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2-hydroxypropyl-β-cyclodextrin extracts 2-phenylphenol from silicone tubing

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Abstract

Cyclodextrins are capable to solubilise lipophilic drugs via (partial) inclusion in their lipophilic cavity. This, however, also provides the potential for the extraction of small molecules from production materials. In the present study, the potency of the commercially available and used cyclodextrin, 2-hydroxypropyl-β-cyclodextrin (HPβCD) to extract the preservative 2-phenylphenol (2-PP) from platinum cured silicone tubing was tested. The presence of 2-PP was structurally confirmed with HPLC–UV and LC/MS/MS in HPβCD solutions after incubation with platinum cured silicone tubing. HPβCD concentration and prior tubing sterilisation were found not to influence the levels of 2-PP extracted. Interestingly, extraction to ethanol was 15-fold higher than observed for HPβCD solutions.

2-PP was extracted from silicone tubing during routine manufacture of a blank dosage form formulated with only HPβCD, resulting in detectable levels of 2-PP in the final product. In a freeze-dried dosage form containing HPβCD and an active pharmaceutical ingredient (exhibiting a stability constant for HPβCD/drug of 1045 L/mol), on the other hand, 2-PP was undetectable.

Keywords: 2-Hydroxypropyl-β-cyclodextrin; 2-Phenylphenol; Silicone tubing; Extraction; Formulation

1. Introduction

Cyclodextrins have been studied extensively for their ability to improve various physico-chemical properties such as solubility and stability of drugs by forming inclusion complexes (Saenger, 1980; Brewster et al., 1989; Frömming, 1994; Loftsson and Brewster, 1996; Szente and Szejtli, 1999). Cyclodextrins are cone-shaped, cyclic oligosaccharides consisting of covalently (α-1,4)-linked α-D-glucopyranose rings with a relatively hydrophilic outer surface and lipophilic cavity. Currently, the cyclodextrins 2-hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutylether-β-cyclodextrin (SBEβCD) are used in the commercially available intravenous formulations of itraconazol and voriconazol, respectively (Slain et al., 2001; Pearson et al., 2003). As cyclodextrins have the capacity to solubilise lipophilic drugs via (partial) inclusion in their lipophilic cavity, they also have the potential for the extraction of small molecules from production materials and administration devices.

Extraction of extraneous substances from these materials into a drug product is undesirable in view

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of toxicity and/or compatibility issues. An example is the leaching of the plasticizer di-2-etylhexyl-phthalate (DEHP) from polyvinyl chloride (PVC) by co-solvents and surfactants (e.g. Nuijen et al., 2001; Jenke, 2001). Recently, the extraction potency of SBEβCD was confirmed by Zimmerman et al. (2003) who recovered 2-phenylphenol (2-PP) from a SBEβCD formulation after exposure to platinum cured silicone tubing (Zimmerman et al., 2003).

Platinum cured silicone tubing is routinely used in the manufacture of several pharmaceutical dosage forms in our facility. In the present study, the potency of HPβCD to extract 2-PP from silicone tubing was tested. Furthermore, platinum cured tubing was evaluated for its applicability in the manufacture of a pharmaceutical dosage form for intravenous use of an active pharmaceutical ingredient (API) with an apparent stability constant ($K_{1:1}$) for HPβCD/drug of 1045 L/mol, formulated with HPβCD.

2. Experimental

2.1. Materials

HPβCD (USP grade, average molecular weight (M_w) of 1399 and a mean degree of substitution of 0.65) was purchased from Roquette Freres (Lestrem, France) and phenylphenol (PP) isomers (2-PP, 3-PP and 4-PP) were purchased from Sigma–Aldrich (Zwijndrecht, The Netherlands). Silicone tubing was platinum cured and complied with the requirements of the United States Pharmacopoeia (USP) ⟨87⟩ (US Pharmacopoeia XXIV, 2000) and European Pharmacopoeia (Ph.Eur.) ⟨3.1.9⟩ (European Pharmacopoeia, 2002), (article no. 913.A048.016, Watson Marlow B.V., Rotterdam, The Netherlands). Ethanol absolute and water for injection (WfI) were of Ph.Eur. grade and purchased from Biosolve B.V. (Valkenswaard, The Netherlands) and B. Braun (Melsungen, Germany), respectively. All reagents used were of analytical grade and used without further purification.

2.2. Methods

2.2.1. Phase solubility diagram

A phase solubility diagram of 2-PP in HPβCD solutions was generated according to the method of Higuchi and Connors (Higuchi and Connors, 1965). An excess amount of 2-PP was suspended in 5.0 mL of solutions containing 0, 5, 10, 15, 20 and 40% (w/v) HPβCD in 20 mL glass vials. The vials were closed with siliconised gray bromobutyl rubber stoppers and subsequently shaken at room temperature and ambient light for 120 h. Experiments were conducted in duplicate. The resulting suspensions were filtered (Millex®-LCR PTFE Syringe filter, 0.45 μm, Millipore, The Netherlands) and analysed for 2-PP concentration.

2.2.2. Extraction

Silicone tubing with an inner diameter of 4.8 mm and a wall thickness of 1.6 mm was used. Prior to extraction studies the tubing was rinsed for 1 min with WfI. Part of the silicone tubing was sterilised by autoclaving for 3 min at 134 °C. Extraction studies were performed in triplicate by filling silicone tubes over a length of 50 cm, corresponding to 9.05 mL of test solution per tube. Both ends of the test tube were closed with clips. The solutions tested were ethanol absolute and 0, 10, 20 and 40% (w/v) HPβCD in WfI. The silicone tubes were stored at room temperature (15–25 °C) and ambient light. Samples were taken after 0.5, 1, 2, 4, 8 and 24 h. Contents of the silicone tubes were emptied into 30 mL polypropylene tubes, mixed to assure homogeneity, sampled, and replaced in the same tubing. Two lots (lot 16549274 and 14936984) of silicone tubing were tested. Moreover, silicone tubes were filled with solutions containing 20% (w/v) HPβCD and 0.3, 3.1 and 31 mM of API ($K_{1:1}$ of 1045 mol/L). The sampling procedure was the same as described for the other solutions.

2.2.3. High performance liquid chromatography (HPLC)

The HPLC system consisted of an 1100 Series binary HPLC pump, Model G1312A (Agilent Technologies, Palo Alto, CA, USA), a Model SpectraSERIES AS3000 automatic sample injection device, equipped with a 100 μL sample loop (Thermo Separation Products, Breda, The Netherlands), and a photodiode array detector (PDA) Model Water™ 966 (Waters Chromatography B.V., Etten-Leur, The Netherlands). Chromatograms were processed using Chromeleon software (Dionex Corporation, Sunnyvale, CA, USA).

Separation was achieved using an Inertsil ODS-2 analytical column (100 × 3 mm i.d., particle size 5 μm, Chrompack, Middelburg, The Netherlands), which was protected by a guard column packed with reversed-phase material (3 mm × 10 mm, Chrompack). The mobile phase consisted of 40/60% (v/v) acetonitrile/water (identification studies) or 60/40% (v/v) acetonitrile/water (quantification studies). A flow rate of 0.4 mL/min, an injection volume of 20 μL and run times of 20 min (identification studies) or 5 min (quantification studies) were employed. For the identification studies, stock solutions of 2-PP, 3-PP and 4-PP of 100 μg/mL in mobile phase were prepared. UV spectra of the PP isomers were recorded from 190 to 400 nm.

For the quantification of 2-PP, a stock solution of 2-PP of 100 μg/mL was prepared in 20% (w/v) HPβCD in water. The stock solution was diluted with 20% (w/v) HPβCD to give standard solutions of 0.02, 0.1, 1.0, 10, 25 and 50 μg/mL 2-PP. Calibration and quality control samples were prepared from two separately weighed stock solutions. UV-detection was performed at 245 nm. 2-PP eluted as a single, sharp peak with a retention time of approximately 3.6 min in the chromatogram. Linear calibration curves were obtained (correlation coefficients > 0.9999) with accuracies between 93.2 and 103%, within- and between-run precisions $\leq$ 2.2% and a limit of detection for 2-PP of 0.02 μg/mL, based on a signal-to-noise ratio of 3:1. Test solutions were injected into the HPLC without further dilution, with the exception of the samples generated for the phase solubility diagram, which were diluted in WfI.

2.2.4. Mass spectrometry (MS)

MS experiments were performed on a Sciex API 365 triple quadrupole LC/MS/MS spectrometer (Sciex, Thornhill, ON, Canada) equipped with an electrospray interface (ESI) ionisation source operating in the negative ion mode. Other parameters were: spray voltage 4.5 kV, heated capillary 250 °C. LC conditions were as described above. For determination of 2-PP/HPβCD complexation, samples were directly infused into the MS system. Product ion scans were obtained by mass-selecting the precursor ion from the Q1 scan. For the optimisation, stock solutions of the PP isomers of 10 μg/ml in mobile phase were prepared. Spectra were processed using Analist™ software (version 1.2, Sciex).

3. Results and discussion

3.1. Phase solubility diagram

Fig. 1 shows that HPβCD is indeed capable of forming inclusion complexes with 2-PP. The aqueous solubility of 2-PP increased up to a factor 90 in HPβCD 40% (w/v), corresponding to 82.4 ± 0.6 mg/mL. The linear curve of the phase solubility diagram can be classified as type A_L, indicating that the complex is first-order with respect to HPβCD and first or higher order with respect to 2-PP. The slope of the curve was found to be greater than unity (1.67), which could indicate that the complexes are of second or higher order with respect to 2-PP. Although, slopes greater than unity do not always reflect higher order complexation with respect to the drug. It has been shown that drug/cyclodextrin complexes form aggregates or micelles in aqueous solution, which can further solubilise the drug molecule (Loftsson et al., 2002). For 2-PP and SBEβCD, an A_L type phase solubility diagram with a slope of 1.26 was acquired (Zimmerman et al., 2003). A 20% (w/v) HPβCD solution was able to solubilise 42 mg/mL 2-PP in comparison with approximately 20 mg/mL 2-PP by 20% (w/v) SBEβCD (Zimmerman et al., 2003). These results indicate that 2-PP complexation is more favourable with HPβCD than SBEβCD, which could result in more extensive 2-PP extraction from silicone tubing.

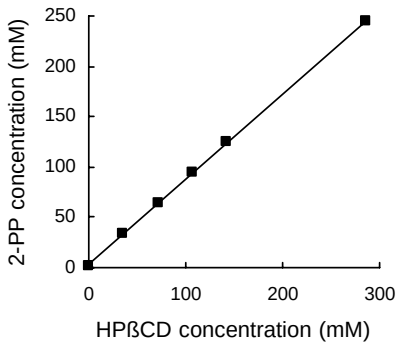

Fig. 1. Phase solubility diagram for the 2-PP/HPβCD system in water.

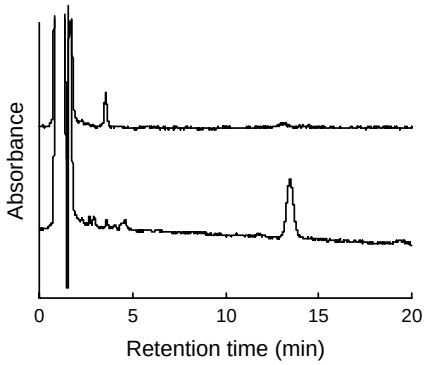

Fig. 2. Chromatogram of a 40% (w/v) HPβCD solution prior to incubation with silicone tubing (top graph) and after 5 days of incubation (bottom graph).

3.2. Identification of the extractable

To examine the possible extraction of 2-PP, silicone tubing was subjected to a 40% (w/v) HPβCD solution for 5 days. The resulting solution was injected into the HPLC system. Indeed, an extraneous peak was obtained in the chromatogram with a retention time of 13.2 min corresponding to 2-PP (Fig. 2). The two other isomers of phenylphenol 3-PP and 4-PP were shown to elute ahead of 2-PP with base-line resolution. The PDA UV spectra of 2-PP, 3-PP, 4-PP and the peak obtained for the extractable are depicted in Fig. 3. Identical UV-spectra were found for 2-PP and the extractable.

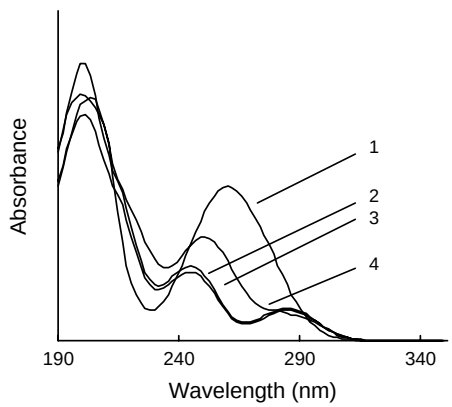

Fig. 3. UV absorbance spectra of (1) 4-PP, (2) the extractable, (3) 2-PP and (4) 3-PP.

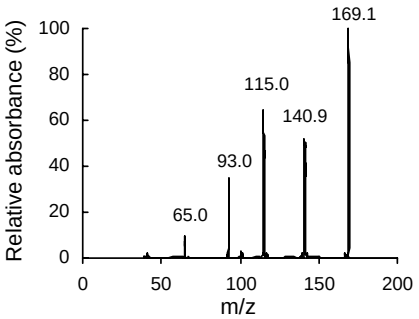

Fig. 4. MS/MS spectrum of 2-PP.

For further identification LC/MS/MS analysis was used. A strong signal (*m*/*z* 169.0, $[M-H]^-$) was seen in the LC/MS spectra of the PP isomers. The product ion scan of 2-PP shows strong signals at *m*/*z* 140.9, 115.0, 93.0 and 65.0 (Fig. 4). The ion at *m*/*z* 140.9 was probably formed by the loss of a C–OH group, resulting in a phenylcyclopentadiene fragment. Cleavage of the bonds between atoms C7–C8 and C7–C12 (Fig. 5) rendered heptanol with a molecular weight of 116 ($[M - H]^{-1} = 115$). The presence of an electrophilic hydroxyl group at the *ortho* position may favour the formation of this fragment. Indeed, both 3-PP and 4-PP showed only a weak signal at *m*/*z* 115, corresponding to the positioning of the hydroxyl group on the *meta* and *para* positions, respectively. The fragments at *m*/*z* 93 and *m*/*z* 65 indicate the formation of a phenol-like structure and pentadiene fragment, respectively.

The LC/MS spectrum of test solution containing the extractable showed a strong signal at *m*/*z* 169, indicating the presence of PP. The fragmentation pattern was indicative for the presence of 2-PP, confirming the results found with HPLC-PDA analysis.

No evidence for the formation of a complex between HPβCD and 2-PP was obtained when a test solution with both compounds was directly infused into the MS

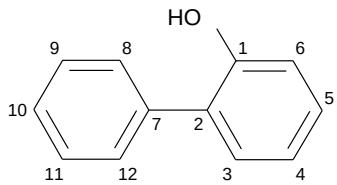

Fig. 5. Chemical structure of 2-PP ($C_{12}H_{23}O$, $M_w = 170$).

interface. Though signals originating from HPβCD were observed in the positive ion mode and from 2-PP in the negative ion mode, no signals originating from the complex between both molecules were observed.

3.3. Extraction simulations

To better understand the implications of the extracting potency of HPβCD during routine manufacture, 2-PP extraction as a function of contact time and HPβCD concentration was investigated. Fig. 6 shows that the extraction process is relatively slow and the amount extracted continuously increases for at least 24 h, with decreasing extraction rate. The maximal 2-PP concentration in the cyclodextrin solutions observed was 0.80 μg/mL, corresponding to 0.096 μg/cm^2 tubing surface area. No 2-PP was recovered from the tubes containing pure water as extraction medium. 2-PP concentrations obtained were in the same order of magnitude as found earlier for SBEβCD (maximal 2-PP concentrations of 0.09–3.89 μg/cm^2 extracted over 24 h into 20% (w/v) SBEβCD for different lots of tubing), (Zimmerman et al., 2003). Although it would be likely that more 2-PP is extracted from tubing exposed to higher HPβCD concentrations, differences were not significant due to the large standard deviations observed.

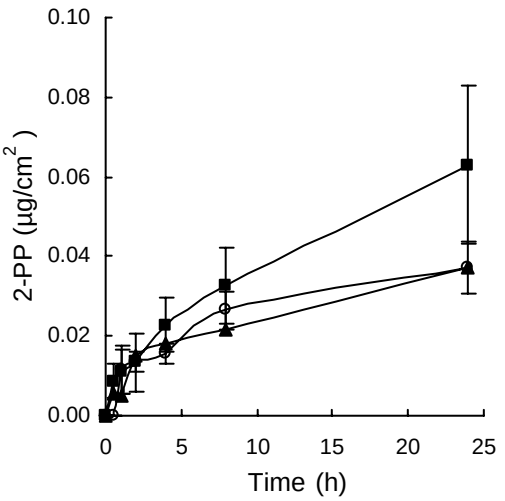

Fig. 6. Extraction of 2-PP from silicone tubing as a function of contact time and HPβCD concentration, with 10% (w/v) HPβCD (■), 20% (w/v) HPβCD (▲) and 40% (w/v) HPβCD (○).

The amount of 2-PP extracted was found to vary with the piece of tubing of the same lot used, suggesting inhomogeneous distribution of the extractable. The same phenomenon was observed between two different lots of tubing extracted with 20% (w/v) HPβCD (Table 1). The effect of exposure of the silicone tubing to one sterilisation cycle was shown not to reduce the 2-PP extraction in 20% (w/v) HPβCD solution (Table 1). Similar results were obtained for 10 and 40% (w/v) HPβCD solutions. Interestingly, extraction with ethanol absolute resulted in an approximately 15-fold increase in the amount of 2-PP extracted (Table 1). This illustrates that the decrease in extraction rate in time observed for the HPβCD solutions was not due to depletion of 2-PP from the tubing, but rather the effect of approaching equilibrium. The partition coefficient of 2-PP between silicone tubing and solution would be significantly higher for ethanol with a solubility of >1000 mg/mL for 2-PP, than for HPβCD solutions with a maximal solubility of 82 mg/mL for 2-PP.

HPβCD is used as an excipient in drug formulations to solubilise or stabilise the drug by complexation. The presence of a drug competing with 2-PP for complexation could reduce the amount of 2-PP extracted from silicone tubing during manufacture. To test this, an API with a $K_{1:1}$ for HPβCD/drug of 1045 L/mol and an aqueous solubility of 0.9 mM was added to the HPβCD 20% (w/v) solution in concentrations of 0.3, 3.1 and 31.0 mM. Although only single pieces of one lot of silicone tubing were tested for each drug concentration, the amounts of 2-PP extracted in the presence

Table 1
Extraction of 2-PP (μg/cm^2 ± S.D.) from silicone tubing after 8 h of incubation

Silicone tubing	Solution	Extracted 2-PP
Lot 16549274	20% (w/v) HPβCD	0.022 ± 0.010
	20% (w/v) HPβCD + 0.3 mM API	0.021
	20% (w/v) HPβCD + 3.1 mM API	0.007
	20% (w/v) HPβCD + 31 mM API	0.006
	Ethanol absolute	0.37 ± 0.14
Lot 16549274 autoclaved	20% HPβCD	0.017 ± 0.002
Lot 14936984	20% HPβCD	0.009 ± 0.001

of 3.1 mM and 31.0 mM of drug molecule were well below those found for all other pieces of silicone tubing tested in the presence of any of the HPβCD solutions (Table 1). The drug was shown not to influence the 2-PP amount extracted when solubilised in a concentration of 0.3 mM in 20% (w/v) HPβCD. This was expected because the drug concentration was below its aqueous solubility.

Two test batches were manufactured to evaluate the amounts of 2-PP extracted from silicone tubing during routine manufacture. For the first test batch, blank dosage forms were freeze-dried from a formulation solution containing 20% (w/v) HPβCD. A second test batch was manufactured from a formulation solution containing API in a concentration of 31 mM in 20% (w/v) HPßCD. During both manufacturing processes, formulation solution was exposed to approximately 150 cm^2 of tubing surface area during filtration and filling for a maximum of 4 h. When analysing the blank dosage form, 0.06 μg of 2-PP per vial was recovered. The presence of 2-PP was identified using LC/MS/MS. The maximum level of 2-PP retrieved from the silicone tubing after 4 h of exposure in the extraction simulation study was found to be 0.036 μg/cm^2 tubing surface area, which would correspond to a maximum extraction of 5.4 μg of 2-PP during manufacturing. For the manufacturing batch size of 100 vials, this would result in 0.05 μg 2-PP per vial. These calculations do not take into account the dynamic flow and constant renewal of formulation solution in the silicone tubing during manufacture, which is expected to result in higher extraction values than found during the static extraction simulation studies.

No 2-PP, however, was recovered from the dosage form containing the API using either HPLC or LC/MS/MS analysis. This result confirms the observation in the static extraction simulation studies that there may be indeed a competition between API and 2-PP for complexation with HPβCD. Therefore, depending on the type of drug, the amount of 2-PP extracted during a manufacturing process could be far less than the amounts extracted without the presence of the drug.

3.4. Toxicity

2-PP is used as a preservative in numerous industrial applications, as a fungicide for citrus fruits, in the rubber industry, as well as a component of household and commercial disinfectant formulations. No information on the parenteral toxicity of 2-PP is available in literature. The only route of administration to man described in literature is dermal exposure (Bartels et al., 1998; Timchalk et al., 1998). Following dermal exposure to a single 8 h dose of 0.4 mg ^{14}C-2-PP, 43% of the applied compound was absorbed. Elimination was found quite rapid ($t_{1/2}$ of 0.8 h), with 99% of the radioactivity excreted in the urine in the first 48 h (Timchalk et al., 1998). In animal toxicity studies, the no-observed-adverse-effect level (NOAEL) for 2-PP was found to be 36 and 750 mg/kg body weight per day for rat and mice, respectively. Acute toxicity of 2-PP in rats, mice and cats treated orally was low, with LD_{50} values ranging from 500 to 3000 mg/kg body weight (Stouten, 1998). The metabolism of 2-PP was found similar in man, mouse and rat (Bartels et al., 1998). Based on the animal toxicology studies, the joint FAO/WHO meeting on pesticide residues (JMPR) established an oral acceptable daily intake (ADI) of 0.4 mg/kg body weight per day using a 100-fold safety factor (JMPR, 1999). Assuming almost complete oral absorption, as also observed in mouse and rat with 80–98% of the administered radioactivity excreted in the urine within 48 h (Bartels et al., 1998), acceptable daily parenteral exposure to 2-PP could be in the same order of magnitude.

The levels of 2-PP extracted from silicone tubing by SBEβCD in the study of Zimmerman et al. (2003) and in the present study with HPβCD, both executed with platinum cured silicone tubing but originating from two different manufacturers, are well below the oral ADI. Though, 2-PP levels were found to be very inhomogeneous distributed within and between different lots of tubing. No specific test for the determination of the extractable amount of 2-PP is described in the Ph.Eur. monograph “silicone tubing elastomer for closures and tubing” ⟨3.1.9⟩ (European Pharmacopoeia, 2002). However, the amount of 2-PP present in tubing would influence the results of two tests specified. The test on “phenylated compounds” is based on the ultraviolet absorption of phenylated compounds present in a hexane extract of silicone tubing. Assuming that 2-PP is the only phenylated compound present in silicone tubing, the limit of specification would correspond to 400 μg 2-PP per gram of silicone tubing extracted (calculated with $\varepsilon_{244} = 8450$ in hexane),

corresponding to 110 μg/cm^2 for the tubing used in the present extraction studies. For the test on "substances soluble in hexane" the maximum value for 2-PP would be 30 mg/g of silicone tubing, corresponding to 51 mg/cm^2 2-PP for the silicone tubing used. These amounts of extractable 2-PP in silicone tubing could result in levels of 2-PP in the final dosage form close to or exceeding the acceptable daily intake. Therefore, monitoring of 2-PP concentration in the starting material(s) (possibly the source of 2-PP) used for the manufacture of silicone tubing or monitoring during in-process control or final control of the tubing is advisable.

4. Conclusions

2-PP was recovered from 10, 20 and 40% (w/v) HPβCD solutions after incubation with platinum cured silicone tubing, with no significant differences found in the extracted amount of 2-PP with increasing HPβCD concentrations. Addition of a selected API able to complex with HPβCD was shown to decrease the amount of 2-PP extracted. Extraction of 2-PP from silicone tubing to ethanol was shown to be 15-fold higher than observed for HPβCD solutions.

2-PP was extracted from silicone tubing during routine manufacture of a blank dosage form freeze-dried from a formulation solution containing 20% (w/v) HPβCD, resulting in a level of 0.06 μg of 2-PP in the final product.

Considering the oral ADI of 0.4 mg/kg body weight per day, values of 2-PP extracted from silicone tubing seem only marginal. Though, no in vivo studies to the effect of intravenously administered 2-PP have been conducted so far. Therefore, extraction of 2-PP from silicone tubing to formulations containing HPβCD and especially formulations containing ethanol should be carefully evaluated.

A freeze-dried dosage form containing HPβCD and an API (exhibiting a stability constant for HPβCD/drug of 1045 L/mol) was found compatible with platinum cured silicone tubing with respect to 2-PP as the API was shown to decrease the amount of 2-PP extracted during manufacture to undetectable, probably due to competition between API and 2-PP for HPβCD complexation.

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