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Original Article

Effect of hydroxypropyl-β-cyclodextrin on the stability of cisapride in oral suspensions

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Abstract

Cisapride (CIS) is a gastrointestinal prokinetic agent. It has been associated with rare, but serious cardiac side effects. However, it does not affect psychomotor functions or induce central depressant adverse effects. As liquid formulations are required in a number of cases, an oral suspension of CIS was developed from CIS tablets. The objective of this study was to investigate the effect of hydroxypropyl-β-cyclodextrin (HP-β-CD) on the stability of CIS in oral suspension with an ultimate aim to formulate a more stable CIS oral suspension. Six batches of CIS oral suspensions, namely, 0 (control), 0.3, 1.6, and 3% HP-β-CD containing formulations were prepared. They were stored at 5°C and 30°C. The amounts of CIS in the suspensions were determined by a validated stability-indicating HPLC-DAD method. The stability was assessed based on the 90% remaining. The changes in the amounts of CIS over time were statistically analyzed by ANOVA and ANCOVA. At 5°C, HP-β-CD had no significant effect on the stability of CIS. CIS in all four formulations was stable for at least 12.5 months. At 30°C, HP-β-CD affected the stability of CIS. CIS was most stable in 0.3% HP-β-CD containing formulation with the observed t_{90} of approximately 11 months as compared to 7 months in control formulation.

Keywords: cisapride, oral suspension, hydroxypropyl-β-cyclodextrin, stability, HPLC

1. Introduction

Cisapride (CIS), (±)*cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxybenzamide (Figure 1; Merck Index, 1996), is a gastrointestinal prokinetic agent. It is effective in the treatment of gastroesophageal reflux disease and non-ulcer dyspepsia in adults, children, and neonates (McEvoy, 2009; Barone *et al.*, 1994; Geldof *et al.*, 1993; Reynolds and Putman, 1992; Sweetman, 2005; Wiseman and Faulds, 1994). CIS has been associated with rare, but serious cardiac side effects including prolongation of QT interval, torsades de pointes, and sudden cardiac death, especially when concomitantly administered with CYP450 3A4 inhibitors or in patients with risk factors of cardiac disorders (McEvoy, 2009; Bedford and Rowbotham, 1996; Thomas *et al.*, 1998; Van Haarst *et al.*, 1998; Wysowski *et al.*, 2001). However, it is largely devoid of central nervous system depressant or antidopaminergic effects as compared to other prokinetic agents such as metoclopramide and domperidone (McEvoy, 2009; Barone *et al.*, 1994; McCallum, 1996; Wiseman and Faulds, 1994). This medicine, therefore,

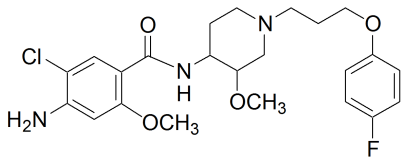

Figure 1. Chemical structure of CIS.

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has been withdrawn in some countries, or its use and indications have been restricted in some countries (World Health Organization, 2001; World Health Organization, 2003). In Thailand, CIS has been severely restricted for prescription use by gastrointestinal physicians and limited use in gastro-esophageal reflux disease patients only (World Health Organization, 2003).

Oral liquid formulations are needed in a number of cases, e.g., to aid patients with difficulty in swallowing tablets, to allow a more convenient way of adjusting dose for pediatric patients, and to facilitate the administration of drugs via nasogastric tube. Therefore, the oral suspension of CIS is developed from cisapride tablets, the only dosage form commercially available in some countries such as Thailand. This formulation is preserved with a combination of methylparaben (MP) and propylparaben (PP), a widely used preservative system in liquid formulations.

CIS is quite unstable in oral liquid formulations (Allen and Erickson, 1998; Horn and Anderson, 1994; Nahata *et al.*, 1995), the most stable of which, when stored under refrigeration, was obtained in a mixture of 1% methylcellulose and simple syrup (1:1). CIS in this formulation was stable for approximately three months under refrigeration, but only for one month at 25°C. Allen and Erickson (1998) reported that the stability of CIS can be enhanced by adjusting the pH of formulation to about 7. In a mixture of Ora-Sweet® and Ora-Plus® (1:1) adjusted to a pH of 7, CIS was stable for more than two months under refrigeration and approximately two months at 25°C (Allen and Erickson, 1998). This might pose a storage problem in countries located in tropical or warm climate zones III and IV (Grimm, 1998) where refrigerator is inevitably needed because of the higher room temperature (approximately 30°C). To increase the stability of CIS in liquid formulation, therefore, a stabilizing agent must be added.

Hydroxypropyl β-cyclodextrin (HP-β-CD), a β-cyclodextrin derivative, has been shown to stabilize a wide variety of compounds via inclusion complex formation (Challa *et al.*, 2005; Loftsson and Brewster, 1996; Loftson, 1995). It has high water solubility and safety profile for use in systemic administration, even at high concentration of 40% for intravenous injection (Irie and Uekama, 1997; Miyake *et al.*, 1999; Szente and Szejtli, 1999). Even though β-cyclodextrin can also improve the stability of a number of drugs, it should not be used for systemic drug formulation due to its low water solubility (1.8% at 25°C) and nephrotoxicity (Kim *et al.*, 2004).

As the complex formation is an equilibrium process, the extent of complex formed depends upon cyclodextrin concentration and inclusion complex formation constant (K_c). For a certain inclusion complex system, increasing the amount of HP-β-CD will shift the equilibrium to the right, i.e., more inclusion complex will be formed. The amount of HP-β-CD in liquid formulation can be as high as 40% (Vandewoude *et al.*, 1997). In this research we investigated the effect of HP-β-CD, as well as its concentration, on the stability of CIS with an ultimate aim to formulate a more stable CIS oral suspension.

2. Materials and Methods

2.1 Materials

Cisapride (CIS) and hydroxypropyl-β-cyclodextrin (HP-β-CD, average MW 1460, molar substitution 0.8) were purchased from Sigma-Aldrich (MO, USA). CIS 5-mg tablets (CIPASID®, Lot No 969270, manufacturing date 12/2006, expiry date 12/2010) were obtained from Siam Pharmaceutical Co., Ltd. (Bangkok, Thailand). Pharmaceutical grade methylparaben (MP) and propylparaben (PP) were purchased from P.C. Drug Center Co., Ltd. (Bangkok, Thailand). Tween 80 was purchased from Srichand United Dispensary Co., Ltd. (Bangkok, Thailand). Viscocel 681 (microcrystalline cellulose with 8.3-13.8% carboxymethylcellulose sodium) was purchased from BASF (Germany). Acetonitrile, methanol, hydrochloric acid, and sodium hydroxide were purchased from Labscan Co., Ltd. (Bangkok, Thailand). *p*-Hydroxybenzoic acid and sodium-1-pentanesulfonate were purchased from Fluka (Buchs, Switzerland). Water was obtained using a Milli-Q water purification system (Millipore Co., MA, USA). All chemicals were pharmaceutical, analytical or HPLC grade, and were used without further purification.

2.2 Equipments

All quantitative measurements of CIS were conducted on an Agilent 1100 series HPLC system (Agilent Technologies, USA) consisting of a quaternary pump, an autosampler, and a photo-diode array detector. The system, data acquisition and processing were performed through Chemstation software. The separation was performed on a C18 column (4.6 mm x 150 mm, 5 μm, BDS C18, Thermo Electron Corporation, MA, USA). Peak purity was assessed from photo-diode array spectral analysis by the instrument software. A Delta 320 pH-meter (Mettler Toledo, Greifensee, Switzerland) was used for pH determination. The viscosity of the formulations was measured using a programmable rheometer (Brookfield DV-III Ultra, Brookfield Engineering, Inc., MA, USA). The temperature-controlled water-bath was manufactured by Scientific Equipment Center, Prince of Songkla University, Songkhla, Thailand.

2.3 Stability-indicating method

A validated stability-indicating HPLC method for the determination of CIS in oral suspension was used. The method was based on an ion-paired, reversed phase HPLC with gradient elution. The mobile phase consisted of solvent A, which was a mixture of 0.13% sodium-1-pentanesulfonate pH 8 and acetonitrile (90:10 v/v) and solvent B, which was acetonitrile. The flow rate of mobile phase was 1.2 mL/min. The gradient program was as follows: 0-5 min; 20 to 56% solvent B; 5-7 min; 56 to 85% solvent B; 7-10 min; 85% solvent B; and re-equilibrated column from 10-13.5 min with 20% solvent B at 2.0 mL/min. Sample injection volume was

20 μL. The photo-diode array detector was set at 275 nm with reference in 360 nm and scan mode in the range of 190-400 nm. The method was validated according to method validation category I described in USP30 (2007) in the range of 50-120% labeled amount of CIS in oral suspensions. The following validation characteristics were addressed: system suitability, selectivity, accuracy, precision, linearity and range.

2.4 Preparation of control formulation of CIS oral suspension

Six batches of a HP-β-CD-free control formulation of 1 mg/mL CIS oral suspension were prepared from the powder of 5-mg CIS tablets according to the formulation published by Niazi (2004) using Viscocel 681 as a suspending agent. A 150 mL suspending vehicle contains Viscocel 681 1.5 g, Polysorbate 80 75 mg, sucrose 30 g, MP 270 mg, PP 30 mg, sodium chloride 150 mg and purified water in sufficient quantity to make 150 mL. It was prepared as follows. Viscocel 681 was dispersed and stirred at high speed in 40 mL of purified water to make a smooth dispersion. MP and PP were dissolved in 30 mL of purified water with the aid of heating to about 90°C to 95°C; sucrose was then dissolved in this solution to give a mixture of syrup and preservatives. This mixture, after being cooled to room temperature, was added into Viscocel 681dispersion followed by Polysorbate 80 and a solution of sodium chloride in 5 mL of purified water while stirring at high speed. The final volume was adjusted to 150 mL with purified water and the resulting mixture was thoroughly mixed to make a homogenous suspending vehicle.

A 1 mg/mL CIS suspension was prepared by triturating the powder of 5-mg CIS tablets (30 tablets) with a small amount of the suspending vehicle in glass mortar until smooth paste obtained. The three-fourths portion of the vehicle was then added and homogeneously mixed. The final volume of 150 mL was adjusted with the vehicle. The initial pH and viscosity (mean ± SD) of these six batches were 7.5± 0.1 and 42.0±0.06 centipoise, respectively. A 120-mL portion of each batch was filled into 120-mL polyethylene plastic prescription bottle with cap.

2.5 Preparation of CIS oral suspensions containing 0.3, 1.6, and 3% HP-β-CD

The 1 mg/mL CIS oral suspensions containing 0.3, 1.6, and 3% HP-β-CD, which correspond to the molar ratio of CIS:HP-β-CD of 1:1, 1:5, and 1:10, respectively, were prepared in the same manner as the control formulation by adding the corresponding amount of HP-β-CD into the formulations. Each of these formulations was prepared in six batches and a 120-mL portion was filled into 120-mL polyethylene plastic prescription bottles with caps. The initial pH of these preparations (mean ± SD) were 7.5±0.1. The initial viscosities of 0.3, 1.6, and 3% HP-β-CD containing formulations (mean ± SD) were 43.2±0.12, 43.2±0.15, and 50.0±0.14 centipoise, respectively. The solubility of CIS in formulations was assessed by directly injecting the clear aqueous supernatant, after centrifugation, of the suspensions into HPLC system.

2.6 Storage conditions

All six batches of each formulation were stored in the temperature-controlled water-bath maintained at 30±1°C and in the refrigerator, the temperature of which ranged from 3°C to 8°C (median 5°C).

2.7 Study of the stability of CIS in oral suspensions

The amounts of CIS in oral suspensions were determined, in duplicate, by the validated stability-indicating HPLC method (Boonleang and Tanthana, 2010) on the day of preparation ($t = 0$) and at 0.5, 1, 2, 3, 4, 5.5, 7, 8.5, 10, and 12.5 months. In addition, pH, physical appearance, and redispersibility of all samples were also determined at room temperature on the day of sample analysis. The redispersibility was determined by vertically inverting the container by hand and recording the number of inversions required to resuspend the sediment completely.

2.8 Data analysis

The remaining amounts of CIS in the various CIS oral suspensions over time were statistically analyzed by one-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) at 95% significance level ($\alpha = 0.05$) to evaluate the effect of HP-β-CD at different concentrations, as well as storage temperatures on the degradation of CIS.

3. Results and Discussion

3.1 Stability-indicating HPLC method

The stability-indicating HPLC method for determination of CIS in oral suspension was selective, accurate, and precise. The chromatographic system provided chromatograms with good peak shape and acceptable resolution of CIS, MP, PP, and the degradation products formed in oral suspensions. CIS peak was pure. All system suitability parameters, i.e.; theoretical plates (N), tailing factor (T), and injection repeatability, met the recommended criteria of CDER reviewer guidance on validation of chromatographic methods (CDER, 1994). The accuracy ranged from 99.20 to 100.6% of the true value. The within-run and between-run coefficient of variations (CV) ranged from 1.11% to 1.38% and from 0.44% to 1.25%, respectively. The calibration curve of CIS was linear over the concentration range of 10.0-75.0 μg/mL with $r^2 > 0.9997$. According to these analytical method validation data, this stability-indicating method for determination of CIS in oral suspensions was considered reliable and suitable for the stability study. The representative chromatograms of freshly prepared and degraded 1 mg/mL CIS suspensions are shown in Figure 2.

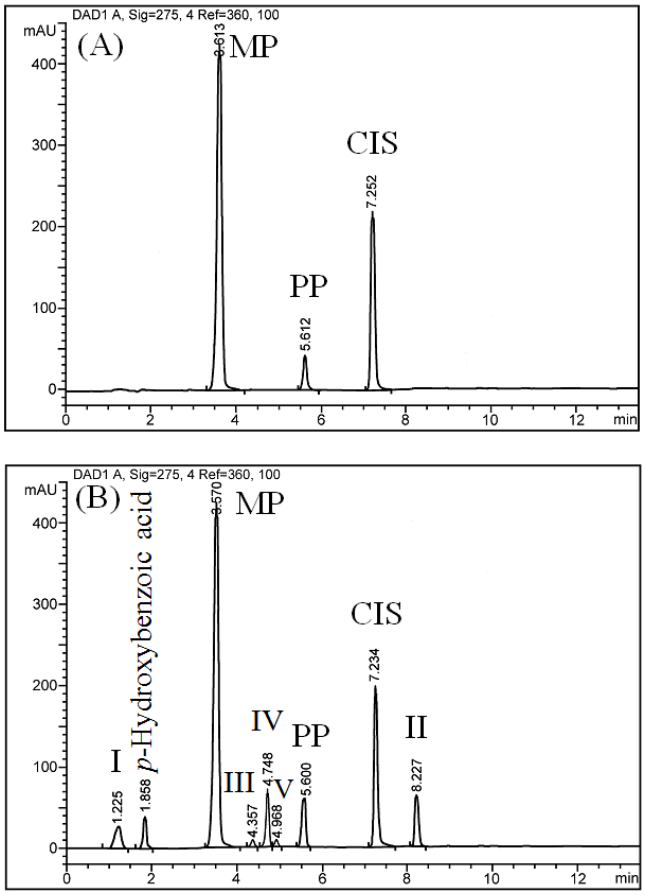


Figure 2. Representative HPLC chromatograms of freshly prepared suspension (A) and degraded 1 mg/mL CIS suspension (B). I and II are CIS hydrolysis product I and II, respectively. III, IV and V are unknown degradation products.

3.2 Physical appearance, viscosity, and redispersibility

No significant changes in physical appearance, viscosity, and redispersibility of all formulations stored under refrigeration were observed for up to 12.5 months. They all were still in white, easily redispersible suspensions. On the other hand, changes in color and odor were observed for all formulations stored at 30°C. A change in color from white to slightly brown of the control formulation and formulations containing 0.3, 1.6, and 3% HP-β-CD was first observed after storage for 10, 12, 8.5, and 7 months, respectively. However, the viscosity and redispersibility of all formulations stored at 30°C did not change significantly.

3.3 Changes in pH of CIS oral suspensions

Figure 3 illustrates the changes in pH over time of all formulations stored at 5°C and 30°C. No significant changes in pH of all formulations kept at 5°C were observed. When stored at 30°C, the pH of all formulations decreased. Up to 12.5 months, sigmoid-like decreases in pH approaching the pH of approximately 3 were observed in control formulation, 1.6%, and 3% HP-β-CD containing formulations. For 0.3% HP-β-CD containing formulation, a trend in pH-decreasing might also be sigmoid-like shape if the study were continued further.

3.4 Effect of HP-β-CD on the stability of CIS in oral suspensions

Figure 4 illustrates the changes in the amount of CIS over time in control and in HP-β-CD containing formulations at 5°C and 30°C. When stored at 5°C, no effect of HP-β-CD on the stability of CIS was observed. The ANOVA suggested that the remaining amounts of CIS in each formulation were not significantly different ($p = 0.69$). CIS in all formulations were stable for at least 12.5 months. The remaining amounts of CIS in the control formulation and formulations containing 0.3%, 1.6%, and 3% HP-β-CD were (mean ± SD) 93.43± 3.58%, 95.29±3.93%, 94.92±3.05%, and 95.99±2.69%, respectively.

When stored at 30°C, CIS in all formulations degraded. The results from ANCOVA suggested that the degradation profiles of CIS in each of the formulations were significantly different ($p<0.0001$). CIS was most stable in 0.3% HP-β-CD containing formulation. The observed t_{90}, i.e., the time at which a drug has decreased to 90% of its initial amount, of CIS in control and in 0.3% HP-β-CD containing formulations were approximately 7 and 11 months, respectively. During the first 120 days the degradation rates of CIS in all formulations were slower than later. This observation corresponded well to the changes in pH of formulations where the degrada-

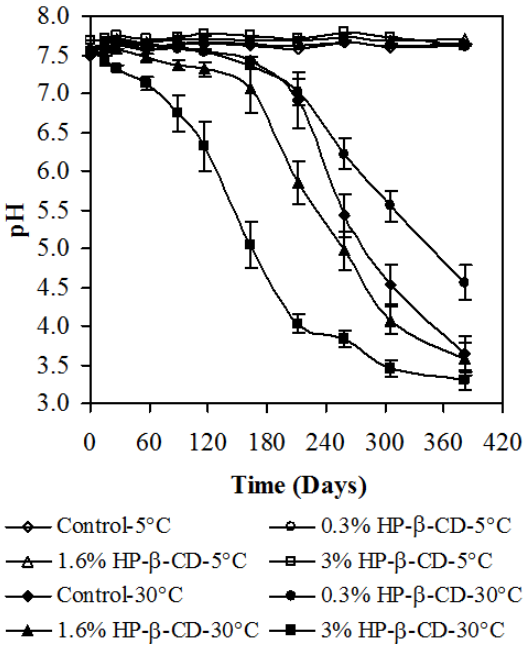


Figure 3. Changes in pH (mean ± SEM) over time of various CIS oral suspensions at 5°C and 30°C.

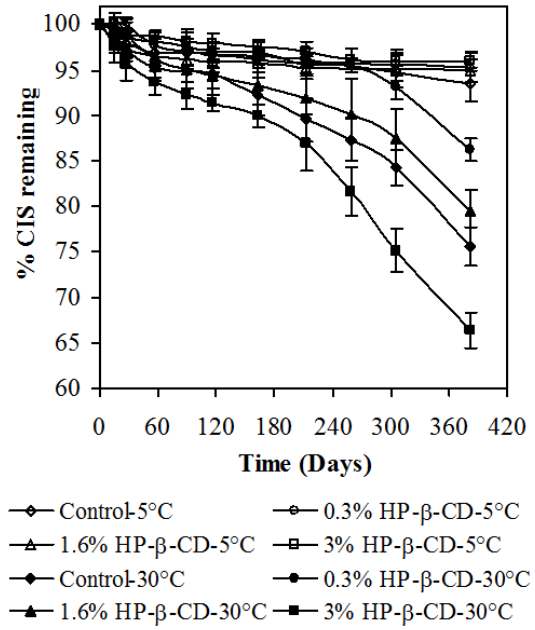


Figure 4. % CIS remaining (mean ± SEM) over time in various CIS oral suspensions at 5°C and 30°C. The profiles at 5°C are not significantly different ($p = 0.69$). The profiles at 30°C are significantly different ($p < 0.0001$).

tion rate of CIS was increased when the pH of formulation was lower than 7. The feasible degradation pathway of CIS might be hydrolysis, as shown in Figure 5. An acidic CIS hydrolysis product I was produced, which lowered the pH of formulations and further accelerated hydrolysis of CIS. *p*-Hydroxybenzoic acid, the hydrolysis degradation product of MP and PP (Connors *et al.*, 1986) also lowers the pH of the formulation. However, since the initial pH decreasing rate of control formulation was slower than that of 1.6% and 3% HP-β-CD containing formulations, it was most likely that the difference in pH-decreasing rate observed in different formulations was from the hydrolysis of CIS. In addition, the suspension excipients, as well as the tablet excipients from CIS tablets used to prepare the suspensions in this study might have some contributions on the degradation of CIS. This was probably evident from the presence of unknown degradation peaks in the chromatogram of degraded suspension (Figure 2).

Cyclodextrins can form in-situ inclusion complexes with a number of drugs in aqueous media and hence increase drug solubility even when there is no complexation in solid state (Higuchi *et al.*, 1965; Rasheed *et al.*, 2008). The inclusion complex formation between CIS and HP-β-CD might be evident from the increasing solubility of CIS as the concentration of HP-β-CD in formulation increased.

0.3% HP-β-CD containing formulation increased the stability of CIS as compared to control formulation. However, increasing the concentration of HP-β-CD decreased CIS stability. This suggests that the less stable inclusion complex

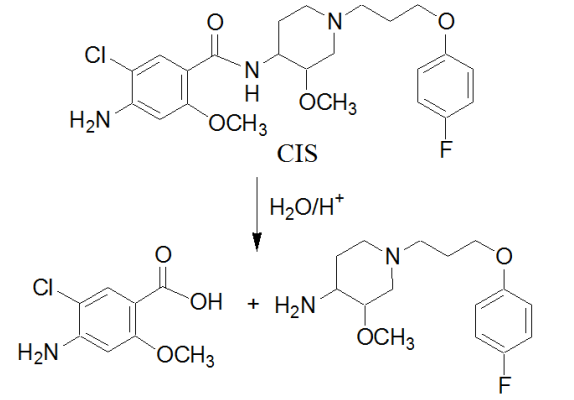
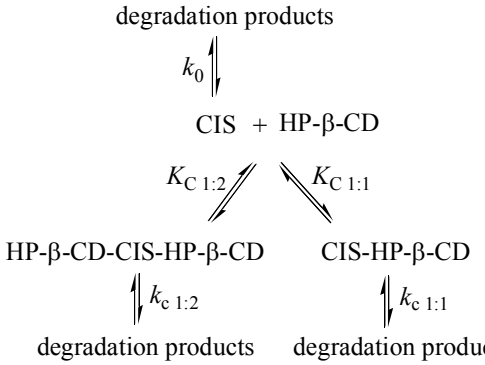


Figure 5. Hydrolysis pathway of CIS.

between CIS and HP-β-CD was formed at higher HP-β-CD concentration. This might be the same situation as the inclusion complex formation between CIS and β-cyclodextrin (β-CD) reported by Omari *et al.* (2007). In this case, CIS forms 1:1 and 1:2 CIS:β-CD inclusion complexes. In 1:1 CIS:β-CD complex, the hydrolysis-sensitive amide bond of CIS is completely included into the β-CD cavity whereas in 1:2 CIS:β-CD complex the amide bond is located between the wider rims of two β-CD molecules outside their cavities. Therefore, the 1:1 CIS:β-CD inclusion complex is more stable to hydrolysis than the 1:2 CIS:β-CD inclusion complex. The same is very likely true for the inclusion complex formation between CIS and HP-β-CD as the chemical structures of HP-β-CD and β-CD are very similar (El-Barghouthi *et al.*, 2006; Peeters *et al.*, 2002). At low concentration of HP-β-CD, the more stable 1:1 CIS:HP-β-CD complex is mostly formed, but at high concentration, the less stable 1:2 CIS:HP-β-CD complex is mostly formed. When compared to free CIS, the destabilizing effect of HP-β-CD on the stability of CIS in 1:2 CIS:HP-β-CD complex might be attributable to the decreased entropy of CIS in the above mentioned complex. Scheme 1 shows the proposed degradation pathway of CIS in HP-β-CD containing formulation.



Scheme 1 Degradation pathway of CIS in HP-β-CD containing formulation.

Where $K_{C\,1:1}$ and $K_{C\,1:2}$ are the inclusion complex formation constants of 1:1 and 1:2 CIS-HP-b-CD complex, respectively; k_0 is the degradation rate constant of uncomplexed CIS; $k_{c\,1:1}$ and $k_{c\,1:2}$ are the degradation rate constants of CIS from 1:1 and from 1:2 CIS-HP-β-CD complexes, respectively.

The observed degradation rate constant (k_{obs}) is a weighted average of all corresponding rate constants as shown in the equation below:

$$k_{obs} = F_f k_0 + F_{C\,1:1} k_{c\,1:1} + F_{C\,1:2} k_{c\,1:2}$$

where F_f, $F_{C\,1:1}$, and $F_{C\,1:2}$ are the mole fractions of uncomplexed CIS, 1:1, and 1:2 CIS-HP-β-CD complexes, respectively. The data obtained in this study apparently supported that the relative degradation rate constant could be as follows: $k_{c\,1:1} < k_0 < k_{c\,1:2}$. In 0.3% HP-β-CD containing formulation where CIS was mostly in the more stable 1:1 CIS:HP-β-CD complex, therefore, the degradation of CIS was slower than in control formulation. On the other hand, in 1.6% and 3% HP-β-CD containing formulations, most of CIS was increasingly in an unprotected 1:2 CIS:HP-β-CD complex, therefore, the increase in CIS degradation rate was observed. Even though CIS degradation rate constant is pH-dependent with higher rate at pH < 7, the relative magnitude of k_0, $k_{c\,1:1}$, and $k_{c\,1:2}$ was unchanged. As a result, CIS in all formulations degraded with faster rate after 120 days of storage correlated with the lower in pH of formulations.

4. Conclusion

CIS in the studied suspensions was more stable when stored at 5°C than at 30°C. At 5°C HP-β-CD had no significant effect on the stability of CIS. CIS in all formulations was stable for at least 12.5 months. At 30°C, HP-β-CD had an effect on the stability of CIS. CIS was most stable in formulation containing 0.3% HP-β-CD, which corresponds to 1:1 CIS:HP-β-CD molar ratio. The observed t_{90} of CIS in this formulation was approximately 11 months. Increasing the concentration of HP-β-CD in formulation decreased the stability of CIS.

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