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Research Article

Excipients and Vehicles in Galenic Practice: Considerations for Neonatology and Pediatrics

Luisetto M[1], Almukthar N[2], Edbey K[3], Hamid GA[4], Mashori GR[5], Cabianca L[6], Ferraioulo A[7], Fiazza C[8], 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.
[5]Professor, Department of Medical & Health Sciences for Woman, 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.

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***Corresponding author:** Luisetto M, IMA Academy, Applied Pharmacologist, Hospital Pharmacist Manager, Italy.

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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 stability. 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.

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

1. Introduction:

Galenic medicine, involving the extemporaneous preparation of customized medications, is vital 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.

2. 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.

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.

3. Results

3.1. 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 considerin 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 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 Neonates

· Aspartame: Contraindicated in patients with phenylketonuria (PKU) as it metabolizes to phenylalanine [3].

Glicerol :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 administrate 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 cause irritation, in some situation since burns, or systemic toxicity [5, 6]. Parabens can cause contacts dermatitis, to be be avoided for small children in cosmetic: silicons products, petrolate, agressive tensioattive and substantie that can alter the skin functions

Povidone-iodine is an effective antiseptic, but its topical use has been associated with a number of 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].

3.2. 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 lanetta) in a cream for a patient with ichthyosis.

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

3.3. Examples of Formulations and Vehicles

Several common pediatric galenic preparations and their bases were identified (See Figures 1-11 in 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 fig. n 3.

· Innovation: Excipient bases for automated compounding and 3D printing (e.g., CuraBlend®) are emerging technologies for producing personalized doses in pediatrics [16].

4. 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, allergies 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. Formulation Factors: 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 esposition to a topical therapy).

5) avoid flavoring oral suspension for very small children (to prevent allergies)

6) To be considered for every substantia is also the thereshold for toxicity: some excipients or at some concentration can be harmful for newborn and not for higher children.

7) Useful to consult the technical sheet of the bases used for every single APIs, not give too much rapid responce inaccurate to physicians according the compatilibility: verify literature, pharmaceutical technique texbook, pharmacopeia, internationla public healthcare website and database and other useful official resource.

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.

5. 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.

Conflict Of Interest: The authors declare no conflict of interest.

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APPENDIX:

Figure 1: Quantitative limits for common excipients in children's medicines. (Adapted from Arthur & Burgess, 2017). Figure 2: Flecainide (20 mg/mL) oral suspension formulation guide. Figure 3: Example of a ready-to-use suspending vehicle formulation (ACEF Base). Figure 4: Propranolol oral suspension formulation. Figure 5: Captopril oral suspension formulation. Figure 6: Sildenafil citrate oral suspension formulation. Figure 7: Caffeine citrate solution for apnea of prematurity. Figure 8: Phenobarbital oral solution. Figure 9: LAT (Lidocaine, Adrenaline, Tetracaine) gel for topical use. Figure 10: Acetylsalicylic acid formulation for Kawasaki disease. Figure 11: Indomethacin oral suspension for patent ductus arteriosus. Table 1: Summary of high-risk excipients and their associated toxicities in pediatrics. Table 2: Toxicity databases and public resources. From Excipients in the Paediatric Population: A Review table 3 : RESEARCH STUDY © 2011 SNL European Study of Neonatal Exposure to Excipients.

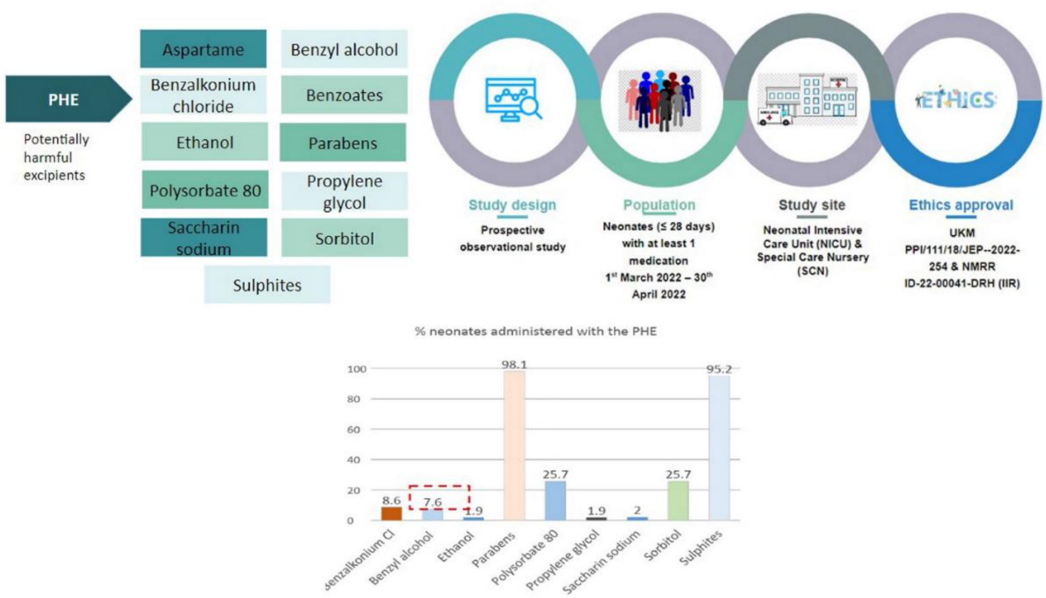


Fig n 1 from https://doi.org/10.1080/03639045.2024.2327462

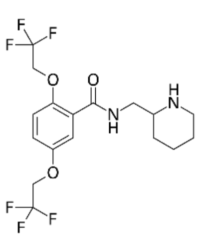


Fig. n 2 Flecainide – Antiarrhytmic medication (oral suspension , capules)

Sospensione NIAPRAZINA 3mg/mL

Niaprazina	300 mg
Base L. x SOSP. pH 4 ml 500 GILIEGIA	Qb a 100.0 mL

Fig. 3 From ACEF website

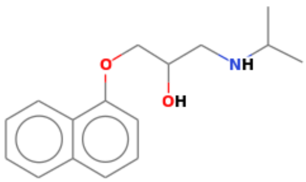


Fig n 4 Propranolol – beta blokers not selective (to treat some heart conditions in newborn and pediatry)Are used in pediatry oral suspension or cps

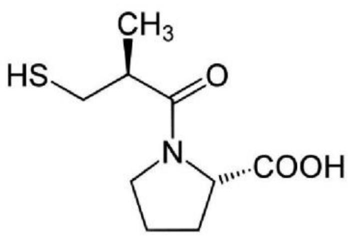


Fig n 5 Captopril (ACE inibithor – antipertensive), cps, oral suspensions

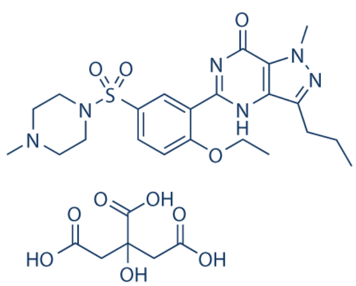


Fig n 6 Sildenafil citrate (PDE5 inibithor, to treat pediatric pulmonary ipertension)

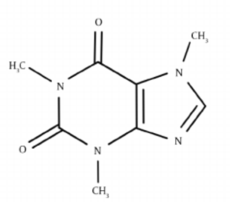


Fig n . 7 Caffeine (to treat apnea of prematurity in premature infants) – galenic papers

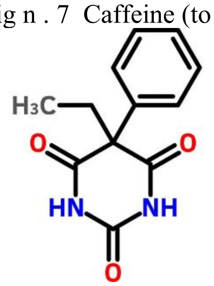
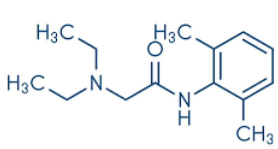


Fig n 8 Phenobarbital (recommended drug for the treatment of seizures in term neonates.)- Galenic papers



lidocaine

Fig n 9 used for l.a.t. gel (lidocaine, adrenalin, tertacaine) in pediatry -emergency (to treat dermatological little wounds)- external use .

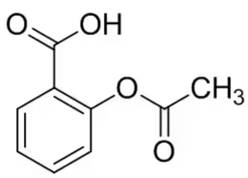
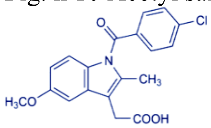


Fig. n 10 Acetyl salicilic acid : used in pediatry (S. KAWASAKY)- galenic papers



11) L'indometacin (used in pediatry to treat the patency of the arterious Botallo hole in new born-premature)- ORAL suspension
E. Ho Cho

Table 2: European Medicines Agency proposed safety limits for propylene glycol [17]

	Neonates up to 28 days (or 44 weeks post-menstrual age for pre-terms)	Children aged 1 month–4 years	Children aged 5–17 years
Safety limits (maximum daily dose)	1mg/kg	50mg/kg	500mg/kg

Table n . 1 from Sara Arthur & Anna Burgess (quantitative limits)

Chart 2: Risks of using topical preparations in newborn babies, infants and children

Compound	Product	Risk
Triclosan	Soap, deodorants, antiseptics	Same risk of toxicity of other phenolic compounds
Propylene glycol	Emollients, cleaning agents	Skin irritation and burning Excessive enteral and parenteral use: risk of hyperosmolality and seizures.
Benzethonium chloride	Cleaning Agents	Poisoning by ingestion, carcinogenesis
Glycerin	Emollients, cleaning agents	Hyperosmolality and seizures
Ammonium lactate	Exfoliating, emollient	Possible lactic acidosis
Coal tar	Shampoos, keratolytic products	Cancer risk due to excessive use of aromatic hydrocarbons
Tetracaine	Topical anesthetic	Contact Dermatitis
Ethanol	Oral cleaning solutions	Oral carcinogenesis
Methylisothiazolinone	Shampoos	Neurological defects
Sodium lauryl sulfate	Soap, shampoos	Skin irritation / contact dermatitis
Sodium laureth sulfate	Toothpaste, soap, shower gel, bath foam	Skin irritation / contact dermatitis

An Bras Dermatol. 2011;86(1):102-10.

×

Table 1. Toxicity databases and public resources.

Name	Website	Creator
ACToR —Aggregated Computational Toxicology Resource	www.actor.epa.gov/actor/home.xhtml (accessed on 15 November 2020)	US Environmental Protection Agency's (EPA) National Center for Computational Toxicology (NCCT)
STEP—Safety and Toxicity of Excipients for Paediatrics *	www.eupfi.org/step-database-info/ (accessed on 15 November 2020)	European Paediatric Formulation Initiative
TOXNET—Toxicology Data Network	www.nlm.nih.gov/toxnet/index.html (accessed on 15 November 2020)	Specialized Information Services (SIS) USA
Vitic	www.lhasalimited.org/products/vitic.htm (accessed on 2 November 2020)	Lhasa Limited

* The purposes of the STEP database can be consulted in the Appendix A.

Table 2 from from https://doi.org/10.3390/pharmaceutics13030387

Known safety concerns of excipients included in the study			
Excipient	**Biochemical/other effects**	**Safety concerns**	**Pharmaceutical issues in neonates**
Sodium benzoate/ benzoic acid		Neonates appear to lack the capacity to conjugate with glycine. This leads to the build up of benzoic acid which can cause metabolic acidosis and neurotoxicity	In the UK all formulations of topical antifungal agents on the market contain sodium benzoate or benzoic acid
Propylparaben (propyl hydroxy-benzoate; propyl parahydroxybenzoate)	May affect protein binding by bilirubin. Suggestion of oestrogenic activity with potential reproductive effects that requires further work	Suggestion that long-term accumulation can occur in some tissues	Widely used in medicines given to healthy babies
Ethanol		Intoxication Effects on neurones	Widely used in medicines given to healthy babies
Polysorbate 80 (polyoxyethylene sorbitan fatty acid ester)		Serious adverse reactions, including some deaths, in low-birthweight infants administered an IV vitamin E preparation containing a mixture of polysorbates 20 and 80	Widely used in medicines given to healthy babies
Propylene glycol	Can intoxicate in same way as ethanol but one third as potent in this regard	Ototoxicity; cardiovascular effects; CNS toxicity; seizures; hyperosmolarity; lactic acidosis	Median exposure of 34mg/kg/24hr for 48hr in preterm neonates did not affect short-term adaptation to birth
Sorbitol		May cause problems in people with congenital fructose intolerance (c. 1:20,000 live births); osmotic laxative effect	

TABLE 2 Summary of available/known toxicity data of the excipients to be studied in the ESNEE project.

Table n 3 from RESEARCH STUDY © 2011 SNL European Study of Neonatal Exposure to Excipients (ESNEE).