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Development and validation of a pediatric dosage form for a commonly used medication

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ABSTRACT

Pediatric children often have difficulty administering their drugs due to a lack of age-appropriate dosage forms, which can result in inadequate therapeutic effects and poor compliance. The creation and validation of a pediatric dosage form for the regularly administered medications acetaminophen and ibuprofen for feverish conditions is the main focus of this study. By creating a kid-friendly dosage form, the study sought to address important formulation issues such as dose accuracy, taste acceptability, and excipient safety. Using a methodical approach, formulations such liquid suspensions and chewable tablets were developed and optimized after excipients were chosen based on pediatric safety criteria. High-Performance Liquid Chromatography (HPLC) and other analytical techniques were validated to guarantee the formulation's quality properties, including solubility, stability, and homogeneity. Pilot tests assessed the product's usability and palatability in the target population, while stability studies conducted under various conditions determined the product's robustness and shelf life. In comparison to previous choices, the final formulation showed enhanced compliance, stability, and acceptable physicochemical qualities. This study establishes the foundation for future clinical testing and large-scale manufacturing while highlighting the significance of novel techniques in pediatric pharmacotherapy.

Keywords: *Acetaminophen, Ibuprofen, pediatric patients, and feverish conditions.*

1. INTRODUCTION

The variability of developing physiology and the ethical issues surrounding a vulnerable population present challenge for pediatric medication dosing. In order to address an unmet medical need and enhance pediatric drug labeling, new regulatory initiatives have encouraged drug sponsors to conduct pediatric-specific programs. Drug dosage recommendations for children are usually derived from adult population research. This paradigm is further complicated by the pathophysiological effects of obesity on medication distribution and metabolism, as well as the roles that body composition and size play in drug dosing. Pediatric patients require specialized dosage formulations that take into account their unique physiological and therapeutic needs. Since children have different pharmacokinetics, have trouble swallowing tablets, and are more sensitive to the taste of medications than adults, compliance and accurate dosing are essential. Despite these requests, there are still a number of commonly used medications without age-appropriate pediatric formulations, which frequently leads to the off-label use of adult formulations that could compromise their efficacy and safety. The need of developing kid-friendly dosage forms that ensure dose flexibility, palatability, and safety has been emphasized by the FDA, EMA, and other regulatory agencies. By creating and licensing a pediatric dose form for the commonly prescribed medications acetaminophen and ibuprofen for feverish conditions, this study aims to solve these issues. When there is no underlying illness that could impair tolerance to temperature, a child's fever is typically a harmless occurrence that doesn't need to be treated. However, when fever causes pain and suffering, parents may get concerned. In this way, two over-the-counter (OTC) antipyretics that are typically used to treat fever and associated pain in children are ibuprofen and acetaminophen (paracetamol).

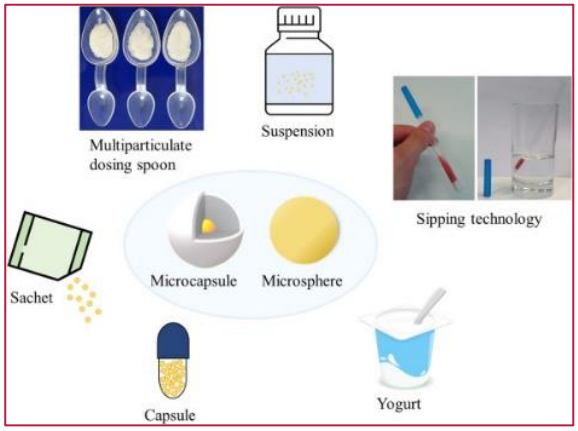

Figure 1: Pediatric dosage

Ibuprofen inhibits cyclooxygenase (COX) isoenzymes in a nonselective and reversible manner, affecting a variety of inflammatory pathways and natural frameworks. Measurement recommendations for children and the antipyretic effects of acetaminophen and ibuprofen are included in the American Foundation of Pediatrics' clinical report on the use of antipyretics in children. There is no proof that there is a significant difference in security at these dosages, and the two drugs are more effective than a fake treatment at reducing fever at specialist coordinated measurements (ibuprofen, 10 mg/kg like clockwork; acetaminophen, 15 mg/kg like clockwork). Additionally, ibuprofen and acetaminophen are available over-the-counter in dosages of 5–10 mg/kg and 10-15 mg/kg, respectively. When used for a variety of acute difficulties and severe and ongoing pain disorders, ibuprofen generally has a positive security profile [1]. However, depending on the patient's demographics, comorbidities, medication use, and measurement, ibuprofen has also been linked to adverse effects on the liver and kidneys. Adolescents were most likely to experience the gastrointestinal antagonistic effects of ibuprofen, which included nausea, heaving, stomach pain, loose stools, obstruction, dyspepsia, and fart. Interesting renal adverse effects (<0.01%) of ibuprofen include severe kidney disappointment, interstitial nephritis, and, following prolonged use, papillary putrefaction. When taken within the recommended therapeutic portion range, acetaminophen has a demonstrated positive impact on wellbeing. It is known that using acetaminophen at dosages higher than the daily maximum might result in hepatotoxicity and severe liver failure. Although acetaminophen and ibuprofen are effective antipyretics when taken separately, they have also been used in combination or replacement regimens, and some authors have even suggested that the combination is more effective than either medication by itself.[2]. Indeed, doctors are increasingly recommending acetaminophen and ibuprofen together, and parents often provide the two drugs at the same time [17]. When both are viewed as coordinated, their combined use can be sustained globally. According to pharmacologic research, acetaminophen and ibuprofen may be widely tolerated when taken together since they have different metabolic pathways that are unaffected by each other.

1.1 Research question

To improve therapeutic outcomes and child compliance, how may acetaminophen and ibuprofen be manufactured and approved in a pediatric dosage form that is safe, efficient, and palatable?

1.2 Objectives

- To develop and validate an acetaminophen and ibuprofen dosage form for children of all ages that is safe, effective, and palatable.
- help locate and select safe excipients that meet pediatric formulation requirements.
- To optimize the acceptability of the dosage form in terms of taste, ease of use, and dosage adaptability.

1. LITERATURE REVIEW

The pediatric population is a broad category with several subsets. Due to the lack of appropriate dose forms for this age group, children are frequently treated with unlicensed and off-label medications. The improvement of pediatric dose structures is negatively impacted by a number of fundamental factors, even though physiological differences associated with the various age groups remain a significant consideration.[3]. These factors include low benefit, lack of administrative clarity, lack of foundational data on the medication particle, excipient wellbeing, taste-veiling issues, innovation requirements, and difficulties in directing clinical preliminary studies. [9]. The most popular dosage type for kids, especially younger ones, is liquid. However, doctors and caregivers are forced to employ off-label, "specials," or impromptu concoctions when appropriate or labeled dose forms are not available. All of these unconventional formulations are dangerous for young patients since they lack pertinent scientific evidence. The situation is far worse in developing countries, where there are little

regulations and standards pertaining to pediatric patients. Pediatric improvement actually has trouble securing a place in the conventional drug advancement programs, even if there are now more secure, compelling, and noticeable measuring structures available. The oral route is frequently the most effective in pediatric formulations [4]. Powder forms for reconstitution are frequently offered for oral pediatric formulations. These forms may need special storage conditions in a refrigerated environment and require clean water for reconstitution, however these requirements aren't usually met. Liquid and powder forms may be problematic for young children since they may be difficult to swallow and indigestible. Children usually have difficulty swallowing solid dosage forms, albeit their swallowing abilities may differ from those of adults.[5]. In general, children younger than five should not consume solid capsules or tablets larger than 10 mm.[10]. It's also critical to remember that children may refuse to take any drug, regardless of tablet size, if they dislike the taste.[13]

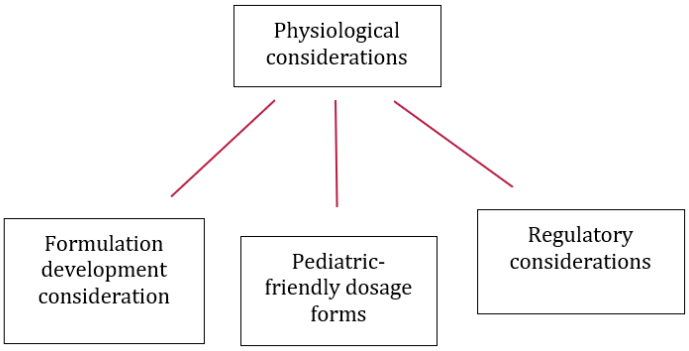

Figure 2: Formulation issues and techniques for creating pediatric dosage forms

For instance, compared to other antibiotics, clarithromycin has a low palatability and a very harsh taste. Drugs with similar disagreeable tastes may therefore make it difficult to follow dosing instructions. If the oral route causes nausea or vomiting, the rectal route may be used as a backup, however this is less common. Although there are many different rectal dosages forms available on the market, such as suppositories, creams, enemas, and ointments, giving them to kids can frequently be uncomfortable. Because of its rapidity, the parenteral route may be used in emergency situations or when the oral route is challenging. The parenteral approach has numerous drawbacks despite its speed advantage, including the requirement for a skilled practitioner to give, the intrusive nature of the procedure, the possibility of blood-borne illnesses, and the possibility of injection-related discomfort or injury. One of the most frequent causes of pediatric care visits is fever. A lot of parents worry unnecessarily about fever. In order to allay these worries, many doctors treat fevers aggressively. advice for taking axilary, rectal, and oral temperatures; a description of fever, including its diurnal variations; a warning that fever alone is rarely dangerous below 41.7°C; and advice for testing the temperature again in children who are feverish; Some areas where parent education may be helpful include recommendations for sponging, when to call the child's doctor, and when to apply antipyretics, including the right dosages, with an emphasis on the child's observation rather than the fever level [6].

2. METHODOLOGY

Study design: The PubMed and Embase literature databases were searched in order to locate relevant publications.

Inclusion criteria: Acetaminophen (including paracetamol and APAP), exchanging dosage, antipyretic, antipyretic specialists, antipyretic/pain relieving specialists, consolidated dosing, similar tests, viability, fever, ibuprofen, ibuprofen/acetaminophen mix item, various/multi-portion, over-the-counter, pediatric, randomized studies, wellbeing, and single portion were among the search terms used both separately and in combination.

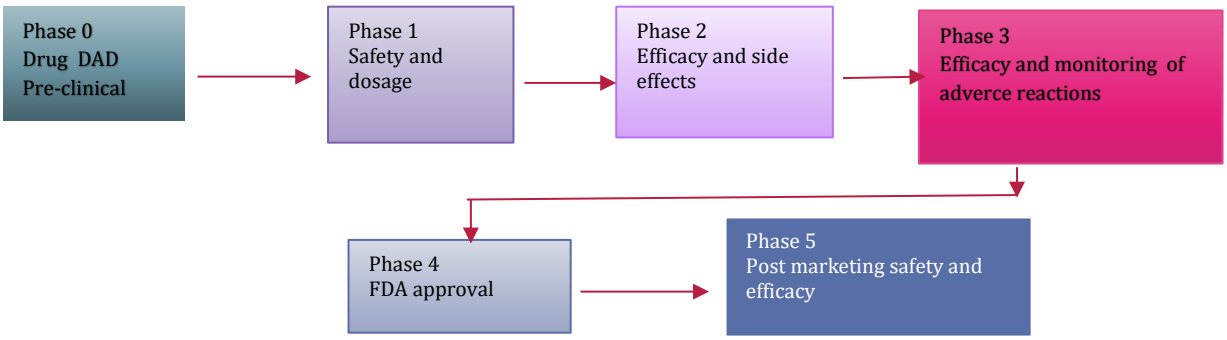

Figure 3: Flow methodology

Limitation: There were no publication date restrictions on the chosen publications, which were restricted to English-language research on over-the-counter oral tablet and syrup forms of ibuprofen and acetaminophen.

Exclusion criteria: Excluded studies included open-label research, nonrandomized research, and trials assessing acetaminophen or ibuprofen suppository or intravenous formulations. Due to differences in patient groups, designs, goals, and techniques, we were unable to perform a thorough systematic review.

Methods: Randomly selected children aged three months to twelve years who had non-severe fevers were given either ibuprofen or paracetamol. To deliver the initial dose in a double-blind fashion, a double-dummy method was employed. Tympanic temperature was collected at baseline and for the next eight hours. For a maximum of three days, parents administered the second and subsequent doses at home under open label. As the doubly visually impaired and open-name time frames came to an end, parents were asked to provide an abstract rating of the item's appropriateness and indicate if they would use it again for their child.

The possibility of pharmacological interactions between ibuprofen and acetaminophen has raised concerns about quiet security. However, when used in combination, the likelihood of drug linkages is minimal. In a surprising way, acetaminophen and ibuprofen pass through specific metabolic pathways and capabilities. Furthermore, when the two medications were administered concurrently, pharmacokinetic analyses revealed no changes in the groups of the various plasma medications.

3. DOSAGE FORM SELECTION

One of the most important considerations when creating oral pediatric drugs is if the measurements are appropriate for the anticipated patient age group without resulting in gulping or agreeability issues.[15]. Taste is without a doubt the most important factor in determining patient consistency. Children may dislike both the type of hidden details and the harsh or metallic flavor of exposed definitions.[8]. They might also reject high-volume measurements. A plan's flavor, sugar, pH, diversity, and tongue sensation all affect how it tastes. When developing pediatric plans, additional considerations include measurements, reliability, conservation, packaging, and the required conveyance tools or techniques.[12]. Understanding the physicochemical characteristics of the drug atom is essential when taking into account buccal measuring structures in order to determine its actual capacity for buccal assimilation.[7] [11] A medication should preferably be in the unionized structure in buccal pH, have a solvency of more than 1 mg/mL, have a sub-atomic size of less than 500 Da, and be lipophilic with a log P greater than 10 and less than 1000 in order to ensure high bioavailability.[16]. The pKa value of a drug becomes crucial since it determines the degree of ionization at different pH levels and affects its dissolvability, ingestion, and bioavailability. [14].

Table 1: Loading dose of acetaminophen for different body weight with various postnatal age to attain the plasma concentration of 10mg/L

Bodyweight (grams)	1	2	3	4	5	6
700	1.84	2.64	3.44	4.24	5.04	5.84
750	2.10	2.90	3.70	4.50	5.30	6.10
800	2.41	3.21	4.01	4.80	5.60	6.40
850	2.76	3.56	4.35	5.15	5.95	6.75
900	3.15	3.95	4.75	5.55	6.35	7.15
950	3.61	4.40	5.20	6.00	6.80	7.60
1000	4.11	4.91	5.71	6.51	7.31	8.11
1050	4.68	5.48	6.28	7.08	7.87	8.67
1100	5.31	6.11	6.91	7.71	8.50	9.30
1150	6.01	6.81	7.61	8.40	9.20	10.00
1200	6.78	7.58	8.37	9.17	9.97	10.77
1250	7.62	8.42	9.22	10.02	10.82	11.62
1300	8.55	9.34	10.14	10.94	11.74	12.54
1350	9.55	10.35	11.15	11.95	12.75	13.55
1400	10.65	11.44	12.24	13.04	13.84	14.64
1450	11.83	12.63	13.43	14.23	15.03	15.82
1500	13.11	13.91	14.71	15.51	16.30	17.10
1550	14.49	15.29	16.09	16.88	17.68	18.48
1600	15.97	16.77	17.57	18.37	19.17	19.96
1650	17.56	18.36	19.16	19.96	20.75	21.55
1700	19.26	20.06	20.86	21.66	22.45	23.25
1750	21.08	21.88	22.67	23.47	24.27	25.07
1800	23.01	23.81	24.61	25.41	26.21	27.01

Table 2: Loading dose of ibuprofen for different body weight with various postnatal age to attain the plasma concentration of 10mg/L

Bodyweight (grams)	5	6	7	8	9	10
700	5.04	5.84	6.63	7.43	8.23	9.03
750	5.30	6.10	6.90	7.69	8.49	9.29
800	5.60	6.40	7.20	8.00	8.80	9.60
850	5.95	6.75	7.55	8.35	9.15	9.94
900	6.35	7.15	7.95	8.74	9.54	10.34
950	6.80	7.60	8.40	9.20	9.99	10.79
1000	7.31	8.11	8.90	9.70	10.50	11.30
1050	7.87	8.67	9.47	10.27	11.07	11.87
1100	8.50	9.30	10.10	10.90	11.70	12.50
1150	9.20	10.00	10.80	11.60	12.40	13.20
1200	9.97	10.77	11.57	12.37	13.17	13.96
1250	10.82	11.62	12.41	13.21	14.01	14.81
1300	11.74	12.54	13.34	14.14	14.93	15.73
1350	12.75	13.55	14.34	15.14	15.94	16.74
1400	15.44	16.24	17.03	17.83	15.44	16.24
1450	16.62	17.42	18.22	19.02	16.62	17.42
1500	17.90	18.70	19.50	20.30	17.90	18.70
1550	19.28	20.08	20.88	21.68	19.28	20.08
1600	20.76	21.56	22.36	23.16	20.76	21.56
1650	22.35	23.15	23.95	24.75	22.35	23.15
1700	24.05	24.85	25.65	26.45	24.05	24.85
1750	25.87	26.67	27.47	28.26	25.87	26.67
1800	27.80	28.60	29.40	30.20	27.80	28.60

Table 3: Maintenance dose of acetaminophen for various body weight to attain the plasma concentration of 10mg/L

Body weight (grams)	Maintenance dose (mg) every 8 hours
700	1.01
750	1.08
800	1.16
850	1.23
900	1.31
950	1.38
1000	1.46
1050	1.53
1100	1.61
1150	1.69
1200	1.76
1250	1.84
1300	1.92
1350	1.99
1400	2.07
1450	2.15
1500	2.22
1550	2.30
1600	2.38
1650	2.46
1700	2.53
1750	2.61
1800	2.69

Table 4: Maintenance dose of ibuprofen for various body weight to attain the plasma concentration of 10mg/L

Body weight (grams)	Maintenance dose (mg) every 8 hours
700	1.01
750	1.08
800	1.16
850	1.23
900	1.31
950	1.38
1000	1.46
1050	1.53
1100	1.61
1150	1.69
1200	1.76
1250	1.84
1300	1.92
1350	1.99
1400	2.07
1450	2.15
1500	2.22
1550	2.30
1600	2.38
1650	2.46
1700	2.53
1750	2.61
1800	2.69

Present study demonstrated the development and validation of Pop-PK models for both aminophylline and caffeine. Before dosage optimization, developed and validated model-based simulations was performed to create dataset separately based on weight stratifications of more than 1500 grams

4. CONCLUSION

Despite its limited restorative benefit, ibuprofen may have a modest advantage over acetaminophen in over-the-counter measurements in terms of a quicker onset of antipyresis, overall survivability, and a shorter duration of fever. This holds true even if over-the-counter oral tablet and syrup forms of acetaminophen and ibuprofen have comparable, generally speaking, antipyretic efficacy in treating hot children at dosages suggested by a specialist. Acetaminophen and ibuprofen both work well when caregivers follow the dosage recommendations on the labels. Because children have different systems of activity, digestion, and end-organ toxic levels, acetaminophen and ibuprofen together or in combination appear to have some advantages in terms of antipyretic viability when compared to either medication alone. They appear to have been suffered everywhere as well. A systematic evaluation of these patient-focused outcomes during acetaminophen or ibuprofen treatment may prove helpful in choosing the best course of action in the management of pediatric fever since improvements in quiet comfort or pain are supposedly more significant outcomes than antipyresis in essence. Pilot studies verified the product's usability and kid acceptance, and analytical techniques were validated to guarantee its quality and dependability. This research advances pediatric pharmacotherapy and supports regulatory objectives for age-appropriate drugs by offering a safe, efficient, and kid-friendly substitute for current formulations. To further validate its effectiveness and usefulness in real-world situations, future research should concentrate on increasing manufacturing, carrying out thorough clinical assessments, and investigating its use in larger pediatric populations.

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