SyrSpend® SF

Age-appropriate personalized formulations for pediatric care

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personalizing medicine

Summary

1. Introduction

Designing oral pharmaceutical dosage forms that prioritize patients and their needs poses a significant challenge, especially when such medicinal products need to be tailored for the pediatric population.[1] Pediatric patients have diverse needs and characteristics.[2] The physical, metabolic, and psychological growth changes from birth to adulthood demonstrate that children cannot be treated as small adults nor as a homogeneous group.[3] Consequently, clinical trials in adults may not provide reliable predictions for pediatric responses. Additionally, pediatric medication presents unique pharmaceutical challenges that may not be seen to the same extent in adult formulations.[4] Developing age-appropriate formulations for pediatric patients, therefore, requires careful consideration of multiple factors, including patient safety and acceptability.[5,6]

Oral liquid preparations are among the few dosage forms considered suitable from birth. They offer dose flexibility and ease of swallowing, which are essential for children. Palatability also plays a key role in a medication's acceptability, defined as the patient and caregiver's ability and willingness to use a medicinal product (Figure 1).[7] Acceptability often faces challenges due to the unpleasant taste of many medications, particularly the liquid ones. The taste can come from the two components of a medication: the active pharmaceutical ingredients (APIs) and the excipients (substances that which, while not therapeutic, enhance the formulation by binding active ingredients, improving taste, aiding absorption, or ensuring stability).[8,9]

Figure 1. School-age girl refusing to take medication.

Furthermore, selecting appropriate excipients in pediatric formulations is critical because excipients used in adult medication may not be suitable for children.[10] During childhood, significant developmental changes occur, including the maturation of biological pathways and organ systems, which can alter how an excipient is metabolized. Notable concerns include the potential toxicity of various alcohols, such as propylene glycol, in children and the possible endocrine-disrupting effects of the preservative propylparaben.[11,12]

Commercially available medication may not be available in the right dose or pharmaceutical form or be palatable enough. Therefore, Fagron has developed a line of oral vehicles for compounding oral liquid dosage forms (Figure 2). Compounding of medication is the creation of custom formulations to meet individual patient needs, addressing gaps in commercially available drugs. This requires a trained (hospital) pharmacist, to mix the API or industrial medication in a vehicle.

SyrSpend® SF is a line of vehicles to enhance the suitability of oral formulations in pediatric care. It was designed following leading (pediatric) guidelines to exclude harmful ingredients and protect young patients. Its formulation is devoid of sugar, alcohol, colorants, parabens, and other risky excipients, reducing toxicological threats and allergic reactions.

This brochure details prevalent pediatric diseases and demonstrates how **SyrSpend® SF** facilitates tailored treatments. It covers the **SyrSpend® SF** range, suitable for various patient groups and APIs, including preservative-free options. Further, we will guide on selecting the appropriate **SyrSpend® SF** product based on patient group and the active substance's chemical properties.

Figure 2. SyrSpend® SF oral vehicle line.

2. SyrSpend® SF

The innovative vehicle line is designed for compounding oral liquid dosage forms, combining dosing flexibility, palatability, and ease of swallowing. All **SyrSpend® SF** products are crafted for taste-masking, providing a pleasant, sweet taste and are available in a neutral flavor, ensuring easy acceptance by patients.

Compatible with a wide range of APIs, **SyrSpend® SF** allows you to choose the most suitable product for your compounding needs, with both acid and alkaline options available, enhancing its versatility and effectiveness in patient care.

The benefits of the SyrSpend® SF vehicles include:

Active Suspending Technology

Safe ingredients

Proven compatibility

High efficiency

Patient comfort

Exceptional Quality

2.1 Active Suspending Technology

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

SyrSpend® SF is expertly designed to address the inherent challenges in pharmaceutical suspensions, which often consist of poorly water-soluble APIs dispersed in an aqueous solution. These suspensions typically face physical stability issues, leading to the settlement of the API after preparation. **SyrSpend® SF**'s superior and patented suspending properties ensure the consistent and accurate dosing necessary for effective treatment.[13] It employs **SyrSpend® SF**'s *Active Suspending Technology* characterized by pseudoplasticity and thixotropy. These rheological properties are crucial in maintaining product quality, with the viscosity being high at rest (like honey) but decreasing under shear forces (like water) (Figure 3).[13,14] These properties enable a suspension with **SyrSpend® SF** to maintain the API suspended at rest and ensure easy homogenization with a simple shake. By facilitating rapid redispersion of APIs with minimal effort and preventing the formation of an irreversible sediment cake, **SyrSpend® SF** ensures that the APIs remain safely suspended and the dosage remains uniform, thus safeguarding the pharmacotherapeutic outcome and the safety of the patient.

This unique combination of properties makes **SyrSpend® SF** an optimal choice for preserving the integrity and efficacy of compounded oral liquid dosages.

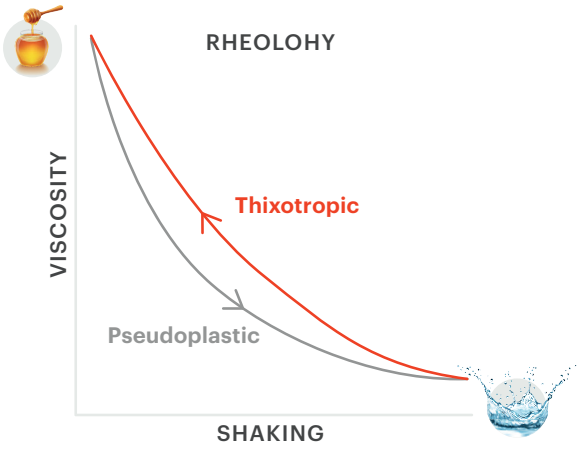


Figure 3. SyrSpend® SF's Active Suspending Technology imparts unique rheological properties: it thickens to a honey-like consistency when undisturbed, preventing API sedimentation, and becomes as fluid as water when shaken, facilitating easy re-homogenization of the suspension.

2.2 Ingredient safety

Many patients, including children, are often treated with medicines not specifically designed, developed, or evaluated for these age groups.[15] This underscores the urgent need for tailored medicine development that considers low and flexible dosing to ensure dose accuracy.[16]

Vulnerable patient groups, including pediatric, chronic patients, and those fed via a (naso)gastric tube, require medicines with exclusively safe ingredients. **SyrSpend® SF** meets this need by adhering to the latest guidelines from the World Health Organization (WHO), European Medicines Agency (EMA), and United States Food and Drug Administration (FDA). This adherence minimizes toxicological effects and allergic reactions, as evidenced by the specific exclusion of harmful excipients.[17,18] Furthermore, the absence of lactose in **SyrSpend® SF**, combined with its low osmolality (<50 mOsmol/kg), significantly reduces gastrointestinal side effects.

In line with WHO, EMA, ANVISA, and FDA guidelines, the formulation of **SyrSpend® SF** includes only safe ingredients, reinforcing its safety profile. All **SyrSpend® SF** vehicles are free of sugar, ethanol, lactose, and other potential hazardous excipients, making them compatible with young children and ketogenic diets (Figure 4). The comprehensive safety profile and compatibility of **SyrSpend® SF** highlight its suitability as a versatile pharmaceutical vehicle for diverse patient groups.

Figure 4. Examples of potentially hazardous excipients.

2.3 Proven compatibility

Over the past years, **SyrSpend® SF** has been rigorously tested with a broad spectrum of Active Pharmaceutical Ingredients (APIs). These studies, conducted in GLP and/or ISO 17025 certified laboratories under Fagron's supervision, primarily utilized stability-indicating high-performance liquid chromatography (HPLC) methods. These methods are primarily derived from the United States Pharmacopeia (USP), with slight modifications when necessary.

The beyond-use date (BUD) is a critical factor, defining the time limit for the safe use of a compounded preparation after its formulation.[19] In the case of **SyrSpend® SF**, extensive stability studies have been conducted on various APIs. These studies, mostly lasting up to 90 days or until a deviation in the required concentration threshold (± 10% of the initial concentration) was observed, were performed under both controlled refrigerated and room temperature conditions.

To date, more than 140 different APIs have been successfully tested with **SyrSpend® SF**, demonstrating its efficacy in delivering accurate doses. The findings from these comprehensive studies have been recognized and published in various peer-reviewed journals.[20–30]

In addition to the compatibility studies with HPLC, the rheological properties of **SyrSpend® SF** have been evaluated and found to be superior compared to other suspending vehicles.[31] These studies underscore the versatility and reliability of **SyrSpend® SF** as a pharmaceutical vehicle suitable for a wide range of APIs and clinical applications.

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 Fagron Formulary.

A key function of a suspending vehicle like **SyrSpend® SF** is to enhance the suspension properties, thereby improving the Content Uniformity of the compound. This aspect is crucial as it directly impacts the accuracy and safety of medication dosages. In our comprehensive analysis, the Content Uniformity of 6,414 samples prepared with **SyrSpend® SF** was meticulously evaluated using high-performance liquid chromatography (HPLC). Impressively, in all instances, the results adhered to the stringent Content Uniformity criteria set by various pharmacopeias.[32]

These findings are particularly significant as they affirm that every sample compounded with **SyrSpend® SF** consistently delivers the correct dose. This consistency is maintained regardless of the API involved, the storage conditions, or the time elapsed before analysis. This level of reliability in Content Uniformity is vital, especially for medications with a narrow therapeutic window where even minor deviations can have substantial implications for patient safety (Figure 5).[32-34]

These findings strongly reinforce the value of **SyrSpend® SF** in boosting the safety and effectiveness of compounded medications. They offer a significant level of confidence to healthcare practitioners and patients regarding the consistent reliability of dosages, ensuring peace of mind about the precision and quality of treatments.

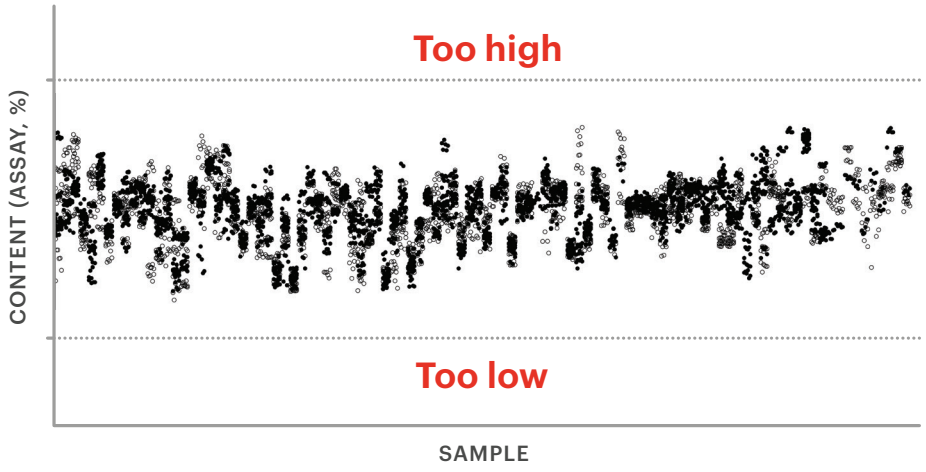
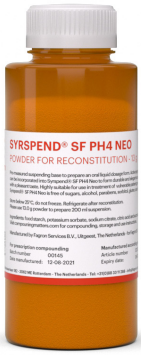


Figure 5. SyrSpend® SF guarantees content uniformity, as evidenced by a study showing its ability to deliver consistent dosages in over 100 formulations with various APIs, under various conditions and times, providing confidence to both healthcare professionals and patients.

2.4 Customized for every oral pharmaceutical need

SyrSpend® SF offers a range of products that ensure convenient, safe, and efficient preparation of oral liquid dosage forms, all while providing taste-masking with a pleasant, sweet taste for easy patient acceptance. Compatible with a wide range of APIs, **SyrSpend® SF** products come with both acid and alkaline options to suit diverse compounding needs.

SyrSpend® SF PH4 (liquid)
Easy-to-use suspension base, gently preserved with less than 0.1% sodium benzoate. It is buffered to pH 4.2 to ensure maximum compatibility and is available in different flavors, including cherry flavor. Each bottle contains 500 mL of suspension, ready for use.



SyrSpend® SF PH4 NEO (dry, for reconstitution)
Meticulously designed with a focus on superior safety, ensuring its suitability for all patients, particularly those who are most vulnerable. It is buffered to pH 4.2 for maximum compatibility. This pre-weighed powder can be used to make a 100 ml or 200 mL suspension, ensuring precise dosing and ease of preparation.

SyrSpend® SF PH4 (dry, for reconstitution)
Tailored for direct compounding in the dispending container. Buffered to pH 4.2, it is completely preservative-free. This product comes in pre-weighed packets, offering the flexibility to prepare either 100 mL or 200 mL suspensions, depending on the patient's needs.

SyrSpend® SF Alka (dry, for reconstitution)
Designed for direct compounding in the dispensing container, is buffered to a pH greater than 7, making it ideal for acid-labile APIs. Like its PH4 counterpart, it is preservative-free and comes in pre-weighed bottles for preparing 100 mL or 200 mL suspensions.

Lastly, the **SyrSpend® SF compounding kits** are designed for maximum efficiency in pharmaceutical compounding. Each kit contains **SyrSpend® SF** (dry, for reconstitution) in a validated dispensing container, pre-weighed API powder, an oral syringe, tip extender, press-in bottle adapter, and comprehensive compounding and cleaning instructions for the syringe and tip extender. These kits streamline the compounding process, ensuring accuracy and convenience. Each of these products in the **SyrSpend® SF** range is formulated to meet the specific needs of pharmacists and patients, ensuring the highest standards of medication safety and efficacy.

Figure 6 details the full spectrum of products and guides the appropriate **SyrSpend® SF** vehicle choice for each situation.

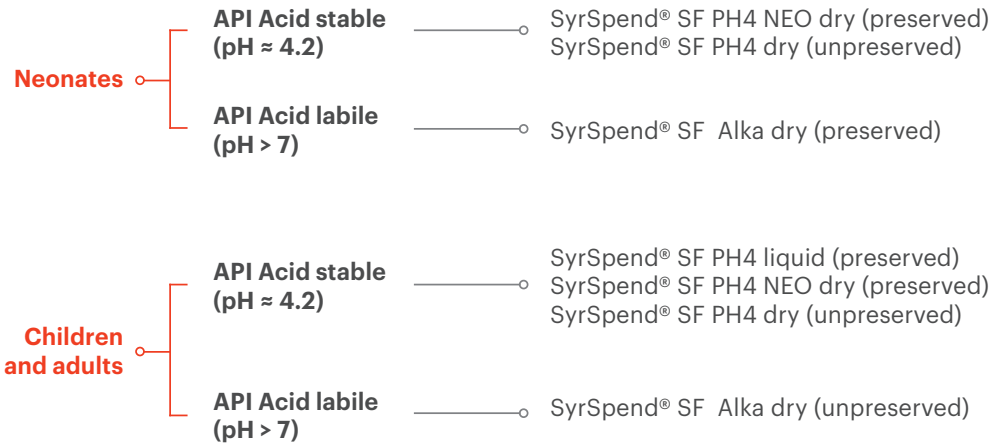


Figure 6. The selection diagram provides a comprehensive guide on choosing the appropriate SyrSpend® SF vehicle based on the patient's specific needs and the chemical characteristics of the active pharmaceutical ingredient (API).

3. Diseases and Treatments

3.1. Infectious diseases

3.1.1. Urinary tract infection

Urinary tract infection (UTI) is among the most common bacterial infections during childhood.[35] It has a bimodal age distribution, peaking in infancy and adolescence. UTI incidence varies with age and gender, with girls being at a significantly higher risk compared to boys, especially in the first year of life.[36] Most cases are caused by *Escherichia coli*; other pathogens, such as *Klebsiella pneumoniae* and *Proteus mirabilis*, are less frequently involved.[37] The infection frequently occurs from the bacterial ascension of the child's endogenous intestinal flora into the urinary tract.[38] Thus, it can affect different parts of the urinary tract, including the urethra, bladder, ureter, and kidneys (Figure 7).

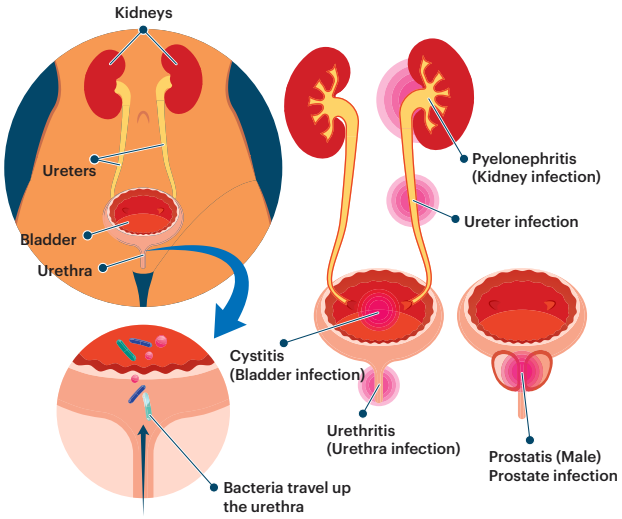


Figure 7. Urinary system (left side).
Infection in different parts of the urinary tract (right side).

The symptomatology depends on the child's age and the site of infection. In young children, symptoms are nonspecific, including fever, irritability, poor feeding, or vomiting.[39] However, older children may complain of urinary frequency, urgency, dysuria, abdominal pain, or back pain.[37] The diagnosis includes clinical evaluation, urinalysis, and urine culture. In some specific cases, renal ultrasonography and other imaging studies might be needed.[40]

UTI treatment consists of antibiotics and supportive care. Antibiotic therapy is typically guided by the pathogen's susceptibility, child's age, and clinical condition.[41] Commonly prescribed antibiotics include nitrofurantoin for uncomplicated lower UTIs, and ciprofloxacin for complicated upper UTIs like pyelonephritis.[42,43]

Compounding nitrofurantoin with **SyrSpend® SF** offers an alternative for patients allergic to excipients like propylparaben in commercial drugs. Unlike standard ciprofloxacin formulations, **SyrSpend® SF** is sucrose-free, aiding diabetic patient treatment and reducing the risk of dental cavities.[44,45]

Prescription example

Nitrofurantoin in **SyrSpend® SF PH4**	2 mg/mL
Typical pediatric dose: 5-7 mg/kg/day orally	
Doses per day: 4 (every 6 hours)	
Duration of treatment: 7 to 10 days (determined by the doctor)	

3.1.2. Pneumonia

Pneumonia is a prevalent and potentially severe lower respiratory tract infection involving the lung parenchyma (Figure 8).[46] Different infectious agents, such as bacteria, viruses, and fungi, might be related to the disease pathogenesis.[47] While pneumonia can affect children of all age groups, it is more common in young children, particularly those below five.[48] According to the WHO, community-acquired pneumonia represents 14.2% of deaths in children younger than 5 years and is the leading cause of death in this age group worldwide.[49]

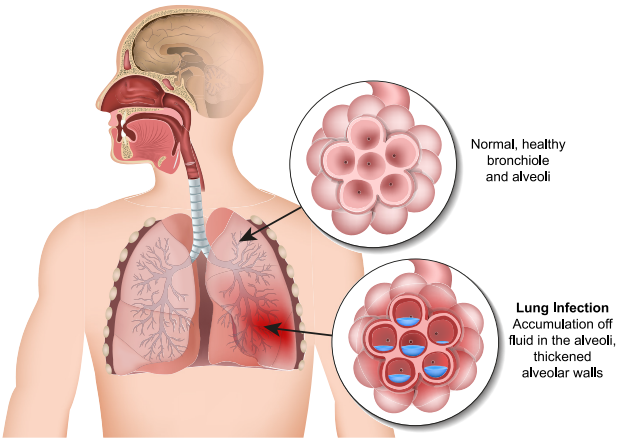


Figure 8. Lower respiratory tract infection involving the lung parenchyma.

The etiology of pneumonia in the pediatric population is variable and changes according to age and disease severity.[47] Among the most frequent pathogens are viruses, such as respiratory syncytial virus (RSV), influenza, and rhinovirus (considered the most common).[50] Although the widespread use of pneumococcal and *Haemophilus influenzae type B* (Hib) vaccines in many countries has reduced the number of pneumonia cases and hospitalizations; bacteria remains a significant infectious agent.[51]

The clinical presentation of pneumonia in children can significantly vary.[52] Common symptoms include fever, cough, tachypnea, thoracic discomfort, wheezing, and signs of respiratory distress.[46] Younger children may exhibit more general clinical manifestations involving poor feeding, vomiting, and irritability.[53]

The diagnosis of pneumonia in pediatric patients is based on clinical symptoms, physical examination, and, if necessary, imaging studies (e.g. X-ray).[54] In some cases, laboratory assessments, including blood tests and culture of respiratory secretion might be performed to identify the causative pathogen.[47]

The management of pneumonia in children depends on the underlying etiology and disease severity.[55] Viral pneumonia is primarily managed with supportive care, which includes rest, hydration, and antipyretic medications.[56] Conversely, bacterial pneumonia requires antibiotic therapy, with amoxicillin being the preferred first-line option.[57] However, rash, a commonly reported adverse reaction, might start in some children after a few days of amoxicillin intake and could potentially jeopardize treatment, as parents are likely to discontinue the medication.[58]

Rashes, urticaria with itching, and photosensitivity are known side effects of β-Lactam antibiotics, often linked to excipients like saccharin sodium rather than the active substance.[59,12] Misidentifying these reactions as penicillin allergies can unnecessarily label patients and limit their access to vital antibiotics. Using **SyrSpend® SF** to compound amoxicillin may help avoid such allergenic excipients.[60]

Prescription example

Amoxicillin in **SyrSpend® SF PH4**	50 mg/mL
Typical pediatric dose (< 40kg): 80-90 mg/kg/day orally	
Doses per day: 2 or 3 (every 12 or 8 hours)	
Duration of treatment: 7 to 10 days (determined by the doctor)	

3.1.3. Skin infections

Impetigo

Impetigo is a contagious, superficial bacterial skin infection that can affect all age groups, but it is more common in children between 2 to 5 years of age.[61] Its occurrence is usually associated with damage to the skin barrier, and it can be classified as a primary or secondary infection.[62] Primary infection is a direct bacterial invasion, while secondary infection is associated with an underlying condition such as scabies or eczema.[63]

There are two presentations of impetigo: nonbullous and bullous.[64] Nonbullous impetigo represents more than 70% of all cases and is caused by *Staphylococcus aureus* or *Streptococcus pyogenes*.[63] Honey-colored crusts on the face and extremities characterized this type of impetigo (Figure 9).[65] Bullous impetigo is usually caused by a single pathogen, *Staphylococcus aureus*, and starts with smaller vesicles, which become flaccid blisters initially with clear content that later becomes purulent.[61] This type of impetigo occurs most commonly in intertriginous regions such as the diaper area, axillae, and neck.[64]

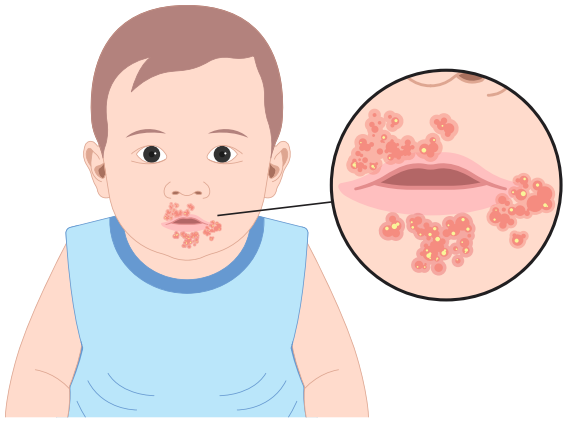


Figure 9. Nonbullous impetigo in a pre-school age boy.

The diagnosis of nonbullous and bullous impetigo is usually clinical.[65] Skin swabs might not be helpful as they poorly differentiate between bacterial infection and normal skin colonization.[66] Culture of the pus or bullous fluid for pathogen identification may be considered in patient in whom first-line treatment fails.[67]

Treatment options for impetigo include topical and systemic antibiotics.[68] Systemic antibiotics are often reserved for more generalized or severe infections in which topical therapy is not ideal.[63] Impetigo is usually a self-limited condition; although rare, complications can occur. If MRSA (Methicillin-resistant *Staphylococcus aureus*) infection is suspected, initial treatment

with a tetracycline antibiotic (e.g., doxycycline) is recommended.[65] Doxycycline, typically available in tablet form and recommended for children over eight, may pose acceptability challenges.[69] A preferable alternative is its liquid formulation in **SyrSpend® SF**, offering a light-textured suspension without a medicinal aftertaste, easing swallowing difficulties.[25]

Prescription example

Doxycycline in **SyrSpend® SF PH4**	50 mg/mL
Typical pediatric dose (> 45kg): 100 mg orally	
Doses per day: 2 (every 12 hours)	
Duration of treatment : 7 days (determined by the doctor)	

Fungal Infections

Fungal infections, also known as mycoses, represent a diverse group of diseases that can affect individuals of different age groups, including children. Among the most common ones in pediatric patients are mucocutaneous candidiasis, pityriasis versicolor, tinea corporis, tinea pedis, and tinea capitis.[70]

Mucocutaneous candidiasis

Mucocutaneous candidiasis constitutes a spectrum of fungal infections predominantly caused by Candida species, particularly *Candida albicans*.[71] It can affect mucosal and cutaneous surfaces and have different clinical manifestations, often involving the oral, esophageal, genital, or nail regions.[72] In children, it commonly presents as oral thrush and diaper rash and is often associated with antibiotics or immunosuppression.[73] The infection can be chronic and recurrent, and its severity can vary from mild and localized to extensive and debilitating.[71] Patients with severe or recurrent infections should be investigated for congenital or acquired immune deficiency.[72] The treatment primarily involves topical antifungal therapy.[74] However, systemic antifungals (e.g., itraconazole) may be considered if conventional topical treatments fail or in moderate to severe cases.[75]

Prescription example

Itraconazole in **SyrSpend® SF PH4**	20 mg/mL
Typical pediatric dose: 2-5 mg/kg/day orally	
Doses per day: 2 (every 12 hours)	
Duration of treatment: 7 to 14 days (determined by the doctor)	

Pityriasis versicolor, or tinea versicolor, is a common and generally benign skin condition caused by a type of yeast called *Malassezia furfur*.[76] This organism is naturally present on the skin, but in some patients, it can overgrow and lead to this skin disorder.[77] Pityriasis versicolor is characterized by scaly hypo- or hyperpigmented lesions on the trunk that may worsen in warm and humid weather.[78] Topical antifungal medications are commonly prescribed; however, oral antifungals (e.g., ketoconazole) are the treatment choice in case of severe and recurrent infections.[79]

Prescription example

Ketoconazole in **SyrSpend® SF PH4**	20 mg/mL
Typical pediatric dose: 3.3 - 6.6 mg/kg/day orally	
Doses per day: 1 (every 24 hours)	
Duration of treatment: determined by the doctor	

Tinea corporis, capitis, and pedis

Tinea is a common fungal infection affecting skin, hair, and nails.[70] Tinea infections are caused by dermatophytes and are classified by the involved site.[80] It has a variety of clinical manifestations and affects all age groups, ranging from tinea corporis and tinea capitis in pre-pubertal children to tinea pedis (athlete's foot) in adolescents and adults (Figure 10).[81,82]

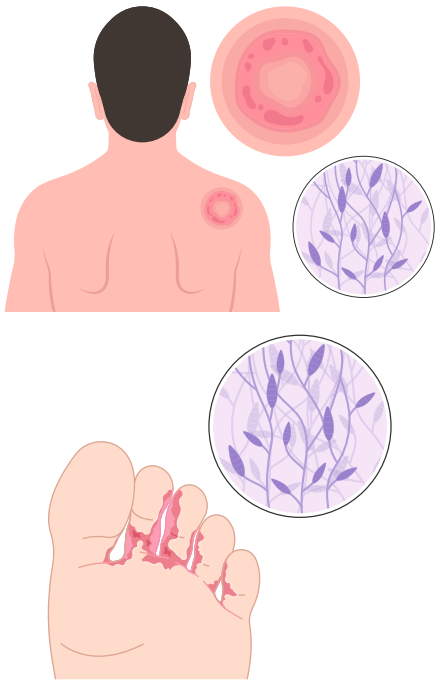


Figure 10. Tinea corporis (top image), and tinea pedis (bottom image).

Common risk factors include close contact with infected individuals and a humid environment.[83] Treatment for tinea infections typically involves the use of antifungal medications, either topical or systemic (e.g., griseofulvin, terbinafine).[84] Both options are available and are selected based on the subtypes and severity of the disease.[85,86]

Overall, systemic antifungal treatment should be restricted to specific conditions, mainly among the pediatric population.[87] For example, despite itraconazole activity against many dermatophytes (e.g., *Candida species, M. furfur*), this medication is still not considered a first-line agent for cutaneous fungal infections in children because of limited data on safety and efficacy.[88] In addition, another challenge regarding antifungal treatment is related to griseofulvin. Griseofulvin has excellent efficacy in tinea capitis but is no longer commercially available in many countries.[89] Moreover, terbinafine has been considered the drug of choice for superficial fungal infections in children, but it is available in tablets only.[90]

Compounded formulations with itraconazole, ketoconazole, griseofulvin, or terbinafine in **SyrSpend® SF** offer an excellent treatment alternative for fungal infections in children.[24,28,45]

Prescription example

Terbinafine in **SyrSpend® SF PH4**	25 mg/mL
Typical pediatric dose: 4-6 mg/kg/day orally (2-6 weeks)	
Doses per day: 1 (every 24 hours)	
Duration of treatment: 2 to 6 weeks (determined by the doctor)	

3.2. Gastrointestinal diseases

3.2.1. Gastroesophageal reflux

Gastroesophageal reflux (GER) is a common and self-limiting condition in children. It is a normal physiological process defined as the retrograde flow of gastric contents into the esophagus, usually related to immaturity of the lower esophageal sphincter (Figure 11).[91] However, when GER becomes pathological, it can lead to frequent or severe symptoms and complications, which is then referred to as gastroesophageal reflux disease (GERD).[92] Although the prevalence of GER in the first six months of life is reported to be as high as 55–73%, a small proportion (5–9%) of all infants with regurgitation have GERD.[93]

During childhood, the prevalence of GERD increases slowly with age, becoming frequent in young adults.[94]

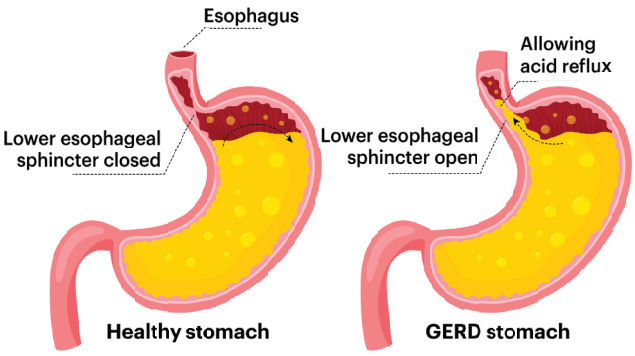


Figure 11. Gastroesophageal Reflux Disease: Pathophysiology.

The symptomatology can vary between infants and children.[95] Most healthy infants typically experience daily regurgitation or vomiting without any complications. However, symptoms that suggest GERD in infants include poor growth or weight gain, as well as signs of esophagitis such as irritability, feeding problems, sleep disturbances, crying episodes, and anemia.[96] In contrast, older children and adolescents often display symptoms similar to those seen in adults, such as heartburn, epigastric pain, chest pain, difficulty swallowing, sour burps, and regurgitation.[97]

GERD management includes a combination of conservative measures (lifestyle and dietary changes), pharmacological treatment, and surgery on rare occasions.[98] For infants diagnosed with GERD who do not improve with the conservative approach, pharmacological therapy using proton pump inhibitors (PPI) is considered.[99]

The lowest available solid formulation of omeprazole, frequently prescribed PPI, is 10 mg, while the starting treatment dose in infants can be as low as 3 mg (based on a recommended dose of 1 mg/kg/day).[100] Moreover, recent studies raise concerns about the effectiveness and safety of the high amounts of sodium bicarbonate used in commercially available omeprazole suspensions for young children.[101]

Compounding omeprazole with **SyrSpend® SF Alka** enables precise dose adjustment.[102] Additionally, this formulation, free from sodium benzoate, utilizes calcium carbonate to protect PPI from degradation.

Prescription example

Omeprazole in **SyrSpend® SF Alka**	2 mg/mL
Typical pediatric dose: neonates and infants: 1 mg/kg/day orally > 5 kg < 10 kg: 5 mg orally > 10 kg < 20 kg: 10 mg orally > 20 kg: 20 mg orally	
Doses per day: 1 (every 24 hours)	
Duration of treatment: up to 4 weeks (determined by the doctor)	

3.2.2. Inflammatory bowel disease

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U), are chronic inflammatory disorders of the gastrointestinal tract (Figure 12).

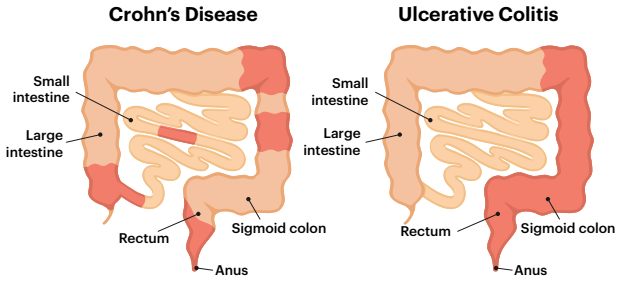


Figure 12. Crohn's disease and Ulcerative colitis clinical presentations.

The disease onset usually occurs during adolescence and young adulthood.[103] In children diagnosed with IBD, 4% manifest the condition before age five, and 18% before reaching ten years, with the highest occurrence observed during adolescence.[104] IBD pathogenesis involves dysregulation of the mucosal immune response to the intestinal microflora in genetically predisposed hosts.[105]

Symptoms of IBD in children are heterogeneous but often include abdominal pain, diarrhea, weight loss, fatigue, and developmental failure.[106] If not adequately followed up, children with IBD may experience delayed puberty and or growth.

IBD diagnosis can be challenging, especially among pediatric patients, due to the potential overlap of symptoms with other conditions.

Diagnostic procedures commonly include blood and stool tests, endoscopic examinations (colonoscopy and/or upper endoscopy), and imaging procedures such as magnetic resonance imaging (MRI) or computerized tomography (CT) scans.

The treatment of IBD in children typically involves a combination of medications and lifestyle adjustments. As malnutrition and nutrient deficiencies can occur due to poor absorption and increased nutrient requirements, proper dietary management is essential to support healthy growth and development. Common medications include anti-inflammatory, immunomodulators, and biologic drugs; surgery might be necessary in severe cases. Among immunomodulating thiopurine drugs, azathioprine is often prescribed.[30,44] However, azathioprine formulations contain lactose and are only available as tablets.

Compounding azathioprine in **SyrSpend® SF** offers a better treatment option for lactose intolerant patients and for those who prefer a liquid medication. In addition, **SyrSpend® SF**'s low osmolality (<50 mOsmol/kg) minimizes gastrointestinal side effects.

Prescription example

Azathioprine in **SyrSpend® SF PH4**	50 mg/mL
Typical pediatric dose: 1-2.5 mg/kg/day orally	
Doses per day: 1 (every 24 hours)	
Duration of treatment: determined by the doctor	

3.3. Rheumatological and autoimmune diseases

3.3.1. Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is the most prevalent pediatric rheumatological disorder and unifies all forms of chronic childhood arthritis, affecting not only joints but extra-articular structures.[107] It is defined as the presence of arthritis of unknown etiology that begins before age 16 and lasts for at least six weeks.[108] It is classified by subtypes depending on the number of joints affected, extra-articular manifestations, systemic symptoms, serology, and genetic factors.[107] The subtypes include systemic, oligoarticular, polyarticular, psoriatic, enthesitis-related, and undifferentiated arthritis.[109]

JIA subtypes are a heterogeneous group of diseases with multifactorial pathogenesis.[110] Environmental factors, such as infectious agents, vitamin D deficiency, trauma, and genetic predisposition, have been proposed as risk factors.[108] However, it is yet to fully know how the combination of environmental and genetic factors disrupts the balance between regulatory and effector cells in the pathogenesis of JIA.[109]

The clinical manifestations depend on the JIA subtype and can vary from mild, self-limiting arthritis to severe

systemic involvement.[111] Common symptoms include joint pain, swelling, morning stiffness, and decreased range of motion (Figure 13).[112] However, systemic JIA may also include high fever, rash, and systemic inflammation.[113] Extra-articular manifestations may affect the skin, eyes, heart, and other organs.[114]

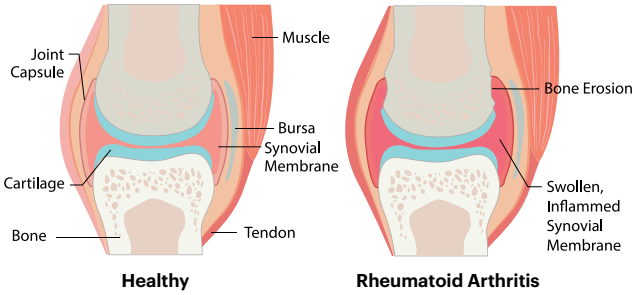


Figure 13. Healthy joint on the left side and joint with arthritis signs on the right side.

JIA diagnosis includes a combination of clinical characteristics and exclusion of other causes of childhood arthritis.[115] In addition, the International League of Associations for Rheumatology (ILAR) classification criteria for JIA are globally accepted and used diagnostic tools.[107]

Management of JIA is multidisciplinary, aiming to reduce pain and inflammation and maintain joint function.[115] The non-pharmacological interventions, such as regular exercise and physical and occupational therapy, focus on keeping muscle strength and flexibility and reducing joint deformities.[116] Pharmacological interventions include non-steroidal anti-inflammatory drugs (e.g., celecoxib), often used to decrease pain and inflammation, and disease-modifying anti-rheumatic drugs (e.g., methotrexate) administrated to control the disease's progression.[117] However, non-steroidal anti-inflammatory drugs should be cautiously used due to an increased risk of gastrointestinal side effects.[118] Sodium lauryl sulfate, an excipient in celecoxib commercial formulation, has been associated with delayed-type hypersensitivity cutaneous reactions.[119] Compounding celecoxib in **SyrSpend® SF** provides an allergen-free treatment alternative.[45]

Prescription example

Celecoxib in **SyrSpend® SF PH4**	10 mg/mL
Typical pediatric dose	>10 kg <25 kg: 50 mg/dose orally
	>25 kg: 100 mg/dose orally
Doses per day: 2 (every 12 hours)	
Duration of treatment: determined by the doctor	

3.3.2. Juvenile systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition that can affect multiple organs and result in significant damage and disability.[120] Approximately 15–20% of patients develop the disease before the age of 18 and are therefore diagnosed with juvenile-onset SLE (JSLE).[121] Juvenile-onset disease is usually associated with more severe organ involvement, increased disease activity, and earlier damage development compared to adult-onset.[122]

The exact pathophysiological mechanisms underlying this condition remain unclear.[123] However, genetic factors, immune complex deposition, hormonal factors, and immune cell dysregulation play an important role.[124] The symptomatology of JSLE can vary widely from cutaneous and musculoskeletal to vital organ involvement.[125] It may include fatigue, arthralgia, skin rashes (especially a butterfly-shaped rash on the face), fever, photosensitivity, and more severe symptoms involving major organs, such as the kidneys or the central nervous system.[126]

The diagnosis includes clinical assessment, laboratory investigations (e.g., ANA-antinuclear and anti-dsDNA antibodies), and imaging studies.[127,128] Management of JSLE is complex and should be tailored to the individual's symptoms and the organs involved.[128] Non-pharmacological measures include lifestyle changes, for example, regular physical activity, a healthy diet, and continuous use of sun protection.[122] Pharmacological treatment includes nonsteroidal anti-inflammatory (NSAIDs), corticosteroids (e.g., prednisolone), immunosuppressive, and antimalarial (e.g., hydroxychloroquine) drugs.[129,130] Commercially available prednisolone and hydroxychloroquine contain excipients, such as sodium bicarbonate, polyethylene glycol, and polysorbate 80, previously associated with skin irritation and renal dysfunction.[131,132] Using **SyrSpend® SF** to compound prednisone or hydroxychloroquine may address these challenges.[20,133]

Prescription example

Prednisolone in **SyrSpend® SF PH4**	1.5 mg/mL
Typical pediatric dose	< 25kg: 0.14-2mg/kg/day orally once a day or in 2-4 divided doses
	>25 kg: 5-60mg orally once a day or in 2-4 divided doses
Doses per day: 1 (every 24 hours) or 2 (every 12 hours) or 3 (every 8 hours) or 4 (every 6 hours)	
Duration of treatment: determined by the doctor	

3.4. Neurological disorders

3.4.1. Epilepsy

Epilepsy is one of the most common neurological disorders in the pediatric population, affecting approximately 5 to 8 per 1,000 children. It exhibits a bimodal distribution, with the highest incidence in the first year of life and during adolescence.[134] However, it is essential to understand the difference between seizure episodes and epilepsy.[135] While seizures are defined as a temporary manifestation of abnormal electrical activity in the brain, epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures, which can have significant physical, psychological, and social consequences for affected children.[136] In addition, seizures can be isolated events that respond to specific triggers, such as fever. Controversially, epilepsy involves a pattern of recurrent seizures that are not associated with particular triggers.[137]

The etiology of epilepsy in children is multifactorial. In some cases, it may result from genetic factors, brain malformations, or perinatal insults, while in others, it may be due to infections, trauma, or metabolic disturbances.[138] The diagnosis of epilepsy includes a documented history of a minimum of two unprovoked seizures occurring > 24 h apart and a detailed clinical history of the child, as well as electroencephalography (EEG) and neuroimaging analysis such as MRI (Figure 14).[139]

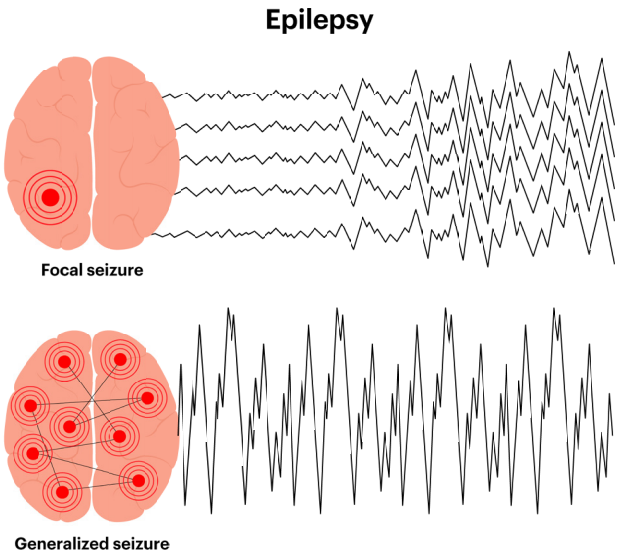


Figure 14. Abnormal electroencephalography signals (e.g., focal and generalized seizures).

The treatment of pediatric epilepsy involves a multifaceted approach, including antiepileptic medications, dietary therapies (e.g., ketogenic diet), and, in some specific cases, surgical interventions.[140] The specific medications and their dosages are related to the type of seizure, the child's age, and overall health.[141] During an acute seizure episode, the main goal of the therapy is to stop seizures before neural cells are irreversibly damaged. First-line medications used in this context are usually benzodiazepines (e.g., clonazepam, lorazepam) and barbiturates (e.g., phenobarbital). However, some children will need continuous anti-epileptic treatment to obtain good seizure control.[142] Common anti-epileptic medications used as monotherapy or combined with other drugs in these cases are carbamazepine and lamotrigine.

It is important to highlight that many liquid therapeutic options contain propylene glycol. This excipient is commonly used to solubilize drugs with limited water solubility, but patients below four years of age may accumulate propylene glycol due to decreased or immature metabolism.[143] Sedation, respiratory depression, and hypotension are frequent side effects that might be related to the presence of propylene glycol. [126,144,145]

Compounding oral medications like clonazepam, lorazepam, phenobarbital, carbamazepine, or lamotrigine in **SyrSpend® SF** provides an effective treatment solution, especially when liquid forms aren't available commercially or to bypass undesirable excipients.[24,27,29]

Prescription example

Phenobarbital in **SyrSpend® SF PH4**	9-15 mg/mL
Typical pediatric dose	Loading dose: 15-20 mg/kg orally
	Maintenance dose: 3-5 mg/kg/day orally
Duration of treatment: determined by the doctor	

3.5. Mental disorders

3.5.1. Attention deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood, and its prevalence is estimated at around 7.2% worldwide.[146] This condition can influence chil-

dren's academic achievement, well-being, and social interactions.[147] In fact, some children with ADHD will persist in experiencing symptoms during adolescence and adulthood.[148]

ADHD is characterized by diverse presentations, often presenting in contrasting forms, and frequently accompanied by underlying conditions.[149] Usually, it also overlaps with other disorders. However, the most common symptoms include persistent pattern of inattention, impulsivity, and hyperactivity that interferes with daily functioning.[146,148] The diagnosis is based on a combination of these symptoms, more than what is normal for age or developmental stage.[150]

Patients with ADHD need an individualized multimodal treatment plan that addresses psychoeducation, pharmacological, and non-pharmacological interventions.[151] Available medications include stimulants (methylphenidate, amphetamines) and non-stimulants (atomoxetine, guanfacine, clonidine).[152,153] However, the commercially available dosage form of clonidine is extended-release tablets.[154] Compounding clonidine in **SyrSpend® SF** is beneficial for children over 6 years who cannot swallow tablets, effectively addressing this challenge .[28]

Prescription example

Clonidine in **SyrSpend® SF PH4**	0.1 mg/mL
Typical pediatric dose	Initial dose: 0.1 mg/day orally
	Maintenance dose: 0.1-0.4 mg/day orally
Doses per day: 1 (every 24 hours)	
Duration of treatment: determined by the doctor	

3.5.2. Anxiety

Anxiety disorders include separation anxiety disorder, selective mutism, specific phobias, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder.[155] The anxiety disorders as a group are the most prevalent mental health condition worldwide.[156] The disease onset is usually during childhood, peaks during adolescence, and often persists into adulthood, with significant effects on quality of life and functioning.[157]

Anxiety disorders encompass a wide range of symptoms with different severity and duration. Common symptoms include fear, excessive worry, restlessness, avoidance behavior, and sleep disturbances.[155,158] The majority of fears experienced during childhood and adolescence are considered a normal part of development, with only approximately 23% indicating the presence of anxiety disorders.[159] In adulthood, temporary episodes of fear or anxiety can emerge during stressful life events; however, these symptoms are not classified as anxiety disorders unless they endure, for example, persisting for at least six months and significantly interfering with daily functioning.[160]

Effective management of anxiety disorders involves a combination of psychotherapy, family and patient education, and pharmacological approaches tailored to the individual's needs.[161] Selective serotonin reuptake inhibitors, such as sertraline and fluoxetine, are considered the first-line pharmacological agents for pediatric anxiety disorders.[162] They have shown efficacy when used as monotherapy or in combination with cognitive behavior therapy.[163] However, some side effects have been reported, including gastrointestinal and renal disturbances, decreased appetite, and weight loss.[162,163] Commercially available sertraline and fluoxetine contain unwanted excipients, such as polysorbate 80, benzyl alcohol, and propylparaben, that might be related to some of the previously mentioned side effects.[164,165] Compounding sertraline and fluoxetine with **SyrSpend® SF** can provide an alternative for pediatric patients to avoid unsuitable or unwanted excipients.[166]

Prescription example

Sertraline in **SyrSpend® SF PH4**	10 mg/mL
Typical pediatric dose: Initial dose: 25 mg/day orally	
Doses per day: 1 (every 24 hours)	
Duration of treatment: determined by the doctor	

3.5.3. Depression

Major depressive disorder is a common, debilitating mood disorder characterized by negative feelings, thoughts, and behaviors.[167] It leads to substantial impairment in one's social, occupational, and educational spheres, resulting in a diminished quality of life and increased morbidity and mortality risks.[168] Childhood and adolescence are critical periods for the development of depression.[169,170] Specifically, the transition from childhood to adolescence is marked by physiological, psychological, and emotional transformations inherent to this phase of life, which can increase an individual's responsiveness and susceptibility to stress exposure.[171,172]

Multiple risk factors are associated with depression, for example, a family history of depression and expo-

sure to adverse events, including the death of a family member and physical or sexual abuse.[173,174] Additionally, parental behaviors such as aversive behaviors (e.g., criticism, punishment, and conflicts), lack of autonomy and warmth given to the child or adolescent, and excessive parental involvement might also heighten the risk of depression.[175] Other factors that play an important role are related to the school community environment, including bullying, limited social bonds with peers and teachers, poor academic performance, and community-related factors such as safety, diversity, and discrimination.[176,177]

Depression among the pediatric population often exhibits distinctive features compared to its manifestation in adults.[178] Common clinical manifestations include frequent expressions of sadness or tearfulness, irritability, anger, withdrawal from interpersonal relationships, including family and peer interactions, diminished interest in previously enjoyable activities and hobbies, profound fatigue or a pervasive lack of energy, and disturbed sleep and eating patterns.[179,180]

The treatment of depression in children and adolescents involves a multifaceted approach that typically includes psychotherapeutic interventions, family, and caregiver support, and, in some cases, medication.[181] The specific treatment plan should be tailored to the individual's needs and the severity of their condition. In some specific cases, antidepressant drugs are prescribed, and the commonly used antidepressants include selective serotonin reuptake inhibitors, such as fluoxetine.[181,182]

Prescription example

Fluoxetine in **SyrSpend® SF PH4**	2 mg/mL
Typical pediatric dose: Initial dose: 20 mg/day orally	
Doses per day: 1 (every 24 hours)	
Duration of treatment: determined by the doctor	

3.6. Oncological diseases

3.6.1. Leukemias

In developed countries, cancer remains the most common cause of disease-related death in children.[183] Leukemia is the most common cancer of childhood, accounting for 30% of all cases.[184] There are three main subtypes of leukemia: acute lymphoblastic leukemia (ALL), accounting for approximately 80% of cases, acute myelogenous leukemia; and the least common chronic myelogenous leukemia.[183,184] ALL occurs in children of all ages, but cases peak at the age of three and four.[185]

The most common symptoms result from the abnormal proliferation of immature white blood cells (called blasts) in the bone marrow, preventing the normal production of erythrocytes, platelets, and neutrophils (Figure 15).[186] For example, a significant anemia can cause pallor, fatigue, headache, and dizziness. Many patients can also have bruising or bleeding, recurrent infections, and fever.[187] In addition, leukemia can infiltrate other organs outside of the bone marrow, leading to lymphadenopathy, hepatomegaly, splenomegaly, and kidney lesions.[183]

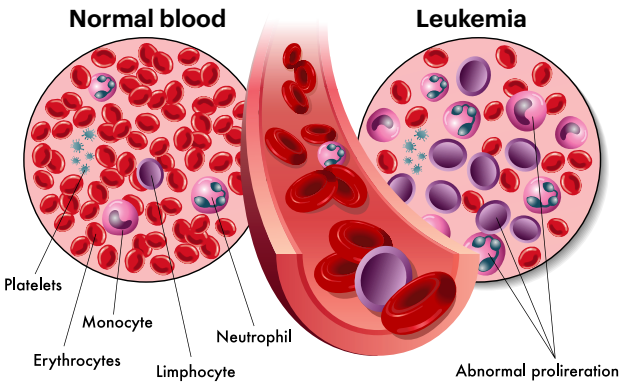


Figure 15. Abnormal proliferation of immature white blood cells.

Diagnosis of leukemia involves clinical evaluation, blood tests, and bone marrow examination.[188] Also, immunophenotyping, cytogenetic analysis, and molecular testing are essential in subtype classification and risk stratification.[189]

The treatment varies greatly depending on the subtype, the type of genetic disorder, the number of leukemia cells in the blood, and the child's age.[183] However, chemotherapy remains the main treatment for most childhood leukemias. Some of the chemotherapeutic drugs used to treat childhood leukemia include methotrexate and 6-mercaptopurine.[190,191] Although both medications are available in tablets and oral suspension, the formulations contain ingredients such as methylparaben, which has been linked to allergic contact dermatitis and other adverse skin manifestations.[192,193]

Compounding methotrexate and 6-mercaptopurine in **SyrSpend® SF**, a paraben-free vehicle, provides an excellent treatment option to circumvent potential skin-related side effects .[194,195]

Prescription example

Methotrexate **in SyrSpend® SF PH4**	2.5 mg/mL
Typical pediatric dose: 20 mg/m² orally	
Doses per week: 1 (every week)	
Duration of treatment: determined by the doctor	

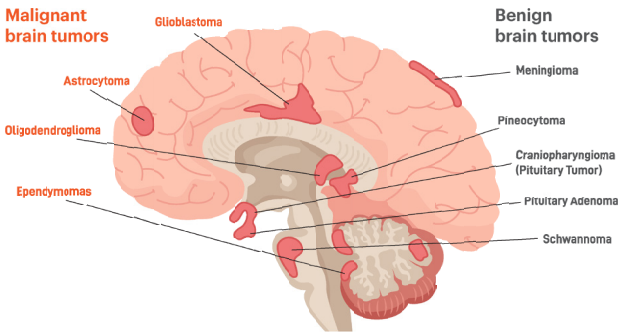


Figure 16. Primary brain tumors.

3.6.2. Brain and spinal cord tumors

Primary tumors of the central nervous system (CNS) constitute the largest group of solid tumors in children.[196] Brain cancer has overtaken leukemia as the leading cause of cancer mortality in children.[184] However, many children are diagnosed with benign brain tumors that can be successfully treated, especially when in a favorable location.[197] The distribution of tumors in children differs markedly from adults.[198] While adult brain tumors usually occur in and around the cerebral hemispheres, the posterior fossa is the most common location in children of all ages.[199] The most common histologic subtype overall in children is glioma (52.9%), and the majority of these glioma are benign tumors (e.g., pilocytic astrocytoma).[197] Following glioma, embryonal tumors are also common during childhood, such as medulloblastoma.[196]

Intramedullary spinal cord tumors in the pediatric population usually are astrocytoma or ependymoma.[200] Astrocytoma is more common in infants and young children, while ependymoma is more common in older children and adults (Figure 16).[201]

In general, the clinical presentation of brain tumors depends on location, the tumor's invasiveness, and the patient's age.[202] Common manifestations include increased intracranial pressure, epilepsy, and progressive neurologic deficit.[197] Increased intracranial pressure may lead to irritability, lethargy, vomiting, and nocturnal headache.[196] The spinal cord tumors can also present with neurologic deficits, such as weakness, numbness, bowel or bladder function changes, back pain, and spinal deformity.[197,198]

Brain and spinal cord tumor diagnosis involves clinical evaluation, blood tests, and imaging studies (e.g., CT and MRI).[203] Usually, the first treatment of brain tumors is surgery. In addition, radiation and chemotherapy might be needed.[199] Chemotherapy is often combined with other types of treatment, such as surgery and radiation therapy.[201] In children younger than three years, it may be preferable compared to radiation therapy.[197] Examples of chemotherapeutics used include lomustine and methotrexate.[191,204] However, lomustine is only available in capsules, which could reduce acceptability among pediatric patients.[204] Compounding lomustine in **SyrSpend® SF** offers a versatile treatment option for pediatric patients, enhancing acceptability, while also broadening the range of available treatments beyond its standard capsule form.[60]

Prescription example

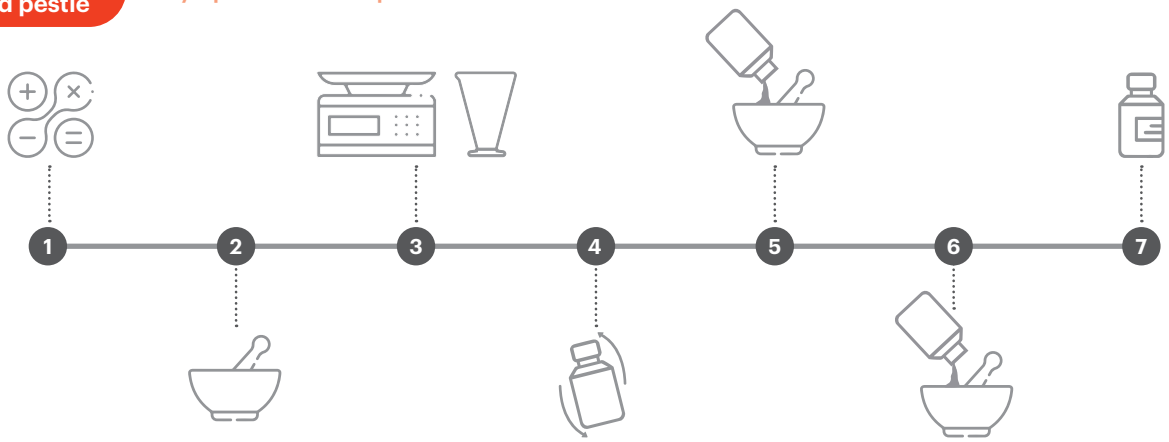
Lomustine in **SyrSpend® SF PH4**	4-10 mg/mL
Typical pediatric dose: 130 mg/m² orally	
Doses per week: 1 (every 6 weeks)	
Duration of treatment: determined by the doctor	

4. Compounding with SyrSpend® SF

SyrSpend® SF provides a range of compounding options, adaptable to its form - be it liquid or dry - and tailored to the chosen method of compounding.

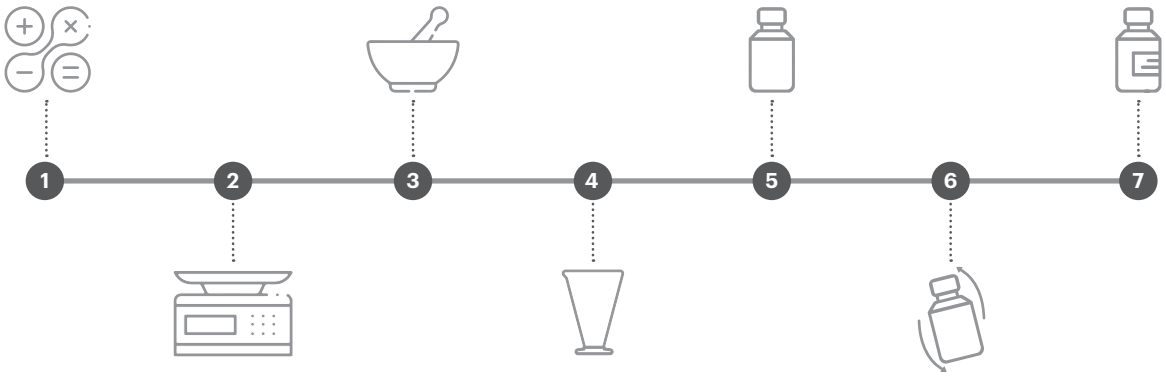
4.1. Compounding steps

Mortar and pestle — SyrSpend® SF PH4 liquid



1. Calculate the required quantity of each ingredient for the total amount to be prepared.
2. Grind the active substance (if necessary) in a mortar until a uniform, fine particle size has formed (not necessary for micronized powders)
3. Weigh and/or measure each ingredient accurately.
4. Shake the **SyrSpend® SF PH4 liquid** before use.
5. Add a small quantity of **SyrSpend® SF PH4 liquid** to the powder ingredients and triturate/mix to form a smooth paste.
6. Add additional **SyrSpend® SF PH4 liquid** geometrically to the final volume and mix well after each addition.
7. Package in an amber bottle and label, including the instruction "Shake before use".

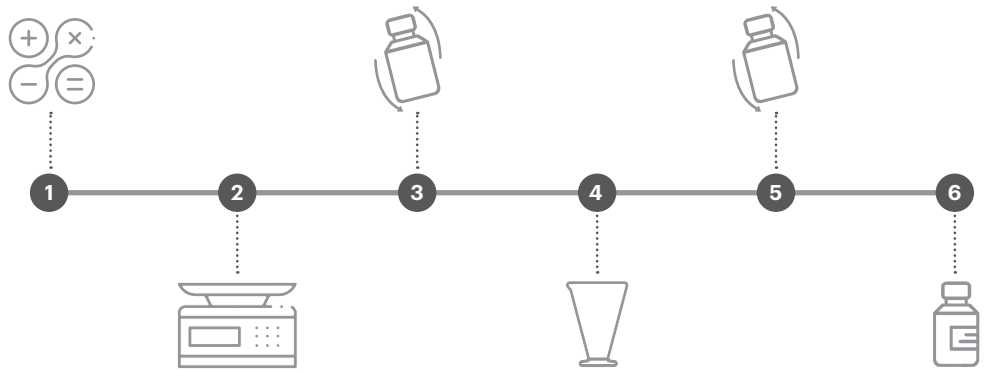
Mortar and pestle — SyrSpend® SF PH4 dry, SyrSpend® SF PH4 NEO or SyrSpend® SF Alka dry



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

SyrSpend® SF PH4 dry, SyrSpend® SF PH4 NEO or SyrSpend® SF Alka dry



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”.

FagronLab™ Mixing PRO

SyrSpend® SF PH4 liquid

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 to approximately 90% of the required volume with **SyrSpend® SF PH4 liquid** to the FagronLab™ jar containing the API.
4. 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 17).
5. When the mixing program is finished, remove the FagronLab™ jar from the device and transfer the suspension into a graduated conical flask.
6. Bring the preparation to the required final volume with **SyrSpend® SF PH4 liquid** and mix it with a glass rod.
7. Transfer to the final package and label accordingly, including the instruction "shake well before use".

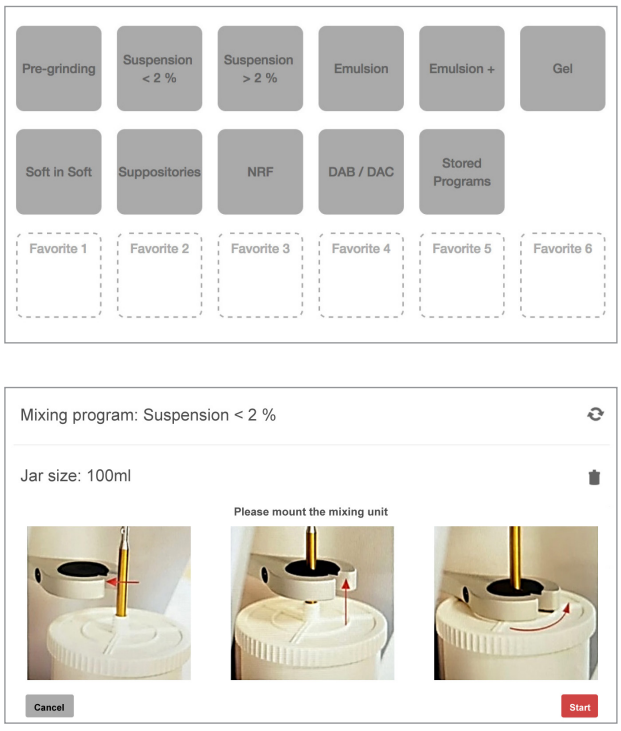


Figure 17. FagronLab™ Mixing PRO display.

FagronLab™ Mixing PRO

SyrSpend® SF PH4 dry, SyrSpend® SF PH4 NEO or SyrSpend® SF Alka dry

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 dry**, **SyrSpend® SF PH4 NEO** or **SyrSpend® SF Alka dry** 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 18).

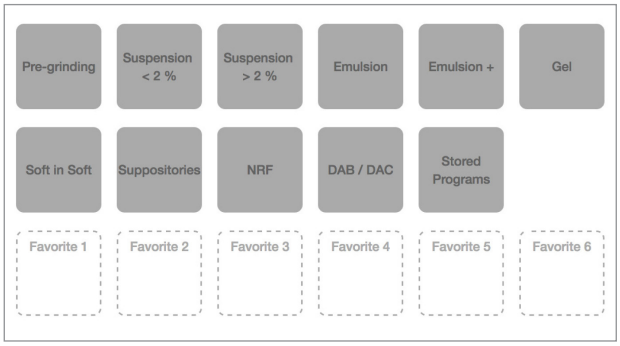


Figure 18. FagronLab™ Mixing PRO display.

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 19).
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".

Figure 19. Display intructions for the attachment of the FagronLab™ jar.

FagronLab™ WetMill Compact

SyrSpend® SF PH4 dry, SyrSpend® SF PH4 NEO or SyrSpend® SF Alka dry

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 20).

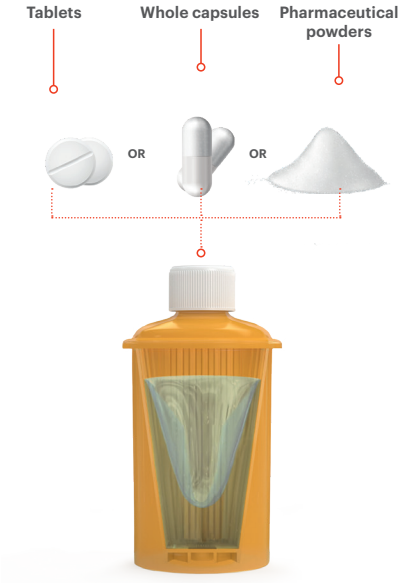
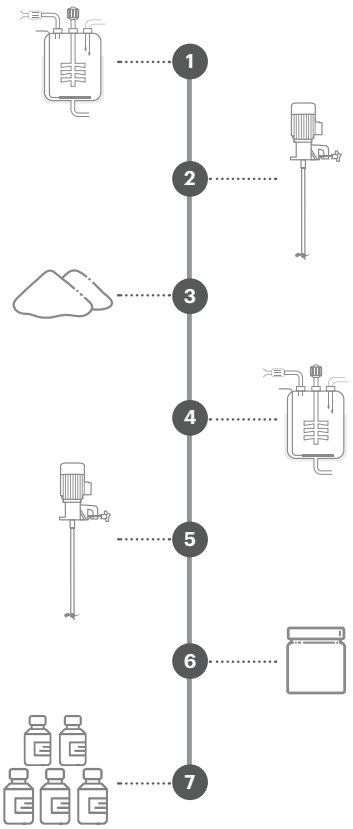


Figure 20. Compounding using the FagronLab WetMill Compact.

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 dry**, **SyrSpend® SF PH4 NEO** or **SyrSpend® SF Alka dry** 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".

Semi-Industrial compounding

SyrSpend® SF PH4 liquid



Equipment

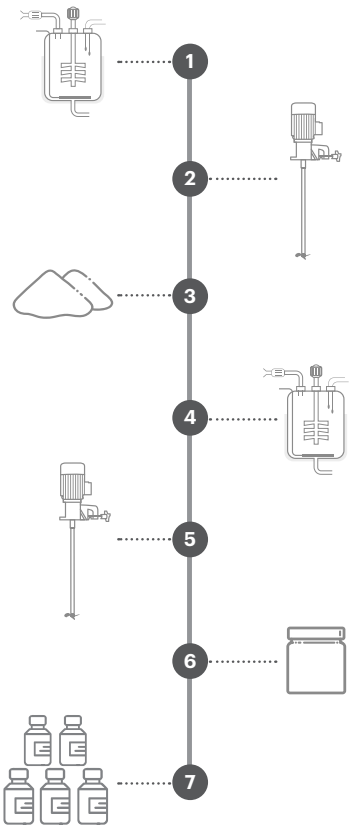
Mixing vessel, mixer, propeller blade, and balance.

Compounding steps

1. Add the 90% of the required amount of **SyrSpend® SF PH4** liquid to a suitable mixing vessel.
2. Start the mixer with a propeller blade at 300-500 rpm.
3. Slowly add the intended API and mix for 10-15 minutes or until all lumps are dispersed.
4. Increase 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.

Semi-Industrial compounding

SyrSpend® SF PH4 dry, SyrSpend® SF PH4 NEO or SyrSpend® SF Alka dry



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 lumps are dispersed.
4. Slowly add the required **SyrSpend® SF PH4 dry**, **SyrSpend® SF PH4 NEO** or **SyrSpend® SF Alka dry** 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. The product will have thickened up during the mixing.
8. 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".

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