PHARMACEUTICAL COMPOUNDING PREPARATIONS: A STUDY ON IBUPROFEN ORAL SUSPENSION

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Abstract: This study examines the formulation of pediatric ibuprofen suspension and the evaluation of its stability, in response to the optimized distribution issues of this drug regarding special patient requirements. The study was based on formulating an Ibuprofen oral suspension in a pediatric suitable dosage form (20mg/ml) using two different bases (sucrose and sodium carboxymethylcellulose) that satisfies the organoleptic properties for the paediatric age group. The formulations were evaluated for stability at two different storing conditions: room temperature (20 - 25°c) and refrigerator temperature (2 - 8°C). Each of the formulated suspension stored at different condition was measured for the concentration of Ibuprofen as the active ingredient and physical parameters (the refractive index and pH) on different periods (1, 3, 9, 12 and 15 days prior the formulation) to determine stability.
The content of Ibuprofen in the two formulations stored at two different conditions reflects within limit of percentege of content of Ibuprofen [90-110%]. The storage conditions significantly impact more the physical stability of ibuprofen, as evidenced by changes in the refractive index during the days after the formulation.
The results show that these galenic formulations can ensures stability and comparable quality to approved products. The pharmaceutical practice sector can still rely on compounding practices for special needs of the patients at special situations. Research focusing on the evaluation of the effectiveness and safety of galenic preparations can help improve the quality and confidence of patients and professionals in this field.
Keywords: Compounded Ibuprofen Suspension; Galenic practice; Non-sterile preparations

1. INTRODUCTION

Ibuprofen is an active ingredient available in different pharmaceutical pediatric form and is used as a non-steroidal anti-inflammatory agent (NSAID) (Tucci et al., 2009). After paracetamol it is the most used most prescribed drug for children in hospital and is widely used for lowering fever and general pain (Moriarty & Carroll, 2016). When it comes to the patient's special needs (such as flavor or allergies to specific ingredients in the industrial formulation) or shortages of the drugs (Shachar, Gruppuso, & Adashi, 2023) compounding ibuprofen suspension by the pharmacist can be useful for the patient. Suspensions of Ibuprofen are generally preferred for their poor taste charac¬teristics; as by minimizing the amount of drug in solution, the palatability of the formulation can be improved (Barbagallo & Sacerdote, 2019).
Oral liquid medications prepared through compounding are crucial in meeting the unique requirements of specific patient groups, such as pediatrics, geriatrics, and individuals reliant on tube feeding (Cutaia, Chablani, & Zhao, 2018). Opting for liquid medicinal products may be preferable since they are easier for children to ingest compared to solid forms (Schirm et al., 2003). Liquid formulations are the most convenient method for administration of oral medication in children, but it can prove difficult to achieve good organoleptic characteristics. Suspensions can minimize the amount of an unpleasant-tasting drug in solution, but solutions are often preferred due to improved texture and dose uniformity (Davies & Tuleu, 2008) . Factors related to medications for the pediatric population can pose challenges, such as excipients, pH, and osmolarity.
The 'art' of compounding pharmaceutical forms is a unique and complex characteristic of the pharmacy practice. However, the regulatory supervision of compounding is fragmented. In the United States, the primary regulatory body and routinely issues standards for appropriate testing, processing, and techniques associated with non sterile pharmaceutical compounding is FDA (Food and drug Association) through the Revision Bulletin of United States Pharmacopeia Chapter 795 (European Association of Hospital Pharmacists, 2020) whereas in Europe the regulatory body that regulates this topic is EMA (European of Medicines Association) according to EAHP's (European Association of Hospital Pharmacist) Position Paper on Pharmacy Preparations and Compounding
(European Parliament & Council, 2001). According to US Pharmacopeia, compounding is defined as 'the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug delivery or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on the practitioner / patient / pharmacist/ compounder relationship in the course of professional practice'.

European legislation encompasses Galenic preparations/compounding and distinguishes between two types: namely, 'magistral formula,' which refers to ‘any medicinal product prepared in a pharmacy following a prescription for an individual patient, and 'official formula,' which denotes any product prepared in a pharmacy in accordance with the descriptions provided in a pharmacopoeia intended to be directly dispensed to pharmacy-served patients’[9].

The term 'compounding' finds frequent usage in English literature, whereas in European pharmaceutical contexts, 'Galenic preparations' predominates. The literature categorizes galenic preparations into two main types: 'adaptations of existing products,' which involve reformulating licensed products into suitable dosage forms tailored for the intended use, and "formulations from raw materials," which entail creating dosage forms from active substances and excipients for the intended use (Boëman-Boer, Fenton-May, & Le Brun, 2015). Past studies highlight varying pharmacy compounding standards in Europe. Many studies request further assessments to ensure alignment with EU legislation and Resolution, with implications based on the evaluation results (European Association of Hospital Pharmacists, 2016).

Galenic preparations or compounding play a vital role in patient care by filling the void between industrially produced licensed medicinal products and the limited treatment options available for certain patient groups and individuals with unique medical conditions or requirements for example limited dosage forms, strength, shtortages, orphan drugs allergic to specific ingredients, elderly individuals, or children unable to swallow tablets and needing a liquid form (Scheepers et al., 2017).

To support galenic preparation activities, EAHP advocates for the ongoing advancement of the profession beyond the requirements of ensuring the quality and safety of pharmacy-prepared medicinal products, emphasizing the need to create an environment enabling the provision of integrated services by hospital pharmacies (Scheepers et al., 2017). The EAHP 2023 Shortage Survey Report underscores the importance of solidifying the role of healthcare professionals, especially hospital pharmacists, in compounding. This emphasizes the need to enhance compounding capabilities to ensure sufficient patient care. Among the responses from hospital pharmacists (N=605) regarding operational changes they find suitable and/or regularly utilize, a significant portion of 40% chose 'increasing on-site compounding of products (Sankeshwari et al., 2023). However, compounded preparations lack FDA approval, meaning the FDA doesn't assess their safety, effectiveness, or quality before reaching patients. Several cases of severe patient injuries have resulted from poorly compounded medications, underscoring the urgent need for rigorous quality control (European Association of Hospital Pharmacists, 2023).

The aim of the study is the formulation of an Ibuprofen oral suspension and determination of its stability in a compounding didactic laboratory. To achieve the main goal, research objectives were investigated, focusing on formulating an Ibuprofen oral suspension in a pediatric usable dosage form with the proper base that satisfies the organoleptic properties for the pediatric age group. Measuring various physical parameters was made to determine stability on different days.

2. MATERIALS AND METHODS

Ibuprofen as an active ingredient along with the solvent NaOH 0,1N and exipients used in the preparation of the suspension (sucrose, sodium carboxymethylcellulose, methylparaben, vanilla) was provided from Albanian University pharmaceutical laboratory. Two different Ibuprofen suspensions 20mg/ml were prepared: Simplex base suspension (F1) and CMC Carboxymethylcellulose based suspension (F2) according to the pharmacy academic literature guidelines formulation methods (U.S. Food and Drug Administration, 2018). Each of the formulation was stored in two different conditions (I and II). Condition I was room temperature (20 – 25°C) and Condition II was below room temperature (2 -8 °C).

The content of the principal active ingredient of Ibuprofen as well as the physical chemical parameters: ph and refractive index were measured at specific days during the period of storage (1, 3, 9, 12 and 15 days prior the formulation). The content of the principal active ingredient was calculated based on the equation of the calibration curve previously constructed. For the pH measurement a Denver Instrument is used with integrated thermometer, and the refractive index is measured with Optika Abbe Refractometre for every formulation stored at different condition.

The data obtained from the measurements were transferred in a working excel sheet and data analysis was performed by Microsoft Excel 365 for statistical and representation purposes.

3. RESULTS

Preparation of the calibration curve for UV-Vis spectrophotometric determination of ibuprofen

This preparation was carried out in the pharmaceutical didactic laboratory. Initially, 0.1g of the active ingredient ibuprofen was taken (provided by the Department of Pharmacy at Albanian University) and added it to a 100 ml flask with 0.1N NaOH solution up to the mark. This preparation is called the stock solution with a concentration of

1mg/ml. From the stock solution, 0.1ml was taken and added it to another 100ml flask, which filled up to the mark with distilled water. After shaking, the first standard solution with a concentration of 0.001mg/ml was created. From the stock solution again, the second and third standard solutions were reconstructed with the respective concentration of 0.002mg/ml and 0.01mg/ml. The absorbance were measured for each of the standard solutions using a spectrophotometer Varian against the blank solution (distilled water), which was set at the maximum absorbance 220nm for Ibuprofen.

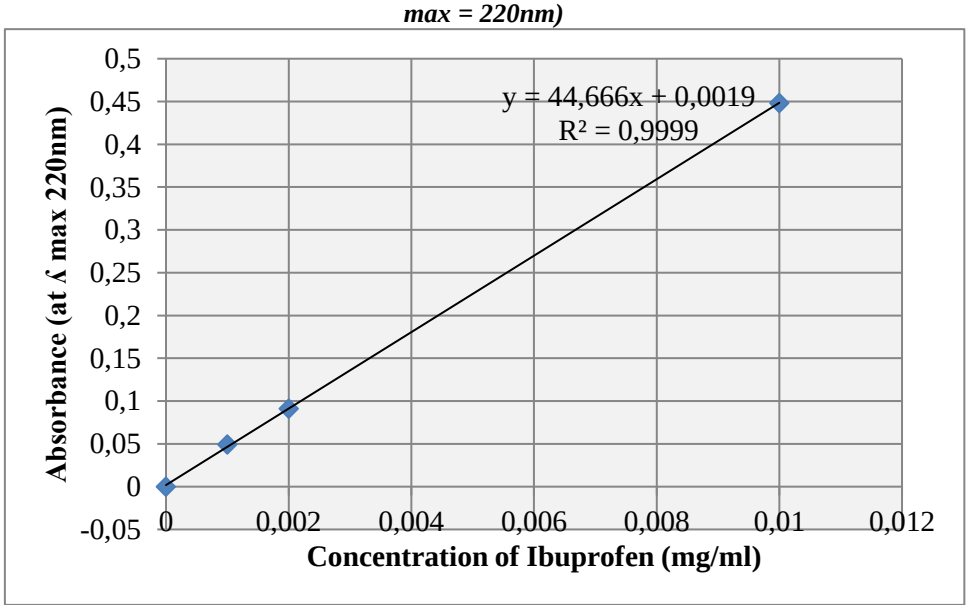
The calibration curve for ibuprofen suspension was constructed using the series of known concentrations and their corresponding absorbance values, as shown in Table 1 The linear relationship between concentration and absorbance is illustrated in Figure 1 **Y=44,66*X + 0,001** (Correlation factor R^2 0,99**)**, indicating a high degree of correlation. This suggests that the method is suitable for quantifying ibuprofen in the formulated suspensions.

Table 1: Measured Absorbance for the different Ibuprofen Solutions for the Calibration Curve

No.	Concentration (mg/ml)	Absorbance (max 220nm)
0	0.000	-0,0003
1	0,001	0,0491
2	0,002	0,0910
3	0,01	0,4483

Source: Author

Fig. 1: Calibration Curve for the UV-Vis Spectrophotometric determination of Ibuprofen in aqueous solution (λ max = 220nm)



Source: Author

Preparation of Ibuprofen suspension formulations

The preparation of Ibuprofen suspension 20mg/ml in two different bases was conducted following compounding guidelines methods for the simple sucrose base (USP32-NF27, p.1367) and for the Na-CMC base (USP 34-NF 29, p. 1416-19). Ibuprofen Suspension 20mg/ml in Simple sucrose base (F1) is prepared by suspending the active ingredient ibuprofen in a simple syrup base of sucrose and includes neither alcohol nor preservatives in it. Ibuprofen Suspension 20mg/ml in Sodium Carboxymethylcellulose (Na-CMC) base (F2) is prepared by suspending Ibuprofen in a Carboxymethylcellulose base which includes the following exipients: Na-CMC (0,5%), alcohol, preservatives and flavoring with vanilla in it. According to Marques Marinho (2013), "Cellulose derivatives are crucial for pharmaceutical compounding due to their versatility" (p. 145).

The steps undertaken to ensure the appropriate formulation of the suspensions with the relevant formula described in the Table 2 and the processes of weighing and mixing, heating and dissolving, filtration, final adjustment and packaging.

Table 2 Formula used for compounding Ibuprofen Suspension 20mg/ml in Simple sucrose base (F1) and Ibuprofen Suspension 20mg/ml in Carboxymethylcellulose (CMC) base (F2)

Ingredient	F1	F2
Ibuprofen	4 g	4 g
Saccharum	128 g	100 g
Natriicarboxymethylcellulosum	-	1 g
Methylii p-hydroxybenzoas	-	0,2 g
Vanillinum	-	0,1 g
Alcoholum 90%	-	2 g
Aqua destillata ad	200 g	200 g

Source: Author

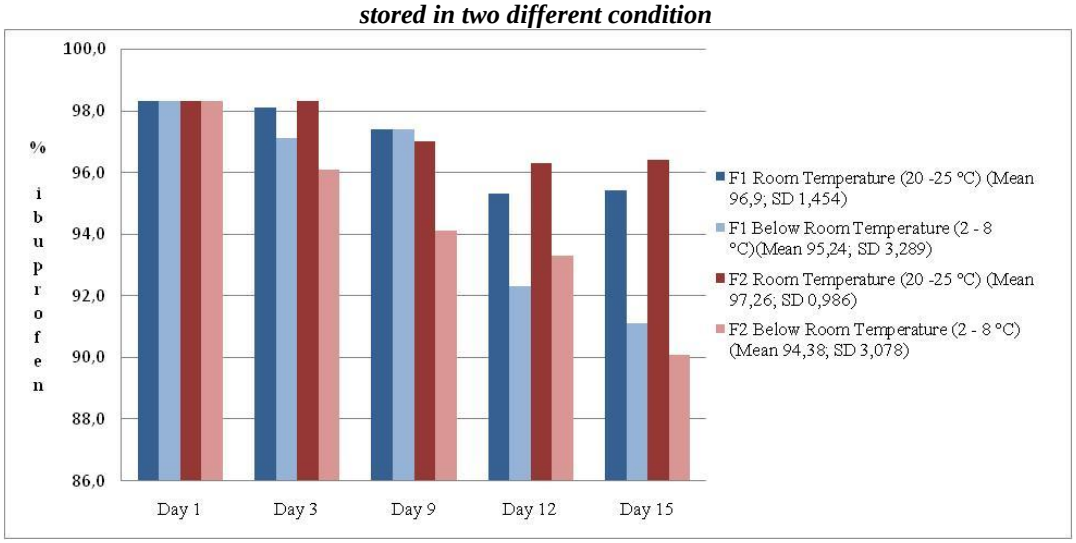
Stability Study

The stability of both formulations was examined for content of active ingredient (concentration in % w/v of Ibuprofen), pH and refractive index under two conditions: room temperature 20 -25°C and below room temperature 2 – 8°C with storage periods of days: 1, 3, 9, 12 and 15.

Concentration of Ibuprofen (in % w/v)

The content of the Ibuprofen active ingredient in each prepared formulation and stored in the specific condition was measured by taking 1ml of aliquot form the suspensions and diluting it in NaOH 0,1N up to 100ml, then filtered. 1ml of this solution was diluted again in NaOH 0,1N up to 100ml. The absorbance of this last solution was measured at the maximum wavelength of 220nm. The content was calculated according to the calibration curve linear equation during the storage days.

Graphic 1 Results of content of Ibuprofen (Concentration in %) in Ibuprofen suspension 20mg/ml (F1 and F2) stored in two different condition



Source: Author

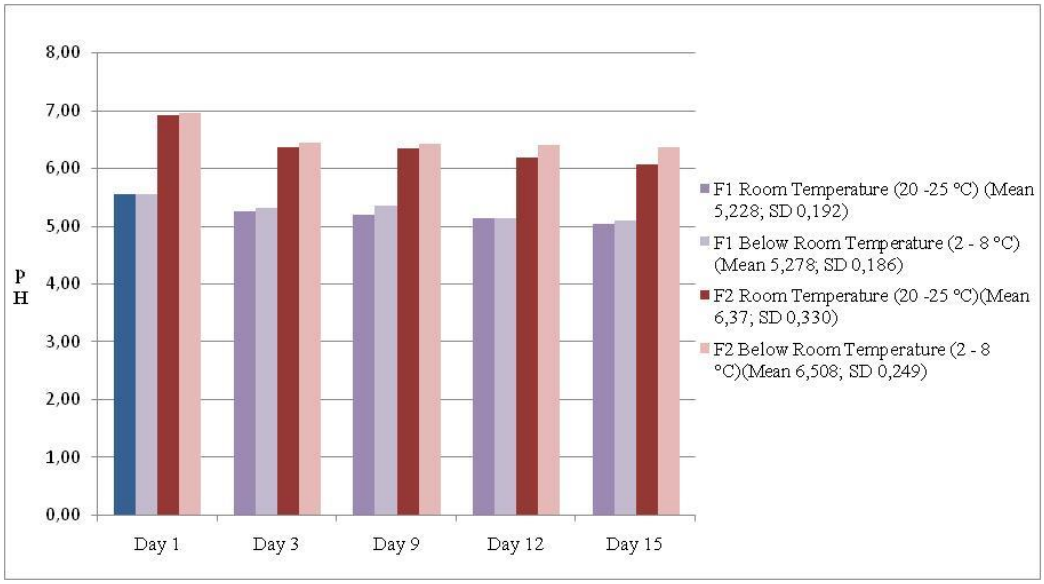
The F2 formulation (both room and below room temperature) maintain a higher concentration e of ibuprofen over 15 days compared to F1 formulations. Room storage conditions tend to show less decline in ibuprofen percentage compared to condition of below room temperature for both formulations. The F1 formulation stored below room temperature shows the most significant decline in ibuprofen percentage over the 15-day period. Overall, F2 formulations, especially at room temperature, appear to provide better stability for ibuprofen over the observed period.

pH measurements

The solubility of Ibuprofen, which is a weak acid with a pKa 4.43±0.03[16], depends on the pH of the medium. The measurement of pH is important for such pharmaceutical suspensions formulations such as Ibuprofen suspension compounded in the pharmacy settings because it affects the solubility, stability, and bioavailability of the drug. As previously studied, Ibuprofen has the optimal stability at pH interval 5, 6 and 7 (Rehman, Ijaz, Murtaza, & Hussain, 2012). Additionally, the pH of the suspension can affect the taste and palatability of the drug, especially for pediatric formulations. A more acidic or alkaline suspension can cause irritation or discomfort in the mouth and throat, which can reduce the patient's compliance.

The measurements of pH were made by using a pH meter (Denver Instuments 9710.1). This instrument is used to measure the acidity of water by comparing readings from a reference electrode and a sample electrode. This pH meter also measure temperature. pH meters generally require frequent calibration, and calibration is part of this laboratory procedure periodically. The results of the pH measurement at different days are represented in Graphic 2.

Graphic 2 The values of pH measured at different days for the Ibuprofen suspension 20mg/ml (F1 and F2) stored at two condition (room temperature and below room temperature) according to the concentration value measurements



Source: Author

The value of the pH of the formulation F1 stored in room temperature (Mean 5,228; SD 0,192) does not differ very much from the same formulation stored below rrom temperature (Mean 5,278; SD 0,186). The same relation is seen in the formulation F2 where the pH of it stored in room temperature (Mean 6,37; SD 0,330) is close to that stored below room temperature (Mean 6,508; SD 0,249). The pH of these formulations are in accordance with the industrial preparation of Ibuprofen discussed in previous studies (Medina, Cortes, & Romo, 2017).

Refractive Index measurements

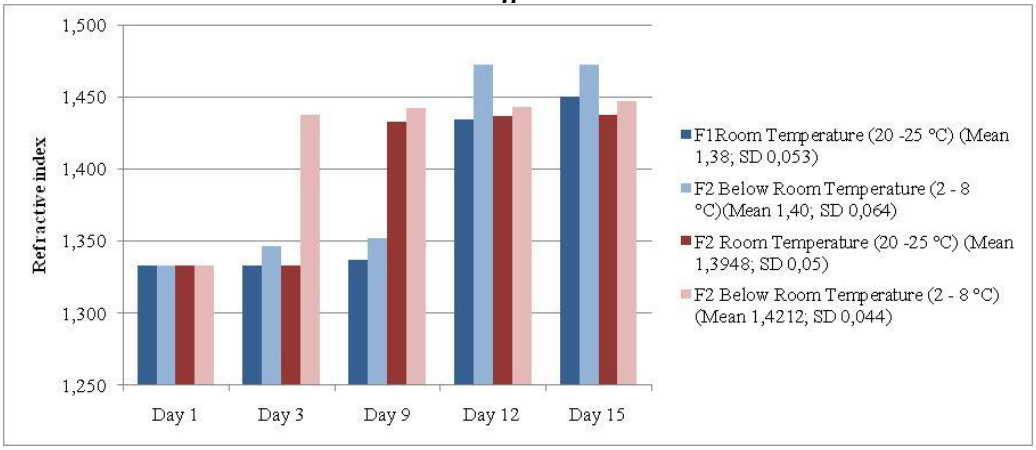
The optical parameter such as the refractive index is important because the optical properties (transparency, turbidity, and color) can influence the appearance and the quality perception of the suspensions by the consumers and the regulators (Mohan, Kato, Drennen, & Anderson, 2019). The stability of the suspensions, such as sedimentation, aggregation, and flocculation, can depend on the refractive index mismatch between the particles and the liquid medium (Wiederseiner, Andreini, Epely-Chauvin, & Ancey, 2011). Therefore, measuring and controlling the index of refraction of the suspensions can help to optimize their performance and quality (McClymer, 2016).

The refractive index of each of the formulation was measured by OptikaAbbe Refractometer by taking direct samples from the suspensions stored in the known condition during the storage days as showed in Graphic 3.

The formulation F1 stored at room temperature (20-25°C) shows a gradual increase, peaking at around Day 12 and maintaining a high refractive index through Day 15, indicating significant changes in the physical properties of ibuprofen under these conditions. Whereas when stored below room temperature (2-8°C) shows the least variation in the refractive index, suggesting this condition maintains the physical properties of ibuprofen more effectively over

time. The F2 formulation stored at room temperature (20-25°C) shows a moderate increase in the refractive index, with a slight decrease by Day 15, indicating a relatively stable condition.

Graphic 3 Refractive Index measurements on different days of Ibuprofen suspension 20mg/ml (F1 and F2) stored in two different conditions



Source: Author

ANOVA-based comparison test

A two-way ANOVA was performed to determine if there were significant differences in the formulation F1 and F2 when stored at different conditions based on the values of concentration of Ibuprofen, pH and refractive index. The results of the test are reflected in the table 4.

According to the data from the two way Anova test, there is no significant difference between the two kinds of Ibuprofen suspensions according to the content of the Ibuprofen concentration (F <F crit, P-value>0,05). Also there is no difference between the types of Ibuprofen suspensions when it comes to the storage conditions (F <F crit, P-value>0,05) and there is no interaction of the storage condition on the concentration of ibuprofen on the two types of suspensions (F <F crit, p>0,05).

Table 3 Two way ANOVA test performed to show if there is significant difference between the F1 and F2 stored at different condition and any interaction between them for the different source of variation (Concentration of Ibuprofen, pH and Refractive index)

Source of Variation	*F*	*P-value*	*F crit*
Concentration of Ibuprofen			
Type of suspension base (F1 vs. F2)	0,053469	0,820064	4,493998
Storage conditions (Room Temperature vs. Below Room Temperature)	4,408333	0,05198	4,493998
Interaction between storage conditions and type of suspension base	0,318333	0,580435	4,493998
pH			
Type of suspension base (F1 vs. F2)	115,9792	0,00	4,493998
Storage conditions (Room Temperature vs. Below Room Temperature)	0,728562	0,405948	4,493998
Interaction between storage conditions and type of suspension base	0,159631	0,69478	4,493998
Refractive index			
Type of suspension base (F1 vs. F2)	0,6369	0,4365	4,4940
Storage conditions (Room Temperature vs. Below Room Temperature)	0,6856	0,4198	4,4940
Interaction between storage conditions and type of suspension base	0,0260	0,8740	4,4940

Source: Author

A two-way ANOVA was performed to determine if there were significant differences in the pH value of ibuprofen based on storage conditions for the respective Ibuprofen suspension 20mg/ml formulated. The type of suspension base has a significant effect on the pH of ibuprofen suspension (F-value is very high 115.9792 and the P-value < 0.05) indicating that the difference between F1 and F2 is statistically significant. The storage conditions (room temperature vs. below room temperature) do not have a significant effect on the pH of ibuprofen suspension (F-value=0.728562; P-value > 0.05), indicating no significant difference due to storage conditions. The interaction between storage conditions and the type of suspension base does not have a significant effect on the concentration of ibuprofen suspension (F-value=0.159631; P-value >0.05), indicating no significant interaction effect. Furthermore, there is no statistically significant interaction effect between storage conditions and the type of suspension base (P > 0.05). This suggests that the effect of storing condition does not depend on the pH value of the two formulated suspensions and *vice-versa*.

A two-way ANOVA was performed to determine if there were significant differences in the refractive index measurements for the respective Ibuprofen suspension 20mg/ml formulated stored at different conditions. The two way ANOVA test performed suggests that the type of suspension base (simple sucrose versus carboxymethylcellulose) nor the storage condition does not significantly affect the refractive index of the suspension and that the effect of the storage condition does not depend on the level of the type of suspension base (Low F value; P value>0.05).

4. DISCUSSIONS

The compounding of Ibuprofen Suspension 20mg/ml can be relatively an easy and quick process that can be achieved in pharmacy practice butchoosing the safe excipients for pediatric dosage form formulation is critical because the pediatric age groups differs when it comes to the toxicity levels of some specific excipients (Sankeshwari et al., 2023). When formulating of a pharmaceutical pedratric form, the notion of 'less is more' need to be applied. Ibuprofen Suspension 20mg/ml can be compounded according to special needs or requests of the patient, for example in simple sucrose base with no preservatives nor alcohol (F1) or with a specific kind of flavouring such as vanilla (F2).

In order to recommend the proper storage and to define the period of time that the formulaion could be used, some easy analysis can be conducted. The content analisys of the concentration of Ibuprofen in % (w/v) for a period of 15 day prior to preparation of the suspensions reflects within limit of percentege of content of Ibuprofen for both storing condition [90 -110%] (United States Pharmacopeia and National Formulary, 2017).

There seems to be no significant difference between the Ibuprofen Suspension 20mg/ml formulated in a simple sucrose base or in carboxymethylcellulose base, but the first version seems to be more stable at room temperature as well as keeping better range values of pH and refractive index. A lower temperature of storage gives to the suspensions a higher viscosity, changing mainly the physical characteristic of refractive index but not the concentration of ibuprofen. Previous studies suggest that many versions of formulations are possible with a good stability and reological properties for the target groups of pediatric or geriatric patient (Sudhir, Divya, Lakshmi Prasanti, & Jyothi, 2016). The storage conditions significantly impact more the physical stability of ibuprofen, as evidenced by changes in the refractive index during the days after the formulation.

5. CONCLUSIONS

Different formulation of Ibuprofen oral suspensions 20mg/ml can be constructed in line with patients needs and desires of the pediatric target group. These formulations could be constructed beginning from simple ingredients reachable at any pharmaceutical practice field as well as didactic pharmaceutical laboratories. Special attention and recommendations for storage are needed to be given in order to maintain the content of the principal active ingredient and physical chemical parameters in the proper limits. The pharmaceutical practice sector can still rely on compounding practices for special needs of the patients at special situations. Similar studies would provide useful information for pharmacists and educators who are involved in compounding practice and teaching to improve this sector to new frontiers. Research dedicated to developing effective marketing strategies for galenics can help increase awareness and use of these products. Research focusing on the evaluation of the effectiveness and safety of galenic preparations can help improve the quality and confidence of patients and professionals in this field. These recommendations aim to improve the understanding and application of galenics in the pharmaceutical market, taking advantage of its potential to provide personalized and effective care to pediatric patients.

ACKNOWLEDGEMENTS

The Authors express gratitude to Albanian University, Faculty of Medical Sciences, Department of Pharmacy for their support in carrying out their work.

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