Choice of Suspending Vehicle for a Pediatric Fit-for-Purpose Formulation

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1 - Introduction

Development of oral dosage forms for children is a special challenge due to the pediatric population's heterogeneity and special requirements like e.g. dosing flexibility, palatability and ease to swallow. In addition, the pediatric formulation should only contain ingredients suitable for children. Suspensions are suitable dosage forms for all age groups as they give a high degree of dosing flexibility, can be easily swallowed and due to the large surface area of the dispersed drug more API is available for absorption. Hydrophobic or poorly soluble drugs can be dispersed so that higher drug loads than in solutions can be obtained.[1] Despite the advantages there are also several challenges concerning suspensions: It is possible that dosage variations occur because of nonuniform mixing of the product. There might be physical instabilities including sedimentation, caking and difficulty in redispersibility. Stability problems of the API due to the aqueous environment may also occur.[2] In order to enhance stability and, especially in early phase clinical trials as a fit-for-purpose formulation a powder-in-bottle-approach may be beneficial. The API itself or a powder formulation is constituted as a suspension by adding an appropriate suspending vehicle. Fruit juices, cola drinks or commercially available suspending solutions like Ora-Sweet®, Ora-Plus® or Syrspend® are examples of suspending vehicles used in studies described in literature.[3]

In the present study the use of different suspending vehicles to constitute a certain amount of model compound to a suspension was evaluated. Physico-chemical characteristics of the API as well as considerations related to the different pediatric age populations were taken into account. The prepared suspensions were characterized directly after constitution as well as after 21 days as part of an in-use stability study to select an optimum suspension vehicle.

Figure 1: Examples of commercially available Syrspend® suspending vehicles

2 - Material and Methods

API: Model compound A is a non-hygroscopic small molecule salt. Characteristics of the compound can be found in table 1.

Suspending Vehicles: Syrspend® SF pH4 liquid, cherry-flavoured, and Syrspend® SF pH4 powder (Fagron GmbH, Glinde, Germany) were chosen as commercially available suspending vehicles. In addition, a commercially available fruit juice Hipp Frucht Plus (Hipp GmbH & Co. KG, Pfaffenhofen, Germany) specially designed as beverage for younger children of six months age and older was chosen. It contains a mixture of different fruit juices including apple juice, banana juice, orange juice and water with addition of vitamin C.

Suspension Preparation Method: Syrspend® suspensions with a concentration of 5 mg/mL were prepared according to the supplier's recommended preparation method. Hipp Frucht Plus formulations with a concentration of 5 mg/mL were prepared by weighing in the correct amount of model compound A, then Hipp Frucht Plus was added and the suspensions were shaken for 2 minutes.

Suspension Characterization:
Samples were immediately analyzed for:

- pH (Mettler Toledo FiveEasy™, n=3)
- Viscosity (Haake-Mars II, n=1)
- PSD in suspension (Malvern Mastersizer 3000, n=3)
- Dose accuracy over a time period of 20 mins (HPLC Waters 2690, Waters Dual λ Absorbance Detector, n=3 bottles)
- Dose uniformity (HPLC, n=2 bottles, 5 times 3 mL each)
- Dissolution (n=3 bottles)
- In-use-stability over 21 days: (Syrspend ® suspensions only)
  - Content
  - Sedimentation behavior (visually)
  - Dissolution

Table 1: Characteristics of compound A

	Attribute	Value
Solubility	Water	0.74 mg/mL
	pH 1	26.0 mg/mL
	pH 6.5	0.8 mg/mL
	pK_a (free base)	8.85

Table 2: Particle size distribution, pH and viscosity of constituted suspensions

Suspending Vehicle	pH	Viscosity (mPa*s)*	Particle Size Distribution (µm) d_{10}	d_{50}	d_{90}
Syrspend SF pH4 *liquid*	4.2	235	26	43	67
Syrspend SF pH4 *powder*	4.2	833	21	74	223
Hipp Frucht Plus	4.2	36	NA	NA	NA

*Viscosity values measured at shear rate of 10 s^{-1}

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3 - Results and Discussion

Characterization of Constituted Vehicles: All formulations show a pH of about 4.2 (table 2). In terms of rheology the vehicles were found to have a large variability. Syrspend® SF powder suspension was found to be the most viscous of all formulations with more than three times the viscosity of Syrspend® SF liquid suspension at a shear rate of 10 s^{-1} with a high degree of thixotropy. Hipp Frucht Plus suspension was found to have the lowest viscosity. In addition, Syrspend® SF pH4 liquid suspension was found to have a tighter particle size distribution and smaller particles compared to Syrspend® SF pH4 powder suspension.

Dissolution: Dissolution testing was carried out and dissolution was found to be fast for all formulations. More than 90% of model compound A was dissolved within 10 mins for all tested suspending vehicles. Results are shown in figure 2.

Dose Accuracy: A dose accuracy test was performed for all suspensions over a period of 20 mins to determine how long after shaking a patient can still get an accurate dose out of a bottle. Results are shown in figure 3. Accurate doses of both Syrspend® formulations could be removed from the bottles for the tested 20 mins, although the overall content of compound A in the Syrspend® pH4 powder formulation was found to be slightly below the target concentration. A different result was found for the Hipp Frucht Plus formulation. Due to the low viscosity of the juice the particles started to settle shortly after suspension preparation so that after 10 mins waiting time a content of only 90% of the compound A target content was measured.

Dose Uniformity: Figure 4 shows dose uniformity results for all formulations. Dose uniformity tests showed the best results for the suspension with Syrspend® SF pH4 liquid as vehicle. With a mean content of 97.7% (all % values in (w/v)), RSD of 0.8% (AV = 2.5) dose uniformity is well given for model compound A. In contrast, the suspension constituted with Syrspend® SF pH4 powder showed an overall low mean value of 90.2% (RSD = 1.5%, AV = 5.2). Hipp Frucht Plus showed least dose uniformity with results higher than 100% indicating early on sedimentation of particles within the formulation. Individual results between 99.6% and 105.7% were found with a mean of 102.4% (RSD = 1.87, AV = 8.51).

In-Use Stability Study: Still after 21 days storage at 2-8°C and room temperature constituted suspensions with Syrspend® SF pH4 liquid showed excellent content values (between 97.0 and 102.8%) indicating a good stability of model compound A in the suspending vehicle. Dissolution was found to be satisfying as well. At the same time formulations with Syrspend® SF pH4 powder showed a drop in content after about 19 days of storage at 2-8°C and after about 14 days storage at room temperature. Dissolution after 21 days was found to be still good with over 90% dissolved after 10 mins. Due to the limited in-use time (consume within 3 days) of Hipp Frucht Plus no in-use stability over 21 days was carried out. For both Syrspend® formulations no sedimentation tendency could be observed within 21 days of storage. However, particles in Hipp Frucht Plus suspension started to settle already after 2.5 mins, which is explainable by the low viscosity of the formulation.

Figure 2: **Dissolution of constituted suspensions**

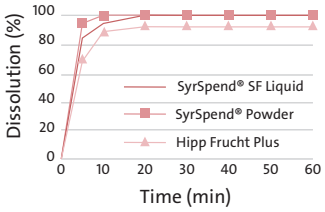


Figure 3: **Dose Accuracy over 20 mins**

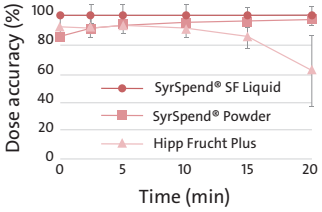


Figure 4: **Dose uniformity results**

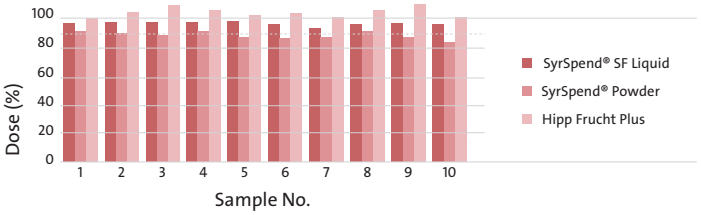


Figure 6: **In-use stability – Content**

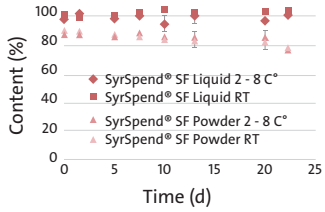
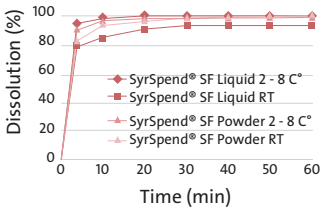


Figure 6: **In-use stability – Dissolution after 21 days**



4 - Conclusions

The study showed that Syrspend® SF pH4 liquid cherry flavoured is an excellent suspending vehicle for compound A to prepare a fit-for purpose pediatric formulation. After constitution of a Syrspend® SF pH4 liquid suspension formulation a patient can draw an accurate dose for at least 20 mins (maximum duration tested) and the suspension was found to be stable for 21 days. Syrspend® SF pH4 liquid cherry flavoured is superior to the Syrspend® SF pH4 powder in terms of dose accuracy and dose uniformity. The overall larger particle sizes and a wider particle size distribution of Syrspend® SF pH4 powder influences the performance of the suspension. Although the taste of Hipp Frucht Plus might be beneficial for palatability, the prepared suspensions were found to be less uniform due to the low viscosity of the juice mixture. Therefore, Hipp Frucht Plus cannot be recommended as supending vehicle. However, the constitution method for Syrspend SF pH4 liquid suspensions needs to be developed carefully due to the high viscosity of the vehicle.

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