HSPI The Open Access Publisher

JAPCH JOURNAL OF ADVANCED PEDIATRICS AND CHILD HEALTH
ISSN 2689-9817

Research Article

Excipients and Vehicles in Galenic Practice: Considerations for Neonatology and Pediatrics: An Overview and Results of a Practical Experience

Luisetto M[1]*, Almukthar N[2], Edbey K[3], Hamid GA[4], Mashori GR[5], Cabianca L[6], Ferraioulo A[7], Fiazza C[8] and Latyshev OY[9]

[1]IMA Academy, Applied Pharmacologist, Hospital Pharmacist Manager, Italy
[2]Professor, Physiology, College of Medicine, University of Babylon, Hilla, Iraq
[3]Professor of Physical Chemistry, Libyan Authority for Scientific Research, Libya
[4]Professor of Hematology oncology Department, University of Aden, Yemen
[5]Professor, Department of Medical & Health Sciences for Women, Peoples University of Medical and Health Sciences for Women, Pakistan
[6]Medical Laboratory, Città della Salute, Turin, Italy
[7]Hospital Pharmacist, PC Area, Italy
[8]Medical Pharmacologist, Hospital Pharmacist Manager, Independent Researcher, Italy
[9]President, IMA Academy International, India

More Information

***Address for correspondence:** Luisetto M, IMA Academy, Applied Pharmacologist, Hospital Pharmacist Manager, Italy, Email: maurolu65@gmail.com

Submitted: September 24, 2025
Approved: Ocotober 01, 2025
Published: Ocotober 02, 2025

How to cite this article: Luisetto M, Almukthar N, Edbey K, Hamid GA, Mashori GR, Cabianca L, et al. Excipients and Vehicles in Galenic Practice: Considerations for Neonatology and Pediatrics: An Overview and Results of a Practical Experience. J Adv Pediatr Child Health. 2025; 8(2): 023-026. Available from: https://dx.doi.org/10.29328/journal.japch.1001075

Keywords: Neonatology; Pediatrics; Excipients; Galenic formulations; Pharmaceutical technology; Safety; Physiology, Toxicology; Pharmacokinetics; 3D printing; Magistral formula

Abstract

Excipients are fundamental components of galenic formulations, critically influencing the safety and efficacy of the final medicinal product. This is of paramount importance in neonatal and pediatric populations, where physiological immaturity results in significant differences in pharmacokinetics and pharmacodynamics compared to adults.

This work provides a comprehensive overview of excipients and vehicles used in galenic preparations for these vulnerable groups. It highlights specific excipients known to be dangerous, detailing their mechanisms of toxicity, and suggests safer alternatives. The discussion covers formulations for oral solutions, suspensions, and topical dermatological use, including ready-to-use vehicles. The role of the prescribing physician and the verifying pharmacist is emphasized, underscoring the necessity of checking for efficacy, safety, incompatibilities, and microbiological compatibility.

The results of a practical five-year local experience with an observational analysis are provided.

Furthermore, innovative technologies such as 3D printing for pediatric dosage forms are discussed. The conclusion asserts that a rigorous, risk-based assessment of excipients is essential in neonatal and pediatric galenic practice to ensure patient safety.

Introduction

Galenic medicine, which involves the extemporaneous preparation of customized medications, is crucial in neonatology and pediatrics. Approximately 40% of drugs used in children are magistral formulations or used off-label, often due to the lack of suitable commercial products [1]. The choice of pharmaceutical form is pivotal; children under 6-8 years often have difficulty swallowing tablets or capsules, making solutions and suspensions the preferred forms to avoid airway obstruction [2].

Excipients are not inert. They serve critical functions: as vehicles to improve drug delivery, ensure stability, facilitate manufacturing, and enhance palatability. However, for neonates and children, certain excipients can pose serious risks due to their underdeveloped metabolic and excretory systems [3,4]. The skin of a newborn, particularly preterm

infants, is thinner and more permeable, offering a poor barrier and increasing the risk of systemic toxicity from topical applications [5,6].

This manuscript reviews the current state of knowledge regarding excipient safety in pediatric populations, identifies harmful substances to avoid, proposes safer alternatives, and discusses practical considerations for the galenic formulation of safe and effective medicines for children.

Materials and methods

This review was conducted from an observational perspective. A comprehensive analysis of relevant scientific literature was performed using major online databases (e.g., PubMed, Scopus, Web of Science) with keywords including "excipients," "neonatology," "pediatrics," "galenic," "safety," and "toxicity." Only peer-reviewed articles, official guidelines from regulatory bodies (EMA, FDA), and authoritative pharmacological texts were considered.

The scientific literature chosen was evaluated for its consistency and relevance with the topics under evaluation.

The team that verified this was multidisciplinary: a Hospital pharmacist, a medical and applied pharmacologist, Physicians, chemists, laboratory professionals, and university professors (physiology, physical chemistry, oncology).

In addition, a five-year observational analysis (2019-2023 external production; 2024 internal production) was conducted in a hospital galenic laboratory. The study monitored official reports concerning excipient or vehicle toxicity in magistral preparations (capsules, oral suspensions, syrups, solutions, gels, powders) for neonatal and pediatric patients.

Results

Literature review findings

The pediatric population exhibits vast pharmacokinetic and pharmacodynamic variability, making them exceptionally vulnerable to excipient toxicity [1,3]. Key findings from the literature include:

- **High-risk excipients:** A consensus identifies the most concerning excipients for neonates as: benzyl alcohol, ethanol, propylene glycol, polysorbate 80, parabens, benzoic acid, sodium benzoate, benzalkonium chloride, sorbitol, and aspartame [3,7,8].

According to Annex 5, WHO TECHNICAL REPORT SERIES 2012

Development of paediatric medicines: points to consider in formulation

"Solubility enhancers; The aqueous solubility of the API may limit the concentration achievable in formulated solutions and, hence, the desirable dose volume. In many cases, an acceptable solution requires solubility-enhancing methods, like the use of non-ionic surfactants and of co-solvents such as glycerol, liquid macrogols, and ethanol. If solubility enhancers are to be used, consideration should be given to the safety of both the agent and the formulation, the risk of irritation and damage of intestinal tissues in neonates caused by hyperosmolality or other local toxicity."

- **Mechanisms of toxicity (some):**
- **Benzyl alcohol:** Associated with fatal "gasping syndrome" in preterm neonates due to metabolic acidosis and CNS depression [9].
- **Propylene glycol:** Can cause CNS depression, seizures, and hyperosmolality; its half-life is significantly prolonged in neonates (~17 hrs *vs.* ~5 hrs in adults) [10].
- **Ethanol:** Causes neurotoxicity and cardiovascular problems; exposure is linked to developmental delays [3].
- **Sodium benzoate:** Can displace bilirubin from albumin, increasing the risk of kernicterus in jaundiced neonates [7].
- **Parabens:** Potential endocrine-disrupting effects, with heightened sensitivity in newborns [11]. Hyperbilirubinaemia, hypersensitivity reactions, and delayed-contact dermatitis in Neonates
- **Aspartame:** Contraindicated in patients with phenylketonuria (PKU) as it metabolizes to phenylalanine [3].
- **Glycerol:** Cases of neurological toxicity have been reported in the paediatric population.
- **Sulfites:** That can cause slight flushing, dermatitis, hypotension, diarrhea, urticaria, and abdominal pain, to life-threatening asthma and anaphylactic reactions.

Water is the most commonly used agent in paediatric formulations, as liquid preparations are easier to administer and allow a more accurate dose adjustment. Water is an ideal medium for the proliferation of microorganisms (bacteria and fungi) despite their purification."

- **Topical formulations:** The immature skin barrier in infants, coupled with a high surface-area-to-weight ratio, increases systemic absorption. Excipients like propylene glycol, sodium lauryl sulfate, and certain preservatives can irritate, in some situations, causing burns or systemic toxicity [5,6]. Parabens can cause contact dermatitis, and should be avoided for small children in cosmetic products: silicon products, petrolatum, aggressive tensioactive, and substances that can alter the skin functions.

Povidone-iodine is an effective antiseptic, but its topical use has been associated with several adverse reactions in burn patients and in neonates as a result of transcutaneous absorption.

- **Databases and resources:** The STEP (Safety and Toxicity of Excipients for Paediatrics) database was developed to compile safety data on excipients for children, addressing a critical knowledge gap [12].

Observational analysis results

Over the five-year observation period in the galenic lab, no official written reports of toxicity directly attributed to excipients were filed. However, several proactive interventions were documented:

1. A request to avoid titanium dioxide in capsules for an oncology patient with a diagnosed allergy.
2. A request for a citrus-free glucose solution for a pregnant woman with a citrus allergy.
3. A specific request for wool wax (cera laninata) in a cream for a patient with ichthyosis.

This suggests that while adverse events are rare, vigilance and individualized assessment are standard practice.

Examples of formulations and vehicles

Several common pediatric galenic preparations and their bases were identified (**Figures 1-11 in the Appendix for examples)**:

- **Ready-to-Use Vehicles:** Commercial vehicles like SyrSpend® SF PH4 (preservative-free or preserved with potassium sorbate), Ora-Blend®, Ora-Plus®, and Ora-Sweet® are commonly used for compounding stable oral suspensions [13,14].
- **Common Preparations:** Examples include extemporaneous suspensions of flecainide, propranolol, captopril, ibuprofen (with Wagner bases), and niaprazine [14,15] and **Figure 3**.
- **Innovation:** Excipient bases for automated compounding and 3D printing (e.g., CuraBlend®) are emerging technologies for producing personalized doses in pediatrics [16].

Discussion

The case of phenytoin intoxication in Australia (1968-69) due to a change from calcium sulfate to lactose excipient starkly illustrates that excipients are pharmaceutically active and can critically influence drug bioavailability and safety [17]. This historical lesson underscores the necessity of meticulous excipient selection for vulnerable populations.

Our review confirms that neonates and preterm infants are at the highest risk due to physiological immaturity. The principle that "the use of excipients in pediatric formulations should be justified through a risk-based assessment" is paramount [18]. This involves:

1. **Patient Factors:** Assessing age, weight, organ function, and comorbidities, allergy, and intolerance (e.g., PKU, lactose intolerance, avoid saccarose in diabetic, global sodium charge provided by the APIs and excipients in CV pathology).
2. **Excipient Factors:** Evaluating the excipient's function, daily intake, duration of therapy, and potential for additive toxicity in polypharmacy.
3. **Glycerol:** Ensuring chemical and physical compatibility between API and excipients, and establishing a valid beyond-use date based on stability studies.
4. The duration of the therapy (short of prolonged exposure to a topical therapy).
5. Avoid flavoring in oral suspension for very small children (to prevent allergy)
6. To be considered for every substance is also the threshold for toxicity: some excipients or at some concentration can be harmful for newborns and not for older children.
7. It is useful to consult the technical sheet of the bases used for every single API, not give too rapid a response, inaccurate to physicians according to compatibility: verify literature, pharmaceutical technique textbook, pharmacopeia, international public healthcare website, database, and other useful official resources.

Verify the quantitative limits admitted (BNF for children) and the route of administration.

For pharmacists, the process is multifactorial:

- **Verification:** Scrutinizing prescriptions for dosage, excipient choice, and potential allergies.
- **Selection:** Choosing the appropriate pharmaceutical form and vehicle (e.g., buffered vehicles for acid-labile APIs).
- **Quality Control:** Using calibrated equipment, purified water, and following aseptic techniques when necessary.
- **Labeling:** Providing clear instructions (e.g., "Shake Well," storage conditions) and a complete list of excipients.
- **Communication:** Educating caregivers on correct administration and collaborating closely with prescribers to select the safest formulation.

The observational study's lack of adverse event reports is positive but likely reflects under-reporting and the effectiveness of preventive risk assessment rather than an absence of risk.

Limitations and future research

Although this work is not a systematic review, the authors have attempted to compile various excipients or vehicles used in galenic formulations, along with their characteristics. These include those that should be avoided for neonates and children, or are potentially harmful in any way, where specific toxicological evaluations are warranted.

Future research will complete this study, adding all excipients and vehicles to be avoided or harmful.

Conclusion

The preparation of galenic formulations for neonates and children is a complex process that demands a deep understanding of pharmaceutical technology, pharmacology, and toxicology. Excipients must be considered active ingredients whose safety profiles are age-dependent.

A proactive, collaborative approach between pediatricians, neonatologists, and pharmacists is essential. This involves:

- Consulting toxicity databases (e.g., STEP).
- Prioritizing licensed products, then off-label use of licensed products, before resorting to unlicensed magistral preparations.
- Selecting excipients with the highest safety margin for the specific age group.
- Avoiding known high-risk excipients like ethanol, propylene glycol, benzyl alcohol, and parabens in neonates whenever possible.
- Utilizing modern, well-characterized, ready-to-use vehicles that minimize harmful additives.
- Embracing new technologies like 3D printing for dose personalization, provided excipient safety is ensured.

Ultimately, the goal is to ensure that every magistral formula is not only therapeutically effective but also unequivocally safe, adhering to the highest standards of pharmaceutical practice.

References

1. Bobillot M, Delannoy V, Trouillard A, Kinowski JM, Sanchez-Ballester NM, Soulairol I. Potentially harmful excipients: State of the art for oral liquid forms used in neonatology and pediatrics units. Pharmaceutics. 2024;16(1):119. Available from: https://doi.org/10.3390/pharmaceutics16010119
2. European Medicines Agency. Reflection paper: Formulations of choice for the paediatric population. EMA/CHMP/PEG/194810/2005. London: EMA; 2006. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-formulations-choice-pa...
3. Rouaz K, Chiclana-Rodríguez B, Nardi-Ricart A, Suñé-Pou M, Mercadé-Frutos D, Suñé-Negre JM. Excipients in the paediatric population: A review. Pharmaceutics. 2021;13(3):387. Available from: https://doi.org/10.3390/pharmaceutics13030387
4. Belayneh A, Tadese E, Molla F. Safety and biopharmaceutical challenges of excipients in off-label pediatric formulations. Int J Gen Med. 2020;13:1051-1066. Available from: https://doi.org/10.2147/ijgm.s280330
5. Kovács A, Péter-Héderi D, Perei K, Budai-Szűcs M, Léber A, Gácsi A. Effects of formulation excipients on skin barrier function in creams used in pediatric care. Pharmaceutics. 2020;12(8):729. Available from: https://doi.org/10.3390/pharmaceutics12080729
6. Fernandes JD, Machado MCR, de Oliveira ZNP. Children and newborn skin care and prevention [Prevenção e cuidados com a pele da criança e do recém-nascido]. An Bras Dermatol. 2011;86(1):102-110. Available from: https://doi.org/10.1590/s0365-05962011000100014
7. Valeur KS, Holst H, Staunsholm L, Greisen G. Excipients in neonatal medicinal products: Never prescribed, commonly administered. Pharmaceut Med. 2018;32(4):251-258. Available from: https://doi.org/10.1007/s40290-018-0243-9
8. Lass J, Naelapää K, Shah U, Käär R, Varendi H, Turner MA, et al. Hospitalised neonates in Estonia commonly receive potentially harmful excipients. BMC Pediatr. 2012;12:136. Available from: https://doi.org/10.1186/1471-2431-12-136
9. Gershanik J, Boecler B, Ensley H, McCloskey S, George W. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med. 1982;307(22):1384-1388. Available from: https://doi.org/10.1056/nejm198211253072206
10. Peleg O, Bar-Oz B, Arad I. Coma in a premature infant associated with the transdermal absorption of propylene glycol. Acta Paediatr. 1998;87(11):1195-1196. Available from: https://doi.org/10.1080/08035259875003211
11. Dupuis A. [Presentation on endocrine disruptors]. GERPAC Conference; 2022 Oct 6; Poitiers, France.
12. Salunke S, Brandys B, Giacoia G, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) database: part 1--a need assessment study. Int J Pharm. 2013;457(1):310-320. Available from: https://doi.org/10.1016/j.ijpharm.2013.09.013
13. Mansourian M, Dijkers E, Silva CCV, Polonini HC. Compatibility of commonly used active pharmaceutical ingredients in a ready-to-use oral suspending vehicle. Pharmaceutics. 2023;15(10):2388. Available from: https://doi.org/10.3390/pharmaceutics15102388
14. Casiraghi A, Centin G, Selmin F, Picozzi C, Minghetti P, Zanon D. Critical aspects in the preparation of extemporaneous flecainide acetate oral solution for paediatrics. Pharmaceutics. 2021;13(11):1963. Available from: https://doi.org/10.3390/pharmaceutics13111963
15. Spennacchio A, Lopedota A, La Forgia F, Fontana S, Franco M, Denora N. Physicochemical stability of the extemporaneous ibuprofen oral suspension in "Wagner" base. Int J Pharm Compd. 2023;27(1):72-77. Available from: https://pubmed.ncbi.nlm.nih.gov/36720064/
16. Sandler Topelius N, Shokraneh F, Bahman M, Lahtinen J, Hassinen N, Airaksinen S, et al. Automated non-sterile pharmacy compounding: A multi-site study in European hospital and community pharmacies with pediatric immediate release propranolol hydrochloride tablets. Pharmaceutics. 2024;16(5):678. Available from: https://doi.org/10.3390/pharmaceutics16050678
17. Bochner F, Hooper WD, Tyrer JH, Eadie MJ. Factors involved in an outbreak of phenytoin intoxication. J Neurol Sci. 1972;16(4):481-487. Available from: https://doi.org/10.1016/0022-510x(72)90053-6
18. Belayneh A, Tadese E, Molla F. Safety and biopharmaceutical challenges of excipients in off-label pediatric formulations. Int J Gen Med. 2020;13:1051–1066. Available from: https://doi.org/10.2147/ijgm.s280330