SyrSpend® SF PH4 NEO

Safe for those who need it the most

Version 1.0

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personalizing medicine

Summary

1. INTRODUCTION

Globally, it is estimated that around 140 million infants are born every year, and 10.6% are prematurely born, according to the World Health Organization.[1] Preterm birth is defined as infants born alive before 37 completed weeks of gestation and is the leading cause of death in children younger than 5 years worldwide.[2,3] This highlights the importance of the first 1,000 days of life, time from conception through 2 years of age, as a critical period of development in which the foundations for healthy growth are established. Accelerated progress for infant survival and promotion of health and well-being during the first years of life requires knowledge of the specific physiology of this pediatric subgroup.[4]

To better understand and target the patient's needs, the pediatric population has been divided into the following subgroups (neonates, infants, toddlers, children, and adolescents).[5]

Figure 1. Pediatric subgroups.

Human growth consists of ongoing physiologic events that result in development and maturation.[6] Across the pediatric groups, organ size and function rapidly change, as does body composition, cellular function, and metabolic activity.[7] These changes are even more pronounced during the first years of life.[8]

The physiological development and maturity of organs are important factors to consider when determining neonates' treatment options.[9] Neonates include term (37-42 weeks), post-term (≥ 42 weeks), and preterm (< 37 weeks) born infants.[10] Even in term born infants, most organs and their functions are still immature at birth. Regarding excretion, neither hepatic clearance nor glomerular tubular secretion is mature at birth, and achieving adult excretion capacity may take up to 12 months.[6,9] In addition, neonates have reduced gastric emptying, intestinal transit time, and surface area, which have relevance for oral medicine delivery.[11] As oral administration is the main route of drug delivery, the latest addition to the successful line of Fagron's oral vehicle bases is **SyrSpend® SF PH4 NEO**. It provides pharmaceutical stability and dosage consistency with each preparation maximizing dose accuracy. In addition, it is free of sugar, alcohol, colorants, parabens, or any other harmful ingredient, making it suitable and safe for neonates and infants.[12]

This brochure describes high-risk diseases during the neonatal period that require hospital admission, as well as common infant conditions managed at home and their specific therapeutic options, and how **SyrSpend® SF PH4 NEO** can facilitate their personalized treatment.

2. DISEASES AND TREATMENTS

2.1 High-risk diseases

In the Neonatal Intensive Care Unit (NICU), high-risk premature and sometimes term and post-term neonates with severe medical or surgical conditions are treated.

2.1.1 Apnea of Prematurity

Apnea of prematurity is one of the most common diagnoses in the NICU. It is usually defined as a cessation of breathing in a premature infant for 20 seconds or longer or a shorter pause accompanied by bradycardia (<100 bpm), cyanosis, or pallor.[13] The incidence varies but is inversely related to gestational age. For instance, it is around 10% in neonates born within > 34 weeks, around 20%-85% in neonates born between 30–34 weeks, and about 90% in those born < 28 weeks as their lungs did not achieve the alveolar phase yet (Figure 2).[14] The treatment to decrease apneic event frequency and duration include respiratory interventions and pharmacologic therapies, such as methylxanthines. Caffeine is the active pharmaceutical ingredient (API) of choice among all methylxanthines because of its efficacy, tolerability, broad therapeutic index, and longer half-life.[9]

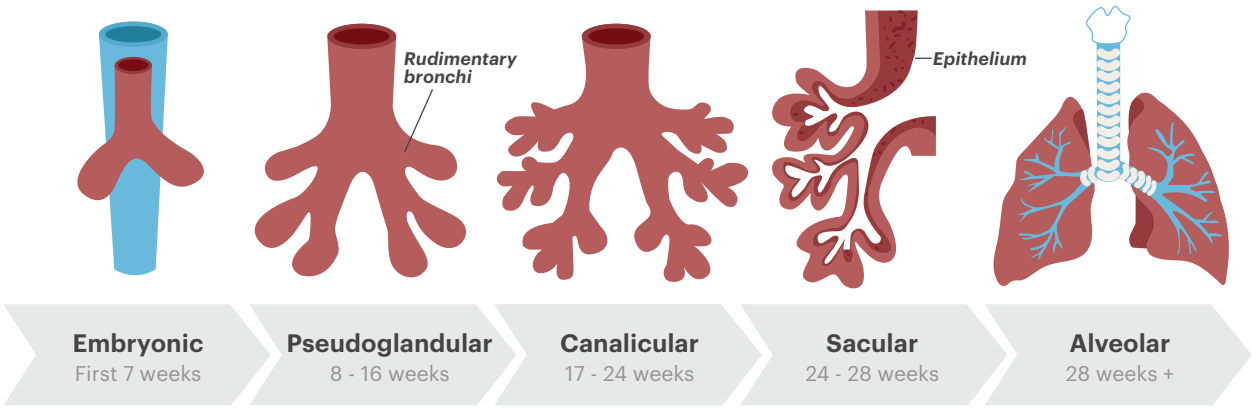

Figure 2. Phases of lung development.

2.1.2 Pain Management

Neonates perceive pain. Pain management is an essential part of medical care known to improve short- and long-term outcomes in the NICU.[15] In addition, fever during the neonatal period requires hospitalization because of the high risk of severe complications. Paracetamol (acetaminophen), one of the most prescribed drugs for pediatric patients, has analgesic and antipyretic effects. It is the only medicine recommended for use as an antipyretic in neonates.[16]

2.1.3 Seizures

Seizures are common in preterm and term neonates affecting 1 to 4 of 1,000 newborns.[17] They may reflect a variety of pre-, peri- or postnatal disorders of the central nervous system. In addition, they can range from self-limited illnesses to prolonged or life-threatening conditions.[18] Seizures are also a common manifestation of infection or metabolic abnormalities. Thus, neonatal seizures' mortality and morbidity rates are attributed mainly to underlying conditions. However, seizures themselves can be harmful, especially for the developing brain.[19] Therapeutic options are still limited; however, phenobarbital remains one of the APIs first-line choices.[9]

2.1.4 Pulmonary Hypertension

Pulmonary hypertension is a chronic pathology characterized by increased pulmonary vascular resistance and blood pressure (Figure 3). Many conditions can lead to pulmonary hypertension, such as pulmonary arterial hypertension, illnesses that emerge from either lung or heart diseases, and chronic

thromboembolism.[20] A prompt and correct diagnosis is essential to effectively treat and improve the child's quality of life. In the presence of shortness of breath, tiredness, or syncopal episodes, pulmonary hypertension should be investigated.[20] In addition, due to the severity of this disease and its complications, it is suggested that treatment is initiated as soon as possible. The European Society of Cardiology recommends sildenafil therapy for pulmonary hypertension in children aged 1 to 17.[21]

In neonates, the condition is characterized by hyperreactivity of the muscle layer in pulmonary arterioles, leading to increased pulmonary vascular resistance and pulmonary blood pressure.[22,23] The incidence varies between 0.43–6.8 per 1000 live-born infants with 10% to 20% mortality. The adverse short-term outcome of this pathology is insufficient pulmonary blood flow and, subsequently, hypoxia.[24,25] Treatment interventions are based on the infant's condition and symptoms. Options include oxygen, intubation/mechanical ventilation, antibiotics, sedation, and blood pressure medications. Although it is still used as an off-label medication, sildenafil is also considered an encouraging treatment option in neonates.[20]

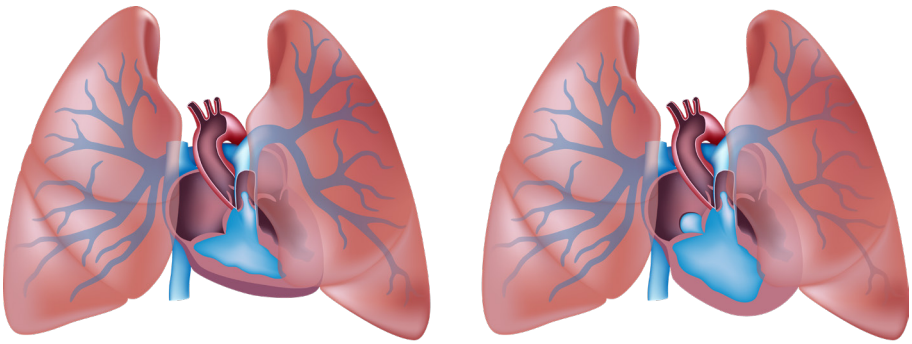

Figure 3. Pulmonary hypertension.

2.1.5 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia is a chronic multifactorial disease affecting over 35% of extremely preterm infants yearly with high morbidity and mortality.[26] Persistent respiratory signs and symptoms, including tachypnoea, tachycardia, increased respiratory effort with chest retractions, nasal flaring and grunting, and frequent desaturations characterize it. The incidence of bronchopulmonary dysplasia has not been reduced, despite the advances in understanding this disease's pathogenesis and the improvement in neonatal clinical care.[27] Several pharmacologic interventions have been studied to prevent or manage bronchopulmonary dysplasia, and corticosteroids, caffeine, bronchodilators, and diuretics, such as furosemide and spironolactone/hydrochlorothiazide remain the most used medications.[28]

2.2 Low-risk diseases

Most of the common health issues among infants during the first 2 years of life are self-limited and can be safely managed at home, with advice and support from a healthcare professional if necessary. Some examples include colds, coughs, fevers, ear infections, vomiting, and diarrhea.

2.2.1 Gastroenteritis

Gastroenteritis in the pediatric population is a prevalent condition, especially in those under 5 years old.[39] It occurs when contaminated water or food is ingested, or via fecal-oral person-to-person contact. The most common pathogen related to gastroenteritis in infants younger than 2 years old is rotavirus; after this age, shigella becomes more prevalent.[40] The clinical manifestations will depend on the pathogen. However, the symptoms usually include vomiting, diarrhea, loss of appetite, nausea, abdominal pain, and mild fever.[41]

Overall, treating and managing children with gastro-

enteritis does not necessarily involve medications.[42] In some specific situations, rehydration, diet selection, and antibiotic therapies are considered. Among the most used antibiotics are ciprofloxacin, and metronidazole.[39,40]

2.2.2 Common cold

Acute upper respiratory tract infection - also called the common cold - is one of the most common diseases in children, especially among those attending daycare.[29] Symptoms are self-limited, often lasting up to 10 days, and include nasal congestion, rhinorrhea, sore throat, cough, and/or low-grade fever (Figure 4).[30] It's usually caused by viruses, such as rhinovirus, and transmitted through contact with the nasal secretions and saliva of infected infants.[31]

Figure 4. Infant with common cold symptoms.

Treatment options are focused on specific symptoms of the common cold in children, but general recommendations include nasal saline irrigation, analgesics, and rest.[29,32] Regarding analgesics, paracetamol has been widely used to reduce fever and fever-related discomfort.[33]

2.2.3 Ear infection

Ear infection or otitis media is one of the most common diseases evaluated by pediatricians. About 50% of all children will have at least one ear infection episode by the age of 2, usually between 3 to 24 months.[34] There are three types of otitis media, acute otitis media, otitis media with effusion, and chronic otitis media with effusion.[35]

Although both bacterial and viral pathogens can cause acute otitis media, it is usually considered to be a bacterial complication of upper respiratory tract viral infection. This upper respiratory tract infection can lead to fluid or mucus accumulation in the eustachian tube. As the eustachian tube is a passage connecting and allowing air to pass between the sinuses and the middle ear space, if it does not work well, fluid can get trapped and infected in the middle ear.[36] Therefore, acute otitis media is characterized by the presence of middle ear effusion and acute onset of signs and symptoms related to middle ear inflammation.[37]

The symptoms can vary depending on the age and developmental status of the child. However, the most specific sign is ear pain. This pain is usually severe and often wakes up the infant during sleep.[36] In addition, acute otitis media is characterized by swelling of the tympanic membrane, and it can be diagnosed based on pneumatic otoscopy (Figure 5).[35]

The treatment includes pain management and antibiotic administration.[34] Antibiotic treatment is recommended for all children from 6 to 24 months of age with confirmed acute otitis media, and oral amoxicillin is one of the first-line treatment options.[38]

Figure 5. Doctor examining infant ear with an otoscope.

3. ROUTES OF ADMINISTRATION

Drugs for neonates admitted to the NICU or infants treated at home can be administered parenterally, orally, rectally, topically, via inhalation, or by any of the usual administration routes.[10] However, the main routes of administration are parenteral and oral.[43] Considering the oral medication, not all options are available and need to be compounded in the hospital pharmacy. Medicines commonly need to be split, crushed, or processed otherwise. All these can lead to inaccurate dosing, potentially threatening patient safety.

In addition, neonates and infants differ in many aspects from the other age groups and require particular considerations regarding pharmacokinetics, formulation composition, and dosage forms.[44] In these age groups, immaturity of enzymes, volume of distribution and clearance may result in differences in pharmacokinetics.[45] Thus, age-appropriate liquid formulations are needed to accurately deliver the right and safe dose considering the specific physiological characteristics of the infants.

3.1 Parenteral delivery: intravenous administration

The neonatal intravenous (IV) administration is a complex process that includes vulnerable patients and IV administration apparatus (Figure 6).[46,47] The IV access in neonates can be obtained via a peripheral cannula or catheter, an umbilical vein, or a peripherally inserted central catheter. However, some remain in situ for several weeks; others may only be patent for hours or days.[46] In addition, all cannulas and catheters require meticulous care to avoid blockage and infection.[47] Therefore, unless fundamental for the care of a critically ill infant, the oral route should replace the parenteral one.

Figure 6. Peripheral IV cannula or catheter.

3.2 Enteral Delivery: oral administration

Drug administration via the oral route to infants can be challenging for both healthcare providers and parents.[48] Although most oral processes are present from birth (rooting, lip, lateral tongue, mouth opening, biting, and emerging chewing behaviors), the main issue of the oral administration is related to the neonate's ability to effectively swallow the medication.[49] The European Medicines Agency guideline suggests that the oral formulation options suitable from birth are powders and granules (administered as a liquid) as well as oral liquid preparations (solution, suspension, and oral drops).[43]

Traditionally, oral liquid formulations have been used in neonates.[50] However, it is important that proper strength medicines are available, ensuring that appropriate doses are accurately administered. In addition, especially in hospitalized patients, enteral tubes might be used to administer oral drugs; thus, liquids are the preferred dosage forms (Figure 7).[51] Palatability considerations are frequently associated with the volume and texture of medicines in addition to taste for infants.[52] However, some taste preferences seem innate (e.g., sweet), and others can even lead to vomiting (e.g., bitter), so also in neonates, palatability should be considered.[53]

Furthermore, the final medicinal product includes active pharmaceutical ingredients and excipients. Excipients are intended to improve the medicines formulation and should be pharmacologically inactive. However, they can cause harm.[54] For this reason, the choice of suitable excipients is one of the key elements of pharmaceutical development for the pediatric age groups.[43] Although the basic considerations regarding the use of a specific excipient might be similar for adult and pediatric formulations, the inclusion of any excipient in pediatric preparations, even those which are normally accepted for use in adults, requires special safety considerations. Neonates may not be able to clear an excipient in the same manner as adults due to their physiological and developmental immaturity.[10,55] Also, the excipient may have a different effect on developing organ systems. For example, excipients known to cause harm to neonates include: propylparaben (hyperbilirubinemia), saccharin sodium (urticaria, photosensitivity), benzyl alcohol (headache, vertigo, nausea, vomiting, diarrhea), benzalkonium chloride (ototoxic), propylene glycol (skin irritation, contact dermatitis), polysor-

bate 80 (thrombocytopenia, renal dysfunction), and ethanol (central nervous system depression).[55] When possible, neonates should receive medicines that are fully adapted to their needs.[56] Therefore, medicines specially designed for children should offer flexible dosing, be easy to swallow, address issues of palatability, and preferably contain safe ingredients only.

Figure 7. Oral liquid formulation administration.

4. SyrSpend® SF PH4 NEO

Dosing flexibility, palatability, and ease of swallowing are crucial determinants of patient acceptability and compliance with treatment, especially in pediatric patients. **SyrSpend® SF PH4 NEO** is an innovative vehicle range for compounding oral liquid dosage forms (Figure 8).

Figure 8. SyrSpend® SF PH4 NEO.

Benefits of SyrSpend® SF PH4 NEO:

- Active Suspending Technology
- Proven compatibility
- Ingredient safety
- Patient comfort

4.1 Active Suspending Technology

SyrSpend® SF PH4 NEO is based on food starch, quick and easy to compound, and provides pharmaceutical stability and dosage consistency with each preparation. In addition, its light texture, safe ingredients, and neutral taste result in a comfortable and easy-to-swallow treatment for infants.

Pharmaceutical suspensions consist of a poorly water-soluble API dispersed in an aqueous solution. The physical stability of suspensions is primarily limited; thus, the suspended API will settle after preparation. Before dosing, the sediment should be resuspended by shaking to yield a suspension with equally distributed drug particles. If improperly resuspended, the uniformity of the dose will be jeopardized, hence the pharmacotherapeutic outcome and safety for the patient.[57]

According to Stoke's law, the physical stability of a suspension can be enhanced by reducing the particle size of the suspended API as well as increasing the viscosity of the vehicle. The rheological properties of the vehicle are an important determinant of product quality.[58] Most favorable for pharmaceutical applications are systems with pseudo-plastic (non-Newtonian) properties. This means that viscosity is relatively high at rest but decreases under the influence of shear forces. Translated for practice, the suspension undergoes thinning during agitation, resembling water, and thickens when left undisturbed, approaching the consistency of honey.[57,58]

Starch is the key component responsible for **SyrSpend® SF PH4 NEO**'s distinctive rheological profile, setting it apart from other oral suspending vehicles. Unlike the majority of such vehicles, which rely on methylcellulose, **SyrSpend® SF PH4 NEO**'s utilization of starch guarantees both precise dosing and consistent performance throughout treatment (Figure 9).

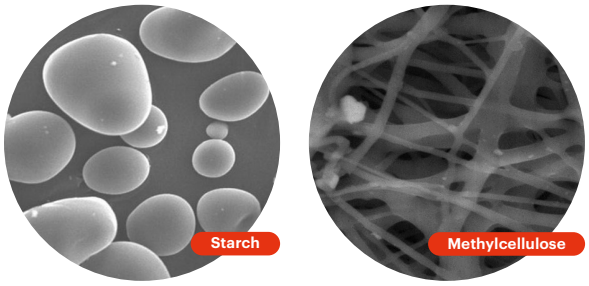

Figure 9. Comparison between starch and methylcellulose bases.

This unique formulation exhibits thixotropic properties, preventing the formation of irreversible sediment caking by increasing viscosity when left undisturbed. Moreover, its pseudoplasticity allows for effortless homogenization by reducing viscosity when shaken, as illustrated in Figure 10. These patented properties, when combined, form what is known as **SyrSpend® SF**'s Active Suspending Technology.

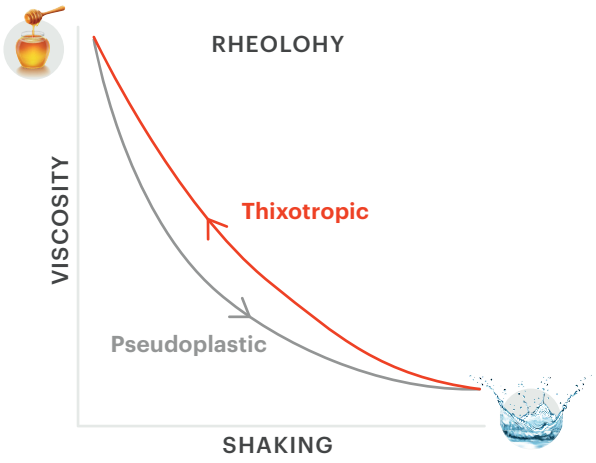

Figure 10. SyrSpend® SF PH4 NEO's unique rheological properties (Active Suspending Technology).

4.2 Enteral Delivery: oral administration

A wide range of APIs has been studied in **SyrSpend® SF** in the last years. Studies have been executed in GLP and/or ISO 17025 laboratories, under the supervision of Fagron. With few exceptions, the studies have been performed using stability-indicating high-performance liquid chromatography (HPLC) methods derived using United States Pharmacopeia (USP), with slight modifications if needed.

The beyond-use date (BUD) is the date after which a compounded preparation shall not be used and is determined from when the preparation is compounded.[59] **SyrSpend® SF** has a vast list of studies performed with different APIs. Most stability studies ran up to 90 days or until the study failed to meet the requirement at the end of the shelf-life (± 10% of the initial concentration). The studies were generally conducted at both controlled refrigerated and room temperature. To date, **SyrSpend® SF** has shown to be capable of delivering the right dose in more than 130 different APIs studied. The results from these studies have been published in peer-reviewed journals.[12,33,61-63,74-78] In addition to the HPLC compatibility studies, the rheological properties of **SyrSpend® SF** were assessed and found superior, when compared to other suspending vehicles.[64]

4.3 Safety

Neonates and infants are still treated with medicines not designed, developed, or evaluated for use in these age groups.[65] As a result, they urgently need tailored medicine development that considers low and flexible dosing to maintain dose accuracy.[66]

As a vulnerable patient group, neonates necessitate exclusively safe ingredients. The excipients in **SyrSpend® SF PH4 NEO** adhere to the latest guidelines from the World Health Organization, European Medicines Agency, and United States Food and Drug Administration, minimizing toxicological effects and allergic reactions.[67,68] The absence of lactose combined with low osmolality (<50 mOsmol/kg) reduces gastrointestinal side effects. In addition, **SyrSpend® SF PH4 NEO** is free from:

One of the purposes of a suspending vehicle is to improve the suspending properties and hence to improve the Content Uniformity of the compound. For **SyrSpend® SF**, we have determined the Content Uniformity for a total of 6,414 samples that were analyzed by high-performance liquid chromatography (HPLC). In all cases, the results were well within the criteria for Content Uniformity as defined by the different pharmacopeias.[12] Therefore, these results highlight that all samples prepared with **SyrSpend® SF** deliver the correct dose, independent of the API used, storage conditions, and time of analysis. This is especially important since many medicines have a narrow therapeutic window and even small deviations in the content uniformity could significantly affect patient safety (Figure 11).[69,70]

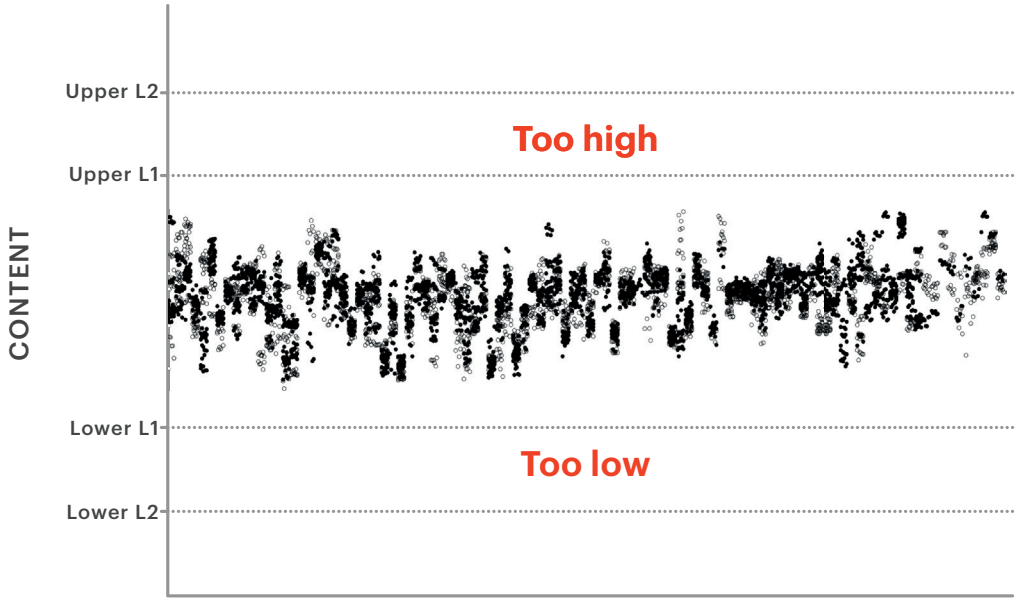

Figure 11. SyrSpend® SF PH4 NEO's content uniformity.

4.4 Patient comfort

Pharmaceutical suspensions are biphasic preparations consisting of solid particles dispersed throughout a liquid phase. Important target groups for oral liquid forms are children and those unable to swallow solid medicine. In case of swallowing difficulties, capsules may be opened, and the content mixed with food or liquid.[71] However, this may have a negative influence on the taste or interact with the prescribed medication.[72] For more than 50 different medicines, for example, drug interactions with calcium have been described.[73]

As taste and ease of swallowing are key factors for pediatric patients' compliance, **SyrSpend® SF PH4 NEO** was designed to target these issues. Its light texture and no medicinal aftertaste as well as viscosity reduction upon shaking makes it easily pourable and swallowable, enhancing patient comfort and adherence.

4.5 Compounding with SyrSpend® SF PH4 NEO

Compounding with **SyrSpend® SF PH4 NEO** allows for tailor-made compounds for infants. **SyrSpend® SF** has proven physicochemical compatibility with a wide range of APIs. The compounding steps are straightforward and can be done in compounding pharmacies, hospital pharmacies, or an industrial environment.

4.5.1 Compounding steps

SyrSpend® SF PH4 NEO can be compounded using various methods:

Using mortar and pestle

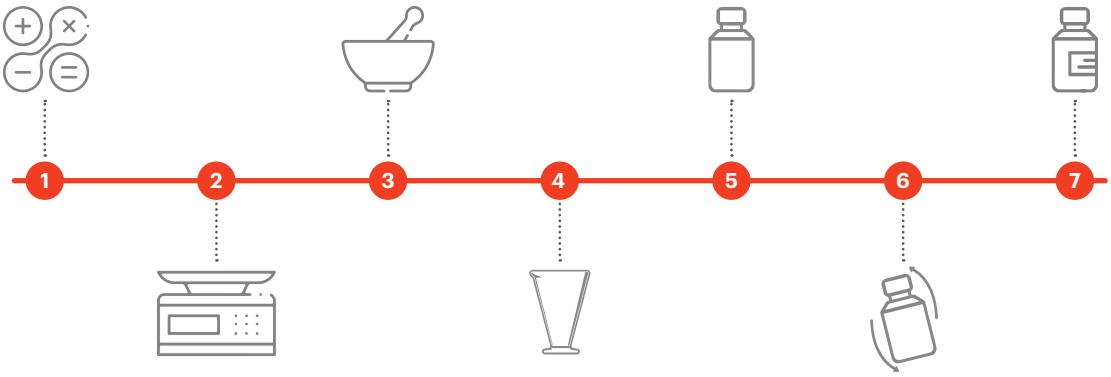

Figure 12. Using mortar and pestle.

1. Calculate the required quantity of each ingredient for the total amount to be prepared.

2. Weigh and/or measure each ingredient accurately.

3. Triturate and mix all ingredients geometrically, passing through a sifter if needed.

4. Geometrically add purified water to reach 70% of the final volume.

5. Transfer the product into an amber bottle and add purified water to the required amount.

6. Shake the product well.

7. Label the bottle, including the instruction "Shake before use".

Direct compounding in a dispensing bottle

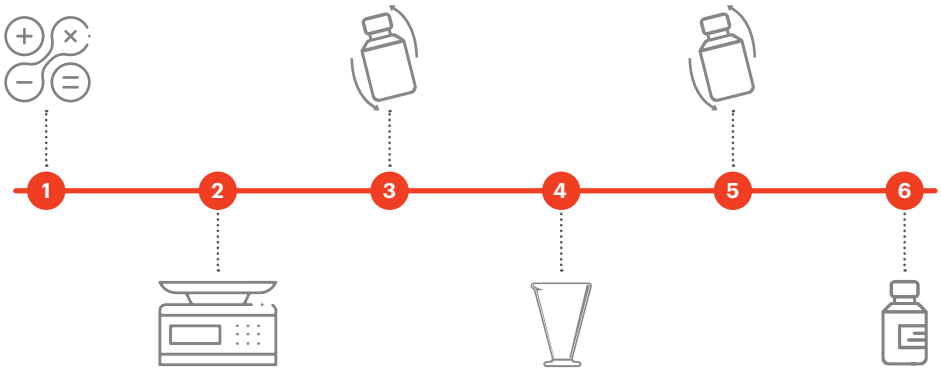

Figure 13. Direct compounding in a dispensing bottle.

1. Calculate the required quantity of each ingredient for the total amount to be prepared.

2. Weigh and/or measure each ingredient accurately. Add all solid ingredients to the bottle, passing them through a sifter if needed.

3. Homogenize the ingredients in the bottle by shaking well.

4. Add purified water to reach 70% of the final volume and shake well.

5. Add purified water to reach the required amount and shake well.

6. Label the bottle, including the instruction "Shake well before use".

Using the FagronLab™ Mixing PRO

1. Consult the FagronLab™ Mixing PRO manual for operational details.

2. Calculate and weigh/measure each ingredient for the total volume of the preparation. The API should be weighed directly into the FagronLab™ jar. Please use the FagronLab™ jars indicated for the compounding of suspensions. If not available, double the jar size compared to the total suspension volume to prevent leakage.

3. Add the required amount of **SyrSpend® SF PH4 NEO** powder to the FagronLab™ jar containing the API.

4. Add approximately 90% of the required volume with purified water.

5. Select on the equipment display the appropriate work program for each suspension, depending on the concentration of API: select “Suspension <2%” mode for formulations containing less than 2% (w/v) of API or “Suspension >2%” mode for those containing 2% (w/v) or more of API (Figure 14).

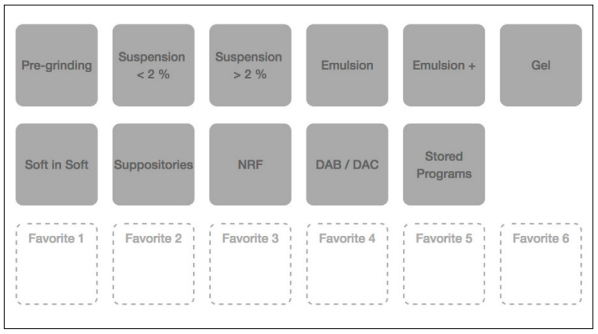

Figure 14. FagronLab™ Mixing PRO display.

6. Attach the mixing blade to the FagronLab™ jar, and then follow the instructions on the display to attach the FagronLab™ jar to the FagronLab™ Mixing PRO device (Figure 15).

Figure 15. Display intructions for the attachment of the FagronLab™ jar.

7. When the mixing program is finished, remove the FagronLab™ jar from the device and transfer the suspension into a graduated conical flask.

8. Bring the preparation to the required final volume with purified water and mix it with a glass rod.

9. Transfer to the final package and label accordingly, including the instruction "shake well before use".

Using the FagronLab WetMill Compact

1. Consult the FagronLab WetMill Compact manual for operational details on the device.

2. Calculate the required quantity of each ingredient for the total amount to be prepared.

3. Weigh and/or measure each ingredient accurately.

4. Add purified water to reach 70% of the final volume. Add less water if a significant volume of tablets, capsules, or powders are added. After adding the API, the total volume should not exceed 90% of the required volume.

5. Add the required amount of tablets, whole capsules, or powder, according to the formulation (Figure 16).

Figure 16. Compounding using the FagronLab WetMill Compact.

6. Ensure all caps are securely tightened on all bottles before inserting them into the device.

7. If an uneven number of formulations are being compounded, ensure that a counterweight bottle of equal weight (use water as a counterweight) is placed in the opposite bottle holder of the compounding bottle. If two formulations are being compounded and have a weight difference of more than 10 g, counterweight bottles of equal weights must be placed on the remaining holders.

8. Install all bottle holder caps securely and select the desired cycle for the operation. The advised cycle can be found in the FagronLab WetMill Compact manual.

9. Once the device has completed the cycle and has come to a complete stop, visually check if all particles are adequately ground and even in size.

10. Add the required amount of **SyrSpend® SF PH4 NEO** for the final volume, close the cap, and homogenize the ingredients in the bottle by shaking well.

11. Add purified water to reach the required amount and shake well.

12. Label the bottle, including the instruction “Shake well before use”.

Using semi-Industrial compounding

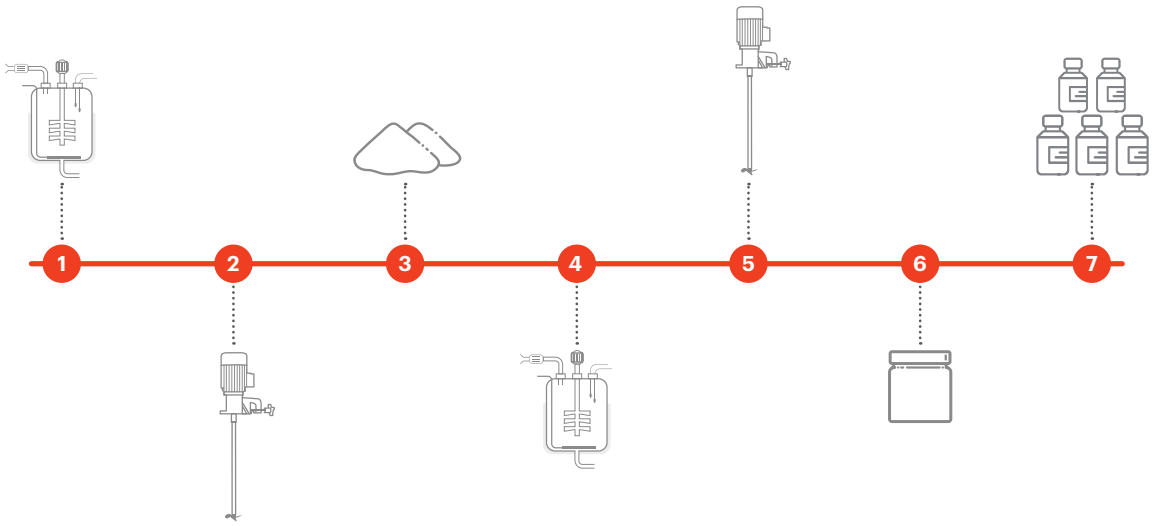

Figure 17. Using semi-Industrial compounding.

Equipment

Mixing vessel, mixer, propeller blade, and balance

Compounding steps

1. Add the required amount of purified water to a suitable mixing vessel.

2. Start the mixer with a propeller blade at 300-500 rpm.

3. Add the intended API and mix for 10-15 minutes or until all clumps are dispersed.

4. Slowly add the required **SyrSpend® SF PH4 NEO** while increasing the speed to maintain a vortex. Observe the complete turnover of this material from side to side and from top to bottom of the mixing vessel. Maintain a strong vortex.

5. Stir for 45-60 minutes observing a strong vortex. Increase the speed if required. The preparation should be free of agglomerations and smooth in appearance. If not, mix for an additional 15-20 minutes and re-evaluate. Repeat if necessary.

6. Check the suspension for homogeneity: no visible agglomerations and smooth appearance.

7. Fill into prescription bottles with continuous stirring.

Remarks

1. Record all values.

2. When adding the dry materials, calculate the displacement value.

3. The total stir time is 45-80 minutes maximum. This could be adjusted accordingly after the validation of the mixing method.

4. Never use a high-shear mixer to mix the suspension: this damages the **SyrSpend® SF**.

5. Fill immediately into finished prescription bottles with continuous mixing to prevent sedimentation of particles in suspension.

6. Label and dispense, indicating to “shake well before use”.

4.6 SyrSpend® SF PH4 NEO example formulations

Formulation	Beyond-use date (BUD)
Caffeine in **SyrSpend® SF PH4 NEO** (10 mg/mL)	90 days[62]
Acetaminophen (paracetamol) in **SyrSpend® SF PH4 NEO** (50 mg/mL)	90 days[33]
Sildenafil citrate in **SyrSpend® SF PH4 NEO** (2.5 mg/mL)	92 days[74]
Phenobarbital in **SyrSpend® SF PH4 NEO** (9-15 mg/mL)	90 days[63,75]
Spironolactone/hydrochlorothiazide in **SyrSpend® SF PH4 NEO** (5-5 mg/mL)	90 days[76]
Amoxicillin Trihydrate in **SyrSpend® SF PH4 NEO** (50 mg/mL)	30 days[77]
Ciprofloxacin Hydrochloride in **SyrSpend® SF PH4 NEO** (50 mg/mL)	60 days[76]
Metronidazole benzoate in **SyrSpend® SF PH4 NEO** (80 mg/mL)	90 days[78]

For a complete list of all APIs studied in **SyrSpend® SF**, and their physical-chemical stability, please refer to our Compatibility Table and or the latest Formulary.

References

1. World Health Organization. Preterm birth. https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed June 14, 2023.
2. Cao G, Liu J, Liu M. Global, Regional, and National Incidence and Mortality of Neonatal Preterm Birth, 1990-2019. JAMA Pediatr. 2022;176(8):787-796. doi:10.1001/jamapediatrics.2022.1622
3. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health. 2019;7(1):e37-e46. doi:10.1016/S2214-109X(18)30451-0
4. World Health Organization. WHO Recommendations for Care of the Preterm or Low-Birth-Weight Infant. https://www.who.int/publications/i/item/9789240058262. Accessed June 16, 2023.
5. European Medicines Agency. Ich e11(r1) Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population. https://www.ema.europa.eu/documents/scientific-guideline/iche11r1- guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1_en.pdf. Accessed June 16, 2023.
6. Allegaert K, van de Velde M, van den Anker J. Neonatal clinical pharmacology. Paediatr Anaesth. 2014;24(1):30-38. doi:10.1111/pan.12176
7. Allegaert K, Verbesselt R, Naulaers G, et al. DEVELOPMENTAL PHARMACOLOGY: NEONATES ARE NOT JUST SMALL ADULTS.... Acta Clin Belg. 2008;63(1):16-24. doi:10.1179/acb.2008.003
8. Silva CC v, el Marroun H, Sammallahti S, et al. Patterns of Fetal and Infant Growth and Brain Morphology at Age 10 Years. JAMA Netw Open. 2021;4(12):e2138214. doi:10.1001/jamanetworkopen.2021.38214
9. Allegaert K, Simons S, van den Anker J. Research on medication use in the neonatal intensive care unit. Expert Rev Clin Pharmacol. 2019;12(4):343-353. doi:10.1080/17512433.2019.1580569
10. O'Brien F, Clapham D, Krysiak K, et al. Making medicines baby size: The challenges in bridging the formulation gap in neonatal medicine. Int J Mol Sci. 2019;20(11). doi:10.3390/ijms20112688
11. Coppini R, Simons SHP, Mugelli A, Allegaert K. Clinical research in neonates and infants: Challenges and perspectives. Pharmacol Res. 2016;108:80-87. doi:10.1016/j.phrs.2016.04.025
12. Dijkers E, Polonini H, Ferreira A de O. Always the Right Dose? Content Uniformity in Over 100 Different Formulations Tested. Int J Pharm Compd. 2020;24(5):408-412
13. Eichenwald EC. Apnea of Prematurity. Pediatrics. 2016;137(1). doi:10.1542/peds.2015-3757
14. Long JY, Guo HL, He X, et al. Caffeine for the Pharmacological Treatment of Apnea of Prematurity in the NICU: Dose Selection Conundrum, Therapeutic Drug Monitoring and Genetic Factors. Front Pharmacol. 2021;12. doi:10.3389/fphar.2021.681842
15. Allegaert K. A Critical Review on the Relevance of Paracetamol for Procedural Pain Management in Neonates. Front Pediatr. 2020;8. doi:10.3389/fped.2020.00089
16. Cuzzolin L, Antonucci R, Fanos V. Paracetamol (acetaminophen) efficacy and safety in the newborn. Curr Drug Metab. 2013;14(2):178-185
17. Sharpe C, Reiner GE, Davis SL, et al. Levetiracetam Versus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial.
18. World Health Organization. Guidelines on Neonatal Seizures. WHO 2011. https://apps. who.int/iris/handle/10665/77756. Accessed June 12, 2023.
19. Spagnoli C, Seri S, Pavlidis E, Mazzotta S, Pelosi A, Pisani F. Phenobarbital for Neonatal Seizures: Response Rate and Predictors of Refractoriness. Neuropediatrics. 2016;47(5):318-326. doi:10.1055/s-0036-1586214
20. Simonca L, Tulloh R. Sildenafil in infants and children. Children. 2017;4(7). doi:10.3390/children4070060
21. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016;37(1):67-119. doi:10.1093/eurheartj/ehv317
22. al Omar S, Salama H, al Hail M, et al. Effect of early adjunctive use of oral sildenafil and inhaled nitric oxide on the outcome of pulmonary hypertension in newborn infants. A feasibility study. J Neonatal Perinatal Med. 2016;9(3):251-259. doi:10.3233/NPM-16161
23. Chakkarapani AA, Roehr CC, Hooper SB, te Pas AB, Gupta S. Transitional circulation and hemodynamic monitoring in newborn infants. Pediatr Res. Published online 2023. doi:10.1038/s41390-022-02427-8
24. Li Z, Lv X, Liu Q, Dang D, Wu H. Update on the use of sildenafil in neonatal pulmonary hypertension: a narrative review of the history, current administration, and future directions. Transl Pediatr. 2021;10(4):998-1007. doi:10.21037/tp-20-277
25. Lavie-Nevo K, Harris KC, Ting JY. Use of sildenafil in an infant with persistent pulmonary hypertension secondary to lung and renal hypoplasia - A case report. BMC Pediatr. 2019;19(1). doi:10.1186/s12887-019-1801-3
26. Schmidt AR, Ramamoorthy C. Bronchopulmonary dysplasia. Pediatric Anesthesia. 2022;32(2):174-180. doi:10.1111/pan.14365
27. Pasha AB, Chen XQ, Zhou G. Bronchopulmonary dysplasia: Pathogenesis and treatment (Review). Exp Ther Med. Published online September 19, 2018. doi:10.3892/etm.2018.6780
28. Mandell EW, Kratimenos P, Abman SH, Steinhorn RH. Drugs for the Prevention and Treatment of Bronchopulmonary Dysplasia. Clin Perinatol. 2019;46(2):291-310. doi:10.1016/j.clp.2019.02.011
29. DeGeorge KC, Ring DJ, Dalrymple SN. Treatment of the Common Cold. Am Fam Physician. 2019;100(5):281-289
30. Ebell MH, Lundgren J, Youngpairoj S. How long does a cough last? Comparing patients' expectations with data from a systematic review of the literature. Ann Fam Med. 2013;11(1):5-13. doi:10.1370/afm.1430
31. Hay AD, Anderson E, Ingle S, Beck C, Hollingworth W. Respiratory tract infections in children in the community: Prospective online inception cohort study. Ann Fam Med. 2019;17(1):14-22. doi:10.1370/afm.2327
32. King D, Mitchell B, Williams CP, Spurling GKP. Saline nasal irrigation for acute upper respiratory tract infections. Cochrane Database of Systematic Reviews. 2015;2015(4). doi:10.1002/14651858.CD006821.pub3
33. Polonini HC, Loures S, de Araujo EP, Brandão MAF, Ferreira AO. Stability of Allopurinol, Amitriptyline Hydrochloride, Carbamazepine, Domperidone, Isoniazid, Ketoconazole, Lisinopril, Naproxen, Paracetamol (Acetaminophen), and

Sertraline Hydrochloride in SyrSpend SF PH4 Oral Suspensions. Int J Pharm Compd. 2016;20(5):426-434

34. Paul CR, Moreno MA. Acute Otitis Media. JAMA Pediatr. 2020;174(3):308. doi:10.1001/jamapediatrics.2019.5664
35. Prasad A, Hasan SMA, Gartia MR. Optical identification of middle ear infection. Molecules. 2020;25(9). doi:10.3390/molecules25092239
36. Venekamp RP, Damoiseaux RAMJ, Schilder AGM. Clinical Evidence Handbook Acute Otitis Media in Children. Vol 95.; 2017. www.aafp.org/afp. Accessed June 12, 2023.
37. Oh JH, Kim WJ. Interaction Between Allergy and Middle Ear Infection. Curr Allergy Asthma Rep. 2016;16(9). doi:10.1007/s11882-016-0646-1
38. Marchisio P, Galli L, Bortone B, et al. Updated Guidelines for the Management of Acute Otitis Media in Children by the Italian Society of Pediatrics. Pediatric Infectious Disease Journal. 2019;38(12S):S10-S21. doi:10.1097/INF.0000000000002452
39. Guarino A, Aguilar J, Berkley J, et al. Acute Gastroenteritis in Children of the World: What Needs to Be Done? J Pediatr Gastroenterol Nutr. 2020;70(5):694-701. doi:10.1097/MPG.0000000000002669
40. Hartman S, Brown E, Loomis E, Russell HA. Gastroenteritis in Children. Am Fam Physician. 2019;99(3):159-165
41. Elliott EJ. Acute gastroenteritis in children. BMJ. 2007;334(7583):35-40. doi:10.1136/bmj.39036.406169.80
42. Schnadower D, O'Connell KJ, VanBuren JM, et al. Association Between Diarrhea Duration and Severity and Probiotic Efficacy in Children With Acute Gastroenteritis. American Journal of Gastroenterology. 2021;116(7):1523-1532. doi:10.14309/ajg.0000000000001295
43. Ema. Committee for Medicinal Products for Human Use (CHMP) Paediatric Committee (PDCO) Guideline on Pharmaceutical Development of Medicines for Paediatric Use Guideline on Pharmaceutical Development of Medicines for Paediatric Use.; 2013. www.ema.europa.eu.
44. Liu F, Ranmal S, Batchelor HK, et al. Patient-Centered Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations. Drugs. 2014;74(16):1871-1889. doi:10.1007/s40265-014-0297-2
45. Hanning SM, Lopez FL, Wong ICK, Ernest TB, Tuleu C, Orlu Gul M. Patient centric formulations for paediatrics and geriatrics: Similarities and differences. Int J Pharm. 2016;512(2):355-359. doi:10.1016/j.ijpharm.2016.03.017
46. Concepcion NDP, Laya BF, Lee EY. Current updates in catheters, tubes and drains in the pediatric chest: A practical evaluation approach. Eur J Radiol. 2017;95:409-417. doi:10.1016/j.ejrad.2016.06.015
47. Farrelly JS, Stitelman DH. Complications in pediatric enteral and vascular access. Semin Pediatr Surg. 2016;25(6):371-379. doi:10.1053/j.sempedsurg.2016.10.006
48. Linakis MW, Roberts JK, Lala AC, et al. Challenges Associated with Route of Administration in Neonatal Drug Delivery. Clin Pharmacokinet. 2016;55(2):185-196. doi:10.1007/s40262-015-0313-z
49. Somani AA, Thelen K, Zheng S, et al. Evaluation of changes in oral drug absorption in preterm and term neonates for Biopharmaceutics Classification System (BCS) class I and II compounds. Br J Clin Pharmacol. 2016;81(1):137-147. doi:10.1111/bcp.12752
50. Ranmal SR, O'Brien F, Lopez F, et al. Methodologies for assessing the acceptability of oral formulations among children and older adults: a systematic review. Drug Discov Today. 2018;23(4):830-847. doi:10.1016/j.drudis.2018.01.038
51. Walsh J, Ranmal SR, Ernest TB, Liu F. Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. Int J Pharm. 2018;536(2):547-562. doi:10.1016/j.ijpharm.2017.07.017
52. Mura Paroche M, Caton SJ, Vereijken CMJL, Weenen H, Houston-Price C. How Infants and Young Children Learn About Food: A Systematic Review. Front Psychol. 2017;8. doi:10.3389/fpsyg.2017.01046
53. Rouse C, Mistry P, Rayner O, et al. A mixed methods study of the administration of flucloxacillin oral liquid; identifying strategies to overcome administration issues of medicines with poor palatability. International Journal of Pharmacy Practice. 2017;25(5):326-334. doi:10.1111/ijpp.12308
54. Turner M, Shah U. Why are Excipients Important to Neonates? Curr Pharm Des. 2015;21(39):5680-5687. doi:10.2174/1381612821666150901110341
55. Turner MA, Duncan JC, Shah U, et al. Risk assessment of neonatal excipient exposure: Lessons from food safety and other areas. Adv Drug Deliv Rev. 2014;73:89-101. doi:10.1016/j.addr.2013.11.003
56. Linakis MW, Roberts JK, Lala AC, et al. Challenges Associated with Route of Administration in Neonatal Drug Delivery. Clin Pharmacokinet. 2016;55(2):185-196. doi:10.1007/s40262-015-0313-z
57. Hinrichs W, Dreijer-van der Glas S. Practical Pharmaceutics : An International Guideline for the Preparation, Care and Use of Medicinal Products.; 2015
58. Sinko P. Rheology. In: Martin's Physical Pharmacy and Pharmaceutical Sciences. 7th ed. Philadelphia, PA: Wolters Kluwer; 2017
59. US Pharmacopeia. Pharmaceutical Compounding—Nonsterile Preparations <795>.; 2023
60. United States Pharmacopeia (2022). General Chapter, 795 Pharmaceutical Compounding—Nonsterile Preparations. USP-NF. Rockville, MD: United States Pharmacopeia. doi:10.31003/USPNF_M99595_05_01
61. Polonini HC, Loures S, de Araujo EP, Brandão MAF, Ferreira AO. Stability of Allopurinol, Amitriptyline Hydrochloride, Carbamazepine, Domperidone, Isoniazid, Ketoconazole, Lisinopril, Naproxen, Paracetamol (Acetaminophen), and Sertraline Hydrochloride in SyrSpend SF PH4 Oral Suspensions. Int J Pharm Compd. 2016;20(5):426-434
62. Polonini HC, Silva SL, de Almeida TR, Brandão MAF, Ferreira AO. Compatibility of caffeine, carvedilol, clomipramine hydrochloride, folic acid, hydrochlorothiazide, loperamide hydrochloride, methotrexate, nadolol, naltrexone hydrochloride and pentoxifylline in SyrSpend SF PH4 oral suspensions. European Journal of Hospital Pharmacy. 2016;23(6):352-358. doi:10.1136/ejhpharm-2016-000903
63. Polonini H, da Silva SL, Brandão MAF, Bauters T, De Moerloose B, Ferreira A de O. Compatibility of Baclofen, Carvedilol, Hydrochlorothiazide, Mercaptopurine, Methadone Hydrochloride, Oseltamivir Phosphate, Phenobarbital, Propranolol Hydrochloride, Pyrazinamide, Sotalol Hydrochloride, Spironolactone, Tacrolimus Monohydrate, Ursodeoxycholic Acid, and Vancomycin Hydrochloride Oral Suspensions Compounded with SyrSpend SF pH4. Int J Pharm Compd. 2018;22(6):516-526
64. Visser JC, Ten Seldam IEJ, van der Linden IJ, et al. Comparison of Rheological and Sedimentation Behavior of Commercially Available Suspending Vehicles for Oral Pharmaceutical Preparations. Int J Pharm Compd. 2018;22(3):247-251

65. Turner MA. Neonatal drug development. Early Hum Dev. 2011;87(11):763-768. doi:10.1016/j.earlhumdev.2011.08.014

66. Allegaert K, Cosaert K, van den Anker J. Neonatal Formulations: The Need for a Tailored, Knowledge Driven Approach. Curr Pharm Des. 2015;21(39):5674-5679. doi:10.2174/1381612821666150901110207

67. Annex 5 Development of Paediatric Medicines: Points to Consider in Formulation.

68. Souza A, Santos D, Fonseca S, et al. Toxic excipients in medications for neonates in Brazil. Eur J Pediatr. 2014;173(7):935-945. doi:10.1007/s00431-014-2272-z

69. Parrish RH. Current Trends and Emerging Priorities in Compounded Preparations for Children. Int J Pharm Compd. 2018;22(5):358-366

70. Engels MJ, Ciarkowski SL, Rood J, et al. Standardization of compounded oral liquids for pediatric patients in Michigan. American Journal of Health-System Pharmacy. 2016;73(13):981-990. doi:10.2146/150471

71. Dijkers E, Nanhekhan V, Thorissen A, Polonini H. Suspensions as a Valuable Alternative to Extemporaneously Compounded Capsules. Int J Pharm Compd. 2017;21(2):171-175

72. Lein A, Ng S. Oral Liquids. Practical Pharmaceutics. An International Guideline for the Preparation, Care and Use of Medicinal Products. (Bouwman- Boer Y, Fenton-May V, Le Brun P, eds.). Switzerland: Springer International Publishing; 2015

73. IBM Corporation; 2023. Available from: www.micromedexsolutions.com. Accessed June 16, 2023.

74. Geiger ChM, Sorenson B, Whaley P. Stability Of Sildenafil Citrate Oral Suspension With Syrspend® Sf. Eur Pharm J. Published online 2018:31-35

75. Geiger CM, Sorenson B, Whaley P. Stability Assessment of 10 Active Pharmaceutical Ingredients Compounded in SyrSpend SF. Int J Pharm Compd. 2015;19(5):420-427

76. Uriel M, Gómez-Rincón C, Marro D. Stability of regularly prescribed oral liquids formulated with SyrSpend® SF. Pharmazie. 2018;73(4):196-201. doi:10.1691/ph.2018.7008

77. Mansourian M, Dijkers E, Silva CC V., Polonini HC. Compatibility of Commonly Used Active Pharmaceutical Ingredients in a Ready-to-Use Oral Suspending Vehicle. Pharmaceutics. 2023;15(10):2388. doi:10.3390/pharmaceutics15102388

78. Vu NT, Aloumanis V, Ben M, et al. Stability of Metronidazole Benzoate in SyrSpend SF One-Step Suspension System. Int J Pharm Compd. 2008;12(6):558-564

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