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FAST-DISSOLVING AND PEDIATRIC-FRIENDLY FORMULATIONS IN CANCER CHEMOTHERAPY: A REVIEW

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Abstract: Chemotherapy remains a cornerstone of cancer treatment, but presents unique challenges in pediatric patients due to poor compliance, swallowing difficulty, dose accuracy, and systemic toxicity. Fast-dissolving (FD) and pediatric-friendly formulations are emerging strategies to improve therapeutic outcomes, compliance, safety, and quality of life. This review provides a comprehensive overview of FD drug delivery systems in cancer chemotherapy, design principles, formulation technologies, clinical considerations, and future perspectives.

Keywords: Fast-dissolving formulations; Pediatric chemotherapy; Orally disintegrating tablets; Oral drug delivery systems; Patient compliance; Cancer therapy

INTRODUCTION

Cancer chemotherapy remains a fundamental 2 yg anxiety related to medication intake significantly affect adherence. Invasive administration routes, including injections, may further increase distress and reduce treatment acceptability. Poor compliance or incomplete dosing in chemotherapy regimens can lead to suboptimal therapeutic outcomes, increased risk of disease progression, and development of drug resistance.

To address these challenges, fast-dissolving and

pediatric-friendly drug delivery systems have gained increasing attention as innovative alternatives to traditional dosage forms. These formulations include orally disintegrating tablets (ODTs), fast-dissolving oral films, buccal and sublingual tablets, and rapidly dissolving granules. Such systems are designed to disintegrate or dissolve rapidly in the oral cavity, usually within seconds, without the need for water. This characteristic makes them particularly suitable for pediatric patients who have difficulty swallowing or are experiencing chemotherapy-induced nausea.

Beyond ease of administration, fast-dissolving formulations offer additional therapeutic advantages. Rapid disintegration enhances drug dissolution and may improve the onset of action. Certain formulations enable partial absorption through the oral mucosa, thereby bypassing first-pass hepatic metabolism and potentially enhancing bioavailability. Moreover, these systems can be engineered to incorporate taste-masking strategies, dose flexibility, and controlled or targeted drug release, which are crucial for chemotherapeutic agents with narrow therapeutic windows.

Consequently, fast-dissolving and pediatric-friendly formulations represent a patient-centric approach to cancer chemotherapy, aiming to improve treatment adherence, minimise dosing errors, and enhance overall therapeutic efficacy while improving the quality of life of pediatric cancer patients.

PEDIATRIC ONCOLOGY: UNIQUE CHALLENGES

Physiological and Psychological Barriers

Pediatric patients differ from adults in terms of gastric pH, enzyme activity, renal clearance, and metabolic rates — factors that influence drug absorption, distribution, metabolism, and excretion (ADME). Swallowing large tablets or managing complex regimens can lead to anxiety, refusal, or incomplete dosing.

Treatment Compliance

Compliance is crucial in chemotherapy due to narrow therapeutic windows. Missed or partial doses heighten the risk of treatment failure and resistance. Palatability, swallowability, and dose accuracy are key drivers of pediatric adherence.

FAST-DISSOLVING FORMULATIONS: DEFINITIONS AND RATIONALE

Fast-dissolving drug delivery systems are advanced solid oral dosage forms specifically designed to disintegrate, disperse, or dissolve rapidly in the oral cavity—typically within a few seconds—without the need for water. Upon contact with saliva, these formulations break down to release the active pharmaceutical ingredient, allowing it to be swallowed easily or absorbed directly through the oral mucosa. This mode of administration is particularly advantageous for pediatric, geriatric, and critically ill patients who experience difficulty in swallowing conventional tablets or capsules.

These systems encompass a range of dosage forms, including **orally disintegrating tablets (ODTs)**, **fast-dissolving oral films**, and **sublingual or buccal tablets**, each offering distinct formulation and therapeutic benefits.

Orally Disintegrating Tablets (ODTs)

ODTs are solid unit dosage forms that rapidly disintegrate in the mouth without chewing or water intake. They combine the stability and dosing accuracy of traditional tablets with the convenience of liquid formulations. The rapid disintegration is typically achieved through the use of superdisintegrants or highly porous matrices. ODTs are particularly suitable for chemotherapeutic agents requiring precise dosing and ease of administration in pediatric patients.

Fast-Dissolving Oral Films

Fast-dissolving oral films are thin, flexible polymeric strips that dissolve quickly when placed on the tongue or buccal mucosa. These films provide excellent patient acceptability due to their small size, absence of choking risk, and pleasant mouthfeel. Oral films allow for dose flexibility, making them especially useful in pediatric oncology, where dosing must be adjusted based on age, weight, or body surface area. Additionally, films can be engineered to incorporate taste-masking agents and permeation enhancers to improve palatability and drug absorption.

Sublingual and Buccal Tablets

Sublingual and buccal formulations are designed to dissolve or release the drug in the sublingual or buccal region of the oral cavity. These systems facilitate direct drug absorption into the systemic circulation through the oral mucosa, thereby bypassing hepatic first-pass metabolism. This route can enhance bioavailability and provide a rapid onset of action, which is beneficial for chemotherapeutic agents with poor oral bioavailability or extensive first-pass metabolism.

Rationale for Use in Pediatric Chemotherapy

The rationale for adopting fast-dissolving formulations in cancer chemotherapy lies in their ability to address major limitations associated with conventional oral dosage forms. Key advantages include rapid onset of action, improved patient compliance, ease of administration without water, and suitability for patients with dysphagia or chemotherapy-induced nausea and vomiting. Furthermore, these formulations enable dose

personalisation, improved taste masking, and potential reduction in gastrointestinal irritation.

Overall, fast-dissolving drug delivery systems represent a patient-centric and clinically effective approach for enhancing the safety, acceptability, and therapeutic performance of chemotherapeutic agents, particularly in pediatric oncology.

PEDIATRIC-FRIENDLY FORMULATION CONSIDERATIONS

Taste Masking

Bitterness is a major barrier in pediatric oncology. Technologies include:

- **Microencapsulation**
- **Cyclodextrin inclusion complexes**
- **Sweeteners and flavours**

Example: Palatable granules with bitterness blockers or coated drug particles improve acceptance.

Dose Flexibility

Pediatric cancer dosing often requires individualised doses based on age, weight, or body surface area. FD systems can be easily tailored — e.g., films can be cut into precise doses.

Reduced Water Requirement

Minimising the need for water benefits patients with nausea or vomiting, common side effects of chemotherapy.

APPLICATIONS IN CHEMOTHERAPEUTIC AGENTS

Several chemotherapeutic agents are suitable for FD formulation:

Drug	Challenges	FD Benefits
Methotrexate	Poor solubility; toxic	Enhanced compliance
5-Fluorouracil	Frequent dosing	Rapid administration
Cyclophosphamide	Bitter taste	Taste masking via films
Temozolomide	Pediatric brain tumours	Buccal delivery

Innovative approaches like nanocrystal suspensions, solid dispersions, and self-emulsifying systems have also been explored to improve solubility and absorption.

DISCUSSION

MECHANISMS OF ENHANCED PERFORMANCE

Fast-dissolving (FD) drug delivery systems enhance therapeutic performance through multiple complementary mechanisms that collectively improve drug absorption, bioavailability, tolerability, and patient compliance. These mechanisms are particularly valuable in cancer chemotherapy, where drugs often possess narrow therapeutic indices and are associated with significant gastrointestinal and systemic adverse effects.

Rapid Disintegration and Absorption

One of the primary mechanisms underlying the enhanced performance of fast-dissolving formulations is their ability to disintegrate rapidly in the oral cavity upon contact with saliva. This rapid disintegration results in the formation of fine drug particles, leading to a substantial increase in surface area available for dissolution. According to the Noyes–Whitney equation, an increase in surface area directly enhances the dissolution rate, thereby promoting faster drug release and absorption.

Additionally, the pre-gastric dispersion of the drug minimises the time required for dissolution in the gastrointestinal tract. In some cases, partial absorption may occur across the oral mucosa, further accelerating systemic availability. This rapid onset of action is particularly beneficial in pediatric chemotherapy, where timely and consistent drug exposure is critical for therapeutic efficacy.

Bypass of First-Pass Metabolism

Buccal and sublingual fast-dissolving systems offer the advantage of delivering drugs directly into the systemic circulation via the rich vascular network of the oral mucosa. Absorption through these routes bypasses hepatic first-pass metabolism, which is responsible for the extensive metabolic degradation of many chemotherapeutic agents.

By avoiding first-pass metabolism, FD buccal and sublingual formulations can significantly improve oral bioavailability, reduce interpatient variability, and lower the required dose to achieve therapeutic plasma concentrations. This is especially important in pediatric patients, where metabolic pathways may be immature or highly variable, increasing the risk of under- or overdosing with conventional oral formulations.

Reduced Gastrointestinal Side Effects

Fast-dissolving drug delivery systems may contribute to a reduction in gastrointestinal adverse effects commonly associated with chemotherapy. Since these formulations dissolve rapidly and require minimal gastric residence time, the exposure of the gastric mucosa to irritating drugs is reduced. This can help minimise gastric irritation, ulceration, and discomfort.

Furthermore, FD systems often allow for lower effective doses due to improved bioavailability, which can further reduce gastrointestinal toxicity. This advantage is particularly relevant for pediatric oncology patients, who frequently experience chemotherapy-induced nausea and vomiting, making conventional oral administration challenging. By improving tolerability and reducing GI distress, fast-dissolving formulations support better treatment adherence and overall patient comfort.

CLINICAL IMPACT AND COMPLIANCE

Studies show that pediatric patients prefer FD forms due to ease of administration and palatability. Improved compliance may translate into better clinical outcomes, fewer dose omissions, and reduced healthcare burden.

REGULATORY AND SAFETY CONSIDERATIONS

The development of fast-dissolving and pediatric-friendly formulations for cancer chemotherapy requires rigorous regulatory oversight and comprehensive safety evaluation. Pediatric patients represent a vulnerable population with distinct physiological, developmental, and behavioural characteristics, necessitating specialised regulatory frameworks to ensure that formulations are both safe and effective.

Safety Assessments

Pediatric formulations must undergo age-appropriate and formulation-specific safety assessments before clinical use. These evaluations extend beyond conventional pharmacokinetic and toxicological studies to include parameters such as palatability, mouthfeel, and ease of administration, which directly influence adherence in pediatric patients. Taste acceptability studies are particularly critical for chemotherapeutic agents, as bitterness and unpleasant sensory characteristics can lead to dose refusal or incomplete administration.

Excipients used in fast-dissolving formulations must be carefully selected and justified for pediatric use. Certain excipients considered safe in adults may pose risks in children due to immature metabolic pathways or limited clearance capacity. Therefore, excipient safety evaluation must consider factors such as maximum allowable daily intake, age-specific exposure limits, and potential for local irritation in the oral cavity. Bioavailability and bioequivalence studies are also essential to ensure consistent drug exposure and to prevent under- or overdosing, especially given the narrow therapeutic window of many chemotherapeutic agents.

Regulatory Guidance

Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have established specific guidelines to promote the safe development of pediatric medicines. The EMA mandates Pediatric Investigation Plans (PIPs), which outline strategies for studying a drug in pediatric populations, including formulation design, dosing regimens, and clinical evaluation. Similarly, the FDA encourages pediatric-focused formulation development through legislation such as the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA).

Both agencies emphasise the importance of acceptability and usability studies, which assess factors such as ease of administration, dosing accuracy, and patient and caregiver preferences. For fast-dissolving formulations, these studies help demonstrate real-world feasibility and therapeutic benefit. Regulatory authorities also encourage early integration of pediatric considerations during formulation development to avoid later reformulation and to ensure timely access to child-appropriate cancer therapies.

FUTURE PERSPECTIVES

The future development of fast-dissolving and pediatric-friendly formulations in cancer chemotherapy is closely aligned with advances in drug delivery science, material engineering, and patient-centred pharmaceutical design. Emerging technologies offer opportunities to further enhance therapeutic efficacy, safety, and treatment acceptability in pediatric oncology.

Nanotechnology Integration

Nanotechnology-based drug delivery systems represent a promising strategy for overcoming key limitations of conventional chemotherapeutic formulations, particularly poor aqueous solubility and low oral bioavailability. Nanoparticles, nanosuspensions, lipid-based carriers, and polymeric nanocarriers can significantly enhance drug dissolution by increasing surface area and improving wettability. When incorporated into fast-dissolving dosage forms, these nano-enabled systems can provide rapid drug release while maintaining improved stability and controlled pharmacokinetics.
Furthermore, nanocarriers can be engineered for sustained or targeted drug release, reducing dosing frequency and systemic toxicity. In pediatric chemotherapy, where minimising adverse effects is critical, nano-integrated fast-dissolving systems may improve therapeutic outcomes by enhancing tumour targeting while sparing healthy tissues. These advanced systems also hold potential for co-delivery of multiple agents, enabling combination chemotherapy in a single, patient-friendly dosage form.

Smart Polymers

The use of smart or stimuli-responsive polymers offers innovative possibilities for precision drug delivery in pediatric oncology. These polymers respond to specific physiological triggers such as pH, temperature, or enzymatic activity, enabling site-specific or controlled drug release. For instance, pH-sensitive polymers can release chemotherapeutic agents preferentially in acidic tumour microenvironments, while enzyme-responsive polymers can be activated by tumour-associated enzymes.

In fast-dissolving formulations, smart polymers can provide rapid initial disintegration in the oral cavity followed by controlled or targeted drug release in systemic circulation. This dual functionality may help optimise pharmacokinetic profiles, reduce off-target toxicity, and enhance therapeutic efficacy, making them particularly suitable for chemotherapeutic agents with narrow therapeutic windows.

Patient-Centered Design

Patient-centred formulation design is increasingly recognised as a critical component of successful pediatric drug development. Actively involving pediatric patients, caregivers, and healthcare professionals in formulation selection and evaluation can lead to dosage forms that better align with real-world needs and preferences. Factors such as taste, mouthfeel, dosage form size, dosing frequency, and ease of administration significantly influence adherence in pediatric patients undergoing long-term chemotherapy.

Incorporating feedback from acceptability and usability studies during early formulation development can improve treatment compliance and reduce medication-related anxiety. Personalised dosing options, such as cuttable oral films or flexible-dose granules, further support individualised therapy. Ultimately, patient-centred design enhances not only adherence but also overall quality of life for pediatric cancer patients, reinforcing the value of fast-dissolving formulations as a holistic and compassionate approach to cancer chemotherapy.

CONCLUSION

Fast-dissolving and pediatric-friendly formulations hold considerable promise for improving cancer chemotherapy in children. By addressing challenges related to swallowability, compliance, taste, and dosing flexibility, these advanced drug delivery systems can enhance therapeutic outcomes and patient quality of life. Continued research, clinical evaluation, and regulatory support are needed to translate these innovations into standard clinical practice.

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