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Review Paper

Novel Approaches in Paediatric Formulations: Recent Advances and Future Perspectives

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ABSTRACT

The Paediatric population has distinct obstacles for drug development owing to its varied physiological, developmental, and pharmacological traits. Notwithstanding regulatory incentives, a substantial disparity persists in age-appropriate medications, resulting in extensive off-label utilization of adult formulations. This study consolidates current advancements (2020-2025) in Paediatric -specific dose forms designed to enhance safety, effectiveness, and adherence. The emphasis is on three transformative technologies: three-dimensional (3D) printing for customized, on-demand production of specific dosages; nanotechnology-based delivery systems (lipid, polymeric, and inorganic nanoparticles) for improved bioavailability, targeted delivery, and diminished toxicity; and orodispersible formulations (mini-tablets, tablets, and films) that address swallowing challenges. The analysis encompasses essential taste-masking techniques and the changing regulatory environments. Although these innovations possess significant potential to transform Paediatric pharmacotherapy, challenges concerning material availability, long-term safety data, manufacturing scalability, and intricate regulatory processes must be resolved to fully actualize their potential and close the existing formulation gap.

INTRODUCTION

The Paediatric population encompasses new-born babies, toddlers, children, and adolescents, each displaying distinct physiological, developmental, and pharmacological traits that set them apart from adults [1]. Creating Paediatric -specific dose forms is particularly difficult due to age-related differences in pharmacokinetics, pharmacodynamics, organ development, and drug metabolism [2]. Notwithstanding legislative initiatives like the Best Pharmaceuticals for Children Act (BPCA) and the Paediatric Research

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Equity Act (PREA) in the United States, as well as analogous laws in the European Union, the provision of age-appropriate Paediatric medications remains inadequate. As a result, the off-label administration of adult drugs to children continues in clinical practice, prompting questions regarding proper dose, safety, and therapeutic effectiveness [3].

The worldwide Paediatric pharmaceutical industry is experiencing significant growth, projected to increase from USD 32 billion in 2024 to USD 95.4 billion by 2033, indicating a compound annual growth rate (CAGR) of 12.7% [4]. This expansion is driven by rising demand for Paediatric medicines, heightened awareness of children's healthcare requirements, increased prevalence of chronic and infectious disorders among children, and technical advancements in Paediatric formulation. Novel dose forms, including chewable, liquids, and orally disintegrating tablets, are increasingly recognized for enhancing adherence in Paediatric patients [4]. Market projections indicate an increase from USD 120.31 billion to USD 179.74 billion from 2023 to 2028, reflecting a CAGR of 8.36%, propelled by escalating birth rates and ongoing issues related to Paediatric diseases such as pneumonia, diarrhoea, malaria, and complications from preterm births [3].

Regulatory frameworks are advancing to enhance Paediatric medication development. In April 2023, the European Commission adopted a new Directive and Regulation, marking a key milestone in the update of pharmaceutical regulation, which includes particular rules for rare illnesses and Paediatric drugs [5]. Concurrent initiatives in the United States augment these modifications, thus improving the domain of Paediatric formulations. The COVID-19 pandemic significantly expedited pharmaceutical innovation, particularly enhancing 3D printing technologies that have potential for individualized Paediatric care.

This study seeks to thoroughly examine current advancements in Paediatric formulation development published from 2020 to 2025. The focus is on: three-dimensional printing applications for personalized therapy; nanotechnology-based delivery systems, including polymeric, lipid-based, and inorganic nanoparticles; orodispersible dosage forms such as tablets, minitablets, and oral films; taste-masking and palatability enhancement strategies; emerging delivery platforms and devices; and regulatory considerations influencing the future of Paediatric pharmaceuticals. This review aims to inform formulation scientists, physicians, and regulatory experts on the latest advancements in Paediatric drug formulation by combining current research and clinical progress.

2. Novel Approaches in Paediatric Formulations

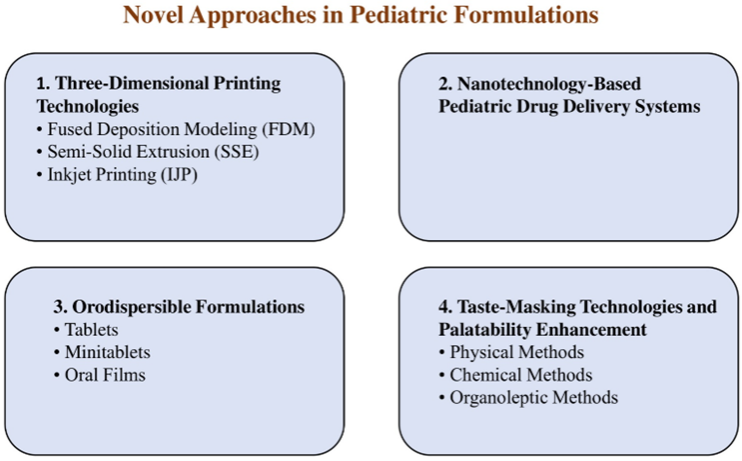
2.1 Three-Dimensional Printing Technologies

Three-dimensional printing (3DP), or additive manufacturing, has emerged as a revolutionary instrument in pharmaceutical formulation, offering novel opportunities for personalized medicine and patient-centric medication creation [1]. This method fabricates three-dimensional medicinal solutions incrementally from digital designs, allowing for exceptional accuracy and adaptability in customizing formulas to meet unique requirements. The Paediatric population, marked by significant diversity in age, physiology, and metabolic capacity, particularly benefits from personalized methods. Frequent dose modifications and differing pharmaceutical needs during developmental phases provide 3DP a viable platform for creating patient-specific formulations that enhance therapeutic efficacy and compliance [1].

The U.S. Food and Drug Administration (FDA) approved Spritam (levetiracetam) in 2015,

representing the inaugural 3D-printed pharmaceutical product to be marketed. Spritam, produced using Drop-on-Powder and Zip Dose Technologies, possesses a very porous structure that facilitates quick breakdown upon liquid contact, hence improving administration for patients with dysphagia. This milestone confirmed the viability of 3D printing for large-scale pharmaceutical manufacture and created opportunities for its use across various active pharmaceutical ingredients (APIs), especially those needed in flexible doses for Paediatric patients [6].

Subsequent to this regulatory achievement, other pharmaceutical businesses have progressed in research and commercialization endeavours in 3D-printed medicine production. Triastek Inc. has unveiled their unique MED 3DP technology, which can manufacture tablets with tailored geometries that regulate medication release patterns, onset timings, and interactions inside the body [1]. Other prominent industry participants, like Aprecia Pharmaceuticals, GlaxoSmithKline (GSK), and FabRx, have also pursued the development and commercialization of 3D-printed pharmaceuticals aimed at diverse therapeutic domains. Their collaborative endeavours indicate an increasing trend towards the incorporation of 3D printing into conventional medication development processes, presenting novel opportunities for accurate, scalable, and patient-specific Paediatric formulations.



2.1.1 Fused Deposition Modelling (FDM)

Fused Deposition Modelling is one of the most often utilized 3D printing methods in pharmaceutical applications. The procedure entails heating thermoplastic filaments to their softening temperature, thereafter extruding them through a nozzle to deposit material layer by layer in accordance with pre-programmed patterns [1]. The integration of hot melt extrusion (HME) allows the insertion of homogenous solid dispersions of thermostable pharmaceuticals and excipients into filament components as printable material, a capability not attainable by alternative methods [1]. The automated manufacturing method provides superior efficiency with less material waste.

The adaptability of FDM in altering medication loading and release profiles by the modification of feedstock % or geometric configuration renders it especially attractive for formulation scientists creating Paediatric -friendly products aligned with patient preferences [1]. Recent advancements involve initiatives to create standardized equipment certification frameworks for FDM printers, essential for expediting and optimizing approval procedures for 3D-printed pharmaceutical products [1].

2.1.2 Semi-Solid Extrusion (SSE)

Semi-solid extrusion, or pressure-assisted micro syringe (PAM) printing, entails the extrusion of semi-solid substances by precision dispensing devices [1]. This approach has demonstrated significant efficacy in Paediatric applications. In 2024, Chachlioutaki and associates created antifungal buccal films with SSE printing as a substitute for commercially available antifungal oral gels [7]. The formulation comprised miconazole with a zein-polyvinylpyrrolidone (zein-PVP) polymer mix as the medication carrier, adding banana flavouring to improve compliance among juvenile patients. Various polymer ratios (60/40, 50/50, and 40/60) were assessed, with all films exhibiting disintegration durations of less than 10 minutes. The formulation including zein and PVP in a 40:60 ratio had the highest mucosal binding capability [7]. Numerous researches have proven the utility of SSE in Paediatric formulations. Herrada-Manchón et al. (2020) created chewable tablets of ranitidine hydrochloride with the SSE approach in attractive designs for children (hearts, bears), fulfilling all criteria for quality homogeneity, dosage precision, and solubility [8]. Tagami et al. (2021) created chewable lamotrigine tablets with hydrogel materials, which are preferred by young patients [8]. Han et al. (2022) developed six distinct sizes of amlodipine besylate tablets for Paediatric patients aged 2-16 years with SSE technology, therefore efficiently meeting clinical requirements for personalized dosage [8].

2.1.3 Inkjet Printing (IJP)

Inkjet printing technique utilizes accurate droplet deposition to create pharmaceutical dosage forms. Industrial IJP print heads are categorized into continuous inkjet and drop-on-demand (DoD) systems [1]. Piezoelectric print heads, frequently employed in inkjet material deposition, provide enhanced control over droplet formation compared to thermal print heads and may utilize a range of inks, whereas thermal heads are restricted to volatile solvents. The DoD IJP offers improved accuracy while reducing ink use [1]. Recent advancements in fast-curing ultraviolet light-emitting diode (UV-LED) inks, coupled with cost-effective drop-on-demand (DoD) technology, present various designs that are expected to meet the growing needs for child-friendly product printing tailored for bespoke applications [1]. These developments establish inkjet printing as a suitable platform for the development of Paediatric formulations.

2.1.4 Stereolithography and Digital Light Processing

Liquid-solidification methods, such as stereolithography and digital light processing, utilize photopolymerization of liquid resins to construct solid structures incrementally. SLA offers high-resolution and precise fabrication of complex structures, rendering it appropriate for elaborate dosage form designs. Nonetheless, exposure to UV radiation during processing may lead to the photodegradation of active compounds, potentially impacting API content and generating hazardous breakdown products [7]. This constraint requires meticulous API selection and formulation design when utilizing photopolymerization methods.

Clinical Applications and Case Analyses:

Three-dimensional printing has demonstrated significant potential in providing customized Paediatric treatments. The initial clinical application entailed personalized isoleucine tablets for Maple Syrup Urine Disease (MSUD), providing bespoke dosages in several tastes and colours to enhance palatability and adherence while sustaining therapeutic plasma concentrations [9,8]. In juvenile epilepsy, 3D printing facilitated adaptable levetiracetam

administration via semi-solid extrusion, permitting accurate, modifiable layer-based configurations that enhance seizure management with less adverse effects [8]. Furthermore, 3D-printed sildenafil orodispersible mini-tablets, optimized through factorial design, have enhanced cardiovascular treatment in Paediatric patients by providing rapid disintegration, mechanical integrity, and dose consistency, especially for pulmonary hypertension [10]. These case studies illustrate the revolutionary influence of 3D printing in producing child-friendly, accurate, and efficacious medicine formulations.

Advantages

1. Dose flexibility: It enables the meticulous customization of form, size, dose, drug release patterns, and multi-drug combinations to accommodate unique patient requirements [5].
2. Personalized medicine: Patient-specific factors, including pharmacogenomic information and medical imaging, can inform the optimization of dosage forms for targeted drug release, administration routes, and dosing regimens [1].
3. Enhanced compliance: The capacity to create child-friendly designs in many forms, tastes, and colours increases acceptance and adherence among Paediatric patients [8].
4. On-demand manufacturing: Formulations may be generated directly at hospitals or pharmacies, enabling rapid, point-of-care preparation and dosage modifications [5].
5. Intricate medication delivery: 3D printing facilitates the fabrication of polypill formulations comprising numerous active pharmaceutical ingredients (APIs) with regulated, separate release characteristics [1].

Limitations and Challenges

1. Restricted material availability: There exists a deficiency of pharmaceutical-grade polymers, binders, and excipients with precisely defined characteristics appropriate for printing [11].
2. Biocompatibility data deficiencies: Insufficient comprehension of material stability and compatibility, particularly in innovative Paediatric designs, heightens safety apprehensions [11].
3. Regulatory obstacles: The approval processes for 3D-printed pharmaceuticals are intricate owing to the novel characteristics of the technology [1].
4. Manufacturing consistency: Fluctuations in printer parameters, including layer thickness and infill density, might affect medication homogeneity, hence hindering repeatable manufacturing [11].
5. Quality control: Maintaining uniformity between batches and establishing approved testing techniques for tailored formulations continue to pose significant hurdles [5].

2.2 Nanotechnology-Based Paediatric Drug Delivery Systems

Nanotechnology-based medication delivery systems have arisen as a viable solution to longstanding issues in Paediatric treatments. Regulatory agencies, such as the United States Paediatric Formulation Initiative and the European Paediatric Formulation Initiative, have advocated for the incorporation of nanotechnology in Paediatric drug development, highlighting the significance of inorganic, polymeric, and lipid-based nanoparticles in enhancing therapies [3]. Nanoscale systems has the capability to surmount restrictions associated with conventional formulations, especially for chemotherapeutic agents and poorly soluble pharmaceuticals. They provide benefits such as regulated or prolonged drug release, enhanced bioavailability, less systemic toxicity, and tailored distribution to disease locations—essential characteristics that can improve clinical results and ensure patient

safety in Paediatric populations [12]. Nanotechnology functions by altering materials at the nanoscale, namely within the range of 10–100 nanometres, where distinctive physicochemical features may be utilized for therapeutic advantages. Particle size is crucial in influencing biodistribution, clearance, and overall pharmacological activity. Nanoparticles larger than 200 nm often collect in the liver and spleen, but those less than 5 nm are swiftly eliminated by renal filtration. Thus, nanoparticles of 10–100 nm are ideal for Paediatric medication administration, striking a compromise between therapeutic effectiveness and minimized off-target toxicity [11].

Lipid-based nanoparticles, including liposomes and solid lipid nanoparticles, are among the most therapeutically verified groups of nanoparticles. Numerous FDA-approved lipid-based pharmaceuticals illustrate their efficacy in Paediatric cancer. Vyxeos, a liposomal co-formulation of daunorubicin and cytarabine in a set molar ratio, improves effectiveness and safety in acute myeloid leukaemia [11]. Oncaspar, a PEGylated variant of L-asparaginase, is extensively utilized in the treatment of acute lymphoblastic leukaemia, exhibiting enhanced pharmacokinetic stability and decreased dose frequency. Likewise, DaunoXome, a liposomal version of daunorubicin, has demonstrated significantly less cardiotoxicity in the treatment of Kaposi's sarcoma, exemplifying how lipid encapsulation can alleviate side effects while maintaining anticancer efficacy.

Polymeric nanoparticles, often made from biocompatible and biodegradable substances like poly (lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG), provide effective platforms for controlled and sustained release formulations. These methods safeguard unstable pharmaceuticals against deterioration, promote improved penetration through biological membranes, and enable surface changes for precise administration. Recent breakthroughs encompass nanoparticle-enhanced formulations of aprepitant for the management of chemotherapy-induced nausea and vomiting (CINV) in Paediatric oncology. These formulations markedly improve bioavailability and extend systemic circulation, hence enhancing treatment efficacy and the quality of life for young cancer patients [14,11]. Inorganic nanoparticles have significant potential in Paediatric medicine, especially for central nervous system tumours. Gold nanoparticles (AuNPs) functionalized with targeting ligands like Angiopep-2 have been developed for the treatment of brain tumours. The Angiopep-2-conjugated PEGylated doxorubicin-loaded gold nanoparticles (An-PEG-DOX-AuNPs) employ LRP1 receptor-mediated transport to penetrate the blood-brain barrier and specifically target glioma cells. Upon arrival in the tumour microenvironment, doxorubicin is locally released, triggering apoptosis and minimizing systemic exposure [13]. This illustrates the significant promise of nanoscale technology in developing safer, more effective treatment options for Paediatric patients.

Clinical Applications

Nanotechnology has substantially progressed Paediatric pharmacology by refining medication targeting, minimizing toxicity, and augmenting patient adherence. In Paediatric oncology, nanoparticle-mediated drug delivery facilitates targeted tumour therapy, prolonged release, and diminished adverse effects, exemplified by liposomal chemotherapies for leukaemia and transferrin-targeted nanoparticles for neuroblastoma [11]. Infectious illnesses have benefited from nanotechnology through enhanced medication bioavailability and dosage convenience, shown by Nano encapsulated antituberculosis drugs in orodispersible films and sustained-release antiretrovirals for Paediatric

HIV. Nanotechnology has revolutionized Paediatric vaccination, shown by virus-like nanoparticle vaccines such as Novavax for COVID-19, which have obtained FDA approval for teenagers, and nanotechnology-enhanced vaccinations like Hepatitis B (Engerix-B) that provide substantial protection. Nanomedicine is facilitating the development of safer, more effective, and Paediatric -friendly treatment and preventative approaches.

Advantages

1. Enhanced patient adherence resulting from decreased dose frequency facilitated by sustained or controlled medication release systems [17,11].
2. Improved bioavailability attained by enhanced solubility, absorption, and systemic distribution, especially for pharmaceuticals with low water solubility.
3. Targeted delivery employing active and passive targeting mechanisms to accurately route pharmaceuticals to affected tissues, therefore reducing systemic exposure and toxicity.

   Alternative administration methods, such as transdermal, nasal, and oral delivery, provide non-invasive choices for medications often necessitating injections, hence enhancing adherence [17].
4. Successful flavour masking accomplished via medication encapsulation, enhancing palatability and acceptability in juvenile patients [18].

Challenges and Safety Considerations

1. Limited long-term safety and toxicity evidence pertinent to Paediatric patients, resulting in ambiguity regarding chronic usage [13].
2. Physiological diversity among Paediatric age groups affects nanoparticle dispersion, metabolism, and excretion, hence challenging dosage optimization.
3. Manufacturing difficulties in increasing nanoparticle output while maintaining quality, stability, and sterility of the final product.
4. Regulatory complexity, due to the absence of established regulatory processes for Paediatric nanomedicines, hinders clinical translation and commercialization.
5. Elevated development and manufacturing expenses, which may hinder accessibility and adoption in resource-constrained healthcare systems.

2.3 Orodispersible Formulations

In 2008, the World Health Organization (WHO) Expert Forum advocated for a paradigm shift towards solid dosage forms, acknowledging the limits of liquid formulations often employed for young patients [19]. This transition was driven by many factors: children's incapacity to ingest big tablets or capsules, stability constraints linked to liquid formulations, concerns over dosage precision, and difficulties in taste masking. Orodispersible formulations have emerged as a viable alternative, merging the benefits of solid dose forms with convenience of administration for young patients [20].

2.3.1 Orodispersible Mini-Tablets

Orodispersible mini-tablets (ODMTs) are a novel Paediatric oral dose form that integrates the benefits of both liquid and solid formulations. ODMTs, with diameters generally between 1 and 3 millimetres, are sufficiently tiny to facilitate swallowing while providing the stability, taste masking, and dosage accuracy characteristic of solid forms [21]. Their shape facilitates customizable dosage, enhances mobility, and ensures high patient acceptance, rendering them especially appropriate for new-born s and young children who struggle with swallowing bigger pills

or tolerating bitter liquids. Global health authorities, such as the World Health Organization (WHO) and the European Medicines Agency (EMA), have acknowledged their potential and advocated the use of mini-tablets in Paediatric Investigation Plans (PIPs) for the creation of age-appropriate therapeutic formulations [21].

Clinical studies have repeatedly demonstrated robust acceptability of ODMTs among Paediatric populations. Thomson et al. (2009) established that 2 mm mini-tablets were favoured over syrups among children aged 6 months to 6 years, but Preis (2015) indicated that babies aged 6–12 months could also swallow mini-tablets with ease [22,19]. Klingmann et al. (2018) further validated the high acceptance of uncoated mini-tablets among babies and toddlers in a randomized controlled experiment [23]. The EU-funded LENA study has examined enalapril ODMTs in 60 Paediatric patients with heart failure, reporting outstanding acceptance, palatability, and clinical effectiveness. After eight weeks, participants demonstrated significant enhancement in left ventricular diastolic dimension and heart failure symptoms, highlighting the clinical feasibility and therapeutic promise of ODMTs [24].

Recent developments in formulation have expanded the variety of Paediatric medicines accessible in ODMT form. Trofimiuk et al. (2024) formulated 2 mm hydrocortisone ODMTs with Paediatric dosages of 0.5 mg and 1.0 mg. The researchers successfully accomplished efficient taste masking using drug-polymer solid dispersions created by ball milling, as proven by differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), electronic tongue testing, and in vitro dissolution study [21]. In a similar vein, Olivera et al. (2024) developed trihexyphenidyl ODMTs for dystonia therapy in Paediatric neurology, assessing six distinct diluents and refining the direct compression method to guarantee consistency and mechanical integrity [25]. Parrish et al. (2020) investigated enalapril maleate ODMTs for juvenile hypertension and evaluated many co-processed excipients, such as Tablettose 80, MicroCe-Lac 100, and StarLac. The formulation with StarLac demonstrated enhanced wetting time and complied with all pharmacopeia standards for Paediatric use [26]. These discoveries together underscore ODMTs as a viable platform for enhancing therapeutic accuracy, stability, and compliance in Paediatric medication administration.

2.3.2 Orodispersible Tablets

Orodispersible tablets (ODTs) are solid dosage forms that rapidly disintegrate or dissolve in the oral cavity without requiring water, rendering them especially beneficial for those with dysphagia. Initially designed for adults, orally disintegrating tablets (ODTs) have garnered increasing attention in Paediatric medication delivery owing to their capacity to improve patient adherence and facilitate administration. These formulations are particularly appropriate for older children who can manage bigger tablets and favour fast-melting dose forms over liquids or chewable. Orally disintegrating tablets (ODTs) provide advantages including precise dosing, enhanced stability, and the ability to conceal undesirable drug flavours through sophisticated manufacturing techniques. Furthermore, the convenience of self-administration and less choking risk provide ODTs a pragmatic option in Paediatric care environments, where compliance and safety are paramount [20].

2.3.3 Oral thin films

Oral thin films (OTFs) have emerged as one of the most rapidly expanding and adaptable dosage forms in contemporary drug administration, providing distinct benefits for Paediatric populations. The worldwide OTF market was valued at USD 3.1 billion in 2024 and is

anticipated to attain USD 7.5 billion by 2034, indicating a compound yearly growth rate (CAGR) of 9.3 percent [27]. Sublingual films dominate the market with a 70.3 percent share, attributed to its capacity for quick drug absorption via the sublingual mucosa, resulting in a swifter start of therapeutic effects relative to traditional oral dose forms. Concurrently, the orally dissolving film (ODF) sector has seen significant growth, with market worth rising from USD 1.49 billion in 2024 to an anticipated USD 2.29 billion by 2032, bolstered by a CAGR of 6.5 percent [28]. The Paediatric medicine sector has significantly contributed to this rise, with Paediatric -specific ODF advancements increasing at an annual pace of 8.2 percent—twice the general growth rate of the pharmaceutical business [28]. The increasing demand is mostly attributable to the easy administration, simplicity of ingestion, and appropriateness for patients with dysphagia or a dislike for traditional tablets and capsules.

The clinical usage of oral film technology has markedly increased, evidenced by recent FDA approvals for therapeutic applications in both adults and children. Rizafilm, which contains rizatriptan in an orally disintegrating film format, received approval on April 17, 2023, for the treatment of migraine with or without aura in adults and children patients weighing 40 kg or more. Zuplenz, an oral thin film formulation of ondansetron, initially licensed in 2010, continues to be a fundamental component of supportive cancer treatment, providing a water-free option for the prevention of chemotherapy-induced nausea and vomiting [27]. Likewise, SYMPAZAN, an oral film formulation of clobazam, obtained FDA clearance in 2011 for use as supplementary treatment in the management of seizures linked to Lennox-Gastaut syndrome, a severe Paediatric epilepsy illness [27]. The proactive measures of the U.S. FDA, including obligatory Paediatric Study Plans (PSPs) mandated by Paediatric law, have further accelerated this spread. As of 2023, twelve novel oral dissolving film formulations have received approval for Paediatric applications, addressing illnesses like attention-deficit/hyperactivity disorder (ADHD), epilepsy, and Paediatric nausea [28]. These regulatory and clinical achievements collectively highlight the increasing significance of oral thin films as a practical, child-friendly, and therapeutically effective advancement in Paediatric medication administration.

Advantages

1. Facilitated administration devoid of water necessity, hence mitigating swallowing challenges
   Swift breakdown and medication absorption in the oral cavity.
2. Precise dosage by accurate film cutting or pre-portioned strips.
3. Improved stability relative to liquid formulations
4. Portability and convenience of storage.
5. Enhanced patient adherence via agreeable flavour and consistency.
6. Appropriate for those with dysphagia or those rejecting traditional dose forms Constraints and Obstacles of Oral Thin Films.
7. Restricted drug loading capacity attributable to the diminutive film size, impeding high-dose medication administration.
8. Vulnerability to moisture and humidity necessitating particular packaging and storage conditions.
9. Mechanical fragility, which may hinder handling, shipping, and dosage precision Complexity in formulating uniform medication distribution and taste masking for bitter active pharmaceutical ingredients (APIs). Regulatory and scalability problems related to innovative pharmaceutical formulations

10. Possible variability in dissolving and absorption affected by saliva volume and oral cavity circumstances.
11. Elevated production expenses relative to traditional pills or liquids, affecting market accessibility.

Manufacturing methods

The manufacturing processes for oral thin films (OTFs) principally encompass solvent casting, hot-melt extrusion (HME), and the innovative application of 3D printing. Solvent casting is the predominant technique, wherein film-forming polymers, plasticizers, and active pharmaceutical ingredients (APIs) are dissolved in appropriate solvents and subsequently cast onto non-adhesive surfaces for regulated drying. This method enables exact regulation of film thickness, consistent drug distribution, and reliable quality, rendering it ideal for large-scale commercial manufacturing [27]. Hot-melt extrusion provides a solvent-free solution, facilitating continuous production with enhanced scalability and decreased processing duration. The lack of solvent utilization and the improved mechanical characteristics of the generated films render it especially beneficial for moisture-sensitive and poorly soluble medicines [28]. Moreover, 3D printing technologies are being tailored for OTF manufacture, allowing individualized dosage, intricate release profiles, and novel film topologies that correspond to patient-specific needs—this combination signifies a new frontier in oral thin film development. The manufacturing processes, whether used singly or in conjunction, enhance the diverse and resilient production framework that facilitates the fast expansion and clinical endorsement of oral thin films, particularly for Paediatric applications.

2.4 Taste-Masking Technologies and Palatability Enhancement

Palatability is a crucial factor influencing treatment adherence in Paediatric populations. Unpleasant taste is identified as a primary factor contributing to medication rejection and non-compliance in children [18]. The unpleasant flavour of several active pharmaceutical compounds presents considerable obstacles in Paediatric formulation development, requiring efficient taste-masking techniques that preserve therapeutic efficacy and enhance patient acceptance.

2.4.1 Physical Methods

Microencapsulation has become a prevalent method for flavour masking in Paediatric formulations by enveloping medication particles with polymeric substances that provide a protective barrier, therefore inhibiting direct contact between bitter active pharmaceutical ingredients (APIs) and taste receptors. Ethyl cellulose (EC) is commonly utilized for its capacity to deliver prolonged taste masking and regulated medication release, whilst Eudragit® polymers enable selective, pH-dependent release in specific areas of the gastrointestinal tract. Polyvinylpyrrolidone (PVP), a hydrophilic polymer, facilitates swift disintegration and efficient flavour masking, rendering it appropriate for rapid-dissolving formulations. In addition to microencapsulation, solid dispersion methods have demonstrated efficacy in mitigating bitterness by dispersing crystalline pharmaceuticals within amorphous carriers, which reduces particle size and modifies the drug's physical state. This not only reduces taste perception but may also improve solubility and bioavailability [21]. Complexation with cyclodextrins, including β-cyclodextrin and hydroxypropyl-β-cyclodextrin, has demonstrated efficacy, since the hydrophobic cavity of these compounds encapsulates the medication, hence reducing direct contact with taste receptors [18].

Moreover, ion exchange resins function as an effective method by adhering drug molecules via electrostatic interactions, inhibiting release in the oral cavity and facilitating regulated release under certain pH values in the gastrointestinal tract [18].

2.4.2 Chemical Techniques

Prodrug creation is an effective approach for taste masking, including the chemical alteration of drug molecules to create derivatives with less bitterness. These altered chemicals are engineered to revert to their active state upon absorption via enzymatic or chemical mechanisms within the body. Likewise, salt production can mitigate bitterness by converting medications into different salt forms that preserve or even augment their therapeutic effectiveness while enhancing palatability, so rendering them more appropriate for Paediatric use.

2.4.3 Organoleptic Techniques

Sweetening compounds are essential in concealing bitterness in Paediatric formulations by activating sweet taste receptors. Natural sweeteners, including sucrose, fructose, and glucose, alongside artificial sweeteners such as aspartame, saccharin, sucralose, and acesulfame potassium, are widely utilized; nonetheless, current trends indicate a preference for natural sweeteners owing to safety apprehensions regarding artificial options in youngsters [18]. Flavouring agents, such as widely favoured fruit tastes including strawberry, banana, orange, and cherry, along with mint flavours, are beneficial in enhancing palatability. The selection of taste must be customized according to variables such as patient age and cultural inclinations to guarantee acceptability [7]. Moreover, flavour enhancers like monosodium glutamate (MSG) and certain amino acids can amplify pleasant tastes and diminish unpleasant flavours, hence enhancing the overall acceptability of the formulation.

2.4.4 Recent Advances in Taste-Masking Technologies

Recent advancements in taste-masking technology have markedly enhanced the palatability of juvenile medication formulations. Multi-layered coating methods employ the progressive application of hydrophobic and hydrophilic polymers to create diffusion barriers that increase taste masking and facilitate regulated medication release [21]. Nanotechnology-based methods, previously outlined in Section 3, enhance taste masking via nanoencapsulation, which diminishes particle size to minimize interaction with taste receptors, amplifies surface area for more effective coating at reduced concentrations, and facilitates controlled release to prevent burst effects in the oral cavity. These Nano systems exhibit versatility and compatibility with various administration methods. Furthermore, contemporary analytical instruments like the electronic tongue have transformed taste evaluation by providing objective, quantitative assessments of sensory characteristics such as bitterness, sweetness, and umami. This sensor-based system emulates human gustatory perception and delivers significant data without the necessity of human taste panels, hence mitigating ethical issues related to the participation of minors in sensory assessment research [21].

3. Challenges and Future Perspective

The widespread use of these advanced Paediatric formulations faces significant challenges that necessitate systematic solutions. Substantial barriers include limited access to pharmaceutical-grade materials suitable for technologies like as 3D printing, which restricts formulation flexibility and exacerbates biocompatibility concerns. A substantial gap exists in long-term safety and toxicity data about nanotechnology in the juvenile population, whose developing physiology may interact with nanoparticles in unpredictable ways. Furthermore, these innovative platforms face

complex regulatory problems because to their novelty, the lack of traditional approval mechanisms, and difficulties in ensuring manufacturing consistency and quality control for individualized or convoluted dosage forms. The high costs related to development and manufacture threaten the accessibility and market viability of these advanced medications, particularly in resource-limited settings.

The future of Paediatric pharmaceutical development is poised for a substantial shift towards hyper-personalized and integrated treatments. The decentralization of manufacturing through point-of-care 3D printing in hospitals and pharmacies would enable real-time, on-demand production of tailored doses tailored to individual patient attributes such as weight, age, and pharmacogenomics. Nanotechnology will progress to "intelligent" delivery systems that may respond to specific disease microenvironment cues, such as pH or enzymes, facilitating ultra-precise targeting that minimizes adverse effects. We will examine the convergence of technology, leading to multi-modal platforms like 3D-printed oral films that include nano-encapsulated pharmaceuticals for enhanced efficacy and adherence. A concerted initiative is essential to establish cohesive global regulatory frameworks, foster collaboration between business and academics, and provide resources for research on novel, safe excipients, guaranteeing that these transformational developments may securely and efficiently benefit every kid in need.

CONCLUSION

The field of Paediatric medication formulation is experiencing a substantial evolution, propelled by technical advancements that emphasize the distinct requirements of children. This analysis emphasizes the significant advancements achieved in the development of child-centric dosage forms from 2020 to 2025. Three-dimensional printing has become an influential instrument for individualized medicine, facilitating dosage adaptability, intricate drug release mechanisms, and enhanced adherence via tailored designs. Nanotechnology provides advanced methods to improve medication absorption, facilitate targeted administration, especially in cancer and central nervous system illnesses, and diminish systemic toxicity. Moreover, orodispersible formulations, such as mini-tablets and oral films, have demonstrated significant acceptability and practicality as alternatives to conventional liquids and tablets, effectively tackling the essential issue of swallowability. In conjunction with sophisticated taste-masking technology, these systems collaboratively enhance palatability and compliance. Facilitated by advancing legal frameworks and an expanding global market, these developments signify a crucial departure from the uniform approach. The ongoing implementation of these new techniques is crucial to address the persistent issues of off-label prescribing and guarantee that the Paediatric population has access to safe, effective, and acceptable medications.

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