eliminated via the biliary tract. Its elimination half-life is relatively prolonged (3 to 4 hours), permitting a convenient twice-daily dosing regimen.
- **Potassium Clavulanate (Extensive Metabolism):** Clavulanic acid is extensively metabolized via hepatic pathways into inactive metabolites and exhibits a remarkably short elimination half-life of

approximately 1 hour. It is rapidly excreted in the urine, with roughly 40% to 60% of the active dose cleared within the first few hours post-administration.

Summary of Pharmacokinetic Parameters

Parameter	Cefixime Trihydrate	Potassium Clavulanate
Route of Administration	Oral	Oral
Bioavailability	40% – 50%	60% – 75%
Time to Peak (*Tmax*)	2 – 6 hours	1 – 2 hours
Plasma Protein Binding	65% – 70%	20% – 30%
Metabolism	Minimal (excreted unchanged)	Extensive hepatic metabolism
Elimination Half-life (*t*~1/2~)	3 – 4 hours	~1 hour
Primary Route of Excretion	Renal and biliary	Mainly renal (and metabolites)

Commercial Formulations, Dosage Forms, and Market Profile[8,9,10]

To contextualize the necessity for widespread analytical quality control, it is pertinent to evaluate the commercial landscape of the cefixime and potassium clavulanate fixed-dose combination (FDC). Since its regulatory approval, this FDC has been aggressively commercialized by multinational and regional pharmaceutical industries. It is primarily formulated as film-coated or dispersible tablets for adult populations and dry powders for oral suspension (dry syrups) for pediatric use.

The table below provides a comprehensive synthesis of the widely prescribed commercial strengths, and respective brands, merging data on their distinct dosage forms, specific manufacturing pharmaceutical companies.

Table 2: Comprehensive Market Profile of Cefixime and Potassium Clavulanate FDC[8,9]

S.No	Brand Name	Dosage Form	Available Strengths(Cefixime /Potassium Clavulanate)	Pharmaceutical Manufacturer
1.	**Taxim-O CV**	Film-Coated Tablet	• 200 mg / 125 mg	Alkem Laboratories Ltd.
	Taxim-O CV DS	Dry syrup / Oral suspension	•50 mg /31.25 mg	Alkem Laboratories Ltd.
	Taxim-O	Dry syrup / Oral suspension	•50 mg	Alkem Laboratories Ltd.
2.	**Zifi CV 200**	Film-Coated Tablet	• 200 mg / 125 mg	FDC Limited
	Zifi CV 50 DS	Dry syrup / Oral suspension	•50 mg /31.25 mg	FDC Limited
	Zifi CV 100 DS	Dry syrup / Oral suspension	•100 mg /62.5 mg	FDC Limited
	Zifi CV 50 DT	Uncoated dispersible Tablet	•50 mg /31.25 mg	FDC Limited
	Zifi CV 100 DT	Film-Coated Tablet	•100 mg /62.5 mg	FDC Limited
3.	**Mahacef-CV 200**	Film-Coated Tablet	• 200 mg / 125 mg	Mankind Pharma Ltd.
	Mahacef 50 DS	Dry syrup / Oral suspension	•50 mg	Mankind Pharma Ltd.
	Mahacef 100 DS	Dry syrup / Oral suspension	•100 mg	Mankind Pharma Ltd.
	Mahacef 50 DT	dispersible Tablet	•50 mg	Mankind Pharma Ltd.
	Mahacef 100 DT	dispersible Tablet	•100 mg	Mankind Pharma Ltd.
4.	**Omnix CV**	Film-Coated Tablet	• 200 mg / 125 mg	Cipla Limited
	Omnix 50DT	dispersible Tablet	•50 mg	Cipla Limited
	Omnix 50 DS	Dry syrup / Oral suspension	•50 mg	Cipla Limited
	Omnix 100 DS	Dry syrup / Oral suspension	•100 mg	Cipla Limited
5.	**Cefolac-CV**	Film-Coated Tablet	• 200 mg / 125 mg	Macleods

	200			Pharmaceuticals Ltd.
	Cefolac-100	Film-Coated Tablet	• 100 mg	Macleods Pharmaceuticals Ltd.
	Cefolac-CV 100 DT	dispersible Tablet	•100 mg /62.5 mg	Macleods Pharmaceuticals Ltd.
	Cefolac-CV 50 DS	Dry syrup / Oral suspension	•50 mg /31.25 mg	Macleods Pharmaceuticals Ltd.
6.	**Milixim CV 200**	Film-Coated Tablet	• 200 mg / 125 mg	Glenmark Pharmaceuticals Ltd.
	Milixim 100 DT	dispersible Tablet	• 100 mg	Glenmark Pharmaceuticals Ltd.
	Milixim 100 DS	Dry syrup / Oral suspension	• 100 mg	Glenmark Pharmaceuticals Ltd.
	Milixim 50 DS	Dry syrup / Oral suspension	• 50 mg	Glenmark Pharmaceuticals Ltd.
7.	**Gramocef-CV**	Film-Coated Tablet Film-Coated Tablet	• 200 mg / 125 mg • 200 mg / 125 mg	Micro Labs Ltd. Micro Labs Ltd.
	Gramocef-O DT	Dispersible Tablet	• 100 mg	Micro Labs Ltd.
	Gramocef-O 100 DS	Dry syrup / Oral suspension	• 100 mg	Micro Labs Ltd.
	Gramocef-O 50 DS	Dry syrup / Oral suspension	• 50 mg	Micro Labs Ltd
8.	**Extacef-200 DT**	dispersible Tablet	• 200 mg	Blue cross lab
	Extacef-DT	Dry syrup / Oral suspension	• 100 mg	Blue cross lab

ANALYTICAL METHODS[15-25]

Table 3: Analytical methods of cefixime trihydrate and potassium clavulanate by RP-HPLC.

S. NO	Methods	Mobile Phase	Flow rate	Wavelength	Correlation Coefficient (r2)
1.	Analytical Method Development and validation of cefixime and clavulanic Acid by RP-HPLC Method	Methanol and orthophosphoric acid of pH (80:20)	1.0 ml/min	278 nm	0.999 each
2.	Studies on Stability and Analysis of cefixime trihydrate and potassium clavulanate Pharmaceutical Dosage Form	25NmM NaH_2PO_4. $2H_2O$	1.0 ml/min	220 nm	0.999 each
3.	Development and Validation of RP-HPLC Method for simultaneous Determination of cefixime and potassium clavulanate in tablet Dosage Form	0.03M Phosphate buffer and methanol (84:16)	1.0 ml/min	220 nm	CEF 0.999 CLV 0.998
4.	A Validation RP-HPLC Method for simultaneous Assay Determination and UV-Spectrophotometric Method for Dissolution Estimation in Film-coated Containing cefixime and clavulanic Acid	3.408 gm of disodium hydrogen phosphate in 800ml of water and 200ml of methanol (20:80)	1.0ml/min	220nm	CEF 0.995 CLV 0.993
5.	Development and validation of a new and economical stability indicating RP-HPLC method for cefixime trihydrate	10 mM disodium hydrogen phosphate (pH 6.3)and methanol (75:25)	1.0 ml/min	289 nm	0.9997
6.	A Validated RP-HPLC Method for simultaneous Determination of Cefixime and clavulanic Acid in Pediatric Oral Suspension	Methanol and water containing disodium hydrogen phosphate (20:80)	1.0 ml/min	220 nm	CEF 0.997 CLV 0.992
7.	Method Development and Validation of cefixime by using RP-HPLC in Pharmaceutical Formulation	Methanol and Acetonitrile (30:70)	1.0 ml/min	220 nm	0.9931

8.	Simultaneous Determination of Potassium Clavulanate and Cefixime in synthetic Mixture by High-Performance Liquid Chromatography	0.03M disodium hydrogen phosphate buffer (Ph 6.5) and methanol (84:16)	1.0ml/min	220 nm	CFE 0.9998 CLV 0.9999
9.	Development and validation of stability Indicating RP-HPLC Method for simultaneous Estimation of Cephalexin and Clavulanic Acid	Sodium dihydrogen phosphate monohydrate buffer (pH 5) And methanol (65:35)	1.0 ml/min	228 nm	CEP 1 CLV 0.9999

Table 4: Analytical methods of cefixime trihydrate and potassium clavulanate by UV-SPECTROPHOTOMETRY.

S. NO	Methods	Solvents	Wavelength	Correlation Coefficient (r^2)
1.	Method Development and validation for Determination of cefixime in Bulk Dosage Form by UV Spectrophotometry	Methanol	287 nm	0.9980
2.	Development and validation of a New Simple and Rapid UV Spectroscopic Method for Cefalexin and Potassium-Clavulanate in pure and Dosage form	Distilled water	262 nm	0.9979

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