SyrSpend® SF – FAQ

Version June 2016

Content

Introduction

SyrSpend® SF is an innovative vehicle product range for compounding of oral liquid dosage forms especially suitable for vulnerable patients and compatible with a broad range of APIs. The vehicles are widely used and supported by scientific evidence. The SyrSpend® SF FAQ is a document created by Fagron to support healthcare professionals in providing optimal care for their patients using SyrSpend® SF.

Should you have any questions or remarks, please contact your local sales representative.

Available information

1. **What SyrSpend® SF vehicles information are available and where can I find these?**
   The following overview includes all information about SyrSpend® SF:

   General information
   - Concept brochure, explaining the benefits of using SyrSpend® SF
   - Target group flyers, SyrSpend® SF is suitable for a broad group of patients:
     - Pediatrics
     - Geriatrics
     - Oncology patients
     - Hospitalized patients
   - Patient specific flyers, syringe cleaning instructions for patients when using SyrSpend® SF at home
   - Compatibility table , scientifically proven compatibility overview of APIs in SyrSpend® SF
   - Compounding formulations, instructions how to compound a specific API with SyrSpend® SF:
     - Compounding Matters online
     - Formulations app
   - SyrSpend® SF compounding instructions, general instructions for the pharmacist:
     - Compounding with SyrSpend® SF PH4
     - Compounding with SyrSpend® SF Alka
   - SyrSpend® SF versus traditional suspending vehicle video, explaining the superior suspending technology of SyrSpend® SF
   - SyrSpend® SF convenience packs instruction video, how to easily compound with SyrSpend® SF ready-to-use packs

   Published studies
   - Stability of Gabapentin in SyrSpend® SF
   - Stability of Metrodanizole Benzoate in SyrSpend® SF
   - Stability of Midazolam in SyrSpend® SF and SyrSpend® SF cherry
   - Stability of Omeprazole in SyrSpend® SF Alka (Reconstituted)
   - Stability of Oseltamivir Phosphate in SyrSpend® SF
   - Stability of Propanolol HCL in SyrSpend® SF
   - Stability of Rifampin in SyrSpend® SF
   - Stability of Ursodiol in SyrSpend® SF cherry flavored
   - Stability of Vancomycin in SyrSpend® SF
   - Stability of Verapamil in SyrSpend® SF
   - Stability assessment of 10 active pharmaceutical ingredients compounded in SyrSpend® SF
   - Feasibility of amlodipine besylate, chloroquine phosphate, dapsone, phenytoin, pyridoxine hydrochloride, sulfadiazine, sulfasalazine, tetracycline hydrochloride, trimethoprim and zonisamide in SyrSpend® SF PH4 oral suspensions
   - Stability of atenolol, clonazepam, dexamethasone, diclofenac sodium, diltiazem, enalapril maleate, ketoprofen, lamotrigine, penicillamine-D and thiamine in SyrSpend SF PH4 Oral Suspensions

- Compatibility of cholecalciferol, haloperidol, imipramine hydrochloride, levodopa/carbidopa, lorazepam, minocycline hydrochloride, tacrolimus monohydrate, terbinafine, tramadol hydrochloride and valsartan in SyrSpend® SF PH4 oral suspensions

Quality documentation:

- SyrSpend® SF Certificate of Analysis (CoA)
- SyrSpend® SF Material safety data sheet (MSDS)

Safety

2. For which patients is SyrSpend® SF suitable?

SyrSpend® SF is a starch based suspending vehicle specifically designed for vulnerable patient groups including:

- Neonates/children
- Hospitalized patients
- Oncology patients
- Elderly
- Diabetics
- Lactose-intolerant patients
- Coeliac patients
- Patients on a ketogenic diet

The WHO, EMEA and FDA guidelines were consulted when developing SyrSpend® SF, and thus the vehicle range is considered safe to use. SyrSpend® SF is based on starch and is gluten and lactose free [FDA 2014].

Sucralose

SyrSpend® SF vehicles contain sucralose derived from sucrose as sweetener. The body does not recognize sucralose as a carbohydrate, as it would for native sucrose. Sucralose does not affect normal carbohydrate metabolism, including insulin secretion and glucose and fructose absorption [McNeil Specialty 1998]. Sucralose is therefore suitable for consumption by diabetic patients and does not contribute to tooth decay. Sucralose is approved for use in food preparations by the FDA after reviewing over 100 safety studies [FDA 2015].

Preservatives

For patients that are sensitive to preservatives, such as neonates and patients with allergies, the SyrSpend® SF PH4 and Alka (dry, for reconstitution) are preservative-free alternatives.

SyrSpend® SF PH4 (liquid) contains the preservative sodium benzoate, but has a value of less than 0.1% [Joint FAO/WHO 2005] Sodium benzoate is Generally Recognized As Safe (GRAS) by the FDA and approved to be used as an anti-microbial agent with a maximum level of 0.1% in food [FDA 2015]. Furthermore, the FAO/WHO Expert Committee on Food Additives allows a limit of 5 mg/kg of sodium benzoate. However, neonates have an immature metabolism capacity for benzoic acid, thus we recommend the use of SyrSpend® SF (dry) [Le Bel 1988].

Modified food starch

Starch is on the FDA GRAS list and not toxic or harmful. The starch used in SyrSpend® SF falls under the FDA 21CFR 172.892 for modified starch and is safe for human consumption [FDA 2015] and is also Halal and Kosher certified.

Upon request a statement with different product characteristics of SyrSpend® SF and Halal/Kosher certificates can be provided by your local Fagron sales representative.

3. **Is SyrSpend® SF PH4 (liquid) cherry flavor suitable for patients with a cherry allergy?**
The flavoring is not advised for patients with a cherry allergy, because SyrSpend® SF PH4 (liquid) cherry flavor contains traces of cherry. The SyrSpend® SF PH4 (liquid or dry) unflavored can be used as an alternative

4. **Is SyrSpend® SF suitable to use for neonates?**
Yes, we especially recommend SyrSpend® SF PH4 (dry, for reconstitution) and SyrSpend® SF Alka (dry, for reconstitution) for neonates because these are preservative free. SyrSpend® SF Alka does contain calcium, for which the maximum recommended daily intake for neonates is 1,000 mg. The calcium value of SyrSpend® SF is far below the daily limit for neonates.

5. **Can SyrSpend® SF be used for patients on a ketogenic diet?**
All types of SyrSpend® SF can be used for patients on ketogenic diets. The carbohydrate content of the different vehicles can be used by healthcare professionals to calculate the daily carbohydrates intake from SyrSpend® SF suspensions. An overview with the nutritional values of SyrSpend® SF can be requested at your local Fagron company.

Compounding

6. **What makes SyrSpend® SF an ideal suspension base?**
SyrSpend® SF is a suspension base with starch as the main ingredient. Starch is responsible for a low viscosity when shaken and a high viscosity at rest. The starch in SyrSpend® SF allows the APIs to stay suspended and easy to (re)homogenize. SyrSpend® SF is compatible with a broad range of APIs as it is practically inert for chemical reactions. This broad compatibility is supported by over 100 scientific stability studies. In addition, SyrSpend® SF has a pleasant mouthfeel and taste and contains ingredients that are generally recognized as safe (GRAS) according to the FDA. It therefore has all the properties that would make the ideal suspending vehicle [Thompson et al 1998] for compounding.
The overview of avoided ingredients can be found in the SyrSpend® SF concept brochure, please contact your local sales representative for this.

7. **How do I prepare a suspension with SyrSpend® SF?**
All API specific compounding instructions can be found in the free Compounding Matters formulations database via www.fagron.com/en/knowledge/compounding-matters.
In general, compounding with SyrSpend® SF is easy and straight forward:

SyrSpend® SF PH4 (liquid)
Compounding instruction:
1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.

3. If necessary and applicable, in a ceramic mortar reduce the particle size of the API to a uniform, fine consistency.
4. Levigate the powder with an appropriate amount of SyrSpend® SF PH4 (liquid) to form a uniform paste.
5. Using geometric dilution, add SyrSpend® SF PH4 in small portions almost to final volume, mixing well after each addition of SyrSpend® SF PH4 to form a homogeneous suspension.
6. Transfer the suspension to a calibrated bottle or container.
7. Add sufficient quantity of SyrSpend® SF PH4 to bring to final volume, and mix well.
8. Label.
9. Dispense.

SyrSpend® SF PH4 and Alka (dry, for reconstitution)
Compounding instruction:

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. If necessary and applicable, in a ceramic mortar reduce the particle size of the API to a uniform, fine consistency.
4. Homogenize the powder with SyrSpend® SF PH4 (dry, for reconstitution) powder in the dispensing container.
5. Add the necessary quantity of purified water to volume and mix thoroughly.
6. Label.
7. Dispense in SyrSpend® SF (dry, for reconstitution) container.

SyrSpend® SF PH4 and Alka kit
Compounding instruction:

1. Prepare according to the compounding instruction.
2. Label and dispense in the original box.

All API specific compounding instructions can be found in the free Compounding Matters formulations database via www.fagron.com/en/knowledge/compounding-matters.

8. Is wetting of the API always necessary when compounding with SyrSpend® SF PH4 (liquid)?

In theory it is not necessary to wet APIs that are soluble in water. However, Fagron always advises to wet any API to make sure a homogeneous preparation is obtained without any lumps. Wetting can in most cases be done with a small amount of SyrSpend® SF PH4 (liquid) or purified water. Wetting with other solvents is also possible, but in that case it is advised to keep the avoided ingredients in SyrSpend® SF in mind to guarantee optimal patient comfort and safety.

For SyrSpend® SF PH4 and Alka dry, it is recommended to triturate APIs into powders in a mortar and shake the API and SyrSpend® SF powder to a homogeneous mixture before adding purified water.

9. If a suspension with an API and SyrSpend® SF is very thick, is it possible to dilute this?

If a suspension based on an API in SyrSpend® SF is too thick for proper administration, up to 50% of purified water can be added to adjust the consistency. This will not harm the active suspending technology. When more than 10% purified water is added, the suspension must be considered unpreserved. It must then be stored in the refrigerator and can be assigned a maximum BUD of 14 days (based on USP chapter 795), provided the API is sufficiently stable.

For immediate administration, a measured single dose can be diluted as desired.

10. Can suspensions with SyrSpend® SF be administered through nasogastric tubes?

All types of SyrSpend® SF can be administered through nasogastric tubes. Fagron has performed an in-house study on the compatibility of different SyrSpend® SF suspensions with nasogastric tubes of polyurethane, silicone and PVC tubes. The results of this study show that SyrSpend® SF is suitable for the administration of high-dosed APIs through even the smallest (external diameter of 5 French = 1.65 mm) nasogastric tubes available. Based on these outcomes, no compatibility issues are expected for SyrSpend® SF when administered through other enteral feeding tubes, such as gastrojejunal, jejunal, nasojejunal or gastric tubes. Upon request this data can be provided by your local sales representative.
Before and after administration of the API, the nasogastric tubes must be flushed with a sufficient amount of water, to prevent interaction with the API.

Note: We always recommend to use API raw material instead of crushed tablets when compounding suspensions for administration through nasogastric tubes, to avoid clogging of the tubes.

11. Is it possible to dilute the suspension when used in nasogastric tubes?

For administration of all API suspensions in SyrSpend® SF through nasogastric tubes, a measured dose of the API in SyrSpend® SF can be diluted with up to an equal amount of water directly before administration to facilitate easy passage of the suspension.
Before and after administration of the API, the nasogastric tubes must be flushed with a sufficient amount of water, to prevent interaction with the API.

12. I would like to prepare a suspension with an API for which there is no study in SyrSpend® SF available, what beyond use date do you recommend?

The starch used in SyrSpend® SF is generally inert for chemical reactions and therefore makes SyrSpend® SF compatible with a broad range of APIs. In cases where a specific study or stability statement is not available for a certain API in SyrSpend® SF we would recommend to use a maximum 14 days BUD and storage in the refrigerator based on USP chapter 795 [USP 2015].

13. What should I do when SyrSpend® SF sticks to the cylinder walls during measuring?

The active suspending technology (high viscosity at rest) can cause (still-standing) SyrSpend® SF to stick a little to cylinder walls. If a pharmacist is concerned about the accuracy of its final preparation, two options are possible:

1. Compound the suspension based on weight instead of volume, densities are available upon request at your local Fagron sales representative.

2. Transfer the suspension to a graduated prescription bottle or flask during the geometric dilution compounding step. With the graduated prescription bottle or flask addition it is easy to bring the suspension to the final volume using SyrSpend® SF.

Compatibility of APIs

14. How can I determine the stability of an API in SyrSpend® SF?

Fagron has studied over 100 APIs of which the compatibility data is available. In case the required API is not listed in our compatibility overview, steps 1-4 as stated below can be performed to estimate the maximum BUD.

For any suspension it is important to look at two types of stability: the microbiological stability of the suspension and the chemical-physical stability of the API in the suspension. The overall stability is always determined by the shortest stability of the two.

Step 1: Determine if the API is stable in acid or alkaline environment. The Martindale or Trissel's are good sources for this type of information. For acid-stable APIs use SyrSpend® SF PH4 (liquid or dry); for alkaline-stable APIs use SyrSpend® SF Alka (dry, for reconstitution)

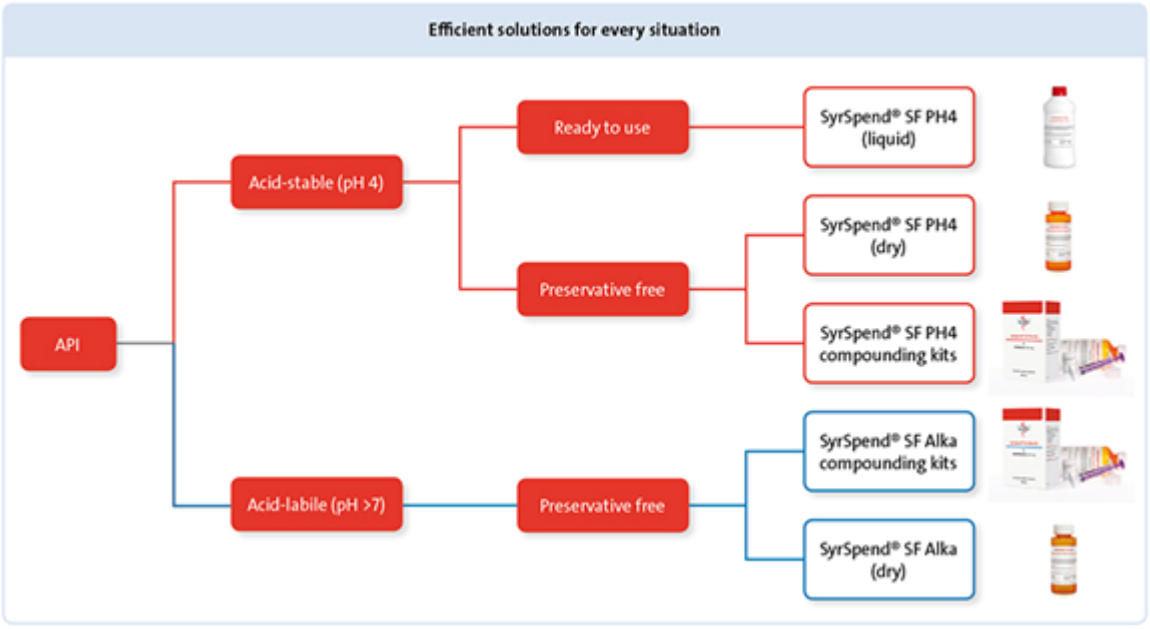

Figure 1. The SyrSpend® SF vehicles are compatible with an extensive range of APIs. It is possible to choose the most suitable product for compounding with both acid and alkaline options.

Step 2: Determine the API's susceptibility to thermal degradation. If susceptible, it is recommended to store in the refrigerator. A PubMed and/or Trissel's search will usually tell whether or not preparations with a specific API are generally stored in the refrigerator.

Step 3: Determine the API's water solubility. Water will be the main cause of API degradation through hydrolyses and oxidation. The amount of API solubilized at any time point, will in most cases be the determining factor in its stability. The Martindale or Trissel's are good aqueous preparations or other

preparations with comparable composition to SyrSpend® SF. Please keep in mind that changing the salt form of an API or the pH of the vehicle can alter its solubility and therefore stability.
Step 4: If based on the steps above you are not sure yet the following can be recommended:
Based on the USP (chapter 795), aqueous oral preparations can be assigned a 14 day beyond use date stored in the refrigerator, when no stability data is available. (see also: 'I would like to prepare a suspension with an API for which there is no study in SyrSpend® SF available, what beyond use date do you recommend?')

Flavoring and taste-masking

15. Is it possible to add flavorings to SyrSpend® SF PH4 (liquid), SyrSpend® SF PH4 (dry, for reconstitution) and SyrSpend® SF Alka?
SyrSpend® SF is believed to be already sufficiently taste-masking for most APIs. Besides, most flavoring available in pharmacies contain ingredients that were avoided in SyrSpend® SF because they are harmful for the patient (e.g. ethanol, propylene glycol, and others). Nevertheless, adding different flavors, including avoided ingredients, to SyrSpend® SF is possible. The flavor of choice generally depends on the specific taste of the API [B. Nayak *et al* 2012; S. Schiffman *et al* 2002; Z. Ayenew (see instructions) 2009].

16. Does the cherry flavor of SyrSpend® SF PH4 (liquid) affect API stability?
No, APIs in either SyrSpend® SF PH4 (liquid) unflavored or cherry flavored have the same stability.
This is also demonstrated in the article:
Stability assessment of 10 active pharmaceutical ingredients compounded in SyrSpend® SF

Working with raw materials, capsules, tablets and other API sources

17. Is it possible to use API-sources other than the API raw material when compounding with SyrSpend® SF?
Yes, this is possible with the professional judgment of the compounding pharmacist.
For most tablets we do not expect issues, however, be careful with tablets containing iodine as these will interact with the starch in SyrSpend® SF. Also, it is not recommended to crush coated tablets in general. Especially in case of using tablets or capsules that are slow-release (to prevent dose-dumping) or gastro-enteric coated (to prevent rapid degradation of the API).

Additionally, it is always recommended to compound from raw materials to avoid:
- Calculation errors
- Additional excipients (chemical reactions, side effects)
- Adding more solid particles than necessary
- Inhomogeneous particle size distribution

The above mentioned compounding errors can result in complications for patients.

18. Which APIs in SyrSpend® SF were tested by using the API from a tablet or capsule?

The aim was always to perform the study with the raw material in SyrSpend® SF, if not available, tablets/capsules were used. The source of the API is indicated on the SyrSpend® SF compatibility statements, which are available upon request at your local Fagron sales representative.

SyrSpend® SF kits

19. What makes the SyrSpend® SF convenience packs (e.g. omeprazole) especially suitable for children?

The composition of the suspension base SyrSpend® SF meets all the requirements of the EMA pediatric guidelines for additives [European Medicines Agency 2006]. The flavor is neutral and it masks the taste of APIs without being cariogenic, which is especially important for children. All SyrSpend® SF convenience packs are free of preservatives and help prevent common medication and compounding errors such as:

- Wrong API
- Wrong dosage strength
- Incorrect preparation
- Incorrect administration

20. What is the expiry date of an SyrSpend® SF Alka & omeprazole convenience pack if left unrefrigerated?

If the kit is left unrefrigerated and the suspension is not yet compounded, the expiry date is maximum 6 months, but no longer than the expiry date mentioned on the packaging.

Microbiological stability

21. Is there a microbial test available for SyrSpend® SF PH4 (liquid) and SyrSpend® SF (dry, for reconstitution)?

Yes, antimicrobial effectiveness tests performed according to pharmacopoeia standard have shown that the sodium benzoate in SyrSpend® SF PH4 (liquid) has sufficient preservative efficacy to allow for a shelf life of 3 years, or 12 months after opening. For the dry versions after reconstitution, the maximum BUD is 60 days if the physical-chemical study allows (under the condition that the suspension is hygienically compounded and used. Statements can be provided by your local Fagron sales representative upon request.

22. Can the study results for SyrSpend® SF PH4 (liquid) be extrapolated to SyrSpend® SF PH4 (dry, for reconstitution)?

SyrSpend® SF PH4 liquid and SyrSpend® SF PH4 (dry, for reconstitution) have similar ingredients in similar concentrations. Their comparable chemical compatibility has been demonstrated in the 'Oseltamivir in SyrSpend® SF study article'.

Microbiological stability studies have shown that SyrSpend® SF PH4 (dry, for reconstitution) and SyrSpend® SF Alka (dry, for reconstitution) remain microbiologically stable for up to 60 days when compounded using purified water (tap water can have a higher microbiological contamination grade from the start). The dry versions do not contain a preservative and therefore can have a shorter BUD than suspensions compounded in the liquid. (see also: 'Is there a microbial test available for SyrSpend® SF PH4 (liquid) and SyrSpend® SF (dry, for reconstitution)')

Unless specifically tested otherwise, we recommend using the suspensions based on SyrSpend® SF PH4 (dry, for reconstitution) or SyrSpend® SF Alka (dry, for reconstitution) for a maximum of up to 60 days when compounded and used hygienically.

Always ensure hygienic use including:

- Cleaning and drying of the oral syringe and tip extender after each use (see instructions).
- Replacement of the oral syringe and tip extender after a maximum of 7 days.
- Storage of the suspension in a clean refrigerator (2-8 °C).

When in doubt about the hygiene conditions the maximum BUD after reconstitution is 30 days.

23. When compounding omeprazole in SyrSpend® SF Alka there are some 'lumps' in the final suspension.

To avoid lumps (agglomerates) when directly compounding omeprazole with SyrSpend® SF Alka in the dispensing container, it is essential that both the omeprazole and SyrSpend® SF Alka powder are quickly and completely wetted. To ensure a homogeneous suspension is obtained, the following compounding steps are crucial:

1. Triturate omeprazole into a powder in a mortar and add the API to SyrSpend® SF Alka powder by shaking both powders in the container before water is added.
2. Add sufficient, but not all purified water. About 50-60 ml works properly. Less than 50 ml usually results in some lumps.
3. Forcefully shake the powders with the added water. No unsuspended powder should be visible at the bottom of the container after shaking. If still some powder is stuck at the bottom, forcefully tapping the bottle on a hard surface and shaking will help. The result after this step is a very thick suspension that sticks to the container walls.
4. Add additional purified water almost to the final volume and shake again forcefully. Directly adding sufficient water to 100 ml mark is difficult, as the marking can be hard to read with the thick suspension sticking to the container walls.
5. Add purified water to 100 ml mark and shake again.

After step 5 no, or only some very small, agglomerates could be visible. If some minor agglomerates are visible, these will usually automatically disappear within 5-10 minutes (and before the patient takes the first dose). These lumps are starch agglomerates that are not yet properly wetted in the suspension.

24. Is it normal that the color of omeprazole in SyrSpend® SF Alka changes over time?

Yes, omeprazole degrades to a grey/purple component in an acid environment or when stored for prolonged periods of time outside the refrigerator (see figure 2). Limited grey/purple discoloration is acceptable, however when there is significant change in color the suspension must be discarded. A statement, including a reference chart for the color of the suspension, is available upon request at your local Fagron sales representative.

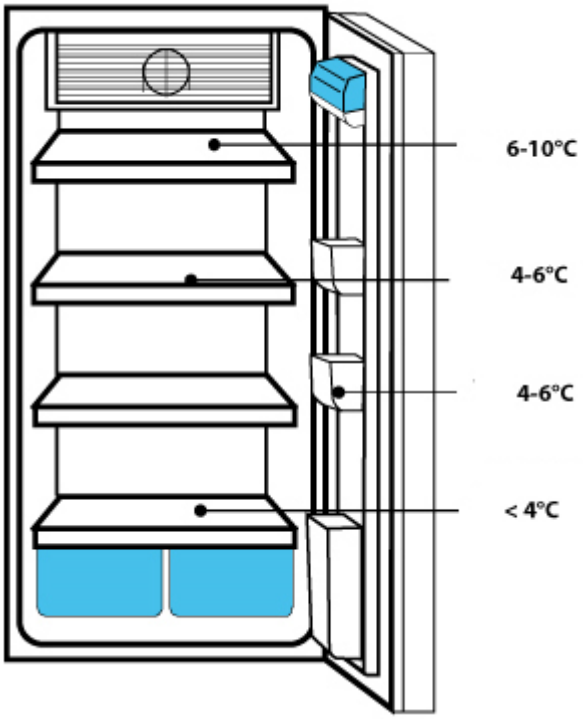

Figure 2. It is recommended to always store the omeprazole suspension at the lowest level (4 °C) in the refrigerator. Ensure the suspension does not touch the backside of the refrigerator as it may freeze the suspension.

25. Can I crush omeprazole tablets for a suspension in SyrSpend® SF Alka?

Fagron does not recommend crushing coated omeprazole tablets for compounding in SyrSpend® SF Alka. There is a risk when using tablets or capsules that are slow-release or gastro-enteric coated. The best option is to use the SyrSpend® SF Alka & omeprazole kit.

Scientific references

- B. Nayak et al, Taste Masking Techniques - An Updated Review (2012).pdf- Overview – taste masking recommendations for APIs. 2012
- European Medicines Agency, Formulations of choice for the pediatric population. 2006
- FDA, Disposition of sodium benzoate in newborn infants with hyperammonemia. 1983
- FDA, Food additives permitted for direct addition to food for human consumption. 2014
- FDA, Sodium benzoate GRAS status. 2013
- Food and Drug Administration. "Title: 21 Food and Drugs - Part 184 Direct Food Substances Affirmed As Generally Recognized as Safe: Subpart 184.1733 Sodium Benzoate." 01 April 2015. Electronic Code of Federal Regulations. 20 12 2015 <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1733>.
- Joint FAO/WHO Expert Committee on Food Additives (JECFA). "Sodium Benzoate". Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives. (2005).
- LeBel, M. et al. "Benzyl alcohol metabolism and elimination in neonates." Developmental pharmacology and therapeutics. 11.6 (1988); 347-356.
- McNeil Speciality, Splenda (promotional information from McNeil Specialty Products Company). 1998
- National Institute of Health – Office of Dietary Supplements, Calcium fact sheet for consumers. 2013
- P.A. Whaley, M.A. Voudrie, B. Sorenson, Stability study omeprazole in SyrSpend® SF Alka. 2012
- S. Schiffman, J. Zervakis, Taste and smell perception in the elderly - effect of medications and disease. 2002
- USP chapter 795, Stability of compounded preparations. 2015
- Thompson, J. E., A Practical Guide to Contemporary Pharmacy Practice, Lippincott Williams & Wilkins, Baltimore, Md., 1998, p. 28.1
- World Health Organization, Benzoic acid JECFA safety status. 1996
- Z. Ayenew et al, Trends in Pharmaceutical Taste Masking Technologies - A Patent Review. 2009

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