Asian Journal of Chemistry; Vol. 26, No. 23 (2014), 7969-7972

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16789

Inclusion Complexation of Lansoprazole with Cyclodextrin Derivatives by ^{1}H NMR, UV Spectroscopy and Phase Solubility

H.Y. FANG[1], X.Y. JIANG[1,*], C.S. ZHOU[2], K.W. TANG[2], T. YANG[2] and P.L. ZHANG[2]

[1]College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, Hunan Province, P.R. China
[2]College of Chemistry and Chemical Engineering, Hunan Institute of Science and Techonlogy, Yueyang 414006, Hunan Province, P.R. China

*Corresponding author: Tel: +86 731 88830833, E-mail: jiangxinyu@csu.edu.cn

Received: 29 November 2013; *Accepted*: 8 April 2014; *Published online*: 15 November 2014; AJC-16274

The inclusion complexes of cyclodextrin derivatives with lansoprazole (LPZ) in aqueous solution were investigated by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy, ultraviolet (UV) spectroscopy and phase solubility analysis. The main factors affecting the inclusion process, such as the structure and concentration of host molecule, temperature and pH, were discussed. A dependable determination of the complex stoichiometry was offered by the continuous variation technique. Thermodynamic parameters for inclusion process of lansoprazole and hydroxypropyl-β-cyclodextrin (HP-β-CD) were also investigated. The chemical shifts of protons of lansoprazole by ^{1}H NMR showed that benzimidazole group was inserted into the cavity of cyclodextrin derivatives. The ultraviolet spectroscopy and phase solubility diagram results revealed that the formation of inclusion complexes with a stoichiometric ratio of 1:1.

Keywords: Inclusion complex, Lansoprazole, Cyclodextrin derivatives, ^{1}H NMR, UV spectroscopy.

INTRODUCTION

As a widely-used acid proton pump inhibitor, lansoprazole (Fig. 1) is a benzimidazole sulfoxide derivarive, which inhibits gastric acid secretion by an interaction with (H+/K+)-ATPase in parietal cells of the stomach[1]. Lansoprazole has been extensively applied in the treatment of gastric and duodenal ulcerative disease with a superior or equivalent clinical efficacy to H_2 receptor antagonist[2,3]. However, the bioavailability of lansoprazole is not stable owing to variation in the genotype of CYP2C19, limited water solubility and sensitivity to acidic condition and light[4,5]. Poorly water-soluble compounds exhibit poor absorption, so enhancement of aqueous solubility is a valuable target to improve therapeutical efficacy. Cyclodextrins (CDs) are extensively used to enhance the aqueous solubility of slightly water-soluble compounds in such way that solubilizing inclusion complexes can be formed in aqueous solutions[6-10].

Cyclodextrins are cyclic glucose oligosaccharides having different numbers glucose units, linked by 1,4-α-glucosidic bonds and comprise α-, β-and γ-cyclodextrin. The size of the cavity of the cyclodextrins permits selectivity for the complexation of guest molecules according to its size, therefore acting as molecular encapsulants. As complexing agents, cyclodextrins are capable of forming inclusion complexes with various guest molecules because of their peculiar molecular

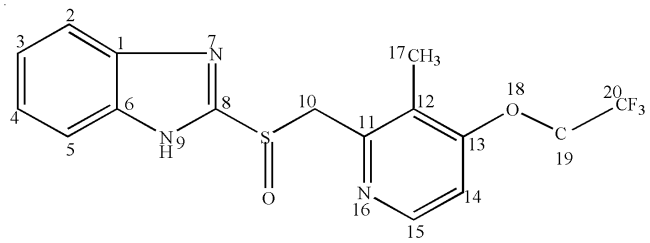

Fig. 1. Chemical structure of lansoprazole

structures with hydrophobic outer surface and a non polar cavity interior[11-13]. The main driving force of the formation of inclusion complex are non-covalent interactions such as van der Waals forces, electronic effects, hydrophobic interactions, conformational energy and steric factors[14,15]. Upon inclusion or partial inclusion of molecules with β-cyclodextrin derivatives (β-CDs), β-cyclodextrins can powerfully shield the excited singlet state of molecules and improve or weaken their ultraviolet absorption (or fluorescence) intensity[16]. The formation of inclusion complex will improve its water solubility, its stability and bioavailability of drugs.

The purpose of this paper was to study the influence of pH and temperature on the inclusion complexation of lansoprazole with different cyclodextrins. Inclusion stability constants were determined using the analysis of the measured phase solubility diagrams by ultraviolet spectroscopy.

EXPERIMENTAL

Lansoprazole (lansoprazole, purity = 99 %) was provided from Yongtai Chemical Company (Linhai Zhejiang, China). β-cyclodextrin (β-CD), hydroxyethyl-β-cyclodextrin (HE-β-CD), methyl-β-cyclodextrin (Me-β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and sulfobutylether-β-cyclodextrin (SBE-β-CD) were purchased from Qianhui Fine Chemical (Shandong, China). All other reagents were of analytical grade and from by different companies.

Study of ultraviolet absorption spectrum of lansoprazole and hydroxypropyl-β-cyclodextrin: Solutions of lansoprazole and hydroxypropyl-β-cyclodextrin with the same concentration were mixed in this way that the total molar concentration of lansoprazole and hydroxypropyl-β-cyclodextrin was held constant, but the molar ratios were varied. The variations of UV absorbance between free and complex lansoprazole were measured at 284 nm.

1×10^{-4} mol/L lansoprazole was prepared by dissolving in methanol as stock solution. 1 mL stock solution was transferred into a 10 mL graduated test tube with stopper, then different volume (0-10 mL) of 2×10^{-2} mol/L hydroxypropyl-β-cyclodextrin solution was added to a solution of lansoprazole and diluting to the mark in a 10 mL graduated test tube using deionized water. The final solution was placed in KQ-300DA ultrasonic to stir for 2 h and in a water-bath shaker to vibrate for 3 h and then kept in a water-bath shaker at 5°C for 12 h to achieve equilibrium.

Phase solubility studies: Phase solubility studies were performed according to the method described by Higuchi and Connors[17]. Lansoprazole, in amount that exceeded its solubility, was added to a 10 mL graduated test tube with stopper containing various concentrations of (0-30 mm/L) cyclodextrins. The suspensions were shaken for 6 h, then kept in a water-bath shaker for 12 h at a fixed temperature to reach equilibrium. The samples were filtered with syringe using a 0.45 μm membrane filter and the concentration of lansoprazole in the filtrate was measured by UV spectroscopy and HPLC at 284 nm.

^{1}H NMR study: ^{1}H NMR is a powerful tool for studying the inclusion complexes of lansoprazole with cyclodextrins. All the ^{1}H NMR experiments were conducted on a Bruker Avance 500 spectrometer at 500 MHz. Samples of β-cyclodextrin and β-cyclodextrin derivatives, lansoprazole and the complex of lansoprazole with β-cyclodextrin (the concentrations of 10 mmol/L) were prepared by dissolving in DMSO. ^{1}H NMR chemical shifts changes (Δd) were estimated to confirm the inclusion of lansoprazole according to the following equation:

$$\Delta\delta = \delta_{\text{complexed state}} - \delta_{\text{free state}} \quad (1)$$

RESULTS AND DISCUSSION

Binding stoichiometry of LPZ/HP-β-CD complex: Mole-ratio plot was constructed by the continuous variation Job's method[13] to investigate the complexation reaction. Fig. 2 shows that the value of absorbance is maximal at about 1:1 the molar ratio of lansoprazole to hydroxypropyl-β-cyclodextrin.

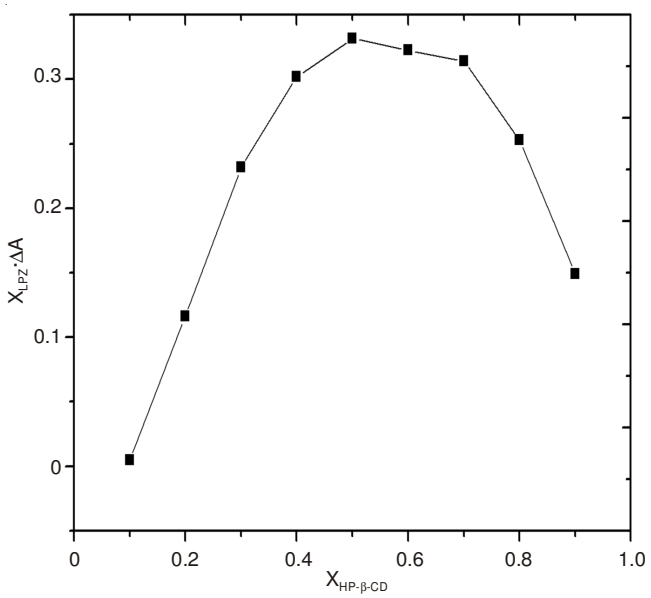

Fig. 2. Illustration of the job plot for the determination of stoichiometry. $X_{HP-β-CD}$ is mole fraction of HP-β-CD in equilibrium mixture; X_{LPZ} is mole fraction of lansoprazole in equilibrium mixture. ΔA is the enhancement of absorbance between free lansoprazole and complexed lansoprazole. The experiment solutions were made over a range of LPZ/HP-β-CD ratios with $C_{HP-β-CD} + C_{LPZ} = 1 \times 10^{-4}$ mol/L

Determination of inclusion stability constant by UV spectroscopy: A straight line is obtained by plotting of 1/ΔA *versus* $1/C_{HP-β-CD}$ (Fig. 3), which shows a 1:1 stoichiometry for inclusion complex. From the ratio of the intercept to the slope in Benesi-Hildebrand plot[18], the inclusion stability constant K was determined with the value of 179.3 L/mol.

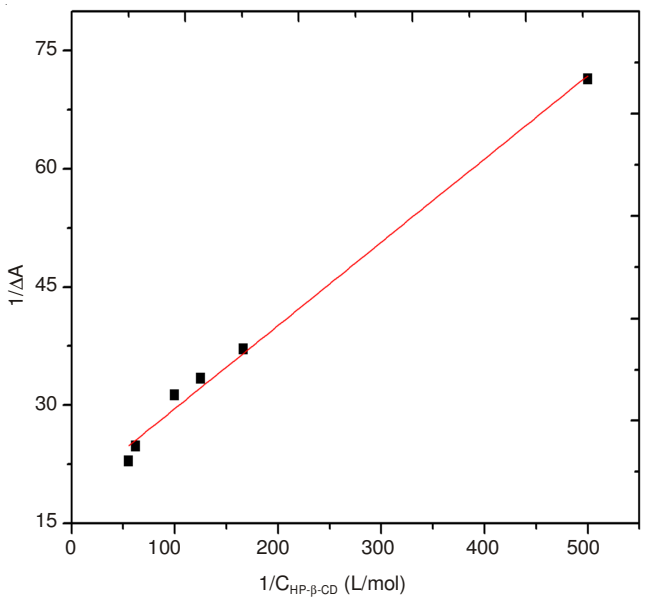

Fig. 3. Benesi-Hildebrand plot of 1/ΔA *versus* $1/C_{HP-β-CD}$

Influence of the type of cyclodextrins: Phase solubility diagrams of lansoprazole with β-cyclodextrin and β-cyclodextrin derivatives are typical A_L type diagrams according to Higuchi and connors and cyclodextrin derivatives are capable of enhancing linearly water solubility of lansoprazole with the increase of cyclodextrins concentrations (5-40 mm). The

reason may be that the cyclodextrins cavity offered a nonpolar environment for lansoprazole molecule.

For the formation of 1:1 inclusion complex, inclusion stability constant can be calculated from the slope and the intercept of the plot of the phase solubility diagrams according to the eqn. (2)[17]:

$$K = \frac{\text{slope}}{S_0 \times (1 - \text{slope})} \quad (2)$$

where K is inclusion stability constant; S_0 is solubility of lansoprazole in absence of β-cyclodextrin. Slope is the slope of the phase solubility diagram for LPZ-CDs.

Table-1 shows that solubilizing efficiency of lansoprazole proves to be different in different cyclodextrins, which indicates that the five cyclodextrins exhibit different inclusion capacity to lansoprazole. It is noted that hydroxypropyl-β-cyclodextrin has the highest stability constant among the five cyclodextrins and it is more efficient than other cyclodextrins. The inclusion capacity of lansoprazole with cyclodextrin derivatives, expressed by the stability constant, follow in the order: HP-β-CD > ME-β-CD > SBE-β-CD > HE-β-CD > β-CD.

TABLE-1
INCLUSION STABILITY CONSTANTS (K) OF LANSOPRAZOLE WITH DIFFERENT CYCLODEXTRINS

Host	β-CD	HE-β-CD	SBE-β-CD	Me-β-CD	HP-β-CD
K/L mol^{-1}	64.16	64.64	71.15	72.27	184.91

Influence of temperature and pH: The influence of temperature in the range of 5-30 °C and pH from 7 to 11 on the inclusion capacity with hydroxypropyl-β-cyclodextrin in water were investigated. The inclusion stability constants of 1:1 complex formation of LPZ/HP-β-CD are listed in Table-2. The inclusion stability constants increased with the increasing of the temperature values and pH values.

TABLE-2
INCLUSION STABILITY CONSTANTS OF LPZ/HP-β-CD COMPLEX AT DIFFERENT TEMPERATURES AND AT DIFFERENT pH VALUES

T (K)	K (L mol^{-1})	ln K	pH	K (L mol^{-1})	ln K
278.15	188.51	5.24	7.0	170.21	5.14
293.15	221.32	5.40	9.0	186.11	5.23
308.15	268.40	5.59	11.0	215.76	5.37

^{1}H NMR studies: The changes of chemical shifts for lansoprazole in the ^{1}H NMR spectrum shown in Fig. 4 confirm formation of inclusion complexes. In the ^{1}H NMR spectrum free lansoprazole, a signal at 7.714 ppm is from the proton of H-2 or H-5. The detailed changes of chemical shifts between free lansoprazole and complexed lansoprazole are given in Table-3.

As shown in Table-3, chemical shifts of lansoprazole protons are changed in the presence of cyclodextrins and either upfield or downfield displacements appear in comparision with those of the pure drug. H-2 or H-5 signal shows upfield displacement, suggesting that this moiety enters into a rich electronic density environment which cause a shielding effect. H-3 or H-4 signal shows downfield displacement as an evidence

TABLE-3
VARIATION OF ^{1}H NMR CHEMICAL SHIFTS (ppm) OF LANSOPRAZOLE IN THE PRESENCE OF CYCLODEXTRINS

Protons of lansoprazole	Δδ (ppm)				
	LPZ /HP-β-CD	LPZ /HE-β-CD	LPZ/ Me-β-CD	LPZ /SBE-β-CD	LPZ/ β-CD
H-3 or H-4	-0.012	-0.006	-0.019	0.001	0.002
H-2 or H-5	-0.065	-0.069	-0.070	-0.062	-0.073

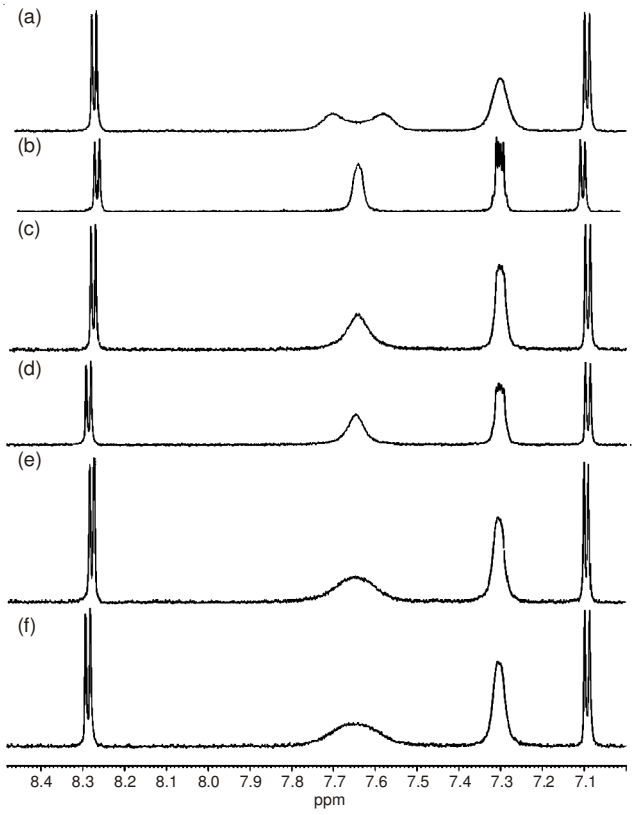

Fig. 4. Expansion of the ^{1}H NMR spectra of lansoprazole in the free state (a) and in the complexed formed with β-CD (b), with HP-β-CD (c), with Me-β-CD (d) with HE-β-CD (e), with SBE-β-CD (f)

of deshielding effect, which may be due to the presence of hydrogen bond. Significant changes of chemical shifts are observed for H-2 or H-5, H-3 or H-4 protons and no changes of significant chemical shifts are observed for other protons, indicating that benzimidazole group of lansoprazole is most probably inserted into the cavity of cyclodextrins.

Conclusion

The formation of inclusion complexes of lansoprazole with cyclodextrins with a stoichiometric ratio of 1:1 is studied. The aqueous solubility of lansoprazole can be enhanced markedly by cyclodextrins. The 1H NMR spectrum results indicate that benzimidazole group of lansoprazole is most probably embedded in the cavity of cyclodextrins. The inclusion stability constants increase with the increase of temperature and pH.

ACKNOWLEDGEMENTS

This work gained the support from the National Natural Science Foundation of China (No. 21176262 and No. 21071052).

REFERENCES

1. Y.F. Luo, L.H. Xu, M. Xu, J. Feng and X. Tang, *Asian J. Pharm. Sci*., **7**, 149 (2012).
2. Y. Lu, T. Guo, J.P. Qi, J.W. Zhang and W. Wu, *AAPS Pharm. Sci. Tech*., **13**, 1222 (2012).
3. C.A. Stedman and M.L. Barclay, *Aliment. Pharmacol. Ther*., **14**, 963 (2000).
4. Y. Ito, H. Arai, K. Uchino, K. Iwasaki, N. Shibata and K. Takada, *Int. J. Pharm*., **289**, 69 (2005).
5. M. DellaGreca, M.R. Iesce, L. Previtera, M. Rubino, F. Temussi and M. Brigante, *Chemosphere*, **63**, 1087 (2006).
6. B. Prabagar, B.K. Yoo, J.S. Woo, J.A. Kim, J.D. Rhee, M.G. Piao, H.G. Choi and C.S. Yong, *Arch. Pharm. Res*., **30**, 249 (2007).
7. T. Loftsson and M. Brewster, *J. Pharm. Sci*., **85**, 1017 (1996).
8. V.J. Stella and R.A. Rajewski, *Pharm. Res*., **14**, 556 (1997).
9. Y.J. Dang, L.N. An, C.H. Hu and C.Y. Zhu, *J. Appl. Polym. Sci.*, **123**, 1557 (2012).
10. R. Vaitkus and S. Sjoberg, *J. Incl. Phenom. Macrocycl. Chem*., **69**, 393 (2011).
11. J. Szejtli, *Chem. Rev*., **98**, 1743 (1998).
12. Z.Y. Sun, G.P. Cao, H. Lv, L. Zhao, T. Liu, L. Montastruc and N. Iordan, *J. Appl. Polym. Sci*., **114**, 3882 (2009).
13. W. Misiuk and M. Zalewska, *J. Mol. Liq*., **159**, 220 (2011).
14. C.S. Zhou, P. Xu, K.W. Tang, X.Y. Jiang, T. Yang and P.L. Zhang, *Chem. Pap*., **67**, 155 (2013).
15. G. Castronuovo and M. Niccoli, *J. Therm. Anal. Calorim*., **103**, 641 (2011).
16. M. Shanmugam, D. Ramesh, V. Nagalakshmi, R. Kavitha, R. Rajamohan and T. Stalin, *Spectrochim. Acta A*, **71**, 125 (2008).
17. T. Higuchi and K.A. Connors, *Adv. Chem. Instrum*., **4**, 117 (1965).
18. H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc*., **71**, 2703 (1949).