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ORIGINAL ARTICLE

Characteristic profiles of the inclusion complex of omeprazole/peracylated-β-cyclodextrin formed in supercritical carbon dioxide

Tamanna Sultana · Jae Mok Jung · Seong-Soo Hong · Won-Ki Lee · Yeong-Soon Gal · Hyun Gyu Kim · Kwon Taek Lim

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Abstract Inclusion properties of the drug omeprazole (OMP) with peracetylated-beta-cyclodextrin (PAc-β-CD) prepared by green method, following supercritical carbon-dioxide ($scCO_2$), were characterized through thermal (TGA and DSC), crystalline (XRD), NMR spectroscopic and dissolution studies. Comparison amongst PAc-β-CD, OMP, physical binary mixture (equimolar ratio of OMP: PAc-β-CD) and the solid inclusion complex (OMP/PAc-β-CD) revealed $scCO_2$ as a successful technique for inclusion complex formation as well, identified characteristics performances of PAc-β-CD/OMP interactions. For instance, absence of characteristic DSC or XRD peaks of either chemical in the complex was quite noticeable with the shift of proton peaks in ^{1}H NMR spectra. The formed inclusion complex also showed an important dissolution performance of OMP for controlled release applications partly due to the hydrophobic nature of PAc-β-CD.

Keywords Omeprazole · Peracetylated-beta-cyclodextrin · Supercritical carbon dioxide · Inclusion complex · In vitro release rate

T. Sultana · J. M. Jung · K. T. Lim (✉)
Department of Imaging System Engineering, Pukyong National University, Busan 608-739, Korea
e-mail: ktlim@pknu.ac.kr

T. Sultana
Department of Applied Chemistry and Chemical Engineering, University of Dhaka, Dhaka 1000, Bangladesh

S.-S. Hong · W.-K. Lee
Division of Chemical Engineering, Pukyong National University, Busan 608-739, Korea

Y.-S. Gal
Polymer Chemistry Laboratory, College of Engineering, Kyungil University, Gyeongsan, Gyeongsangbuk-Do 712-701, Korea

H. G. Kim
Korea Basic Science Institute, Busan Center, Busan 618-230, Republic of Korea

Introduction

Omeprazole (OMP), a primary member of proton pump inhibitors, has been extensively used to control acid disorders like- peptic ulcer, reflux disease, erosive esophagitis, Zollinger-Ellison syndrome, duodenal ulcer, multiple endocrine adenomas, dyspepsia and also in the treatment of *Helicobacter pylori* infection and systematic mastocytosis etc. The molecular structure of OMP contains tri-coordinated sulfur atom in pyramidal structure (Fig. 1) and thus, exist in both the S and R enantiomers, i.e. as a racemate. In human body, the ultimate mediator of acid secretion is the H^+/K^+ ATPase and this pump is unique to the parietal cells and also to specific inhibitors it has. In the acid space of the secreting parietal cells, pharmacologically, OMP is converted to achiral products (i.e. thiofilic sulfon amide or sulfenic acids), which reacts mainly with the cysteine-813 residue in the catalytic subunit of the H^+/K^+ ATPase and this create a situation which is critical for enzyme inactivation and ultimately inhibit parietal cells to produce gastric acid. However, OMP is very slightly soluble in water ($\sim$0.5 mg/mL) and this is a fact for small dissolution rates as well as, low bioavailability of this drug [1]. More pharmaceutical drawbacks of omeprazole are mainly related to the

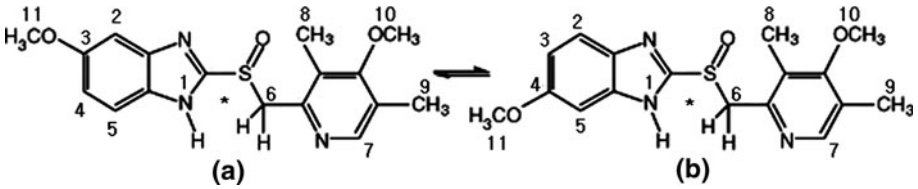

Fig. 1 Molecular structure of omeprazole (OMP, 5(6)-methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl}-1*H*-benzimidazole) as **a** 5-methoxy tautomer structure and **b** 6-methoxy tautomer structure

physico-chemical instability to heat, light, moisture, solvents, exposure to UV light, various salts, metal ions and acidic media even with coated formulations [2–4]. To overcome these stability and solubility limitations of drugs several approaches had been carried out in the past on different drugs using derivatives of natural cyclodextrins (CDs) and utilizing various methods like spray drying, kneading, freeze drying and physical mixing etc. [1]. However, not many works have been reported in the past focusing the delayed release applications for avoiding frequent doses, though capsules formulated with enteric coated granules and covered with a shell containing a large number of inactive ingredients could work. It is well known that, the most important features of the CDs is the ability to form inclusion complexes with a large variety of guest molecules and ions that have a suitable size and shape to be fully or partially accommodated in their central cavities [5] and thereby, enlighten the favorable properties as complex by improving or altering aqueous solubility, bio-adaptability and stability of a variety of poorly soluble and labile drugs [6, 7]. Chemically these CDs are cyclic oligosaccharides containing at least 6 D (+) glycopyranose units attached by α (1, 4) glycosidic bonds. The four natural CDs as α, β, γ and δ with 6, 7, 8 and 9 glucose units, respectively, differ in their ring sizes and solubility [8]. The cavity size of α CD is insufficient for many drugs, whereas, γ CD is expensive and δ CD has weaker complex forming ability. On the other hand, β CD because of its ready availability and suitable cavity size for wide range of drugs is the most popular for pharmaceutical applications. However, most of the preparation methods used in previous investigations for inclusion complex formation was time consuming, need multistage processing, used expensive solvents and required evaporation of large volume of liquid solvents to ensure no harmful residue in the final product.

Recently, supercritical carbon dioxide ($scCO_2$) based technology has emerged as a favored option in food, pharmaceutical and chemical process industries mainly for the replacement of organic solvents by non flammable, non toxic and inexpensive CO_2, which avoid chance of toxic solvent residues, the absence of gas liquid phase

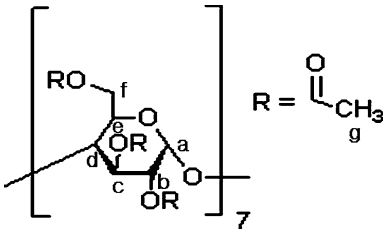

Fig. 2 Molecular structure of peracetylated beta cyclodextrin (PAc-β-CD)

boundary and ease of product recovery etc. [9]. Several trials for medicine β-cyclodextrin complexes have been successfully performed in $scCO_2$ for enhanced solubility and dissolution rate [10–14]. More recently we reported the complex of water-soluble drug molsidomine and CO_2-soluble peracylated-β-cyclodextrin (PAc-β-CD) (Fig. 2) [15].

The characterization of the prepared complex of OMP and PAc-β-CD using $scCO_2$ was carried out following thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray diffractometry (XRD), ^{1}H NMR and drug dissolution studies. This work also included comparison of analytical parameters among the drug, the physical mixtures and the complex formed with OMP and PAc-β-CD in $scCO_2$. OMP is a poor water-soluble drug but its solubility and half life is highly pH dependent. Therefore, most oral preparations available are enteric coated due to the rapid degradation of OMP in the acidic conditions of the stomach. Theoretically, hydrophilic CDs are targeted with limited aqueous soluble drugs for complex formation, whereas hydrophobic CDs are considered as controlled release carrier. It has been reported that peracetylated CDs are hydrophobic in nature and exhibits high degree of miscibility with dense CO_2 over a broad range of concentration [15, 16]. The solubility of PAc-β-CDs in $scCO_2$ was comparable to those oligomers of poly (vinyl acetate), containing an equivalent number of acetate groups, which are known to be the most CO_2-soluble vinyl homopolymers composed solely of carbon, hydrogen and oxygen [17]. For example, 5 wt% of PAc-β-CD is soluble about 34.5 MPa at 45 °C. In these contexts, we have

envisaged to use PAc-β-CDs with OMP to investigate the performances of inclusion complex formed in $scCO_2$.

Experimental

Materials

PAc-β-CD (2,3,6-tri acetyl-β-cyclodextrin/heptakis, $C_{84}H_{112}O_{56}$, Mw 2017.75 g/mol) and OMP drug ($C_{17}H_{19}N_3O_3S$, Mw 345.4 g/mol) were purchased from Sigma-Aldrich (Korea) and used as received. All other reagents (chemicals and solvents) used in this study were of analytical reagent grade.

Formation of inclusion complexes in $scCO_2$

The supercritical CO_2 technique used in this study for the complex formation contains a 10 mL high pressure stainless steel reactor equipped with sapphire quartz window. A high pressure syringe pump (ISCO model 260D series) was used to introduce densified carbon dioxide into the reactor. Heating was provided by a water bath and temperature was recorded with a thermocouple (Doric Trendicator 400A). Teflon coated magnetic stir bar was used to mix the cell contents. In a typical inclusion experiment, equimolar mixture of OMP and PAc-β-CD were placed in the high pressure reactor and carbon dioxide was charged into the cell using the syringe pump until the pressure reached to 34.5 MPa at 45 °C. After 2 h of stirring CO_2 was slowly vented off and the product was collected as powder.

The physical mixture of OMP and PAc-β-CD were prepared by simply blending both solids at 1:1 molar ratio (12 mg of PAc-β-CD and 2 mg of OMP) uniformly in a mortar at room temperature.

Characterization of inclusion complexes

Pure materials (i.e. OMP, PAc-β-CD), the inclusion complexes, and physical mixtures of OMP and PAc-β-CD were investigated for the thermal behavior of each sample using TGA (with a Perkin-Elmer TGA7) and DSC (with a DSC 60 Shimadzu, Japan). Crystallinity of the samples was determined using powder XRD (with a Philips X" Pert MPD, Japan). ^1H NMR spectra were recorded using a JNM-ECP 4000 (JEOL) spectrometer with DMSO-d_6 solvent. The concentration of OMP in DMSO-d_6 was fixed at 0.93 mg/mL.

In vitro drug dissolution studies

The in vitro release rate of OMP from an oily suspension of drug/PAc-β-CD complex was measured according to the paddle method of dissolution test described in Japanese pharmacopeia XIV. OMP or its 1:1 molar complex of PAc-β-CD (equivalent to 2 mg of OMP) was suspended in 10 mL of peanut oil for 30 min, which was used as a vehicle for sustained release preparations. 30 mL of acidic water (pH 4) then added to the suspension and the mixture was kept at 37 °C. Sample solutions (1 mL) were drawn with a cotton plug and diluted with 2 mL of acidic water. The release rate of OMP from the oily phase into water was assayed by spectrometrically (Lambda 40 UV–Vis spectrometer, Perkin Elmer) at a wavelength of ca. 332 nm where linearity pf the concentration versus absorption relation was ascertained as reported previously [15].

Results and discussion

Prior to the inclusion experiment, the solubility of PAc-β-CD and OMP was examined by using a variable volume cell equiped with sapphire window [18]. 12 mg of PAc-β-CD was fairly soluble in 10 mL of supercritical CO_2 at 34.5 MPa and 45 °C. The solution became transparent immediately after mixing and the cloud point of the solution was detected at 18.6 MPa from isothermal expansion. On the other hand, OMP was completely insoluble at this condition, as white power was clearly observed through the sapphire window and the cloud point was not detected upon expansion. However, 2 mg of OMP was put in the cell together with 12 mg of PAc-β-CD, the solid drug slowly disappeared in the reactor and the whole system became homogeneous in 40 min under the experimental conditions (34.5 MPa and at 45 °C). The cloud point of the solution was found at 21.0 MPa from isothermal expansion. This result clearly indicates the phenomena of molecular complexation of the drug with PAc-β-CD in the presence of $scCO_2$. It has been known that PAC-β-CD rarely showed inclusion behavior possibly due to the self-inclusion and its low solubility in water [5]. Here the complexation mechanism is not clear, but it is assumed that CO_2-philic acetate groups favor bulk $scCO_2$ phase to result in strong interaction between the host and guest molecules. To investigate the pharmaceutical characteristics, the inclusion complex, OMP/PAc-β-CD, obtained after venting $scCO_2$ was subjected to TGA and DSC analysis. The TGA thermograms of OMP, PAc-β-CD, and the complex of OMP/PAc-β-CD recorded up to 800 °C at a heating rate of 10 °C/min under nitrogen atmosphere are shown in Fig. 3. OMP started to decompose at ca. 165 °C and the weight loss continued to around 500 °C, while a rapid weight loss was found at ca. 350 °C for PAc-β-CD. The complex showed the combined weight loss behavior of OMP and PAc-β-CD upon heating. For DSC analysis, the samples were heated up to 300 °C with a rate of 10 °C/

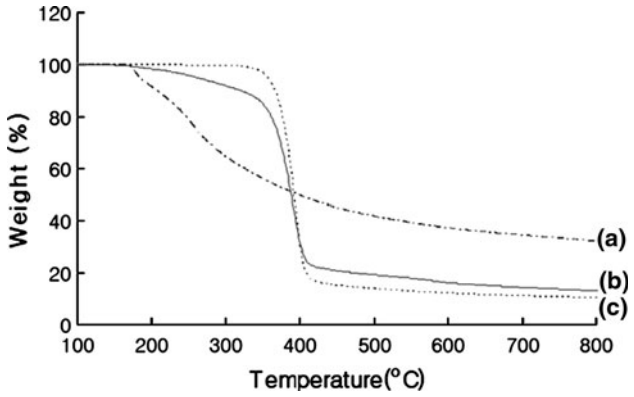

Fig. 3 Thermogravimetry of **a** OMP, **b** the OMP/PAc-β-CD complex, and **c** PAc-β-CD

min. As shown in Fig. 4a, free OMP exhibits sharp fusion endothermic at 160 °C corresponding to its melting points. The exothermic peaks between 170 and 190 °C are attributed to decomposition. In the DSC of PAc-β-CD (Fig. 4b), an endothermic peak appears at 205 °C, which can be assigned to solid–liquid phase transition [19]. Similarly, two peaks corresponding to the melting of OMP and PAc-β-CD were observed in the same range of thermograms for the physical mixture, consisting of 1:1 molar ratio of the OMP and PAc-β-CD (Fig. 4c). It is worth notice the absence of exothermic peaks at around 170–190 °C on the DSC, which may be attributable to the increased thermal stability of OMP in the physical mixture. In contrast, there were no such detectable peaks for the inclusion complex prepared with the similar composition in $scCO_2$ and this absence of peaks indicated a more stable and strong interaction of OMP with PAc-β-CD (Fig. 4d). As it is well known that the disappearance or shifting of endo- or exothermic peaks is a strong evidence of thermal behavioral for the encapsulation of host species by the cyclodextrin at the molecular level [20]. Further,

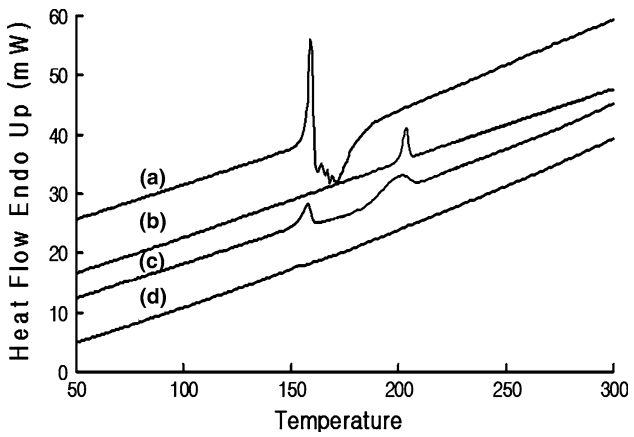

Fig. 4 DSC thermograms of **a** OMP **b** PAc-β-CD **c** physical mixture of OMP and PAc-β-CD and **d** the OMP/PAc-β-CD complex

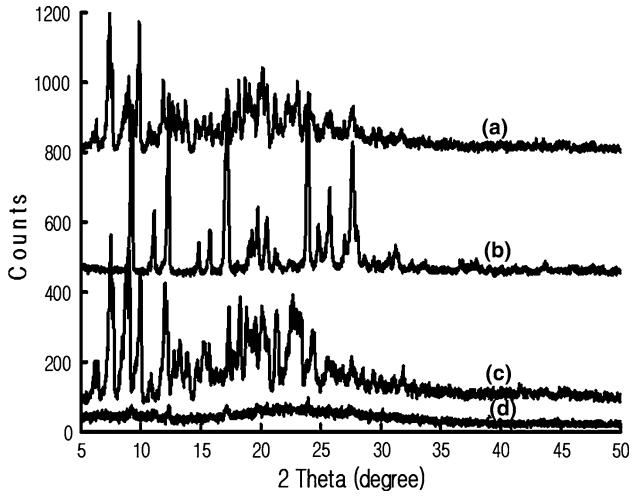

Fig. 5 XRD diffractograms of **a** PAc-β-CD **b** OMP **c** physical mixture of OMP and PAc-β-CD and **d** the OMP/PAc-β-CD complex

crystalline behavioral observations with XRD showed additional support for the formation of the complex in $scCO_2$ (Fig. 5). For instance, XRD patterns of both OMP and PAc-β-CD powder showed sharp peaks, which suggested the high crystallinity of individual compounds. In the XRD of the physical mixture of OMP and PAc-β-CD (Fig. 5c), the wide peak of amorphous phase is not apparent, indicating that it is mostly additive sum of the XRD of pure OMP and PAcCD. In contrast, very wide peaks are seen in the amorphous complex between OMP and PAc-β-CD from $scCO_2$ (Fig. 5d). These results confirm that OMP is no longer present as a crystalline material and its solid inclusion complexes exist in the amorphous state.

Theoretically, H bonding and non specific forces change in both the drug and the carrier molecules when these host and guest molecules form inclusion complex and which ultimately affects the chemical shift of nuclear magnetic resonance [21]. Therefore, the use of equimolar amounts of OMP and PAc-β-CD in the complex is expected to cause detectable complexation shifts of both OMP and PAc-β-CD protons. The ^{1}H NMR spectra presented in Fig. 6 shows a comparative displacement of ^{1}H-chemical shifts among individual bulks, the physical mixture and the complex to extract additional supportive information for the OMP/PAc-β-CD complex. The NMR spectra of the complex and equimolar physical mixture were almost identical at the same concentration of OMP. Even though the differences in characteristic peaks are extremely small, the detectable changes observed are chemical shifts of both guest and host peaks in the complex formed. For instance, considering the host (carrier PAc-β-CD) molecule first, chemical shift changes of ca. 0.001 ppm were measured for the ring proton peaks in the OMP/PAc-β-CD complex For

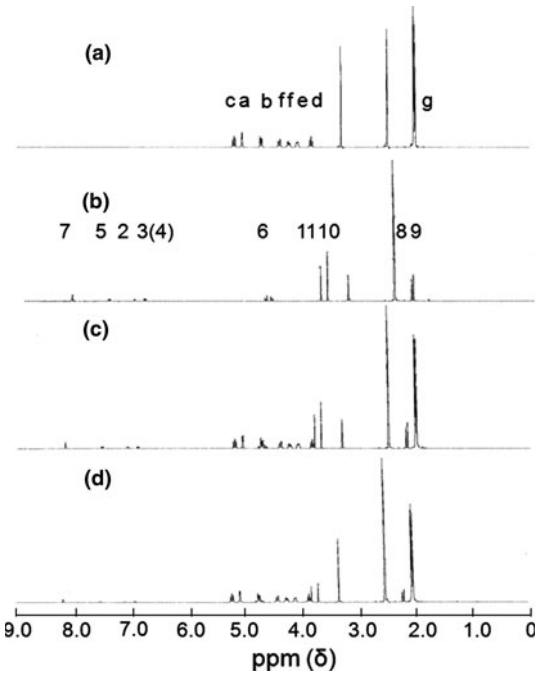

Fig. 6 ^{1}H NMR spectra of **a** PAc-β-CD, **b** OMP, **c** physical mixture of OMP and PAc-β-CD, and **d** the OMP/PAc-β-CD complex in DMSO-d_6

the drug molecule (OMP), four protons attached to the aromatic ring (H-2, H-3(4), H-5, and H-7) in the complex are too weak in the NMR spectra to compare with those of pure OMP. However, the complexation shift ($\Delta\delta$) of 0.01 ppm was shown for the peak 11 (–OCH_3) of OMP in the complex, whereas the chemical shift of the peak 10 (–OCH_3) was negligibly changed, indicating that the presence of PAC-β-CD much affected the H-11 protons of OMP. Therefore, methoxy groups of benzimidazole moiety might be involved in the complexation with PAc-β-CD. The result suggests that complexation involving an inclusion of the benzimidazole fragment into the cavity of the host. This is in accord with the experimental results and ab initio calculations from the OMP and β-CD complex produced in aqueous NaOH [22].

OMP is amphoteric with p*K*a values of 3.98 for accepting a proton on the pyridine nitrogen atom, and 8.7 for releasing a proton from the NH group of the benzimidazole [23]. Basically it has poor aqueous solubility, thus the release test in neutral water did not give appreciable change in UV peaks in the time interval. On the other hand, inconsistent result was obtained at pH 2 where OMP was fairly soluble, possibly due to decomposition of OMP in strong acidic condition. Therefore the release experiment was performed at weak acidic water (pH 4), which is the pH environment between in stomach and small intestine. OMP itself was also fairly soluble in this condition. The dissolution profiles of the drug OMP from the

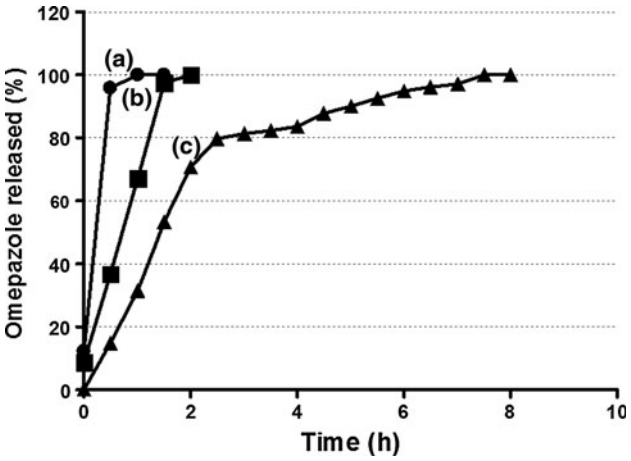

Fig. 7 *In vitro* drug dissolution profiles of OMP from the oily suspension in acidic water (pH 4) at 37 °C containing **a** OMP alone, **b** physical mixture, and **c** the OMP/PAc-β-CD complex

oily suspension containing the drug alone, physical mixture and inclusion complex into the acidic water phase are compared in Fig. 7. It is apparent that in vitro release rate of OMP retarded slightly by the addition of PAc-β-CD as can be observed from the physical mixture of equimolar ratio. This can be partly explained by the fact that a few complexes may be produced in the mixture [24]. However, comparing to the release pattern of the inclusion complex, the dissolution rate of both drug alone or the physical mixture were very fast as the released percentage of the drug after 2 h was 100%. Whereas, 65% release of drug was measured after 2 h from the inclusion complex, which slowly reached to 82% and the maximum 100% after 4 and 7.5 h respectively. Therefore, it is noticeable that interfacial transfer of OMP was significantly retarded by the complexation with PAc-β-CD. Moreover, the complexation might contribute to the stability of OMP in the acidic condition. OMP was insoluble in peanut oil and its solubility was not increased by complexation with PAc-β-CD. As a consequence, the drug is dispersed with an oily matrix through a moderate drug/CD interaction and/or the affinity of hydrophobic CDs to the vehicle. The extended duration of the drug release is attributed to the slow dissolution of the inclusion complex at oil/water interface due to poor water solubility of PAc-β-CD.

Conclusions

In this study, application of green technology using $scCO_2$ was a successful approach for the formation of inclusion complex of drug OMP, a major proton pump inhibitor with PAc-β-CD. The prepared OMP/PAc-β-CD complex was characterized by DSC, XRD, ^{1}H-NMR and release rate analysis through comparison with other samples, which

were pure drug, pure carrier and the equimolar physical mixtures of those. The complex showed no detectable and characteristic DSC and XRD peaks like individual OMP or PAc-β-CD sample as successfully treated in $scCO_2$, however, noticed peaks were identified from the physical mixture. The investigation of the proton peak shift in ^1H NMR spectra suggested that the inclusion process involves encapsulation of the benzimidazole fragment of OMP in the PAc-β-CD cavity. The OMP dissolution pattern from peanut oil into acidic aqueous phase was remarkably sustained and the stability of OMP was increased by the complexation with PAc-β-CD mainly due to the hydrophobic properties of the host molecules. Therefore, this green method could be applied for the sustained/controlled release formulations of clinically demanded OMP drugs.

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References

1. Figueiras, A., Ribeiro, L., Teresa, M.: Preparation and physicchemical characterization of omeprazole: methyl beta cyclodextrin inclusion complex in solid state. J. Incl. Phenom. Macrocycl. Chem. **57**, 173–177 (2007)
2. Figueiras, A., Carvalho, R.A., Ribeiro, L., Torres-Labandeira, J.J., Veiga, F.J.B.: Solid state characterization and dissolution profiles of the inclusion complexes of omeprazole with native and chemically modified β-cyclodextrin. Eur. J. Pharm. Biopharm. **67**, 531–539 (2007)
3. Marzocchi, L., Moyano, J.R., Rossi, A., Munoz, P., Arias, M.J., Giordano, F.: Current status of ATPase proton pump inhibitor complexation with cyclodextrins. Biol. J. Armen. **53**, 176–193 (2001)
4. Riedel, A., Leopold, C.S.: Degradation of omeprazole induced by enteric polymer solutions and aqueous dispersions: HPLC investigations. Drug Dev. Ind. Pharm. **31**, 151–160 (2005)
5. Anibarro, M., Gessler, K., Uson, I., Sheldrick, G.M., Harata, K., Uekama, K., Hirayama, F., Abe, Y., Saenger, W.: Effect of peracylation of α-cyclodextrin on the molecular structure and on the formation of inclusion complexes: an X-ray study. J. Am. Chem. Soc. **123**, 11854–11862 (2001)
6. Castronuovo, G., Niccoli, M.: Thermodynamics of inclusion complexes of natural and modified cyclodextrins with propranolol in aqueous solution at 298 K. Bioorg. Med. Chem. **14**, 3883–3887 (2006)
7. Yang, X., Kim, J.C.: pH-Dependent release of blue dextran from carboxymethyl-β-cyclodextrin hydrogels. J. Ind. Eng. Chem. **16**, 763–766 (2010)
8. Loftsson, T., Brewester, M.: Pharmaceutical applications of cyclodextrins, drug solubilization and stabilization. J. Pharm. Sci. **85**, 1017–1025 (1996)
9. Beckman, E.J.: Super critical and near critical CO_2 in green chemical synthesis and processing. J. Supercrit. Fluids **28**, 121–191 (2004)
10. Van Hees, T., Piel, G., Evrared, B., Otte, X., Thunnus, L., Delattre, L.: Application of supercritical carbon dioxide for the preparation of a piroxicam-β-cyclodextrin inclusion compound. Pharm. Res. **16**, 1864–1870 (1999)
11. Tozuka, Y., Fujito, T., Moribe, K., Yamamoto, K.: Ibuprofen-cyclodextrin inclusion complex formation using supercritical carbon dioxide. J. Incl. Phenom. Macrocycl. Chem. **56**, 33–37 (2006)
12. Bounaceur, A., Rodier, E., Fages, J.: Maturation of ketoprofen/β cyclodextrin mixture with supercritical carbon dioxide. J. Supercrit. Fluids **41**, 429–439 (2007)
13. Al-Marzouqi, A.H., Solieman, A., Shehadi, I., Adem, A.: Influence of the preparation method on the physicochemical properties of econazole-β-cyclodextrin complexes. J. Incl. Phenom. Macrocycl. Chem. **60**, 85–93 (2008)
14. He, J., Li, W.: Preparation of borneol-methyl-β-cyclodextrin inclusion complex by supercritical carbon dioxide processing. J. Incl. Phenom. Macrocycl. Chem. **65**, 249–256 (2009)
15. Lee, M.Y., Ganapathy, H.S., Lim, K.T.: Controlled drug release applications of the inclusion complex of peracetylated-b-cyclodextrin and water-soluble drugs formed in supercritical carbon dioxide. J. Phy. Chem. Solids **71**, 630–633 (2010)
16. Filardo, G., Di Blasi, M., Galia, A., Ponchel, A., Bricout, H., Sayede, A.D., Monflier, E.: Peracetylated-β-cyclodextrin as solubilizer of arylphosphines in supercritical carbon dioxide. J. Supercrit. Fluids **36**, 173–181 (2006)
17. Potluri, V.K., Hamilton, A.D., Karanikas, C.F., Bane, S.E., Xu, J., Beckman, E.J., Enick, R.M.: The high CO_2-solubility of peracetylated α-, β-, and γ-cyclodextrin. Fluid Phase Equilib. **211**, 211–217 (2003)
18. Hwang, H.S., Heo, J.Y., Jeong, Y.T., Jin, S.-H., Cho, D., Chang, T., Lim, K.T.: Preparation and properties of semifluorinated block copolymers of 2-(dimethylamino)ethyl methacrylate and fluorooctyl methacrylates. Polymer **44**, 5153–5158 (2003)
19. Veiga, M.D., Merino, M., Fernandez, D., Lozano, R.: Characterization of some cyclodextrin derivatives by thermal analysis. J. Therm. Anal. Calorim. **68**, 511–516 (2002)
20. Herchuelz, A., Carreer-Bruhwyler, F., Crommen, J., Chiam, P., Hubert, P., Messim, R., Dubois, C., Famaui, F.P., Gecjy, J.: Clinical pharmacokinetics of once-daily molsidomine: from immediate-release to prolonged-release once-daily formulations. Am. J. Drug Deliv. **2**, 131–141 (2004)
21. Schneider, H., Hacket, F., Rudiger, V., Ikeda, H.: NMR studies of cyclodextrins and cyclodextrin complexes. Chem. Rev. **98**, 1755–1786 (1998)
22. Braga, S.S., Ribeiro-Claro, P., Pillinger, M., Gonçalves, I.S., Fernandes, A.C., Pereira, F., Romão, C.C., Correia, P.B., Teixeira-Dias, J.J.C.: Interactions of omeprazole and precursors with β-cyclodextrin host molecules. J. Incl. Phenom. Macrocycl. Chem. **47**, 47–52 (2003)
23. Brändström, A., Lindberg, P., Bergman, N.A., Alminger, T., Anker, K., Junggren, U., Lamm, B., Nordberg, P., Erickson, M., Grundevik, I., Hagin, I., Hoffmann, K., Johnsson, S., Larsson, S., Löfberg, I., Ohlson, K., Persson, B., Skänberg, I., Tekenbergs-Hjelte, L.: Chemical reactions of omeprazole and omeprazole analogues I. A survey of the chemical transformations of omeprazole and its analogues. Acta Chem. Scand. **43**, 536–548 (1989)
24. Nozawa, Y., Kishimoto, H.: Complex formation in amorphous powder mixture of β-cyclodextrin with medicinal drug by roll mixing procedures. J. Soc. Powder Technol. **29**, 460–464 (1992)