Development and verification of standard vehicles for investigating the compatibility of oral paediatric drug products with fruit juices

Carolin Eckert[1], Cordula Stillhart[2], Leonie Wagner[2], Emmanuel Scheubel[2], Isabelle Prevot[2], Marc Lindenberg[2], Sandra Klein[1]

[1] University of Greifswald, Germany
[2] F. Hoffmann-La Roche Ltd., Switzerland

sandra.klein@uni-greifswald.de

Purpose

The co-administration of oral medicines with small amounts of liquids and soft foods, also referred to as dosing vehicles (Figure 1), is a common practice to ensure acceptability in oral paediatric drug therapy [1]. However, given the large number of vehicles that are theoretically available for this purpose, it is very difficult to ensure which vehicle can be safely used for this type of administration [2]. Also, commonly used vehicles vary both between product types and within vehicle types in terms of their nutritional composition and physicochemical properties and can therefore exert different impacts on the quality and performance of a drug product [3]. Conducting compatibility studies with all types and variants of vehicles would be ideal but is not feasible. This consideration gave rise to the idea of a standard vehicle toolbox for *in vitro* experiments, which could be used to combine as many vehicle properties as possible in compatibility studies in a targeted and reproducible manner to enable a sound risk assessment regarding the co-administration of a drug product with different vehicles of the same type. Standard vehicles that mimic the composition and physicochemical properties of fruit juices (simJuice) were chosen as a starting point.

Figure 1. Mixing medicines with dosing vehicles before administration.

Materials and Methods

For the development of the standard vehicles, different original fruit juices (n = 30) were characterised regarding their nutritional composition and physicochemical properties, i.e., pH, buffer capacity, osmolality and surface tension, as described in [4]. All tests were performed in sextuplicate (n = 6) and except for osmolality, the parameters were recorded at 25 °C. To avoid simulating every single original vehicle, a DoE, which combines and varies the minima (MIN) and maxima (MAX) of the measured properties of the original vehicles, was used to design a set of simulated fruit juice vehicles (simJuice vehicles) and is shown in Table 1. In addition to the simJuice vehicles obtained by combining different MIN and MAX properties, a so-called centre point (CP) simJuice, represented by physicochemical properties reflecting the midpoint between the MIN and the MAX value of each of the values, was considered (Table 1). The development procedure for the standard vehicles is illustrated in Figure 2. After preparation of the individual simJuice vehicles, physicochemical properties of all simJuice vehicles were determined using the same test methods as for the original vehicles. In Addition, for initial verification, *in vitro* dissolution experiments (Figure 3) with furosemide mini-tablets were performed with an original vehicle and a set of simJuice vehicles according to Freerks *et al.* [5].

Table 1. DoE for the development of the simJuice vehicles; Θ = centre point (CP), + = maximum, - = minimum of target property, (MAX) = maximum and (MIN) = minimum target values only.

run	pH	buffer capacity	osmolality	surface tension
1 (CP)	Θ	Θ	Θ	Θ
2	+	-	-	+
3	-	-	+	+
4	-	+	+	-
5 (MAX)	+	+	+	+
6	+	-	+	-
7	+	+	-	-
8 (MIN)	-	-	-	-
9	-	+	-	+

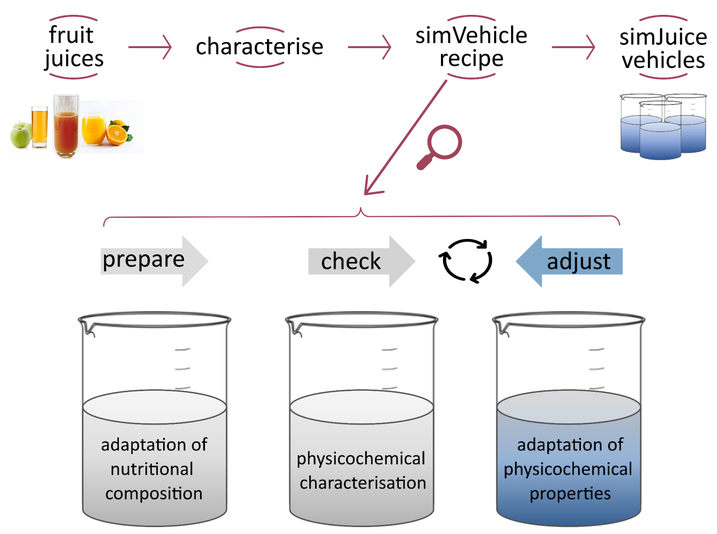

Figure 2. Procedure of the standard vehicle development.

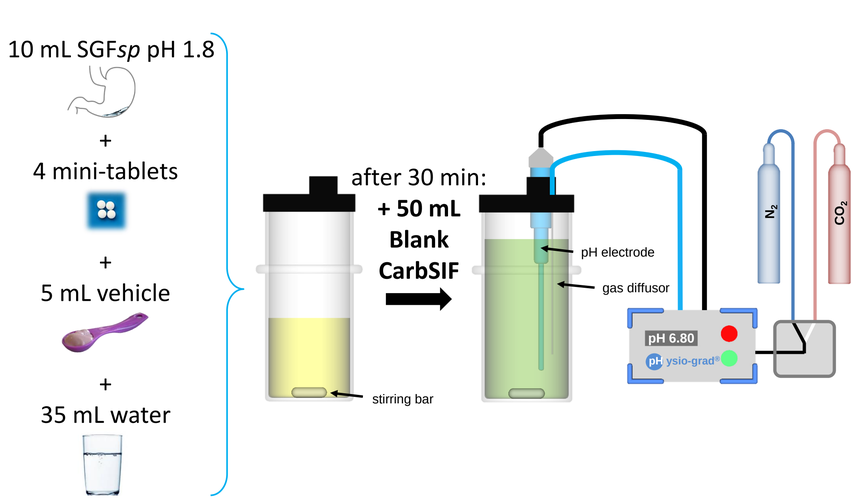

Figure 3. Dissolution setup using the Kiddy-Size Dissolution System (KiDS) with a previously reported dissolution method [5].

Results

A total of nine liquid simJuice vehicles comprising physicochemical properties that represent selected combinations of MIN and MAX values of the target parameters pH, buffer capacity, osmolality and surface tension of the original vehicles, or the respective CP values only, were developed. The idea was to keep the media preparation as simple as possible and to use the same components for all media. The nutritional values for carbohydrate, fat, and protein content could be set very precisely. The liquid simVehicles, for which all target values of the physicochemical properties were either the CP (simJuiceCP), the MAX (simJuiceMAX) or the MIN (simJuiceMIN) represented the three main simVehicles and only the results of the characterisation of these vehicles are presented hereinafter. The physicochemical properties of these three simJuice vehicles are shown in Figures 4. With all the presented, but also with all other simJuice vehicles of the DoE, the target values for each physicochemical parameter could be properly matched.

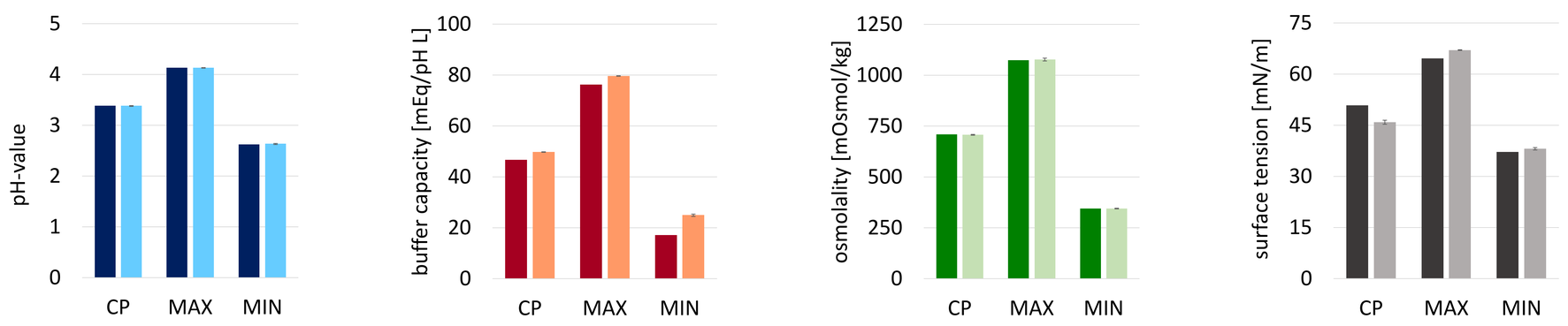

Figure 4. Target values (dark columns) and actual values (light columns, mean of n = 6 (±S.D.)) of the physicochemical properties of simJuiceCP, -MAX and -MIN.

The results of the *in vitro* dissolution experiments, conducted with one original fruit juice and the three main simJuices, are presented in Figure 5. As can be observed, similar release profiles were obtained when simulating co-administration of furosemide mini-tablets with original and standard vehicles.

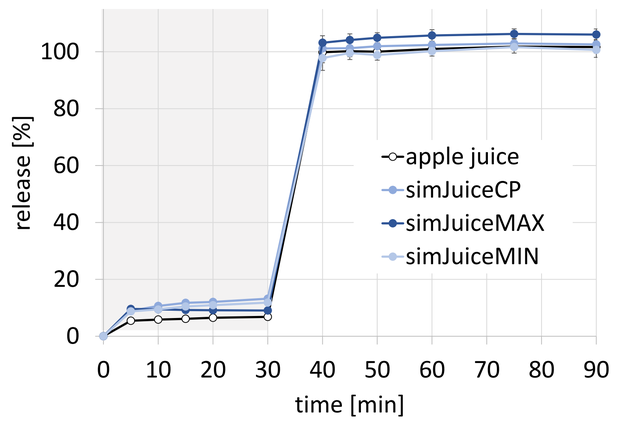

Figure 5. Furosemide release of the mini-tablets in simulated gastric- (0-30 min) and small intestinal conditions (30-90 min) of infants when simulating tablet co-administration with original and standard vehicles for fruit juice; mean of n = 3 (±S.D.).

Conclusion

The aim of the present study was to develop a first set of standard vehicles for a toolbox that can be used for *in vitro* experiments to obtain reliable information on the compatibility of oral paediatric dosage forms with different dosing vehicles. The established simVehicles represent the basic composition and variable physicochemical properties of fruit juices and the results of the *in vitro* experiments clearly show that with a set of standard vehicles it is possible to simulate the co-administration of the investigated dosage form with the corresponding vehicle type. Of course, further dosage forms will need to be investigated for validation, but the first important step has been taken towards establishing a standard vehicle toolbox that can be used worldwide to assess drug product-vehicle interactions.

References

1. Freerks, L. *et al.,* Pharm Res 39:497–509 (2022)
2. FDA Draft Guidance. Use of Liquids and/or Soft Foods as Vehicles for Drug Administration (2018)
3. Matir, J. *et al.*, AAPS PharmSciTech 21:287 (2020)
4. Freerks, L. *et al*., Journal Pharm Sci 111:51-61 (2022)
5. Freerks, L *et al.*, Eur J Pharm Biopharm 156:11-19 (2020)

Acknowledgements

The financial support of this work through a PhD Grant from F. Hoffmann-La Roche Ltd is gratefully acknowledged. Further, we would like to thank Anne Brechlin and Maike Penkuhn for their support in the development of part of the standard vehicles.