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The Use of Cyclodextrins in Preparing a Pediatric Oral Liquid Dosage Form of Loratadine

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Introduction

The importance of pediatric dosage form development has been increasing since the European Medicinal Agency in 2006[1] and the United States FDA[2] in 2007 issued regulations requiring the development of pediatric dosage forms for new prescription drugs. Oral liquid dosage forms [OLDF] are preferred for use with children. The preparation of oral liquid solutions is a challenge when taking into account that the liquid should be palatable and the excipients used in it must be both safe[3] and able to increase solubility of poorly soluble drugs. The aim of this work was to investigate the use of cyclodextrins [CDs] as excipients for OLDF. CDs are known for their ability to increase drug solubility by formation of both inclusion and non-inclusion complexes[4], as well as for their taste-masking properties[5]. Loratadine was chosen as a model drug, known for its high LogP, low solubility and bitter taste. γ-cyclodextrin (GCD), 2-hydroxypropyl-γ-cyclodextrin (HPGCD) and 2-hydroxypropyl-β-cyclodextrin (HPBCD) were chosen for their high water solubilities, which make them suitable for use in OLDF. Tartaric acid[6] and citric acid, as alpha hydroxy acids; hydrochloric acid, as a mineral acid; L-arginine[7], an amino acid; sucrose[8] and sorbitol were used for investigating the possibility of further increasing API solubility by enhancing the complexation efficiency in ternary systems.

Experimental Methods

Materials

Loratadine (LOR) was obtained from RIA International LLC (East Hanover, NJ, USA). CAVAMAX W8 γ-cyclodextrin, CAVASOL* W7 2-hydroxypropyl-β-cyclodextrin and CAVASOL* W8 2-hydroxypropyl-γ cyclodextrin were produced by Wacker Chemie (Burghausen, Germany); L-tartaric acid (TAR) was obtained from Bernd Kraft (Duisburg, Germany); L-arginine (ARG) and citric acid (CIT) from Applichem Panreac (Darmstadt, Germany); hydrochloric acid (HCl) from VWR Chemicals (Radnor, PA, USA); Neosorb P150DC sorbitol (SORB) from Roquette Frêres (Lestrem, France); sucrose (SUCR) from Südzucker (Mannheim, Germany); Natrosol™ 250 G Pharm hydroxyethylcellulose (HEC) from Ashland Inc. (Covington, KY, USA); sorbic acid from Carl Roth (Karlsruhe, Germany) and sucralose from Niutang Chemicals (Jiangsu, China).

Note: This work was presented in part as posters at 10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology 2016, Glasgow, UK and UK PharmSci 2016, Glasgow, UK.

Phase-Solubility Experiments (Binary systems)

Excess amounts of LOR (400 mg or 1.04 mmol), were added to 15 ml of unbuffered aqueous solutions of cyclodextrins in demineralized water: GCD 0–150 mmol/L, HPBCD 0–300 mmol/L and HPGCD 0–250 mmol/L. Solutions were stirred for 48 hours. Aliquots were taken from the solutions and filtered with 0.22 µm

filters. They were then analyzed using UV-spectrophotometry or high-performance liquid chromatography (HPLC) with UV detection.

Solubility of Ternary Systems

Ternary systems were prepared and evaluated in the same manner as that used in the phase solubility study, however, with a much lower drug addition of only 20 mg (0.05 mmol) to reflect usual dosing for OLDF (1 mg/mL) and only with HPBCD at lower concentrations (1–80 mmol/L, 0–112.8 mg/mL). ARG was added equimolar to the drug. Sucrose and sorbitol were added at 10% concentration (292 and 459 mmol/L respectively). pH values of solutions were measured using a FiveEasy FE20 (equipped with LE409 electrode) pH-meter (Mettler Toledo, Greifensee, Switzerland).

Solutions for the acidic ternary systems were prepared by adding 26.7 mg (= 0.07 mmol) of LOR to 20 ml of solutions with increasing concentrations of HPβCD (0–108.75 mg/ml = 0–77 mmol/l) in demineralized water. Acids were added to the mixture to achieve a pH value of around 3 (0.07 mmol TAR, 0.08 mmol CIT, 0.04 mmol HCl). The solution was stirred for 24 h on a magnetic stirrer.

UV-Spectrophotometry

The filtrates were diluted with methanol:water (1:1) and measured with a UV-Vis spectrophotometer (Specord 200 Plus, Analytik Jena, Jena, Germany) at 230 nm for binary systems or 247 nm for ternary systems.

Preparation of a Model Oral Liquid Formulation

The final model formulation for a pediatric oral liquid dosage form of loratadine was prepared in two different approaches as described in Table 1.

Table 1:Final oral liquid formulations

Component	Formulation A	Formulation B
Loratadine	100 mg	100 mg
Citric acid	50 mg	50 mg
HPβCD	2400 mg	2400 mg
Sorbic acid	100 mg	100 mg
Sucralose	4 mg	4 mg
Natrosol™ 250 G HEC	2100 mg	2100 mg
Ethanol	2.5 ml	
Water	100 ml	100 ml

Formulation A

Loratadine was dissolved in 2.5 ml of ethanol. HPβCD and citric acid were added to water at 80°C and stirred until fully dissolved. Both solutions were mixed and stirred until the solution cleared. Sorbic acid, sucralose and Natrosol 250 G HEC were added. The solution was stirred while it cooled. Water was added to a final volume of 100 ml and the solution was stirred for 24 h.

Formulation B

Loratadine, HPβCD and citric acid were added to water at 50°C. The solution was heated (50°C) and stirred for 2.5 h until LOR was fully dissolved. Sorbic acid, sucralose and Natrosol 250 G HEC were added. The solution was stirred while it cooled. Water was added to a final volume of 100 ml and the solution was stirred for 24 h.

Assay analysis of final model formulations with HPLC / UV

A 0.1 g amount of each LOR formulation was accurately weighed into a 20 ml sample vial. The mass was converted into a volume based on the density of the formulation, and 10 ml of acetonitrile was added to the vial followed by shaking and sonication for 30 minutes. This left a clear water-acetonitrile mixture (1:100 v/v) and some insoluble material made up of HEC, sucralose, HPβCD and any other acetonitrile-insoluble components. Solutions were filtered through 0.45 µm. The concentration of LOR in the filtrate was quantified by an HPLC HP 1100 system (Agilent, Santa Clara, CA, USA) with a diode array detector. Using 10 mM phosphate buffer, pH 7.2, and acetonitrile as mobile phases, the percentage of acetonitrile was increased from 40% to 100% in 7 min then held for 3 min at 100%. Column: Agilent Poroshell 120 C18 and UV Detection: 254 nm, 360 nm.

Rheology of final model formulations

Samples were measured using a Malvern Kinexus Pro Rheometer (Malvern Instruments S.A., Worcestershire, UK) using a cup and bob geometry and a shear rate ramp of 0.01 s^{-1} to 1000 s^{-1}.

Ethanol content in final model formulations

The samples were diluted with water to reduce their viscosity, before direct analysis using the gas chromatograph/flame ionization detector (GC/FID) model CP9104 (Agilent, Santa Clara, CA, USA) with the VF-624 column (Agilent, Santa Clara, CA, USA) and aqueous ethanol standards.

Results

Phase-Solubility Experiments (Binary systems)

Phase solubility results showed that HPBCD is the most effective cyclodextrin of the three tested for increasing the solubility of LOR (as shown in Figure 1). These results are generally in accordance with those obtained by Omar et al.[9] in terms of the ranges and types of CDs used in their study. This study, however, examined higher concentrations of CDs and included HPGCD, which was not tested before. GCD and HPGCD yielded an A_L[9] type isotherm, whereas HPBCD had an A_N type interaction. A linear regression line was used to calculate the complex stability constant ($K_{1:1}$) and complexation efficiency (CE)[10] for complexes with HPBCD: $K_{1:1}$ = 201.7 and CE = 0.33718. Preliminary taste (n=1, by author) results showed that the solutions with HPBCD were sweet with no bitter taste component. HPLC showed comparable results to those of UV, except for HPBCD, for which the dissolved LOR concentration dropped at 400 mg/mL HPBCD (data not shown).

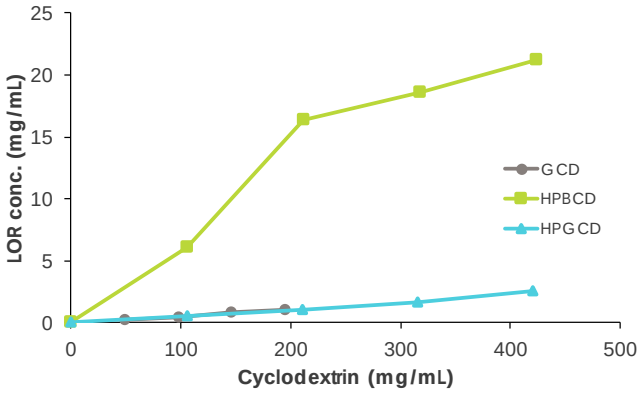

Figure 1: Phase solubility of loratadine in CD solutions

Ternary Systems

Results of the ternary systems of HPBCD with TAR, ARG, SUCR and SORB can be seen in Figure 2. TAR increased the solubility of the drug considerably, whereas ARG did not have an impact. SUCR and SORB, on the other hand, decreased the solubility of LOR.

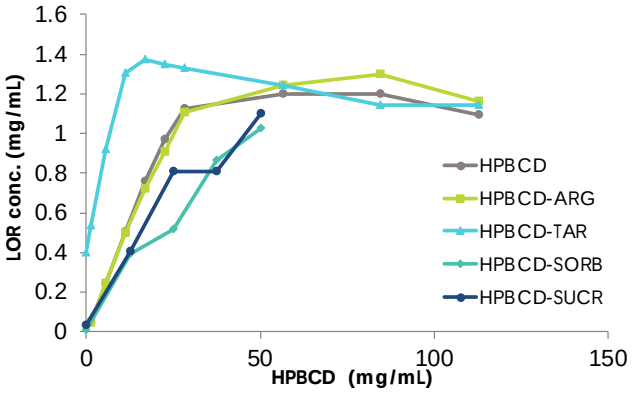

Figure 2: Ternary systems with HPBCD

Acidic Ternary Systems

The results of the measurements on ternary systems revealed an increase in solubility of LOR with the addition of the hydroxy acid TAR. On the basis of these findings, CIT, as another hydroxy acid, and HCl, a mineral acid, were added to solutions of LOR and HPBCD to investigate the influence of other acids at the same pH on complexation efficiency. Figure 3 shows the results of these solubility studies.

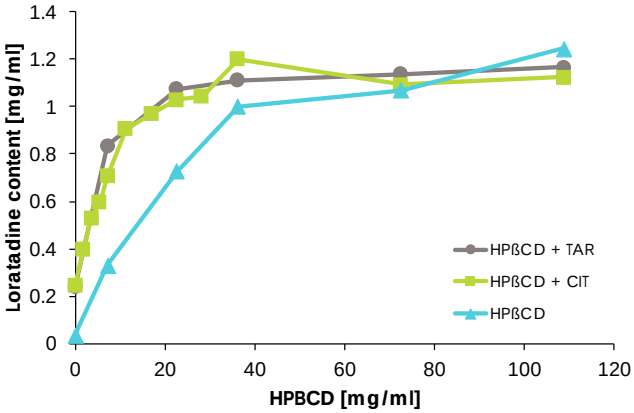

Figure 3:Acidic ternary systems with HPBCD

All acids increased the solubility of LOR in demineralized water due to protonation of the basic API. The results show an increase in complexation efficiency of HPBCD, i.e., a smaller amount of HPBCD needed to dissolve the same amount of LOR, when TAR and CIT were added (22.5 mg/ml HPBCD needed with CIT compared with 72.5 mg/ml without additional acid for 1.1 mg/ml of LOR).

HCl, on the other hand, decreased the amount of dissolved LOR after initially increasing it at lower concentrations of HPBCD. Adding HCl to achieve a pH of 4 decreased the effectiveness of HPBCD even further (Figure 4).

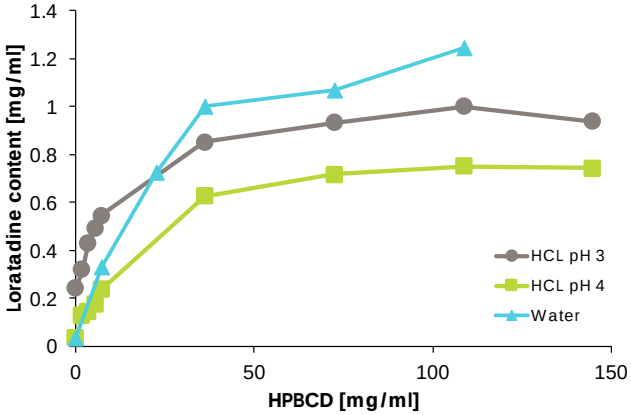

Figure 4:Comparison of HPBCD and HCl at pH 3 and pH 4

Model liquid oral formulations

Model formulations for a pediatric OLDF of LOR were prepared with two different approaches. Formulation A used ethanol to initially dissolve LOR and therefore decrease the time until it was fully dissolved in water. The ethanol was mostly removed from the formulation by heating it to 80°C while stirring for a short period of time. LOR was added directly to water for formulation B and the solution was stirred at 50°C for 2.5 h to successfully dissolve the full amount of LOR.

Ethanol contents in formulations are listed in Table 2.

Table 2: Ethanol content of final formulations

Formulation	Ethanol content
A	0.81%
B	<100 ppm

Assay of drug in the final formulation was analyzed 30 days after preparation, with samples kept on a shelf at room temperature. Results can be seen in Table 3.

Table 3: Ethanol content of final formulations after 30 days

Sample	Assay (mg/mL)
Formulation A	1.009
Formulation B	1.007

Sorbic acid was chosen as a preservative in this concentration at the used pH because cyclodextrins diminish the activity of most preservatives by complexing them, especially benzoic acid derivatives[11]. Sucralose was chosen as a sweetener to replace cariogenic sucrose. Natrosol™ 250 G HEC was used as a viscosifier with pseudoplastic properties to optimize flow properties of the formulation and to increase palatability and create the mouthfeel of a syrup. Figure 5 shows the viscosity of both formulations versus the shear rate. They show a shear thinning rheological behavior with a slightly higher viscosity for formulation A.

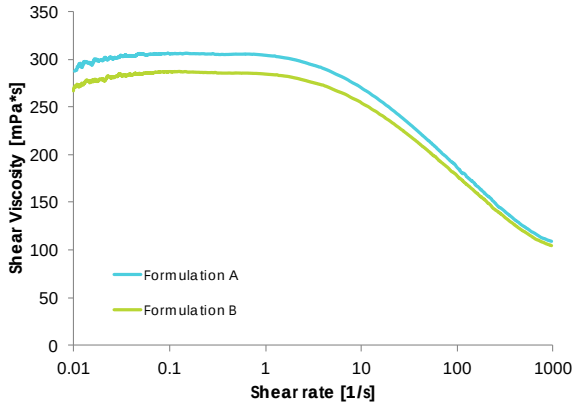

Figure 5: Rheology of both model pediatric liquid oral formulations of loratadine

The use of heat seems to have possibly helped to build the structural system of hydroxyethylcellulose in solution for formulation A, which therefore shows increased viscosity compared with formulation B.

Discussion and Conclusion

Loratadine is a basic drug with a benzocycloheptapyridine structure, making it a possible good candidate for building a complex with GCD or HPGCD. Neither of those formed a highly soluble inclusion compound, however, leaving HPBCD as the best solubilizer.

Both organic hydroxy acids (TAR, CIT) showed a positive effect on the complexation efficiency of HPBCD for loratadine, hence the amount of HPBCD needed in a liquid oral formulation can be effectively reduced by adding CIT or TAR. This could be mainly attributed to a possible further stabilization of the complex by fixing LOR into the cavity with the formation of hydrogen bonds between the hydroxyl of the hydroxy acid and the hydroxyl groups located on the external rim of HPBCD[12], as depicted in the possible schematic representation shown in Figure 5.

The inorganic acid HCl, on the other hand, cannot stabilize the complex with hydrogen bonds. This reduced complexation efficiency might also be attributed to the fact that ionized molecules form weaker complexes[13]. The addition of HCl increased the dissolved free drug portion but decreased the complexed drug on the other side.

Strengthening water structure with SUCR and SORB might be the reason for the negative impact on solubility[14]. ARG, on the other hand, had no effect on the solubility of LOR, or on water structure or any other effect that might have led to an enhancement of non-inclusion complexation and a subsequent increase in solubility.

The decrease of drug solubility after surpassing a certain HPBCD concentration could be attributed to formation of CD-aggregates and/or undissolved complex. These results should make it clear that the addition of commonly used excipients into the formulation might have a considerable impact on the solubilization behavior of CDs.

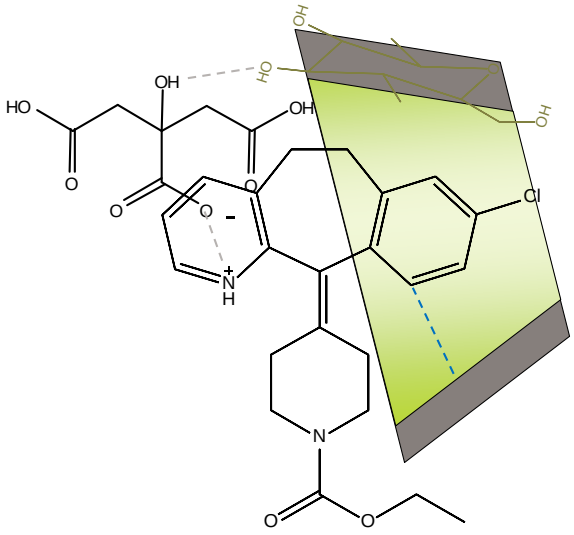

Figure 5: Possible schematic representation of the interaction of loratadine with HPBCD and citric acid

Using the findings of the solubility studies, the necessary amount of HPBCD to solubilize 1 mg/ml LOR for a pediatric oral liquid dosage form was successfully reduced to one third of the amount needed without the hydroxy acid. This solubilization approach was used to create a sophisticated model formulation for a pediatric oral liquid formulation, which was prepared via two different manufacturing approaches. Even though formulation A can be manufactured in a considerably shorter amount of time, while still containing an ethanol residue of 0.81%, it was possible to manufacture a pediatric oral liquid dosage form of loratadine in a reasonable amount of time without any components that might be less safe for use with young children, such as alcoholic or polyolic ingredients, by using the approach for formulation B.

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