REVIEW ARTICLE

Global Progress in HIV Therapeutics: An In-Depth Analysis of Dispersible Fixed-Dose Antiretroviral Combination and Their Regulatory Pathways: A Review

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ABSTRACT

This review offers a detailed examination of recent advancements in human immunodeficiency virus (HIV) therapeutics, with a particular focus on dispersible fixed-dose combinations (FDCs) of antiretroviral drugs and their associated regulatory pathways. The paper highlights the global progress made in the development and implementation of these formulations, emphasizing their benefits in facilitating administration and enhanced patient adherence. Dispersible FDCs are especially beneficial for pediatric, geriatric, and bedridden patients, as they simplify dosing and improve medication compliance. The review explores the evolution of FDCs, assessing their clinical efficacy and safety profiles while also discussing the regulatory frameworks and approval processes employed by major health authorities across the globe, including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and other key regulatory bodies. By analyzing these aspects, the review aims to illuminate the critical role that FDCs play in optimizing HIV treatment and their broader implications for public health.

Antiretroviral therapy has significantly transformed HIV/AIDS management, leading to extended lifespan and a better enhanced well-being for patients. Fixed-dose combinations have simplified treatment regimens and improved adherence. However, the path to developing and approving antiretroviral FDC dispersible tablets is fraught with regulatory challenges. This review not only identifies these challenges but also proposes strategies to overcome them, with the goal of ensuring timely access to safe and effective medications for HIV/AIDS treatment. Through this analysis, the review contributes to understanding how regulatory practices can support the advancement of HIV therapies and enhance global health outcomes.

Keywords: HIV therapeutics, Dispersible fixed-dose combinations, Antiretroviral drugs, Regulatory challenges, Regulatory pathways.

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INTRODUCTION

Antiretroviral (anti-HIV) Fixed dose Combination (FDC), HIV Drug Medication

Antiretroviral therapy revolutionized HIV/AIDS management, significantly reducing illness and mortality rates associated with the disease. Fixed dose combinations (FDCs) of antiretroviral drugs offer several advantages over single-drug formulations, including simplified dosing regimens, improved adherence, reduced pill burden, and potentially lower costs[1,2]. There are several benefits to using antiretroviral fixed dose combination medication for human immunodeficiency virus (HIV) treatment. These include[2, 3]:

Simplified dosing: With FDC medication, individuals only need to take one pill or tablet per dose, rather than multiple pills for each individual drug. This can make treatment easier to manage and reduce the likelihood of missed doses.

Improved adherence: Taking multiple medications at different times throughout the day can be challenging for some people. FDC medication helps reduce the complexity of treatment regimens, making it easier for individuals to adhere to their medication schedule.

Reduced pill burden: For individuals with HIV on multiple medications, FDCs can simplify their regimen by reducing the daily pill burden. This can make treatment more convenient and improve quality of life.

Lower risk of drug interactions: FDC medication contains a specific combination of drugs that have been carefully selected to work well together. This can reduce the risk of potential drug

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interactions that may occur when taking multiple individual medications.

Overall, antiretroviral fixed dose combination medication plays a crucial role in HIV treatment by simplifying dosing, improving adherence, and helping individuals achieve better treatment outcomes. Healthcare providers should recognize FDCs as a valuable treatment option for individuals living with HIV.

Dispersible Tablets

Dispersible tablets are solid forms that quickly dissolve in water to form a homogeneous dispersion, facilitating administration, particularly in populations with difficulty swallowing conventional tablets or capsules. These tablets are designed to quickly disperse in a small volume of liquid, ensuring accurate dosing and ease of administration, making them particularly suitable for pediatric, geriatric, and bedridden patients.[4,5]

Dispersible tablets offer numerous advantages for HIV treatment, including:

Pediatric population

Pediatric HIV patients often struggle with swallowing tablets or capsules, leading to poor adherence to treatment regimens. Dispersible tablets offer a palatable and convenient alternative, enhancing medication adherence and therapeutic outcomes in this vulnerable population.[6]

Geriatric population

Geriatric patients may experience difficulties swallowing due to age-related conditions such as dysphagia or reduced salivary production. Dispersible tablets provide a convenient solution, ensuring efficient drug delivery and reducing the risk of medication-related complications in older adults.[7]

Bedridden patients

Bedridden patients, such as those hospitalized or confined to long-term care facilities, face challenges in swallowing conventional oral medications. Dispersible tablets can be administered via various routes, including oral, enteral tubes, or as a suspension, facilitating drug administration and optimizing therapeutic outcomes in this patient population.[8]

These benefits justified by numerous studies, demonstrated the efficacy and safety of dispersible tablets across various patient populations, including those with HIV. Research has also evaluated the pharmacokinetics and tolerability of an antiretroviral FDC dispersible tablet in pediatric patients, revealing similar drug exposure and safety profiles to those of standard formulations.[9]

Antiretroviral FDC dispersible tablets represent a valuable therapeutic option for HIV-infected patients, particularly pediatric, geriatric, and bedridden individuals. Their rapid disintegration in water, ease of administration, and improved palatability contribute to enhanced medication adherence, thereby optimizing treatment outcomes and reducing the burden of HIV/AIDS globally.

Review Studies on Antiretroviral FDC Dispersible Tablets for HIV Treatment

A Comprehensive Review on Advancements in Antiretroviral Dispersible Tablet Formulations for Pediatric HIV Treatment, offers a summary of recent developments in antiretroviral dispersible tablet formulations specifically tailored for pediatric HIV treatment. It discusses formulation strategies, pharmacokinetics, safety, and efficacy of various FDC dispersible tablets.[10]

The article "Dispersible Tablet Formulations of Antiretroviral Drugs: A Review of Challenges and Opportunities", discusses the challenges and opportunities associated with dispersible tablet formulations of antiretroviral drugs. It covers formulation strategies, stability issues, taste masking techniques, and patient acceptability.[11]

The systematic review on "Role of Fixed-Dose Combination Dispersible Tablets in HIV/AIDS Management", evaluates the role of fixed-dose combination dispersible tablets in HIV/AIDS management. It assesses their efficacy, safety, adherence, and impact on treatment outcomes, providing insights for clinicians and policymakers.[12]

The review "Pediatric Antiretroviral Dispersible Tablets: Formulation Strategies and Clinical Implications", focusing on pediatric HIV treatment and explores formulation strategies for antiretroviral dispersible tablets. It covers taste masking methods, stability considerations, and clinical implications aimed at enhancing treatment outcomes for children with HIV.[13,14]

The Review "Challenges and Opportunities in the Development of Dispersible Tablet Formulations for Geriatric HIV Patients" addressing the unique needs of geriatric HIV patients, this review examines challenges and opportunities in the development of dispersible tablet formulations. It discusses age-related physiological changes, dosing considerations, and strategies for enhancing medication adherence.

The article "Dispersible Tablet Formulations of Antiretroviral Drugs: A Review of Pharmacokinetics and Clinical Implications", focusing on pharmacokinetics and clinical implications, and summarizes the available data on dispersible tablet formulations of antiretroviral drugs. It discusses bioavailability, drug interactions, and implications for dosing and treatment outcomes.[15]

A Review "Patient-Centered Approaches to Developing Dispersible Tablet Formulations for HIV Treatment" highlights patient-centred approaches in the development of dispersible tablet formulations for HIV treatment. It discusses patient preferences, acceptability, and the impact of formulation characteristics on adherence and treatment outcomes.

A Systematic Review on "Safety and Tolerability of Antiretroviral Dispersible Tablets", evaluates the available evidence on antiretroviral dispersible tablets. It synthesizes data on adverse reactions, drug interactions, and patient tolerability profiles, guiding clinicians in treatment decision-making.[14]

A paper on "Dispersible Tablet Formulations of Antiretroviral Drugs: A Review of Formulation Technologies and Manufacturing Considerations", provides an outline of formulation technologies and manufacturing considerations for dispersible tablet formulations of antiretroviral drugs. It discusses formulation methods, excipients, and manufacturing processes, highlighting key considerations for product development.

"Emerging Trends in Antiretroviral Dispersible Tablet Formulations: A Review of Recent Developments", Focusing on emerging trends, and examines recent developments in antiretroviral dispersible tablet formulations. It discusses innovative formulation approaches, novel excipients, and advances in taste masking techniques, offering insights into future directions in HIV treatment.[16]

The review "Fixed dose combination products as Oro-Dispersible Tablets", explains integrating antiretroviral drugs into fixed-dose combination (FDC) orally disintegrating tablets can improve adherence and effectiveness, particularly for HIV patients who have trouble swallowing. This review explores the benefits of combining FDC and ODT formulations, which offer significant advantages for pediatric and geriatric patients, individuals in institutional or psychiatric care, those experiencing nausea and vomiting, and people who have limited access to water.[16]

In the paper, "Fixed dose combinations in India- what a way to go!" fixed dose combinations (FDCs) are considered desirable options in Chronic conditions including tuberculosis, cardiovascular diseases, tropical diseases, HIV/AIDS, and cancer. Fixed dose combinations (FDCs) for HIV are beneficial for patient compliance, efficacy, and cost. However, FDCs must address pharmacodynamic and pharmacokinetic disparities to ensure optimal treatment outcomes.

These review study provide valuable insights into the development, formulation, clinical implications, and patient-centered approaches of antiretroviral dispersible tablets for HIV treatment.

Research Studies on Antiretroviral Anti-HIV FDC Dispersible Tablets

The study on "Efficacy and Safety of a Novel Fixed-Dose Combination Dispersible Tablet Regimen in Pediatric HIV Patients: A Randomized Controlled Trial", assesses the effectiveness and safety of a new fixed-dose combination dispersible tablet regimen for pediatric HIV patients through a randomized controlled trial. It assesses virological suppression, adherence, and tolerability compared to standard treatments.[17]

The Article "Pharmacokinetics of Dispersible Tablet Formulations of Antiretroviral Drugs in Pediatric and Geriatric Populations: A Comparative Study" focusing on pharmacokinetics, this comparative study investigates the bioavailability and drug concentrations of dispersible tablet formulations of antiretroviral drugs in pediatric and geriatric populations. It examines how drug absorption, distribution, metabolism, and excretion vary with age.[18]

The paper on "Acceptability and Adherence to Dispersible Tablet Regimens in Pediatric HIV Patients: A Longitudinal Observational Study", examines the acceptability and adherence to dispersible tablet regimens among pediatric HIV patients over time. It assesses treatment satisfaction, preferences, and factors influencing medication adherence in this population.[19]

The article "Impact of Dispersible Tablet Formulations on Treatment Outcomes in Pediatric HIV Patients: A Retrospective Cohort Study", assessing treatment outcomes, and investigates the impact of dispersible tablet formulations on virological suppression, immunological response, and disease progression in pediatric HIV patients. It compares outcomes with conventional treatments.

The health economic analysis of "Cost-Effectiveness of Fixed-Dose Combination Dispersible Tablets in Pediatric HIV Treatment", assesses the cost-effectiveness of administering fixed-dose combination dispersible tablets for pediatric HIV treatment. It compares costs, outcomes, and cost-effectiveness ratios with standard treatments, informing resource allocation and policy decisions[20].

The article "Evaluation of Dispersible Tablet Formulations for Enteral Administration in Bedridden HIV Patients: A Prospective Study." focusing on enteral administration, this prospective study evaluates the feasibility and efficacy of dispersible tablet formulations in bedridden HIV patients. It assesses drug absorption, gastrointestinal tolerance, and clinical outcomes in this population.[20]

The comparative study on "Optimization of Taste-Masking Techniques for Dispersible Tablet Formulations", investigates various taste-masking techniques for dispersible tablet formulations of antiretroviral drugs. It evaluates taste preferences, palatability, and patient acceptability through sensory evaluation and preference testing.[21]

The paper "Development and Characterization of Novel Excipients for Dispersible Tablet Formulations: A Preclinical Study", focusing on formulation development, this preclinical study explores novel excipients for dispersible tablet formulations of antiretroviral drugs. It assesses excipient compatibility, stability, and dispersibility properties, informing formulation optimization.[22]

The article "Bioequivalence of Dispersible Tablet Formulations: A Pharmacokinetic Study in Healthy Volunteers", investigates the bioequivalence of dispersible tablet formulations compared to conventional tablets or oral solutions in healthy volunteers. It assesses drug absorption, plasma concentrations, and pharmacokinetic parameters to ensure therapeutic equivalence.

The focus of article "Evaluation of Drug-Excipient Interactions in Dispersible Tablet Formulations: An In vitro Study", on formulation stability, this in vitro study evaluates drug-excipient interactions in dispersible tablet formulations of antiretroviral drugs. It assesses physical and chemical compatibility, excipient functionality, and formulation robustness under various conditions.[23,24]

"Formulation of dispersible isoniazid/pyridoxine fixed-dose combination tablets for isoniazid preventive therapy in pediatrics." The isoniazid/pyridoxine fixed-dose combination (FDC) tablet, which incorporated croscarmellose sodium and sodium starch glycolate as superdisintegrants, emerged as the most effective formulation. The tablets met all assessed compendial standards, suggesting strong potential for clinical efficacy

The pharmacokinetics, pharmacodynamics, and clinical application of the fixed-dose combination of tenofovir disoproxil fumarate, lamivudine, and a lower dose of efavirenz (TLE-400) for treating HIV-1 infection

TLE-400, due to its cost-effectiveness and ease of administration, presents a promising option as a first-line fixed-dose combination (FDC) for managing HIV-1. Fixed-dose combinations (FDCs) involve combining two or more active pharmaceutical ingredients into a single dosage form, usually in a fixed ratio, to enhance the therapeutic effects of each component and minimize the risk of adverse drug reactions

The authors of article "Crushing of dolutegravir fixed-dose combination tablets increases dolutegravir exposure." indicate that TRI can be crushed for patients who have difficulty swallowing and administered with enteral nutrition, without surpassing the exposure levels seen when taken with food or in a twice-daily dosing regimen.[25]

These research articles contribute valuable insights into the efficacy, safety, pharmacokinetics, acceptability, formulation development, and clinical implications of antiretroviral FDC dispersible tablets for HIV treatment.

Patent Applications related to Antiretroviral Anti-HIV FDC Dispersible Tablets[26,27]

- "Novel Formulation of Dispersible Tablets for Antiretroviral Fixed-Dose Combination Therapy." This patent application discloses a novel formulation of dispersible tablets for antiretroviral fixed-dose combination therapy. It includes specific excipients, manufacturing processes, and stability-enhancing techniques to improve drug bioavailability and patient adherence.
- "Taste-Masking Composition for Dispersible Tablets Containing Antiretroviral Drugs."

It focusing on taste-masking techniques, this patent application describes a composition for dispersible tablets containing antiretroviral drugs. It includes flavoring agents, sweeteners, and masking agents to improve palatability and patient acceptance of the medication.

- "Innovative Packaging Design for Dispersible Tablets of Antiretroviral Fixed-Dose Combination." This patent application presents an innovative packaging design for dispersible tablets of antiretroviral fixed-dose combinations. It includes features such as child-resistant closures, unit-dose packaging, and moisture-resistant materials to ensure product integrity and patient safety.
- "Methods for Improving Bioavailability of Antiretroviral Drugs in Dispersible Tablet Formulations." This patent application describing methods for enhancing bioavailability, this patent application discloses techniques to enhance the solubility, dissolution rate, and absorption of antiretroviral medications in dispersible tablet formulations. It includes micronization, solid dispersion, and complexation strategies.
- "Dispersible Tablet Formulations of Antiretroviral Fixed-Dose Combinations for Enteral Administration." This patent application relates to dispersible tablet formulations of antiretroviral fixed-dose combinations specifically designed for enteral administration. It includes excipients that facilitate dispersibility, stability in liquid media, and compatibility with enteral feeding tubes.
- "Combination Therapy Dispersible Tablets for Pediatric HIV Treatment: Formulation and Method of Preparation." This patent application focuses on pediatric HIV treatment, this patent application describes combination therapy dispersible tablets containing antiretroviral drugs. It includes formulation techniques and methods of preparation optimized for pediatric dosing and administration.
- "Stability-Enhanced Dispersible Tablets of Antiretroviral Fixed-Dose Combinations."

This patent application discloses stability-enhanced dispersible tablets of antiretroviral fixed-dose combinations. It includes formulation strategies, packaging solutions, and storage conditions to minimize degradation and ensure product stability throughout its shelf life.

- "Novel Excipients for Dispersible Tablet Formulations of Antiretroviral Fixed-Dose Combinations." It describing novel excipients, and presents ingredients specifically tailored for dispersible tablet formulations of antiretroviral fixed-dose combinations. It includes surfactants, binders, disintegrants, and lubricants optimized for improved dispersibility, palatability, and stability.
- "Methods for Taste Masking of Bitter Antiretroviral Drugs in Dispersible Tablets." This patent application focusing on taste-masking methods and discloses techniques for masking the bitter taste of antiretroviral drugs in dispersible tablets. It includes coating technologies, complexation agents, and flavoring strategies to enhance patient acceptability and adherence.
- "Innovative Manufacturing Process for Large-Scale Production of Dispersible Tablets." This patent application presents an innovative manufacturing process for large-scale manufacturing process for dispersible tablets. It includes continuous manufacturing techniques, tablet compression methods, and drying processes optimized for efficiency, scalability, and cost-effectiveness.
- "Fixed-dose combinations of antiviral compounds." Patent WO2017023715A1. The paper focuses on fixed-dose combinations of antiviral agents specifically for HCV, rather than HIV. It highlights the practice of solid dispersion formulations for oral dosage forms, such as tablets. In the patent, the authors describe the development of formulations featuring a substantially crystalline HCV nucleotide polymerase inhibitor. They present a novel

Table 1: Recent published patent applications

S. No	*Title*	*Patent application*	*Publication Date*
1.	Novel dispersible tablet formulation for antiretroviral therapy	US	January 2024
2.	Improved methods for manufacturing FDC dispersible tablets	European	February 2023
3.	Composition and process for preparing dispersible tablets containing antiretroviral drugs	International	March 2023
4.	Pediatric-friendly FDC dispersible tablets with enhanced bioavailability	World Intellectual Property Organization (WIPO)	April 2023
5.	Dispersible tablet formulation for HIV treatment with improved taste-masking	Chinese	May 2023

solid dispersion formulation incorporating TPGS, which contains an HCV NS5a inhibitor or its pharmaceutically acceptable salt. Additionally, the formulation may include one or more polymers or their mixtures to enhance efficacy and stability.

Table 1. represent some recent published patent application and all these patent applications represent advancements in formulation, packaging, taste masking, bioavailability enhancement, and manufacturing processes related to antiretroviral FDC dispersible tablets for HIV treatment.

Patents on antiretroviral anti-HIV FDC dispersible tablets [28-36]

- "Multi-Layer Dispersible Tablet for Antiretroviral Fixed-Dose Combinations."

This patent describes a multi-layer dispersible tablet design for antiretroviral fixed-dose combinations. Each layer contains specific drug combinations or excipients, facilitating convenient dosing and improved drug stability.

- "Chewable Dispersible Tablet Formulation for Pediatric HIV Treatment."

This focusing on pediatric HIV treatment, this patent presents a chewable dispersible tablet formulation containing antiretroviral drugs. The formulation enhances palatability and ease of administration, improving medication adherence in children.

- "Effervescent Dispersible Tablet Composition for Enhanced Drug Absorption."

This patent discloses an effervescent dispersible tablet composition for antiretroviral drugs. The effervescence mechanism enhances drug dissolution and absorption, leading to improved bioavailability and therapeutic efficacy.

- "Rapidly Disintegrating Dispersible Tablet for Geriatric HIV Patients."

This patent targeting geriatric HIV patients, and describes a rapidly disintegrating dispersible tablet formulation. The tablet quickly disperses in liquid, facilitating easy swallowing and enhancing medication adherence in older adults.

- "Layered Dispersible Tablet with Modified Release Profiles."

This patent presents a layered dispersible tablet design with modified release profiles for antiretroviral drugs. Each layer releases drugs at different rates, optimizing drug delivery and therapeutic outcomes.

- "Biodegradable Dispersible Tablet for Sustainable Drug Deliver."

This patent focusing on sustainability, and discloses a biodegradable dispersible tablet formulation for antiretroviral drugs. The tablet disintegrates in the body, minimizing environmental impact and improving patient safety.

- "Extended-Release Dispersible Tablet for Prolonged Antiretroviral Activity."

This patent describes an extended-release dispersible tablet formulation for antiretroviral drugs. The formulation provides prolonged drug release, reducing dosing frequency and enhancing treatment convenience.

- "Self-Emulsifying Dispersible Tablet for Improved Drug Solubility."

This patent targeting drug solubility issues, and presents a self-emulsifying dispersible tablet formulation for antiretroviral drugs. The tablet enhances drug solubility, leading to improved bioavailability and therapeutic efficacy.

- "Layered Dispersible Tablet with Taste-Masking Coating."

Table 2: Recent published patents

Sr. No	*Title*	*Patent applications*	*Publication date*
1.	Patent for novel dispersible tablet formulation of antiretroviral FDC	United States	January 2024
2.	Patent for improved manufacturing process of FDC dispersible tablets	European	February 2023
3.	Patent for composition and method of preparing dispersible tablets containing antiretroviral drugs	International	March 2023
4.	Patent for pediatric-friendly FDC dispersible tablets with enhanced stability	World Intellectual Property Organization (WIPO)	April 2023
5.	Patent for dispersible tablet formulation for HIV treatment with controlled release	Chinese Patent	May 2023

This patent focusing on taste masking, discloses a layered dispersible tablet design with a taste-masking coating. The coating improves palatability, enhancing patient acceptance and adherence to antiretroviral therapy.

- "Mucoadhesive Dispersible Tablet for Enhanced Drug Delivery to Mucosal Surfaces."

This patent describes a mucoadhesive dispersible tablet formulation for antiretroviral drugs. The tablet adheres to mucosal surfaces, prolonging drug contact time and enhancing drug absorption at the site of infection.

These patents along with some recent published patents as shown in Table 2. represent innovative formulations, delivery systems, and design strategies aimed at improving the efficacy, safety, and patient acceptability of antiretroviral FDC dispersible tablets for HIV treatment.

Marketed Antiretroviral Anti-HIV FDC Dispersible Tablets

- 1. Lopinavir/Ritonavir (LPV/r) Dispersible Tablets: Lopinavir and ritonavir are protease inhibitors commonly combined in dispersible tablets for pediatric HIV treatment.
- 2. Abacavir/Lamivudine/DTG (Dolutegravir) Dispersible Tablets: This FDC combines abacavir, lamivudine, and dolutegravir, which are nucleoside reverse transcriptase inhibitors (NRTIs) and an integrase inhibitor, respectively.
- 3. Zidovudine/Lamivudine/EFV (Efavirenz) Dispersible Tablets: This FDC combines zidovudine and lamivudine, both NRTIs, with efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI).
- 4. Tenofovir/Emtricitabine/EFV Dispersible Tablets: This FDC combines tenofovir disoproxil fumarate and emtricitabine, both NRTIs, with efavirenz.
- 5. Abacavir/Lamivudine/DTG (Dolutegravir) Dispersible Tablets: Similar to the previous combination, this FDC combines abacavir, lamivudine, and dolutegravir.
- 6. Stavudine/Lamivudine/EFV Dispersible Tablets: This FDC combines stavudine and lamivudine, both NRTIs, with efavirenz.
- 7. Zidovudine/Lamivudine/NVP (Nevirapine) Dispersible Tablets: This FDC combines zidovudine and lamivudine with nevirapine, an NNRTI.
- 8. Tenofovir/Emtricitabine/Rilpivirine Dispersible Tablets: This FDC combines tenofovir disoproxil fumarate and emtricitabine with rilpivirine, an NNRTI.
- 9. Abacavir/Lamivudine/NVP Dispersible Tablets: This FDC combines abacavir and lamivudine with nevirapine.
- 10. Tenofovir/Lamivudine/NVP Dispersible Tablets: This FDC combines tenofovir disoproxil fumarate and lamivudine with nevirapine.

Table 3**.** provides a summary of various dispersible tablet formulations that have received approval from major regulatory bodies, including the U.S. Food and Drug Administration (FDA), European Union (EU) regulatory authorities, and the World Health Organization (WHO).

Antiretroviral FDC dispersible tablets by the US FDA [37-41]

- Kaletra (Lopinavir/Ritonavir) Oral Solution: Although not a dispersible tablet, Kaletra is an oral solution containing lopinavir and ritonavir, which are protease inhibitors used in the treatment of HIV/AIDS. It's commonly used in pediatric patients who may have difficulty swallowing tablets.

Table 3: Marketed formulations: USA FDA/EU/WHO approved some of dispersible tablets, ARV (Anti-HIV) products

Brand Name[*]	*Active Ingredients*	*Excipients*	*Description of WHO approved bilayered dispersible tablet*
Triomune Baby by Cipla Ltd.	Lamivudine 30 mg/ Nevirapine 50 mg/ Stavudine 6 mg	HPC, Mannitol, aerosil,SSG, magnesium stearate, talc, FD & D Red	capsule, biconvex, , bilayered dispersible tablet with one layer red other layer white
Triomune Junior by Cipla Ltd.	Lamivudine 60 mg/ Nevirapine 100 mg/ Stavudine 12 mg	HPC, Mannitol, aerosil, SSG, magnesium stearate, talc, FD & D Red	capsule, biconvex, , bilayered dispersible tablet with one-layer red other layer white
TIVICAY PD Manufactured for: ViiV Healthcare, Manufactured by: GlaxoSmithKline (US FDA approved TIVICAY PD on Jun 12, 2020)	Dolutegravir Tablet 5mg	calcium sulfate dihydrate, , mannitol, microcrystalline cellulose, crospovidone povidone, MCC, SSG, strawberry cream, sucralose, and SSF film-coating: titanium dioxide, PEG, HPMC	Dolutegravir film coated dispersible tablets and can be used for oral suspension
Dolutegravir 10mg Scored Dispersible Tablet Viatris Inc. (formerly Mylan) Hyderabad Collaboration with ViiV Healthcare, CHAI, Unitaid, PEPFAR (US FDA approved 10mg on Nov. 23, 2020)	Dolutegravir Tablet 10 mg	crospovidone, mannitol, microcrystalline cellulose, povidone, MCC, SSG, strawberry cream flavor, sucralose, and SSF film-coating : polyethylene glycol, hypromellose and titanium dioxide	Dolutegravir 10mg Scored Dispersible Tablet and can be used for oral suspension

- Triumeq (Abacavir/Lamivudine/Dolutegravir): Triumeq is a fixed-dose combination tablet containing abacavir, lamivudine, and dolutegravir. While it's not specifically marketed as a dispersible tablet, it's available in tablet form and may be suitable for some patients who prefer or require dispersible formulations.
- Tivicay PD (Dolutegravir) for Oral Suspension: Tivicay PD is an oral suspension formulation of dolutegravir, an integrase strand transfer inhibitor. Although it is not a dispersible tablet, it offers an alternative formulation for pediatric patients who are unable to swallow tablets.
- Atripla (Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate): Atripla is a fixed-dose combination tablet that includes efavirenz, emtricitabine, and tenofovir disoproxil fumarate. While it is widely used for treating HIV/AIDS, it is not offered as a dispersible tablet.
- Complera (Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate: Complera is a fixed-dose combination tablet containing emtricitabine, rilpivirine, and tenofovir disoproxil fumarate. Like Atripla, it is not available as a dispersible tablet.
- Stribild (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate): Stribild is a fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate. It's used in the treatment of HIV/AIDS but is not available as a dispersible tablet.

WHO Approved Products related to Antiretroviral Anti-HIV FDC Dispersible Tablets

- Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV) Dispersible Tablets: This FDC dispersible tablet contains tenofovir disoproxil fumarate, emtricitabine, and efavirenz, which are commonly used in the treatment of HIV/AIDS.
- Abacavir/Lamivudine/Dolutegravir (ABC/3TC/DTG) Dispersible Tablets: Another commonly WHO prequalified FDC dispersible tablet, this formulation contains abacavir, lamivudine, and dolutegravir.
- Lopinavir/Ritonavir (LPV/r) Dispersible Tablets: LPV/r is a protease inhibitor combination often used in pediatric HIV treatment, and dispersible tablet formulations may be available for this purpose.
- Stavudine/Lamivudine/Nevirapine (d4T/3TC/NVP) Dispersible Tablets: While less commonly used due to side effects, this FDC dispersible tablet combines stavudine, lamivudine, and nevirapine.
- Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP) Dispersible Tablets: This FDC dispersible tablet contains zidovudine, lamivudine, and nevirapine, commonly used in resource-limited settings for HIV treatment.
- Tenofovir/Emtricitabine/Rilpivirine (TDF/FTC/RPV) Dispersible Tablets: A newer FDC formulation, this combination includes tenofovir disoproxil fumarate, emtricitabine, and rilpivirine.
- Abacavir/Lamivudine (ABC/3TC) Dispersible Tablets: This FDC dispersible tablet contains abacavir and lamivudine and is commonly used in pediatric HIV treatment.

EMEA (European Medicines Evaluation Agency), and MHRA (Medicines and Healthcare products Regulatory Agency) approved products specifically related to antiretroviral anti-HIV fixed-dose combination (FDC)

- Kaletra (Lopinavir/Ritonavir) Oral Solution: Kaletra is an oral solution containing lopinavir and ritonavir, approved by the MHRA and EMEA for the treatment of HIV/AIDS. While not a dispersible tablet, it may be used in pediatric patients who have difficulty swallowing tablets.
- Triumeq (Abacavir/Lamivudine/Dolutegravir): Triumeq is a fixed-dose combination tablet containing abacavir, lamivudine, and dolutegravir. While not specifically marketed as a dispersible tablet, it's approved by the MHRA and EMEA and may be suitable for some patients who prefer or require dispersible formulations.
- Tivicay PD (Dolutegravir) for Oral Suspension: Tivicay PD is an oral suspension formulation of dolutegravir, approved by the MHRA and EMEA. While not a dispersible tablet, it provides an alternative formulation for pediatric patients who cannot swallow tablets.
- Atripla (Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate): Atripla is a fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate, approved by the MHRA and EMEA.
- Complera (Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate): Complera is a fixed-dose combination tablet containing emtricitabine, rilpivirine, and tenofovir disoproxil fumarate, approved by the MHRA and EMEA.
- Stribild (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate): Stribild is a fixed-dose combination tablet containing elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate, approved by the MHRA and EMEA.

Pharmaceuticals and Medical Devices Agency (PMDA) approved products specifically related to antiretroviral anti-HIV fixed-dose combination (FDC)[42]

- Abacavir/Lamivudine/Dolutegravir (ABC/3TC/DTG): This FDC dispersible tablet contains abacavir, lamivudine, and dolutegravir, and may have received approval from the PMDA for use in Japan.
- Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV): Another potential FDC dispersible tablet approved by the PMDA, this combination contains tenofovir disoproxil fumarate, emtricitabine, and efavirenz.
- Lopinavir/Ritonavir (LPV/r): LPV/r is a protease inhibitor combination, and while it's not specifically marketed as a dispersible tablet, it may have been approved by the PMDA for use in Japan.
- Tenofovir/Emtricitabine/Rilpivirine (TDF/FTC/RPV): This combination includes tenofovir disoproxil fumarate, emtricitabine, and rilpivirine, and it may have been approved in dispersible tablet form for use in Japan.

- 5. Abacavir/Lamivudine (ABC/3TC): This FDC contains abacavir and lamivudine, and while not specifically marketed as a dispersible tablet, it may have been approved by the PMDA for use in Japan.

Regulatory Issues in the Development and Approval of Fixed-Dose Combination (FDC) Dispersible Tablets for Antiretroviral HIV Treatment [43-46]

Antiretroviral therapy (ART) has significantly transformed HIV/AIDS treatment, converting it from a fatal disease into a manageable chronic condition. The fixed-dose combination (FDC) formulations, which consolidate several antiretroviral medications into one tablet, has played a crucial role in simplifying treatment regimens and enhancing patient adherence. Dispersible tablets, designed to dissolve quickly in liquid, offer additional benefits, particularly for populations such as pediatric, geriatric, and bedridden patients. However, the journey from drug development to regulatory approval of antiretroviral FDC dispersible tablets is fraught with challenges, including scientific, technical, and regulatory hurdles.

The regulatory pathway for approving pharmaceutical products, including antiretroviral drugs, differs by region and country. Key regulatory agencies, such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and South Korea's Ministry of Food and Drug Safety (MFDS), are essential in assessing the safety, efficacy, and quality of medications. These agencies set forth guidelines and requirements for drug development, clinical trials, manufacturing, and marketing authorization.

Challenges in Regulatory Approval of Antiretroviral FDC Dispersible Tablets[47-50]

Pediatric formulation development

Developing pediatric-friendly formulations poses unique challenges, including palatability, dosing accuracy, and safety considerations. Dispersible tablets must be formulated to appeal to children's taste preferences while maintaining therapeutic efficacy. Meeting regulatory requirements for pediatric formulations adds complexity to the development process.

Stability and bioavailability

Dispersible tablets should maintain stability and drug content uniformity over their shelf life. Formulation challenges such as moisture sensitivity, chemical degradation, and physical instability need to be addressed. Ensuring consistent drug release and bioavailability across different storage conditions presents additional regulatory hurdles.

Manufacturing considerations

The manufacturing process for dispersible tablets requires specialized equipment and technologies to achieve uniform particle size distribution and optimal tablet characteristics. Regulatory agencies scrutinize manufacturing processes to guarantee obedience with good manufacturing practices (GMP) and product quality standards. Scale-up from laboratory to commercial production introduces challenges related to process scalability and reproducibility.

Clinical trial design

Conducting clinical trials for antiretroviral FDC dispersible tablets involves specific considerations, particularly in vulnerable populations such as pediatric and geriatric patients. Regulatory agencies emphasize the need for well-designed studies that demonstrate safety, efficacy, and pharmacokinetic profiles tailored to the target patient population. Recruiting and retaining participants for pediatric clinical trials present logistical challenges.

Regulatory documentation and submission

Developing comprehensive regulatory documentation is crucial for obtaining approval for antiretroviral FDC dispersible tablets. Regulatory submissions must provide data on preclinical studies, clinical trials, manufacturing processes, stability testing, and quality control procedures. Ensuring compliance with regulatory requirements and addressing agency inquiries in a timely manner is essential for successful approval.

Strategies to Address Regulatory Challenges

Collaboration and partnerships

Collaboration among pharmaceutical companies, regulatory agencies, research institutions, and patient advocacy groups facilitates knowledge sharing, resource pooling, and collective problem-solving. Public-private partnerships can accelerate drug development and streamline regulatory processes.

Regulatory harmonization

Aligning regulatory requirements and standards across regions fosters consistency and minimizes redundant efforts. Initiatives like those by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) aim to standardize guidelines and simplify global drug development

Pediatric drug development incentives

Regulatory agencies provide incentives and regulatory pathways to incentivize pediatric drug development. Programs such as Pediatric Investigation Plans (PIPs) in Europe and Pediatric Exclusivity in the United States encourage sponsors to conduct pediatric studies and obtain pediatric labeling for approved drugs.

Innovative formulation technologies

Investing in innovative formulation technologies such as taste-masking techniques, controlled-release systems, and nanotechnology enhances the development of pediatric-friendly dispersible tablets. These technologies improve palatability, stability, and drug delivery characteristics, addressing regulatory concerns.

Expedited regulatory pathways

Regulatory agencies provide expedited pathways for reviewing and approving medications as shown in Table 4, that address

Table 4: Regulatory process in various regulatory agencies

Agency	*WHO*	*US FDA*	*Japan PMDA*	*EMEA*	*MHRA*	*MFDS*	*China NMPA/SAMR*
Dossier Format	WHO prequalification dossier, including data on quality, safety, and efficacy.	Common Technical Document (CTD) format, including modules on quality, nonclinical, and clinical data.	Pharmaceutical Affairs Law (PAL) application dossier, including CTD format modules.	CTD format, typically following ICH guidelines.	CTD format, following ICH guidelines.	CTD format, following ICH guidelines.	New Drug Application (NDA) dossier, including data on quality, safety, and efficacy.
Timeline	Variable, depending on dossier completeness and review workload.	Generally 10-12 months for Priority Review, longer for Standard Review.	Approximately 12-18 months, depending on review category.	Approximately 12-18 months, depending on review category.	Approximately 12-18 months, depending on review category.	Approximately 12-18 months, depending on review category.	Variable, depending on dossier completeness and review workload.
Process	Review of dossier by WHO experts, including assessment of manufacturing facilities. May involve on-site inspections.	Review of dossier by multidisciplinary teams, including assessment of clinical trial data and manufacturing processes.	Review of dossier by PMDA experts, including evaluation of clinical trial data and manufacturing facilities. May involve on-site inspections.	Centralized or decentralized assessment by EMEA committees, including review of clinical data and manufacturing processes.	Assessment by MHRA experts, including review of clinical data and manufacturing facilities.	Review of dossier by MFDS experts, including evaluation of clinical trial data and manufacturing processes. May involve on-site inspections.	Review of dossier by NMPA/SAMR experts, including assessment of clinical trial data and manufacturing facilities.
Strategies	Collaboration with manufacturers and other stakeholders to expedite dossier preparation and review.	Engagement with sponsors to address regulatory requirements early in the development process.	Implementation of priority review and sakigake designation programs for innovative therapies.	Alignment with other regulatory agencies through mutual recognition agreements and work-sharing initiatives.	Implementation of accelerated assessment and adaptive pathways for innovative therapies.	Engagement with sponsors to facilitate dossier preparation and review. Utilization of	Alignment with international standards and best practices.
Requirements	Compliance with WHO prequalification guidelines, including stringent quality, safety, and efficacy criteria.	Compliance with US FDA regulations and guidelines, including demonstration of safety, efficacy, and quality.	Fulfillment of PMDA requirements for drug approval, including submission of comprehensive data on quality, safety, and efficacy.	Adherence to EMEA guidelines and regulations, including demonstration of quality, safety, and efficacy through clinical trials and manufacturing processes.	Adherence to MHRA regulations and guidelines, including submission of robust clinical and nonclinical data.	Compliance with MFDS regulations and guidelines, including demonstration of quality, safety, and efficacy through clinical trials and manufacturing processes.	Fulfillment of NMPA/SAMR requirements for drug approval, including submission of comprehensive data on quality, safety, and efficacy.

Table 5: Comparison of the regulatory processes

Regulatory agency	*Dossier format*	*Timeline*	*Process*	*Strategies*	*Requirements*
India CDSCO	Common technical document (CTD) format, including modules on quality, safety, and efficacy.	Approximately 12–18 months, depending on review workload and completeness of dossier.	Review of dossier by CDSCO experts, including clinical trial data, manufacturing processes, and labelling.	Collaboration with sponsors to address regulatory requirements early in the development process.	Compliance with CDSCO regulations and guidelines, including demonstration of quality, safety, and efficacy
China NMPA/ SAMR	New Drug Application (NDA) dossier, including data on quality, safety, and efficacy.	Variable, depending on dossier completeness and review workload.	Review of dossier by NMPA/SAMR experts	Engagement with sponsors to facilitate dossier preparation and review.	Compliance with NMPA/ SAMR requirements for drug approval, including safety, and efficacy data
Japan PMDA	Pharmaceutical Affairs Law (PAL) application dossier, including Common Technical Document (CTD) format modules.	Approximately 12-18 months, depending on review category. Expedited reviews may be available.	Review of dossier by PMDA experts, including evaluation of clinical trial data	Implementation of priority review and sakigake designation programs for innovative therapies.	Fulfillment of PMDA requirements for drug approval, including submission of safety, and efficacy data
Indonesia BPOM	Common Technical Document (CTD) format, including modules on quality, safety, and efficacy.	Approximately 12-18 months, depending on review workload and completeness of dossier.	Review of dossier by BPOM experts, including assessment of clinical trial data, manufacturing processes, and labelling.	Engagement with sponsors to facilitate dossier preparation and review. Utilization of expedited review pathways for urgent medical needs.	Compliance with BPOM regulations and guidelines, including demonstration of quality, safety, and efficacy
Malaysia NPRA	Common Technical Document (CTD) format, including modules on quality, safety, and efficacy.	Approximately 12-18 months,	Review of dossier by NPRA experts, including assessment of clinical trial data, manufacturing processes, and labelling.	Engagement with sponsors to facilitate dossier preparation and review. Utilization of expedited review pathways for urgent medical needs.	Compliance with NPRA regulations and guidelines, including demonstration of quality, safety, and efficacy data

unmet medical needs or public health emergencies. Programs like Priority Review in the United States and Accelerated Assessment in Europe accelerate the regulatory evaluation process for promising therapies.

Comparison of the regulatory processes for the approval of antiretroviral anti-HIV fixed-dose combination (FDC) dispersible tablets in Asian countries, including India

The difference in regulatory processes as mention in Table 5, highlights the differences and similarities in the regulatory processes for the approval of antiretroviral FDC dispersible tablets by various regulatory agencies, emphasizing the importance of understanding and addressing each agency's specific requirements and expectations.

CONCLUSION

Developing and obtaining regulatory approval for antiretroviral FDC dispersible tablets presents multifaceted challenges, ranging from formulation development to clinical trial design and regulatory submission. Addressing these challenges requires collaboration, innovation, and regulatory alignment across regions. By overcoming regulatory hurdles and implementing strategic approaches, stakeholders can accelerate access to safe, effective, and pediatric-friendly antiretroviral medications, ultimately contributing to the global fight against HIV/AIDS.

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