



Formulating a poorly water soluble drug into an oral solution suitable for paediatric patients; lorazepam as a model drug



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ABSTRACT

Introduction: Many drugs are unavailable in suitable oral paediatric dosage forms, and pharmacists often have to compound drugs to provide paediatric patients with an acceptable formulation in the right dose. Liquid formulations offer the advantage of dosing flexibility and ease of administration to young patients, but drug substances often show poor aqueous solubility. The objective of this work was to study different solvents and matrices to design a liquid formulation for poorly water soluble drugs, using lorazepam as model drug.

Methods: Three different formulation strategies were explored to improve the solubility. Firstly, water-soluble organic solvents were used to improve the aqueous solubility directly, secondly, ionic surfactants were used to solubilise the model drug, and thirdly, complexation of lorazepam with cyclodextrin was studied. Specific attention was paid to excipients, adequate taste correction and palatability. For the final formulation, physical and chemical stability and microbiological quality were assessed for 12 months.

Results: An organic solvent based formulation, containing a mixture of polyethylene glycol and glycerol 85%, with a minimum amount of propylene glycol, proved to be physically and chemically stable. Development of the non-ionic surfactants formulation was discontinued due to taste problems. The cyclodextrin formulations were physically stable, but lorazepam content declined to 90% within five months. The final formulation contained in volume concentration (%v/v) 87% glycerol, 10% polyethylene glycol 400 and 3% propylene glycol. Orange essence was the preferred taste corrector. The formulation remained stable for 12 months at 4 °C, with lorazepam content remaining >95%. Related substances increased during the study period but remained below 2%. In-use stability was proven up to 4 weeks.

Conclusion: An organic solvent based oral formulation was shown to be superior to a non-ionic surfactant based formulation or a cyclodextrin formulation. These results may help to formulate paediatric formulations of other poorly water soluble drugs, to aid pharmacy compounding.

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1. Introduction

Many drugs are unavailable in suitable oral paediatric dosage forms (van Riet-Nales et al., 2011), therefore, pharmacists often have to compound drugs to provide paediatric patients with an acceptable formulation in the right dose. In the reflection paper released by the paediatric working party of the European Medicines Agency (EMA) on formulations of choice for the paediatric population, solutions/drops and effervescent dosage forms are considered to have the highest applicability in a population of young patients (Committee for Human Medicinal Products

(CHMP), 2006). Capsules can be compounded extemporaneously in the dosage needed, but they need to be dissolved before administration and are difficult to administer through feeding tubes. Another disadvantage of extemporaneously compounded capsules is the difficulty in obtaining adequate content uniformity at low dosages.

Liquid formulations have the advantage of dosing flexibility and a reduced risk of choking. They can also be applied in other populations, such as geriatric patients with swallowing difficulties, or in a palliative setting. Possible disadvantages of liquid formulations are issues with stability and palatability, parameters that need to be considered in the design. As an alternative for liquid formulations, the development of mini-tablets has been given a lot of attention in the past years (Aleksowski et al., 2015). They provide dosing flexibility and ease of

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administration, and generally solid formulations are more stable than liquid formulations. However, for most compounding pharmacies, tableting is not an available technique. Liquid formulations are therefore still commonly applied by pharmacist that need to compound for paediatric patients, both on individual and batch scale.

Drug substances sometimes show poor aqueous solubility. The use of solubilizing excipients can improve this, but especially in the paediatric population, the use of excipients needs to be considered carefully, with respect to safety and palatability. The objective of this study was to explore different formulation strategies for a poorly water soluble drug substance, lorazepam was chosen as a model drug.

Lorazepam (7-chloro-5-(2-chlorophenyl)-3-hydroxy-2,3-dihydro-1H-1,4-benzodiazepin-2-one) is a benzodiazepine indicated for the treatment of generalized anxiety disorder and pre-surgical (Lexicomp Online®, 2016). Off-label, it is applied in a wide range of indications and patient categories, because of its sedative and anticonvulsive activity and absence of active metabolites. Within paediatrics, it is administered to children from the age of one month for acute anxiety, sedation, chemotherapy induced- or associated nausea, status epilepticus or for weaning purposes (Lexicomp Online®, 2016).

Currently, no liquid dosage form of lorazepam is available in the EU. An extemporaneous suspension of 1 mg/ml, prepared from 2 mg tablets, distilled water, Ora-Plus® and Ora-Sweet®, has been proven to be chemically stable for up to three months when stored at 4 °C (Lee et al., 2004). However, a subsequent study using this suspension proved that dosage measurement by paediatric intensive care nurses led to significant deviations from the intended dose (Lee et al., 2005). These inaccurate dosage measurements are less likely to occur in the case of an oral solution, but the physical and chemical characteristics of lorazepam make this a challenge.

There are different strategies to formulate a poorly water soluble drug substance into an oral solution. pH Adjustment can be used to ionize a compound, which generally will result in increased aqueous solubility. In the case of lorazepam (aqueous solubility 0.08 mg/ml) (O'Neil, 2006), with pKas of 1.3 and 11.5 (Clarke's Analysis of Drugs and Poisons [Internet], 2016), pH adjustment is not a feasible method to increase the solubility. It is also sensitive to hydrolysis in both acidic and basic environments (Siddegowda et al., 2012) and shows temperature-dependent degradation (McMullan et al., 2013). Organic solvents can be used as an alternative to water, but specific attention has to be paid to safety in paediatric patients. A distinction can be made between water-soluble and water-insoluble organic solvents. Water-soluble co-solvents, like ethanol (lorazepam solubility 14 mg/ml) and propylene glycol (lorazepam solubility 16 mg/ml) (O'Neil, 2006), create a mixed aqueous/organic solution. These excipients are readily available and easy to process, but they can convey a risk of toxicity to children (Committee for Human Medicinal Products (CHMP), 2006). A combination of water-insoluble organic solvents, such as medium-chain and long-chain triglycerides and oleic acid, can be used to disperse lipophilic drugs.

Alternatively, a poor water-soluble drug can be solubilized using surfactants, like polysorbate 20 and 80 (Tween) or polyoxyl hydrogenated castor oil (Cremophor), to obtain micelles in an aqueous environment. Similarly, surfactants can be used to obtain a microemulsion, when combined with a polar solvent, an oil, and a cosurfactant. Lastly, complexation of poorly soluble drugs with cyclodextrins has been a strategy to increase the aqueous solubility and bioavailability of compounds, while at the same time masking the taste (Committee for Human Medicinal Products (CHMP), 2014a), an important aspect in the design of paediatric formulations.

The objective of this study was to explore different formulation strategies to process a poorly soluble drug substance into a clear oral solution, using lorazepam as a model drug. The formulation needed to be suitable for paediatric patients from the age of one month, and have adequate stability to allow for individual and batch production within the pharmacy.

2. Material and methods

2.1. Materials

Lorazepam drug substance was bought from Fagron BV (Capelle a/d IJssel, The Netherlands) and Duchefa Farma BV (Haarlem, The Netherlands). Lorazepam related compound B and hydroxypropyl- β -cyclodextrin (HP- β -CD, substitution degree 0.6) were bought from Sigma-Aldrich Chemie BV (Zwijndrecht, The Netherlands). Lorazepam related compounds C and D were bought from USP Switzerland (Basel, Switzerland). Colour Reference Solutions Y were bought from Merck Millipore (Amsterdam, The Netherlands). Lorazepam drug substance and all other excipients were European Pharmacopoeia grade.

2.2. Formulation development

The dosage strength was chosen based on the target population of children from the age of one month to 18 years old, receiving a maximum dose of 0.6 mg/kg/day (Lexicomp Online®, 2016). To limit the volume needed and excipients administered, we aimed for a strength of 1 mg/ml. Three different formulation strategies were explored to improve the solubility. Firstly, water-soluble organic solvents were used to improve the aqueous solubility directly, secondly, non-ionic surfactants were used to solubilise the model drug, and thirdly, complexation of lorazepam with cyclodextrin was studied. Parameters that were studied were; physical stability (by visual inspection), chemical stability, using the analytical assay described in Section 2.5, and palatability (see Section 2.3). Physical instability was defined as the presence of visible precipitation. The visual inspection of the samples was performed according to Ph. Eur. 2.2.1., with use of commercial reference solutions. The physical and chemical stability were initially studied for 5 months.

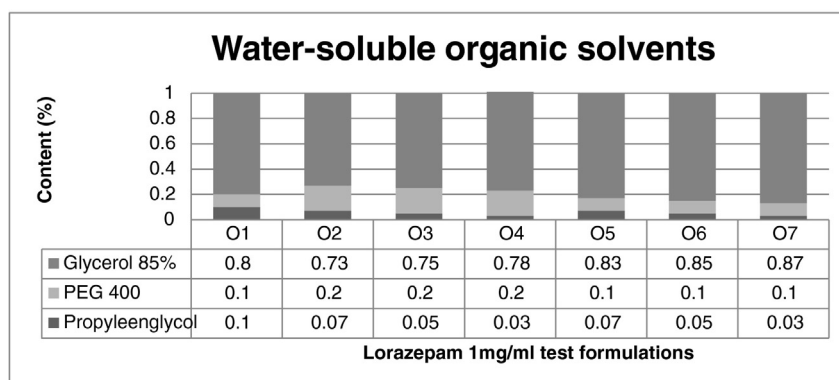


Fig. 1. Lorazepam 1 mg/ml test formulations containing water-soluble organic solvents.

2.2.1. Organic solvents

For the organic solvents-based formulation, we experimented with different ratios of propylene glycol (PG), poly ethylene glycol 400 (PEG400) and glycerol 85%. Efforts were directed towards a glycerol/PEG400 based mixture containing minimal amounts of propylene glycol (Fig. 1).

2.2.2. Non-ionic surfactants

The second strategy that was explored was the use of non-ionic surfactants to create a micellar solution. Polysorbate 80 and sorbitan monooleate were mixed in a ratio to obtain a hydrophilic/lipophilic balance (HLB) of 11.5. The total surfactant content in the test formulations ranged from 1 to 5%. PEG400 was used to dissolve lorazepam, after which the micellar solution was slowly added to the PEG400. The volume per test formulation was 50 ml, the composition of the excipients is displayed in Fig. 2.

2.2.3. Cyclodextrin

For the cyclodextrin formulation, HP- β -CD was chosen as the complexing agent, because of its high water solubility, lower cost compared to other cyclodextrins, low toxicity (Committee for Human Medicinal Products (CHMP), 2014a), and based on previous work investigating different cyclodextrins for inclusion complexation of lorazepam (Holvoet et al., 2005). A phase solubility diagram was made to measure the solubility of lorazepam as a function of the HP- β -CD concentration. This revealed that a minimum of 54 mg/ml HP- β -CD was required to obtain a 1 mg/ml lorazepam solution after 4 h of ultrasonification. However, a HP- β -CD solution of 60 mg/ml (formulation C1) proved not sufficient to maintain a stable product after one week, therefore the HP- β -CD concentration was increased to 100 mg/ml (formulation C2). Glycerol 85% was added as a preservative in an amount of 35% m/v.

2.3. Palatability

The palatability of the test formulations was assessed by three adults, experienced in taste assessment. Characteristics that were evaluated were smell, taste, aftertaste and mouthfeel, and they were independently and qualitatively described by the taste panel. Taste correction possibilities were assessed with formulation C2, O6 and O7, using lemon, banana, raspberry and orange essence. Raspberry and banana were chosen as they are regularly applied in paediatric formulations. Lemon and orange flavours are good taste maskers for bitter drug substances.

2.4. Long-term stability studies

After the preliminary formulation studies, a decision was made to continue the development with formulation O7 (Table 3). To this

end, two batches of 3000 ml each were compounded, to investigate the influence of temperature and packaging material on long term stability. The test formulations were prepared with active pharmaceutical ingredient (API) from two different suppliers (Fabbrica Italiana Sintetici S.p.A and Cambrex Profarmaco Milano S.r.l.). Samples were stored in climate cabinets at 4 °C (VTL650K, range 2–8 °C) and 25 °C 60% relative humidity (Elbanon type LC 500, range 23–27 °C, 55–65% RH) in amber-coloured polyethylene terephthalate (PET) and glass containers. In each cabinet the temperature was registered hourly. Because of the known temperature dependent degradation of lorazepam, stability studies at 40 °C were omitted. Samples were tested against the release or end-of-shelf life specifications, based on the United States Pharmacopeia (USP) monograph for lorazepam oral concentrate and the general Ph. Eur. monograph for microbiological quality of non-sterile pharmaceutical preparations, shown in Table 1. Samples stored at 25 °C were analysed at 0, 1, 2, and 3 months. Samples stored at 4 °C were also analysed at 6, 9 and 12 months.

2.5. Analytical assay

For the quantitative analysis of lorazepam and lorazepam related compounds (USP) B, C and D [2-amino-2,5'-dichlorobenzophenone, 6-chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde and 6-chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic acid, respectively] a high performance liquid chromatography combined with UV (HPLC-UV) detection method was used. The components were separated using a Shimadzu LC20 system, on a C18 analytical column (Inertsil ODS-3.5 μ m 150 \times 4.6 mm) with a mixture of acetonitrile, methanol and ammonium acetate solution (100 mM, pH 6.0 \pm 0.04 adjusted with 1 M acetic acid) in the ratio 1:1:1 (v/v/v) as mobile phase, at a flow rate of 1.0 ml/min. Column temperature was kept at 30 \pm 0.1 °C and UV detection for quantification was performed at 230 nm using a Shimadzu M20A diode array detector, while the wavelength range of 200–400 nm was continuously monitored for unidentified peaks. The injection volume was 20 μ l. The method was validated for the quantification of lorazepam in the cyclodextrin and PG/PEG 400/glycerol sample matrices and in the presence of related compounds B, C and D, for the parameters shown in Table 2. The response factors of related compounds B, C and D were determined to allow for accurate quantification of these compounds on lorazepam calibration curves.

2.6. Calibration and sample analysis

Samples were diluted 40 times to 25 μ g/ml with mobile phase and quantified on a calibration curve (20–30 μ g/ml) of freshly prepared standard solutions of lorazepam RS in mobile phase using the validated HPLC method. All duplicate sample analyses were preceded by a system

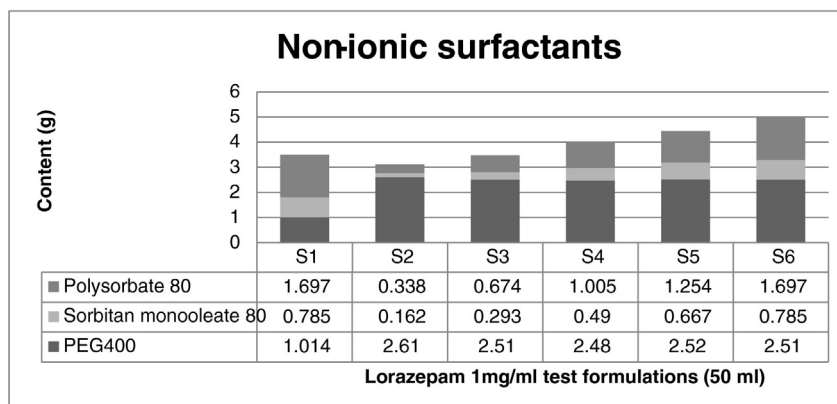


Fig. 2. Lorazepam 1 mg/ml test formulations containing non-ionic surfactants.

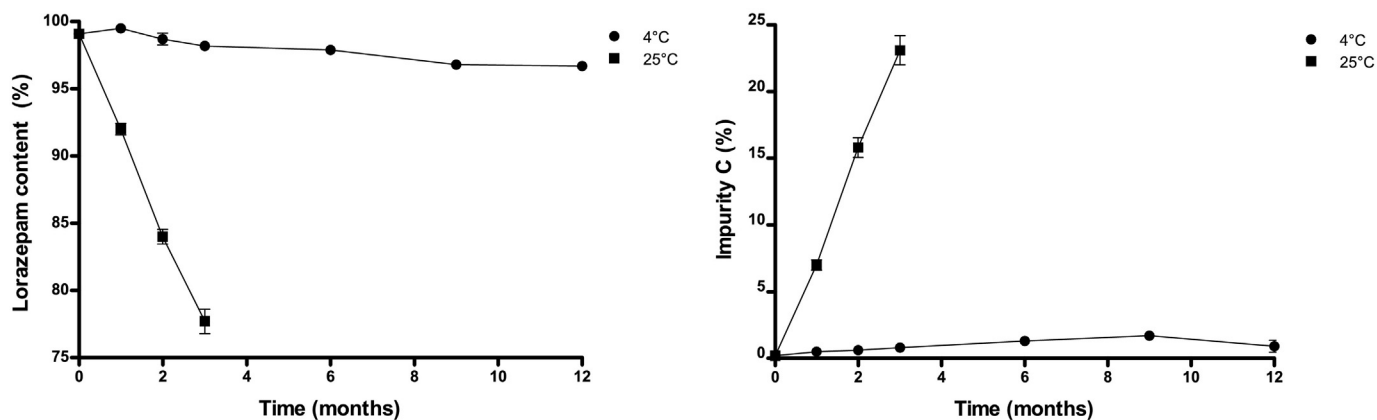


Fig. 3. Average lorazepam content (left graph) with SD (n = 4) and related compound C content (right graph) with SD (n = 4) of formulation O7 at 4 and 25 °C.

suitability test consisting of replicate (n = 5) injections of an equal mixture of lorazepam RS 25 µg/ml in mobile phase and lorazepam related compound D, 25 µg/ml RS in mobile phase. Specifications for the relative standard deviation in the lorazepam peak areas and the resolution between the lorazepam and lorazepam related compound D peaks were ≤0.5% and 3.8–4.6, respectively. If unavailable, lorazepam related compound D can be created in situ by diluting a lorazepam RS 1000 µg/ml solution in methanol 40 times with 1 M sodium hydroxide and exposing it to a temperature of 70 °C for two hours, then neutralized by mixing with an equal volume of 1 M hydrochloric acid.

2.7. In-use stability

An in-use test was performed on the final formulation (O7) based on a four-times daily dosing schedule. The containers were stored at 4 °C (range 2–8 °C) and based on the application in our PICU, four-times daily removed from the climate chamber to be exposed to air, light and ambient temperature for 15 min at every dosing simulation. Samples of 0.25 ml were withdrawn. After 28 days the samples were analysed in accordance with the specifications in Table 1. Microbiological quality was tested in accordance with the bioburden filtration method of Ph. Eur. 2.6.1.

2.8. Manufacturing procedure

The manufacturing procedure was developed with the intention to be suitable for individual and batch compounding. The lorazepam drug substance was levigated in a mortar with the solvent mixture. The remaining solvent was added by geometric dilution. Orange essence was added and the solution was magnetically stirred for one hour to achieve complete solution of the lorazepam.

Table 1
Release and end-of-shelf life specifications.

Test item	Method	Reference	Acceptance criteria
Identification	According to assay	Ph. Eur. Lorazepam Monograph	Spectra should be identical to reference
Appearance	Visual observation	Ph. Eur. 2.2.1	Clarity ≤ Susp. I
		Ph. Eur. 2.2.2	Coloration ≤ Y5
Assay	HPLC-UV	Modified Ph. Eur. method	Lorazepam 90–110%
			Related compound C ≤ 4%
Microbiological quality	Bioburden filtration	Ph. Eur. 2.6.1.	<i>E. coli</i> Absent
			TAMC (CFU/ml) < 100
			TYMC (CFU/ml) < 10

CFU Colony-forming unit TAMC Total aerobic microbial count TYMC Total combined yeasts/moulds count.

3. Results

3.1. Formulation development

The organic solvents-based formulations O1–O7 all resulted in physically stable products for at least 5 months. In formulation O1–O4, the lorazepam content declined to around 80–90% after 5 months at 4 °C. Formulations O5–O7 were also chemically stable, with lorazepam content remaining around 100% after five months at 4 °C. For this reason, we chose formulation O7, with the lowest propylene glycol content, to take into further development (Table 3).

The surfactant-based formulations gave variable results. Formulations S1–S3 precipitated within a few days (S1) to two months (S3). Formulations S4–S6 remained physically stable during the study period. The content of S4 declined towards the end-of-shelf life limit of 90% within 3 months at 4 °C. S5 and S6 remained chemically stable, but development of these formulations was discontinued due to the bad soapy taste of the liquid.

The cyclodextrin formulation C2 containing 100 mg/ml HP-β-CD remained physically stable during the 5 month study period. The

Table 2
Validation parameters of the developed HPLC-UV analytical assay. LLOQ lower limit of quantification, LOD limit of detection.

Parameter	Test	n	Specification	Result
Accuracy (12.5–37.5 µg/ml)	Recovery (%)	12	98.0–102.0	100.0
	Coefficient of variation (%)	12	<1.0	0.5
Linearity (0–1.25 µg/ml)	F-value (12;1 p = 0.05)	14	<4.747	1.508
	Correlation coefficient	14	>0.9950	0.9978
Linearity (12.5–37.5 µg/ml)	F-value (10;1 p = 0.05)	12	<4.965	2.050
	Correlation coefficient	12	>0.9950	0.9997
Limits	LLOQ (µg/ml)	26	–	0.055
	LOD (µg/ml)	26	–	0.018
Intra-assay precision (0.25 µg/ml)	Coefficient of variation (%)	6	<1.0	0.2
	Coefficient of variation (%)	6	<1.0	0.1
Intra-assay precision (25 µg/ml)	Coefficient of variation (%)	6	<2.0	1.4
	Coefficient of variation (%)	6	<2.0	1.4
Response factors	Related compound B	4	–	0.707
	Related compound C	4	–	1.085
	Related compound D	4	–	0.999
	Lorazepam (%)	2	>99.5	99.7
Specificity	Related compound B (%)	2	>99.5	99.9
	Related compound C (%)	2	>99.5	99.8
	Related compound D (%)	2	>99.5	99.6
	Lorazepam (%)	2	>99.5	99.7

Table 3
Composition of the lorazepam formulation studied for long-term and in-use stability.

Lorazepam	100	mg
Poly ethylene glycol 400	10	g
Propylene glycol	3	g
Orange essence	100	mg
Glycerol 85%	ad 108,1	g (= 100 ml)

lorazepam content declined to around 90% after 5 months at 4 °C with formation of related substance C up to 2,9%.

3.2. Palatability

The taste assessment results within the panel were consistent. Both cyclodextrin formulations had a neutral scent, slightly sweet taste, and a faint bitter taste caused by the lorazepam. There was no obvious aftertaste, but a prickly sensation on the tongue was sometimes observed. The lemon essence was the preferred taste corrector for formulation C2. Formulations S4 and S4 both had an overpowering soapy smell and taste, which was the reason for discontinuing the development of the surfactant-based formulations. All organic solvent-based formulations had a neutral scent, a sweet taste and a bitter aftertaste. Formulations with 20% PEG400 had a stronger bitter taste than formulations with 10% PEG400. Orange essence was the preferred taste corrector for formulation O6 and O7.

3.3. Long-term stability

The long-term chemical stability studies of formulation O7 showed that lorazepam content declined over time as displayed in Fig. 3. A gradual increase in related compounds, mainly related compound C, was seen in all samples, but was notably higher at 25 °C. Therefore, stability studies at 25 °C were stopped after 3 months. At 12 months, related compound B was first measured in the 4 °C samples and also an unknown impurity was found. Related compound C remained below 2.0%. The packaging material did not influence the chemical degradation of lorazepam. No changes in colour and clarity were observed in any of the samples.

3.4. In-use stability

The samples of formulation O7 remained stable during the in-use study, no visual changes were observed. The content of lorazepam did not decrease during the in-use study. Related substance C reached a maximum of 0.5% and the remaining related substances were all below the quantification limit. The total aerobic microbial count and total yeast and mould counts were <1 colony forming unit per sample (the total remaining liquid per vial) at day 28 of the in-use study in all samples.

4. Discussion

In this study, we explored different formulation strategies to compound a poorly water-soluble drug into a clear oral liquid formulation, using lorazepam as a model drug. With the intended application in paediatric patients, specific attention was paid to child-friendly excipients and adequate palatability. We developed an oral solution of lorazepam at a concentration of 1 mg/ml with adequate physical and chemical stability, and a shelf-life of at least 12 months. This clear solution can be expected to provide good dosing accuracy.

In our final, organic solvent based formulation, a small volume (3% m/v) propylene glycol was still needed to ensure adequate stability. Recently the European Medicines Agency has published a

new assessment report concerning the safety of propylene glycol in paediatric formulations (Committee for Human Medicinal Products (CHMP), 2014b). In this report, new safety limits were set, expressed in terms of maximum daily doses that are considered to be safe whatever the duration and the route of administration. For neonates up to 28 days, this limit is set at 1 mg/kg, for children 1 month to 4 years old it is set at 50 mg/kg, and for children aged five years and up it is set at 500 mg/kg. Even in the rare occasion that the maximum dose of 0.6 mg/kg/day is required, the intake limits for patients above 28 days old will not be reached with our formulation. If administration to neonates is required, the propylene glycol limit of 1 mg/kg/day may be exceeded, and therefore its use is not recommended for neonates.

In the last decades, an increasing amount of research has been performed into cyclodextrins as a pharmaceutical excipient. The best known example of cyclodextrin in a commercial formulation, is itraconazole (Trisporal®) 10 mg/ml oral solution, containing 40% HP-β-CD and 2,5% propylene glycol, which is used off-label in children. HP-β-CD seems to be a promising option for a lorazepam solution. However, our results showed a restricted stability of maximum of 5 months, most likely due to hydrolysis of lorazepam. The compounding method, needing 4 h of ultrasonification, proved impractical for individual preparations. The high amount of HP-β-CD required in this composition also makes it expensive. A possible solution that is currently being studied is the spray-drying of lorazepam-cyclodextrin 1:1 complexes, to provide a dry, and thus stable, semi-finished product, which can be compounded by pharmacist for individual patients.

Besides the technical challenges, there are also uncertainties around the safety of cyclodextrins in children below the age of 2 years. The oral bioavailability of HP-β-CD is very low, and high doses could cause reversible diarrhoea. For children below the age of 2 years, the currently suggested permitted daily exposure of HP-β-CD is set at 16 mg/kg/day for oral ingestion (Committee for Human Medicinal Products (CHMP), 2014a). This is set at one tenth of the adult value, as there are insufficient data in this age group. It corresponds with a maximum allowable lorazepam intake of 0.16 mg/kg/day, which may be surpassed in clinical practice. In summary, a cyclodextrin formulation is a feasible option, but would require considerable additional research.

Our efforts to create a micellar solution of lorazepam resulted in a physically and chemically stable product, and the high amounts of surfactants required to obtain a stable solution would not exceed the Acceptable Daily Intake (ADI) limits for food additives set by the WHO (Joint FAO/WHO Expert Committee on Food Additives Meeting, World Health Organization, International Program on Chemical Safety, editors, 1982; Joint FAO/WHO Expert Committee on Food Additives, editor, 1974). However, the taste of the formulation made it unacceptable for use in children. The development of this formulation was therefore discontinued.

With regard to the palatability assessment by healthy volunteers, it is known that children experience different taste sensations than adults (Mennella and Beauchamp, 2008). In this stage of development we considered a first screening by an adult tasting panel acceptable. A palatability assessment is included in the clinical trial that is currently performed with our formulation in paediatric ICU patients.

In conclusion, we have studied different options for an oral solution of a poorly water soluble drug, using lorazepam a model drug. The organic solvent based formulation showed adequate stability, taste and dosing flexibility, rendering it suitable for the paediatric population above the age of one month. Our final, organic solvent-based formulation is currently used in a paediatric clinical trial to study the oral pharmacokinetics of lorazepam in PICU patients from the age of 1 month to 12 years old. This formulation is preferable to manipulation of commercial dosage forms and non-standardized extemporaneously compounded formulations, and may serve as an example for the development of comparable drug substances into oral liquid formulations.

Conflict of interest

The authors have no conflict of interest to declare.

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References

- Aleksovski, A., Dreu, R., Gasperlin, M., Planinsek, O., 2015. Mini-tablets: a contemporary system for oral drug delivery in targeted patient groups. *Expert Opin. Drug Deliv.* 12 (1), 65–84.
- Clarke's Analysis of Drugs and Poisons [Internet]. Pharmaceutical Press ([cited September 8, 2016]. Available from:). <https://www.medicinescomplete.com/mc/clarke/2010/>.
- Committee for Human Medicinal Products (CHMP), 2006. Reflection Paper: Formulations of Choice for the Paediatric Population London: European Medicines Agency.
- Committee for Human Medicinal Products (CHMP), 2014a. Background Review for Cyclodextrins Used as Excipients. European Medicines Agency, London.
- Committee for Human Medicinal Products (CHMP), 2014b. Background review for the excipient propylene glycol. London: European Medicines Agency.
- Holvoet, C., Vander Heyden, Y., Plaizier-Vercammen, J., 2005. Inclusion complexation of lorazepam with different cyclodextrins suitable for parenteral use. *Drug Dev. Ind. Pharm.* 31 (6), 567–575.
- Joint FAO/WHO Expert Committee on Food Additives, editor, 1974. *Toxicological Evaluation of Certain Food Additives with a Review of General Principles and of Specifications*. Food and Agriculture Organization of the United Nations, Rome.
- Joint FAO/WHO Expert Committee on Food Additives Meeting, World Health Organization, International Program on Chemical Safety, editors, 1982W. *Toxicological Evaluation of Certain Food Additives*. WHO/FAO, Geneva.
- Lee, W.M., Lugo, R.A., Rusho, W.J., Mackay, M., Sweeley, J., 2004. Chemical stability of ex-temporaneously prepared Lorazepam suspension at two temperatures. *J. Pediatr. Pharmacol. Ther.* 9 (4), 254–258.
- Lee, W.M., Lugo, R.A., Cash, J., Rusho, W.J., Mackay, M., Welkie, K., 2005. The accuracy and precision of measuring Lorazepam from three liquid preparations. *J. Pediatr. Pharmacol. Ther.* 10 (1), 36–42.
- Lexicomp Online®, 2016. *Pediatric & Neonatal Lexi-Drugs®*. Lexi-Comp, Inc, Hudson, Ohio.
- McMullan, J.T., Pinnawin, A., Jones, E., Denninghoff, K., Siewart, N., Spaite, D.W., et al., 2013. The 60-day temperature-dependent degradation of midazolam and Lorazepam in the prehospital environment. *Prehosp. Emerg. Care* 17 (1), 1–7.
- Mennella, J.A., Beauchamp, G.K., 2008. Optimizing oral medications for children. *Clin. Ther.* 30 (11), 2120–2132.
- O'Neil, M.J., 2006. *The Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologicals*. Merck, Whitehouse Station, NJ.
- Siddegowda, M.S., Ramakrishn, R.A., Yathirajan, H.S., 2012. Facile thermal rearrangement of Lorazepam and Oxazepam. *Indian J. Chem. Sect. B Org. Med. Chem.* 51 (11), 1628–1632.
- van Riet-Nales, D.A., de Jager, K.E., Schobben, A.F., Egberts, T.C., Rademaker, C.M., 2011. The availability and age-appropriateness of medicines authorized for children in The Netherlands. *Br. J. Clin. Pharmacol.* 72 (3), 465–473.