Original Article

Simultaneous stability-indicating HPLC method for the determination of cisapride, methylparaben and propylparaben in oral suspension

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Abstract

A simultaneous stability-indicating HPLC method for the determination of cisapride, methylparaben and propylparaben in oral suspensions has been developed and validated. Baseline separation was achieved on a C18 column at room temperature (25°C) by gradient elution with mobile phase consisting of solvent A: 10% v/v acetonitrile in 0.13% w/v sodium-1-pentanesulfonate pH 8 and solvent B: acetonitrile. 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. The flow rate of mobile phase was 1.2 mL/min. The injection volume was 20 μL. Detection and peak purity assessments were performed by photo-diode array detector set at 275 nm with scan mode in the range of 190-400 nm. The method was selective, accurate and precise. It provided chromatograms with good peak shape and acceptable resolutions of greater than 4.4 for all analytes including the degradation products formed in oral suspensions in about 8.5 min. All analyte peaks were pure. The accuracy of all analytes was in the range of 99.20-100.6%. The within-run and between-run relative standard deviations were less than 1.50%. The calibration curves for cisapride, methylparaben, and propylparaben were linear over the concentration range of 10.0-75.0 μg/mL, 8.0-100.0 μg/mL, and 0.8-10.0 μg/mL, respectively with r^2 greater than 0.999. This developed method was successfully applied to the stability study of cisapride, methylparaben and propylparaben in oral suspension formulations.

Keywords: cisapride, parabens, HPLC, oral suspension, stability-indicating

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 (Reynolds and Putman, 1992; Geldof *et al.*, 1993; Wiseman and Faulds, 1994; Onat *et al.*, 1994; Barone *et al.*, 1994; Sweetman, 2005). 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 (Bedford and Rowbotham, 1996; Thomas *et al.*, 1998; Van Haarst *et al.*, 1998; Wysowski *et al.*, 2001). However, it does not affect psychomotor function or induce central depressant adverse effect as compared to other prokinetic agents such as metoclopramide and domperidone
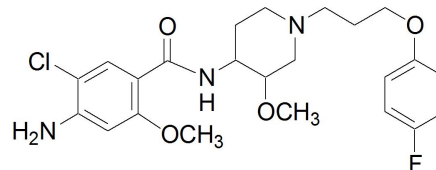
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Figure 1. Chemical structure of cisapride.

(McCallum *et al.*, 1988). This medicine, therefore, 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 gastroesophageal reflux disease patients only (World Health Organization, 2003)

     An oral suspension of CIS has been developed from cisapride tablets in order 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 the drug via the nasogastric tube. This formulation is preserved with a combination of methylparaben (MP) and propylparaben (PP), the widely used preservative system in liquid formulations. In our study, hydroxypropyl-β-cyclodextrin (HP-β-CD) is added into the formulation to increase the stability of CIS.

     The preservative system is an important part of liquid formulations in preventing the deterioration of formulations from microbial contamination. To establish their effectiveness throughout the shelf life of the product, the actual concentrations of preservatives must be determined, as also required by regulatory agencies. Stability-indicating methods have been reported for the determination of MP, PP and other drugs by HPLC (Kollmorgen and Kraut, 1998; Beasley *et al.*, 2005; Ali *et al.*, 2006; Grosa *et al.*, 2006). A limited number of stability-indicating HPLC methods have been reported for the determination of CIS in pharmaceutical preparations (Nahata *et al.*, 1995; Allen Jr. and Erickson III, 1998; Argekar and Sawant, 1999). Belgaied and Trabelsi (2003) postulated that CIS is easily oxidized to give cisapride *N*-oxide, and developed a HPLC method for simultaneous determination of CIS, cisapride *N*-oxide, PP and butylparaben in suspension. However, in our study, other degradation products of CIS have been found. As per bibliographical revision, no analytical methods for simultaneous determination of CIS, MP and PP that account for the presence of these other degradation products of CIS and *p*-hydroxybenzoic acid, a known degradation product of parabens, have been reported. The aims of this study were to develop and validate a stability-indicating HPLC method for simultaneous determination of CIS, MP and PP in oral suspension in the presence of degradation products of CIS and *p*-hydroxybenzoic acid for use in the stability study of CIS, MP and PP in oral suspension.

2. Material and Methods

2.1 Chemicals

     Cisapride (CIS), hydroxypropyl-β-cyclodextrin (HP-β-CD, average MW 1460, molar substitution 0.8), methylparaben (MP) and propylparaben (PP) were purchased from Sigma-Aldrich (MO, USA). Acetonitrile, methanol, hydrochloric acid and sodium hydroxide were obtained 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 analytical or HPLC grade, and were used without further purification.

2.2 Samples

     A 1 mg/mL CIS oral suspension was prepared from the powder of 5-mg CIS tablets (CIPASID®, Siam Pharmaceutical Co., Ltd., Bangkok, Thailand) according to the formulation published by Niazi (2004) with 3% w/v HP-b-CD added. This oral suspension contains 0.18% w/v MP and 0.02% w/v PP. A placebo suspension was prepared in the same manner as the 1 mg/mL CIS oral suspension using powdered placebo tablets without MP and PP added. The 1 mg/mL CIS oral suspension was kept at 30°C to allow degradation over a period of 12.5 months.

2.3 Equipments and chromatographic conditions

     The HPLC system (Agilent 1100 Series, Agilent Technologies, USA) consisted 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) at room temperature (25°C) by gradient elution with mobile phase consisting of solvent A, which was a mixture of 0.13% w/v 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. The mobile phase was filtered through a 0.22 μm membrane filter and degassed by ultrasonication before use. Sample injection volume was 20 μL. The photo-diode array detector was set at 275 nm with reference in 360 nm with scan mode in the range of 190-400 nm. Peak purity was assessed from photo-diode array spectral analysis by the instrument software.

2.4 Preparation of stock and calibration standard solutions

     The individual stock standard solutions of CIS, MP, and PP were prepared in methanol at the concentrations of 250 μg/mL, 200 μg/mL, and 20 μg/mL, respectively. All stock solutions and calibration standard solutions were freshly prepared on the day of analysis. A series of five concentrations of standard mixture of CIS, MP and PP were then prepared by appropriately diluting the respective stock solution with methanol to give the concentration of CIS, MP, and PP in the range of 10.0-75.0 μg/mL, 8.0-100.0 μg/mL, and 0.8-10.0 μg/mL, respectively.

2.5 Preparation of analytical sample

Immediately after thorough mixing, a sample of 1.0 mL suspension was transferred into a 25-mL volumetric flask. The appropriate amount of methanol was then added. The mixture was sonicated for 10 min and allowed to cool to room temperature before adjusting to volume with methanol. The resulting mixture was centrifuged at 3500 rpm for 5 min and 20 μL of the clear supernatant was injected directly onto the column.

2.6 Method validation

The method was validated according to method validation category I described in USP30 (2007). The following validation characteristics were addressed: system suitability, selectivity, accuracy, precision, linearity and range.

2.6.1 System suitability

System suitability standard solution was prepared by diluting appropriate volume of respective stock solutions with methanol to give a mixture of 40.0 μg/mL CIS, 40.0 μg/mL MP and 4.0 μg/mL PP. The system suitability parameters, i.e., injection repeatability, theoretical plates (N) and tailing factor (T) were evaluated from six replicate injections of the system suitability standard solution. The parameters N and T were calculated according to the formulae specified in USP30 (2007) as follows.

$$N = \left(\frac{t_R}{W_{0.5}}\right)^2 \qquad T = \frac{W_{0.05}}{2f}$$

where t_R is the retention time of the analyte, $W_{0.5}$ is the peak width at half-height, $W_{0.05}$ is the peak width at 5% of peak height, and f is the distance between the perpendicular line dropped from the peak maximum and the peak front at 5% of peak height. The injection repeatability was determined from the relative standard deviation (RSD) of peak areas from replicate injections.

2.6.2 Selectivity

Selectivity of the method was evaluated by comparing the chromatograms from MP- and PP-free placebo suspension, freshly prepared CIS suspension, controlled-30°C real time degraded CIS suspension and standard mixture of CIS, MP and PP in methanol to investigate any interference from sample matrix as well as degradation products on the analysis of CIS, MP and PP. The resolution factors between the analytes of interest and the adjacent resolved peaks were calculated according to USP30 (2007). The selectivity was also evaluated from peak purity analysis established from spectral analysis by the instrument software.

2.6.3 Accuracy and precision

Accuracy and precision of the method were determined from replicate analysis of placebo suspension spiked with known amount of CIS, MP and PP at 50, 100 and 120% labeled amount. The within-run accuracy and precision were determined from five replicate determinations of samples in a single analytical run. The between-run accuracy and precision were determined from five replicate determinations of five analytical runs performed on five different days (one batch of sample per day). The accuracy was expressed in term of % accuracy calculated as the percentage of the estimated analyte concentration obtained from standard calibration curve and the known added concentration. The precision of the method was expressed as RSD of the estimated concentrations from replicate determinations.

2.6.4 Linearity and range

Five concentrations of calibration standard solutions containing the mixture of CIS, MP, and PP, at the concentration range of 10.0-75.0 μg/mL, 8.0-100.0 μg/mL, and 0.8-10.0 μg/mL, respectively, were analyzed. Linear regression analysis was used to evaluate the linear relationship between peak area of the analyte (y) and concentration (x).

2.6.5 Solution stability

The system suitability standard solution and analytical sample solutions were left in the autosampler at ambient temperature (25°C). These solutions were repetitively injected every 4 h for 24 h. The percentage change of analyte peak area at each time point with respect to the initial peak area ($t = 0$) was calculated. The RSD of peak area from repeated injections was also estimated. The analyte is considered stable if the percentage change of analyte peak area is within 2% (Green, 1996).

2.7 Application of the developed method

The developed method was applied to the stability study of CIS, MP and PP in 1 mg/mL CIS oral suspension with and without 3% w/v HP-β-CD to investigate the effect of HP-β-CD on the stability of these three compounds in oral suspension. The samples were stored at 5°C and 30°C, and the amount of CIS, MP and PP were simultaneously determined by the proposed method at the specified intervals over a period of about 12.5 months.

3. Results and Discussion

3.1 Method Development and optimization

This aim of this study was to develop a stability-indi-

cating HPLC method for simultaneous determination of CIS, MP and PP in the presence of *p*-hydroxybenzoic acid, a known degradation product of parabens, and degradation products from CIS to be used in the stability study of CIS, MP and PP in oral suspension. Ion-paired reversed phase HPLC with isocratic elution was initially selected in method development, using forced degradation solution of CIS in 1 M HCl, 1 M NaOH and 3% H_2O_2. The optimum separation of CIS, MP, PP, *p*-hydroxybenzoic acid and degradation products from CIS was achieved with the mobile phase consisting of 0.1% w/v sodium-1-pentanesulfonate pH 8 and acetonitrile (55:45, v/v). However, when this separation system was applied for the analysis of samples of 1 mg/mL CIS oral suspension from the stability study, other degradation products were found to co-elute with MP and PP, as evidenced from peak purity analysis. Therefore, gradient elution was developed, based on the mobile phase consisting of 10% v/v acetonitrile in 0.13% w/v sodium-1-pentanesulfonate pH 8 as solvent A and acetonitrile as solvent B. The addition of 10% v/v acetonitrile into the aqueous part of mobile phase was to prevent microbial growth during the analysis of a large number of stability samples. This chromatographic system provided chromatograms with good peak shape and acceptable resolution of all analytes in about 8.5 min. Figure 2(B) and 2(C) show typical chromatograms from the freshly prepared and degraded samples of 1 mg/mL CIS oral suspension, respectively.

3.2 Method validation

3.2.1 System suitability

The system suitability parameters, *N*, *T* and injection repeatability, from six replicate injections are presented in Table 1. All parameters met the recommended criteria of the CDER reviewer guidance on validation of chromatographic methods (CDER, 1994), i.e., *N* should be > 2000, *T* should be ≤ 2 and RSD of five or more (n $\geq$ 5) replicate injections should be $\leq$ 1%.

3.2.2 Selectivity

Figure 2 illustrates the selectivity of the method. No interferences from sample matrix and degradation products on the peak of CIS, MP and PP were observed. Spectral analysis also indicated that all of these peaks were pure. The chro-
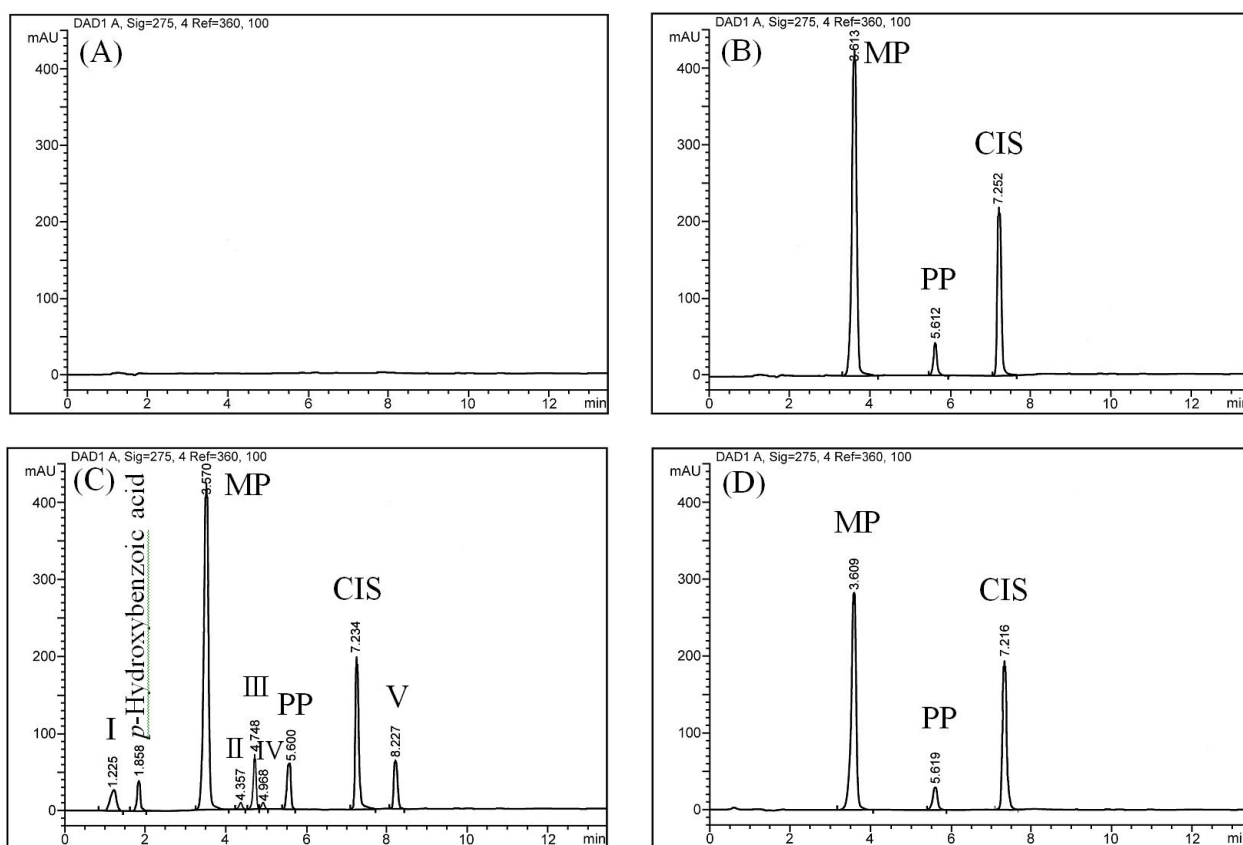

Figure 2. HPLC chromatogram of (A) MP- and PP-free placebo suspension, (B) freshly prepared 1 mg/mL CIS suspension, (C) degraded 1 mg/mL CIS suspension, and (D) standard mixture of CIS (40.0 μg/mL), MP (40.0 μg/mL) and PP (4.0 μg/mL) in methanol. I, II, III, IV, and V are CIS degradation product I, II, III, IV, and V, respectively.

Table 1. System suitability parameters

Parameters	CIS	MP	PP
Theoretical plates $(N)^a$	45798 (2.37)	7206 (1.75)	22895 (2.29)
Tailing factor $(T)^a$	1.08 (1.47)	0.92 (1.07)	0.94 (0.64)
Injection repeatability[a]			
Peak area	1256.86 (0.34)	1939.59 (0.60)	184.74 (0.65)
Retention time	7.242 (0.23)	3.600 (0.43)	5.600 (0.34)

[a] Expressed as mean from six replicate injections of system suitability standard solution with RSD (%) in the parentheses.

matographic system used in this study can effectively resolve CIS, MP, PP and degradation products with baseline separation. The retention times of MP, PP, and CIS were approximately 3.6, 5.6, and 7.2 min, respectively. Peak at retention time about 1.8 min was identified as *p*-hydroxybenzoic acid based on the retention data and UV-spectrum obtained by injecting *p*-hydroxybenzoic acid-spiked authentic sample. Peaks at retention time of 1.2, 4.3, 4.7, 4.9, and 8.2 min were from CIS degradation product I, II, III, IV, and V, respectively. The CIS degradation product I and V were the same as those obtained from acid hydrolysis of CIS in 0.1 N HCl, whereas CIS degradation product II, III and IV were formed in the suspension during storage at 30°C. The resolution factors of five critical pairs, namely, *p*-hydroxybenzoic acid-MP, MP-CIS degradation products II, CIS degradation products IV-PP, PP-CIS, and CIS-CIS degradation products V were 13.08, 5.12, 4.44, 10.96, and 7.52, respectively.

3.2.3 Accuracy and precision

The within- and between-run accuracy and precision are shown in Table 2. The developed method was very accurate and precise. The within- and between-run accuracy for the determination of CIS, MP and PP were within 98.0-102.0%.

The within- and between-run precision of the method, as determined from RSD, were less than 2% for all analytes.

3.2.4 Linearity and range

The linear relationship between peak area (*y*) and analyte concentration (*x*) of CIS, MP, and PP over the five studied concentrations ranged from 10.0-75.0 μg/mL, 8.0-100.0 μg/mL, and 0.8-10.0 μg/mL, respectively, was established. These concentration ranges covered the concentration range of 50-120% labeled amount of CIS, MP and PP in oral suspension at which the method has been validated to provide acceptable accuracy and precision. The equations for mean of five calibration curves of each analyte from linear regression were: CIS; $y = 33.5958x - 21.1420$ ($r^2 = 0.9998$), MP; $y = 42.3487x + 9.7861$ ($r^2 = 0.9998$), and PP; $y = 36.7967x + 1.9250$ ($r^2 = 0.9997$). That the coefficient of determination (r^2) of calibration curve for all analytes was greater than 0.999 indicated the excellent fit of the regression line.

3.2.5 Solution stability

The results of solution stability are shown in Table 3. CIS, MP and PP in standard solution, as well as in sample

Table 2. Accuracy and precision for the simultaneous determination of CIS, MP and PP in oral suspension (n = 5)

Analytes	Nominal % labeled amount	Accuracy (%)		Precision (RSD, %)	
		Within-run	Between-run	Within-run	Between-run
CIS	50	99.93	99.95	1.21	1.25
	100	99.68	99.20	1.11	0.44
	120	100.2	100.6	1.38	0.87
MP	50	100.0	99.53	0.29	1.33
	100	100.0	101.1	0.41	1.41
	120	100.3	99.93	0.59	1.14
PP	50	99.99	100.1	0.30	0.52
	100	99.86	100.6	0.48	0.92
	120	100.0	100.3	0.38	0.82

Table 3. Stability of standard and sample solutions in the autosampler at 25°C for 24 h

Solutions	Change in peak area (%) at 24 h			RSD (%) of repetitive injections (n = 7)					
				Peak area			Retention time		
	CIS	MP	PP	CIS	MP	PP	CIS	MP	PP
Standard solution	-0.70	0.54	0.05	0.51	0.32	0.61	0.23	0.43	0.34
Sample solution of freshly prepared suspension	0.53	-0.79	-1.18	0.62	0.50	0.52	0.27	0.17	0.28
Sample solution of degraded suspension	0.57	-1.03	0.42	0.55	0.62	0.37	0.19	0.17	0.42

solutions, were stable in autosampler at 25°C for at least 24 h. No significant changes in retention time, peak area and peak purity were observed.

3.3 Application of the validated method

The validated method was applied to the simultaneous determination of CIS, MP and PP in oral suspensions with and without 3% w/v HP-β-CD in the stability study. Representative chromatograms of freshly prepared suspension and degraded suspension are shown in Figure 2B and 2C, respectively. The changes in the amount of CIS, MP and PP over time in the above mentioned oral suspensions at 5°C and 30°C are shown in Figure 3. Stability was assessed based on the 90% of drug remaining. The results demonstrated that, when stored at 5°C CIS, MP and PP in oral suspension with and without 3% w/v HP-β-CD were stable for at least 12.5 months. When stored at 30°C, HP-β-CD at this concentration increased the stability of MP and PP, but decreased the stability of CIS as compared to the oral suspension formulation without HP-β-CD. At 30°C, CIS, MP, and PP in oral suspension containing 3% w/v HP-β-CD were stable for at least 160 days, 60 days, and 360 days, respectively.

4. Conclusion

The developed simultaneous stability-indicating HPLC method for determination of CIS, MP and PP in oral suspension is selective, accurate and precise. The chromatographic system provided chromatograms with good peak shape and acceptable resolution of all analytes including the degradation products formed in oral suspension in about 8.5 min. It was successfully applied in the stability study of CIS, MP and PP in oral suspension formulations.
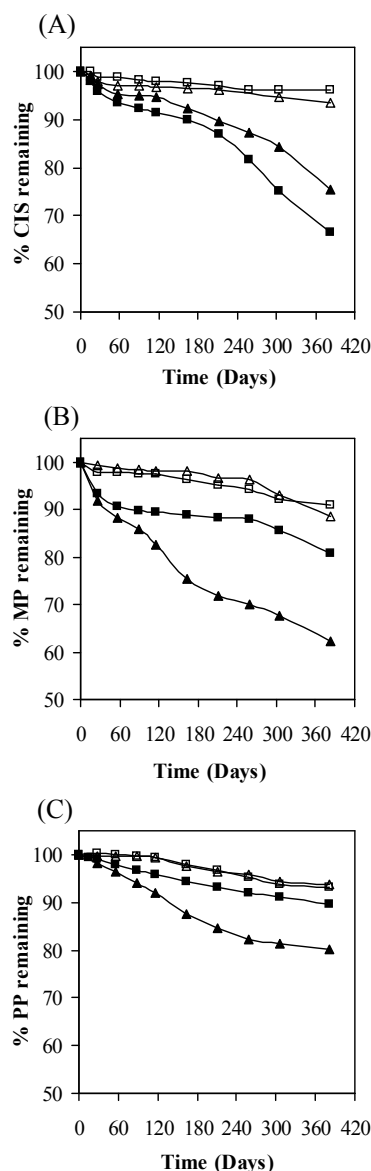
Figure 3. % Remaining of CIS (A), MP (B) and PP (C) over time in two formulations of 1 mg/mL CIS oral suspension; formulation without HP-β-CD at 5°C (△) and at 30°C (▲) and formulation with 3% w/v HP-β-CD at 5°C (□) and at 30°C (■).

References

Ali, M.S., Ghori, M. and Khatri, A.R. 2006. Stability indicating simultaneous determination of domperidone (DP), methylparaben (MP) and propylparaben by high performance liquid chromatography (HPLC). Journal of Pharmaceutical and Biomedical Analysis. 41, 358-365.

Allen Jr., L.V. and Erickson III, M.A. 1998. Stability of alprazolam, chloroquine phosphate, cisapride, enalapril maleate, and hydralazine hydrochloride in extemporaneously compounded oral liquids. American Journal of Health-System Pharmacy. 55, 1915-1920.

Argekar, A.P. and Sawant, J.G. 1999. Determination of cisapride in pharmaceutical dosage forms by reversed-phase liquid chromatography. Journal of Pharmaceutical and Biomedical Analysis. 21, 221-226.

Barone, J.A., Jessen, L.M., Colaizzi, J.L. and Bierman, R.H. 1994. Cisapride: a gastrointestinal prokinetic drug. The Annals of Pharmacotherapy. 28, 488-500.

Beasley, C.A., Shaw, J., Zhao, Z. and Reed, R.A. 2005. Development and validation of a stability indicating HPLC method for determination of lisinopril, lisinopril degradation product and parabens in the lisinopril extemporaneous formulation. Journal of Pharmaceutical and Biomedical Analysis. 37, 559-567.

Bedford, T.A. and Rowbotham, D.J. 1996. Cisapride: Drug interactions of clinical significance. Drug Safety. 15, 167-175.

Belgaied, J.E. and Trabelsi, H. 2003. Determination of cisapride, its oxidation product, propyl and butyl parabens in pharmaceutical dosage form by reversed phase liquid chromatography. Journal of Pharmaceutical and Biomedical Analysis. 33, 991-998.

Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration. 1994. Reviewer Guidance, Validation of Chromatographic Methods, FDA, Rockville, MD, U.S.A.

Geldof, H., Hazelhoff, B. and Otten, M.H. 1993. Two different dose regimens of cisapride in the treatment of reflux oesophagitis: a double-blind comparison with ranitidine. Alimentary Pharmacology and Therapeutics. 7, 409-415.

Green, J.M. 1996. A practical guide to analytical method validation. Analytical Chemistry. 68, 305A-309A.

Grosa, G., Grosso, E.D., Russo, R. and Allegrone, G. 2006. Simultaneous, stability indicating, HPLC-DAD determination of guaifenesin and methyl and propylparabens in cough syrup. Journal of Pharmaceutical and Biomedical Analysis. 41, 798-803.

Kollmorgen, D. and Kraut, B. 1998. Determination of methylparaben, propylparaben and chlorpromazine in chlorpromazine hydrochloride oral solution by high-performance liquid chromatography. Journal of Chromatography B. 707, 181-187.

McCallum, R.W., Prakash, C., Campoli-Richards, D.M. and Goa, K.L. 1988. Cisapride: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use as a prokinetic agent in gastrointestinal mobility disorders. Drugs. 36, 652-681.

The Merck Index, 1996. The Merck & Co., Inc. Whitehouse Station, New Jersey, U.S.A., p. 390.

Nahata, M.C., Morosco, R.S. and Hipple, T.F. 1995. Stability of cisapride in a liquid dosage form at two temperatures. The Annals of Pharmacotherapy. 29, 125-126.

Niazi, S.K. 2004. Handbook of Pharmaceutical and Manufacturing Formulations: Liquid Products, CRC PRESS, New York, U.S.A., p. 105.

Onat, F., Yegen, B., Berkman, K. and Oktay, S. 1994. The hypotensive effect of cisapride in rat. General Pharmacology. 25, 1253-1256.

Reynolds, J.C. and Putnam, P.E. 1992. Prokinetic agents. Gastroenterology Clinics of North America. 21, 567-596.

Sweetman, S.C. 2005. Martindale: The Complete Drug Reference. The Royal Pharmaceutical Society of Great Britain, London, UK, p. 1259.

Thomas, A.R., Chan, L.N., Bauman, J.L. and Olopade, C.O. 1998. Prolongation of the QT-interval related to cisapride-diltiazem interaction. Pharmacotherapy. 18, 381-385.

The United States Pharmacopeia (USP30) - The National Formulary (NF25) 2007. United States Pharmacopeial Convention Inc., Rockville, MD, U.S.A.

Van Haarst, A.D., Van't Klooster, G.A., Van Gerven, J.M., Schoemaker, R.C., Van Oene, J.C., Burggraaf, J., Coene, M.C. and Cohen, A.F. 1998. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clinical Pharmacology and Therapeutics. 64, 542-546.

Wiseman, L.R. and Faulds, D. 1994. Cisapride: An updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal mobility disorders. Drugs. 47, 116-152.

World Health Organization. 2001. Pharmaceuticals: Restriction in Use and Availability, Essential Drugs and Medicines-Quality Assurance and Safety of Medicines, Health Technology and Pharmaceuticals, Geneva, Switzerland.

World Health Organization. 2003. Pharmaceuticals: Restriction in Use and Availability, Essential Drugs and Medicines Policy-Quality Assurance and Safety: Medicines Health Technology and Pharmaceuticals, Geneva, Switzerland.

Wysowski, D.K., Corken, A., Gallo-Torres, H., Talarico, L. and Rodriguez, E.M. 2001. Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and food and drug administration regulatory actions. The American Journal of Gastroenterology. 96, 1698-1703.