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STABILITY CONSIDERATIONS IN EXTEMPORANEOUSLY COMPOUNDED PREPARATIONS FROM COMMERCIALLY AVAILABLE PRODUCTS FOR PEDIATRIC POPULATIONS

[1]Dr. M. Radhakishan,[2]Mr. M. Ranadheer Kumar,[3]Ms. T. Sneha

[1]Principal,[2,3]Assistant Professor

[1,2,3]Department of Pharmaceutics

Vaagdevi Institute of Pharmaceutical Sciences, Bollikunta, Warangal. Telangana.

ABSTRACT:

When commercially accessible, licensed, and age-specific dosage forms are not available, pharmacists can create appropriate pharmacological compositions through a process known as "extemporaneous compounding." These preparations carry a lot more risk than using prescription medications. One of the main things to consider while preparing impromptu formulations is stability. The purpose of this work was to analyze all of the existing stability studies in order to investigate the stability of pediatric extemporaneous formulations of standard solid dosage forms that are sold in the market. Approach. The Web of Science, PubMed, Scopus, EMBASE, Cochrane Library, and Google Scholar databases were searched for articles. Based on the inclusion criteria, a total of 28 experimental trials documenting the stability of oral pediatric extemporaneous formulations were selected from all of the searched papers. Oral spontaneous formulations using pure pharmaceuticals and commercially accessible dose forms were taken into consideration. As per the United States and British Pharmacopeia (USP and BP), the majority of spontaneous formulations are deemed chemically stable if they preserve ≥90% of the initial drug quantity, physically stable if there is no discernible alteration in physical attributes, and microbiologically stable if the prepared formulations do not exhibit any microbial growth. Discovering. The majority of the study's impromptu oral formulations for children maintained over 90% of the original substance while also being chemically, physically, and microbiologically stable. There are very few studies that did not involve a microbiological or physical stability test. In conclusion. This comprehensive analysis indicates that there are relatively few published experimental experiments that show microbial growth, chemical instabilities, or physical instabilities on pediatric oral extemporaneous formulations. Extemporaneous preparations are stable at the ICH-recommended storage conditions and duration, according to the majority of investigations. In general, the most promising alternative for child drugs will be oral formulations that are spontaneously prepared.

1. INTRODUCTION

1.1. Background

The shortage of suitable pharmaceutical dosage forms specifically designed for children is the major challenge for pediatric treatment. Most FDA-approved adult pharmaceutical dosage forms are not appropriate formulations for pediatric use. .e lack of sufficient information on pediatric administration often leads to the unauthorized use of adult preparations by

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healthcare professionals [1]. In some cases, there are no licensed or substitute products that fully meet the clinical needs of specific patients, so it is necessary to temporarily prepare a limited number of customized products for individual patients. About 15% to 80% of all drugs used by hospitalized children are either unlicensed or used outside of the product's license specifications ("off-licence") [2].

Extemporaneous formulation describes the use of traditional compounding techniques by pharmacists to manipulate various drugs and chemical ingredients to produce suitable drugs when commercial forms are not available. .ese techniques are widely used in the practice of pediatric pharmacy. Most approved oral medications for adults are provided in tablet or capsule form, usually in a single adult dose form or in a liquid form that is not suitable for infants. However, the dose size of pediatric medications should change proportionally to body surface area and body weight during childhood. Also, most of the pediatric population cannot swallow pills, capsules, and other conventional dosage forms. To prevent the inappropriate use of unlicensed and unapproved adult medications, pharmacists will prepare suitable pediatric preparations [3]. .is can be accomplished by grinding approved adult solid dosage forms such as tablets or by using capsule contents (powder and granules). .en, the powder can be prepared in the form of oral solution or suspension preparations using appropriate excipients and a suitable vehicle to produce, or it can be diluted into lower strength solid dosage forms using inert diluents. Sometimes the tablets are segmented into lower portions (half or a quarter) to get a suitable dosage unit for children [2].

1.2. Stability of Extemporaneous Pediatric Formulation. .e physical, chemical, and microbiological stability should be considered during the quality assessment of extemporaneous preparation. It is very important to meet the storage conditions indicated on the label. Even if it has been proven that a given pharmaceutical preparation has sufficient physical, chemical, and microbiological stability, the bioavailability and palatability of the formulation may not be proven. Few pharmaceutical formulations are supported by evidenced data that determine sufficient absorption curves and/or bioequivalence with licensed formulations. Insufficient access to raw materials and equipment is also another concern during the compounding of good quality extemporaneous pharmaceutical products. In order to reduce degradation and deterioration, the maximum shelf life of the product is 28 days, unless the product is chemically unstable, so the shelf life is based on the stability of the respective products. Stability studies of these formulations are usually conducted in a short period of time. .e lack of stability data limits the availability of many pediatric drugs. .e candidate formulations available for extemporaneous preparations are highly dependent on the accessibility of stability data and the ingredients required for the compounding [2].

.e objective of this study was to systematically review the stability of pediatric extemporaneous pharmaceutical formulations. .e specific aim of this study was first to assess the stability of oral pediatric extemporaneous formulations by reviewing the currently available experimental literature and to provide evidence-based or best practice guidance about the chemical, physical, and microbiological stability of

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extemporaneous oral preparations of medicines for pediatrics. .is helps policy makers and clinical practitioners who use extemporaneous preparations for pediatrics. Pharmacists, the main concerned professionals of pharmaceutical compounding, will benefit from the findings of this systematic review.

2. Methods

2.1. Literature Searching Strategy

The systematic reviews follow the Cochrane Collaboration guidelines, and we record the results according to the PRISMA guidelines for systematic reviews and meta-analysis preferred reporting project (PRISMA flowchart) [4]. We searched related experimental works of literature according to the study objectives from reliable databases of the Web of Science, PubMed, Scopus, EMBASE, Cochrane Library, and Google Scholar databases, written in English from June 1, 2021, to July 5, 2021. We combined the search strategy for free text terms and exploited the MESH title for the topics "Extemporaneous formulation OR Extemporaneous preparation OR Extemporaneous compounding," "stability," and "Peadiatric OR child OR Neonate OR Infant" using the Boolean operators like "AND" or "OR."

2.2. Study Selection and Eligibility Criteria.

All currently online available experimental works conducted on the stability of extemporaneous pediatric formulations were included in the study. .e articles and records which had no stability data, not focused on pediatric formulations, not focused on oral formulations, and articles without an informative abstract or full document were excluded from the study.

2.2.1. Eligibility Criteria

(1) Inclusion Criteria. Two researchers (AB and ZT) independently and carefully reviewed the content of each retrieved article. Finally, documents that meet the following criteria are included in the study.

Population: studies on the stability of pediatric extemporaneous formulations were included

Study area: all articles were included irrespective of the specific study area and year of the study

Study design: original experimental works of literature which have data on the stability of pediatric extemporaneous preparations were eligible

Language: documents published in English were considered

Publication condition: documents that fulfill the inclusion criteria were considered regardless of their publication status

(2) Exclusion Criteria. Two independent reviewers performed blind data extraction after evaluating the abstract and full text of the literature. After reading the full text and abstract, articles with methodological issues were excluded by two independent researchers. Due to incomplete data, inaccessible full-text articles were not included in the review

(3) Data Extraction. Using the previously tested data extraction format, the researchers extracted the necessary data. Data extracted from included studies are as follows: author, study area, method of chemical stability test, source drug for extemporaneous formulation, storage condition of extemporaneous formulation, chemical stability result, physical stability result, and microbiological stability study.

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Any differences between the two authors on data extraction are resolved through discussion.

3. Results and Discussion

We reviewed all available studies which focused on the chemical, physical, and microbiological stability of pediatric oral extemporaneous formulations. We considered whether

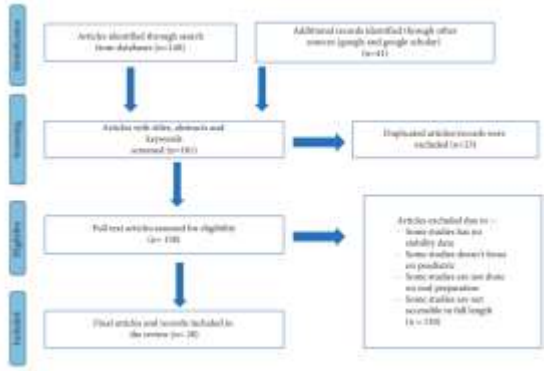

Figure 1: PRISMA diagram showing studies utilized for systematic review of stability of pediatric oral extemporaneous oral formulations.

or not instability problems occurred in such preparations. A limitation of our review is that the protocol was not previously registered. We found encouraging research on the stability of many drugs for pediatric oral formulations.

3.1. Selection of Included Studies

The search for the database has brought a total of 181 research items. Duplicate research (n = 23) was eliminated through its titles and summaries. .e research approved by the abstract review was also examined with its title. Finally, a total of 28 studies (experimental articles) were included in this systematic review (Figure 1).

3.2. Source of Pediatric Extemporaneous Oral Liquid Formulations

. In this systematic review, commercially available tablets and capsules are the most commonly used sources for pediatric extemporaneous preparations. Pure drugs, injectable preparations, and pellets are also used as sources of pediatric extemporaneous preparations. .e results are consistent with other studies (Table 1). Research conducted at the Malta Hospital shows that most improvised pediatric compounding is made by converting capsules and tablets into oral liquids or powder. Others are made from active ingredients in bulk, such as oseltamivir powder to make an oseltamivir phosphate solution [2]. Preparation of children's oral medicines is subject to much variation in hospitals throughout Europe, and there is little harmonization of formulations or information on the stability of products. .e European Union could be the focus for improving the availability of appropriate authorized medicines for children and ensuring that when extemporaneous preparation is necessary, it is of a common high standard [3].

3.3. Methods for Stability Testing.

For this study, high-performance liquid chromatography (HPLC) is the frequently used method to check the chemical stability of most extemporaneous preparations. .e UV-spectrophotometer and other methods are also used rarely to check the stability of these preparations (Table 1). HPLC and UV-spectrophotometer are the recommended methods for stability test of pharmaceutical formulations by all pharmacopeias including United States Pharmacopeia (USP) and British Pharmacopeia (BP) [7]. .e stability of the peaks of the analyte and the degradation product that are completely separated from

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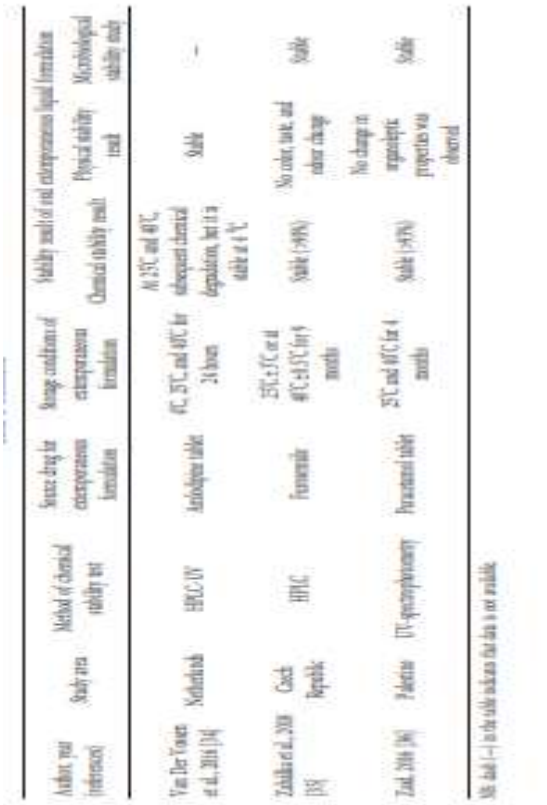
each other is indicative of the chromatogram of the HPLC method. [8].

3.4. Storage Condition of Pediatric Extemporaneous Formulations.

During storage, pharmaceuticals are prone to physical and chemical degradation. .ese degradations may change the pharmacological properties of the drug, reducing its benefits and increasing its harmful effects. .e physical factors which affect the stability of the drug are light, solvent, heat, oxygen, and humidity [9].

In this review, most of the pediatric extemporaneous formulations were stored at temperatures of 4, 25, and 40°C with and without light before testing. Some were stored at

able 1: .e stability of oral liquid extemporaneous preparations compounded from commercially available formulations



Authors, year (reference)	Study area	Method of chemical stability test	Source drug for extemporaneous formulation	Storage conditions of extemporaneous formulation	Stability result of oral extemporaneous liquid formulation		
					Chemical stability result	Physical stability result	Microbiological stability study
Van Der Vossen et al., 2016 [34]	Netherlands	HPLC-UV	Amlodipine tablet	4°C, 25°C, and 40°C for 24 hours	At 25°C and 40°C, subsequent chemical degradation, but it is stable at 4°C	Stable	-
Zaidan et al., 2020 [35]	Czech Republic	HPLC	Paracetamole	25°C ± 2°C or at 40°C ± 2°C for 6 months	Stable (<90%)	No color, taste, and odour change	Stable
Zaid, 2016 [36]	Palestine	UV-spectrophotometry	Paracetamol tablet	25°C and 40°C for 4 months	Stable (<95%)	No change in organoleptic properties was observed	Stable

Nb: dash (—) in the table indicates that data is not available

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storage conditions comply with the ICH guideline which focuses on the storage conditions of pharmaceuticals for the purpose of stability testing of APIs [10].

3.5. Chemical Stability of Pediatric Oral Extemporaneous Liquid Formulations. Stability studies to ensure pharmaceutical product safety, quality, and efficacy are preserved throughout the shelf life and are considered as a precondition for approval of any pharmaceutical preparations. Experimental stability studies should be done in a wellorganized manner according to the World Health Organization (WHO) and International Conference on Harmonization (ICH) guidelines. Stability refers to the degree to which a product maintains the same characteristics during its storage and use within the specified limits. Each drug maintains chemical integrity and labeled efficacy within the specified range [8].

More than 96% of pediatric oral extemporaneous liquid formulations in this review are stable at all storage conditions (4°C, 25°C, 40°C, and room temperature). .ey retain more than 90% of their initial content of the active drug after the storage duration. But, some drugs are unstable in some specific conditions. For instance, nifedipine and pyridoxal phosphate oral liquid extemporaneous preparations were degraded in the exposure of light. Amlodipine was also degraded at 25 and 40°C. From twenty-eight pediatric oral extemporaneous formulations, only three formulations showed chemical degradation (Table 1).

The USP, BP, and European Pharmacopeia have established that the acceptable range of most compounded preparations is typically ±10%, or within the range of 90.0%– 110.0%. Even for some drugs, if they retain 85% of their original content, it is acceptable [8].

3.6. Physical Stability of Pediatric Oral Extemporaneous Liquid Formulations.

The appearance, consistency, uniformity of content, solution clarity, moisture content, particle size and shape, pH value, and integrity of pharmaceutical packaging may change, which may affect its stability. Such physical changes can be caused by shock, vibration, wear, and temperature fluctuations (such as freezing, thawing, or shearing) [37]. To conclude a pharmaceutical product as physically stable, the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, must be retained [8].

3.7. Microbiological Stability of Pediatric Oral Extemporaneous Liquid Formulations.

The stability of a pharmaceutical product can also be affected because of microbiological changes such as the growth of microorganisms in nonsterile products and changes in preservative efficacy. Microbiological tests include sterility, preservative efficacy, and microbial count as applicable. Resistance to microbial growth is retained according to the specified requirements [37].

We also discuss the factors that affect microbial contamination in popular dosage forms (e.g., tablets, sterile products, cosmetics). When these products are contaminated, the microorganisms can cause changes. .e effects range from mild changes (e.g., discoloration, texture alteration) to severe effects (e.g., changes in activities, toxicity). In this study, most pediatric oral extemporaneous preparations in this review are stable (no growth of microorganisms at the storage temperature

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during the storage conditions). But some studies do not include microbiological stability study (Table 1)).

4. Conclusion

There is a serious lack of commercial medications that are safe for kids, thus last-minute oral preparations are required. Hospital pharmacists rely heavily on stability study results to ensure the quality and safety of the impromptu concoctions they distribute, particularly for pediatric patients. The impromptu pharmaceutical preparation needs to be physically, chemically, and microbiologically stable in order to be utilized as a substitute for commercial pharmaceuticals and to be therapeutically safe and efficacious.

This systematic review states that microbial growth and chemical and physical instabilities on pediatric oral spontaneous formulations are extremely uncommon, based on multiple experimental experiments. The majority of research showed that spontaneous preparations are stable for the length of time and under the ICH-recommended storage settings. All impromptu formulations should have an expiration date of no more than one month (or less if specified in the published study or if antimicrobial preservatives cannot be utilized). It will promote the use of fresh preparation on a regular basis and support the maintenance of safety and efficacy. Additionally, it enables the physician to routinely assess how the patient is utilizing the preparation.

For pediatrics, the most promising choice will typically be impromptu oral formulations (medications) made from commercially available tablets, capsules, powders, and other dosage forms.

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